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FURTHER STUDIES OF THE HEMOLYTIC-UREMIC PHASE OF SHIGELLA DYSENTERIAE 1 (SHIGA'S BACILLUS)

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In the past four months we have studied, in detail, 10 children with the hemolytic-uremic syndrome. The coagulation studies were initiated by Dr. Bill Adams and Dr. Rahaman, Now, I will illustrate (with four case histories) the sequence of events and the clinical spectrum we have seen, then summarize the coagulation study data, and conclude with our hypothesis of pathogenesis.

First a typical case. Slide 1 illustrates the hospital course of a four-year old well-nourished boy admitted with a five-day history of bloody diarrhea. Shigella dysenteriae Type 1 was cultured from the stool on the first and second days of hospitalization. Blood culture was negative. On admission the child was toxic-appearing, anorectic, had a rectal prolapse, hypoproteinemia, hyponatremia, and was severely oliguric. However, excepting the leukemoid reaction, the hematologic picture was normal-normal hematocrit, normal platelet count, no red cell fragmentation (or schistocytemia) seen on peripheral smear. Over the next five days, the boy remained toxic, purulent stool continued, and total serum proteins dropped to 4.3 gm%. Platelets and hematocrit fell as schistocytes appeared in the peripheral blood. A battery of four coagulation assays (not shown on slide) were done on days 2,4 and 6. The protamine sulfate test (a screening test DIC) became positive on day 4 and the thrombin time became prolonged on day 6. Following whole blood transfussion there was temporary remission, followed by gradual recovery to normal 2 weeks later.

The second case (SLIDE) again illustrates some of the coagulation abnormalities and effect of transfusion. This is a seven month old well-nourished breastfeeding girl

presenting with a history of four days of bloody loose motion. Severe hemolysis was already apparent on admission, with 15% of the circulating red cells fragmented. In a three-week hospital course, requiring two transfusions, steady improvement was documented. Decreasing percent schistocytemia was paralleled by a decreasing titre of fibrin degradation products, measured by the tanned sheep red cell hemagglutination inhibition immunoassay. Transfusion had no effect on the fibrin degradation product titre. Recent follow-up revealed complete loss of schistocytemia and proteinuria. Note that the white cell count never exceeded 35,000 during our period of observation.

The third case (SLIDE) was a 4½ year old poorly-nourished girl admitted after a 10-day history of diarrhea with blood and mucous, with normal hematologic parameters. In contrast to the previous case, her hospital course was marked by progressive deterioration. Striking was the accelerating hemolysis, documented by the increasing rate of fall of the hematocrit and increasing schistocytemia. Despite this, and persistent thrombocytopenia serial coagulation tests revealed only a marginally prolonged partial thromboplastin time and positive protamine test.

Parralleling the accelerating hemolysis was colitis. The perirectum became purple, apparently ischemic, and she died on the 20th day of toxic megacolon and peritonitis. Her clinical course suggests that the microvasculature of the colon may be a significant site of hemolysis.

Despite severe oliguria, BUN of 75, her serum Creatinine never rose. The post-mortem renal biopsy is striking. The vast majority of glomeruli visualized are engorged with red cells. Lacking is hypercellularity, crescent formation, basement membrane thickening, tubular degeneration or intestitial disease. PAS strain has not yet been done, but if it reveals heavy fibrin deposits, one would conclude that DIC was present before death.

Permanent renal damage following the typical hemolytic-uremic syndrome has been seen only once in our hospital. A three year old boy presented typically as outlined above, required only one transfusion, but was anuric for 10 days. When hemolysis ceased and uremia resolved, heavy proteinuria and hypertension remained. His proteinuria has abated little during four months of follow-up.

The last case illustrates (SLIDE) severe dysentery culturing Shigella flexneri from the stool. Hemostatic abnormalities typical of the cases described earlier, although less marked, were present - thrombocytopenia, persistent leukemoid reaction, hypofibrinogenemia, and elevated titre of fibrin degradation products. When the patient absconded, schistocytemia and hemolysis had not yet appeared. We have seen patients who show no evidence of hemolysis until the 8th hospital day. Three other patients with flexneri dysentery have had a leukemoid reaction but no schistocytemia.

The next slide (SLIDE) summarizes our coagulation studies in diarrhea patients. For each patient, only the assay taken at the height of clinical disease is tabulated. Nine patients were studied with dysentery culturing the Shiga Bacillus. Seven of these had the leukemoid reaction and some degree of hemolysis. None had a prolonged prothrombin time, and only three of the seven hemolyzing patients had a prolonged thrombin time uncorrectable with normal plasma, indicating circulating anticoagulant. The single case with abnormal PTT was in the girl who died, described earlier. The most consistent abnormalities were the positive protamine sulfate paracoagulation test and elevated titres of fibrindegrad. products (FDP). It is likely that the prolonged thrombin times were due solely to high titres of FDP.

No dysentery patients culturing Shigella flexneri demonstrated coagulation abnomalities, but 3/3 studied had mild elevation of FDP. The last group, marked negative culture, is a mixture. Four patients had dysentery and leukemoid reaction (two of these had severe hemolysis) and all four of these had prolonged thrombin times and positive

protamine tests. Three others of this group had dysentery alone, and only one had a positive protamine test. The 22 remaining cases had culture negative clinical cholera, all of whom had normal coagulation tests. In 10 dysentery cases measured to date, fibrinogen measured by radial ~~diffusion immunoassay was reduced~~ only in Shiga Bacillus dysentery, excepting the single flexneri dysentery described earlier.
(SLIDE OFF)

We have demonstrated that our brand of hemolytic uremi syndrome is characterized by red cell fragmentation, thrombocytopenia, hypofibrinogenemia, and circulating fibrin degrad. products that is, results of thrombosis and fibrinolysis accompanying disseminated intravascular coagulation. Unlike the typical DIC our syndrome lacks the coagulation test abnormalities-prolonged prothrombin time and PTT indicative of clotting factor consumption. This, coupled with retarded fibrinolysis (untested) may account for our observation that bleeding never occurs in our patients.

DIC or Defibrination without clotting factor deficiencies are uncommon clinically. It has been reported of co[illegible] the idiopathic hemolytic-uremic syndrome (500 cases rep[illegible] in the literature), + in the so-called subacute or chro[illegible] DIC associated with some metastatic carcinomas and syst[illegible] lupus. The explanation may be (a) slower rate of clotting factor turnover or (b) the activation of the clotting case[illegible] late in the sequence, (c) directly stimulating conversio[illegible] of fibrinogen to fibrin.

The next slide (SLIDE) presents an over-simplification of possible mechanisms in the pathogenesis of this syndrome. Bacterial invasion of the colonic mucosa induces either loc[illegible] inflammatory events or bacteremia or circulating endotoxin, or less likely, immune complexes, and one or all of these trigger the coagulation cascade. In the microcirculation, i.e. capillary beds like the renal glomerulus, fibrin strands shred red cells as they pass through, producing hemolysis, and fibrin clots plug capillaries producing oliguria and uremia. At this time, toxic megacolon and

nephrotic syndrome remain interesting associated findings, without clear relation to the run-of-the-mill syndrome.

A word about the leukemoid reaction. We have only this clue to its origin. The highest leukocyte counts occur in the more malnourished patients. Conversely we have seen several better nourished patients with severe hemolysis who generate a leukocyte count no greater than 30 to 50,000. The reticuloendothelial system of the liver is responsible for clearing fibrin monomers from the bloodstream. Perhaps malnourished patients with compromised RE system must call forth from the bone narrow a greater leukocyte response to sweep the bloodstream.

The last slide (SLIDE) is an incomplete list of intended studies. Several other mechanisms of hemolysis must be ruled out. Auto immune hemolysis detected by the Coombs test, and G6PD deficiency will be sought. I have already Coombs-tested three patients with anti-IgG, anti-IgM, and anti-complement sera and detected no hemolysis. Further attempts at obtaining autopsy material will be made, and plans are made to study several patients with percutaneous renal biopsy.

Many features of this syndrome mimic the classic Schwartzman reaction-glomerular histapathology, occurrence only in children, presence of abundant leukocytes, platelet consumption, etc. - incriminate endotoxin, which can be detected either as bacteremia or by the Limulus assay. Serum complement levels, enterotoxin production by strains from hemolyzing patients, and possibly circulating immune complexes will be assayed.

The last four months has seen the completion of the first phase of our studies. We have established that the coagulopathy and sequence of events in our cases parrallel those reported for the idiopathic hemolytic-uremic syndrome, i.e. do not involve detectable clotting factor consumption. Marked leukocytosis remains the best flag for impending hemolysis, and usually but not always followed by hemolysis. The degree of schistocytemia best predicts the need for transfusion. The case material is abundant - we will make use of this unusual opportunity.