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Risk of Posttransfusion Hepatitis in the United States

See

A Prospective Cooperative Study

WAO

NATIONAL TRANSFUSION HEPATITIS STUDY

The Coordinating Center

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Lemuel Shattuck Hospital (1966 to July 1969) and Biologic Laboratories of the State Laboratory Institute (August 1969 to the present), the Massachusetts Department of Public Health, and the departments of medicine and preventive medicine, Tufts University School of Medicine, Boston.

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Transfusion of 4,984 cardiovascular surgery patients with an average of 7.7 units of blood at 14 university medical centers resulted in symptomatic hepatitis in 2.8% and death in 0.1%. Among additional patients receiving fibrinogen and blood, the hepatitis incidence and mortality were 19% and 4%, respectively. These figures do not include 0.1% incidence of hepatitis within 15 days of receiving halogenated anesthetics, and 0.1% incidence of "postperfusion" syndrome. The risk of typical symptomatic posttransfusion hepatitis among the 14 centers varied, in order of correlation, with (1) the incidence of hepatitis type B antigen in donor blood, (2) the proportion of commercial donors, and (3) transfusion volume, and ranged from 0 to 8.6 per 100 patients, or 0 to 1.56/100 units of blood. Hepatitis was not prevented by intramuscular injections of immune serum globulin (γ-globulin) containing conventionally low amounts of hepatitis-B antibody.

Posttransfusion viral hepatitis was studied by a common protocol at 14 university hospital centers in order to maximize the total number of observations and to permit inferences about risk factors associated with local variations in hepatitis incidence. Cardiovascular surgery patients were studied because they receive large but variable transfusion volumes and are easily followed up. The study design included an attempt to determine whether intramuscular injections of up to 30 ml of immune serum globulin (immune serum globulin, human, γ-globulin) would prevent or attenuate posttransfusion hepatitis.

Methods

From March 15, 1966, through Nov 15, a pilot study at hospitals (identified in the organization listing of this study) in Boston, Denver, Los Angeles, and Rochester, Minn, was undertaken to determine whether hepatitis could be detected accurately among cardiovascular surgery patients whose psychological suitability for study and probability of survival for six months had to be estimated within a few days after surgery. Successful follow-up of the 316 patients led to expansion of the study to include hospitals in Atlanta, Baltimore, Cleveland, Chicago, Columbus (Ohio), Houston, Indianapolis, Lexington (Ky), Minneapolis, and San Francisco. The first patient in the expanded study was enrolled Nov 25 and the last patient completed six-month follow-up on Jan 15, 1970. Selection was limited to those at least 15 years old who received at least 2 units of blood and who had not had hepatitis or transfusions within six months prior to surgery. A history indicating no hypersensitivity to injectable protein biologicals had also been obtained prior to randomization of patients for receipt of a three-injection series of up to 30 ml of either normal human serum albumin or standard 16% immune serum globulin in order to determine whether the latter could reduce the incidence of posttransfusion hepatitis. A preliminary report[1] has summarized the number of patients receiving various lots and doses of immune serum globulin and its failure to reduce the incidence of hepatitis. The current report excludes 47 of the 5,189 patients at risk identified in the preliminary report[1] because careful review of transfusion records failed to substantiate receipt of at least 2 units of blood. The remaining 5,142 patients are defined as the population at risk because they completed at least three months of follow-up (by which time 75% of hepatitis cases had occurred) and 4,976 of them completed six months of follow-up.

As patients entered the study, their age, sex, weight, and available preoperative liver function test values were recorded. Determinations of total serum bilirubin, glutamic pyruvic transaminase (SGPT) or glutamic oxaloacetic transaminase (SGOT) levels had been obtained in 73%, including 95% of patients with passive congestion of the liver. Notation was made of the total duration of anesthesia and whether the major inhalation anesthetic agent was halogenated. Exposure to potentially infective sources was tabulated in regard to single-donor transfusion products, such as whole blood, packed red blood cells, and single-donor plasma, and in regard to plasma and fibrinogen prepared from pooled donations. The donors of single-donor products were classified as (1) Red Cross, (2) other volunteer, (3) paid but known to the transfusionist, or (4) paid but unknown to the transfusionist ("prebottled" commercial blood). The amount of blood that had been collected within 48 hours of transfusion and the use of a pump oxygenator for cardiopulmonary bypass (open-heart surgery) were noted. A history of transfusion or hepatitis more than six months prior to surgery was also recorded.

The injections of immune serum globulin or normal human serum albumin solutions provided the first set of checkpoints with patients and their physicians. If the day of surgery is designated as the first study day, the first, second, and third injections, respectively, were given on study days 3 to 10, 25 to 35, and 45 to 55. Ninety-six percent of patients received two injections and 94% received all three. Postcards accompanying injection materials alerted physicians to note and report signs of hepatitis and to discreetly remind patients to report symptoms consistent with hepatitis. At three and six months postoperatively, patients received a letter inquiring about 20 symptoms or signs, 13 of which were intended to disclose possible hepatitis and seven of which were intended to reflect cardiovascular decompensation or a tendency to overrespond to all queries.

"hepatitis attributable" queries uded hepatitis by name, any new ness, "flu," "bad cold or virus," fe- er or chills, yellowing of eyes or skin, dark urine, upset stomach, vomiting, loss of appetite, weight loss, diarrhea, and unusual weakness. "Cardiac attributable" queries included racing heart beat, shortness of breath, and swollen ankles. General queries included pneumonia, kidney infection, headache, and insomnia. Telephoning was used to supplement responses that were incomplete or uninterpretable, or suggested that hepatitis had occurred. Patients answering affirmatively regarding hepatitis, jaundice, or any four of the other hepatitis-attributable symptoms were urged to be examined by their private physicians and to have records of pertinent clinical and laboratory findings forwarded to the local study center. These reports were condensed into a standardized candidate-case history and forwarded for review by a three-member committee of hepatologists if the candidate cases met one or more of the following criteria: one or more symptoms or signs of hepatitis as defined above and severe enough to necessitate a sharp restriction of activity for at least three days or to cause medical attention to be sought other than by regularly scheduled visits; definite jaundice in the opinion of the patient's physician; elevation of serum total bilirubin, SGPT, or SGOT levels to 2.5 times the upper limit of normal or 2.5 times base-line values if abnormal; or liver biopsy findings showing features consistent with acute viral hepatitis. Cases were sought for review if the first detection of abnormal clinical, biochemical, or histological findings occurred between study days 1 to 180; but by arbitrarily agreed definition, only cases with onset between days 16 to 180 were accepted as viral hepatitis. Sources of exposure other than transfusions were sought but we were unable to implicate any clearly identifiable family or community contacts in any hepatitis cases.

At 11 study centers, selected patients living nearby were followed up by biweekly SGPT level determinations. The general criteria for the definition of patients at risk described in the first paragraph of the methods section were met by 494 patients who followed the schedule of biweekly SGPT content determinations with no lapse of more than 35 days during the specified follow-up period. Further sampling was done to confirm any SGPT value as high as 80 units (a limit defined by the Coordinating Center with the use of lyophilized pig-liver standards [Hyland Laboratories, Los Angeles]) to monitor and calibrate values for the Study Center laboratories. Patients whose SGPT value was greater than 100 units on two occasions seven days apart and had sulfobromophthalein retention of greater than 11% at 45 minutes or a newly palpable or tender liver, or who met the general criteria in the paragraph above, were considered candidate cases of hepatitis.

The three hepatologists serving the coordinating center as the Clinical Review Board (identified in the organization listing of this study) reached a consensus that 223 of the 249 candidate cases from the combined questionnaire and SGPT follow-up groups were more likely to represent posttransfusion viral hepatitis than liver disease of any other cause. Severity was classified in three categories: "severely symptomatic" was defined as hepatitis sufficient to confine the patient to bed for one week or more; "symptomatic" included patients whose symptoms lasted less than one week; and "asymptomatic" patients were those with evidence only biochemically or from biopsy. Liver biopsy or autopsy findings reviewed independently by four experienced pathologists (see organization listing) were available regarding 60 of the 249 candidate cases. All decisions of clinical reviewers and pathologists were made without knowledge of whether the patients under review had received immune serum globulin.

"Hepatitis B" (HB) is the nomenclature used throughout this report to identify the antigen (and corresponding antibody) originally called Australia antigen and also known as hepatitis-associated antigen or serum hepatitis antigen because of its specific association with long-incubation hepatitis commonly transmitted parenterally. In 1969, the last year of study, the prevalence of HB antigen was sought by the immunodiffusion technique in random samples of donor bloods from several centers.[2] Immunodiffusion tests for HB antigen in acute-phase serum of hepatitis patients, not necessarily recipients of the blood known to contain HB antigen, identified the antigen in 7 among the 28 cases sampled at the two centers having the capability to test by 1969.

Results

Short-Incubation Hepatitis or Post-anesthetic Hepatitis.—By definition, acceptable cases of posttransfusion viral hepatitis were those which occurred between 16 and 180 days postoperatively, but cases of "hepatitis" were also sought within the first 15 days. Clearly demarcated cases were difficult to identify during the immediate postoperative period because

Table 1.—Possible Hepatitis Relation to Anesthetics Given Within 15 Days Before Onset

Major Anesthetic	Mean Duration of Anesthesia, hr	Patients at Risk	Hepatitis	
			Cases	Deaths
Halothane	4.8	2,459	3	1
Methoxyflurane	4.1	1,552	1	0
Other	4.8	902	0	0
Unspecified	...	229	0	0
Totals	**4.6**	**5,142**	**4**	**1**

Table 2.—Relation of Postperfusion Syndrome to Cardiovascular Surgery and Use of Fresh* Blood

Type of Surgery	No Fresh Blood (Cases/at Risk)	Some Fresh Blood (Cases/at Risk)	Totals (Cases/at Risk)
Open-Heart (Cardiopulmonary bypass)	0/1,639	7/1,405†	7/3,044
Other	0/2,068	0/30	0/2,098
Totals	**0/3,707**	**7/1,435**	**7/5,142**

*Blood collected within 48 hr of transfusion.
† $P < .01$.

Table 3.—Posttransfusion Viral Hepatitis and Method of Follow-Up, Prophylactic Immune Serum Globulin, and Diagnostic Certainty

Hepatitis cases:	2,310 Globulin Recipients				2,338 Placebo Recipients				4,648 Total Patients			
	All	Symptomatic	Severe	Fatal	All	Symptomatic	Severe	Fatal	All	Symptomatic	Severe	Fatal
Patients Followed Up by Questionnaire Only												
Possible	75	74	63	5	82	79	64	1	157	153	127	6
Probable	65	65	58	4	69	66	58	1	134	131	116	5
Patients Followed Up by Serial SGPT Determinations												
Possible	32	17	10	2	34	23	9	1	66	40	19	3
Probable	28	17	10	2	26	19	9	1	54	36	19	3
Total Patients Followed Up by Questionnaires or SGPT Determinations												
Possible	107	91	73	7	116	102	73	2	223	193	146	9
Probable	93	83	68	6	95	85	67	2	188	167	135	8

Table 4.—Influence of Multiple-Donor Blood Products on the Incidence of Posttransfusion Viral Hepatitis

Product Transfused and Follow-Up Method	Average No. of Units of Single-Donor Transfusion Products Per Patient	Patients at Risk	Hepatitis Cases			
			All	Symptomatic	Severe	Fatal
Blood or other single-donor products						
Questionnaire only	7.8	4,532	115 (2.5%)	112 (2.5%)	101 (2.2%)	4 (0.1%)
Serial SGPT tests	7.0	452	42 (9.3%)	28 (6.2%)	13 (2.9%)	1 (0.2%)
Total	7.7	4,984	**157** (3.2%)	**140** (2.8%)	**114** (2.3%)	**5** (0.1%)
Plasma (multiple donor)						
Questionnaire only	9.8	100	7 (7%)	7 (7%)	5 (5%)	0 (0)
Serial SGPT tests	7.4	36	9 (25%)	5 (14%)	3 (8%)	0 (0)
Total	9.2	136	**16** (12%)	**12** (9%)	**8** (6%)	**0** (0)
Fibrinogen* (multiple donor)						
Questionnaire only	22.9	16	12	12	10	1
Serial SGPT tests	9.6	6	3	3	3	2
Total	19.2	22 (80)†	**15** (19%)†	**15** (19%)†	**13** (16%)†	**3** (4%)†
Totals						
Questionnaire only	7.9	4,648	134 (2.9%)	131 (2.8%)	115 (2.5%)	5 (0.1%)
Serial SGPT tests	7.1	494	54 (10.9%)	36 (7.3%)	19 (3.8%)	3 (0.6%)
Total	7.8	5,142	**188** (3.7%)	**167** (3.2%)	**135** (2.6%)	**8** (0.2%)

*There were three patients at risk and one hepatitis case (severe) who received multiple-donor plasma in addition to fibrinogen.
†Incomplete recording of the use of fibrinogen at the time of surgery was confirmed by a detailed review of hospital charts of 640 patients in order to derive an estimate (80) of actual use.

many patients had passive congestion of the liver from temporary cardiac decompensation. However, Table 1 shows that four of the 5,142 patients had a pattern of acute hepatocellular dysfunction compatible with viral hepatitis or postanesthetic hepatitis. An incidence of approximately 1/1,000 was recorded among recipients of the halogenated anesthetics, halothane and methoxyflurane, and no cases were noted among others. In three of the four suspect cases, a history of exposure to halogenated anesthetics could be excluded. All four patients had a complicated postoperative course and one died.

Postperfusion Syndrome.—During review of the descriptions of candidate cases of hepatitis, the Clinical Review Board noted seven instances in which fever, splenomegaly, and atypical lymphocytosis were more prominent than indications of liver dysfunction. In each instance the syndrome began within 21 to 35 days of cardiotomy and cardiopulmonary bypass. In all instances some portion of the blood used had been collected within 48 hours of transfusion ("fresh" blood). These cases were tentatively labelled "postperfusion syndrome" (Table 2) and have not been included in the analyses in any other Tables or in Fig 1. Two of the seven patients had been randomly selected to receive immune serum globulin and one of these had received a second injection of 10 ml before onset of the postperfusion syndrome. One patient developed typical postperfusion syndrome one month postoperatively, recovered completely, and then developed typical severe posttransfusion hepatitis two months later.

Immune Serum Globulin: Adverse Reactions and Failure as Prophylaxis.—Not only did immune serum globulin injections of up to 30 ml fail to reduce the incidence or severity of hepatitis following transfusion (Table 3), but adverse reactions to the injections were noted in 24 (1%) of the 2,551 recipients. Eight of the 24 had severe pain at the injection site and three of the eight developed large hematomas, possibly related to potentiation of anticoagulant therapy by salicylates given to control initial pain at the injection site. Sixteen patients had one or more signs or symptoms of allergic reactions thought not to be attributable to serum hepatitis (arthralgia, 2; erythema nodosum, 1; urticaria, 4; rash, 13; unexplained fever, 5). Five of the 16 had also received other highly suspect medications and all study patients routinely received a wide variety of drugs.

The failure of immune serum globulin to prevent hepatitis permits the

Table 5.—Posttransfusion Viral Hepatitis by Age and Sex of Recipients of Single-Donor Transfusion Products Only

Age, yr, Sex	Average Transfusion Volume*	Patients at Risk	Hepatitis Cases			
			All	Symptomatic	Severe	Fatal
15-39						
Male	8.7	539	15 (2.8%)	11 (2.0%)	8 (1.5%)	0
Female	7.5	469	12 (2.6%)	9 (1.9%)	9 (1.9%)	0
Total	8.1	**1,008**	**27** (2.7%)	**20** (2.0%)	**17** (1.7%)	**0**
40-59						
Male	7.6	2,089	73 (3.5%)	69 (3.3%)	54 (2.6%)	0
Female	8.1	942	29 (3.1%)	25 (2.7%)	21 (2.2%)	0
Total	7.8	**3,031**	**102** (3.4%)	**94** (3.1%)	**75** (2.5%)	**0**
60 or more						
Male	6.9	687	23 (3.3%)	21 (3.1%)	19 (2.8%)	5 (0.7%)
Female	7.8	241	5 (2.1%)	5 (2.1%)	3 (1.2%)	0
Total	7.2	**928**	**28** (3.0%)	**26** (2.8%)	**22** (2.4%)	5 (0.5%)
Totals						
Male	7.7	3,315	111 (3.3%)	101 (3.0%)	81 (2.4%)	5 (0.2%)
Female	7.9	1,652	46 (2.8%)	39 (2.4%)	33 (2.0%)	0
Total	7.7	**4,967†**	**157** (3.2%)	**140** (2.8%)	**114** (2.3%)	**5** (0.1%)

*Average number of units of single-donor transfusion products received by each patient.
†Among the 4,984 patients receiving single-donor transfusion products, 17 were of unspecified age and no hepatitis was detected among them.

entire population at risk to be pooled for analysis (Table 3). The 223 "possible" cases are an estimate of maximum incidence including all instances in which viral hepatitis is as likely as any alternative diagnosis. Among the 223 are 188 "probable" cases in which viral hepatitis is the most likely diagnosis and in 151 of these no other type of hepatitis had to be excluded. Although the "probable" cases provide a minimum estimate of incidence, the minimum is only slightly less than the maximum estimate, and the greater precision of diagnosis of "probable" cases has led to their use as the basis for the subsequent analyses.

Incubation Periods.—The distribution of incubation periods of the 188 "probable" hepatitis cases is in the Figure. Among the 188 were 31 whose operative record indicated receipt of multiple-donor (pooled) plasma or fibrinogen in addition to blood. Incubation periods were calculated as if all transfusions had been given during the major transfusion episode at surgery although 4% of cases received transfusions beyond the first postoperative week. Onset was defined as the first detected sign or symptom of hepatitis or abnormal result of liver function test. Recipients of immune serum globulin are not shown separately because there was no reduction in the incidence of hepatitis regardless of incubation period.

Incidence and Severity of Hepatitis From Whole Blood.—The operative records of the 5,142 patients indicated that no multiple-donor blood products had been used to supplement transfusions of 4,984 patients receiving whole blood, packed blood cells, or single-donor plasma (Table 4). Five of the 4,984 died of hepatitis, a death rate of approximately 1/1,000 patients or 1/7,700 donor exposures (units of blood or single-donor products). Hepatitis symptoms lasting one week or more ("severe" hepatitis) occurred in 2.9% of patients followed up by SGPT determinations and in 2.2% of the questionnaire follow-up group, a combined incidence of 2.3% (Table 4). Serial testing in the SGPT follow-up group was required in order to estimate the incidence of hepatitis that was asymptomatic or minimally symptomatic (6.4% in addition to the 2.9% having symptoms lasting one week or more). Fortuitous SGPT test findings also identified three asymptomatic hepatitis cases in the questionnaire follow-up group.

Incidence and Severity of Hepatitis From Multiple-Donor Blood Products.—Notation of the use of fibrinogen is sometimes omitted from the operative record because fibrinogen is often dispensed by the hospital pharmacy rather than the blood bank. When the hospital charts of patients developing hepatitis were reviewed, the initial underreporting of the use of fibrinogen became evident and the case reports were corrected appropriately. In addition, a corrected esti-

Table 6.—Incidence* and Severity of Posttransfusion Viral Hepatitis by Follow-Up Method at Each Study Center

Study Center	Serial SGPT Follow-Up				Questionnaire Follow-Up Only			
	Patients at Risk	Hepatitis Cases			Patients at Risk	Hepatitis Cases		
		All	Symptomatic	Severe		All	Symptomatic	Severe
Lexington, Ky	3	0	0	0	145	0	0	0
Rochester, Minn	...	...	...	...	834	4 (0.5%)	4 (0.5%)	4 (0.5%)
Minneapolis	...	...	...	...	163	1 (0.6%)	1 (0.6%)	1 (0.6%)
Atlanta	...	...	...	...	150	3 (2.0%)	3 (2.0%)	3 (2.0%)
San Francisco	4	0	0	0	283	6 (2.1%)	6 (2.1%)	6 (2.1%)
Houston	14	0	0	0	260	6 (2.3%)	6 (2.3%)	6 (2.3%)
Baltimore	14	1 (7.1%)	1 (7.1%)	1 (7.1%)	161	4 (2.5%)	3 (1.9%)	2 (1.2%)
Boston	9	1 (11.1%)	1 (11.1%)	0 ...	379	8 (2.1%)	8 (2.1%)	8 (2.1%)
Indianapolis	12	1 (8.3%)	1 (8.3%)	1 (8.3%)	139	3 (2.2%)	3 (2.2%)	3 (2.2%)
Columbus, Ohio	48	2 (4.2%)	2 (4.2%)	2 (4.2%)	112	3 (2.7%)	3 (2.7%)	3 (2.7%)
Cleveland	108	4 (3.7%)	3 (2.8%)	2 (1.9%)	1,488	51 (3.4%)	50 (3.4%)	42 (2.8%)
Denver	62	5 (8.1%)	5 (8.1%)	4 (6.5%)	195	7 (3.6%)	7 (3.6%)	6 (3.1%)
Chicago	50	6 (12.0%)	4 (8.0%)	2 (4.0%)	223	19 (8.5%)	18 (8.1%)	17 (7.6%)
Los Angeles	128	22 (17.2%)	11 (8.6%)	1 (0.8%)	...	...	...	...
Totals	**452**	**42** (9.3%)	**28** (6.2%)	**13** (2.9%)	**4,532**	**115** (2.5%)	**112** (2.5%)	**101** (2.2%)

*From blood and other single donor products only (see Table 4).

mate of the number of patients at risk was derived from an equally careful review of the charts of 640 patients who did not develop hepatitis. The correction factor derived from the sample was used to estimate that in the entire study population, 80 patients had actually received fibrinogen rather than 22 as initially reported. The estimated number of unreported fibrinogen recipients (58) was thought to be so small and so difficult to apportion among study centers as to obviate the need for correction of the number of patients originally thought to have received single-donor products only.

Patients receiving multiple-donor (pooled) plasma and fibrinogen also received an above-average amount of whole blood or other single-donor transfusion products (Table 4) but the latter was insufficient to account for the excess incidence of hepatitis observed. Symptomatic hepatitis occurred in 9% of recipients of pooled plasma and 19% of the estimated number of recipients of fibrinogen. There were no deaths among the relatively small number of plasma recipients but the death rate among the estimated number of recipients of fibrinogen was 4%.

Risk as Related to Age, Sex, and History of Hepatitis or Transfusion.—Table 5 shows that males predominated in the population risk and that all hepatitis deaths occurred among men more than 60 years old. Although the effect of advanced age upon outcome is statistically significant ($P<.01$), there were too few females at risk to conclude that they have a better chance of surviving hepatitis. Recipients of fibrinogen and the three deaths among them (Table 4) were also concentrated among older men. However, the incidence of hepatitis (Table 5) was no higher among older patients and did not differ significantly according to sex.

Among the 4,984 patients who received whole blood only, 479 (10%) had a history of transfusion more than six months before entering the current study and 108 (2%) had a history of hepatitis. The histories did not affect the currently observed incidence of symptomatic hepatitis (2.8% [3/108] among those with prior hepatitis and 4.0% [19/479] among those with earlier transfusions) as compared to an overall incidence (see Table 4) of 2.8% (140/4,984).

Variation in Incidence Among Study Centers.—Table 6 ranks the 14 study centers according to the observed incidence and severity of hepatitis and according to the method of follow-up. The variations in incidence among centers is clearly nonrandom ($P<.001$) and some clustering of rates is noted with regard to the three lowest and possibly the two highest. However, comparison of centers must include consideration of the respective numbers of patients followed up by serial SGPT deter-

Table 7.—Posttransfusion Viral Hepatitis According to Transfusion Volume*

Units Transfused (Donor Exposures)	Patients at Risk	Hepatitis Cases		
		All	Symptomatic	Severe
2	441	11 (2.5%)	10 (2.3%)	5 (1.1%)
3	453	9 (2.0%)	8 (1.8%)	7 (1.5%)
4	498	13 (2.6%)	12 (2.4%)	12 (2.4%)
5	465	14 (3.0%)	12 (2.6%)	9 (1.9%)
6	517	13 (2.5%)	10 (1.9%)	8 (1.5%)
7	485	14 (2.9%)	14 (2.9%)	11 (2.3%)
8	425	8 (1.9%)	7 (1.6%)	6 (1.4%)
9	364	13 (3.6%)	11 (3.0%)	10 (2.7%)
10	280	11 (3.9%)	11 (3.9%)	9 (3.2%)
11	198	7 (3.5%)	5 (2.5%)	5 (2.5%)
12	176	6 (3.4%)	5 (2.8%)	4 (2.3%)
13	103	7 (6.8%)	7 (6.8%)	5 (4.9%)
14	115	5 (4.3%)	5 (4.3%)	2 (1.7%)
15	87	3 (3.4%)	1 (1.1%)	1 (1.1%)
Subtotals	4,607	134 (2.9%)	118 (2.6%)	94 (2.0%)
>15	377	23 (6.1%)	22 (5.8%)	20 (5.3%)
Totals	**4,984**	**157** (3.2%)	**140** (2.8%)	114 (2.3%)

*Number of units of single-donor transfusion products.

Table 8.—Posttransfusion Viral Hepatitis According to Source of Donor Blood

	Average No. of Units of Blood* Per Patient	Patients at Risk	Hepatitis Cases		
			All	Symptomatic	Severe
In Patients Receiving All Transfusions From a Single Category					
Group 1: Red Cross donors only	7.4	715	10 (1.4%)	10 (1.4%)	9 (1.3%)
Group 2: Other volunteer donors only	6.4	354	6 (1.7%)	6 (1.7%)	6 (1.7%)
Group 3: Paid donors, known to transfusionist	6.3	396	13 (3.3%)	12 (3.0%)	11 (2.8%)
Group 4: Prebottled blood from paid donors	4.9	625	33 (5.3%)	27 (4.3%)	19 (3.0%)
In Patients Receiving Transfusions From Mixed Sources					
Groups 1, 2, 3 above but no prebottled blood from paid donors	9.3	1,550	35 (2.3%)	35 (2.3%)	28 (1.8%)
Prebottled blood from paid donors and some blood from groups 1, 2, or 3	8.1	1,314	57 (4.3%)	47 (3.6%)	38 (2.9%)
Single Sources and Mixed Sources					
Totals	7.7	4,954‡	**154** (3.1%)	**137** (2.8%)	111 (2.2%)

*Includes single-donor transfusion products.
†Among the 4,984 patients receiving single-donor transfusion products (see Tables 4 and 6), the sources of blood were unspecified regarding 30 including 3 who developed hepatitis.

Table 9.—Symptomatic Posttransfusion Hepatitis by Proportion of Prebottled Paid-Donor Blood and by Proportion Containing Hepatitis-Associated Antigen

Study Center	Prebottled Blood From Paid Donors, %	Hepatitis Cases Per 100 Patients	Average Transfusion Volume (Units)*	Hepatitis Cases Per 100 Units of Blood*	Hepatitis-Associated Antigen Detected by Immunodiffusion†
Lexington, Ky	3	0	8.9	0	...
Rochester, Minn	<1	0.5	9.3	0.05	0.06(5/8,816)
Minneapolis	<1	0.6	6.9	0.08	...
Atlanta	0	2.0	11.9	0.17	...
San Francisco	0	2.1	6.4	0.34	...
Houston	100	2.2	3.6	0.61	...
Baltimore	24	2.3	11.7	0.19	0.28(1/354)
Boston	0	2.3	11.3	0.20	0.22(4/1,800)
Indianapolis	36	2.6	7.0	0.39	...
Columbus, Ohio	0	3.1	7.6	0.44	...
Cleveland	44	3.3	7.0	0.47	...
Denver	<1	4.7	5.6	0.85	0.66(4/600)
Chicago	38	8.1	5.2	1.56	1.47(9/611)
Los Angeles	57	8.6	7.0	1.23	1.08‡
All centers	21	2.8	7.7	0.36	...

*Includes single-donor transfusion products (see Tables 4 and 6).
†Rate per 100 units of donor blood.*
‡Composite calculated from known local rates, 16/1,000 for prebottled blood from paid donors, and 4/1,000 for blood from other sources.

minations, a technique which enhances detection and also results in a larger proportion of cases being classified as symptomatic.

Relation of Incidence to Transfusion Volume.—Table 7 examines the possibility that variations in the incidence of hepatitis from blood and other single-donor products could relate to variations in the average transfusion volume among centers. Patients receiving very large numbers of transfusions have a definitely increased risk of contracting hepatitis but an ascending risk is less clear when the number of transfusions (donor exposures) per recipient is considered in lower ranges. The results and conclusions are not appreciably altered when analyses are adjusted to compensate for distortions introduced into pooled data by anomalous average transfusion volumes at atypically high-risk or low-risk centers.

Relation of Incidence to Blood Source.—Table 8 shows that the source of blood is one of the most easily demonstrable determinants of hepatitis risk. Among the 1,069 patients who received only volunteer donor blood from the Red Cross or other sources, the incidence of hepatitis was 1.5%. This is significantly lower than the rate of 3.3% ($P=.03$) observed when paid known "walk in" donors are the source of blood used in the same hospital where the donors are bled. The highest rate of all, 5.3% ($P<.001$) was observed regarding commercially supplied blood received prebottled from unknown donors. The same trend was seen when mixed sources, including prebottled commercial blood, were compared to mixed sources in which prebottled commercial blood was not included ($P=.002$).

Risk at Each Study Center in Relation to Use of Commercial Blood and With Regard to the Prevalence of HB Antigen in Randomly Sampled Donor Bloods.—Table 9 again ranks the 14 study centers according to the incidence of symptomatic hepatitis as in Table 6 but also expresses the incidence per 100 units of blood and other single-donor transfusion products. The proportion of blood obtained prebottled commercially showed a broad correlation with risk but there were notable exceptions. The risk correlated more precisely with rates of detection of HB antigen at the six centers where immunodiffusion tests for the antigen were performed on the blood of randomly selected donors.

Comment

Short-Incubation Hepatitis Syndromes.—Hepatitis occurring within 15 days of surgery was noted among only those patients who had received halogenated inhalation anesthetics. Previous reports of such an association[3-5] could have led to selective ascertainment. However, the prospective nature of the current study may permit a better estimate of risk, approximately one case per thousand exposures, than is known to be available from other studies.

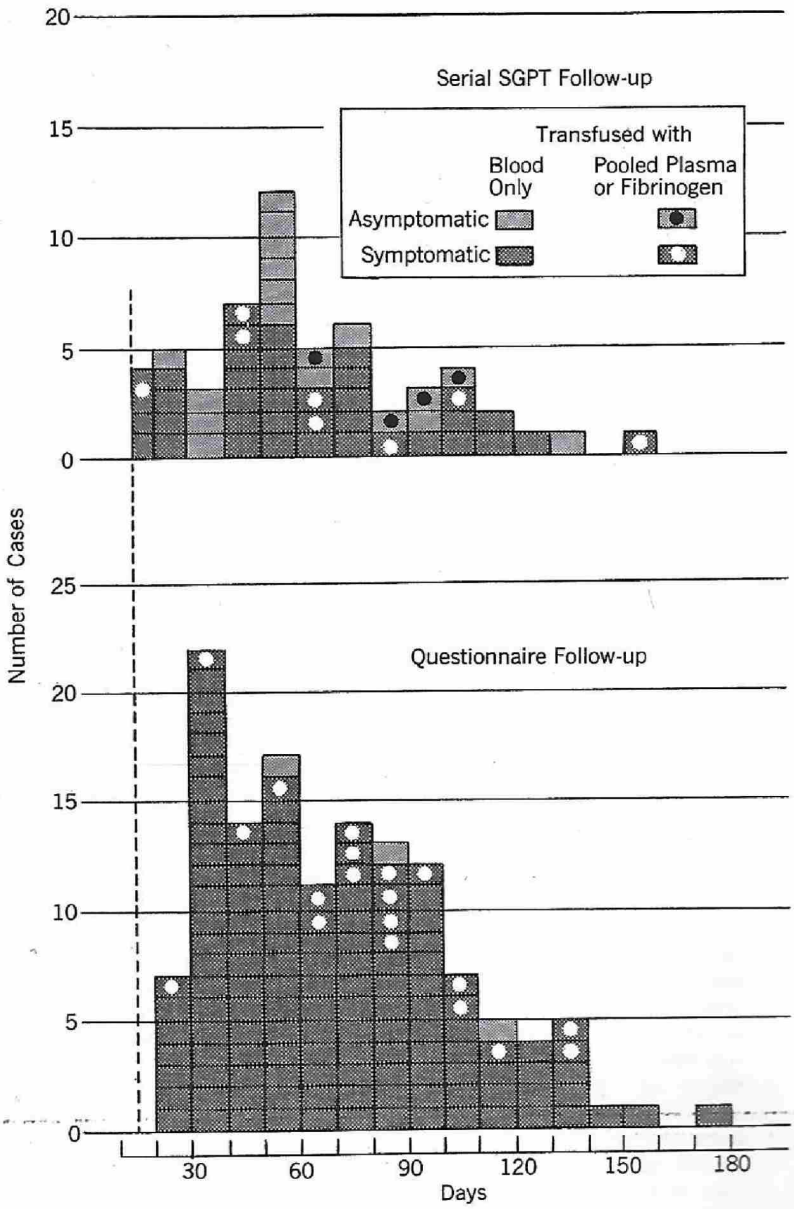
No serologic techniques were used to identify transfused viruses other than by limited testing for HB antigen. With rare exceptions[6] cytomegalovirus appears to survive only in fresh blood[7,8] and may cause splenomegaly, fever, and lymphocytosis, sometimes called "postperfusion syndrome."[6-8] Further evidence that the postperfusion syndrome is not simply an atypical response to infection with serum hepatitis virus was provided by the patient who developed a discrete episode of classical serum hepatitis shortly after recovering from postperfusion syndrome.

Interpretations in the Light of Newly Available Tests for HB Antibody and Antigen.—We have recently been able to show that the lots of immune serum globulin used in the current study have typically low titers of specific antibody against hepatitis (type B) antigen.[9] After the pilot study was completed, the first major lot of immune serum globulin tested clinically was one fractionated from the plasma of outdated blood collected nationwide by the American National Red Cross Blood Program from volunteer donors denying a history of hepatitis. Recent analyses using a hemagglutination technique[9] indicate that the reciprocal titer of HB antibody in the globulin is 16, an antibody concentration below the threshold of detectability by immunodiffusion and counterelectrophoresis. Neverthe-

less, the globulin, when mixed with a small inoculum of serum containing the HB antigen-positive MS-2 strain of Krugman, appeared to be mildly protective,[10,11] although not as protective as against the short-incubation HB antigen-negative MS-1 strain tested by a similar protocol.[10]

The lots of immune serum globulin tested in the second main portion of the current study were fractionated from the plasma of prisoners and commercial donors, a population often exposed to serum hepatitis from contaminated illicit-drug injections. Prince et al[9] showed that commercial donors had higher HB antibody titers than volunteer donors. Conrad[12] used some lots of prisoner-derived globulin that had an HB antibody titer considerably above average and prevented enterically transmitted HB antigen-positive hepatitis among US military personnel stationed in Korea. For reasons that are unclear, the globulin derived from prisoners and commercial donors that was used in the current study had less than an average titer of HB antibody.[9]

Katz et al[13] have recently reported the prevention of posttransfusion hepatitis by immune serum globulin modified for intravenous administration with blood. The HB antibody titer was less than that detectable by immunodiffusion or complement fixation but was not measured by more sensitive methods. Creutzfeldt et al,[14] using another modified immune serum globulin of unknown HB antibody titer, observed protection that was not quite statistically significant among a smaller study population, half of whom also received intramuscular injections of nonmodified immune serum globulin four weeks after transfusion. Since the dose of virus transmitted by an infective transfusion is probably much larger than that acquired by subjects in the studies of Krugman and Giles[10] and Conrad et al,[12] immune serum globulin preparations expected to prevent posttransfusion hepatitis may have to contain unusually large amounts of specific HB antibody or be given by especially advantageous methods. The present study was undertaken in large part because earlier attempts to prevent posttransfusion hepatitis with intramuscular injections of conventional globulin, as previously summarized,[1] had yielded such variable results.



Onset of hepatitis by 10-day intervals following transfusion among cardiovascular surgery patients followed up by serial determinations of SGPT or by questionnaire only. By definition, acceptable cases occurred within 16 to 180 days following surgery. Representation of cases occurring within five-day interval between days 16 to 20 has been adjusted appropriately. Cases occurring within first 15 days are presented in Table 1.

The distribution of encountered incubation periods is similar to that found in several other studies.[15-18] Half the cases in the SGPT follow-up group began within 50 days after transfusion and within 60 days in the questionnaire follow-up group. Results of testing of hepatitis cases for HB antigen were too limited in the current study to be correlated with incubation period. However, from other unpublished studies, Grady et al have found HB antigen by precipitin

s in 61% of symptomatic patients ch incubation periods more than 45 ays and 30% of those with shorter incubation periods, figures which yield a composite of 55% and are in close agreement with 58%, as found by Prince et al.[19] Thus, with some allowance for insensitivity of the method of testing, one can estimate the proportion of posttransfusion hepatitis cases associated with HB antigen and potentially preventable by large amounts of HB antibody. Similarly, one can estimate the proportion of posttransfusion hepatitis cases that, by virtue of being HB antigen-positive, might be prevented if the respective donors can be identified and excluded by screening for HB antigen.

A striking correlation between the incidence of overt hepatitis and the prevalence of HB antigen in the blood of randomly sampled donors at six of the study centers (Table 9) indicates how useful testing may be in guiding selection of specific populations of low-risk donors. The greater prevalence of HB antigen among commercial and prisoner donors than among volunteer donors[20,21] correlates with the greater incidence of hepatitis among recipients of commercial and prisoner blood.[15-17] The importance of recruiting volunteer donors is obvious, but in urban areas where this is most difficult, testing for HB antigen can at least serve as a monitor of the degree of excess risk of hepatitis expected. The variation in risk is so great, as illustrated in the current study, that estimates of average risk[22] are nearly meaningless and local factors must be considered.

Although the incidence of hepatitis at the Denver center (Table 9) was higher than expected, considering the nearly complete avoidance of prebottled commercial blood, the local donor population which included paid donors was characterized by a higher than average prevalence of HB antigen. Testing of donors for HB antigen has become routine recently and in spite of enhanced sensitivity of the tests now used, fewer persons whose serum contains HB antigen are presenting themselves as prospective paid donors.[23]

Among the group followed up in the current study with serial transaminase level determinations, approximately two cases of hepatitis with minimal or absent symptoms occurred for every case that was severe enough to come to general attention, and if screening of donor blood by insensitive methods such as immunodiffusion will detect only one third of infective units of blood,[2] the coincidence would contribute to the nearly exact correlation between the apparent prevalence of HB antigen in donor blood and the incidence of hepatitis among recipients (Table 9). Such correlation does not imply that exclusion of all bloods containing detectable amounts of HB antigen would eliminate hepatitis. Indeed, no such complete success has been observed.[24] However, Barker et al[25] showed that undiluted plasma, in which HB antigen could be detected by methods no more sensitive than those currently used to screen blood, caused more severe hepatitis than that arising from plasma diluted so much that HB antigen was not detectable. Thus, insensitive methods which fail to detect all bloods containing HB antigen may nevertheless permit elimination of the most severe cases of posttransfusion hepatitis or be more effective[26] than expected.

Other Factors Affecting Risk.—Plasma pooled from thousands of donors presents an obviously excessive risk since plasma from a single infective donor contaminates the entire pool. The incidence of hepatitis among patients in the current study who received multiple-donor plasma along with whole blood was 9%. Data were limited to the first half of our study because multiple-donor plasma was removed from interstate commerce by a ruling of the federal Division of Biologic Standards in 1968 following Redeker's demonstration[27] that hepatitis virus is not completely inactivated in plasma stored six months at 32 C (89.6 F), and by renewed recognition that serum albumin solutions, which can withstand effective sterilization at 60 C (140 F) for ten hours, are a preferable alternative.

Multiple-donor fibrinogen is still used widely, although the current study confirms the excessive risk of hepatitis associated with it[28] and dramatizes the formidable mortality that can result. The high risk of fibrinogen-transmitted hepatitis is often balanced against the grave prognosis of some hypofibrinogenemic syndromes, but it is becoming increasingly apparent that many of the syndromes are related to consumption coagulopathy for which fibrinogen administration is controversial.[29] Screening for HB antigen of all plasma intended for manufacture of blood products, a proposed regulation of the Division of Biologic Standards, will hopefully result in fibrinogen with a lower risk of transmitting hepatitis, but judicious use will remain equally important.

Judicious use of blood and other single-donor products is also necessary. Even if the data in Table 9 are adjusted for the variable proportion of open-heart operations performed among the 14 centers, there are wide differences in the average amount of blood used. There was little drop in the average transfusion volume during the three years of study, although it is possible that attempts to minimize blood use were offset by larger transfusion requirements for increasingly complex surgical procedures.

A previously demonstrated lack of difference in the incidence of posttransfusion hepatitis among men and women, respectively,[16] was confirmed, as was the propensity for older patients to succumb to the disease.[16-18] No difference in age-specific incidence of hepatitis was noted, although the current study did not include children as young as those among whom Allen and Sayman[16] found a decreased incidence. Despite the large number of patients at risk in the current study, the number with a history of hepatitis was too small to conclude whether the apparent lack of immunity to posttransfusion hepatitis is meaningful. Nor was immunity evident clinically among the larger group with a history of transfusion although Lander et al[30] have detected low titers of HB antibody in 83% of multiply transfused patients as contrasted with 14% of the general population.

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Nonproprietary and Trade Names of Drug

Normal human serum albumin—*Albumisol, Albuminate, Albuspan, Pro-bumin, Proserum.*