blood 1985 66: 367-372

A study of liver biopsies and liver disease among hemophiliacs

LM Aledort, PH Levine, M Hilgartner, P Blatt, JA Spero, JD Goldberg, L Bianchi, V Desmet, P Scheuer and H Popper

Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published semimonthly by the American Society of Hematology, 1900 M St, NW, Suite 200, Washington DC 20036.

A Study of Liver Biopsies and Liver Disease Among Hemophiliacs

By Louis M. Aledort, Peter H. Levine, Margaret Hilgartner, Philip Blatt, Joel A. Spero, Judith D. Goldberg, L. Bianchi, Valeer Desmet, Peter Scheuer, Hans Popper, and Paul D. Berk

Hepatic histologic materials (biopsy or autopsy) and associated clinical data from 155 hemophiliacs were collected by an ad hoc hemophilia study group and analyzed retrospectively in an effort to determine the spectrum of liver disease in this population and to examine the relationship between the severity of liver disease and treatment history. Clinical information on the frequency of complications from 126 biopsies in 115 hemophilic patients provided a unique opportunity to assess the safety of liver biopsy in such patients. The incidence of cirrhosis (15%) and chronic active hepatitis (7%) was lower than previously reported. The frequency of severe liver disease (chronic active hepatitis or cirrhosis) in patients receiving large pooled concentrates was no greater than in patients treated principally with cryoprecipitate or plasma. The risks of liver biopsy in this setting are relatively high: clinically significant hemorrhage followed 12.5% of the procedures.

IN THE PAST TEN YEARS there has been increasing recognition of, and concern over, the high incidence of abnormal liver function test results, as well as markers for hepatitis B, in hemophiliacs.[1,2] Several early studies, reviewing deaths and in some instances autopsy material from hemophiliacs, reported essentially no deaths from liver disease.[3-5] However, recent studies demonstrating that a large majority of hemophilic patients have biochemical evidence of hepatic dysfunction correspond in time with the introduction of concentrated antihemophilic factor replacement materials for these patients and have led to concern about the use of products prepared from pooled plasma.

Increasing numbers of liver biopsies are being performed on hemophiliacs throughout the world. The published results, based principally on a small series, emphasize the severity of the pathologic lesions observed as well as the safety of the procedure.[6-10] However, we were aware of many biopsy specimens with minimal findings and of at least two unreported deaths following the procedure. Accordingly, an ad hoc group sought to collect and review all available liver biopsy samples on hemophiliacs in an attempt to determine (1) the spectrum of liver disease in hemophiliacs, (2) whether the nature and severity of the liver disease depended on the type and magnitude of prior transfusion therapy, and (3) whether safety warranted the continued performance of liver biopsies on hemophiliacs.

MATERIALS AND METHODS

Patient population. A small group, designated the Ad Hoc Hemophilia Study Group (AHHSG) initiated this study by contacting all major hemophilia treatment centers listed by the World Federation of Hemophilia in the United States and Western Europe. Additional centers were identified and contacted if they had published data on liver biopsies in hemophilia or were personally known to the investigators. Institutions were asked to submit for review all liver biopsy tissue available from hemophiliacs and to complete a questionnaire for each biopsy patient. The questionnaire sought data about the type of hemophilia (A or B); severity of factor deficiency using standard criteria (severe hemophilia, <1% factor VIII; moderate, 1% to 3%; mild, >3%)[11]; age at time of biopsy; clinical status; prior blood replacement therapy; hepatic biochemical data (expressed as multiples of the upper limits of normal for each institution); hepatitis B marker status (HB_sAg and anti-HB_s); biopsy techniques; and factor coverage for procedure and complications. All biopsies performed at each participating center prior to and within one year after inception of the study (ie, through January 1981) were accessioned.

Criteria for performance of a biopsy were those of the participating institutions. In no case was a biopsy performed solely for the purposes of this study. In addition to biopsies, autopsy materials were also accessioned whenever available. A total of 115 patients on whom biopsies were performed and 40 patients on whom autopsies were performed were entered into the study. Nine patients underwent biopsies on two occasions and one underwent biopsy three times. One patient who underwent liver biopsy was subsequently examined at autopsy. Intervals between procedures, where reported, ranged from three months to three years. Except when noted, the data presented below describe the results of the initial histologic examination on each patient.

Patient classification. Prior to interpretation of histologic features and data analysis, patients were classified by their history of previous replacement therapy into the following four categories: (1) those who had never received concentrates and had been treated only with cryoprecipitate and/or plasma; (2) those who had received a lifetime exposure of <100,000 units of factor VIII or IX concentrate; (3) those who received a cumulative lifetime dose of >100,000 units of concentrate; and (4) those without sufficient data for classification.

Morphological categorization. The clinical data for each patient were reviewed and collated by a clinical subcommittee

From the Departments of Medicine (Polly Annenberg Levee Hematology Center) and Biostatistics, and the Stratton Laboratory for the Study of Liver Disease, Mt Sinai School of Medicine, New York; the Department of Medicine, University of Massachusetts Medical School, Worcester; the Department of Pediatrics, Cornell University Medical Center, New York; the Department of Medicine, University of North Carolina, Chapel Hill; the Department of Medicine (Division of Coagulation), University of Pittsburgh School of Medicine and Central Blood Bank of Pittsburgh; the Departments of Pathology of the Universities of Basel, Switzerland, and Louvain, Belgium; and the Department of Histopathology at the Royal Free Hospital and School of Medicine, London.

Presented in part at the American Society of Hematology meeting, San Antonio, Tex, December 1981.

Supported in part by a contract from the National Heart, Lung, and Blood Institute; by a generous grant from the Merieux Institute; by Health Services Administration grant No. MCB-360001-04-01; by the Regional Comprehensive Hemophilia Diagnostic and Treatment Center, the Margie Boas Fund, and the International Hemophilia Training Center of the World Federation of Hemophilia; and by gifts from the Polly Annenberg Levee Charitable Trust and the Jack Martin Fund.

Submitted July 5, 1983; accepted Feb 13, 1985.

Address reprint requests to Dr Louis M. Aledort, Mt Sinai School of Medicine, Fifth Ave and 100th St, New York, NY 10029.

0006-4971/85/6602-0023$03.00/0

without knowledge of the biopsy interpretations. All hepatic histologic materials were blinded, coded, and distributed in sequence to the four participating pathologists, each of whom was a specialist in hepatopathology. The histologic materials included, for every patient, a hematoxylin and eosin-stained section. Most cases also included a reticulin stain and/or a connective tissue stain (Masson or chromotropic aniline blue), and lesser proportions of the cases included stains for iron, copper, periodic acid-Schiff (PAS) (with or without diastase digestion), and the Shikata stain for hepatitis B surface antigen. All histologic materials received on a given patient were circulated for interpretation.

Each of the four pathologists initially read the coded biopsy/autopsy materials blindly and independently, without any clinical information. Data for each case were recorded on a self-coding computer form in four sequential steps. First, 15 separate histologic features were sought (eg, acidophilic bodies, steatosis, bridging or piecemeal necrosis) and graded (absent, mild, moderate, severe). Second, a diagnosis was offered—acute hepatitis, acute hepatitis with transition to chronicity, chronic lobular hepatitis (CLH), chronic persistent hepatitis (CPH), chronic active hepatitis (CAH), and other forms (specified where possible). The criteria for classification of the various forms of chronic hepatitis were those previously reported.[12] The presence of cirrhosis was specifically indicated. Finally, the pathologist was asked to speculate about the etiology of any observed lesions (hepatitis A, hepatitis B, non-A/non-B, drug, alcohol, other, cannot specify).

Subsequent to analysis of the coded data, all four pathologists met to review the cases together. At this meeting, all cases were classified, by consensus, with respect to the severity of the hepatitic component of the observed histologic lesion (trivial, mild to moderate, severe) and the presence or absence of cirrhosis. All clinical and histologic data were merged for statistical analysis. Data were compared for autopsy cases and biopsy cases using cross-classification methods and χ^2 tests. Similarly, χ^2 tests were used to compare groups with respect to exposure to concentrate and consensus diagnosis.

RESULTS

Demography. Of the patients entered into the study, 80% were factor VIII deficient and 17% factor IX deficient. Three percent of all autopsy cases were unclassified. This older autopsy material, derived from well-known clinicians with a particular interest in hemophilia, antedated the time when specific factor VIII and IX assays were available. Using each institution's local classification based on factor level and clinical symptoms, 79% were classified as severe, 15% mild, and 2% moderate. Collectively, the 115 patients who underwent biopsies and the 40 patients autopsied were comparable with respect to type and severity of hemophilia. Liver disease as a clinical complication of hemophiliac care was unrecognized during the period when most of the autopsy material was collected. In addition, availability of tests for hepatitis B markers followed that era. Hence, no analysis was attempted of the scanty laboratory data available on the autopsied patients.

In the biopsy material, biochemical abormalities equal to or greater than twice the upper limit of normal were present in 47% of cases for SGOT, 57% for SGPT, and 9% for bilirubin. The percentage of cases with abnormal values for each test was substantially higher than previously reported.[2] Twenty-four percent of the patients undergoing biopsies showed positive results for serum HB_sAg, in contrast to the usually reported low incidence of 5% to 7% for all hemophiliacs.[2] The higher incidence in our study may represent selection of patients for liver biopsy because of persistent antigenemia as part of the clinical picture. Splenomegaly, hepatomegaly, or both were found in 49% of the patients receiving biopsies. The median age was 28 years at biopsy and 26 years at autopsy.

Treatment history. Seventeen percent of all patients in the study were never exposed to concentrate, 20% had a cumulative lifetime total of <100,000 units of concentrate, and 53% had been exposed cumulatively to >100,000 units of concentrate prior to biopsy or autopsy. Exposure was unknown for 10% of the cases. In contrast to the total study population, only 5% of those who had liver biopsies had never received any concentrate, whereas 53% of the patients whose autopsy material was supplied had never received concentrate. This difference in the pattern of the replacement therapy between these two groups was statistically significant ($\chi^2_1 = 47.5$, $P = .0001$) and reflects the fact that the patients who underwent biopsies were current cases, whereas autopsy materials often reflected cases retrieved from older files. Available data were inadequate to examine differences in liver function or hepatitis B markers between biopsy and autopsy cases, again reflecting the paucity of modern test data submitted on the autopsied patients.

Biopsy findings. Although there was good agreement among the four pathologists with respect to the histologic features they observed in each case, there was a surprising amount of disagreement on the final diagnosis. Thus, all four pathologists agreed on a specific pathologic entity in only 55% of the cases, and at least three of four agreed in only 76% of the cases. There was considerable disagreement in the classification of cases representing CPH and CAH. Accordingly, at the consensus meeting, patients were further classified into those whose hepatitic lesions were trivial, mild to moderate, or severe; those with cirrhosis (which superseded any coexistent diagnosis); and those with other pathologic features. The spectrum of histopathologic diagnoses that fell into each of these consensus categories is indicated in Table 1.

As shown in Table 2, 64% of all cases had trivial, mild, or moderate hepatitic lesions, and only 7% had severe lesions. Fifteen percent had cirrhosis and 14% had other lesions.

Table 1. Hepatic Disease in Hemophiliacs

Consensus Classification	Histologic Diagnosis
Chronic hepatitis	
Trivial	Spotty liver cell injury
	Minimal inflammatory infiltrate
	Minimal nonspecific hepatitis
Mild/moderate	Chronic lobular hepatitis (CLH)
	Chronic persistent hepatitis (CPH)
	Chronic active hepatitis (CAH)
Severe	Chronic active hepatitis
Cirrhosis	
Other conditions	Acute viral hepatitis, drug-associated lesions, fatty liver, alcoholic liver disease, cancer, terminal ischemia (autopsy cases)

Table 2. Consensus Diagnosis by Group

Chronic Hepatitic Lesion	Biopsy of Patients (%)	Autopsy of Patients (%)	Total of Patients (%)
Trivial, mild, and moderate	65	60	64
Severe	9	2	7
Cirrhosis	16	13	15
Other	10	25	14
Total (%)	100	100	100
Total No.	115	40	155

Within this classification the distribution of lesion types and severity was comparable for the autopsy and biopsy cases ($\chi^2_3 = 7.26$, $P = .06$). Among patients ultimately classified as severe, there was virtual unanimity among the four pathologists in classifying these cases as CAH in their initial review. The overall lower level of agreement in the initial review was seen to reflect principally subtle differences in the weight given by each pathologist to various histologic features in arriving at a specific diagnosis in the majority of cases with borderline disease. Such borderline cases are now known to be common in non-A, non-B hepatitis,[13,14] a condition in which the value of the conventional classification into CPH and CAH based on the presence or absence of piecemeal necrosis has recently been questioned.[15] Because of the lack of agreement on the diagnosis of CAH in patients with mild to moderate hepatitic lesions, it is not possible to be more specific than the consensus diagnosis with respect to histologic severity. A comprehensive review of the histologic features in this patient population will be reported elsewhere.

It was of interest that no etiologic speculation was possible in many cases. However, features considered suggestive of non-A, non-B hepatitis[15] (Table 3) were frequently noted to predominate in some HB_sAg-positive patients in whom histologic features of hepatitis B virus (HBV) infection (eg, ground glass hepatocytes) were lacking. This may suggest that the non-A, non-B agent(s), rather than HBV, caused the ongoing liver disease in such cases, despite the serologic evidence of HBV infection.

For the total population, there was no association between the history of therapeutic products received and the histologic severity of the liver disease (χ^2 9–1.9; $P = .99$). Because of their different treatment histories, a possible association between treatment history and severity of hepatic histologic lesions was examined separately in the biopsy and autopsy cases. As summarized in Table 4, only six biopsy cases had

Table 3. Histologic Features—Chronic Non-A, Non-B Hepatitis

- Lobular
  - Focal liver cell damage (centrilobular prominence)
    - Eosinophilic bodies/eosinophilic cytoplasm
    - Cell swelling
    - Microvesicular fat
  - Variable degree of inflammatory infiltrate
    - Often intense in sinusoids ("infectious mononucleosis")
    - Prominent Kupffer cells and ceroid-containing macrophages
- Portal
  - Lymphocytic/plasma cell infiltration
  - Follicle formation ± germinal centers
  - Changes in bile duct epithelium
- Periportal
  - Mild piecemeal necrosis

no exposure to concentrate. Of these, four (67%) had severe hepatitis or cirrhosis. By contrast, only five of 26 patients (19%) with exposure to <100,000 units of concentrate, and 18 of 72 patients (25%) with exposure to >100,000 units of concentrate had severe chronic hepatitis or cirrhosis. Thus, from this selected group of patients on whom biopsies were performed for some indication of suspected liver disease, no apparent increase in severity of disease is seen with increased exposure ($P = .6$). Although no significant association was observed either among the 40 autopsied cases ($P = .8$), 21 of these had received no concentrate. Among the 15 autopsied patients known to have received concentrate, the incidence of severe chronic hepatitis or cirrhosis was 20%. Thus, the prevalence of severe liver disease is comparable for reported levels of any exposure to concentrate in both the biopsy and autopsy groups.

The frequency of exposure to various levels of concentrate, consensus histologic diagnosis, and severity of hemophilia were examined within all age groups, and possible associations among these variables were explored (Table 5). Other than an increased proportion of mild hemophiliacs among patients beyond the age of 40, presumably reflecting reduced survival of severe cases, no association between age, severity of hemophilia, product exposure, and histologic severity was discernible, although the number of childhood cases <10 years old was small.

Sequential histologic examinations. The single patient on whom three biopsies were performed showed a progression from acute hepatitis, with evidence of transition to chronicity to mild chronic hepatitis (CPH) to severe chronic hepatitis (CAH) over a three-year period. Of the 11 patients examined twice, five were unchanged—three with mild

Table 4. Consensus Diagnosis for Patients Who Underwent Biopsies, by Exposure to Concentrate

	Exposure to Concentrate									
	No Exposure		<100,000 U		≥100,000 U		Not Enough Data		Total	
Consensus Diagnosis	No.	%	No.	%	No.	%	No.	%	No.	%
Trival, mild to moderate	2	33.3	18	69.2	47	65.3	8	72.7	75	65.2
Severe	1	16.7	2	7.7	6	8.3	1	9.1	10	8.7
Cirrhosis	3	50.0	3	11.5	12	16.7	1	9.1	19	16.5
Other lesions	0	—	3	11.5	7	9.7	1	9.1	11	9.6
Total	6	100.0	26	100.0	72	100.0	11	100.0	115	110.0

Table 5. Frequency of Exposure to Concentrate, Consensus Histologic Diagnosis, and Level (Severity) of Hemophilia Within Age Groups

	Age Group											
	<10 yr		10-19 yr		20-29 yr		30-39 yr		≥40 yr		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Exposure to concentrate												
None	1	10.0	0	—	1	2.6	1	5.0	3	12.5	6	5.2
<100,000	5	50.0	5	22.7	6	15.4	3	15.0	7	29.2	26	22.6
≥100,000	4	40.0	15	68.2	27	69.2	15	75.0	11	45.8	72	62.6
Not enough data	0	—	2	9.1	5	12.8	1	5.0	3	12.5	11	9.6
Consensus diagnosis												
Trivial, mild to moderate	5	50.0	17	77.3	27	69.2	12	60.0	14	58.3	75	65.2
Severe	1	10.0	1	4.5	4	10.3	2	10.0	2	8.3	10	8.7
Cirrhosis	3	30.0	2	9.1	5	12.8	4	20.0	5	20.8	19	16.5
Other lesions	1	10.0	2	9.1	3	7.7	2	10.0	3	12.5	11	9.6
Level (severity)												
<1% (severe)	9	90.0	18	81.8	34	87.2	18	90.0	14	58.3	93	80.9
≥1-<3% (moderate)	1	10.0	1	4.6	0	—	0	—	0	—	2	1.7
≥3% (mild)	0	—	3	13.6	3	7.7	1	5.0	10	41.7	17	14.8
Unknown	0	—	0	—	2	5.1	1	5.0	0	0	3	2.6
Total	10	100.0	22	100.0	39	100.0	20	100.0	24	100.0	115	100.0

CPH, one with severe CAH, and one with cirrhosis—and one each showed evolution from acute hepatitis to acute hepatitis with evidence of chronicity, from the latter diagnosis to mild CAH, and from mild chronic hepatitis (borderline CPH/CAH) to cirrhosis. By contrast, in two patients, initial biopsies showing mild to moderate CAH improved to milder hepatitic lesions (CPH). In the final patient, mild CPH improved to a trivial lesion showing only minimal spotty necrosis. As in the total population (see below), changes in the results of hepatic biochemical tests did not predict alterations in hepatic history.

Biopsy Sequelae. Study participants reported that 12.5% of the biopsy procedures led to a prolongation of the planned hospitalization or to an appreciable increase in coagulation factor replacement beyond what had been planned for the biopsy in order to control hemorrhage. No deaths occurred as a result of the 126 biopsy procedures on 115 patients reported to the AHHSG.

Biochemical and serologic studies. Seventy-eight percent of the biopsy cases considered to have cirrhosis and 70% of the cases with severe hepatitic lesions had SGOT activities at least two times normal compared with 37% of those with trivial and mild lesions and 45% of those with other lesions ($\chi^2_3 = 11.8$, $P = .008$). Similarly, the proportion of cases with abnormal SGPT activities (at least two times normal) appears higher in those cases with severe lesions (89%) and cirrhosis (68%) compared to those with trivial and other lesions (51% to 60%; $\chi^2_3 = 6.0$, $P = .11$). Only 13% of trivial cases were HB_sAg positive, compared with 27% of other lesions, 40% of severe lesions, and 61% of cirrhosis ($\chi^2_3 = 19.7$, $P = .0002$). Although there are statistically significant differences in hepatic test abnormalities or the presence of HB_sAg between the different histologic groups, blood testing in the individual patient did not, however, reliably predict either the type or severity of the hepatic histologic lesions.

DISCUSSION

This study reports the largest series of hepatic histologic materials in hemophiliacs assembled for review. It would have been preferable to examine a more homogeneous population, followed with current and standardized diagnostic modalities, treated prospectively according to well-defined protocols, and biopsied only under predetermined criteria. Nevertheless, the risks of performing additional biopsies prospectively appeared sufficiently formidable to encourage this retrospective analysis of available materials.

Accordingly, the goals of this review were (1) to define the spectrum of liver disease in hemophiliacs, (2) to examine the relationship between the severity of histologically documented disease and treatment history, and (3) to estimate the risk-benefit ratio for liver biopsy in this population.

Results of our histologic evaluation reveal that the incidence of cirrhosis in our large series is 15%, less than previously reported.[7-9] In the noncirrhotic biopsy specimens, the incidence of severe necro-inflammatory disease, mainly CAH, was also lower than previously described.[7-9] Most slides showed CPH, CLH, or mild borderline CAH. Many cases with serologic markers for hepatitis B lacked the histologic features of B hepatitis (eg, ground glass cells)[16] and showed features of non-A, non-B hepatitis.[13-15,17,18] The lack of agreement on diagnosis reflects a high proportion of cases with mild to moderate disease, with features suggestive of both CPH and mild CAH, as well as of a non-A, non-B etiology. These cases differ histologically from the more florid types of chronic hepatitis observed in autoimmune

HBV-associated chronic liver disease, and it was from studies of the latter that the current diagnostic criteria for CPH and CAH largely evolved.[12,16] Studies of histologic materials from patients with presumptive non-A, non-B disease, including the present biopsies and autopsies, have led hepatopathologists to recognize the need for new descriptive and diagnostic criteria,[13,15] but no generally accepted schema is currently available. The consensus classification developed during this study is at best an interim measure with respect to precise histologic classification, but appears suitable for addressing the more clinically oriented goals of the present study.

The lack of severity of the histopathologic findings in the current materials may not be entirely reassuring. Some recent evidence suggests insidious progression of non-A, non-B hepatitis to cirrhosis,[19] although other studies suggest the possibility of reversion toward normal hepatic architecture.[20] Both progression and reversion, as well as a static picture, were observed in patients examined repeatedly in the present study. As in previous reports, hepatic biochemical and serologic tests did not predict the histologic lesions.

There was no association in this study between the treatment regimen and histologic severity. Specifically, there was no evidence of more severe liver disease in patients receiving concentrates prepared from large pools of donor plasma. Thus, at this time there appears to be no indication to alter current therapy patterns because of concern over plasma product-related liver disease. Whether pooled plasma-derived products may present a greater risk for the acquisition of acquired immune deficiency syndrome (AIDS) by hemophiliacs[21] was not addressed in this study.

These data are of particular interest, as it is now clear that the use of large amounts of cryoprecipitate and concentrate leads to identical patterns of hepatitis B markers in recipients as well as produces similar patterns of biochemical abnormalities.[2] This was not originally predicted since patients receiving cryoprecipitate or plasma are exposed to far fewer donors compared to those receiving concentrate. For example, the average factor VIII-deficient patient receives 40,000 units of factor per year.[11] The maximum annual exposure to donors is 400 when plasma and/or cryoprecipitate are used, whereas a single vial of 1,000 units of factor VIII concentrate is derived from a pool of between 2,500 and 22,500 donors. These findings may be of particular importance when attempting to make rational treatment decisions for hemophiliacs at a time when serologic screening tests for type III human T cell leukemia virus—the presumptive cause of AIDS—are not widely available, nor their efficacy established.

The risks of liver biopsy in hemophiliacs are not insignificant. Despite the experience of the participating centers with both liver biopsy and hemophilia, one of every eight procedures (12.5%) reported to the present study was complicated by prolonged hospitalization and/or requirements for appreciably increased factor use because of hemorrhage. Beyond this high morbidity rate, we are aware of two deaths from uncontrollable bleeding following liver biopsy at two centers, in New York and London, which did not contribute histologic materials to the study. Hence, based on our estimate of approximately 200 liver biopsies in hemophiliacs worldwide at the time of our review, the fatality rate from the procedure may approximate 1%, compared to <0.01% in nonhemophiliacs.[22] This is of great concern. As the vast majority of biopsy specimens showed histologically unimpressive lesions, and as there is in any case no currently effective therapy for CAH,[23] the information obtained by liver biopsy in this patient population only occasionally justifies the increased risk of this procedure.

ACKNOWLEDGMENT

The authors would like to thank the following physicians who kindly contributed material to this study: Drs Anjela Miser, Thomas Kisker, Oscar Ratnoff, Jack Lazerson, Teri Holbrook, Arthur Thompson, Richard Counts, Eric Lian, John Lukens, Piero Mannucci, Ronald Weinger, Gerald Gilchrist, Marion Dugdale, Ralph Gruppo, M.J. Larrieu, Jeanne Lusher, and Klaus Shrimpf.

REFERENCES

1. Hasiba U, Spero JA, Lewis JH: Chronic liver dysfunction in multitransfused hemophiliacs, in Fratantoni J, Aronson D (eds): Proceedngs of a Workshop on Unsolved Therapeutic Problems in Hemophilia. Bethesda, Md, US Department of Health, Education and Welfare, 1976, p 81

2. Cederbaum AI, Blatt PM, Levine PH, and the Hemophilia Study Group: Abnormal serum transaminase levels in patients with hemophilia A. Arch Intern Med 42:481, 1982

3. Aledort LM: The cause of death in hemophiliacs, in Fratantoni J, Aronson D (eds): Proceedings of a Workshop on Unsolved Therapeutic Problems in Hemophilia. Bethesda, Md, US Department of Health, Education and Welfare, 1976, p 9

4. Forbes CD, Prentice CRM: Mortality in haemophilia—a United Kingdom survey, in Fratantoni J, Aronson D (eds): Proceedings of a Workshop on Unsolved Therapeutic Problems in Hemophilia. Bethesda, Md, US Department of Health, Education and Welfare, 1976, p 15

5. Lewis JH, Spero JA, Hasiba U: Deaths in hemophiliacs, in Fratantoni J, Aronson D (eds): Proceedings of a Workshop on Unsolved Therapeutic Problems in Hemophilia. Bethesda, Md, US Department of Health, Education and Welfare, 1976, p 29

6. Spero JA, Lewis JH, Van Thiel DH, Hasiba U, Rabin BS: Asymptomatic structural liver disease in hemophilia. N Engl J Med 298:1373, 1978

7. Mannucci PM, Ronchi G, Rota L, Colombo M: Liver biopsy in hemophilia. Ann Intern Med 88:429, 1978 (letter)

8. Schimpf K, Dohnert G, Thamer G, Zeltsch P, Zimmerman K: Hepatic histology and serological findings in 22 patients with severe hemophilia A, hemophilia B, and factor VIII deficiency. Results of 25 biopsies. XVII Congress of the International Society of Hematology. 1978, p 212

9. Preston FE, Underwood JCE, Mitchell VE, et al: Percutaneous liver biopsy and chronic liver disease in hemophiliacs. Lancet 2:292, 1978

10. White GC, Zeitler KD, Lesesne HR, et al: Chronic hepatitis in patients with hemophilia A: Histologic studies in patients with intermittently abnormal liver function tests. Blood 60:1259, 1982

11. Aledort LM, Goodnight SH: Hemophilia treatment: Its relationship to blood products, in Brown E (ed): Progress in Hematology, vol 12. Orlando, Fla, Grune & Stratton, 1981, pp 125–141

12. Leevy CM, Popper H, Sherlock S (eds): Diseases of the Liver and Biliary Tract: Standardization of Nomenclature, Diagnostic

Criteria, and Diagnostic Methodology. Washington, DC, US Government Printing Office, US Department of Health, Education and Welfare, Publication NIH 76–725, 1976

13. Dienes HP, Popper H, Arnold W, Lobeck H: Histologic observations in human hepatitis non-A, non-B. Hepatology 2:562, 1982

14. Fagan EA, Williams R: Non-A, non-B hepatitis. Semin Liver Dis 4:314, 1984

15. Popper H: Changing concepts of the evolution of chronic hepatitis and the role of piecemeal necrosis. Hepatology 3:758, 1983

16. Bianchi L, Zimmerli-Ning M, Gudat F: Viral hepatitis, in MacSween RNM, Anthony PP, Scheuer PJ (eds): Pathology of the Liver. London, Churchill-Livingstone, 1977, p 164

17. De Wolf-Peeters C, De Vos R, Desmet V, et al: A light microscopic marker of non-A, non-B viral hepatitis. J Clin Pathol 34:814, 1981

18. Bamber M, Murray AK, Weller ND, et al: Clinical and histological features of a group of patients with sporadic non-A, non-B hepatitis. J Clin Pathol 34:1175, 1981

19. Koretz RL, Stone O, Gitnick GL: Non-A, non-B transfusion hepatitis: Disaster after decades. Hepatology 2:687, 1982 (abstr)

20. Mannucci PM, Colombo M, Rizzetto M: Nonprogressive course of non-A, non-B chronic hepatitis in multitransfused hemophiliacs. Blood 60:655, 1982

21. Desforges JF: AIDS and preventive treatment in hemophilia. N Engl J Med 308:94, 1983 (editorial)

22. Lindner H: Grenzen and Gefhren der perkutanen Leberbiopsie mit der Menghini-Nadel: Erfahrungen bei 80,000 Leberbiopsien. Dtsch Med Wochenschr 92:1751, 1967

23. Hoofnagle JH: Chronic hepatitis: The role of corticosteroids, in Szmuness W, Alter HJ, Maynard JE (eds): Viral Hepatitis. Philadelphia, Franklin Institute Press, 1981, p 575