IMPAIRED FUNCTION OF MACROPHAGE Fcγ RECEPTORS AND BACTERIAL INFECTION IN ALCOHOLIC CIRRHOSIS

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Abstract *Background.* Bacterial infection is a frequent and often fatal complication in patients with cirrhosis. Macrophages play an important part in the host defense against infection because their Fcγ receptors recognize antibody-coated bacteria.

Methods. We prospectively studied macrophage Fcγ-receptor function in vivo and in vitro in 49 patients with alcoholic cirrhosis, 10 alcoholics without cirrhosis, and 20 normal volunteers.

Results. The clearance of IgG-sensitized autologous red cells was decreased in 37 of the 49 patients with cirrhosis but in none of the subjects without cirrhosis. In the 49 patients clearance was inhibited by a mean (±SE) of 47±3 percent at 1 hour and 53±3 percent at 1½ hours, as compared with the clearance in the normal controls ($P<0.001$). The impairment of macrophage Fcγ-receptor–dependent clearance correlated with the degree of liver insufficiency but not with age, sex, nutritional status, HLA haplotype, or the presence of circulating immune complexes. The clearance of unsensitized and heat-altered autologous erythrocytes was normal. In vitro recognition of IgG-sensitized red cells by monocytes from the patients was not significantly decreased. During a two-year follow-up period, 11 patients had severe bacterial infections, and in 4 they were fatal. The mean clearance of IgG-sensitized red cells in these 11 patients (half-time, 126.2±22 hours) was significantly impaired, as compared with that in the 38 patients without severe infection (half-time, 32.2±18 hours, $P<0.001$).

Conclusions. The function of macrophage Fcγ receptors is impaired in patients with alcoholic cirrhosis, and this impairment probably contributes to the high incidence of bacterial infections among such patients. (N Engl J Med 1994;331:1122-8.)

PATIENTS with cirrhosis have an increased incidence of bacterial infection.[1] Although immunologic abnormalities have been observed in such patients, the precise mechanisms responsible for the increased frequency of infection are uncertain. Macrophage Fcγ receptors are important in the host defense, since they participate in the clearance of IgG-coated microorganisms. We studied the clearance of IgG-sensitized cells by macrophage Fcγ receptors in patients with alcoholic cirrhosis, the most common type of cirrhosis.[2]

The functional integrity of Fcγ receptors has been widely studied in patients with autoimmune disease through measurement of the clearance of radiolabeled IgG-sensitized erythrocytes by splenic macrophages.[3,4] Macrophage Fcγ-receptor function has been observed to be decreased in patients with certain HLA haplotypes and in patients with such autoimmune disorders as systemic lupus erythematosus, Sjögren's syndrome, and dermatitis herpetiformis.[3,4] This finding has been attributed to the occupation of these receptors on the macrophages by immune complexes. We have previously observed that macrophage Fcγ-receptor function is impaired in patients with end-stage renal disease who are undergoing hemodialysis, and that this impairment probably contributes to the observed immunodepression and high prevalence of infection among such patients.[5]

METHODS

Patients

We studied 49 consecutive patients in Spain (16 women and 33 men) whose mean (±SD) age was 55.2±8.3 years. All patients had alcoholic cirrhosis confirmed by biopsy and were followed for a minimum of two years. Ten alcoholic subjects without cirrhosis (4 women and 6 men; mean age, 45±7 years) and 20 healthy volunteers (6 women and 14 men; mean age, 52±12 years) served as concurrent controls. Patients who had undergone portosystemic shunting or liver transplantation, had active infection or acute hypovolemia, or were receiving immunosuppressant medications were excluded from the study. The patients were divided into three groups according to whether the degree of hepatic insufficiency was mild (group 1), moderate (group 2), or severe (group 3), according to established criteria.[6]

Study Protocol

All patients gave informed written consent, and the study was approved by the appropriate institutional review boards.

Blood samples were obtained from the patients and controls on admission for the following measurements: blood glucose and urea nitrogen, sodium, potassium, chloride, total calcium, phosphate, magnesium, creatinine, uric acid, total cholesterol, triglycerides, cholesterol (high- and low-density lipoprotein), serum aspartate and alanine aminotransferases, γ-glutamyltransferase, 5′-nucleotidase, alkaline phosphatase, serum protein electrophoresis, complete blood count, prothrombin time, activated partial-thromboplastin time, fibrinogen, and alpha-fetoprotein. Serum IgG, IgA, and IgM concentrations were determined by radial immunodiffusion (Behring Diagnostics, Madrid). Serum C4 concentrations were determined by hemolytic titration,[7] and serum C3 and C3a desarginine concentrations by radial immunodiffusion (Behring Diagnostics). Plasma zinc levels were measured by absorption spectrophotometry (Pye Unicam SP 190). Circulating immune complexes were determined by ^{125}I-labeled C1q binding.[8] A peripheral-smear examination was performed after Wright–Giemsa staining to detect the presence of Howell–Jolly bodies, an index of splenic function[9] (negative in all patients). Macrophage Fcγ-receptor–dependent clearance was determined in vivo, and Fcγ-receptor–mediated recognition of IgG-sensitized cells by blood monocytes in vitro. Abdominal ultrasonography was performed to detect splenomegaly,[9] which was present in 27 of the 49 patients and in none of the controls. The study protocol was the same for the patients and the controls. The results of all the above studies were normal in the 10 alcoholic subjects without cirrhosis, except for the mean corpuscular volume.

Preparation of Human IgG Anti-RhD Antibodies

Human IgG anti-RhD antibodies were prepared from serum from a single donor by ammonium sulfate precipitation followed by Sephacryl S-300 gel filtration and quartenary aminoethyl ion-

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exchange chromatography (Pharmacia, Madrid). No IgM was detected by double immunodiffusion (Ouchterlony analysis[3]). The final IgG fraction was passed through a Millipore filter and tested for pyrogenicity and sterility. The final IgG fraction was negative for human immunodeficiency virus type 1 (HIV-1) by the enzyme-linked immunosorbent assay (Pasteur Institute, Madrid), the Western blot technique (Pasteur Institute), and the quantitative end-point dilution method.[10] The number of IgG (anti-RhD) molecules per red cell was determined as previously described with ^{125}I-labeled anti-IgG antibodies.[11] Clearance studies were performed with erythrocytes sensitized so that approximately 600 molecules of IgG were present on each red cell. When Fcγ-receptor–dependent recognition by blood monocytes was studied in vitro, each red cell was coated with 400, 800, or 1600 molecules of IgG.

Macrophage Fcγ-Receptor–Mediated Clearance

Clearance studies were performed as previously described.[5,12,13] In brief, erythrocytes (RhD-positive) were isolated from all subjects, washed three times in physiologic saline, spectrophotometrically standardized to a concentration of 6.6×10^8 cells per milliliter, and radiolabeled with ^{51}Cr (potassium dichromate, Amersham, Buckinghamshire, United Kingdom). An aliquot of cells was sensitized by adding to it drop by drop an appropriate dilution of purified human IgG anti-RhD antibodies. The mixture was incubated at 37°C for 30 minutes, and the sensitized ^{51}Cr-labeled erythrocytes were washed four times in saline and resuspended to a concentration of 3.3×10^6 cells per milliliter in Hanks' balanced salt solution (M.A. Bioproducts, Madrid). An aliquot of cells (10±0.3 ml with 2.5 μCi of radioactivity) was injected through an antecubital vein, and the survival of red cells was determined in serial blood samples obtained over a period of 48 hours. Neither the specific activity of the radiolabeled erythrocytes nor the volume injected differed significantly between the patients and the controls.

Clearance curves were plotted by expressing the number of counts per minute at each point in time as a percentage of the number of counts at 10 minutes, the zero point. The time required for the clearance of 50 percent of the IgG-coated red cells (the half-time) was calculated and then correlated with the clinical and serologic data. In addition, to determine the clearance on each day, the percentage of inhibition of clearance above the control value was calculated at 1, 1½, 2, 8, 24, and 48 hours, according to the formula

$$\%\ \text{inhibition} = 100 \times 1 - \left(\frac{\text{CPMb} - \text{CPMx}}{\text{CPMb} - \text{CPMc}}\right),$$

where CPMb denotes the number of counts per minute in a control subject who received an injection of unsensitized autologous red cells, CPMx the number of counts in a patient who received IgG-coated (sensitized) autologous red cells, and CPMc the number of counts in a control subject who received autologous IgG-sensitized red cells. Controls with body weights comparable to those of the patients were studied simultaneously with them, and the counts per minute at the zero point (10 minutes) were similar. By means of the above formula, patients could be compared with controls studied on the same day, and the results could be expressed as the percentage of the change in clearance; thus, 100 percent inhibition of clearance indicated that clearance in a patient who received IgG-coated red cells was identical to that in a control who received unsensitized red cells.[5,14] Serum C3, C3a des-arginine, and C4 concentrations were measured to assess complement activation during the clearance of IgG-coated red cells. No marked complement activation was observed in any of the patients.

In three subgroups (five patients with alcoholic cirrhosis, five alcoholic subjects without cirrhosis, and five controls) we examined the clearance of autologous ^{51}Cr-labeled but unsensitized red cells and the clearance of ^{51}Cr-labeled heat-damaged (i.e., heated for 30 minutes at 56°C) autologous red cells.

Monocyte Recognition of IgG-Coated Cells

The recognition of IgG-coated red cells by isolated blood monocytes was determined as previously described.[15,16] In brief, confluent monolayers of 5.5×10^5 monocytes were obtained from defibrinated blood after density-gradient centrifugation (Ficoll–Isopaque) and plastic adherence to petri dishes (Nunc, Amsterdam). An aliquot of 2×10^7 ^{51}Cr-labeled, IgG-coated red cells was added to each monocyte monolayer. The petri dishes were then incubated at 37°C in 5 percent carbon dioxide for 45 minutes, washed to detach unbound red cells, and treated with 0.086 M EDTA solution to remove adherent monocytes and monocyte-bound IgG(anti-RhD)-sensitized red cells. The treatment with EDTA removed all adherent monocytes and all radioactivity. The percentage of ^{51}Cr-labeled and IgG-sensitized red cells recognized by peripheral-blood monocytes was determined according to the formula

$$\%\ \text{of red cells bound to monocyte monolayers} = \frac{\text{cpm for IgG(anti-RhD)-coated red cells removed with EDTA}}{\text{cpm for IgG(anti-RhD)-coated red cells added to monocyte monolayers}} \times 100.$$

No phagocytosis of anti-RhD–sensitized erythrocytes by peripheral-blood monocytes occurs under these experimental conditions.[15,16]

IgG2b-antibody–sensitized sheep erythrocytes were also prepared as previously described.[17] In brief, 1×10^9 sheep red cells in 1.0 ml of 0.01 M EDTA buffer were sensitized by adding mouse anti-sheep red-cell monoclonal antibody Sp2/HL, subclass IgG2b (Serotec, Bicester, United Kingdom), in 0.1 ml at 37°C for one hour. The final antibody dilutions used to prepare these cells were between 1:10 and 1:80. The IgG-sensitized sheep red cells were washed twice and resuspended in Hanks' balanced salt solution to a final concentration of 1×10^8 cells per milliliter.

Monocyte recognition of rabbit IgG-sensitized red cells in vitro was assessed as previously reported.[17,18] In brief, 1×10^8 IgG-coated red cells or unsensitized control red cells were added to monocyte monolayers containing 1×10^6 cells. These cells were incubated at 4°C or 37°C in phosphate buffer at an ionic strength of $\mu = 0.07$ or $\mu = 0.15$, respectively. After two hours, the plates were washed and stained with Wright–Giemsa. Two hundred monocytes were counted under light microscopy in a blinded fashion to assess the number of IgG-sensitized red cells bound to each monocyte. Monocytes binding more than 3 red cells per monocyte were determined. These experiments were performed in five patients from each group of subjects with alcoholic cirrhosis (groups 1, 2, and 3), eight alcoholic subjects without cirrhosis, and eight normal volunteers.

The studies were repeated in both patients and controls. Both the clearance studies and the in vitro studies with blood monocytes were repeated six months after the original studies in nine of the patients with cirrhosis in whom severe infection had developed, in six of the patients with cirrhosis who did not have a history of infectious complications, in six of the alcoholic subjects without cirrhosis, and in six normal volunteers. In each subject the results of the repeated studies were the same as those of the original studies.

HLA Typing

HLA typing was performed by the tissue-typing laboratory of the Virgen del Rocio University Hospital in Seville, Spain.

Assessment of Nutritional Status

Nutritional status was evaluated according to anthropometric, biochemical, and immunologic measurements.[19-22] Dry body weight, relative body weight, and the percentage of ideal body weight were also determined. The anthropometric data were compared with standard values for the local population.[23] Serum albumin and transferrin were measured to evaluate the serum protein level. Malnutrition was classified, according to previously established criteria,[19-24] as marasmus, kwashiorkor, or a mixed type. All malnourished patients had malnutrition of the mixed type. There was a high incidence of protein-calorie malnutrition of the mixed type (in 17 of the 49 patients [35 percent]). The total body weight did not change.

Cutaneous hypersensitivity responses to standard concentrations of four antigens — purified protein derivative, *Trycophyton rubrum*, *Candida albicans*, and streptokinase–streptodornase — were used to evaluate cell-mediated immunity, as previously described.[20,25] A response was considered positive when the diameter of induration was more than 5 mm. A normal response was indicated by positive

responses to three or four antigens, an abnormally low response by a positive response to one or two antigens, and anergy by negative responses to all four antigens.

Statistical Analysis

The in vivo clearance curves at the designated times were analyzed with Student's t-test to calculate P values for the differences between the controls and the patients. The in vitro Fcγ-receptor–dependent recognition of red cells by monocytes and the clearances in patients and controls were assessed with the Wilcoxon rank-sum test for unpaired data. The relation of the clearance rate (half-time) or monocyte Fcγ-receptor–dependent recognition of IgG-coated red cells in vitro to the results of serologic tests was analyzed with the Spearman rank-correlation test. The data are presented as means ±SE.

Results

Clearance studies were performed in the 49 patients with alcoholic cirrhosis who met the criteria for inclusion in the study. The results demonstrated that the clearance of IgG-coated red cells by macrophage Fcγ receptors was significantly impaired ($P<0.001$) (Fig. 1). At 1 and 1½ hours, clearance was inhibited by 47±3 and 53±3 percent, respectively, as compared with the clearance in the normal volunteers and the alcoholic subjects without cirrhosis. Clearance was inhibited by 15 to 83 percent in 37 patients and by 5 to 12 percent in 6. In contrast, the clearance of unsensitized and heat-damaged red cells in the patients did not differ from that in the alcoholic subjects without cirrhosis and the healthy volunteers (Fig. 1).

The patients with cirrhosis were classified according to the degree of hepatic insufficiency. Clearance studies in these three groups of patients are presented in Figure 2. The clearance of IgG-coated red cells was significantly impaired ($P<0.001$) in the patients with moderate (group 2) or severe (group 3) hepatic insufficiency. At 1 and 1½ hours, the mean inhibition of macrophage Fcγ-receptor–mediated clearance was 47±3 and 66±4 percent, respectively, for group 2 and 59±5 and 81±6 percent, respectively, for group 3. At 1 and 1½ hours, Fcγ-receptor–mediated clearance of IgG-coated red cells was impaired in the patients with mild hepatic insufficiency (group 1), but the difference was not significant.

Patients were followed for at least two years after the clearance studies. Six patients died: two of massive hemorrhage from ruptured esophageal or gastric varices (in the 15th and 17th months of follow-up), two of spontaneous bacterial peritonitis with *Escherichia coli* (in the 14th and 20th months of follow-up), and two of gram-negative sepsis due to *E. coli* and *Serratia marcescens* (in the 16th and 21st months of follow-up). Eleven patients had severe infection: five had spontaneous bacterial peritonitis (*E. coli*), and six had sepsis (due to *E. coli* in three, *Staphylococcus aureus* in one, *Pseudomonas aeruginosa* in one, and *S. marcescens* in one). When the clearance of IgG-coated red cells in the patients with severe infection was compared with the clearance in the patients without infection, those with infection were found to have a significantly longer half-time (126.2±22 vs. 32.2±18 hours, $P<0.001$) (Fig. 3) in the clearance studies performed at the time of their enrollment in the study. Of the 11 patients with half-times of 100 hours or more, 10 later had severe bacterial infections. In contrast, of the 38 patients with half-times under 100 hours, only 1 had a severe bacterial infection. Thus, a defect in macrophage Fcγ-receptor–mediated clearance identified patients in whom severe infection subsequently developed.

We analyzed the clearance (half-time) of IgG-coated red cells in relation to several indications of liver impairment (abnormal values for serum aspartate and alanine aminotransferases, γ-glutamyltransferase, 5′-nucleotidase, bilirubin [total, direct, and indirect], prothrombin time, activated partial-thromboplastin time, fibrinogen, and serum albumin). None of these values, or the presence of splenomegaly, correlated with the extent of impairment of clearance of IgG-coated red cells.

Seven patients had elevated levels of circulating immune complexes. The clearance of IgG-coated red cells in these patients did not differ from that observed in the other 42 patients (data not shown). Furthermore, there was no correlation between the level of circulating immune complexes and the extent of impairment of the recognition of IgG-coated red cells by monocytes (see below).

We also studied peripheral-blood

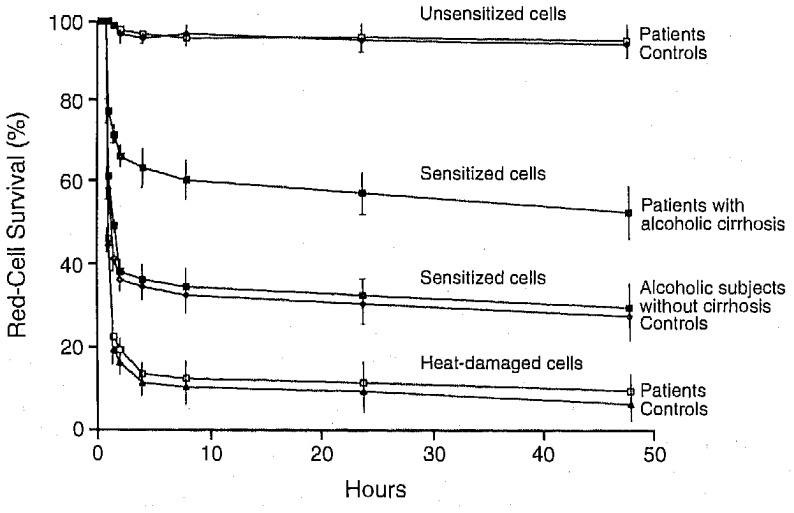

Figure 1. Macrophage Fcγ-Receptor–Mediated Clearance of IgG-Sensitized Radiolabeled Red Cells in 49 Patients with Alcoholic Cirrhosis, 10 Alcoholic Subjects without Cirrhosis, and 20 Normal Controls; Clearance of Unsensitized Autologous Red Cells in 5 Patients and 5 Controls; and Clearance of Heat-Damaged Red Cells in 5 Patients and 5 Controls.
Values are means ±SE.

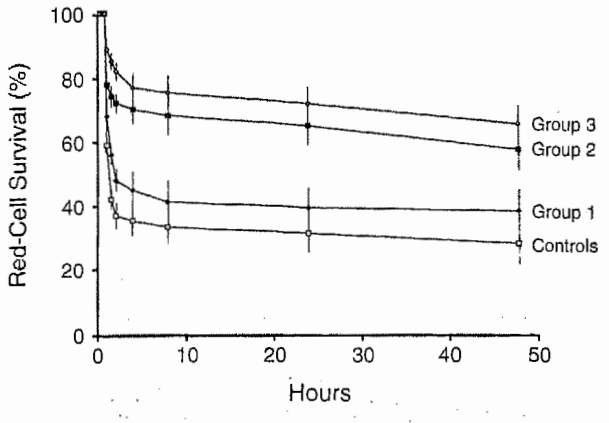

Figure 2. Macrophage Fcγ-Receptor–Mediated Clearance of IgG-Sensitized Radiolabeled Red Cells in 17 Patients with Mild Hepatic Insufficiency (Group 1), 17 Patients with Moderate Hepatic Insufficiency (Group 2), 15 Patients with Severe Hepatic Insufficiency (Group 3), and 20 Controls.
Values are means ±SE.

monocytes from our patients (Fig. 4). Erythrocytes from a single RhD-positive donor were sensitized with three different concentrations of IgG anti-RhD antibodies. Monocytes isolated from the patients bound fewer IgG-coated red cells than did those from the controls, but the differences were not significant. There was no correlation between the extent of binding by monocytes and the degree of impairment of clearance. No differences were observed between the monocytes from patients in whom severe infection developed and those from patients without severe infection. Similarly, peripheral-blood monocytes isolated from the patients with cirrhosis did not bind significantly fewer IgG2b-sensitized red cells than monocytes from the alcoholic subjects without cirrhosis or those from the normal volunteers (Fig. 5).

Neither the clearance of IgG-sensitized red cells nor the in vitro recognition of IgG-coated red cells by monocytes from the patients correlated with sex, age, time elapsed since the diagnosis of alcoholic cirrhosis, or any of the serologic measurements, including the immunoglobulin level. Furthermore, there was no relation between the clearance of IgG-coated red cells or their recognition in vitro by monocytes and the HLA haplotype or the nutritional status of the patients.

The plasma zinc level was 120±4.6 μg per deciliter (18.4±0.7 μmol per liter) in the healthy volunteers and 83.3±3.7 μg per deciliter (12.7±1.3 μmol per liter) in the patients with alcoholic cirrhosis ($P<0.001$). However, there was no correlation between the plasma zinc level and the degree of impairment of clearance in vivo or the recognition of IgG-coated red cells by monocytes in vitro. Similarly, malnutrition was not associated with impairment of the clearance rate or with in vitro recognition of IgG-sensitized red cells by monocytes. Neither the macrophage Fcγ-receptor–mediated clearance nor the binding by monocytes of IgG anti-RhD antibodies or IgG2b-coated red cells correlated with the nutritional status of the patients, as indicated by anthropometric, biochemical, and immunologic values.

Discussion

Infection is a major cause of morbidity and mortality in patients with cirrhosis.[1,26-28] Cirrhosis is primarily due to consumption of alcohol,[2] and the incidence of infectious complications among hospitalized patients with alcoholic cirrhosis is very high. In several studies 30 to 50 percent of patients presented with bacterial infection on admission or infection developed during their hospital stay — an incidence far in excess of that reported for the general hospital population.[1] Most bacterial infections in patients with cirrhosis are acquired in the hospital, with nosocomial infections developing in 20 to 35 percent of patients — again, an incidence far above that in the general hospital population.[1] In our study, severe infection developed in 11 of 49 patients over a two-year period, with fatal complications in 4.

We observed that the clearance of IgG-coated red cells is impaired in patients with alcoholic cirrhosis. Since this clearance is mediated by splenic macrophage Fcγ receptors,[5,12-14,29-31] our data indicate that splenic macrophage Fcγ-receptor function is impaired in such patients. This abnormality was found in the majority of patients (43 of 49), particularly in those with advanced liver insufficiency (Fig. 2), as assessed by an established clinical-staging protocol.[6] Furthermore, impairment of splenic macrophage Fcγ-receptor function predisposes such patients to bacterial infection. The patients in whom severe infections sub-

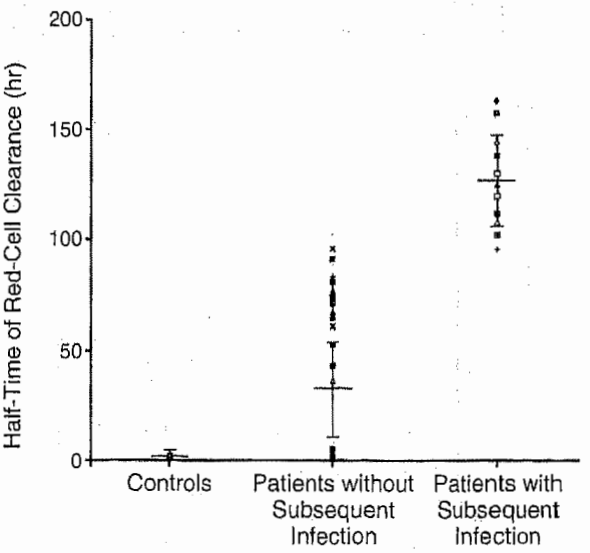

Figure 3. Macrophage Fcγ-Receptor–Mediated Clearance of IgG-Coated Red Cells (Half-Time) in 49 Patients with Alcoholic Cirrhosis and 20 Controls.
The half-time was significantly longer in the 11 patients in whom severe infection developed during follow-up than in the 38 patients without subsequent infection or the controls. The symbols represent individual subjects. Values are means ±SE.

sequently developed had the most marked abnormalities of splenic macrophage Fcγ-receptor–dependent clearance (Fig. 3).

Macrophage Fcγ-receptor–dependent clearance was previously examined in two[29] and five[30] patients with alcoholic cirrhosis. The extent of disease in these seven patients was comparable to that in our patients in group 1. Like our patients in group 1, the seven patients had no evidence of defective macrophage Fcγ-receptor–dependent clearance. In a study of patients with another cirrhotic disorder, primary biliary cirrhosis, a related defect, an abnormality in C3b-receptor–dependent clearance, was observed.[29] The relation of this receptor abnormality to infection in the patients was not studied.

Patients with systemic lupus erythematosus also have defective macrophage Fcγ-receptor–dependent clearance, and this defect correlates with the level of circulating immune complexes.[12,31] We observed defective macrophage Fcγ-receptor function in our patients with alcoholic cirrhosis in the absence of circulating immune complexes. Patients with systemic lupus erythematosus have an increased incidence of infection.[32] However, to our knowledge, there has not been a systematic study of the incidence of infection in relation to the defect in Fcγ-receptor–dependent clearance in such patients.

Splenomegaly has been associated with alterations in the clearance of radiolabeled particulate material by the reticuloendothelial system.[1] Like other investigators,[29,30] however, we found no correlation between the clearance of IgG-coated or heat-damaged red cells and the presence of splenomegaly. Low plasma zinc levels and protein-calorie malnutrition have been associated with immunodepression in cirrhosis.[1,33] However, we found no relation between plasma zinc levels

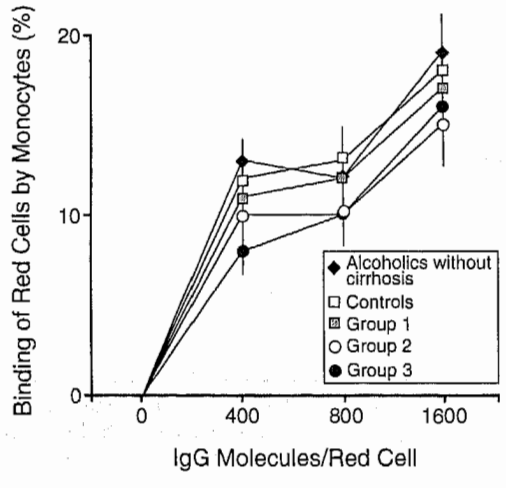

Figure 4. Recognition of Human IgG (Anti-RhD)–Coated Red Cells by Monocytes from 49 Patients with Alcoholic Cirrhosis, 10 Alcoholic Subjects without Cirrhosis, and 20 Normal Controls.

IgG-sensitized, ^{51}Cr-labeled erythrocytes (2×10^7) were added to monolayers of monocytes, and the percentage of red cells bound by monocytes was determined. Values are means ±SE.

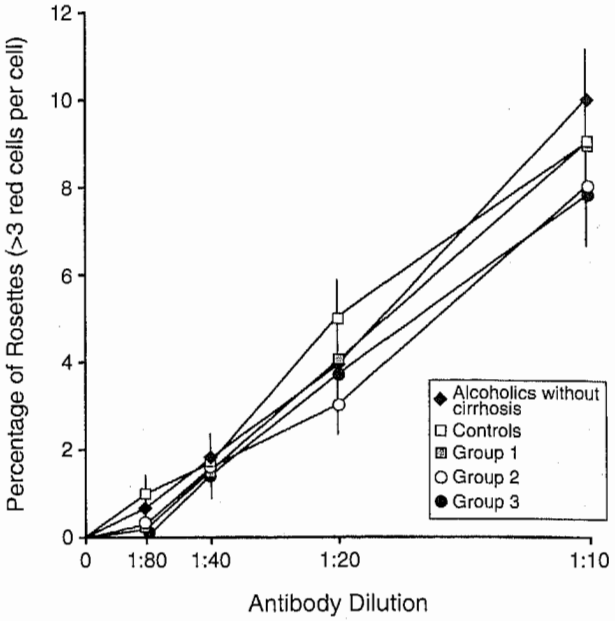

Figure 5. Recognition of Mouse IgG2b-Coated Red Cells by Monocytes from 49 Patients with Alcoholic Cirrhosis, 10 Alcoholic Subjects without Cirrhosis, and 20 Normal Controls.

IgG2b-sensitized erythrocytes were added to monolayers of monocytes, and the percentage of monocytes binding more than three red cells was determined. Values are means ±SE.

or malnutrition and the alteration of Fcγ receptors in our patients either in vivo or in vitro. Abnormalities in the expression or function of Fcγ receptors have been observed in association with certain HLA haplotypes.[3,12,31] In our study there was no correlation between the HLA haplotype and either macrophage Fcγ-receptor–dependent clearance or the recognition of IgG-coated cells by monocytes. Similarly, defective Fcγ-receptor–dependent clearance has been observed in patients with the acquired immunodeficiency syndrome (AIDS),[34] but none of our patients had antibodies to HIV or any evidence of diseases related to AIDS.

Several predisposing factors have been proposed in the development of bacterial infection in patients with cirrhosis. Significantly increased numbers of gram-negative bacilli have been reported in the jejunal flora of patients with cirrhosis.[35] Several in vitro and in vivo studies have demonstrated a reduction of cell-mediated immunity,[36,37] as well as reduced metabolic activity and neutrophil phagocytic and killing capacity.[38] Reduced serum[39] and ascitic-fluid[40,41] opsonic activity has been noted.[1] In addition, patients with cirrhosis frequently have malnutrition[24,36] or acute hypovolemia, which may exacerbate the dysfunction of the reticuloendothelial system.[1,33,42]

Previous studies of macrophage function in cirrhosis have focused on the rate of clearance of radiolabeled colloid or microaggregated human serum albumin.[1,39,43] Abnormalities in hepatic circulation have been reported in association with increased intrahepatic shunting, and such abnormalities may con-

tribute to this nonspecific clearance.[44] Such studies demonstrating an alteration in reticuloendothelial-system clearance did not assess macrophage Fcγ-receptor function. Infection with pyogenic organisms is very common in patients with cirrhosis, and the Fcγ receptors probably have a critical role in the specific clearance of IgG-coated microorganisms, as part of the host defense against bacterial infection.[5]

We further explored the Fcγ-receptor abnormality in our patients. Since tissue macrophages from our patients were unavailable for study, we examined their peripheral-blood monocytes, which are related to tissue macrophages. The peripheral-blood monocytes bound normal amounts of the same human IgG-coated red cells whose clearance was impaired in vivo. Monocytes express two Fcγ-receptor proteins, FcγRI and FcγRII.[45,46] Data from our laboratory indicate that the recognition of IgG anti-RhD–coated erythrocytes by monocytes is mediated primarily by FcγRI.[47] Thus, the binding of IgG-coated cells by monocyte FcγRI is not intrinsically defective in patients with alcoholic cirrhosis. The in vitro binding of mouse IgG2b-coated erythrocytes by human peripheral-blood monocytes has been shown to be mediated primarily by the monocyte receptor FcγRII.[17,47] Our results demonstrate that monocytes from patients with alcoholic cirrhosis bind normal amounts of IgG2b-coated red cells. Thus, the binding of IgG-coated cells by monocyte FcγRII is also not defective in such patients.

In addition to FcγRI and FcγRII, tissue macrophages express a third Fcγ-receptor protein, FcγRIII.[45,46] The alteration in the clearance of IgG-coated cells by splenic macrophage Fcγ receptors, which predisposes patients with alcoholic cirrhosis to severe bacterial infection, may be accounted for by an abnormality in this third class of Fcγ receptors. We have previously reported that patients with end-stage renal disease have a defect in splenic macrophage Fcγ-receptor–dependent clearance that correlates with the incidence of severe infection.[5] Studies of blood monocytes from these patients with renal failure suggested that FcγRI was not responsible for the alteration in clearance.[5] Thus, the results of studies in patients with chronic renal disease are similar to those in patients with alcoholic cirrhosis, indicating the presence of a macrophage Fcγ-receptor defect that predisposes these patients to severe bacterial infection.

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