34

Transfusion-Transmitted Viruses: Interim Analysis of Hepatitis Among Transfused and Nontransfused Patients

Richard D. Aach, Jerrold J. Lander, Laurence A. Sherman, William V. Miller, Richard A. Kahn, Gary L. Gitnick, F. Blaine Hollinger, Jochewed Werch, Wolf Szmuness, Cladd E. Stevens, Aaron Kellner, John M. Weiner and James W. Mosley

The Transfusion Transmitted Viruses (TTV) Study is a multicentered collaborative effort initiated in July 1974, with the following objectives:

1. To determine in a prospective fashion the incidence and etiologies of transfusion-associated hepatitis at different medical centers, and relate these to different blood donor populations.
2. To assess the relationship between blood transfusion and hepatitis by following a control group of patients who were cross-matched to receive blood, but did not require transfusion.
3. To establish a "bank" of well-pedigreed serum samples from all patients enrolled in the TTV Study, both recipients and controls, as well as all blood donors. This bank is of particular value because it includes serial samples of all patients developing hepatitis and all implicated donors.
4. To evaluate the effectiveness of present methods of donor screening, and examine additional methods which might lead to a further reduction in posttransfusion hepatitis.

At its inception in July 1974, the TTV Study Group consisted of three participating centers: The Center for the Health Sciences, University of California, Los Angeles, Barnes Hospital at the Washington University Medical Center in St. Louis, and Ben Taub Hospital, Baylor College of Medicine in Houston, Texas. The Hepatitis Epidemiology Laboratory at the University of Southern California has served as the coordinating center for the TTV Study. In January 1976, the New York Blood Center (NYBC) joined the TTV Study.

METHODS OF STUDY

Patients admitted to each participating hospital are screened for entry into a 10-month prospective study. The criteria for enlistment are designed to

minimize those factors which might confuse subsequent interpretation of clinical and serologic data. Thus, patients with a history of chronic liver disease, patients receiving medication or drugs which might affect liver function, those with a history of jaundice or hepatitis, an occupational exposure to hepatitis, transfusion within the previous 12 months, certain malignancies which might metastasize to the liver or require chemotherapy, and patients with any illness having a life expectancy of less than 10 months were excluded. Only those patients with one or more normal serum alanine aminotransferase (ALT) levels were enrolled in the study after informed consent was obtained. An additional prerequisite was that aliquots of blood were available from each donor unit transferred as well as a sample from all patients prior to transfusion and/or surgery.

Subsequent specimens were collected at the time of clinical evaluation which occurred at 2-week intervals for the first 3 months, at 3-week intervals for the next 3 months and at 40 weeks or 10 months. If symptoms of hepatitis occurred, or if laboratory studies became abnormal, an additional blood sample was obtained for testing within a 3- to 10-day period.

All recipients' specimens were tested within a 24- to 72-hour period following collection. Donor units were stored at 4°C and tested for ALT activity by the Beckman TR automated kinetic method within 48 hours of transfusion[1].

All participating centers used the same ALT reagents and standards and performed all determinations using a standardized protocol. Evaluation of representative donor units had shown that the level at ALT activity observed at the time of transfusion is not excessively influenced by dilution, anticoagulation or storage at 4°C. By using identical standards at the time of each determination, the coefficient of variation for ALT determinations was less than 5% both within and between participating centers. The upper limit of normal was considered to be 45 International Units (I.U.), a value two standard deviations above the geometric mean. All samples were tested for HBsAg by solid phase radioimmunoassay (RIA) (Ausria II, Abbott Laboratories). All donor units, as well as recipient samples drawn before transfusion and at 20 and 40 weeks, were screened for anti-HBs by radioimmunoassay (Ausab, Abbott Laboratories). The same samples were also screened for anti-HBc by one of two methods of RIA: one, a microtiter solid phase RIA similar to that described for anti-HA detection using purified liver-derived HBcAg[2]; and by Corab (Abbott Laboratories). All patients with ALT abnormalities were also screened for anti-HA seroconversion by RIA[2].

The diagnosis of hepatitis was made if within 14 to 180 days after transfusion, or surgery for the control group, two sequential ALT levels greater than 45 I.U. were observed in the absence of other probable causes. These abnormal samples had to be drawn 3 to 17 days apart with at least one sample equal to or greater than 90 I.U., two times the upper limits of normal.

Patients were considered to have icteric hepatitis if they became visibly jaundiced during acute illness and/or the serum bilirubin exceeded 2% mg.

Serologic requirements for diagnosis of viral HB included the de novo

appearance of HBsAg, anti-HBs and/or anti-HBc not related to passive transfer by transfusion. Seroconversion to the HA agent unrelated to passive transfer was used as the criteria for HAV infection. The designation "non-A/non-B", was applied to those presumptively viral hepatitis cases for whom the criteria for type A or type B infection were not met.

The onset of hepatitis was the interval from first transfusion for the recipients, and surgery for the controls, to the first abnormal ALT value. The duration of illness was defined as the period of time that the ALT value remained elevated, i.e., from the first to the last observed elevation.

RESULTS

Incidence of Hepatitis

Between July 1974, and December 1976, a total of 1,307 patients were successfully followed; 595 recipients, and 712 nontransfused controls (Table 34-1). Ten of the 595 recipients had received only autologous blood. There were 75 episodes of hepatitis among the transfused patients, and incidence of 12.6%. The attack rates varied between 5.4% at Washington University to 18.5% at UCLA.

HBV was the etiologic agent in 10 or 1.7% of the recipients and represented 13.3% of the episodes of posttransfusion hepatitis. Six of those with HB had demonstrable HBsAg, five with the subsequent appearance of both anti-HBc and anti-HBs. Two patients were non-antigenemic but developed anti-HBs and anti-HBc, while one patient each had the de novo appearance of anti-HBs and anti-HBc respectively. No instance of posttransfusion HA was found.

The overall incidence of hepatitis among the 712 control patients was 2.2% with attack rates ranging between 0.7% at Baylor to 3.8% at NYBC. None of the 16 control cases had evidence of HA infection. One control HB case was identified at Washington University. HBsAg was detected in this patient's serum 121 days after surgery, followed by the appearance of anti-HBc and anti-HBs.

Clinical Characteristics

The time of onset of disease (incubation period) among recipients developing HB ranged between 28 and 120 days with a mean of 72 days (Table 34-2). The incubation period of those recipients developing non-A/non-B hepatitis was shorter, 44 days, with a range of 14 to 91 days. The mean incubation period was 39 days for the 15 non-A/non-B control cases.

The peak ALT of the 10 HB recipients was 625 I.U. For the 65 non-A/non-B recipients the mean peak ALT value was 647 I.U. The one control patient developing HB had a peak ALT of 121 I.U. associated with

Table 34-1. Hepatitis Cases Among Recipients and Controls, TTV Study July 1974-December 1976

Participating Centers	No. of Recipients	Viral Hepatitis		Total Cases	% Attack Rate
		Hepatitis B	Hepatitis Non-A/non-B		
Washington University	205	0	11	11	5.4
NYBC	67[a]	0	6	6	9.0
Baylor	139	4	20	24	17.2
UCLA	184	6	28	34	18.5
Total	595	10	65	75	12.6

a: Includes nine recipients at UCLA and one at NYBC who received autologous blood.

Participating Centers	No. of Controls	Viral Hepatitis		Total Cases	% Attack Rate
		Hepatitis B	Hepatitis Non-A/non-B		
Washington University	276	1	5	6	2.2
NYBC	80	0	3	3	3.8
Baylor	143	0	1	1	0.7
UCLA	213	0	6	6	2.8
Total	712	1	15	16	2.2

HBs antigenemia 120 days after surgery. The mean peak ALT level of the non-A/non-B hepatitis patients was 249 I.U. This value was significantly different from both the non-A/non-B and HB recipients with a P value of $<.05$.

Symptoms and jaundice occurred in 20% of the HB patients. Twenty-nine percent of the non-A/non-B recipients had symptoms and 25% became jaundiced. Forty-six percent of the 15 controls who developed non-A/non-B hepatitis were symptomatic but none were jaundiced.

The duration of illness averaged 7.2 weeks for recipients acquiring self-limited HB and 10 weeks for those recipients with non-A/non-B disease. All but two of the 29 patients with self-limited non-A/non-B hepatitis illness were clinically and chemically well within a 16-week period. The 15 individuals who developed non-A/non-B hepatitis among the control group had elevated ALT levels for an average of 8.6 weeks with a range of 2 to 31 weeks.

Of note is the proportion of patients whose hepatitis was unresolved at the end of the follow-up period. Five of the 10 HB recipients and 55% of the non-A/non-B recipients still had ALT elevation at 40 weeks. This represented a mean duration of observed disease activity of 35 weeks (16 to 54 weeks) for

Table 34-2. Clinical Features of the Patients Developing Hepatitis Among Recipients and Controls, TTV Study July 1974-December 1976

						Resolved		Unresolved	
	No.	Incubation Period (Days)	Peak ALT (I.U.)	% Symptoms	% Jaundice	No.	Weeks Abnormal ALT ± SEM	No.	Weeks Abnormal ALT (range)
Recipients									
Hepatitis B	10	72 ± 11	625 ± 185	20	20	5	7.2 ± 1.9	5	35(16–54)
Non-A/non-B	65	44 ± 2	647 ± 75	29	25	29	10 ± 1	36	47(26–108)
Controls									
Hepatitis B	1	120	121	(+)	(−)	—	(1)	—	—
Non-A/non-B	15	39 ± 9	249 ± 42[a]	46	0	15	8.6 ± 2.4	0	—

[a] $P < .05$

patients with HBV infection and 47 weeks (26 to 108 weeks) for those with non-A/non-B hepatitis. Median figures for continued ALT abnormalities were 34 and 40 weeks for HB and non-A/non-B cases, respectively.

Although five of ten HB recipient cases had continued ALT elevations throughout the 40-week period of observation, none had sustained HBsAg positivity. There were no appreciable differences in the incubation period (42.2 versus 45.9 days), occurrence of symptoms, presence of icteric disease (44% versus 33%) or the peak ALT values (736 I.U. versus 591 I.U.) between non-A/non-B patients with self-limited illness and those whose illness had not resolved.

To date, no hepatitis patient among the control population has had evidence of chronic hepatitis, although one patient after having evidence of hepatic dysfunction for 31 weeks has had two subsequent normal ALT determinations.

A plot of the incubation period of the posttransfusion non-A/non-B hepatitis among recipient patients indicates a peak during the seventh week following transfusion and a possible clustering at 12 weeks (Figure 34-1). ALT elevations were first seen between 3 and 19 weeks in the control non-A/non-B patients. Although the number of control cases is small, onsets were observed at 6 and 7 weeks as well as one case each at 13 and 14 weeks corresponding to the pattern seen among recipients. However, there were six cases with the onset of ALT abnormalities during the third and fourth week of follow-up. This suggests a postoperative or postanesthetic event which also must be taken into consideration in evaluating the etiology of the recipients with early onsets.

Relation of Posttransfusion Hepatitis to the Source of Blood

The TTV Study provides an opportunity to directly compare the incidence of hepatitis associated with different blood donor populations. Blood from volunteer donors was used exclusively at the centers in St. Louis and New York, whereas both commercial (paid) donors as well as volunteer donors provided the blood administered at UCLA. Donor units collected by a hospital blood bank, usually family or friends of hospitalized patients, were utilized at Baylor.

The incidence of hepatitis by source of donor blood is shown in Table 34-3. Recipients receiving only commercial units had a hepatitis attack rate of 42.3%. This is in sharp contrast to the 7.5% incidence of hepatitis among recipients given blood obtained from volunteer donors only. Patients at UCLA who received both volunteer and commercial blood had a hepatitis incidence of 35.5%, similar to the attack rate of recipients of commercial blood. Recipients at Baylor, given hospital donor blood, had an intermediate rate of 17.2%. A total of 118 recipients at UCLA received units from volunteer donors exclusively and 10.2% developed hepatitis. Corresponding figures at the St. Louis and New York centers were 5.4% and 9.1%, respectively. The

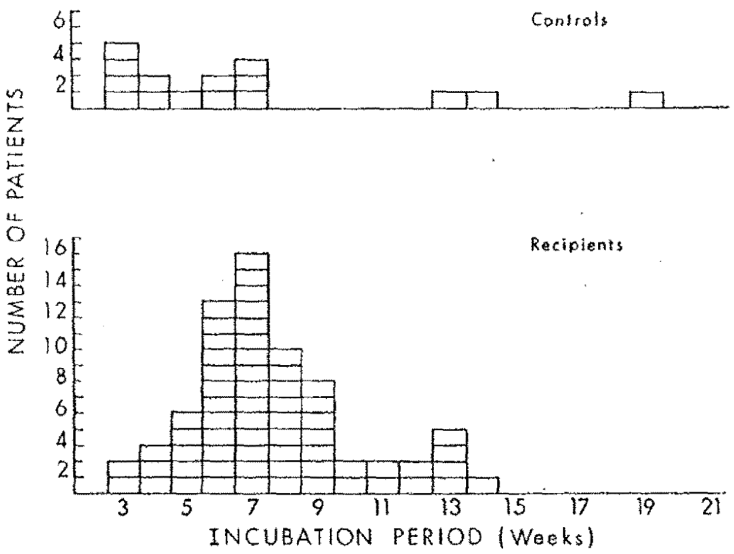

Fig. 34-1. Histogram showing the time of onset (first ALT elevation) of non-A/non-B hepatitis among recipients and controls (TTV Study, July 1974 - December 1976).

same patterns were observed for the rates of non-A/non-B posttransfusion hepatitis in patients given either volunteer, commercial, or hospital donor units. Recipients of only volunteer blood had non-A/non-B hepatitis rates of 5.4% at Washington University, 9.1% at NYBC and 7.6% at UCLA. The overall non-A/non-B hepatitis attack rate was 6.7% compared to an incidence of 34.6% among recipients of commercial blood only.

The variation in the incidence of hepatitis among recipients given only volunteer blood suggests regional differences, but this appears to be much less important than the type of donor, i.e., commercial versus volunteer.

Relationship of Posttransfusion Hepatitis and the Transfusion Volume

The effect of the number of units of blood transfused on the incidence of non-A/non-B hepatitis is shown in Table 34-4. The overall attack rate was 8.9% for patients receiving 1 to 3 units, 12.7% for those given 4 to 6 units and 17% for recipients of more than 6 units. A relationship between transfusion volume and the risk of hepatitis was most noticeable for recipients of hospital donor blood in Houston and patients at UCLA given both volunteer

Table 34-3. Relationship of Posttransfusion Hepatitis and Type of Blood Donors

	No. recipients	No. HB	Non-A/non-B hepatitis		Total cases hepatitis	% attack rate
			No.	%		
Volunteer only						
Washington University[b]	205	0	11	5.4	11	5.4
NYBC	66	0	6	9.1	6	9.1
UCLA	118	3	9	7.6	12	10.2
Total	389	3	26	6.7	29	7.5[a]
Commercial	26	2	9	34.6	11	42.3[a]
Both volunteer and commercial	31	1	10	32.2	11	35.5[a]
Hospital blood bank (Ben Taub, Houston)	139	4	20	14.4	24	17.2

a: $P < .05$ in attack rates involving commercial donor blood versus volunteer blood only.
b: Red Cross Regional Blood Centers.

Table 34-4. Non-A/non-B Posttransfusion Hepatitis According to Source and Transfusion Volume

Donor	Total recipients	1–3 Units			4–6 Units			>6 Units		
		No. recipients	Non-A/non-B hepatitis		No. recipients	Non-A/non-B hepatitis		No. recipients	Non-A/non-B hepatitis	
			No.	%		No.	%		No.	%
Volunteer only[a]	389	183	10	5.4	121	7	5.8	84	9	10.3
Hospital blood bank	139	105	11	10.5	22	5	22.7	12	4	33.3
(Ben Taub)	26	19	5	26.3	5	2	40	2	2	100
Commercial										
Both volunteer and commercial	31	14	1	7.1	10	6	60	7	3	42.9
Total	585	321	27	8.4	158	20	12.7	105	18	17.1

[a] Red Cross Regional Centers and NYBC.

Table 34-5. Relation Between Maximum Donor ALT and Non-A/non-B Posttransfusion Hepatitis Among Recipients of Volunteer Blood Only

Maximum donor ALT (I.U.)	No. recipients	No. non-A/non-B hepatitis	% hepatitis attack rate
<45	353	12	3.4[a]
45–80	26	11	42.3
81–100	6	2	33.3
100+	4	1	25.0

a: P < .05 # difference in attack rate compared to recipients given blood with higher maximum ALT values.

and commercial units. Recipients of commercial blood only had a high attack rate at all three levels of transfusion volume, although the data were derived from a much smaller sample size.

Of the 10 HB cases, five had received 1 to 3 units, two were given 4 to 6 units, and 3 had been transfused with more than 6 units.

Maximum Donor ALT Level and Posttransfusion Hepatitis

To search for additional risk factors which might be associated with non-A/non-B posttransfusion hepatitis, a number of donor and recipient characteristics were evaluated by discriminant multivariate analysis. Recipients given volunteer blood exclusively and their donors were selected for study. The factors analyzed included the age and sex of the recipient, history of prior transfusion, the type of surgery or reason for crossmatch, the anesthetic administered, the anti-HBs status of the donor and the recipient, and the maximum donor ALT value. Of these characteristics, only the maximal donor ALT correlated with the development of non-A/non-B posttransfusion hepatitis. Of 353 recipients given volunteer units with normal ALT activity, 12 or 3.4% developed non-A/non-B posttransfusion hepatitis (Table 34.5). In contrast, non-A/non-B hepatitis occurred among 14 of 36 (38.9%) recipients given at least 1 unit with an elevated ALT level.

Discriminant analysis of the recipients given only volunteer donor blood, and their donors, also showed that the maximal donor ALT was a far more important determinant in the occurrence of posttransfusion hepatitis than the number of units transfused. The non-A/non-B hepatitis attack rate was 3.4% for both the 175 recipients given 1 to 3 units of volunteer donor blood and the 178 recipients given more than 4 units with normal ALT values (Table 34-6). The incidence of hepatitis was approximately 10 times greater among recipients of volunteer units with an elevated ALT value; 40% for patients given 1 to 3 units and 38% for those receiving more than 4 units.

In all, 34 of the 75 total recipients (or 45%) developing hepatitis received

Table 34-6. Relation of Non-A/non-B Posttransfusion Hepatitis to Maximum Donor ALT and the Number of Volunteer Units Administered

	<45 I.U.				>45 I.U.			
	1–3 Units		4+ Units		1–3 Units		4+ Units	
Total recipients of volunteer blood	175		178		10		26	
	No.	%	No.	%	No.	%	No.	%
Non-A/non-B hepatitis	6	3.4	6	3.4	4	40	10	38

at least 1 unit with an elevated ALT level—31 of the 65 non-A/non-B cases and three of the 10 cases of HB infection.

DISCUSSION

Data from the first 2½ years of the TTV Study affirm that posttransfusion hepatitis remains a serious and continuing problem. The 12.6% overall incidence of hepatitis among the 595 recipients is comparable to the 11.3% rate observed in the VA Cooperative Study of posttransfusion hepatitis which was conducted between January 1969 and July 1974[3]. Although the rate of HB declined following routine screening of donors for HBsAg, the overall incidence of HBsAg-negative posttransfusion hepatitis in the VA Study remained unchanged. Only 13.3% of our posttransfusion hepatitis cases were attributable to HB infection, all from donors whose blood were HBsAg-negative by RIA. Four of the 10 posttransfusion HB cases, all with abnormal ALT elevations, were diagnosed by the appearance of anti-HBc and/or anti-HBs in the absence of demonstrable antigenemia. In keeping with the observations of Feinstone and his associates at NIH [4], none of the other 65 posttransfusion cases in our study could be attributed to HA infection. The clinical characteristics of these non-A/non-B hepatitis cases were similar to those patients with posttransfusion HB, except for a shorter time of onset (44 versus 72 days, respectively). Although most were asymptomatic and not jaundiced, ALT abnormalities were sustained for a mean of 10 weeks, more than 2 months, among those whose illness had resolved by the end of the study period.

The high proportion of recipients whose hepatitis was unresolved is of special note. Approximately half of the patients with posttransfusion hepatitis still had ALT elevations at 40 weeks. At least 12 of the non-A/non-B cases had continued evidence of hepatitis of greater than 1 year's duration and five for more than 2 years. These observations are in keeping with recent reports that

10 to 30% of patients with acute non-A/non-B hepatitis subsequently developed chronic hepatitis [5,6]. No clinical features during the acute phase of illness were found to be predictors of prolonged hepatitis.

The introduction of a nontransfused control population followed in an identical fashion makes it possible to evaluate the role that hospitalization and surgery might play in the risk of acquiring hepatitis. Of the 712 controls, 16 cases (2.2%) developed hepatitis. No patients had serologic evidence of acute HA infection, but one control had HB. The mean incubation period of 39 days for the remaining 15 cases was comparable to the 44 day average of the non-A/non-B cases in the transfused group. However, several observations were not comparable and need further study. These include a lower peak ALT, the absence of control cases with apparent chronic hepatitis and the small cluster of cases with onsets during the third and fourth week after enrollment. Although a hospital-related etiology other than non-A/non-B infection is suggested, factors such as anesthetic (e.g., halothane), drugs associated with liver function abnormalities, and a complicated postoperative course could not be identified. However, these preliminary findings do demonstrate the occurrence of a low incidence of hepatitis among nontransfused hospitalized patients undergoing surgery who are closely followed prospectively.

Although this is an interim analysis of an on-going study, certain interesting observations pertaining to risk factors for the transmission of hepatitis by blood have emerged. The incidence of posttransfusion hepatitis varied substantially between the four participating centers, but this appears to be related primarily to the source of blood. The high rate of hepatitis associated with the commercial (paid) donor has been well described[7-9]. Hepatitis occurred in 42.3% of recipients transfused with only commercial units, a rate eight times greater than that associated with the use of all-volunteer blood. Patients receiving both volunteer and commercial blood had a hepatitis rate closely approximating blood from commercial donors alone. Blood collected by a hospital blood bank (Ben Taub, Houston) was associated with an attack rate of 17.2%. The lower socioeconomic status of the donors and perhaps the recipients at this participating center are factors which might have influenced the risk of acquiring hepatitis following transfusion in this population.

In previous studies, the number of units of blood transfused was found to be an important risk factor for the transmission of hepatitis[10, 11]. In our study, a higher rate of posttransfusion hepatitis was observed for patients receiving 4 or more units, but the effect appeared to be largely restricted to patients given blood obtained from replacement donors. Using discriminant multivariate analysis of the recipients receiving only volunteer blood, a more striking correlation was found with the maximal donor ALT value and the occurrence of non-A/non-B posttransfusion hepatitis than with transfusion volume. A similar relationship was also found for recipients of commercial units only but the sample size was small. Factors such as the age and sex of the recipient, prior transfusion, type of surgery, the anesthetic agent used, and the

anti-HBs status of the recipient and donor were not correlated with non-A/non-B hepatitis transmission.

Recently, a non-A/non-B carrier state has been demonstrated[12]. In addition, three independent groups of investigators[13,15], including the TTV Study Group, have successfully transmitted human non-A/non-B hepatitis to chimpanzees by inoculation of serum from implicated donors. The observation that several of these donors had ALT abnormalities on repeated sampling suggests that an elevated ALT level might be a marker for the non-A/non-B agent(s).

Since the TTV study is an on-going effort our sample size will continue to grow. Although our study suggests that screening donor units for ALT levels might be useful in reducing the incidence of non-A/non-B posttransfusion hepatitis, the data must be interpreted with caution since the number of patients analyzed to date is small. Also, there are a number of causes for an elevated ALT other than viral hepatitis, one possible reason why 41 of the 75 patients given blood with an abnormal ALT level did not develop evidence of hepatitis in serial follow-up. Furthermore, 30 of the 65 non-A/non-B cases received blood with normal ALT values.

More data on this point are obviously required and our observations need to be confirmed. Clearly, careful standardization of technique and reagents is a prerequisite for future investigations.

SUMMARY

During its first 2½ years, the TTV Study Group has prospectively followed 595 recipients and 712 nontransfused controls. Seventy-five (12.6%) of the recipients developed posttransfusion hepatitis (10 type B and 65 non-A/non-B). Among controls, 16 (2.2%) developed hepatitis including one patient with type B.

Hepatitis rates among recipients by donor source were 7.5% volunteer blood, 17.2% blood from the hospital blood bank at Ben Taub and 42.3% commercial blood. A relationship between transfusion volume and the risk of hepatitis was noted, primarily among recipients given blood collected by the hospital blood bank. Recipients of volunteer blood had a relatively constant low risk by comparison, while recipients of commercial blood had a high risk at all transfusion volumes.

Discriminant multivariate analysis showed that of the multiple risk factors studied, an elevated donor ALT value correlated most closely with the development of non-A/non-B hepatitis in recipients of volunteer donor blood. Hepatitis occurred in 3.4% of recipients who received donor units with normal ALT values in contrast to 38.9% among those given an elevated ALT donor unit(s). Maximal donor ALT was a more important determinant than the number of units transfused. Screening volunteer donor units for ALT may be

useful in reducing the incidence of hepatitis although further study is warranted.

REFERENCES

1. Wolf, P.J. Clin. Pathol. *26*:587, 1975.
2. Skinhøj, P., Mikkelsen, F., and Hollinger, F.B. Am. J. Epidemiol. *105*:140, 1977.
3. Seeff, L.B., Wright, E.C., Zimmerman, H.J., et al. Am. J. Med. Sci. *270*:355, 1975.
4. Feinstone, S.M., Kapikian, A.Z., Purcell, R.H., et al. New Engl. J. Med. *292*:767, 1975.
5. Koretz, R.L., Suffin, S.C., and Gitnick, G. Gastroenterology *77*:797, 1976.
6. Knodell, R.G., Conrad, M.E., Ginsberg, A.L., et al. Lancet *i*:557, 1976.
7. Alter, H.J., Holland, P.V., Purcell, R.H., et al. Ann. Intern. Med. *77*:691, 1972.
8. Goldfield, M., Black, H.C., Bill, J., et al. Am. J. Med. Sci. *270*:335, 1975.
9. Seeff, L.B., Zimmerman, H.J., Wright, E.C., et al. Gastroenterology *72*:111, 1977.
10. Allan, J.G. and Sayman, W.A. JAMA. *180*:1079, 1962.
11. Risk of post-transfusion hepatitis in the US. JAMA *220*:692, 1972.
12. Hoofnagle, J.H., Gerety, R.J., Tabor, E., et al. Ann. Intern. Med. *87*:14, 1977.
13. Hollinger, F.B., Aach, R.D., Lander, J., et al. Intervirology *10*:60, 1978.
14. Alter, H.J., Purcell, R.H., Holland, P.V., and Popper, H. Lancet *i*:460, 1978.
15. Tabor, E., Gerety, R.J., Drucher, J.A., et al. Lancet *i*:463, 1978.