Mechanism of Anemia in Zieve's Syndrome*

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Abstract: The mechanism of anemia occurring during an illness associated with alcoholism, jaundice, fatty infiltration of the liver, and hyperlipemia was investigated in six men. Increased erythrocyte destruction for the patients' cells and for transfused, normal, compatible donor cells was found during the acute illness. During abstinence and remittance of jaundice and hyperlipemia, erythrocyte survival was normal. In vitro incubation of erythrocytes obtained from this period of remission with plasma preserved from the acute illness did not produce erythrocytes with shortened survival. These erythrocytes did not develop the increased lipid concentrations characteristic of erythrocytes in the acute illness. Present findings support previous impressions that anemia in these patients results primarily from increased erythrocyte destruction, and add two previously unreported features to the description of the hemolysis. One feature is the involvement in the hemolysis of an extracorpuscular abnormality which, by the methods used herein, is not demonstrable in plasma. The second feature is the temporal limitation of accelerated hemolysis to the interval of acute illness. These results suggest that an unidentified, extracorpuscular factor develops during the acute illness and subsides during remission. Whether this factor is unique to patients whose illness conforms to the description of Zieve remains uncertain.

KEY INDEXING TERMS:

Liver disease *Alcoholism* *Hemolysis*
Zieve's syndrome *Hyperlipemia*

Anemia is common in patients with liver disease and various mechanisms may cause its development.[1,2] One type of hemolytic anemia has been reported in patients characterized by Zieve[3,4] as having alcoholism, fatty infiltration of the liver, jaundice and hyperlipemia. In the present study red cell survival was measured in patients with the illness described by Zieve, both during their acute illness and during remission. Results of these studies established for the first time that the excessive hemolysis may be limited temporally to the acute illness and that an extracorpuscular abnormality was responsible at least in part for the increased red cell destruction. In vitro incubation experi-

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ments did not reveal the extracorpuscular defect to be in the plasma preserved from the acute illness.

Methods

Six men with an illness having the features described by Zieve were studied (Table 1). The patients were followed for at least six months after their acute illness.

Standard hematologic procedures,[5] Coombs' test,[5] analysis of stools for occult blood,[5] serum iron measurement,[6] serum folic acid assay,[7] serum amylase determination,[8] liver function measurements,[8] bone marrow aspiration and biopsy,[9] and hepatic biopsy[10] were performed by previously described methods. Techniques for determining plasma and red cell lipids are given in another report.[11]

Survival of the patient's erythrocytes and of normal red cells transfused into the patient was measured simultaneously during the acute illness. The patient's cells were labeled in vivo by the intravenous injection of 140 to 180 μc of diisopropylfluorophosphate^{32} (DFP^{32}).* One hour later the patient was transfused with packed red cells to increase his red cell mass to normal as predicted from body weight. At the same time his plasma volume was brought to normal by plasmaphoresis. The plasma was stored at −70°C for further studies. Following this, fresh, normal, compatible donor erythrocytes tagged in vitro with 100 μc of Cr^{51}† were infused. Half-life values for cells of both the patient and the donor were estimated using both radioactivity per milliliter whole blood and radioactivity per milliliter red cells.[12,13] In all except Subject R, however, subsequent reduction in red cell mass was small enough to make little difference which method was used to calculate survivals. Normal half-life was taken as 25 to 31

TABLE 1

Clinical features of patients

Subject	Age (years)	Duration of Illness	Previous Similar Episodes	Evidence of Chronic Liver Disease	Hepatomegaly	Splenomegaly
D	48	2 months	None	Few spider angiomata	Moderate	Spleen not palpable
A	58	1 week	None	None	Moderate	Slight
W	54	4 days	None	Facial telangiectasia	Moderate	Spleen not palpable
B	39	1 week	None	Few spider angiomata	Marked	Slight
P	43	2 months	1–1 year before	Thin	Moderate	Spleen not palpable
R	40	1 week	2–2 years before	Thin	Moderate	Spleen not palpable

* Obtained monthly in sterile propylene glycol with specific activity of about 200 μc per mg from New England Nuclear Corporation, Boston, Massachusetts.

† Obtained as $Na_2Cr^{51}O_4$ with specific activity 35 μc per μg from E. R. Squibb and Sons, New York, New York.

days for Cr^{51} tagged cells and 40 to 50 days for DFP^{32} labeled cells. Cr^{51} activity was counted using a crystal scintillation counter with a discriminator adjusted so as to exclude P^{32} counts. The Geiger-Muller tube used to measure P^{32} activity did not detect Cr^{51} radiation.

After recovery from their acute illness, three patients (D, A and W) had additional red cell survival measurements. All three patients had an incubation experiment done. In this study the survival of red cells taken from the patient during his remission was determined after sterile incubation with plasma preserved from his acute illness. To do this 400 ml of blood were drawn into plastic bags containing ACD solution. Plasma was removed after centrifugation and replaced by 350 ml of the previously frozen, ACD-containing, acute phase plasma. After anaerobic incubation at room temperature for 24 hours, 100 μc of Cr^{51} were injected into the bag. An hour later 50 mg of ascorbic acid were added, the blood was infused, and red cell survival was measured as before. Aliquots of blood were removed for measurement of red cell and plasma lipids at the beginning and end of the incubation. Subject D had an additional survival study done during remission, but

TABLE 2

Course of patients

Subject	*Course in Hospital*	*Course after Discharge*
D	Appetite excellent; recovery prompt; liver function normal by day 28; maximum reticulocytosis when first measured (day 3); reticulocytosis present on discharge (day 31).	Nearly complete abstinence from alcohol for over 1 year; hematocrit and reticulocyte count normal by day 71; no recurrence; persistent hepatomegaly.
A	Appetite excellent; recovery prompt; liver function nearly normal by day 19; reticulocyte count less on day 1 than day 4; reticulocytosis present on discharge (day 22).	Abstinence from alcohol after discharge; liver and spleen not palpable by day 80; hematocrit and reticulocyte values normal by day 80.
W	Appetite excellent; recovery rapid but liver function not normal until day 40; reticulocyte count less on day 1 than day 6; hematocrit and reticulocyte normal by discharge (day 40).	Abstinence from alcohol after discharge; abnormal bromsulphalein test on day 425.
B	Appetite excellent; recovery rapid but liver function not followed long enough; peak reticulocyte count on day 1; discharged day 18.	Resumption of drinking after discharge; hematocrit level not normal at any time.
P	Appetite fair; clinical recovery delayed by delirium tremens; liver function nearly normal by day 28; reticulocyte count less on day 1 than day 5; reticulocytosis still present on discharge (day 50).	Resumption of drinking after discharge requiring two subsequent admissions; on day 162 admitted again for anemia which was not associated with hypercholesterolemia.
R	Appetite poor; clinical recovery delayed by delirium tremens but liver function normal by day 30; maximum reticulocytosis delayed until day 18; discharged on day 38 with reticulocyte count still increased.	Resumption of drinking after discharge requiring admission again on day 115 with recurrence; never seen when normal hematologically.

TABLE 3

Nonhematologic laboratory data

Subject	Day	Serum Bilirubin (mg/100 ml) Direct	Total	Serum Cholesterol (mg/100 ml)	Serum Alkaline Phosphatase (K.A. units)	SGOT (units)	BSP Retention at 45 min (%)	Liver Biopsy
D	0	3.1	4.6	468	90	157		Slight fatty change; minimal portal fibrosis; intralobular bile stasis; increased stainable iron. (Biopsied day 14).
	7	1.0	1.9	324	34	86		
	14	0.7	1.4		20	26		
	28	1.0	1.8		10	6	2.0	
	71	0.1	0.3	224	9	18		
	436			215				
A	1	8.0	11.0	454	97	202		Marked fatty change; minimal periportal fibrosis. (Biopsied day 11).
	4				56	60		
	11	2.1	3.2	306	32			
	19	0.9	1.7	310	17	32		
	80	0.5	0.2	275		67	1.5	
	180			185			1.0	
W	1	11.0	17.5	560	22	340		Moderate fatty change and cholestasis; mild periportal fibrosis and hemosiderosis. (Biopsied day 7).
	7	3.5	4.8	480	15	87		
	17	2.0	2.6	327		45		
	40		1.0	270	6	26		
	425	0.3	0.6	250	7	20	11.0	

B	1	2.3	4.0	500	62	214		Laennec's cirrhosis with marked fatty change and hemosiderosis. (Biopsied day 4).
	10	0.7	1.5		27	58		
	16						14.0	
	225			418				
P	1	1.1	2.6	348	37	132		Laennec's cirrhosis. (Biopsied day 28).
	5	0.4	0.8	252	15			
	28	0.4	0.6	224	10	22	8.8	
	162	0.6	1.2	288	14	68		
	285			105				
R	2	14.0	24.0	980	61	112		Periportal fibrosis, minimal fatty change; bile stasis. (Biopsied day 16).
	9	8.0	11.0	707	34			
	16	1.4	1.8	316	21			
	30	0.6	0.9	270	13			
	65	12.8	18.0	560	47	200		
	115	0.4	0.6	302	12	28		
	300			218				
Normal range		0.1–0.4	0.3–1.1	150–330	5–13	5–40	<5	

Abbreviations: SGOT=serum glutamic oxaloacetic transaminase, BSP=bromsulphalein.

prior to the incubation experiment. This study measured the life span of his cells tagged in vivo with DFP^{32} and normal, compatible cells labeled in vitro with Cr^{51}.

Results

Summaries of the courses of these patients are given in Table 2. Three patients (D, A and W) abstained from alcohol while being followed and remained well. The remaining three resumed drinking on discharge from the hospital and two (P and R) subsequently required hospitalization. These latter two subjects had also been admitted with the same illness on occasions prior to this study (Table 1).

On admission all patients had elevated serum bilirubin, cholesterol, alkaline phosphatase, and glutamic oxaloacetic transaminase values which rapidly decreased (Table 3). Plasma total lipid, total phospholipid and lecithin concentrations also were increased during the acute illness in all except Subject P, whose plasma lipid elevations were confined to cholesterol and lecithin. Studies of plasma and red cell

TABLE 4

Hematologic data

Subject	*Day*	*Hematocrit (%)*	*Reticulocytes (%)*	*Platelet Count (No./mm³)*	*Serum Folic Acid (mμg/ml)*
D	3*	35	7.1	210,000	28.0
	31	38	3.8	236,000	
	71	47	0.8	252,000	10.0
	436	45	0.4		
A	1	29	2.2	166,000	22.0
	4*	27	9.4	182,000	
	22	39	2.1	348,000	
	80	45	0.2		
	180	41	0.6	314,000	
W	1	28	2.3	128,000	4.9
	6*	30	5.5	188,000	
	17	35	3.4	438,000	
	40	41	1.2	394,000	
	425	45	0.3	412,000	
B	1*	38	5.1	154,000	13.5
	16	40	1.9	236,000	
	225	37	3.0		
P	1	26	3.9	352,000	9.3
	5*	27	12.2	348,000	
	50	40	2.0	398,000	
	62	42			
	162	30	4.4	492,000	
	285	39	1.1		
R	2*	38	1.9	88,000	39.0
	18	30	7.8	570,000	
	38	39	2.9	488,000	
	65	38	0.7	182,000	49.0
	115	39	2.1	288,000	
	300	40	3.4		
Normal range		40–54	0.5–1.5	200,000–440,000	7–16

* Transfusions were given on the indicated day; hematologic tests done on that date were performed prior to transfusion.

lipids are to be reported in greater detail elsewhere.[11] All subjects had some degree of fatty change in liver biopsy specimens except Subject P, who was biopsied later than the other patients. Additionally, most subjects initially showed increased serum lactic acid dehydrogenase, abnormal cephalin flocculation, decreased serum albumin, and normal prothrombin time values. Serum amylase levels were normal in all patients except B, whose value initially was 336 units.

All patients were anemic on admission and showed reticulocytosis at some time in their hospital course (Table 4). The highest reticulocyte count most often occurred at some time after the initial measurement (Subjects A, W, P and R). This pattern was observed despite transfusion which would blunt further reticulocytosis. Findings on the peripheral blood smear in these six patients varied widely (Table 5) and included macrocytes, spherocytes, target red cells, cells containing Howell-Jolly bodies and siderotic granules, and nucleated red cells. Marrow biopsy specimens showed only modest erythroid hyperplasia. Vacuolated erythroid precursors indicated a toxic effect of alcohol on the marrow in two patients (W and R).[14]

The normal or increased serum folic acid levels, the presence of stainable iron in bone marrow and/or liver biopsy specimens as well as normal to high serum iron values, the consistent absence of occult blood in the stools, and numerous negative Coombs' tests provided evidence against folic acid deficiency, iron deficiency, acute bleeding, or immune hemolysis playing a role in the anemia of these patients.

Significant shortening of the half-life for DFP^{32} tagged cells indicated excessive hemolysis as a major factor in the pathogenesis of the anemia (Table 6). The decreased survival of Cr^{51} labeled donor cells provided evi-

TABLE 5

Findings on initial peripheral blood smears and bone marrow examinations

Subject	*Peripheral Smear*	*Bone Marrow*
D	Frequent polychromatophilic macrocytes and spherocytes; occasional fragmented cell.	Slight erythroid hyperplasia; vacuolated reticulum cells containing green granules; increased stainable iron.
A	Moderate numbers of macrocytes, target cells, polychromatophilic cells; few nucleated red cells, cells with Howell-Jolly bodies, and cells with Pappenheimer bodies.	Slight erythroid hyperplasia; plasmacytosis; vacuolated reticulum cells containing green granules; increased stainable iron.
W	Occasional macrocyte and polychromatophilic cell.	Moderate erythroid hyperplasia; vacuolated erythroid precursors; reticulum cells with green granules.
B	Few polychromatophilic macrocytes; occasional macrocytes.	Slight erythroid hyperplasia; few reticulum cells with green granules.
P	Marked anisocytosis with polychromatophilic macrocytes; microspherocytes; occasional nucleated red cell and cells with Howell-Jolly bodies; frequent Pappenheimer bodies.	Moderate erythroid hyperplasia; reticulum cells with green granules; increased stainable iron.
R	Frequent polychromatophilic macrocytes and target cells.	Slight erythroid hyperplasia; vacuolated erythroid precursors; reticulum cells with green granules; decreased stainable iron.

dence for participation of an extracorpuscular factor in the erythrocyte destruction. To determine whether plasma from the acute illness contained a factor which could induce both accelerated hemolysis and characteristically increased red cell lipid concentration,[11,15] incubation experiments were performed as outlined under Methods. Red cells incubated with acute phase plasma had neither increased lipid levels (Table 7) nor underwent premature death in vivo (Table 6).

Increased hemolysis appeared to occur only during the interval of acute illness in those patients who abstained from alcohol after discharge (D, A and W). During this period of abstinence and apparent good health, hematocrit, reticulocyte count, and erythrocyte survival values were normal. These normal red cell life spans were found despite incubation of the cells with plasma preserved from the acute illness. The three who continued to drink alcohol (B, P and R) continued to show hematologic abnormalities. In Subject R clear evidence of increased hemolysis was provided by a repeat survival study done at a time when he again had elevated serum bilirubin, alkaline phosphatase and cholesterol values. Continued accelerated hemolysis was not established by repeat measurement of red cell life span in Subjects B or P or on day 300 in Subject R, but reticulocytosis and anemia were intermittently found.

Discussion

Anemia in patients with alcoholism and liver disease may be caused by one or more mechanisms including acute bleeding, iron deficiency, folic acid deficiency, impaired erythropoiesis and hemolysis. The patients described herein had evidence implicating the last two mechanisms but not the others. Serum folic acid levels were in fact increased in three patients. The reason for these high values is unclear, but similar observations have been recorded previously.[16] Release of folate from liver stores is a possibility, but

TABLE 6

Erythrocyte half-life

Subject	*Day**	*Patient's Cells DFP³²* *(days)*	*Donor's Cells Cr⁵¹* *(days)*	*Remission Phase, Incubated Cells Cr⁵¹* *(days)*
D	3	†	11 (11)‡	
	71	52 (50)	34 (31)	
	436			31 (29)
A	4	22 (19)	16 (16)	
	180			32 (29)
W	6	25 (24)	20 (21)	
	425			28 (27)
B		†	15 (19)	
P	5	20 (19)	12 (14)	
R	2	9 (21)	13 (26)	
	65	11 (11)	13 (12)	
Normal range		40–50	25–31	25–31

*Indicates day survival study was begun.

†Radioactivity was too low for accurate measurement.

‡Half-life values determined using radioactivity per milliliter of red cells are given in parentheses.

TABLE 7

Effect of acute phase plasma on red cell lipid concentrations

Subject	Time (hours)	Red Cell Lipid Concentrations ($mg \times 10^{-11}$/red cell)				Plasma Lipid Concentrations* (mg/100 ml)			
		Total lipid	Phospho-lipid	Choles-terol	Lecithin	Total lipid	Phospho-lipid	Choles-terol	Lecithin
D	0	672	325	143	74	940	215	212	133
	24	466	190	147	47	1,370	440	325	259
A	0	584	382	143	103	710	173	185	88
	17	463	245	138	60	1,430	572	351	350
	24	414	222	109	85	1,450	572	344	410
W	0	596	316	139	80	620	101	189	48
	24	475	220	138	55	1,520	503	330	374
Normal mean		479	300	112	72.2	705	220	227	
SD		± 85	± 36	± 9	± 9.2	± 120	± 31	± 40	
Range									28.6–90.7

*Zero time plasma lipid concentrations were those found in remission phase; plasma lipid concentrations thereafter reflect levels found in acute phase plasma after its incubation.

no proof for this occurrence is available.

Quantification of erythropoiesis was not done by ferrokinetic measurements, but relative impairment of erythropoiesis was suggested by the modest erythroid hyperplasia in the presence of brisk hemolysis. Vacuolated erythroid precursors in two patients indicated recent alcoholism,[14] a condition known to suppress erythropoiesis.[16,17] Because alcohol consumption in most patients probably would continue until hospitalization, suppression of erythropoiesis would likely continue until admission. This may account for the delay in peak reticulocyte count in four of the six patients studied. A similar effect on thrombopoiesis possibly may be responsible for the increasing platelet counts seen during hospitalization.[18]

Accelerated hemolysis clearly constitutes a major factor in the anemia, as shown by the results of this study and by those of previous ones in which reticulocytosis, prompt improvement on hospitalization and shortened red cell survival have been reported.[3,4,19,20] These earlier findings have been viewed as clear evidence of excessive red cell destruction. Little consideration has been given to the possibility that these results might be manifestations of recovery of erythropoietic activity previously suppressed by alcohol. In this situation erythrocyte survival would appear to be diminished because of the rapidly increasing red cell mass if radioactivity was calculated in the usual manner; i.e., per milliliter red cells. In the present study this possible artifact was circumvented (see Methods) and still red cell half-life was found to be short.

To determine whether the increased hemolysis involved an intracorpuscular or an extracorpuscular defect required cross-transfusion studies. Since testing for an intrinsic red cell defect necessitated transfusion of patient's cells to a normal recipient and incurred the risk of transmitting hepatitis, this portion of the cross-transfusion studies was not done. Survival of normal, compatible, transfused donor cells, however, was tested in these patients and found consistently impaired during the acute illness. This clearly indicates an extracorpuscular abnormality although a concomitant intracorpuscular defect could be present. In an effort to determine the nature of the extracorpuscular factor, the effect of incubation of acute phase plasma on the life span and lipid concentration of red cells obtained during a remission phase was tested. Although an in vitro incubation does not duplicate in vivo conditions, the incubated erythrocytes did not assume the characteristics of acute phase cells; i.e., shortened survival and increased lipids, suggesting the extracorpuscular factor is not a circulating one.

At least in certain patients with this syndrome the extracorpuscular abnormality is present only during the acute illness because survival studies done during remission in three subjects (D, A and W) gave normal results. Erythrocyte life spans were normal during remission despite incubation of the cells with plasma preserved from the acute illness. Erythrocyte survival apparently does not return to normal in all patients whose illness is in remission. Holt and Korst[19] have reported two patients whose red cell life spans remained short during remission. Whether the course of these two patients more closely resembled that of Subjects D, A and W; i.e., abstinence from alcohol and good health, or that of B, P and R; i.e., continued drinking and persistent hematologic abnormalities, cannot be determined from published information. A course of illness in the patients of Holt and Korst similar to that observed in Subjects D, A and W would suggest that more than one factor might be responsible for increased hemolysis during the acute episodes. Nevertheless, the present study indicates that excessive red

cell destruction may be limited to the interval during which jaundice, fatty infiltration of the liver, and hyperlipemia occur.

Until the pathogenesis of anemia in liver disease is more fully understood, the pathophysiologic implication of the syndrome described by Zieve remains uncertain. Hemolytic anemia, jaundice, hyperlipemia, and fatty infiltration of the liver occur commonly in alcoholic patients in varied combinations.[21] This variable expression of illness could possibly be indicative of other toxic agents besides ethanol in alcoholic beverages. One such toxin might be responsible for the transient hemolysis described in the present patients. To determine whether the extracorpuscular abnormality described herein is unique to patients whose illness fits the description of Zieve will require studies to further characterize this factor.

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