

The New England Journal of Medicine

©Copyright, 1981, by the Massachusetts Medical Society

Volume 304

APRIL 23, 1981

Number 17

SERUM ALANINE AMINOTRANSFERASE OF DONORS IN RELATION TO THE RISK OF NON-A, NON-B HEPATITIS IN RECIPIENTS

The Transfusion-Transmitted Viruses Study

RICHARD D. AACH, M.D., WOLF SZMUNESS, M.D., JAMES W. MOSLEY, M.D., F. BLAINE HOLLINGER, M.D.,
RICHARD A. KAHN, PH.D., CLADD E. STEVENS, M.D., VIRGINIA M. EDWARDS, B.S.,
AND JOCHEWED WERCH, M.D.

Abstract To evaluate the incidence of post-transfusion hepatitis and factors influencing its occurrence, the Transfusion-Transmitted Viruses Study prospectively followed 1513 transfusion recipients from 1974 through 1979. The attack rate for non-A, non-B hepatitis was 10 per cent. The incidence of hepatitis was directly related to the alanine aminotransferase (ALT) level in blood donors. In recipients of multiple transfusions of blood that had no donor-ALT level above 29 IU per liter the attack rate was 6 per cent or less; at

higher donor-ALT levels the attack rate increased progressively, reaching 45 per cent in recipients of units with an ALT of 60 IU or greater. A similar relation was observed among recipients of single units of blood. Moreover, hepatitis developed in 10 of 11 recipients of two units with an ALT level of 45 IU or greater. These data indicate that screening blood for ALT levels would reduce the incidence of non-A, non-B post-transfusion hepatitis. (N Engl J Med. 1981; 304:989-94.)

IN the mid to late 1950s it was recognized that some donors whose blood was probably responsible for post-transfusion viral hepatitis had persistent abnormal values in one or more tests for hepatic dysfunction.¹ In addition, certain donors who were associated with an increased likelihood of transmitting post-transfusion hepatitis had a high rate of these abnormalities.^{2,3} Thus, it seemed plausible that screening donors for laboratory evidence of subclinical hepatic damage could be useful in reducing the occurrence of hepatitis in transfusion recipients.⁴

The test initially favored was thymol turbidity because the proportion of positive results among implicated donors was the highest.¹ However, studies evaluating its efficacy provided conflicting results,⁵⁻⁷ and

routine application of the test would have required blood banks to discard a substantial proportion of donations. Furthermore, many technical aspects of the procedure were difficult to standardize.⁸

The advent in 1955 of practical techniques for the clinical measurement of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT),⁹ which have high sensitivity in detecting liver damage,^{10,11} rapidly led to attempts at donor screening with these procedures. Once again, however, there were conflicting observations,¹²⁻¹⁵ and the controversy that resulted provided little incentive for blood banks to assay these enzymes as a routine method of donor evaluation.

Awareness of the association of Australia antigen with viral hepatitis^{16,17} and its importance in donor screening^{18,19} caused a decline in interest in nonspecific indexes. When the Transfusion-Transmitted Viruses Study began in 1974, however, it was recognized that not all cases of post-transfusion hepatitis could be eliminated, even when blood banks used sensitive methods to detect hepatitis B surface antigen (HBsAg)-positive donors.²⁰ That observation directed the attention of the Study Group back to ALT screening of donors as one approach to reducing further the incidence of hepatitis in recipients. The recognition in 1974 of non-A, non-B post-transfusion hepatitis,²¹ for which specific tests are still lacking, provided additional support for the promising initial results obtained by this Study Group.²²

The Transfusion-Transmitted Viruses Study Group consists of the following:

Participating Institutions: the Lindsley F. Kimball Research Institute of the New York Blood Center, the New York Hospital, and the Hospital for Special Surgery, New York; Washington University School of Medicine-Barnes Hospital and the Missouri-Illinois Regional Red Cross, St. Louis; Baylor College of Medicine, Ben Taub General Hospital, and Methodist Hospital, Houston, Tex.; and the UCLA Center for the Health Sciences, Los Angeles.

Coordinating Center: University of Southern California School of Medicine, Los Angeles.

Advisory Committee: Dr. Paul Holland (chairman), Dr. William Bancroft, Dr. Lawrence Shaw, and Dr. Hyman Zimmerman.

Address reprint requests to Dr. Aach at the Department of Medicine, Sinai Hospital of Baltimore, Belvedere Ave. at Greenspring, Baltimore, MD 21215.

Supported under a contract (N01-HB 42972) with the National Heart, Lung, and Blood Institute, National Institutes of Health.

Systematically collected data for the period 1974 through 1979 now provide substantial evidence that the level of donor ALT is related to the occurrence of non-A, non-B hepatitis in transfusion recipients. The extent of the association is sufficient to raise the question of whether ALT screening of donors should be reconsidered. This report summarizes the data.

METHODS

The Transfusion-Transmitted Viruses Study is a prospective investigation that has as two of its major goals the definition of the incidence of post-transfusion viral hepatitis at four medical centers in different areas of the United States and the evaluation of factors influencing its occurrence. Patient recruitment and follow-up were carried out in these cities within the following intervals: New York, January 1976 through November 1979; St. Louis, July 1974 through November 1979; Houston, July 1974 through November 1979; and Los Angeles, July 1974 through June 1977.

Patient Recruitment and Follow-up

Recruitment was begun before anticipated transfusion. The major criteria for eligibility of each patient included the following: age of at least 16 years; no problems likely to result in death or a need for transfusion during follow-up; no transfusions within the preceding nine months; no history of viral hepatitis or other liver disease, no recognized exposure to hepatitis within the previous six months, no recognized potential for occupational exposure; and no administration or likelihood of administration of drugs commonly associated with an elevation in serum ALT.

Once the patient had provided informed consent for participation in the study, a sample of blood was obtained for definition of base-line serum ALT and for specific serologic indexes of infection with hepatitis A virus or hepatitis B virus before transfusion. In most instances, a sample was also collected seven days after transfusion.

Final evaluation for entry into the study was based on the recipient's status 14 days after transfusion. The hospital chart was reviewed to confirm that the previously applied eligibility criteria were still met. Entry into the follow-up study, however, was also contingent on the following conditions: no transfusion volume exceeded 15 units of whole blood or blood components (or both); no clotting-factor concentrates prepared from multiple donors were given; transfusions were limited to units negative for HBsAg by reverse passive hemagglutination (New York Blood Center) or by radioimmunoassay (all other blood banks); all donors could be identified, and a sample of blood from the donation was available for additional testing; evaluation during hospitalization had uncovered no cause for a poor prognosis (e.g., metastatic neoplasm) or need for treatment likely to produce ALT elevations; at least one serum ALT level before transfusion or within 14 ± 3 days after transfusion was less than 45 IU per liter (micromoles per minute per liter) at 37°C; any transient elevation of ALT could be explained by known self-limiting factors such as the patient's condition (e.g., trauma) or the effects of surgery or anesthesia; and, finally, the patient's blood sample taken before transfusion was HBsAg negative by radioimmunoassay.

For eligible patients, 10 additional visits were routinely scheduled at four, six, eight, 10, 12, 15, 18, 21, 24, and 40 weeks after transfusion. At each visit, the patient's status was reviewed and a blood sample obtained. Follow-up was discontinued if there was retransfusion or any other recognized exposure to viral hepatitis.

Visits were made weekly if symptoms or signs compatible with the presence of viral hepatitis developed, if the ALT activity increased to 45 IU or more, or if the HBsAg test became positive.

Case Evaluation

A patient was suspected of having viral hepatitis if between 11 and 180 days after transfusion there were at least two consecutive blood samples with elevated ALT levels, one of 45 IU or more and another of 90 IU or more. The specimens had to be collected not less than three days and no more than 17 days apart.

Periodically, records for each patient with a suspected episode of hepatitis were evaluated by a panel consisting of the investigators and the advisory committee. All available information, including results of serologic tests specific for infections from hepatitis A and B, was considered in classifying each episode. The diagnosis of non-A, non-B hepatitis was made after the following possible explanations of ALT elevations had been excluded: a diagnosis of hepatitis B as shown by the appearance of HBsAg or hepatitis B core antibody (anti-HBc) (or both), with or without the appearance of hepatitis B surface antibody (anti-HBs) unrelated to passive transfer by transfusion; an underlying disease; drug-induced hepatitis; or chronic liver injury undetected during recruitment but detected by review of the patient's history and laboratory studies before and after this period.

Characteristics of Donors and Recipients

The blood transfused at the medical centers in St. Louis and New York was obtained from volunteers donating at a community agency. These donors were derived primarily from a white, middle-level socioeconomic population. From 1974 until 1976, the hospital in Los Angeles acquired most of its blood from a similar population, but some units were also obtained from three commercial collection agencies that depended on paid donors. At the Houston facility, blood was obtained from volunteers through a county-hospital blood program; the donors were mainly from a lower socioeconomic group and included families and friends of recipient. The mean age of all donors was 34 ± 12 years (\pm S.D.), with a male:female ratio of 2:1.

Recipients were predominantly patients scheduled for elective surgery. In New York, St. Louis, and Los Angeles, recipients were mainly from a middle to upper-level socioeconomic population, whereas those in Houston were largely from a lower socioeconomic stratum served by a county hospital. The mean age of the recipients was 52 ± 16 years, with a male:female ratio of 1:1.

Laboratory Procedures

Careful attention was given to standardization and quality control of all laboratory procedures. Samples were processed and usually tested in triplicate for ALT levels within 24 hours of collection. If testing was delayed for 48 to 72 hours, the serum was stored at 4°C. ALT levels were measured in the Study Group laboratories at each participating institution and at the coordinating center, with an automated kinetic assay (Beckman TR System, Fullerton, Calif.) that used reagents (including distilled water) from the same lots by the same manufacturers. Two standards were routinely measured in triplicate with each run. Results of ALT testing were monitored by a computer program to ensure that values within and among laboratories were consistent over time. In addition, serum aliquots in randomly sequenced panels were tested as "unknowns" for evaluation of intralaboratory and interlaboratory variation.

Patients' blood samples were tested for HBsAg, anti-HBs, and anti-HBc with commercially available assays (Ausria I-125 or Ausria II-125, Ausab, and Corab, respectively; Abbott Laboratories, North Chicago, Ill.) and serum samples for antibody to hepatitis A with a radioimmunoassay previously described.²³

Data were analyzed by the chi-square test with Yates' correction in all 2-by-2 contingency tables.

RESULTS

The 1513 patients included in this analysis were followed for a minimum of 21 weeks (median, 40 weeks). Excluded from analysis were 164 recipients who were followed for less than 21 weeks, five recipients for whom all donor specimens were not available for ALT testing, and 15 recipients in whom hepatitis B infection developed. There were no cases of hepatitis A infection. The number of recipients followed at each participating center was 428 in New York, 504 in St. Louis, 384 in Houston, and 197 in Los Angeles. These patients received an average of 3.7 units of blood; the

mean transfusion volume at two of the centers (St. Louis and Los Angeles) was nearly identical (4.2 and 4.3 units), but recipients in New York received an average of 3.8 units and those in Houston one of 2.4 units. Among all recipients, 156 (10 per cent) acquired non-A,non-B hepatitis. The incidence of hepatitis ranged from 4 per cent in St. Louis to 18 per cent in Houston.

Among the 5564 donors ALT levels were distributed in the following way: 1 to 14 IU, 66 per cent; 15 to 29 IU, 25 per cent; 30 to 44 IU, 6 per cent; 45 to 59 IU, 1.5 per cent; and 60 to 284 IU, 1.6 per cent. Of these 5564, 638 were donors to a recipient who later had non-A,non-B hepatitis. Table 1 compares the ALT levels of these implicated donors with those of all donors. The frequency of donors associated with a case progressively increased, from 9 per cent in the group with 1 to 14 IU of ALT to 47 per cent in the group with values of 60 IU and higher.

To study the possibility that the level of donor ALT influenced the occurrence of post-transfusion hepatitis, we grouped each recipient according to the donor

Table 1. Frequency of Association between Donors and Recipients with Non-A,non-B Hepatitis According to Donor ALT Level.

ALT LEVEL OF DONOR	NO. OF DONORS	DONORS ASSOCIATED WITH NON-A,non-B HEPATITIS IN RECIPIENTS
<i>IU</i>		<i>no. (per cent)</i>
1-14	3680	329 (9)
15-29	1397	179 (13)
30-44	315	59 (19)
45-59	85	30 (35)
60-284	87	41 (47)

whose blood had the highest ALT activity (Table 2). When the highest donor ALT level ranged between 1 and 14 IU, the attack rate of non-A,non-B hepatitis was 5 per cent. Recipients given donor units with ALT levels that were <30 IU had a substantially lower incidence of non-A,non-B hepatitis than recipients given units with higher levels ($P < 0.005$). At ALT levels ≥ 30 IU the incidence of non-A,non-B hepatitis progressively rose as the maximum donor ALT level increased. Among patients receiving at least one unit of blood with an ALT level ≥ 60 IU the attack rate was 45 per cent.

Table 2 also shows the hepatitis attack rate per 1000 units transfused; the rate was calculated in this way to control for variation in the number of units received. The relation of this attack rate to the highest donor ALT was similar to that of the rate expressed per hundred recipients; the rate per 1000 units rose from a low of 17 to a high of 101 cases in the group of recipients whose donor ALT levels were ≥ 60 IU.

To eliminate the possibility that units other than the one with the highest ALT level was the source of infection, the investigators examined the association between donor ALT and the incidence of non-A,

Table 2. Relation between Highest ALT Level of Donor and the Incidence of Non-A,non-B Post-Transfusion Hepatitis among 1513 Recipients.

HIGHEST ALT LEVEL OF DONOR	NO. OF RECIPIENTS	AVERAGE NO. OF UNITS TRANSFUSED	RECIPIENTS WITH NON-A,non-B HEPATITIS		
			TOTAL NO.	NO./ 100 RECIPIENTS	NO./ 1000 UNITS
<i>IU</i>					
1-14	531	2.7	24	5	17
15-29	584	4.0	37	6	16
30-44	238	4.7	35	15	32
45-59	76	4.8	22	29	60
60-284	84	4.5	38	45	101

non-B hepatitis in recipients of single units (Table 3). Although the number of patients was much smaller, the same relation between donor ALT and attack rate was observed. Moreover, the attack rate was eight times higher among recipients given a unit with an ALT level ≥ 45 IU than among recipients given blood with a lower ALT level (42 vs. 5 per cent).

Table 4 shows the relation between non-A,non-B hepatitis and the number of units with an elevated (≥ 45 IU) ALT level given to recipients of multiple units. Patients receiving one unit with an elevated level had more than a fourfold higher rate of hepatitis than did recipients of blood with a lower level (33 vs. 8 per cent; $P < 0.01$). Among patients into whom two units with elevated ALT levels had been transfused, 10 of 11 (91 per cent) contracted hepatitis.

The relation between the highest donor ALT level and the incidence of non-A,non-B hepatitis was observed among recipients of blood obtained from all three types of donors (Fig. 1). Transfusion of blood with an ALT level below 45 IU resulted in a lower attack rate when it was obtained from community agencies (5 per cent) than when it was collected from a county-hospital blood program (13 per cent) or from commercial agencies with paid donors (23 per cent). A similar pattern in the incidence of hepatitis as related to donor source was seen in recipients to whom at least one unit of blood with an elevated ALT level was given. However, the attack rates in each donor group were much higher (28, 43, and 63 per cent, respectively).

Table 3. Relation between ALT Level of Donor and Incidence of Non-A,non-B Post-Transfusion Hepatitis among 275 Recipients of Single Units.

ALT LEVEL OF DONOR	NO. OF RECIPIENTS	RECIPIENTS WITH NON-A,non-B HEPATITIS
<i>IU</i>		<i>no. (per cent)</i>
1-14	167	7 (4)
15-29	72	5 (7)
30-44	24	2 (8)
45-59	6	2 (33)
60-284	6	3 (50)

Table 4. Relation between Number of Donor Units with an Elevated ALT Level and Incidence of Non-A,non-B Post-Transfusion Hepatitis among 1238 Recipients of Multiple Units.

NO. OF UNITS WITH ELEVATED ALT (>45 IU)	NO. OF RECIPIENTS	RECIPIENTS WITH NON-A,non-B HEPATITIS
		no. (percent)
None	1090	82 (8)
One unit	137	45 (33)
Two units	11	10 (91)

DISCUSSION

The first study to determine whether the aminotransferase level in blood donors could predict an increased risk of post-transfusion hepatitis was that of Bang and his co-workers.¹² They found that the incidence of overt hepatitis was increased 2.3 times in patients transfused with blood that had an AST level of ≥ 41 Karmen units and increased 3.7 times in those receiving blood with an AST > 100 Karmen units. The serious problems that they encountered were AST elevations due to hemolysis of the donor specimen and the incompleteness of donor follow-up. However, on the basis of their results they recommended further study.

Brandt et al. studied AST and ALT levels in a community-based volunteer-donor population in the Netherlands.¹³ The frequency of elevated values was 2.8 per cent; the incidence of icteric post-transfusion hepatitis based on follow-up through family physicians was only 0.3 per cent. In view of the low rate of disease detected, it is not surprising that they concluded that the use of either aminotransferase assay was not justified in terms of cost-benefit.

Miller and his colleagues also evaluated the AST and ALT assays for their ability to detect infectious donors, but did so by determining mean levels in a group of 100 donors to six patients who contracted hepatitis and comparing them to enzyme levels in 160 donors to 11 patients who did not contract the disease.¹⁴ AST levels were notably higher in the former than in the latter; ALT values were virtually the same. The large number of units transfused into each recipient (mean, 15.3) and the small number of patients followed up precluded any definite conclusion.

Otto-Servais et al. examined outcomes in nine recipients of blood with an enzymatic profile typical of viral hepatitis (ALT and AST > 30 IU, with ALT levels greater than AST levels) and compared the results with those from 10 recipients of blood with normal aminotransferase levels.¹⁵ All recipients were examined twice a month for five months. No cases of post-transfusion hepatitis occurred among the recipients of "normal" donor units. In contrast, anicteric hepatitis developed in five of the nine patients who were given blood containing elevated levels of aminotransferases. Three of these five patients received HBsAg-positive blood. Further study showed that six

of nine asymptomatic HBsAg-positive donors had changes in their aminotransferase levels.

Other investigators focused on the prevalence of abnormal levels of ALT or AST in blood donors, but did not examine the outcome after transfusion.²⁴⁻²⁶

From this survey, we conclude that no previous study prospectively evaluated a large enough number of patients who had been given low volumes of blood and who had an incidence of post-transfusion hepatitis that was sufficiently high to render a trial meaningful. The data reported here indicate that the proportion of donors associated with patients with non-A,non-B hepatitis increased progressively in relation to the level of donor ALT activity (Table 1). Alternatively, the recipients' chance of contracting non-A,non-B hepatitis increased in a progressive fashion if at least one donor ALT level was ≥ 30 IU (Table 2). This relation could not be attributed to the number of units transfused, because it was also apparent when single-unit recipients were examined. Finally, patients who received two units with an ALT level ≥ 45 had a higher incidence of hepatitis than did patients who were transfused with only one such unit.

The source of donor blood is another variable that has been shown to influence the risk of post-transfu-

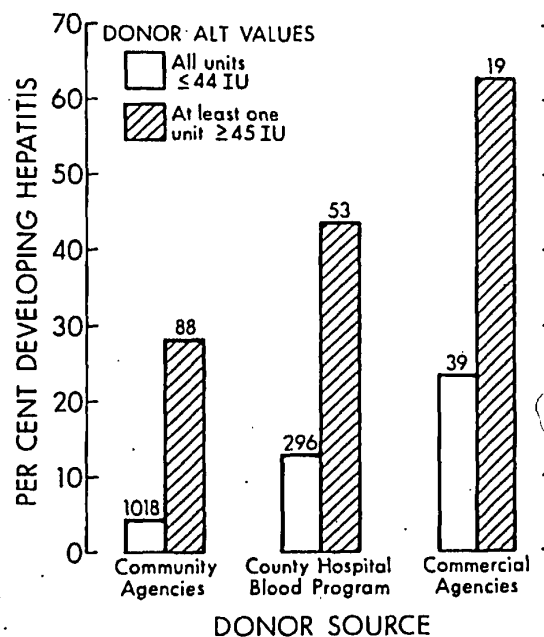


Figure 1. Relation between Highest Donor ALT Level and Incidence of Non-A,non-B Hepatitis, According to Donor Source.

Each hatched or open bar indicates a hepatitis attack rate, and the value at the top of a bar represents the number of recipients. Donors to the county-hospital blood program were mainly from a lower-level socioeconomic population and included families and friends of recipients. Patients transfused with commercial blood may also have received blood from community agencies.

sion hepatitis in previous studies²⁷⁻³⁰ as well as this one. This risk is almost certainly due to the inverse relation between socioeconomic status and rate of infection with hepatitis viruses.³¹ Although the source of blood was clearly an influence in this study, the relation between the highest donor ALT level and the incidence of hepatitis was observed for all three sources of blood (community agencies, county-hospital blood programs, and commercial blood banks).

We also conclude, on the basis of the results in this study, that ALT testing is a potentially useful method of screening donors to reduce the incidence of non-A,non-B hepatitis. The advantages of the test are that it is available in an automated form applicable to testing large numbers of samples, that it is equally valid for plasma or serum samples and is not influenced by the postprandial state, that hemolysis has no appreciable effect (in contrast to its effect on AST determinations), and that the enzyme is sufficiently stable to make extreme care in the handling of specimens unnecessary.

The observations in this report suggest that about 40 per cent of the cases of non-A,non-B post-transfusion hepatitis among recipients in this study could have been prevented by discarding units with an ALT level in the upper 3 per cent of the distribution (i.e., ALT \geq 45 IU). A larger number of cases could have been prevented by lowering the "cutoff" to 30 IU, but that procedure would have required discarding about 9 per cent of the blood collected. If ALT screening is initiated nationwide, there will be fewer units of blood for transfusion than are presently available, no matter what cutoff level is chosen. The increased number of rejected units will undoubtedly require improved efforts in recruiting donors to meet the transfusion needs of this country.

Consequently, the benefits of initiating ALT screening must be carefully weighed against the number of potential donors that would be excluded, the overall incidence of hepatitis in recipients, and the severity of the disease. Although non-A,non-B post-transfusion hepatitis is most often subclinical, approximately 20 to 40 per cent of patients who contract this disease are symptomatic.³²⁻³⁴ At least 25 per cent of all affected patients have aminotransaminase elevations lasting longer than six months.^{32,35} Moreover, a chronic non-A,non-B carrier state that is often asymptomatic has been documented^{34,36}; a recent report described a patient who was infectious over a six-year period.³⁷ The development of chronic hepatitis and progression to cirrhosis have been observed,³⁸⁻⁴¹ although the precise frequency of these complications is uncertain.

Other considerations must be taken into account if widespread ALT testing of blood donors is to be initiated. These include the uncertainty about how long to defer a donor whose blood was rejected, as well as the problems that might occur in the quality control and proficiency of ALT testing on a nationwide basis. Advising donors of the implications of the ALT level

would also pose a special problem. In addition, adjustments might have to be made for the observed differences between ALT levels in male and female donors and for the ages of donors.⁴² Nonetheless, it appears from this study that screening donor blood to eliminate units with elevated ALT levels would result in a substantial reduction in non-A,non-B post-transfusion hepatitis.

Although ALT screening lacks the sensitivity to detect all infectious units and lacks the specificity to detect only infectious units, the high correlation between an elevated ALT level and infectivity of transfused blood provides a compelling argument that such screening should be instituted. Obviously, if there were sensitive and specific serologic tests for the identification of the non-A,non-B agent or agents, ALT testing would be unnecessary. However, efforts to date to identify such a test have not been rewarding, despite extensive research.

We are indebted to Dr. John Weiner for help in the design of the methods used in data handling, and to Dr. Aaron Kellner for support throughout the study.

REFERENCES

- Norris RF, Kassouny D, Reinhold JG, Neefe JR. Persistence of abnormal hepatic tests in carriers of viral hepatitis. *JAMA*. 1956; 160:1118-21.
- Potter HP Jr, Cohen MN, Norris RF. Chronic hepatic dysfunction in heroin addicts: possible relation to carrier state of viral hepatitis. *JAMA*. 1960; 174:2049-51.
- Bowers GN Jr, Potter HP Jr, Norris RF. The prevalence of an increased isocitric dehydrogenase (ICD) activity in a segment of the blood donor population with a low social and economic status. *Am J Clin Pathol*. 1960; 34:513-7.
- Norris RF, Kassouny D, Hunter DT Jr, Reinhold JG. Selection of blood donors: value of hepatic function tests for the detection of carriers of viral hepatitis. In: Hartman FW, LoGrippo GA, Mateer JG, Barron J. *Hepatitis frontiers*. Boston: Little, Brown, 1957:263-75.
- Jennings ER, Hindman WM, Zak B, Reed J, Brines OA. The thymol turbidity test in screening of blood donors. *Am J Clin Pathol*. 1957; 27:489-502.
- Strumia MM, Burns ME, Sample AB, McGraw JJ Jr. The incidence of posttransfusion hepatitis. II. A 13-year survey including 2 years during which blood donors were screened by means of liver function studies. *Am J Clin Pathol*. 1958; 30:133-42.
- Maxwell NG. Incidence of serum hepatitis in recipients of thymol turbidity-screened blood or aged liquid plasma. *Am J Clin Pathol*. 1960; 34:518-25.
- Reinhold JG. Turbidity reaction mechanisms and turbidity measurements in the study of hepatitis. In: Hartman FW, LoGrippo GA, Mateer JG, Barron J, eds. *Hepatitis frontiers*. Boston: Little, Brown, 1957:255-61.
- Karmen A, Wróblewski F, LaDue JS. Transaminase activity in human blood. *J Clin Invest*. 1955; 34:126-33.
- Wróblewski F. The clinical significance of transaminase activities of serum. *Am J Med*. 1959; 27:911-23.
- De Ritis F, Mallucci L, Coltorti M, Giusti G, Caldera M. Anicteric virus hepatitis in a closed environment as shown by serum transaminase activity. *Bull WHO*. 1959; 20:589-602.
- Bang NU, Rueggsegger P, Ley AB, LaDue JS. Detection of hepatitis carriers by serum glutamic oxalacetic transaminase activity. *JAMA*. 1959; 171:2303-6.
- Brandt K-H, Meulendijk PN, Poulie NJ, et al. Data on the determination of SGOT and SGPT activity in donor blood for the possible prevention of post-transfusion hepatitis. *Acta Med Scand*. 1965; 177:321-5.
- Miller WV, Watson LE, Holland PV, Walsh JH. Evaluation of the effectiveness of hepatitis screening tests. *Vox Sang*. 1971; 21:1-10.
- Otto-Servais M, Plomteux G, Brocteur J, et al. Interest of enzymatic determinations: OCT, GOT, GPT and observations of the presence of Australia antigen relating to viral hepatitis in blood donors. *Vox Sang*. 1970; 19:338-44.
- Blumberg BS, Gerstley BJS, Hungerford DA, London WT, Sutnick AI. A serum antigen (Australia antigen) in Down's syndrome, leukemia,

- and hepatitis. *Ann Intern Med.* 1967; 66:924-31.
17. Prince AM. An antigen detected in the blood during the incubation period of serum hepatitis. *Proc Natl Acad Sci USA.* 1968; 60:814-21.
 18. Okochi K, Murakami S. Observations on Australia antigen in Japanese. *Vox Sang.* 1968; 15:374-85.
 19. Gocke DJ, Greenberg HB, Kavey NB. Hepatitis antigen: detection of infectious blood donors. *Lancet.* 1969; 2:248-9.
 20. Hollinger FB, Aach RD, Gitnick GL, Roche JK, Melnick JL. Limitations of solid-phase radioimmunoassay for HB Ag in reducing frequency of post-transfusion hepatitis. *N Engl J Med.* 1973; 289:385-91.
 21. Prince AM, Brotman B, Grady GF, et al. Long-incubation post-transfusion hepatitis without serological evidence of exposure to hepatitis-B virus. *Lancet.* 1974; 2:241-6.
 22. Auslander MO, Gitnick GL, Lander JJ, Aach RD, Hollinger FB, Mosley JW. Post-transfusion hepatitis in relation to SGPT levels in blood donors. *Gastroenterology.* 1975; 69:804. abstract.
 23. Hollinger FB, Dienstag JL. Hepatitis viruses. In: Lennette EH, Balows A, Hausler WJ Jr, Truant JP, eds. *Manual of clinical microbiology.* 3d ed. Washington, D.C.: American Society of Microbiology, 1980:899-921.
 24. Prince AM, Gershon RK. The use of serum enzyme determinations to detect anicteric hepatitis. *Transfusion.* 1965; 5:120-34.
 25. Pintera J, Valnicek S, Vacl J, et al. A new screening test for the activity of serum glutamic oxalacetic transaminase in blood donors performed before blood collection. *Blood.* 1969; 19:226-31.
 26. Nordby G, Foss OP. The alanin aminotransferase activity as screening test for blood donors. *Vox Sang.* 1974; 26:265-71.
 27. Kunin CM. Serum hepatitis from whole blood: incidence and relation to source of blood. *Am J Med Sci.* 1959; 237:293-303.
 28. Allen JG, Dawson D, Sayman WA, Humphreys EM, Benham RS, Havens I. Blood transfusions and serum hepatitis: use of monochloroacetate as an antibacterial agent in plasma. *Ann Surg.* 1959; 150:455-68.
 29. Grady GF, Chalmers TC. Risk of post-transfusion viral hepatitis. *N Engl J Med.* 1964; 271:337-42.
 30. Alter HJ, Holland PV, Purcell RH, et al. Post-transfusion hepatitis after exclusion of commercial and hepatitis-B antigen-positive donors. *Ann Intern Med.* 1972; 77:691-9.
 31. Cherubin CE, Purcell RH, Lander JJ, McGinn TG, Cone LA. Acquisition of antibody to hepatitis B antigen in three socioeconomically different medical populations. *Lancet.* 1972; 2:149-51.
 32. Alter HJ, Purcell RH, Feinstone SM, Holland PV, Morrow AG. Non-A, non-B hepatitis: a review and interim report of an ongoing prospective study. In: Vyas GN, Cohen SN, Schmid R, eds. *Viral hepatitis.* Philadelphia: Franklin Institute Press, 1978:359-69.
 33. Seeff LB, Wright EC, Zimmerman HJ, et al. VA cooperative study of post-transfusion hepatitis, 1969-1974: incidence and characteristics of hepatitis and responsible risk factors. *Am J Med Sci.* 1975; 270:355-62.
 34. Aach RD, Lander JJ, Sherman LA, et al. Transfusion-transmitted viruses: interim analysis of hepatitis among transfused and non-transfused patients. In: Vyas GN, Cohen SN, Schmid R, eds. *Viral hepatitis.* Philadelphia: Franklin Institute Press, 1978:383-96.
 35. Knodell RG, Conrad ME, Ginsberg AL, Bell CJ, Flannery EP. Efficacy of prophylactic gamma-globulin in preventing non-A, non-B post-transfusion hepatitis. *Lancet.* 1976; 1:557-61.
 36. Hoofnagle JH, Gerety RJ, Tabor E, Feinstone SM, Barker LF, Purcell RH. Transmission of non-A, non-B hepatitis. *Ann Intern Med.* 1977; 87:14-20.
 37. Tabor E, Seeff LB, Gerety RJ. Chronic non-A, non-B hepatitis carrier state: transmissible agent documented in one patient over a six-year period. *N Engl J Med.* 1980; 303:140-3.
 38. Koretz RL, Suffin SC, Gitnick GL. Post-transfusion chronic liver disease. *Gastroenterology.* 1976; 71:797-803.
 39. Knodell RG, Conrad ME, Ishak KG. Development of chronic liver disease after acute non-A, non-B post-transfusion hepatitis: role of γ -globulin prophylaxis in its prevention. *Gastroenterology.* 1977; 72:902-9.
 40. Berman M, Alter HJ, Ishak KG, Purcell RH, Jones EA. The chronic serology of non-A, non-B hepatitis. *Ann Intern Med.* 1979; 91:1-6.
 41. Iwarson S, Lindberg J, Lundin P. Progression of hepatitis non non-B to chronic active hepatitis: a histological follow-up of two cases. *J Clin Pathol.* 1979; 32:351-5.
 42. Siest G, Schiele F, Galteau M-M, et al. Aspartate aminotransferase and alanine aminotransferase activities in plasma: statistical distributions, individual variations, and reference values. *Clin Chem.* 1975; 21:1077-87.

HYPERGONADOTROPIC HYPOGONADISM IN FEMALE PATIENTS WITH GALACTOSEMIA

FRANCINE RATNER KAUFMAN, M.D., MAURICE D. KOGUT, M.D., GEORGE N. DONNELL, M.D.,
UWE GOEBELSMANN, M.D., CHARLES MARCH, M.D., AND RICHARD KOCH, M.D.

Abstract We evaluated gonadal function in 18 female and eight male patients with galactosemia due to transferase deficiency; it was normal in the males, but 12 females had signs of hypergonadotropic hypogonadism. All female patients had a 46,XX karyotype, normal levels of thyroid hormone and prolactin, and no anti-ovarian antibodies. The biologic activity of urinary gonadotropins was normal. Ultrasonography of the pelvis revealed that ovarian tissue was diminished or absent. Total estrogens increased in one of two patients after administration of human menopausal gonadotropin. The fre-

quency of hypergonadotropic hypogonadism was higher in females in whom dietary treatment for galactosemia was delayed. Clinical course and mean erythrocyte galactose-1-phosphate and urinary galactitol levels did not correlate with ovarian function.

We conclude that female patients with galactosemia have a high incidence of ovarian failure due to acquired ovarian atrophy. Galactose or its metabolites may be toxic to the ovarian parenchyma, particularly during the immediate neonatal period. (*N Engl J Med.* 1981; 304:994-8.)

GALACTOSEMIA, a disorder due to a deficiency of the enzyme galactose-1-phosphate (Gal-1-P) uridylyl transferase (transferase), represents an inborn error in the major pathway of galactose metabolism. As a consequence of the transferase defect, galactose and its metabolites accumulate in various

tissues in untreated children with this condition and result in hepatic, renal, lenticular, and neurologic abnormalities. Early diagnosis and institution of dietary treatment permit survival and good health over the long term.¹⁻³

Many galactosemic women who have been treated since early childhood are now reaching childbearing age, and although their fertility rate is not known, several have borne healthy children.^{4,5} Because hypogonadism was noted in one of our patients, we evaluated gonadal function in 26 patients who attended the Galactosemia Clinic at Childrens Hospital of Los Angeles. This report describes the finding of hypergonadotropic hypogonadism with a surprisingly high

From the divisions of Endocrinology and Metabolism and Medical Genetics, Childrens Hospital of Los Angeles; the Department of Pediatrics, USC School of Medicine; and the Department of Obstetrics and Gynecology, LAC-USC Medical Center, USC School of Medicine. Address reprint requests to Dr. Kaufman at the Division of Endocrinology and Metabolism, Childrens Hospital of Los Angeles, P.O. Box 54700, Los Angeles, CA 90054.

Supported in part by a grant (05932) from the National Institute of Child Health and Human Development.