HOST FACTORS CAUSING INCREASED SUSCEPTIBILITY TO INFECTION IN PATIENTS WITH LAENNEC'S CIRRHOSIS

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Infection is one of the common precipitating factors of hepatic coma in patients with cirrhosis. It is also the immediate cause of death of about $\frac{1}{4}$ of the patients with Laennec's cirrhosis.[1] This paper will deal with the effects of cirrhosis on host-defense mechanisms that increase the risk of infection, but it will not cover the influences of acute alcoholic intoxication on these mechanisms.

The types of infections found in cirrhotics are many, but pyogenic bacterial infections as a group tend to predominate. Organisms arising from the gastrointestinal tract, such as gram-negative bacilli and anaerobes, are most common, but pneumococcal, staphylococcal, and streptococcal infections frequently occur.[1-4] Pneumonia, peritonitis, bacteremia, and pyelonephritis are the most common sites of these infections. The facets of the host-defense mechanisms that appear to be most important in preventing pyogenic infections are (1) the reticuloendothelial system (fixed macrophages), (2) antibodies, (3) complement, and (4) neutrophilic granulocytes. The major steps in the prevention of pyogenic infections are the phagocytosis of bacteria by granulocytes and fixed macrophages and the subsequent intracellular killing of these organisms. The serum factors primarily serve to facilitate these activities. Current knowledge about the functional capacity of these systems in cirrhotics will be reviewed individually.

The reticuloendothelial system is important for clearing organisms from the blood that enter from the gastrointestinal tract, lungs, skin, and other sites. Since the liver is the major organ of the reticuloendothelial system, it would not be surprising if function were abnormal in cirrhotic patients. In a study of cirrhotic rats, Rutenberg et al.,[5] demonstrated that intravenously injected bacteria were normally cleared from the blood; however, there was a delay in bacterial killing in these animals. As cirrhosis progresses, additional difficulty probably results from shunting of blood around the cirrhotic liver and thereby bypassing this very important reticuloendothelial organ.

Antibodies function as opsonins to facilitate phagocytosis of bacteria by granulocytes and to initiate the inflammatory process that ultimately limits and controls the infection. The antibody-forming ability of the cirrhotic does not appear to be deficient and may even be greater than normal. Cirrhotic patients commonly have a polyclonal hypergammaglobulinemia.[6] Triger et al.[7] found increased levels of antibodies to *E. coli* in patients with liver disease; however, the antibody levels to *Hemophilus influenzae* were within the normal range. They concluded that patients with liver disease are unable to degrade the antigen from bacterial products that arise in the gastrointestinal tract and consequently make antibodies to this increased level of bacterial antigen. Since *Hemophilus influenzae* is not a normal inhabitant of the gastrointestinal tract, it would not be ex-

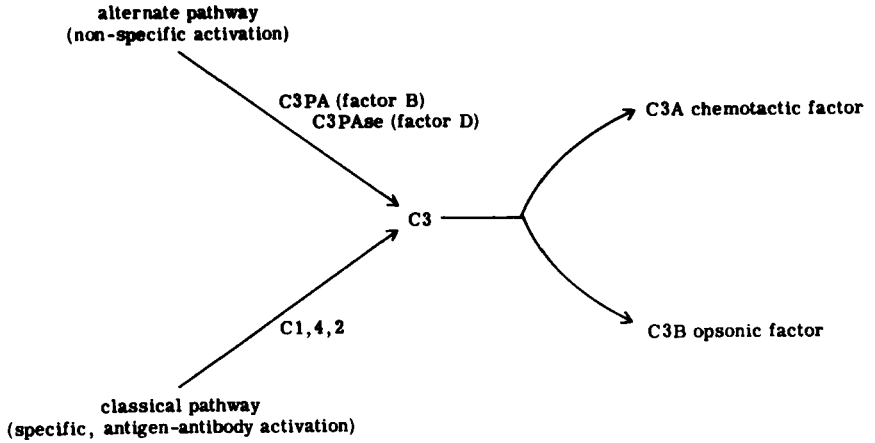

FIGURE 1. Pathways of C3 activation.

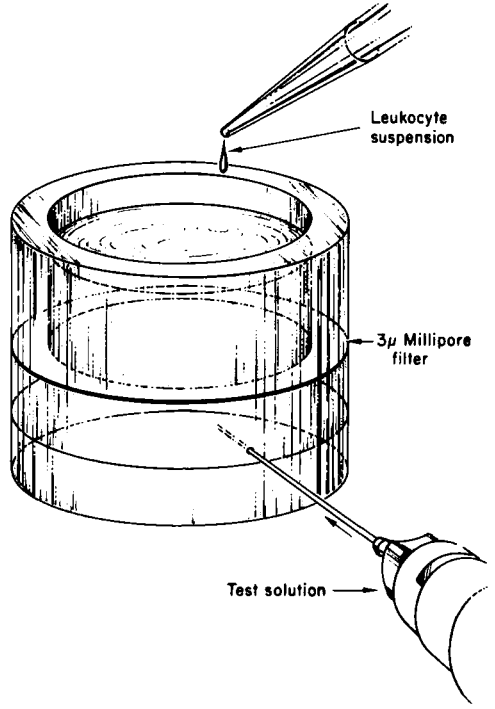

FIGURE 2. The chamber used in determining the chemotactic ability of granulocytes and the chemotactic activity of serum.

pected to be present in increased amounts. Havens,[8] however, reported an increased secondary immunologic response in patients with alcoholic cirrhosis who were immunized with tetanus toxoid. The cause of the increased antibody response is unclear at the present time, but for the purposes of this discussion, there is clearly no deficiency in this facet of the host-defense mechanisms.

The importance of the complement system in pyogenic infections is that, with appropriate activation, factors will be produced that attract granulocytes to the site of an infection and will increase the rate of phagocytosis of bacteria by the granulocytes. They are referred to as chemotactic and opsonic factors, respectively. The complement system may be activated either by the classic route with bacterial antigens and their antibodies or by the nonspecific alternate pathway (FIGURE 1). The alternate pathway is particularly important in the early phases of an infection before the host has had time to mount an immunologic response to the invading organism. In a study of 12 cirrhotic patients at the West Side VA Hospital, a number of the complement components were found to be decreased.[6] Seven of the 12 patients had levels of C3 well below the normal range. Half of the patients had decreased C4 levels, while only 3 patients had reduced levels of the C5 component. Four of 12 patients had C3 proactivator (C3PA) levels that were depressed, and among 11 patients who had total hemolytic complement assays performed, 8 had levels that were below the normal range. These comple-

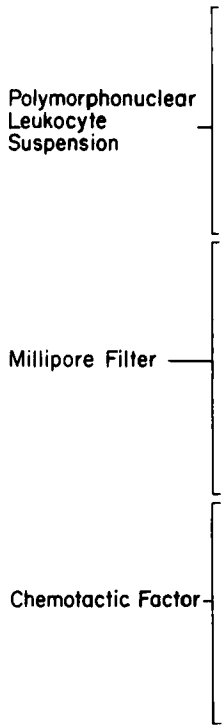

FIGURE 3. Diagram of granulocytes moving through a micropore membrane toward a chemotactic factor diffusing up from the lower compartment of a chemotaxis chamber.

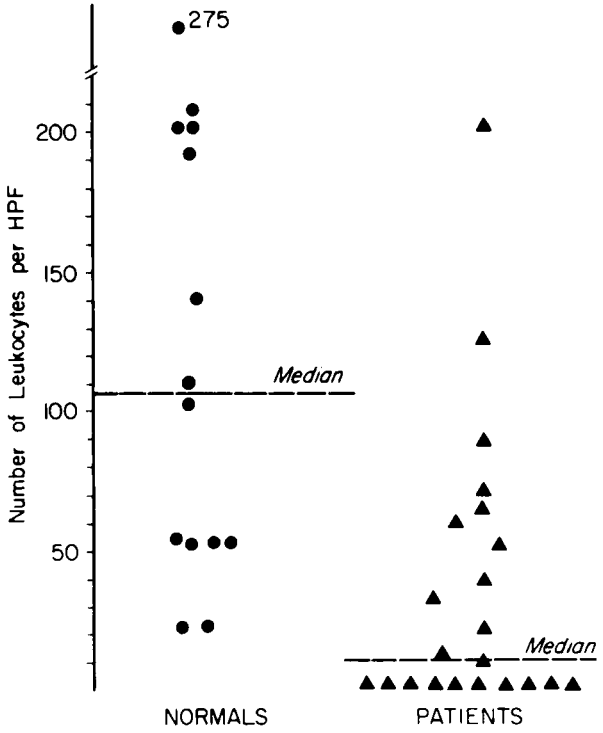

FIGURE 4. The chemotactic index of normals and patients with Laennec's cirrhosis. Serum (as the source of chemotactic factors) and granulocytes from the same individual were used in this chemotaxis assay.

ment deficiencies, therefore, may serve to provide a less than optimal chemotactic and phagocytic stimulus for the granulocytes of the cirrhotic patient.

Evidence to date does not seem to indicate that granulocytes of cirrhotic patients have any significant functional defect. In an earlier study,[6] 2 important functional characteristics of granulocytes were observed, namely chemotactic capacity and the intracellular killing ability of granulocytes. The chemotactic ability of the cirrhotic's granulocytes when exposed to an active chemotactic attractant was entirely normal in most cases. When the intracellular killing ability was tested with *Candida albicans* as the test organism, there was no evidence that the granulocytes from these patients had any difficulty in killing the *Candida albicans.* Occasionally cirrhotic patients have granulocytopenia as an additional defect in host defense.

It was apparent from an earlier study[6] that the cirrhotic patients' granulocytes demonstrated a poor chemotactic response to their own serum. The ability of a patient's serum to attract normal and his own granulocytes was tested using a chemotaxis chamber requiring only small volumes of serum and granulocytes (FIGURE 2). The granulocytes that moved through the micropore membrane (FIGURE 3) toward the serum chemotactic factors in the lower chamber were counted following staining with hematoxylin. The degree of chemotactic response was determined by calculating the average number of granulocytes pres-

ent per high-power field on the under surface of the micropore membrane. In many cases there was virtually no demonstrable movement of either normal or the patients' granulocytes. FIGURE 4 shows the response of normal granulocytes to normal serum chemotactic activity and the response of granulocytes from 22 cirrhotic patients to their own serum chemotactic factors. The chemotactic responsiveness of the cirrhotic patients' granulocytes to normal serum was in most cases entirely normal. Since it had been demonstrated that complement components were depressed in many patients with cirrhosis, especially C3, C4, and C3 proactivator, it was initially thought that the poor chemotactic response was due to these deficiencies. However, normal serum added to the patients serum failed to correct the problem. A seruminhibitor of chemotaxis was demonstrated in most of the patients with advanced Laennec's cirrhosis. This inhibitor was quite labile and was lost quickly at room temperature and even with prolonged freezing. Some patients lost the inhibitor as their clinical condition improved.

The studies described above have identified a number of defects in the host-defense mechanisms of patients with Laennec's cirrhosis. At the present time it is impossible to determine their relative importance in increasing the incidence of pyogenic infections in cirrhotic patients. This question probably will be answered as we develop the means to correct these deficiencies and observe changes in the course and prognosis of the disease.

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