when combined with paracentesis accurately predicted the need for operation.

Sudden hyponatremia and metabolic acidosis indicated deterioration. If these abnormalities did not respond to appropriate therapy within four hours in patients when first seen or if they occurred in adequately treated patients already on therapy, operation was generally needed.

The most striking finding was related to the course of the platelet count and the PTT. Modest falls in platelet counts to a level above 100,000 without further fall and modest prolongation of the PTT did not indicate a need for operation. However, platelet counts which fell below 100,000 or which continued to fall from higher levels over a period of hours were invariably associated with gangrenous bowel. The PTT data were similar to the platelet findings. It may be that gangrenous intestine releases sufficient tissue thromboplastin to initiate clotting and utilization of platelets. Similarly intravascular gas may produce thrombotic effects because of altered hemodynamics.[9] Finally, excessive binding of platelets with endotoxin may result in platelet injury and loss.[2] Regardless of the causal relationship, profound, sustained falls in the platelet count which could not be explained on another basis reliably predicted that gangrene with or without bowel perforation had occurred.

The surgical experience gained with these patients would indicate that exteriorization resection and anastomosis after a few months is likely to be the best approach. Anastomosis of potentially compromised bowel has been hazardous in our experience. Precise evaluation of the vascular status of the intestine in these patients is difficult, and the late occurrence of stenosis, especially in the distal colon, is another reason to stage the anastomosis.[7]

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Discussion

Dr. Thomas V. Santulli (New York): Dr. O'Neill and his group, I believe, have made an important contribution to this knotty problem of surgical indications in these desperately ill infants. They are to be congratulated for their excellent overall results.

The role of surgical intervention in this disease has been unclear. Pneumo-peritoneum or peritonitis resulting from perforation but without free air are clearcut indications. However, a decision to operate on the basis of progressive clinical deterioration may be very difficult.

Dr. O'Neill has placed emphasis on the development of metabolic acidosis, sudden hyponatremia and abnormalities in blood coagulation in these infants, as more objective evidence of intestinal gangrene, than the clinical examination which is so frequently unreliable in these very sick and small infants. I think this is an important contribution.

But, I would hasten to point out that these infants are usually suffering with many other problems as well. They may have hyaline membrane disease with periodic apnea, hyperbilirubinemia, and, especially sepsis, all of which or any one of which could account for some of these abnormal parameters. Hence, they must be evaluated in conjunction with the clinical picture.

Although we have had difficulty in interpreting most of the blood clotting parameters in the very young premature infant, the one reliable value is the platelet count since anything under a 100,000 is clearly abnormal, even in the tiniest premature infant.

In this regard, our data do not totally support Dr. O'Neill's conclusion that a drop in platelet count below a hundred thousand is indicative of intestinal gangrene and therefore requires operation. In 26 of our 69 patients whose platelet counts were under a hundred thousand, 20 died, six survived. In three of the survivors, no operation was done. They were managed on the type of intensive, aggressive, medical regimen that Dr. O'Neill has shown you. Their severe thrombocytopenia was on the basis of gram negative sepsis; they did not have gangrene of the intestine.

Finally, I wish to discuss the prophylaxis which I think is eminent in this very serious problem in the newborn infant. The laboratory data is quite convincing. It now remains to be documented in the human subject and a good deal of information is beginning to filter in.

Very briefly, in our laboratory, my resident, Barbara Barlow, was able to produce the disease in newborn rats which were made hypoxic. Three separate litters were used. One was contaminated by the environment, the second by introduction of an inoculum of klebsiella by mouth soon after birth, and the third by the transvaginal route in the mother about 24 hours before delivery. These were all split litters.

One group was allowed to feed on the mother's breast; another group was fed simulated breast milk formula which we had tried in many preliminary experiments.

None of the newborn rats that were fed breast milk developed the disease, whereas *all* that were fed the formula died two to five days later

of enterocolitis, with similar findings as those seen in the newborn infant.

In the formula group, all rats that were contaminated by the environment had heavy growth of *E. coli* in their stool and in the postmortem peritoneal cultures and those that had been contaminated with klebsiella had heavy growth of klebsiella in their stool and in the postmortem peritoneal cultures.

In the breast fed group, stool cultures either had a light growth of *E. coli* or no growth at all.

(Slide) The total protection offered is shown in this schema of the pathogeneis of enterocolitis. In the newborn rat it comes about by the host resistance factors in the breast milk and by its control of the enteric flora. There is repair at a stage when there was already mucosal damage by auto-digestion, whereas in the formula fed there is overgrowth of gas-forming bacteria and then the sequence of pathologic events going on to necrotizing enterocolitis.

It's too early to be sure that this is a preventable disease, but it is my own feeling that it will prove to be so. However, until such time as we can prevent it, we must treat this disease early and aggressively as has been outlined by Dr. O'Neill, and we must refine our operative indications by such sophisticated and thorough studies that have been presented so beautifully tonight.

DR. R. KENNEDY GILCHRIST (Chicago): I am reminded of the fact that the agricultural community is well aware of this kind of problem. The most important thing in keeping your baby pigs or your baby calves from dying from scours and so forth is to see that they get the mother's colostrum in the first half-hour and if they do not get this, you may lose half of these young immediately.

The most important fact is that the newborn has no immunity while the first secretion of the breast, called colostrom, has a very high concentration of all antibodies that the mother possesses. The concentration drops to low levels by the fifth day. Thus, these poor risk infants should be given the colostrom, by bottle if need be, as soon as possible. Colostrom can be preserved by refrigeration for some time.

DR. HARRY H. LEVEEN (Brooklyn): As I listened to Dr. O'Neill's presentation and Dr. Santulli's comments, I thought that perhaps some of the work that we're doing in the laboratory might have some significance in this respect.

We have found that the primary toxic effect of colonic bacteria flora was due to the production of bacteria uriase. The bacteria uriase converts urea to ammonia. The ammonia is very highly toxic to the colonic cell and if we take the kidneys out of dogs, we routinely produce a uremic colitis. If we immunize these dogs to uriase so that no ammonia is formed, this colitis does not form. Also, we are unable to produce ulcerative colitis in the guinea pig with carragheenum that is immunized to uriase.

Furthermore, if we study the turnover rate, which we have done with tritiated thymadine of colonic mucosa, we find that in the uriase immunized animal the chronic mucosal cell lives twice as long as it does in the normal animal. In other words, it approaches the bacteria-free animal.

Perhaps it is not merely the anoxia, but the diminution of renal blood flow, the elevation of blood urea nitrogen, and since 20% of all body urea turns itself over in the colon, in a 24-hour period, the excessive formation of ammonia in the colon might well account for this particular syndrome. It might be wise either to treat these patients with exchange resins or to acidify their colonic tract with polyachroic acid. The reason for this is that the ammonia per se is only toxic in the form of NH-3 and the pH for this reaction is 9.1.

If one acidifies the colonic mucosal content, one raises the oxygen content by shifting the oxyhemoglobin dissociation curve. Also one reduces the toxicity of the ammonia by putting it in the form of ammonium instead of NH-3.

DR. THOMAS K. HUNT (San Francisco): Perhaps it is worth reminding this audience that many of the advances in surgery are put forward for us by basic scientists. One of the great revolutions in basic science at the moment is occurring in the field of white cell physiology, particularly in the manner in which white cells kill bacteria. At least five or six separate mechanisms have been identified.

Today, we tend to emphasize those which pivot on immune mechanisms and tonight, of course, the association of breast feeding and immunity to infection tends to focus our attention still closer to immune mechanisms. We tend to neglect the importance of so-called "natural immunity."

One of the more powerful, potent and important means by which white cells kill bacteria depends on conversion of atmospheric oxygen to high energy derivatives by the white cell which then modify the bacterial cell wall and set it up for killing. In this particular case, klebsiella, Staphylococcus aureus, and some other bacteria which we identify as causing enterocolitis, causing wound infections and so forth, are those which cannot be killed well by white cells in the absence of oxygen. One of these papers points to hypoxia as contributing to infectability but the discussion points toward antibodies.

When one adds an immune defect to an opsonization defect, one then has paralyzed at least two of the major killing mechanisms. No doubt, in this disease just as in most infectious diseases, there are multiple, additive factors which depress resistance. When two or more resistance factors are impaired, we have a child who is in trouble. I fail to see any real conflict between the various views expressed here.

DR. JAMES A. O'NEILL, JR. (Closing discussion): With respect to Dr. Hunt's comments, they are very well taken and well-directed. Certainly, these are areas we need to look into. One additional point that might be made with respect to speculation that there might be poor neutrophil function and even poor intracellular killing in these infants, would be the fact that infants in the range of three to four pounds potentially have poor immunologic function and response anyhow. This may be an additive factor over and above the physiologic problems of hypoxia on the cellular level and poor white cell function on that basis.

Dr. Le Veen, I'm afraid you have thoroughly overwhelmed me with organic chemistry. Certainly this is something that we should examine more closely. I'm afraid I would have to know a bit more about the details of the pathology of your preparation in comparison with the very well known details of pathologic features of necrotizing enterocolitis, pneumatosis and the like. I believe the model you are referring to is different.

Dr. Gilchrist, none of these infants received breast feeding initially. This is a disease of neonatal intensive care units whereby these very tiny infants are taken from their mothers, placed in isolated atmospheres on respirators and the like and thus don't get that kind of feeding. However, virtually all of them have received some enteral feedings. Most were not the true hyperosmolar type which is known to cause difficulty, but most of the feedings were slightly hyperosmolar.

Finally, Dr. Santulli, thank you, very much, for your gracious remarks, especially since you and your group described the syndrome. I was reminded of something that Dr. Cope said in a Surgical Forum session I participated in several years ago. He was talking about shock and said, "Well, you know, it's a very complicated business. All you fellows are trying to look at one feature and really you're going to have to spend a lifetime looking at many!" I suspect this is a similar situation.

The question about why platelets decrease is a good one. I would hasten to add that I was very careful to say that sudden decreases in platelet counts correlated with gangrenous colon in this particular group of patients. I didn't say that the gangrenous colon caused the decrease in platelets although it might very well have. For example, gangrenous colon might very well be releasing tissue thromboplastin and initiating clotting, but by the very same token, intravascular gas collections which we know occur may induce thrombosis and utilization of clotting factors as well.

Finally, gangrenous colon has to be associated with sepsis, toxemia and the well-known phenomenon of binding and loss of platelets as shown by Roger DesPrez at our own institution in Nashville several years ago.

Breast milk may be helpful. We note that many of our infants have severe and prolonged malabsorption defects in the postoperative period which is an entirely different story. We have given breast milk, as Dr. Santulli's group has, as a prophylactic measure, but are now also using this in the postoperative period as a therapeutic measure giving something which is essentially isosmolar if you will, and it appears to be helpful.