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Discussion

DR. JOHN DELANEY (Minneapolis, Minnesota): This is a very nice paper with potential clinical usefulness. I was asked to discuss it because I have had an interest in radiation injury and its prevention in the small bowel. Methotrexate and radiation have similarities. Both inhibit Crypt cell replication and therefore restitution of the mucosa.

The small bowel has some unique characteristics that are difficult to interpret. One of those characteristics is extremely rapid replacement of the mucosa, every 2 days in the rat. In addition, the intestine contains myriad bacteria which can elaborate toxins that get into the circulation when the bowel is injured. When you perturb one variable in the small bowel, everything else is perturbed as well. It is incidentally a huge reservoir of lymphoid tissue, as the transplanters have found out. The gut is also the largest endocrine organ in the body. So anything that you disturb changes numerous other variables. That is what makes this experiment difficult to explain.

For example, giving the bombesin at time of the methotrexate injury had the same effect as when it was given prior to the injury. Either the bombesin had to block the effects on the enterocytes or it caused a tremendous acceleration of enterocyte replication following the injury. I would be interested in speculations from the authors.

Methotrexate has multiple actions, one of which is to inhibit bone marrow and induce leukopenia. We know that leukopenia itself can lead to enterocolitis. I would ask the authors if they studied hematologic parameters and were they influenced by bombesin? They mentioned the possibility of bacterial translocation; was that studied that as a possible cause of death?

We heard in an earlier paper at this meeting that glutamine had some influence on replication of tumor cells. Glutamine is a trophic factor for the small bowel, like bombesin. Jim Thompson's lab has had an interest in cancer trophic factors. I would ask if they have delved into the possibility that bombesin has trophic effects on malignancies? In other words, this agent cannot be used clinically to protect the intestine until we are confident that the bombesin does not interfere with the desired effects of the methotrexate on the target tumor.

DR. KENNETH R. SIRINEK (San Antonio, Texas): I would like to congratulate Dr. Chu on his presentation and to thank the authors for providing a copy of their manuscript for my review prior to the meeting.

This study represents another contribution by my University of Texas colleagues at Galveston for the understanding of the physiology, pathophysiology, and now possible clinical applications of gut peptides. I would like to ask two questions and to disagree with one of their conclusions.

Are the authors aware of any effect of bombesin on the absorption of an elemental diet? And secondly, why was the jejunum protected, and the only site of enterocolitis was the ileum?

I thoroughly agree that they have shown a decreased mortality from the methotrexate-induced enterocolitis by the administration of bombesin. However, I disagree with their conclusion that the beneficial effect occurred by preventing gut mucosal atrophy.

Group 3 rats did not get bombesin until day 14, the same day that the methotrexate was given. Mucosa in this group of animals should have atrophied during that 14-day period just like the control group. For this group of animals it would appear more plausible that bombesin may have acted as a competitive inhibitor of methotrexate-induced enterocolitis. This could be the same receptor that is responsible for stimulating cell growth or for its destruction.

Could this hypothesis of competitive inhibition be demonstrated by giving additional doses of methotrexate to displace the bombesin from this receptor site?

DR. ARTHUR H. AUFSES, JR. (New York, New York): I would also like to congratulate Dr. Chu and his colleagues on a very interesting study which, as Dr. Delaney pointed out, may have very significant clinical implications.

I notice, however, that although they describe this as a model of enterocolitis, the only slides that we saw were of the jejunum and ilium. And I wonder what the changes actually are in the colon.

The clinical implication of this is clearly related to antibiotic-induced colitis, which in our own institution is becoming almost of epidemic proportions. Therefore, I wonder whether they have done any work on any other models of colitis and could tell us what those results might be.

DR. KYO U. CHU (Closing discussion): First, I'd like to thank all the discussants for their important questions and comments. I will answer each in the order it was asked.

First, Dr. Delaney has questioned the rate of gut mucosal proliferation after bombesin injection since a group that was injected with bombesin after methotrexate injection significantly improved survival, along with a group that was pretreated with bombesin. Although we have not examined the rate of mucosal proliferation after bombesin treatment, our first experiment indicates that bombesin produces a significant gut mucosal proliferation within 7 days in rats fed an elemental diet. In addition, other parts of our study have revealed that even in chow-fed rats that were injected with methotrexate, bombesin produced significant gut mucosal proliferation in less than 7 days. These data suggest that bombesin may have a role in gut mucosal regeneration after injury produced by an elemental diet and methotrexate. Also, bombesin is able to produce a significant amount of gut mucosal proliferation to have protective effect in a short period of time, less than 7 days.

Dr. Delaney's second question was whether we had looked at any immunologic parameters. No, we have not looked at any immunologic parameters in this study. I think this question of the effect of bombesin on immune system is very important. There is evidence that bombesin has immune-enhancing properties and this may be the mechanism involved in improving the survival from this methotrexate-induced enterocolitis.

Dr. Delaney also asked about the possible role of bacterial translocation in this model. Yes, that is certainly one possibility. This can be related to improved immune function after bombesin treatment as speculated in the previous question. Previously, Fox and colleagues have observed improved survival from this methotrexate-induced enterocolitis after glutamine supplemented elemental diet. They also observed a significant decrease in bacterial translocation with glutamine supplementation.

The fourth question Dr. Delaney asked dealt with the effect of bombesin on different malignant tissues. This is an area that our group has extensively studied and found that there are different growth effects in different malignant tissues. As you well know, bombesin stimulates growth of small cell lung carcinoma and has autocrine growth effects on these cancer cells. Bombesin stimulates growth of breast and prostate cancer. However, we have found that the effect of bombesin on the growth of gastrointestinal malignancies is more unpredictable. Bombesin stimulates the growth of colon cancer, pancreatic cancer, stomach cancer and gastrinoma; however, we have also found that bombesin actually inhibits the growth of different lines of colon and pancreatic cancer. So there are many questions to be answered concerning the effects of bombesin on the growth of cancer. Certainly this is one area that needs to be addressed before this kind of therapy can be considered and implemented in oncology patients.

Dr. Sirinek asked about the effects of bombesin on gut absorption. A recent work of Dr. Hodin and his colleague, presented at the Society of University Surgeon meeting, demonstrated that bombesin increased mRNA for gut enzymes such as lactase and intestinal alkaline-phosphatase. Therefore, bombesin, while having a growth effect on the gut mucosa, may simultaneously have some beneficial effect as far as providing better function.

Dr. Sirinek also asked why jejunum is not affected. Previously, Dr. Evers performed a study examining the effect of bombesin and neurotensin on gut mucosal atrophy induced by a more severe form of an elemental diet. In our study, we have used a more clinically relevant form of the elemental diet, Vivonex TEN which contains glutamine and a small amount of fat. Better nutrients and growth promoting factors in the proximal gut may have contributed to maintenance of mucosal mass despite the elemental diet. Also, because the nutrients are exposed and absorbed in the proximal gut, investigators have observed slower development of mucosal atrophy in the proximal gut and much more significant atrophy in the distal intestine and colon.

Dr. Aufses inquired about the colon. We have examined the colon and found that, as expected, an elemental diet led to significant atrophy of colonic mucosa. Bombesin marginally increased mucosal growth in the proximal colon but had no effect in the distal colon. These observations are currently under further investigation.