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Discussion

DR. ALAN G. JOHNSON (Sheffield, England): This is an important paper with profound implications if it is true. The hypothesis is that all cardiac-type mucosa is abnormal and metaplastic, even at the junctional zone, and that it is very common. If this is also associated with intestinal metaplasia, which is premalignant, it may well go a long way toward explaining the increasing incidence of adenocarcinoma of the lower esophagus. My questions are threefold. How does this abnormal mucosa actually relate to the sphincter itself and to the respiratory reversal point? Is it in the abdominal part or the esophageal part? Because if this is in the lower part, would a fundoplication, for example, make any difference to this very minimal reflux? My second question is whether there was dysplasia in this intestinal metaplasia, because this is the important predictor of premalignant change.

Third, did you correlate the changes and, in particular, the intestinal metaplasia with alkaline or, as we prefer to call it, duodenal juice reflux? This may be important in the change to an intestinal-type mucosa.

DR. THOMAS P. J. HENNESSY (Dublin, Ireland): I am pleased to have the opportunity to comment on this paper, and I would like to congratulate the authors, Dr. Peters and Dr. DeMeester and the rest of the group, on what I think is a very important paper that contributes further to our knowledge of the pathophysiology of gastroesophageal reflux disease. It may also account for the development of adenocarcinomas around the cardia in the absence of any apparent Barrett's metaplasia.

In our experience for a long period looking at Barrett's esophagus, we have found that the most potent combination to provoke metaplasia and also dysplasia is bile and acids. I wonder whether the authors have looked at the possibility of bile reflux in this situation, because, as Professor Johnson has already remarked, the acid reflux here is minimal. I also wondered whether there was any alteration in motility of the esophageal body, as well as whether there were motor disorders in the sphincter.

The other thing that surprised me about this paper is the very high frequency of hiatal hernia. I noticed that in those patients who were relatively normal with no reflux changes, no inflammatory changes, and no cardiac mucosa, even they had a 25% incidence of hiatal hernia. So I wonder how relevant these hernias are.

Finally, I would like to inquire, do the authors think it is possible to reverse the process or have they tried to do so? One wonders what would be the response to intensive medical treatment at this stage of the condition.

DR. JOHN HUNTER (Atlanta, Georgia): This is a tremendous amount of exciting and provocative material. As I try to understand the story that lies beneath all this data, what I understand is that early gastroesophageal reflux is manifested by the development of columnar metaplasia in the region of the lower esophageal sphincter. That is to say, in a patient without Barrett's esophagus, our assumption that the stomach starts below the squamocolumnar junction is wrong. The cardiac glands belong to the esophagus. They are a result of acid injury to the squamous esophagus, they are usually inflamed when they exist, and their presence predicts gastroesophageal reflux disease.

If we are to believe this story, and I think we should, I have about a million questions. But I will try to ask just a few.

If the presence of intestinal-type epithelium represents healing of erosive disease in severe reflux and esophageal erosions are not seen in early disease, how does the cardiac metaplasia occur in patients with carditis? Is carditis, which is so uniformly found in patients with cardiac glands, really an epiphenomenon? If you took biopsies of their lower esophagus, do these patients have microscopic inflammatory changes above the squamocolumnar junction grade 1 injury in the Savory-Miller classification? As these studies progress, there are several other issues that need to be addressed. One is, how specific are these findings? Do the normal controls, patients without foregut symptoms or patients undergoing endoscopy for endoscopic retrograde cholangiopancreatography (ERCP), have any of these findings? What about omeprazole? We know it causes histologic changes to the stomach. Does it influence any of the histology of these cardiac glands? Lastly, in the methods section it was suggested that these biopsies were obtained sometimes by retroflex—some of the biopsies were obtained retroflex and some antiflex. Was there any difference in the biopsy findings when the scope was retroflexed or straight on?

DR. THOMAS R. GADACZ (Augusta, Georgia): Were any of the changes you describe with gastroesophageal reflux disease

found in patients with duodenal or gastric ulcer or in patients with hypergastrinemia? Patients with Barrett's and mild dysplasia have healed the Barrett's lesion when the Barrett's mucosa is destroyed and then either an antireflux operation is performed or effective intense medical treatment is followed. Have you followed up any of these patients who have shown these changes and then were either treated with H2 blockers or a proton pump inhibitor? Was there any reversibility of the changes you describe?

DR. ANDRE DURANCEAU (Montreal, Canada): I have two questions to ask the presenter. First, I am pretty sure that you have a controlled population in your laboratory. In this controlled population, did you look at your incidence of intestinal metaplasia in retroflex biopsy samples? Second, do you have any data to show us the effect of duodenal gastric reflux on lower esophageal function itself?

DR. PAUL H. JORDAN (Houston, Texas): This paper is terribly important because of the increased frequency of carcinoma in this area of the esophagus.

What bothers me is that only a few years ago people working with Barrett's said you had to biopsy the esophagus 2 to 3 cm proximal to the esophageal-gastric junction to make sure you were biopsying in the esophagus.

A question was raised just a minute ago about how biopsies were taken. My question just duplicates that, but it does represent my concern. How do you know what you are biopsying? Is it really the cardia that is being biopsied?

DR. DAVID L. NAHRWOLD (Chicago, Illinois): I have one question. The entry into the study was determined by foregut symptoms, so that it is a very heterogeneous group of patients. It would seem essential to define the various subgroups against a control group, which in this instance would have to be normal patients. Thus, I would ask again, what are the findings in normal individuals?

DR. JEFFREY H. PETERS (Closing Discussion): I would like to thank the discussants for their comments and questions.

Dr. Johnson asked about the relationship of cardiac mucosa to the structure of the lower esophageal sphincter (LES). Historically it has been difficult to correlate the anatomic and physiologic features of the lower esophagus and upper stomach; as such, it has not been done well. There are data, however, to suggest that what we are looking at is actually within the sphincter. Dr. Attila Csendes from Chile has attempted to correlate lower esophageal biopsies with manometric measurements in a large number of patients with reflux disease. In general, the LES was within the area of cardiac mucosa. We think that we are biopsying within the sphincter, although proving it is a very difficult thing to do.

He also asked whether we found dysplasia as a precursor to adenocarcinoma in these patients. The answer is, there was no dysplasia in this population of patients, but we have seen it. During the last few years we have seen several patients who have both low- and high-grade dysplasia in intestinal metaplasia limited to the gastroesophageal junction. This, of course, represents a very interesting finding and almost certainly relates to the incidence of adenocarcinoma of the cardia.

Dr. Johnson, as well as several of the other discussants, also asked about the relationship between cardia histology and alkaline reflux. This relationship is more difficult than may meet the eye, largely because we really should be measuring the presence of bile and alkalinity in the stomach and not in the lower esophagus. To date, we have studied lower esophageal exposure to bile and duodenal juice, but not gastric exposure. We do think there is a correlation, which will be the topic of future presentations.

Dr. Hennessy asked whether this had any effect on the alterations in esophageal body motility. I didn't show the data, but there was also a fairly high prevalence of defective sphincters in patients with carditis, but no esophagitis. In this group of patients, the distinguishing feature between those who got esophagitis and those who didn't was poor esophageal clearance and altered esophageal body function.

Dr. Hennessy also queried the high incidence of hiatal hernia in our study population. There are several reasons for this. First, these are patients with symptoms of foregut disease. Second, hiatal hernia is common in the general population. Finally, we had a fairly sensitive definition for the presence of hiatal hernia, that is, a 2-cm difference between the crura and the gastroesophageal junction by endoscopic examination.

Several discussants asked about the potential for reversal of cardiac metaplasia. We don't know yet the natural history of this phenomenon, although it will certainly be a topic of interest for the next several years. We have had some patients who have had intestinal metaplasia limited to the cardia and have undergone laparoscopic fundoplication. I wish I could, but I can't, tell you yet whether we have been able to reverse it in these patients. It will be interesting to see what happens as the years go by.

Dr. Hunter asked what the origin of this tissue is. We think that it probably does arise, John, from erosions at the gastroesophageal junction, in a similar fashion to the present concept of how Barrett's esophagus occurs in the esophageal body.

Is this an epiphenomenon, and what do we find in esophageal biopsy samples of the lower esophagus in comparison? The problem is that the biopsy samples of the lower esophagus, as I pointed out in the presentation, are very nonspecific. If one limits the definition of esophagitis to intraepithelial eosinophils or plasma cells as indicators of inflammation (as opposed to the Ismail-Beigi criteria), we don't find much correlation.

The important question is, what is the specificity of cardiac mucosa as a measure of reflux disease? Several other discussants asked about this also. What do we find in a control population? A control population, as you all know, is difficult to come by. But we do have one. And in conjunction with Para Chandrasoma, our pathologist, we have studied an autopsy population for evidence of cardiac mucosa. It is often absent, particularly true in those less than 20 years old. He has collected 60 or 70 such cases. In 9 of 11 less than 20 years old, there was an abrupt transition from squamous to fundic mucosa. The other two had very small segments of cardiac mucosa. This is probably the best control population that we can identify. We have

tried to study a nonspecific population of patients undergoing upper endoscopy. The problem is that many have unrecognized reflux disease, and, thus, also have cardiac mucosa.

Dr. Gadacz asked about the possibility of ablation. Remember that these changes are not readily evident endoscopically. We don't know if we can ablate it, nor do we know the effects of omeprazole or a Nissen fundoplication.

Finally, I would like to address Dr. Jordan's question about how we know where we are biopsying. A careful endoscopist can distinguish the end of the stomach and the beginning of the esophagus by looking for the end of the rugal folds in the retroflexed position. We then try very carefully to biopsy this anatomic gastroesophageal junction whether or not there is a hiatal hernia.