

II. HISTORY OF HEPATITIS

**Robin Biswas, M.D., Medical Officer
Division of Emerging Transfusion Transmitted Diseases, OBRR, CBER, FDA**

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8777 Georgia Avenue
Silver Spring, MD

Blood Products Advisory Committee Meeting: March 16, 2000

Blood Donor Deferral for a History of Hepatitis

Current Situation

Regulations 21 CFR 640.3 (c) (1) and 640.63 (c) (11) preclude persons with a history of viral hepatitis from donating Whole Blood or Source Plasma.

FDA's prior interpretation of the above, is as follows:

1. Donors with a history of *clinical* viral hepatitis after 11 years of age should be deferred.
2. The term "viral hepatitis" might include jaundice, or a clinical diagnosis of hepatitis.

Note: While lab tests may assist a physician in arriving at a clinical diagnosis of hepatitis, in the absence of clinical history or medical diagnosis, laboratory results alone need not be interpreted as a history of hepatitis for the purposes of the regulations, *i.e.*, "*history of viral hepatitis*" means the occurrence of *clinical, symptomatic, hepatitis*.

3. In a donor with a history of jaundice, after the age of 11, if it is not possible to rule out viral hepatitis as a cause, the donor is deferred.

Background

A regulation precluding the use of blood donors who have a history of hepatitis has been in place since the late 1950s, and blood establishments have used a history of hepatitis or jaundice as a criterion for determining donor suitability since the early 1950s. This was long before any hepatitis viruses had been identified, before tests were developed for their detection, and before much was known about the infections caused by these viruses: for example, it was not known whether individuals who had had clinical hepatitis were chronically infected after apparent clinical recovery.

Since that time several hepatitis viruses have been identified and tests for their detection developed; in particular very sensitive and specific serologic assays for HBV and HCV (the two blood borne hepatitis viruses which are known to cause disease in recipients) have been licensed and implemented in blood establishments for donor screening. For donors of Whole Blood or components these tests include hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc) and antibody to hepatitis C virus (anti-HCV). Source Plasma for further manufacture into injectable products is tested for HBsAg and anti-HCV. Most blood for transfusion is also tested for alanine aminotransferase (ALT). Almost all Source Plasma is tested for ALT.

In addition, all Source Plasma donations and almost all Whole Blood donations in the U.S. are screened for HCV RNA by NAT under IND, using a pool-testing format.

Preliminary results show that such testing detects a certain number of units containing HCV RNA prior to seroconversion. _____

_____ Testing of pools is considered to be an interim measure until single unit NAT testing replaces it.

Because of this increasingly sensitive and specific testing for viral hepatitis, the risk of post-transfusion hepatitis is rapidly being reduced to barely detectable levels. This fact, together with advancing knowledge about viral hepatitis, has raised questions about the necessity for excluding donors with a history of clinical hepatitis. Therefore, FDA sponsored a workshop to discuss the issue and to examine any relevant data.

FDA Workshop: July 21, 1999

The specific question discussed at the workshop was whether there was sufficient information to consider eliminating the exclusion of donors with a history of hepatitis. At the meeting the following points emerged:

1. Studies in the 1970s and 1980s showed that markers for hepatitis A, B, and C, and elevations of ALT, were more frequently detected in potential donors with a history of hepatitis than in donors with no such history. There are no recent comparable data.
2. The regulations were probably of use in the past.
3. The number of Whole Blood donors who were deferred in 1998 solely because of donor history of hepatitis was about 13,000.
4. The theoretical residual risk for post-transfusion hepatitis B (9 per million units) and C (3 per million units) expected once implementation of NAT is complete is extremely low. Transfusion transmitted hepatitis B and C are already so rare that their incidence is approaching zero. (Moreover, the reported U.S. population incidence of hepatitis B and C from all causes has declined dramatically from the mid-to-late 1980s to now: hepatitis B, from 400,000 to 200,000 cases/year; hepatitis C, from 200,000 to 40,000 cases/year.)
5. At the present time, it appears that most, if not all known viral hepatitis agents, apart from HBV and HCV, do not cause significant health risks to blood recipients, except in very rare situations.
6. However, according to CDC, 3% of reported U.S. cases of hepatitis are hepatitis non A-E, and may be related to the virus referred to as "SEN-V", about which very little has been reported. (Is it a single species; does it cause acute disease, does it cause chronic, inapparent infection; does it pose a health risk to recipients?)
7. Any increase in post-transfusion hepatitis resulting from elimination of the history of hepatitis question from the donor screening interview would be very difficult to detect if the change were as slight as anticipated.

Options

1. Entirely eliminating the exclusion for a history of hepatitis

This would stop deferral of about 13,000 Whole Blood donors per year nationally. Many of these excluded donors are not currently infected with any transmissible agent, and they probably represent a loss of useful present and future donations.

However, the problems doing this are CDC's report of 3% of acute non A-E viral hepatitis together with the preliminary data on SEN-V virus. Eliminating the exclusion would also eliminate an extra layer of safety. However, it is highly probable that a very high proportion of donors (and their donations) excluded solely on the basis of this question are safe, when all other donor suitability criteria are met.

2. Keeping the exclusion.

This would retain a layer of safety with continued loss of many safe donors and their present and future donations.

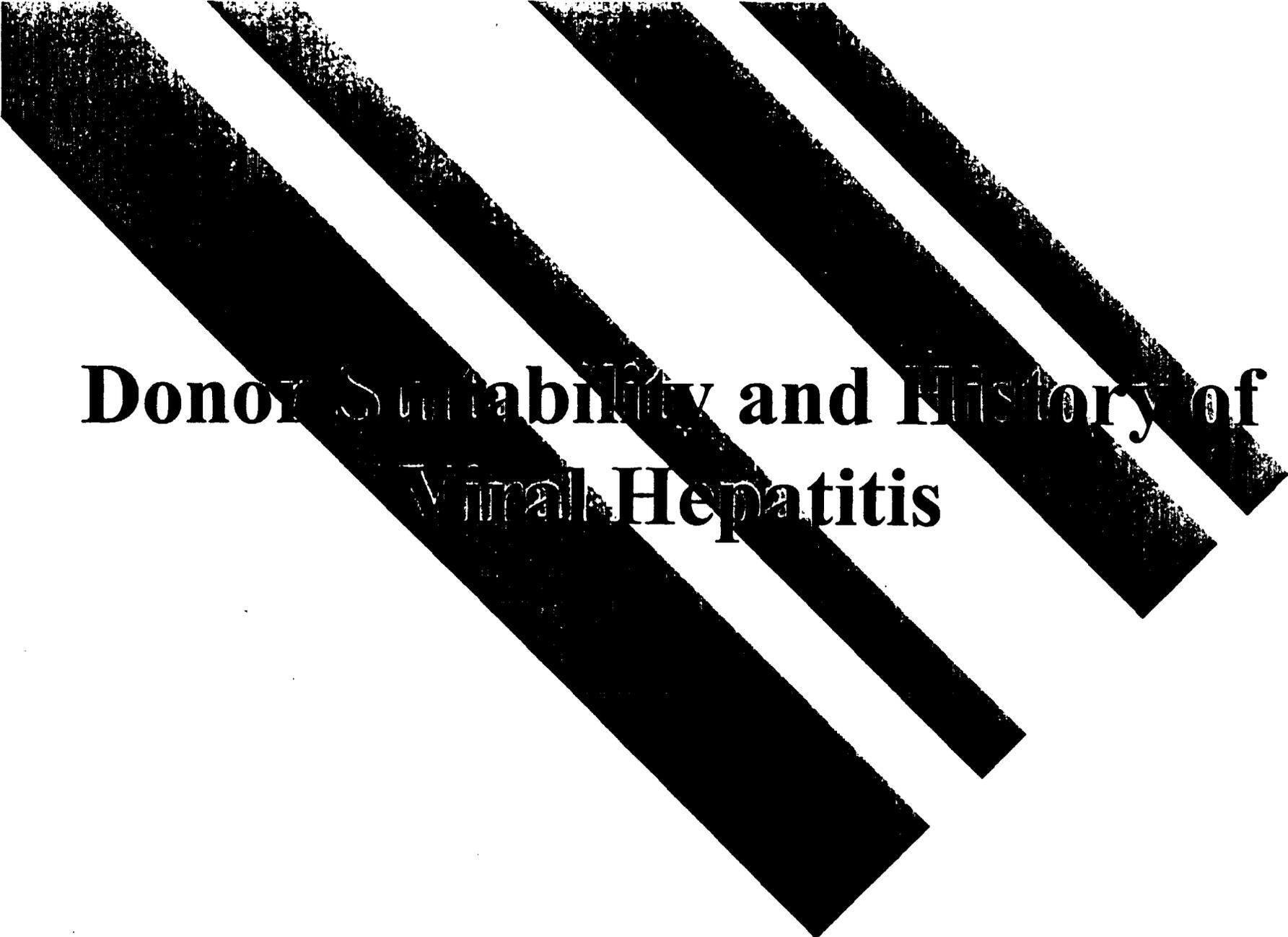
3. Modifying the exclusion by excluding donors with a history of clinical hepatitis that occurred during a limited time period, e.g., during the past one year.

This should be easy to do and would probably retain many donors currently excluded by the question. However, it could miss unknown or emerging agents, e.g., chronic non A-E hepatitis agent(s). Moreover, its scientific basis is not firm, inasmuch as it carries the assumption that the period of infectivity (if any) is known.

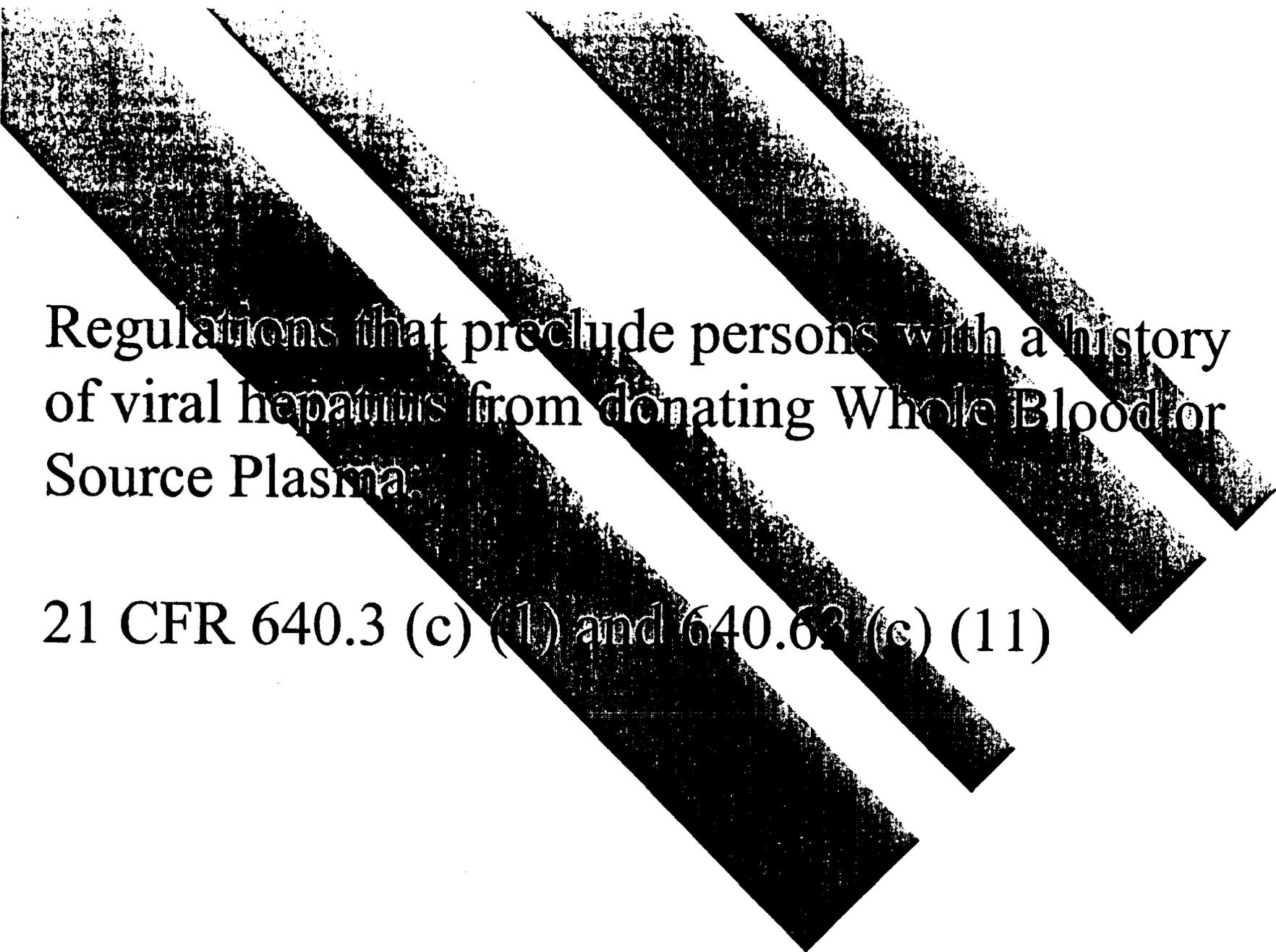
4. Modifying the exclusion by accepting donors whose previous viral hepatitis (e.g., hepatitis A, CMV, etc.) could be documented not to pose a current significant risk for recipient hepatitis; i.e., require documentation that demonstrated the identity of the etiologic agent at the time the potential donor was diagnosed with viral hepatitis.

In principle, this would be a safe way of retaining some safe donors and excluding potential carriers of new or unknown agents who had hepatitis symptoms in the past. Although, acquiring sufficient evaluable documentation might be difficult, this could be a first step in reconciling the current interpretation of the regulation with well established medical knowledge.





Donor Suitability and History of Viral Hepatitis



Regulations that preclude persons with a history of viral hepatitis from donating Whole Blood or Source Plasma:

21 CFR 640.3 (c) (1) and 640.63 (c) (11)

At least since the early 1950s, blood establishments have used a history of hepatitis criterion for determining donor suitability.

At least since the late 1950s, a history of hepatitis donor exclusion regulation has been in place.

At least since the early 1960s, blood establishments included a history of jaundice, or yellow jaundice.

Testing Donors for Viral Hepatitis

Blood and blood components for transfusion:

Hepatitis B surface antigen (HBsAg)

Antibody to hepatitis B core antigen (Anti-HBc)

Antibody to hepatitis C virus (Anti-HCV)

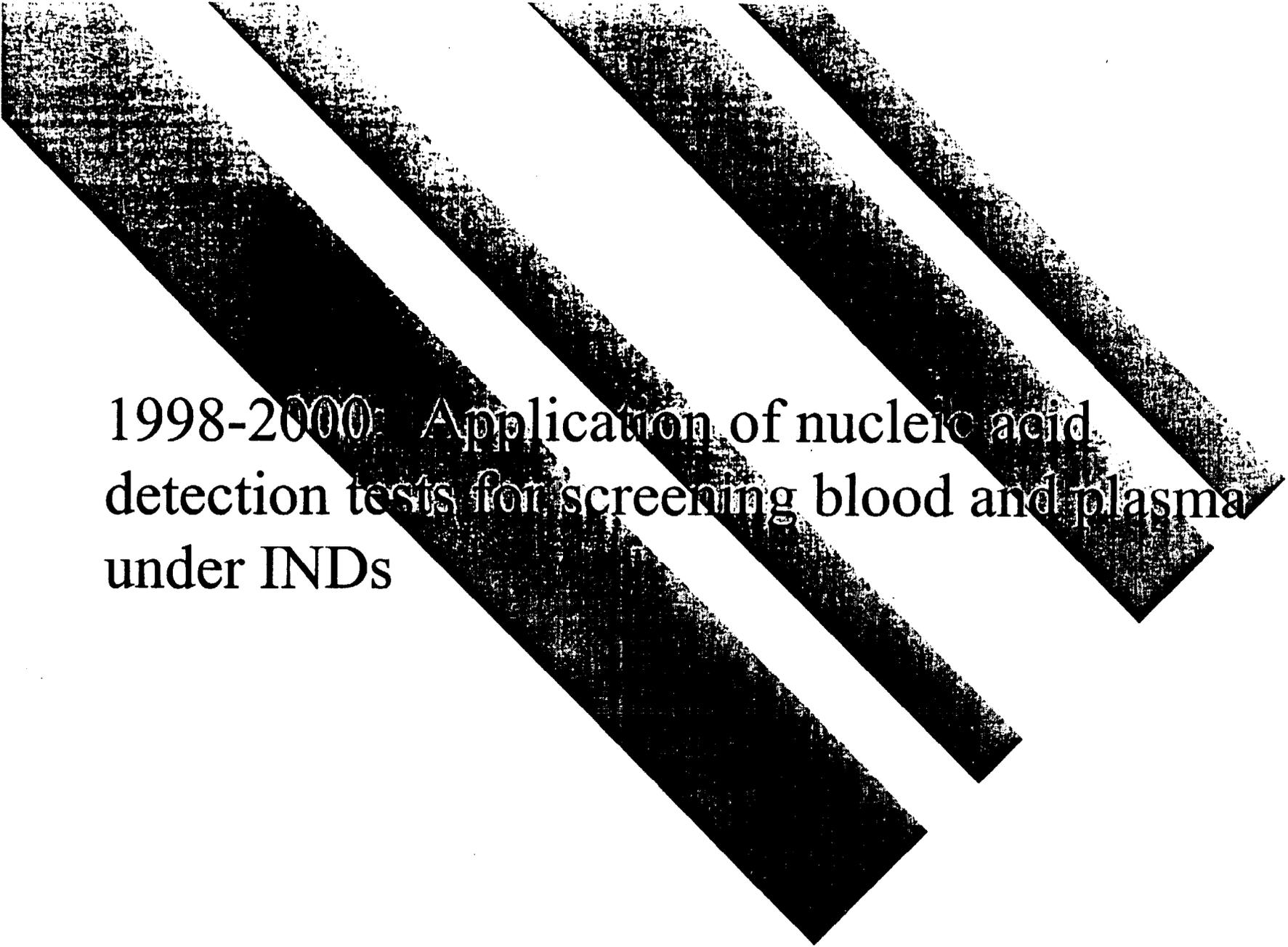
Alanine aminotransferase (ALT)

Plasma for further manufacture into injectable products:

HBsAg

Anti-HCV

ALT



1998-2000: Application of nucleic acid
detection tests for screening blood and plasma
under INDs

Consistent with BPAC recommendations, the regulations are currently interpreted as follows:

Donor with a history of clinical viral hepatitis after 11 years of age should be deferred

At present “viral hepatitis” might include jaundice, or clinical diagnosis of hepatitis

In a donor with a history of jaundice, after the age of 11, if it is not possible to rule out viral hepatitis as a cause of jaundice, defer donor

Goals of July 21, 1999 Workshop

Is there sufficient information today to consider eliminating the exclusion of donors who have a history of viral hepatitis?

HDA Workshop: July 21, 1999

- Studies in the 1970s and 1980s showed that markers for hepatitis A, B and C, and ALT, more often present in donors with history of hepatitis/jaundice than in donors with no such history.
No recent data.
- Regulations probably useful in the past.

- 13,000 WB donors deferred in 1998 solely for history of hepatitis/jaundice.

- With inclusion of NAT testing of donors, remaining residual risk:

HBV 9: 1,000,000. HCV 3: 1,000,000

- Incidence of HBV and HCV declining in the United States:
Mid-to-late 1980s to late 1990s
HBV 400,000 to 200,000 cases per year
HCV 200,000 to 40,000 cases per year.
- Apart from HBV and HCV, known viral hepatitis agents do not cause significant recipient risk.

However,

- 30% of reported acute viral hepatitis cases in U.S. are hepatitis non A-E.
- Accounts of a hepatitis virus referred to as "SEN-V".
- Any increase in post-transfusion hepatitis resulting from elimination of questions would be difficult to detect, if change is slight.

Options

1. Entirely eliminating the exclusion for a history of hepatitis.
2. Keep the exclusion.
3. Modify the exclusion by excluding donors with a history of clinical hepatitis for a limited time period, e.g., for one year after disappearance of symptoms.

(Continued)

Options (Continued)

4. Modify the exclusion by accepting donors whose previous viral hepatitis, e.g., hepatitis A, could be documented not to pose a current risk for recipient hepatitis, i.e., require documentation to demonstrate what the etiologic agent was at the time the potential donor was diagnosed with viral hepatitis.

1. Eliminate exclusion for history of viral hepatitis.

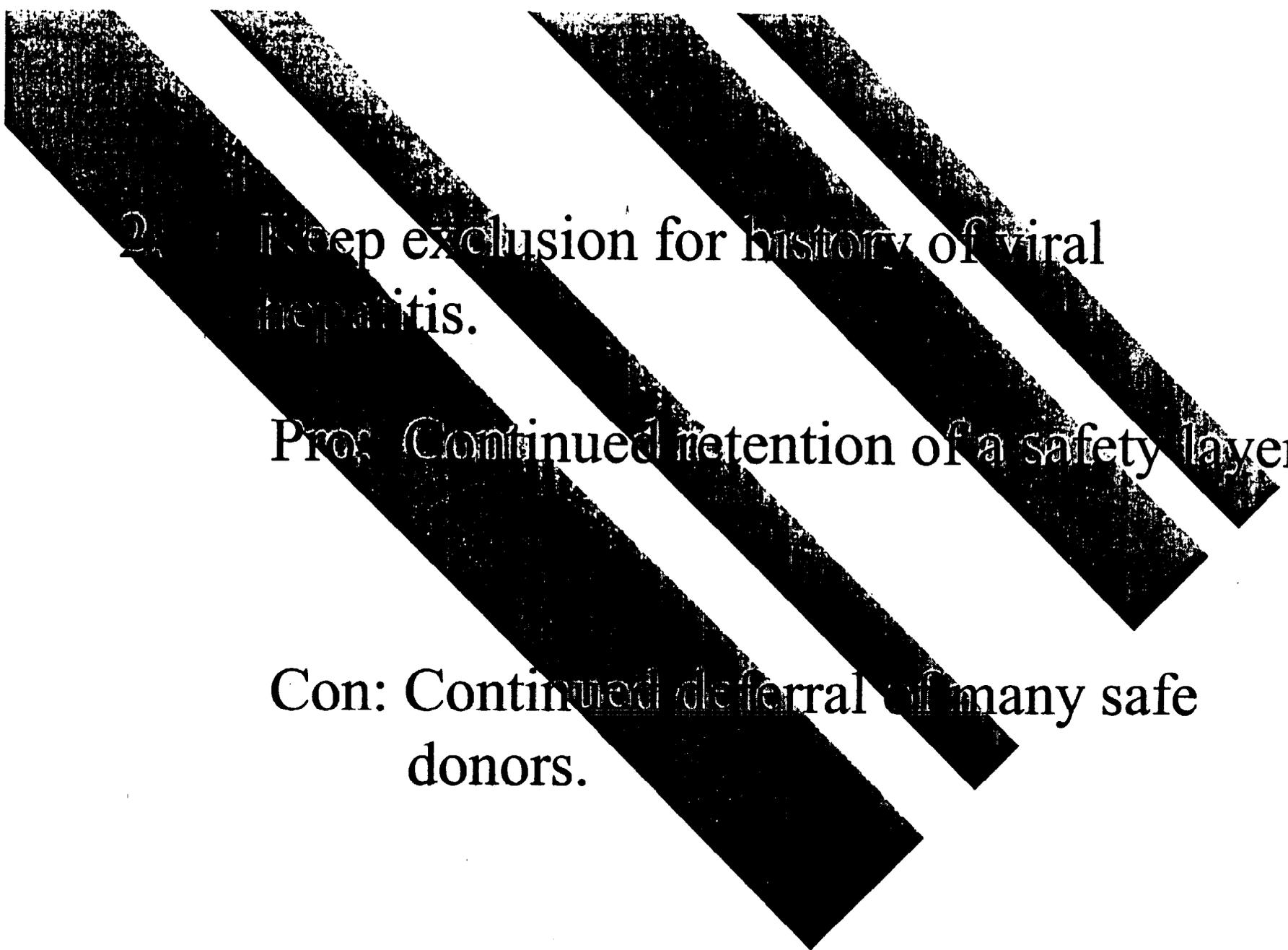
Pro: Would stop denial of 13,000 donors who are highly likely safe.

Con: Lack of information about CDC's reported 3% of acute non A-B hepatitis.

Accounts about SEN

1 (Continued) Eliminate exclusion for a history of hepatitis

- Utility of the question about history of hepatitis is low if utility absent.
- In the absence of data on utility of question for elimination of hepatitis non A-E transmission, appears premature to drop question.
- "SEN-V"?



2. Keep exclusion for history of viral hepatitis.

Pro: Continued retention of a safety layer.

Con: Continued deferral of many safe donors.

2 (Continued). Keep exclusion for history of hepatitis.

- Not useful for known agents.
- Sensitive tests for HBV and HCV.
- Probably inefficient for unknown agents.
- In the absence of data on utility of question for elimination of hepatitis non A-E transmission, appears premature to drop question.

3. Modify exclusion by excluding donors with a history of viral hepatitis for a limited time period, e.g., for one year after disappearance of symptoms.

Pro: Should be easy to do.

Retain many (all?) safe donors.

Con: Could miss unknown emerging agents, e.g., SEN-V or CDC's 39% unknowns, if chronic.

3 (Continued). Modify exclusion by excluding donors with a history of viral hepatitis for a limited time period, e.g. one year after disappearance of symptoms.

- Would not capture non-A-E hepatitis that became chronic and persisted > 1 year.
- If the assumption is that an infection is chronic, setting 1-year limit is arbitrary.

4. Modify exclusion by accepting donors whose previous viral hepatitis, e.g., hepatitis A, could be documented not to pose a current significant risk for recipient hepatitis.

Pro: Safe and scientifically sound way of reconsidering deferred donors.

Con: Acquiring evaluable documentation might be difficult.

4 (Continued) Modify exclusion by accepting donors whose previous viral hepatitis, e.g. hepatitis A, could be documented not to pose a current significant risk for recurrent hepatitis.

While acknowledging difficulties in implementation, it is a sound, scientific way for reconsidering deferred donors.

- FDA is considering permitting this approach.
- Some donors could be re-entered.
- A step forward in permitting safe donors to donate.

1. Does the Committee agree that the Food and Drug Administration should permit exemptions from the regulatory requirements to allow blood establishments to accept donors who report a history of viral hepatitis after the age of 11 years, if there is documentation that the hepatitis was caused by an agent (other than hepatitis B virus or hepatitis C virus) for which the donor is no longer infectious?

2. Please comment on any studies that could be useful to further clarify the utility of donor deferral based on a history of viral hepatitis.

**STATEMENT OF THE AMERICAN ASSOCIATION OF BLOOD BANKS
BEFORE THE BLOOD PRODUCTS ADVISORY COMMITTEE**

March 16, 2000

History of Hepatitis in Blood and Plasma Donors

**Presented by Louis Katz, MD
Chair, AABB Transfusion Transmitted Disease Committee**

The American Association of Blood Banks (AABB) is the professional society for over 9,000 individuals involved in blood banking and transfusion medicine and represents roughly 2,200 institutional members, including community and Red Cross blood collection centers, hospital based blood banks, and transfusion services as they collect, process, distribute, and transfuse blood and blood components and hematopoietic stem cells. Our members are responsible for virtually all of the blood collected and more than 80 percent of the blood transfused in this country. For over 50 years, the AABB's highest priority has been to maintain and enhance the safety and availability of the nation's blood supply.

The AABB appreciates this opportunity to provide comment to the Blood Products Advisory Committee (BPAC).

**AABB Statement Regarding Deferral of Volunteer Blood Donors for a
History of Hepatitis**

The American Association of Blood Banks supports eliminating the requirement to permanently defer potential volunteer blood donors with a history of viral hepatitis after the age of eleven years.

Our rationale is based on accumulated lines of evidence suggesting that this action will not decrease recipient safety. Further, it will reduce the unneeded loss of around 10,000 donors yearly at a time when the demand for blood components is poised to outstrip the supply. We have reached a point where donor historical screening should focus on current rather than historically remote risks, when simplification of donor historical screening can allow us to focus on material threats to blood and donor safety in a more straightforward fashion.

In the 1960s, with paid donors of untested blood, hepatitis was a common outcome of transfusion. Since 1990, using sensitive assays for HBV and with the identification of HCV and implementation of successively more sensitive and specific HCV screening test(s), post-transfusion hepatitis has become so rare that prospective studies have had to be replaced by mathematical modeling to estimate its frequency. After the implementation of HCV RNA screening in minipools under IND, credible estimates suggest the risk for this virus is in the range of 1:1,000,000. The use of current HBsAg screening for HBV infections is far more sensitive than a history of hepatitis for this virus given the high rate of asymptomatic and unrecognized infection in those destined to become chronically infected.

Current rates of post-transfusion hepatitis are exceedingly low. Ongoing prospective surveillance for clinically significant post-transfusion hepatitis at the NIH Clinical Center, in the interval after effective anti-HCV screening was implemented, is unable to demonstrate a persistent problem. In the UK, donors with a history of jaundice are permitted to donate, provided that they are Hepatitis B surface antigen negative and more than one year has elapsed since acute hepatitis B. In addition, since 1997, donors who provide a history of Hepatitis B are tested for anti-HBc. If anti-HBc is negative, they are qualified. If anti-HBc is positive, an anti-HBs is done, and those with levels above 100 mIU are qualified to donate blood. Recently published data from the UK (Regan FAM et al. BMJ. 2000. 320:403) reported the prospective evaluation of 5,579 recipients of 21,923 units of blood for post-transfusion viral infection. No viral infection attributable to transfusion was found in this ongoing prospective cohort.

With regard to the putative non A-E agents of hepatitis, the evidence that clinically recognized hepatitis would allow deferral of these donors is lacking; that is, the history of hepatitis is an insensitive "test" that will miss the majority of these individuals who had no clinically consistent illness and are characterized only by abnormal transaminase levels. It is estimated that the proportion of clinically apparent non-A-E cases is very low based on studies at NIH and the CDC. Also, as yet there is no convincing evidence of clinically significant chronic sequelae.

Data from a number of sources have documented the non-specificity of the history of hepatitis which defers donors with prior HAV, or donors who have been told by their physicians they had hepatitis associated with EBV or CMV infections. These donors represent no additional threat to blood recipients.

In summary, the AABB recommends...

- Elimination of the requirement to exclude donors with a history of hepatitis as an insensitive and nonspecific donor screening tool.
- Failing this, adoption of a system similar to that in the UK that might allow blood collection facilities the option to salvage many thousands of safe donors yearly.