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DISCUSSION.—DR. C. STUART WELCH, Albany, New York: Again Dr. McDermott is to be congratulated for the excellent work he has done in this field of the investigation of ammonia metabolism in patients with liver disease.

I would like to show, in two slides, some of our experiments along the same line and some of our experiences with clinical cases.

(Slide) This shows that in Eck fistula dogs we have found the same rise in blood ammonia when blood has been fed to these animals. This rise does not occur in milk and mash fed dogs as indicated by the low values for blood ammonia.

(Slide) Here we have some figures on patients. We have now studied some 36 patients who have had gastro-intestinal bleeding with severe liver disease. The point I would like to make, corroborating Dr. McDermott's work, is that the high mortality in patients bleeding from varices occurs in the patients who have an elevated blood ammonia.

As you can see, only five of 20 survived when the ammonia was elevated, in contrast to ten survivals out of 16 when there was no elevation of blood ammonia. So, the coma which ensues and the ammonia intoxication are very significant in the causation of death.

Another important point is shown here. Nine patients died with continuing hemorrhage and coma. Therefore, it is very important that the bleeding be stopped.

The last point is that no patients in our series died in coma after hemorrhage was stopped, showing again the extremely important significance of bleeding and continued bleeding and blood in the intestinal tract.

DR. CHAMP LYONS, Birmingham, Alabama: It is a great privilege to acknowledge the very real help Dr. McDermott has been to Dr. Tom Patton and myself in similar studies. We are in complete accord with his conclusions.

I arise to ask one question. We have been concerned about the role of bacterial production of urease in the gastro-intestinal tract as a contributing factor to the ammonemia. We have been unable to demonstrate the presence of such bacterial enzymes, but the intestinal tract does have a great deal of intracellular urease. The question of antibiotic therapy in these patients hinges a good deal, I think, upon whether or not such enzymes have been demonstrated.

DR. BEN EISEMAN, Denver, Colorado: Our clinical experience has been very similar to that reported by Dr. McDermott. Of 57 patients in hepatic coma in our current series, 12 have had massive gastro-intestinal hemorrhage at the onset of their coma. In all of these cases the blood ammonia levels were elevated, and in 10 patients we feel that the ammonia load resulting from absorption of blood within the intestinal tract probably precipitated coma.

In our experience cases of hepatic coma precipitated by exogenously administered ammonia salts usually have a good prognosis; however, this has not been our experience in patients thrown into hepatic coma following massive gastro-intestinal bleeding. Indeed, as a group their prognosis is among the worst and although the administration of sodium glutamate to these people will temporarily lower the blood ammonia levels following its discontinuance we have found little change. For this reason our practice is to employ a slow infusion over a 24 hour period.

We have recently completed experimental studies on the effect of hemorrhage on ammonia metabolism—that is extra corporeal hemorrhage not bleeding into the intestinal tract. Following bleeding the portal blood ammonia concentration is markedly elevated, but simultaneous portal blood flow measurements indicate that this is merely a reflection of decreased blood flow and that there is no increased endogenous production of ammonia

in the portal bed. Bacterial sterilization of the intestinal tract does not alter this pattern. The normal liver has a tremendous reserve in converting portal blood ammonia to urea even in advanced stages of shock or when an abnormal ammonia load is thrown upon it.

The patient with a liver bordering on failure will go into coma, however, when the insult of diminished hepatic blood flow resulting from gastro-intestinal hemorrhage is added to the injury of an ammonia load resulting from the absorption products of blood within the intestinal tract.

In closing, may I congratulate Drs. McDermott, Wareham and Riddell, and thank them and the Association for the privilege of discussing this interesting paper.

DR. ALERED BLALOCK, Baltimore, Maryland: Dr. McDermott, I would like to ask you a couple of questions.

In view of your observations in doing a portacaval shunt, do you now recommend that end-to-side anastomosis or side-to-side anastomosis be done?

Secondly (and this question does not have to do with the methods of stopping bleeding), after bleeding has occurred and the intestinal tract is filled with blood, do you have any good way of getting rid of that blood so that it won't be absorbed?

DR. WILLIAM V. MCDERMOTT, JR., Boston, Massachusetts: I would like to thank the discussors for their most interesting comments. I have been very interested in the work being done by Drs. Welch, Lyons and Eiseman, and I certainly appreciate what has come out of their laboratories in clarifying this field.

In trying to answer some of the questions Dr. Lyons raised, one was the question of bacteria in the gastro-intestinal tract as the source of amino acid oxidase and urease, which presumably is the enzymatic pathway by which ammonia is produced. We have done no direct work on this problem, but Dr. Baird Hastings in the Department of Biochemistry at Harvard, in association with Dr. Pinsis, has been studying this problem for the past several years, and they are quite convinced that it is intestinal bacteria which is the source of these enzymes that lead to the production within the lumen of the gastro-intestinal tract of ammonia from any source of pooled nitrogenous material.

Dr. Eiseman raised the question of the use of L-glutamic acid and the mechanisms by which it is effective—if it is effective. I think this is an extremely long subject, and I was rather reluctant to get into it. At the moment it appears to us as if the use of L-glutamic acid is that of a binding mechanism in the peripheral blood. The administration of L-glutamic acid as a sodium or potassium salt, in the presence of a high ammonia level, seems to be associated with a sharp rise in the glutamine and sometimes the alpha-keto-glutarate. As long as the feeding of ammonia into the circulation continues, the administration of L-glutamic acid will only temporarily control the level of the blood ammonia. Therefore, it is imperative that the source of blood ammonia be stopped at the same time that the administration of L-glutamic acid is being used.

Dr. Blalock raised the most difficult question (which I am not competent to answer) as to the type of shunt. Anything I could say in regard to that would be purely an opinion, and I don't feel very strongly about it myself.

From the point of view of hemodynamics, I think an end-to-side portacaval shunt is the most effective type of decompression for portal hypertension. I think without any question the greater the decompression you get, the more metabolic problems you have associated with the absorption of ammonia and very probably of other materials from the gastro-intestinal tract by-passing the liver.

How you balance these pros and cons, I don't know, but I think that with the increasing knowledge of the metabolic changes associated with a direct end-to-side portacaval shunt, and our increasing ability to control these metabolic derangements, I think we can utilize the more successful type of hemodynamic decompression.

As far as the elimination of the pooled blood in the gastro-intestinal tract is concerned, after immediate control of the hemorrhage through a balloon tamponade we have administered cathartics through the tube, and shortly after this we try, by the use of colonic irrigations, to remove the blood that is pooled. This is not always highly successful, but I think it does accomplish something.

Again I would like to thank the Association for the privilege of presenting this paper.