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DISCUSSION

DR. JOSEF E. FISCHER (Cincinnati, Ohio): As usual, this is a very elegant, well-designed work that further explores the relationship of putative gut hormones with growth of the gut and gut components in both benign and malignant conditions.

If I can take a few liberties with the experimental design, what the authors have done is taken three different types of putative gut hormones—one clearly endocrine, one perhaps paracrine, and one perhaps neurocrine, *i.e.*, the three modes of action of gut hormones—and tried to measure their effects on gut growth.

There is a paradox that when elemental diets are given or TPN is given, the atrophy of the gut mucosa is disproportionate to the lack or presence of protein and calories, and therefore they invoke another

mechanism other than simply a protein and caloric dependence, one of which could be the relationship between gut hormones and the gut mucosa.

I have one comment and two questions. I think the thesis that gut hormones or other substances have a controlling effect on gut mucosa is shown not only by this work but also from the recent demonstration of some of the laboratories that have been most enthusiastic about substances like glutamine. In a recent paper from Wilmore's laboratories they point out very clearly that as compared with supplemental glutamine, even on an enteral basis, the administration of epidermal growth factor is more efficacious in preventing the atrophy of gut as compared to glutamine, so that there is evidence from the literature to support this hypothesis.

The critical thing I would like to focus on is the finding that neurotensin, although it does have an effect on releasing biliary pancreatic secretion, clearly has a direct effect on the mucosa, which is not mediated by biliary pancreatic secretions, so I have two questions.

The first relates to the finding that neurotensin, although it stimulated the growth of mucosa in 5 days, by 10 days this particular trophic effect on ileal mucosa was no longer present. I find that difficult to comprehend, and I wondered whether Drs. Townsend and Thompson have any thoughts on why this occurred.

My second question has to do with this peculiar effect that biliary pancreatic secretion has on the gut mucosa and perhaps the suggestion of the mechanism.

David McFadden of our department recently showed that when bile is placed in a bypassed loop, you have a paradoxic effect of some of the pancreatic polypeptide hormones, specifically NPY and PYY, which accumulate in the cells. They may not be released in the blood, but they are present in rather large concentration in the cells, and these two hormones, or at least PYY, have been shown to be very trophic in regard to the gut mucosa.

I know that Dr. Thompson's and Dr. Townsend's laboratories have worked extensively with pancreatic polypeptide, and I wonder what they think of the suggestion that perhaps this mechanism may be mediated by some of the pancreatic peptides, and whether they have any data as to this.

I like the paper very much. I think it is important work not only in its specific nature but to the suggestion that when we are dealing with shortened gut or atrophied gut, or maybe even gut poisoned by chemotherapy or radiation, that perhaps in addition to nutrients we really should look to gut putative peptides to maintain the gut mucosa.

DR. EDWARD A. COPELAND (Gainesville, Florida): Our group, both in Houston and in Gainesville, has had an interest in the GI tract.

I would like to compare and contrast our results with those presented today. In our experiements, rodents on TPN are compared to chow-fed animals.

As you can see, the animals on TPN have atrophy of the small bowel, oxyntic gland area of the stomach, and the pancreas.

The addition of pentagastrin to the TPN solution ameliorates the atrophy in all three organs, in contrast to some of the data presented by Dr. Townsend. We evaluated the entire small bowel, whereas Dr. Townsend evaluated mucosa only. Other experiements evaluating small bowel mucosa only indicated that the addition of pentagastrin to the TPN solution would prevent the expected mucosal atrophy, as well.

Histologically, what did the small bowel of the animals that received gastrin show?

When receiving TPN, antral tissue gastrin and serum gastrin concentrations fell. Since the addition of pentagastrin to the TPN solutions prevented gut and pancreatic atrophy, tell us the interplay among the hormones gastrin, Bombesin, and neurotensin in your experiments. Were concentrations of these hormones decreased in the organ of origin?

The colon atrophies, as well, when a rodent is fed either by TPN or with an elemental diet. Pentagastrin will ameliorate the atrophy somewhat, but the addition of non-nutritive bulk to an elemental diet eliminates the atrophy entirely.

How should we evaluate the absence of bulk in your experiments?

From a practical point of view, how should we begin to refeed patients after a prolonged period of bowel rest? Do we go the clear liquid, full liquid, regular diet route? If so, will the patients get diarrhea? What exactly happens from the standpoint of your data? Does the pancreas quit making pancreatic juice, the stomach quit making acid, and the jujunum lose its ability to absorb?

You predict that gut atrophy may cause bacterial translocation. Do you have data to support this hypothesis, and if so, do neurotensin and Bombesin eliminate it?

DR. LESTER WILLIAMS (Nashville, Tennessee): Yesterday we heard a good deal on gut mucosal barrier, as has already been mentioned by Ted Copeland. Although there was discussion of what is cause, what is effect, and what is mechanism, there was the implication in almost every presentation that metabolic phenomena were important. In those discussions elemental diets were used because they improved metabolic phenomena of the gut mucosa. Now we have a model in which the use of the elemental diet is the mechanism whereby the metabolism of the mucosa is deranged. Clearly there is some concern generated by these two diverse observations.

The second comment relates to how complicated these issues are because the neurotensin data are very variable in terms of what is happening in the jejunum and in the ileum. This leads me to my only question. In the bypass group, the ileal response is substantial, and yet in the original data the ileal response to neurotensin is so variable that you conclude there is no response.

Why is it that ileum, when it is in a bypass segment, shows an effect but it does not when the intestinal tract is intact?

DR. JOHN M. KELLUM (Richmond, Virginia): I want to ask Dr. Townsend to reassure us that these rats actually ate the elemental diet. Even a starved Texas wharf rat would be too discriminating to eat the elemental diet.

The reason I am skeptical is that when we did some clinical studies in our center, we have found that elemental diet put through a nasogastric tube into the stomach in humans causes a vigorous response in terms of CCK release and pancreatic secretion.

The second question I wanted to ask relates to the role of the ileal peptide, enteroglucagon, which has gained some currency as a physiologic trophic hormone for the colon and perhaps the distal small bowel. Did you look at enteroglucagon, and if so, what were your findings?

DR. EDWIN A. DEITCH (Shreveport, Louisiana): Most of us believed for a long time that enteral feeding is superior to parenteral feeding, since Dr. Sheldon clearly showed that enterally fed animals survived a septic challenge better than parenterally fed animals. This concept was verfied recently in trauma patients by Dr. Moore in Colorado. However what is apparent is that not all enteral feedings are equally protective. Specifically elemetnal diets do not appear to be very different from parenteral nutrition as far as supporting distal intestinal function and metabolism is concerned. Now we have to ask why is it that elemental diets are not beneficial. There are two potential explanations for this phenomenon: first that these diets may not contain glutamine, and second that they do not contain bulk or fiber.

Recently we found that fiber-free elemental diets cause mucosal atrophy, loss of intestinal barrier function, and bacterial translocation. However, by adding fiber to these elemental diets, we can preserve intestinal barrier functiona and prevent bacterial translocation, even though mucosal atrophy is not reversed. The work presented today by Dr. Townsend offers one explanation for why fiber works because fiber-containing diets induce higher levels of intestinal hormone release than fiber-free diets.

With this background, I would like to ask the following question. Do you believe that there is a direct relationship between intestinal barrier function and intestinal atrophy? Because we have not found a direct relationship between mucosal mass and barrier function, I wonder whether one can extrapolate measurements of mucosal protein or DNA to function.

DR. B. M. EVERS (Closing discussion): Dr. Fischer, you asked whether we have studied the effects of the pancreatic polypeptide family of hor-

mones on gut mucosal growth. Investigators in our laboratory have studied the effects of both pancreatic polypeptide and peptide YY administration. No effect was noted with PP; however a preliminary study suggests that PYY, when given at a dose that is equimolar to the effective dose of neurotensin, can stimulate mucosal growth of the distal small bowel and colon of mice. We are presently evaluating possible mechanisms of action.

Dr. Williams, you asked why mucosal growth in the ileum was greater after intestinal bypass compared to the ileum in the intact gut. Previous studies have demonstrated that the ileum, during periods of mucosal atrophy, is very sensitive to pancreaticobiliary secretions and growth is stimulated when these secretions are specifically diverted to this segment. Our current hypothesis is that the increases in ileal growth that have been noted after both bypass and administration of neurotensin are indirectly mediated by an increase in pancreatic exocrine secretions and are not due to a direct effect of neurotensin.

Dr. Kellum, you asked about the palatibility of the elemental diet preparation. The elemental diet was given as the sole source of food and liquid, and after a 1- to 2-day adaptation period, the rats readily took the diet, consuming approximatlely 60 to 70 calories a day.

Dr. Copeland, when you were at the University of Texas at Houston, you and your colleagues provided important information about gastrin and gut growth, and we appreciate your comments on our present study. We found no histologic differences in the small bowel of rats treated with pentagrastrin compared to controls. This was consistent with our findings that mucosal weight and biochemical growth parameters were unchanged.

You also asked about the effects of bulk. We think that the whole issue of bulk and gut growth is interesting. It appears that bulk has its greatest effect on the colon, and we are studying its effects on small bowel growth.

Finally, Dr. Deitch, you asked about the atrophy and overall gut function. We have not addressed this question specifically, but hope to do so in the future.