Discussion

Dr. Kirby I. Bland (Gainesville, Florida): I wish to thank Dr. Garrison and his colleagues for the opportunity to discuss this paper and for forwarding the manuscript to me in advance for review.

I encourage the membership and the students of this disease to look at the comprehensive manuscript that was presented at the Association for Academic Surgery last month with regard to their animal model, which, together with this paper, allows much more insight into the pathophysiology of malignant ascites formation.

These clinical observations and the experimental data presented appear to support a tumor-produced factor that alters host blood vessel growth and permeability, rather than a more simplistic explanation of subdiaphragmatic venous obstruction. The authors provide supportive data in the Walker 256 carcinoma model that angiogenesis is primarily responsible for the major component of the increase in preoperative peritoneal and hepatic leakage of malignant ascitic fluid. Dr. Garrison acknowledges, and I feel correctly so, that other tumor-induced factors are present that alter vascular permeability, but these have not as yet been elucidated.

Neal, I have one comment and two questions for you. You have acknowledged that patients with tumors that have a high protein concentration within the ascitic fluid have longer survivals than those with tumors that form a simple transudate within the peritoneal cavity. Indeed, this was statistically different in the rats that were infused intraperitoneally with a cell-free malignant ascites. We appreciate that the net transfer of protein toward the peritoneal third space compartment occurs at the expense of the intra- and extravascular compartments. Thus, in effect, in your model of this ratio of the ascitic fluid protein to the serum protein, the ratio reflects an increase in the numerator of that ratio. As a result, we see a shift to a higher value and one that is greater than 0.4, which would convey a meaningful explanation of an increase in survivorship for these patients. As a matter of fact, that is a paradoxical effect. You are actually observing that you have an increased survivorship in patients who are nutritionally depleted, hypoproteinemic, catabolic, and preterminal. This is difficult to explain in view of the dynamic fluctuations of both intra- and extravascular fluid components and their contributions to the ascitic fluid protein compartment.

Could you give us more insight into that issue, and, finally, could you please explain the survival differences in these patients who are all categorically stage IV disease? Would you think that a better interpretation of these observations could be best explained by the tumor volume of these patients?

I enjoyed this paper very much, and thank the Association for the privilege of the floor.

Dr. Harvey J. Sugerman (Richmond, Virginia): This study of the tragic course of malignant ascites from the University of Louisville represents the ideal in academic surgery: to evaluate a clinical problem and then go to the laboratory to answer the basic questions raised so that improved therapy might be developed that will prolong the productive lives of all of our patients.

I suspect that the reason Dr. Garrison asked me to discuss his paper was because of my interest in pulmonary protein permeability in adult respiratory distress syndrome. Perhaps I could offer a few suggestions for future studies regarding the protein permeability data.

In that context I would like to ask several questions:

First, you stated that the ascites to serum protein ratio of 0.4 or more implied increased peritoneal permeability to protein in 71% of the cases. Could not this increased ratio have been secondary to protein secretion by the malignant cells rather than permeability in the human studies? This was certainly ruled out as a possibility in the animal data, where the studies involved the use of cell-free malignant fluid. Perhaps, and maybe you could comment on this in regard to Dr. Bland's question also, the increased duration of survival in patients with protein-rich fluid was possibly secondary to more well-differentiated tumor cells that retained their protein synthetic and secretory functions.

Second, in the animal studies, did you examine the peritoneal fluid itself, in addition to the eluted omental fluid, for the presence of Evans blue dye?

Third, although you found an increase in the wet weight to dry weight ratio in the omental tissue, could this not have been due in part to an increased blood volume in the omentum? In future studies, I would like to suggest a technique borrowed from the pulmonary extravascular lung water literature, namely, the Pierce gravimetric method of correcting for blood contamination by homogenizing the tissue and measuring its hemoglobin content. One can then correct back to the original tissue extravascular water volume.

Fourth, you corrected for the effect of plasma Evans blue contamination by dividing the eluted Evans blue optical density by the plasma Evans blue optical density. I question if this solves the problem of blood volume changes. Again, you can get around this issue by using the Pierce gravimetric technique, and subtracting the effect of plasma extravasation.

Finally, would you mention your interesting hypothesis regarding neovascularization and its effect on malignant ascites formation?

Again, I would like to compliment the authors for combining a clinical study with basic animal sleuth work.

Dr. Eugene H. Shively (Campbellsville, Kentucky): Thank you very much for the opportunity to discuss this paper. I would like to thank Dr. Garrison for letting me read the manuscript before it was presented.

Last year we had the opportunity to review the literature on this subject. (Slide) There are many different ways of treating this problem, none of which work very well. (Slide) We attempted to come up with a normogram for treating these patients, but first I would like to emphasize that it is important to determine the etiology of malignant ascites. Patients with carcinoma of the ovary, testes, and lymphomas can be treated and sometimes cured. We have two patients with stages III and IV carcinoma of the ovary who have been treated with cytoreductive surgery and intensive chemotherapy. At second look operations, they have no evidence of tumor.

If it is not possible to give definitive treatment, then the best treatment is diuretics; and if the patient responds, then he should be sent home on maintenance dosage. If this does not work, occasionally a paracentesis in an attempt to get all the ascitic fluid out will work.

Patients who get recurrences are then divided into four categories. Those with large abdominal masses have a very short life expectancy because of the massive volume of tumor and probably are best treated with repeat paracentesis. Patients who have negative cytology but have normal liver functions with bilirubin greater than 4 or a protime greater than 4 minutes beyond the control are best treated with paracentesis. If these patients are shunted, they often develop DIC or hepatic failure. Patients with positive cytology are probably best treated with a P32. Patients with no malignant cells and normal liver function are probably best treated with peritoneal venous shunting.

I have a couple of questions for Dr. Garrison. What do you postulate to be the factor causing the capillary permeability change? In your experience, what has been the best palliation for these patients?

Thank you very much.

Dr. Harold J. Wanebo (Charlottesville, Virginia): Mr. President and Members of the Association, I rise partly out of naivete.

First of all, I would compliment the authors on their approach of examining difficult clinical problems and taking it to the lab. I would like to ask them whether the omentum may be a major factor in the ascites in these patients. The reason I say this is that frequently in exploring patients with carcinomatous ascites, one is struck by the fact that many of them will have massive omental metastases. One wonders whether there may be additional factors, aside from the ones that were mentioned, which may have some effect on the omentum itself (and secondarily limit lymphatic drainage from the peritoneal cavity).

Secondly, of course, numerous factors have been described in the omentum, including a recent report of angiogenesis factors. As many of you remember, years ago people transplanted the omentum to edematous extremities in an effort to reduce lymphedema. Thus, one would wonder whether the tumor could be releasing factors that have direct effect on the omentum (*i.e.*, promote edema).

In your model, you directly infused the extract into the peritoneal cavity, which did have an effect on the tissues you had happened to measure, *i.e.*, the omentum. One wonders whether you would have seen the same changes in other tissues in the cavity such as the peritoneum itself. Thus, one might pose questions that could be addressed in your model. For example, by injecting the material intravenously, would this actually induce the effect in a target organ? And would the omentum be

that target organ that I suggest it might be? (Or would you also see it in other tissues?)

Also, are there any clinical applications of your experimental data?

I want to thank the authors for allowing me to discuss their paper and the Association for the privilege of the floor.

DR. R. NEAL GARRISON (Closing discussion): Thank you, Dr. Cerise. I will try to direct these questions one at a time if I might.

Dr. Bland, you asked the question about the peritoneal to serum protein ratio of 0.4 and whether this might be due to serum hypoproteinemia. We used 0.4 because we felt that that did correct for those patients who were hypoproteinemic. The classic description of a transudative fluid is one of less than 2½ milligrams per decaliter of protein. That does not account for where the protein is coming from, and, if you have a hypoproteinemia patient, then 2 grams or 2.2 grams of protein within the peritoneal fluid might be a better indication of active protein leakage or secretion into the abdominal cavity.

I am not really sure of the reason why the high protein ratio patients survived longer other than that, potentially, the small volumes of tumor that secrete this factor increase the survival simply because a smaller tumor mass can express itself earlier with fluid accumulation. This would be opposite to obstruction of lymphatics, which is a process that takes a lot of tumor and tumor volume in order to obstruct all of the lymphatics that drain through the diaphragmatic lymphatics.

Dr. Sugerman, possibly active protein secretion is an explanation for the high protein concentrations within the peritoneal fluid. Certainly, that is something that we have not looked at. We simply postulated that it was coming from the intravascular space. I am not quite sure how we would get a handle on active protein secretion. Certainly, most of these tumor cells are viable cells and do actively have metabolic processes going on.

There was very little peritoneal fluid in the cavities of the rats that we studied at the time they were killed. Most of this fluid is picked up by the diaphragmatic lymphatics because there is no obstruction, and so there is really very little fluid to measure the Evans blue dye. Most of the abdomens are quite dry except for just a glistening surface.

We chose the omental tissue because of the large blood supply in that tissue as compared to some of the other tissues that we might have sampled. We have measured the small bowel mesentery, the diaphragm muscle, and the liver. Our problem with these tissues comes in the amount of blood and plasma present in those tissues. Our results lean toward statistical significance but do not correlate as well as does the omental tissue. We look forward to the use of the Pierce gravimetric technique to better define the degree of true permeability change.

Dr. Shively, your review was quite helpful in the preparation of this manuscript. In view of our clinical findings, I recommend only temporary measures for those tumors of the alimentary tract where the protein ratios are low, while tumors of the ovary and lymphatics systems might very well benefit from a peritoneal-venous shunt or an ablative procedure with radioactive phosphorus based on the presence or absence of tumor cells in the ascitic fluid.

I suspect that there are a variety of tumor factors present to account for the permeability changes that we have measured. One that we tried to delineate in a previous paper was that of tumor angiogenesis factor. We were able to inhibit partially this permeability change by the topical infusion of protamine into these animals along with the malignant ascitic fluid. We implied from these experiments that some degree of this leak is due to new vessel growth and the subsequent fragility of these new vessels.

Dr. Wanebo, I appreciate your comments. The omentum certainly could be a target organ in this process. It is not thought to be a primary drainage lymphatic organ. Again, we used it basically because it had a lot of tissue vessels that are very small. Yet, there was very little blood volume and plasma involved in the tissue itself.

We have wanted to do some experiments using intravascular fluid infusions of the ascitic fluid. However, we have had a hard time deciding exactly how we will measure the permeability changes. Certainly, we are going to do that in the omental tissue, but we wanted to do it concomitantly in the lung. We hope to do that in the near future.

Thank you very much.