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Discussion

Dr. J. Lynwood Herrington, Jr. (Nashville, Tennessee): It has been my experience that patients with pronounced subjective symptoms of reflux, coupled with severe and widespread gastric mucosal inflammation, do gain benefit from the remedial operation. If these operative criteria are not rigidly met, the operative results are, indeed, disappointing. Satisfactory results have been obtained in approximately 80% of the patients in our series, which now totals 96 patients. Fifty-five of those patients obtained excellent results, and the conditions of 25% have improved.

Most of us will agree that severe reflux gastritis occurs more commonly after a Billroth II type reconstruction than after a Billroth I or a pyloroplasty, and it is virtually nonexistent after a proximal gastric vagotomy.

I present for your consideration, and I am not the first to suggest the use of, a Roux-en-Y diversion as a primary operation for duodenal ulcer, when proximal gastric vagotomy or a Billroth I type of reconstruction is not feasible. We are all aware that a Roux-en-Y diversion alone is ulcerogenic, but not so when accompanied by an adequate vagotomy and an adequate resection. The primary operation can then prevent the distressing complications of reflux gastritis that we so frequently encounter.

If we combine the resection with a selective gastric vagotomy, the possibility of severe postvagotomy diarrhea developing is, indeed, small. Furthermore, as you know, Dr. Edward Woodward has shown that a Roux-en-Y gastrojejunostomy empties slowly, and the dumping syndrome is, thus, diminished considerably. Emptying problems, however, can be of great concern in a small number of patients with Roux-en-Y diversions. Therefore, this primary operation could serve to diminish considerably the three distressing, long-range postgastrectomy problems that we face today.

In our series of 96 Roux-en-Y diversions, only two marginal ulcers have occurred, and each was due to incomplete vagotomy.

I congratulate Dr. Warshaw on a splendid presentation, and would like to have a later follow-up on a larger number of patients.

How do you explain the negative test response in your six patients with clinical symptoms and documented reflux? Did these six patients have severe and extensive mucosal changes?

Also, in your positive test cases, did the gross appearance of the gastric mucosa change on endoscopic study?

Dr. David Fromm (Syracuse, New York): Dr. Warshaw, I am left with more confusion than solution. The term alkaline is probably, as you admit, a misnomer. It is not, at least by current concepts, the alkalinity of the refluxed duodenal contents that is responsible for the symptoms. It is either the bile salts or bile acids or perhaps lysolecithin; it is the pH in the gastric lumen that is responsible for whether or not these agents cause mucosal alterations and symptoms.

I fail to understand how a solution of pH 13 can be responsible for symptoms, or responsible for an alkaline gastritis, if the patient's own gastric juice does not cause symptoms. Did you give any of your successfully treated patients your pH solution of 13 postoperatively to see if that correlated with their improvement?

Dr. A. Rahim Moossa (Chicago, Illinois): In the early 1950s (slide) Charles Wells of Liverpool suggested that bile acid reflux following a Billroth II gastrectomy is the result of an afferent loop syndrome. Intermittent emptying of bile from the afferent loop into the stomach, sometimes precipitated by eating, leads to alkaline gastritis/esophagitis and bilious vomiting. Because of this hypothesis we studied the problem using Tc-HIDA. This radiopharmaceutical agent is administered intravenously to the patient, and the abdomen is scanned. The liver parenchyma is first visualized followed by the appearance of isotope in the common bile duct and into the afferent loop (slide). The afferent loop is filled and distended; suddenly the afferent loop empties, especially in response to a meal, and the isotope refluxes into the stomach and sometimes into the esophagus. Bilious vomiting may occur at this stage.

This method was the most useful way of diagnosing bile acid reflux. Bile remains in the stomach and the afferent loop for quite a long time, even after 3 hours.

(slide) Following the Roux-en-Y diversion, repeat Tc-HIDA scan demonstrates bile coming into the afferent loop and bypassing the stomach without inducing the patient's symptoms.

In regard to the pain provocation tests suggested by Dr. Warshaw, I share the same reservations that Dr. Fromm mentioned, and I have two additional questions: 1) I am worried about the control group. I would have preferentially chosen as controls persons who have had a Billroth II gastrectomy but who have symptoms. 2) Have you tried using bile or a bile acid solution as the test solution?

We see a fair number of these patients referred to us with a provisional diagnosis of recurrent pancreatitis, because they often have elevated serum amylase levels during an attack of pain and vomiting.

Dr. Wallace P. Ritchie, Jr. (Charlottesville, Virginia): Stimulated by those who believe that alkaline reflux gastritis is a real entity, and not just a diagnosis in search of a disease, several fairly sophisticated methods have been developed to identify patients with excessive enterogastric reflux after gastrectomy. As Dr. Moossa has indicated, and in my opinion as well, the most specific and sensitive of these is gamma camera scintography, using tecnitium-labeled HIDA or PRIDA.

As Dr. Way and others have pointed out, none of these techniques is a reliable predictor of the clinical efficacy of remedial operative procedures, and therein, of course, lies the rub, and therein too, on the surface of it, lies the significance of Dr. Warshaw's contribution, a provocative test that, apparently, when positive predicts a 90% success rate, and that when negative predicts a 100% failure rate.

Now, this paper raises two issues, both of which have been raised before but deserve reiterating. The first relates to whether or not we can accept Dr. Warshaw's conclusions. Despite the somewhat serpentine way at which the definition of a positive test was arrived, I am tempted to hope that we can. My enthusiasm is somewhat tempered, however, by some methodologic problems, which could have confounded the results.

First, the sequence in which the solutions were instilled in the stomach was not randomized. Second, more important, this means that the individual responsible for assessing and grading symptomatic response was fully aware of which solution was being instilled, and that circumstance is ripe for the introduction of bias.

Third, like Dr. Moossa, I believe that a more appropriate control group could have been studies, patients who do not have symptoms after gastrectomy. These may be minor objections, but I believe they should be raised.

The second issue, I think, is far more interesting. If the observations are correct, how can we account for them? There are few sheets of epithelial cells in the body, even if healthy, which can tolerate exposure to a pH of 11.5, the pH of tenth normal sodium hydroxide, even for a brief period, and this includes the gastric mucosa, at least of the rat, according to André Robert. What is surprising, therefore, is not that the patients with reflux gastritis respond, but that normal individuals do not.

This raises the interesting possibility that the mucous membrane of the responders is already sensitized to the alkali. Could some factor in refluxed upper intestinal content be responsible? Since, as we and others have shown, a Roux limb of the length used here completely eliminates reflux, this possibility could be tested by doing what Dr. Fromm suggested; that is, repeating the study after operation at a time when the responding patients are completely without symptoms.

Perhaps Dr. Warshaw could enlighten us on what his results have been with this technique so far.

I hope that others with an interest in this disease will attempt to verify its conclusions in the near future.

DR. JAMES C. THOMPSON (Galveston, Texas): I am a bit uneasy to follow this parade of enthusiasts because I am a little bit skeptical about this condition. I wonder what we used to do with these people before we had this name to tag them with. I think we looked upon them as people who were dissatisfied with their gastrectomy and decided that "For God's sake, let's try not to operate on them any more." A major problem with most of these patients is that they have been operated upon many times.

Whenever an operation is proposed and the cure rate turns out to be only 40–60%, there is a problem in selecting those patients who properly should be operated on. I have managed to avoid operating on all but one patient in the last 8 years.

It bothers me to advocate this apparently nihilistic approach when such splendid surgical scientists as Dr. Ritchie and Dr. Warshaw have promulgated scientific theses that purport to provide a way to identify this problem and to help us select those who will be helped. I am speaking more from prejudice than from any kind of intellectual base, but I worry about patients who are going to undergo an operation and not be cured. I would like to propose a prophecy, that in a dozen years we will not see many of these patients being operated on.

The question that Dr. Warshaw asked on one of the slides was: Does alkali cause the symptoms? Well, if you require a pH of 10 or 11 to do it, I'll say, unequivocally no, in real life, alkali does not cause the symptoms. It is rare to have any pH above 8 within the stomach, even if bile and pancreatic juice are diverted directly through the stomach.

About ten years ago, my colleagues and I wondered about the effects of changes in pH on the antrum on the release mechanisms, first of all, of gastrin, and later of somatostatin, and then of pancreatic polypeptide. One of the things we showed was that if the mucosa of the stomach is exposed to a pH above 10, it will be uniformly damaged, and a pH of 12 will almost curdle the superficial layers of the mucosa. Has Dr. Warshaw happened to look at any mucosal biopsy specimens after the alkali? I suspect he has not been able to talk anybody into undergoing both intubation and biopsy at the same time, but it is a good question.

I would also like to know how long the test period is, because we found out that not only was the high pH itself dangerous, but the longer the pH was applied, the worse trouble it caused.

DR. LAWRENCE W. WAY (San Francisco, California): Alkaline gastritis presents an interesting clinical dilemma. All of us see patients with postgastrectomy abdominal pain who are candidates for this diagnosis. I suppose one could be a complete skeptic and say that the condition does not exist. However, two-thirds of patients improve substantially after surgical therapy, and it is difficult to dismiss the impression that the operation has corrected the cause of their symptoms.

After my associates and I analyzed our patients, we concluded that reflux gastritis was a real entity, but that the traditional methods of diagnosis were grossly imprecise. Therefore, I am interested in Dr. Warshaw's findings and am hopeful that they represent progress in diagnosing this condition.

I have a couple of questions. First, why were six of the patients with a positive test not operated on? How is Dr. Warshaw doing on late follow-up results? How was the control group, called nonalkaline gastritis, selected? Was selection performed before or after the test was performed? Last, did he also try bile infusion?

DR. ANDREW L. WARSHAW (Closing discussion): Dr. Herrington, the idea of performing primary reconstruction on all patients with a Roux-en-Y limb is one that has been suggested before. Perhaps Dr. Thompson would like to take you on later since he argues against operating on these patients at all. To make a more complex operation, perhaps with more postoperative problems such as delayed emptying, may be more than he can tolerate.

The interpretation of a negative test in patients who carried a clinical endoscopic diagnosis of alkaline reflux gastritis is critical to the understanding of what I am trying to say, which is that not all patients who receive that label have the disease. In Dr. Way's published experience and in that of others, at least a third of such patients probably do not. Perhaps in Dr. Thompson's experience, 90% do not. We are trying to get the incorrectly diagnosed patients out of the group, and therefore our interpretation of a negative test implies that those patients do not have the disease.

Dr. Fromm, you bring up the question, as did others after you, about whether alkali or bile is the offending agent. We all talk about "bile reflux," but in the literature on this subject, starting with Ritchie and going back, every one of the papers produced by members of this society is entitled "Alkaline Reflux Gastritis" and not "Bile Reflux Gastritis." Attempts to measure bile reflux in these patients, on the assumption that it quantitatively increases in those who have symptoms, have been limited in their success. Ritchie was able to show increased bile reflux in the highly selected end of the spectrum among those patients who had the most severe gastritis endoscopically, but in two-thirds of his patients, as in two-thirds of most other series, the amount of bile reflux really was not different in patients with or those without symptoms. Therefore, there is some question about what bile itself is really contributing to this syndrome.

I have been asked several times today why we did not use bile acids instead of alkali in the test. The answer is, it has been done by others. In a report during this past year, Meshkinpour found that gastric contents reproduced the symptoms when reinfused into his highly selected group of patients, but that purified bile acid solutions did not. That raises the interesting question whether bile acids have anything to do with this syndrome at all, at least at this stage of the game.

Dr. Fromm, you asked why the patients' own gastric contents did not reproduce the symptoms. My guess is that we are dealing here with a provocative test that exceeds normal physiologic conditions, and that for a provocative test, gastric contents might not be strong enough. Gastric contents were strong enough in Meshkinpour's study, but, again, his patients were highly selected to be the most severely affected. It may be that less severely affected patients can have the disease but not respond to applied gastric contents. Our

observations of whether or not these patients remain sensitive to the alkali even after surgical diversion and presumed healing is at too preliminary a stage to tell you anything about it.

Incidentally, the pH of gastric contents in those with bile reflux is between 6 and 7. That is far lower than the pH of 11 to 12 of the solution used for the provocative test. Robert's observations of gastric mucosal necrosis with alkali were made with 0.2 normal alkali. We used 0.1 normal. All I can tell you is that, no matter what the biopsy specimen might show right after the test, we do not observe symptoms in most individuals. A few endoscopic examinations performed 24 hours later have not shown notable evidence of mucosal damage. The time factor of exposure to alkali may be important. We leave it there for only three minutes and then wash it out. Perhaps that is why we do not see more trouble from it.

Dr. Moossa has shown us his nice scintigraphic studies. This is similar to the work published by Tolin, who showed an extraordinarily high correlation of excessive bile reflux as detected by scintigraphic techniques with patients with symptoms. Again, it was a highly selected group of patients on the one hand, and on the other we have no follow-up data to show what happened to those patients in terms of results from operative treatment. That is the nitty-gritty of what we are talking about today. We are trying to pick patients for an operation and pick them well. Certainly the assumption that the culprit is the amount of total bile reflux, rather than some other specific factor within the bile-stained duodenal contents, is as yet unproved.

Dr. Moossa asked why we did not choose asymptomatic postgastrectomy patients for our controls. There were eight such controls in this study. They appeared in the "other abdominal pain" group. Three had chronic pancreatitis, and that is why they were being operated on for this hospital admission. They had no gastritis-type symptoms, and they were included in our control group. So eight patients who had previously had a Billroth II gastrectomy were included and did not respond to the test.

In reference to how we picked that control group and whether the picking might have been done after the fact and, therefore, biased the results—a legitimate question—all patients were categorized before the test was performed into putative alkaline reflux gastritis or into other abdominal pain groups. There was no realignment on the basis of test results.

There is no question but that this test depends on the subjective interpretation of a subjective response, and therefore has all of the traps built into that kind of a test. We are dependent upon the excessive response of the patient, and on the patient's blindness to the identity of the test solutions. Whether this approach will turn out to be applicable in other peoples' hands obviously remains to be seen.

Again, to answer all of you, we are really trying to deal with problems of patient selection. We are starting with the assumption that the syndrome exists, but we have had trouble up to now picking out patients who really have it from the morass of psychiatric problems and emotional problems and other organic factors that may be playing a part. We hope that this test can help to do it.

There is no question but that there is a spectrum of symptoms; that many of these patients can be held off without having an operation, and that many patients who have an operation do not benefit. Our own long-term follow-up data on patients who have not been operated on, who had the diagnosis of alkaline reflux gastritis made but then treated medically, shows that a high percentage, more than 50%, will not have symptoms two or more years later. This means either that the syndrome goes away or they never had it in the first place. The syndrome and these patients are complex.

I was asked by Dr. Way why six of the patients with a positive test were not operated on. The answer is that I did not make the decision for operation in any of the patients except those who were my personal patients, and those six patients were not my personal patients. The referring doctors have chosen to follow them for the time being and not believe the results of the test. That is their decision. We have tried not to influence the decision for surgical intervention when that possibly could be avoided on the basis of the test.