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Based on Your Analysis of the Benefits and Costs of Routine Donor Screening for ALT-GPT to Reduce the Incidence of Post-Transfusion Non-A, Non-B Hepatitis in Your Blood Services Region, what Action Would You Recommend on This Matter?

R.D. Aach. Two recently conducted prospective studies have shown a close relationship between the risk of non-A, non-B (NANB) post-transfusion hepatitis (PTH) and the donor serum alanine amino-transferase (ALT, SGPT) value [1, 2]. The transfusion transmitted viruses (TTV) study with participating centers located in four different regions of the United States, observed this association over a 5-year period (1974–1979); 1,513 recipients given 5,564 units of blood were evaluated [1]. The risk of NANB-PTH was found to be directly related to the serum ALT level of the blood donor. In all, approxiamtely 40% of the cases of NANB-PTH appeared to be associated with units of blood with an ALT value equal to or greater than 45 IU/l, i.e., the upper 3% of the distribution. After correcting for the expected NANB hepatitis risk from the substitution of units with ALT values less than 45 IU, a 31% decrease among multidonor recipients and a 23% reduction among 275 single unit recipients could still be expected.

These observations and the absence of a specific NANB test, led the TTV Study group, including this author, to conclude that '...the high correlation between the elevated ALT level and the infectivity of transfused blood provides a compelling argument that such screening should be instituted'. Unfortunately, circumstances are much the same now as they were almost a year ago when the TTV study observations were published, and my views have not changed. A specific NANB test has still not appeared with certainty. On the other hand, the association of an elevated donor ALT value and NANB-PTH risk has now been confirmed by *Alter* et al. [2]. Their findings were very similar to the TTV study. In their study, a donor ALT exclusion value of 53 IU, i.e. 2.25 standard deviations above the mean log of their volunteer donor population, identified the greatest proportion of NANB cases per number of units that would have to be eliminated. This ALT exclusion level '...could prevent 29% of the post-transfusion hepatitis cases at a loss of 1.6% of donor units'.

Appropriately, a number of issues have been raised about the possible implementation of wide-scale donor ALT screening [3]. These include the objections that the investigations cited were predictive and that an

interventive prospective randomized control study should be initiated for confirmation. In addition, there has been serious concern about the nonspecificity of the test and the substantial loss of noninfectious donors that would result from ALT screening. The cost of performing the ALT determination is yet another concern. Current estimates are that ALT screening would cost approximately $ 20,000,000 per year in the United States alone. Difficulty in establishing appropriate cut-off levels and assuring proper standardization, as well as the questions of how long should the ALT elevated donor be deferred and what should he and his doctor be told are problems that also have been voiced.

Taken together all of these concerns argue strongly for caution. Obviously, if there were a sensitive and specific serologic test for the identification of NANB agent(s), ALT testing would not be a consideration. Unfortunately, such a test does not appear immediately on the horizon, despite more than 6 years of intensive effort. Even if the promise of a specific NANB serologic test is realized at the time of this writing, at least 3 years and likely, 5 years would be required for the independent confirmation, acquisition of reagents in limited supply and the transition from an investigative procedure to a commercial one that lends itself to large scale use. During this time and perhaps even longer, NANB-PTH, approximately 30–40% of cases presumably preventable, will continue to occur. Although most cases will not be prevented by routine screening, there is reason to suspect that 100,000 cases per year might be eliminated in the US alone. Of concern, 30–50% of the recipients who acquire acute NANB-PTH develop chronic hepatitis and some go on to develop cirrhosis. In a recent compilation 12% of patients biopsied with chronic NANB hepatitis had evidence of cirrhosis [4].

Although the studies published to date are predictive rather than interventive, the investigations were well designed, made almost identical observations and were the same type as those which led to implementation of HBsAg donor screening. Indeed, the climate is such that serious objections have been raised to initiating a prospective randomized interventive study at the present time.

The problem posed by removal of 1.5–3% of donors is very real, but a reduction of this or even a greater number can be expected when a specific NANB test becomes available. The TTV study suggested that the NANB carrier rate may even exceed 3% among US donors; 19 of 275 or 6.9% of the recipients of a single unit of blood subsequently developed NANB hepatitis in the TTV study [1].

Admittedly, the cost-benefit ratio cannot be assessed at the present time. The vast majority of NANB cases appear to have asymptomatic or mild illness, and few require hospitalization. However, the cost of medical care of those who are symptomatic, the cost due to absence from work, and above all, the cost of long-term disability resulting from chronic hepatitis may be substantial. If adopted, the cost of ALT testing would be only a small fraction of the total cost of a single unit of blood, no more than the cost of HBsAg screening which represents a preventative measure for what is now a much lesser risk to the recipient than NANB hepatitis.

Instrumentation and standardization certainly are challenges, but the success of other laboratory tests such as HBsAg detection,

once of similar concern, suggests that given the proper initiative, these goals could be accomplished for ALT detection as well. Since the relatively undocumented policy of rejecting donors with a history of hepatitis or jaundice is currently in effect, it would seem reasonable to reject donors found to have an elevated ALT value, for which there is a documented risk.

A decision must soon be made regarding donor ALT screening. Either the issue is not resolved and requires a properly designed randomized study which should be initiated now, or a target date for routine ALT testing should be set for those donors populations in which an association with NANB PTH has been identified. It is unfair to postpone the decision, possibly indefinitely, because of the expectation that a specific and sensitive NANB test will soon come along to lead us out of the wilderness.

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W.L. Bayer. The emotionalism that prevails over the ALT-GPT issue exists because medicine has had a specious belief that it could and would guarantee good health to everyone. Unfortunately, no individual and certainly no society can be guaranteed what is impossible to control. Transmission of infectious agents can be moderated by a transfusion service but transfusion makes up only a small portion of the overall risk of exposure to infectious agents that might lead to disease. We must remember, however, that infection in itself does not mean disease, a word whose meaning in the English language can be expressed as DIS-EASE or without comfort. We can agree that there is a risk of infection with non-A, non-B hepatitis agents from transfusion.

The issue at hand that must be faced by blood distribution agencies is whether action in regards to ALT-GPT testing of donors should be taken at this time and if taken what should be done with the units and the donors defined as positive. What is the scale of this risk and how does it compare with the risk of nontransfused patients, to the public at large, and in different regions.

We know that the incidence of elevated ALTs varies according to geographic region, socioeconomic status, sex, and ethnic subgroups [1, 2]. These differences have to be considered for their impact on the reduction of an available blood supply by all parties concerned, particularly as the test is nonspecific for non-A, non-B hepatitis and as Paul Holland emphasized, has a 70% false-positive and 70% false-negative rate.

The risk to transfused patients of infection also varies between geographical region and is reported to be 4% in St. Louis where the donors were primarily a white, middle level socioeconomic population and the re-

cipients a middle upper to upper-level socioeconomic population and 18% in Houston where both the donors and recipients were from lower socioeconomic populations. The severity of acute clinical disease in the patients is not described and the long-range effects in terms of the amount of liver caused debilitation in populations that have had an infection with non-A, non-B agents is not known other than to say it does occur. The vast majority of patients admitted to the hospital, however, do not receive transfusions; in 1980 there were 39 million admissions to US hospitals. If we consider 20% to be readmissions and an attack rate to non-transfused patients of 2.2% for non-A, non-B [3], then 686,400 people will develop infection during hospitalization. Approximately three million patients are transfused annually in the US and so one might assume that 300,000 minus 66,000 patients would develop an infection associated with transfusion.

Thus, about one million people can be expected to develop non-A, non-B hepatitis infection in the US each year by virtue of being hospitalized or transfused. The Center for Disease Control annual summary for 1980 published an incidence of 5.25 per 100,000 in the US for clinical hepatitis unspecified, presumably non-A, non-B, so there therefore would be approximately 11,500 clinical cases annually. Our transfusion region has a clinically reported incidence of approximately 1:5,000 transfused patients. We transfuse 25,000 patients annually, and represent 1% of the US population. For argument's sake we will say all the transfusion-associated cases are non-A, non-B and they are not. But to put clinical incidence in perspective then five cases yearly out of a potential 115 are attributed to transfusions in our region.

Even if the assumption is made, and it is probably true, that direct infusion of a larger amount of infectious material is a greater danger to an individual than exposure within the environment, it can still be stated that in terms of reducing the number of people who will develop non-A, non-B hepatitis that interdiction of donors with elevated ALTs will have only a small impact.

When we add to this that we have no real knowledge of the long-term effect of mild or intermittent transaminitis in the single transfusion episode patient, but do know that in hemophilia A that asymptomatic patients with intermittent transaminitis have for the most part only milder forms of liver disease on biopsy [4], we then have to recognize that the evidence for implementation of ALT testing on medical or public health grounds is still weak.

There are other problems with establishing a donor screening program using ALT. Test costs for the transfusion service might be the least of these problems, but at $ 1.00 per test could add $ 11 to $ 12 million annually to expenses in the US.

Other costs for the collecting agency would include the cost for the blood and components discarded; the cost of increased recruiting to replenish supply; and the cost of time and money in explanation to 2–3% of all blood donors. In an open society, the donor is entitled to know that his or her unit will not be used because of a finding which may affect the recipient or the donor's health.

The latter may well be the most significant in cost, if not to the collection agency then to society. These donors may seek additional medical follow-up from their own physicians, which would not only increase the amount of money expended but would

also create anxiety and emotional distress for many people for no real reason.

The ALT issue demands that realism be applied so that cost and availability of a necessary resource be weighed against risk. The facts should be made available to governing boards, physicians and the public, and final decisions should not be made indiscriminately in the hope that if enough money is spent the world will be perfect. These decisions will depend on local rather than national or international circumstances and should be made locally. In our region we have decided not to use ALT testing to reject donors and will continue our present policy of collecting blood from volunteer donors who are the mainstream of our society. If other regions decide differently, we will review their results over time but hope that in making such a decision they do not permanently defer donors with elevated ALTs and establish a precedent such as now exists in the permanent rejection of donors with past histories of proven hepatitis A and for donors who have completely resolved hepatitis B antigenemia.

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R.J. Gerety. Before deciding what action, if any, should be taken in regard to the routine screening of blood donors for serum alanine aminotransferase (ALT) activity to reduce the incidence of post-transfusion non-A, non-B hepatitis, it is worth reviewing some characteristics of the 'ideal' screening test. Such a screening test would yield reproducible results in different laboratories, would require minimal technical skills, be easily standardized, possess a cut-off value which distinguishes those who do and do not transmit non-A, non-B hepatitis, and would be readily available at low cost. The currently available ALT test is specific for liver damage but it is not specific for non-A, non-B hepatitis. In fact, most individuals who transmit non-A, non-B hepatitis have normal or near normal ALT levels [1, 2 and below]. Problems related to technical aspects of the ALT test as well as its cost have yet to be fully discussed or appreciated [3]. Preliminary data suggest that establishment of an ALT cut-off value to distinguish acceptable from unacceptable donors will not be easy [4–6]. ALT levels can be elevated by the use of ethanol, nearly every analgesic, anti-inflammatory, tranquilizer, antipyretic, sedative, antihypertensive, and oral hy-

poglycemic or contraceptive, as well as by intensive physical activity. ALT levels also appear to differ in different geographical areas and populations [4–6].

No prospective study has demonstrated that eliminating donors with elevated ALT would reduce the incidence of either elevated ALT or post-transfusion non-A, non-B hepatitis in recipients. Currently available data come in large part, from the multicenter, prospective, transfusion-transmitted viruses study (TTV). Non-A, non-B hepatitis in recipients was defined in this study by an abnormal ALT plus the absence of serologic markers for hepatitis A and hepatitis B viruses. Blood recipients were candidates for elective surgery lacking a history of either hepatitis or liver disease, without exposure or potential exposure to drugs affecting ALT. Each had a normal ALT prior to transfusion. Blood donors included volunteers, county hospital donors and commercial blood donors. Data from 1,513 blood transfusion recipients [1] showed the average attack rate of non-A, non-B hepatitis to be approximately 10% and to be directly related to the ALT level in blood donors. The attack rate in recipients of blood which had an ALT below 29 IU/l was 6% or less compared to a 45% attack rate in recipients of blood with at least 1 U having an ALT of 60 IU/l or more. This association also held for recipients of single units of blood although 74% of non-A, non-B hepatitis cases occurred in individuals who received blood from a donor with a normal ALT. In addition to the ALT levels of donor blood, the source of blood also appeared to relate to the risk of post-transfusion hepatitis. 23% of recipients of blood from commercial sources compared to 5% of recipients of blood from volunteer sources (all with normal ALT) got non-A, non-B hepatitis [1]. Of 137 recipients who received multiple units of blood and who developed non-A, non-B hepatitis, 60% received only blood units with normal ALT, while the remainder received some blood units with normal and some blood units with elevated ALT levels.

The clinical significance of transient or even prolonged elevations of ALT levels after a single blood transfusion episode is not clear. Is the risk of transmitting non-A, non-B hepatitis associated with an absolute ALT level or is it associated with donors whose ALT levels are elevated with respect to the geographic, sex or age subgroup from which they come or to their own baseline value? What is the variation in donor ALT levels considering the variety of known confounding factors outlined above? Are abnormal ALT values found consistently when serial samples are obtained from one individual? ALT screening will only reduce, and not eliminate, the incidence of post-transfusion non-A, non-B hepatitis. Can some individuals who transmit non-A, non-B hepatitis be identified more easily and more cheaply than by ALT screening, i.e., by history, demographics or another nonspecific test [7]? Does antibody to hepatitis B core antigen in the absence of other serologic markers for hepatitis B increase the risk of post-transfusion non-A, non-B hepatitis as a result of the epidemiologic association of these viruses? What would be the effect of elimination of nonreplacement fees for blood, using all volunteer blood donors and eliminating certain known high-risk donor groups? Studies to evaluate these alternative approaches have not yet been accomplished. There appear to be more questions than answers regarding ALT screening [8]. Only after the answers become known can a decision be made re-

garding the value of ALT screening or of other nonspecific measures to reduce the incidence of non-A, non-B post-transfusion hepatitis until a specific screening test is developed, approved and generally available.

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P. V. Holland. The use of an ALT-GPT test to screen blood donors in an effort to reduce the incidence of transfusion-associated hepatitis is not a new idea [1, 2]. Recent studies have, however, restimulated interest in this *potential* means to reduce the risk of transfusion-associated hepatitis [3, 4]. In most of these studies, the authors found that transfusion of blood which came from donors with elevated levels of ALT correlated with an increased risk of hepatitis in recipients. The conclusions and recommendations of these authors are somewhat at variance, however. In addition, no one has actually carried out a study to see if the predicted efficacy of ALT screening is actually realized when put into practice. This is the first problem with ALT testing; its actual efficacy in hepatitis prevention has not been proven. For this and other reasons to be detailed below, I do not feel that routine donor screening for ALT-GPT should be performed at this time.

Schmitt et al. [1] found the risk of clinical hepatitis after transfusion of blood with an elevated ALT (>39 units, approximately equal to 7 SD above their mean) to be 7.35%, compared to 4.74% for patients who received all blood without an elevated ALT. With 0.6% of untransfused patients developing hepatitis, it can be calculated that 27% of their transfusion-associated hepatitis might have been prevented if blood with an elevated ALT were not transfused. However, these authors did not allow for the fact that the more transfusion patients received, the more likely they were to receive blood with an elevated ALT. *Schmitt* et al. [1] did point out that they would lose 1% of their blood but 4% of their donors (12% of their donors in some regions) with ALT screening.

Creutzfeldt et al. [2] prospectively evalu-

ated the risk of both icteric and anicteric hepatitis after the transfusion of blood tested for ALT (in retrospect). They found that 25% of patients who had received at least one blood with an elevated ALT (>17 units, or more than 2 SD above their mean) developed hepatitis compared to 13.5% for recipients of blood without an elevated ALT. However, the former group received more blood and was thus more likely to receive some with an elevated ALT; when the risk of hepatitis was expressed per pack of blood, patients who had received blood with an elevated ALT had a risk of 3.4% compared to 4.6% for patients who had received no elevated ALT blood. Despite the conclusion of these authors that they could not prove an increased risk of hepatitis after administration of blood with a pathologically high ALT, they instituted routine ALT screening of blood donors and recommended against using blood with an ALT of over 50 units (more than 9 SD above their mean).

In the TTV Study [3], the risk of transfusion-associated hepatitis increased progressively with higher donor ALT levels. When all donor blood had an ALT of less than 30 IU/l (about 1.5 SD above the mean), the hepatitis attack rate was 6%; this rose to 45% for recipients of at least one blood with an ALT of 60 IU/l or greater (about 2.5 SD above the mean). These authors suggested that about 40% of their cases of non-A, non-B hepatitis could have been prevented by not using blood with an ALT of 45 IU/l or higher (about 2 SD above their mean). This prediction did not allow for replacement of the discarded blood with some without an elevated ALT, which would have reduced the efficacy of ALT screening to 28.5% for multiply transfused patients (actually only 21% for single unit transfusions). These authors estimated that 3% of their blood would be discarded because of an elevated ALT. In our study [4] of multitransfused recipients at the NIH, we also found that the frequency of hepatitis increased when bloods with an elevated ALT level were transfused; we predicted that 29% of transfusion-associated hepatitis might be prevented by rejecting blood with an ALT of over 53 IU/l (2.25 SD above our mean).

In each of these four studies [1–4], the majority of transfusion-associated hepatitis occurred in recipients of blood which did not have an elevated ALT. In fact, rejection of elevated ALT blood would not have eliminated 70% or more of the hepatitis in these studies. In addition, in each study, most patients who received blood with an elevated ALT did not develop hepatitis. While it is impossible to know how many of the recipients might have been immune to non-A, non-B hepatitis, it is likely that many blood donors with elevated levels of ALT are not carriers of a non-A, non-B hepatitis virus. So, the second problem with the ALT test is that it is too nonspecific to be used routinely as a screening test to identify hepatitis carriers among blood donors; it has too many 'false-negatives' and too many 'false-positives'. Hopefully, a more specific test to identify non-A, non-B hepatitis carriers is forthcoming [5].

The third problem with ALT screening is the actual performance of the test. There are a variety of methods for ALT testing (with little information on their comparability), there are no standards for determining absolute values, and there are insufficient data to establish a reliable cut-off level to separate donors to be accepted or rejected. Blood donors may be acceptable by one test and not by another (or acceptable at one time or

cut-off and rejected on another occasion by a different, arbitrary cut-off level). It is not established whether the donor or his blood pack should be rejected if the ALT test is elevated.

The fourth problem with implementing routine ALT testing is that the effects on the rejected blood donor and the donor population, in general, have not be assessed. Little is known about the significance of an elevated ALT in an otherwise healthy, asymptomatic blood donor. What should the blood bank tell a donor with an elevated ALT? How should the donor be further evaluated, and by whom? The medical and psychological effects of notifying donors that they have an elevated ALT level have not been investigated. What impact will testing have on donor motivation? How many donors will actually be rejected and how many blood packs discarded (which will have to be replaced)? The practicalities of ALT testing and the impact on blood donors and donor sources must be thoroughly thought out and evaluated before routine testing is instituted.

My feelings about routine ALT testing of blood donors are incorporated into the recommendations of an ad hoc committee of the AABB which was asked to address this problem. Our conclusions have been published [6]. The final statement summarizes our collective opinions and is as follows: 'At this time we do not advise routine donor testing for ALT as a means of reducing the incidence of non-A, non-B hepatitis. Furthermore, we strongly advise that any testing that is undertaken be done in a way that will increase our information concerning the significance and natural course of elevated levels of ALT in donors and the relationship to the transmission of non-A, non-B hepatitis.' At this time, the NIH Blood Bank is screening donors for elevated levels of ALT to assess the impact of the measure on our hepatitis incidence, to identify donors with elevated ALT levels, and to study such donors to learn more about them and the medical implications of an elevated ALT. We are also looking at other possible means to identify non-A, non-B hepatitis virus carriers.

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D.B.L. McClelland. The only action which I would recommend at present is that there should be a thorough prospective study to determine the frequency with which post-transfusion hepatitis occurs in the regions served by this centre, or in a closely comparable population.

If the results of such a study indicate that post-transfusion hepatitis due to non-A, non-B viruses (PTH) occurs sufficiently frequently to cause concern, I would recommend further study be carried out to determine whether the introduction of a donor ALT screening programme does in fact reduce the attack rate for PTH. As an alternative, it may well be possible to study simultaneously the attack rate for PTH in the recipients of ALT screened or nonscreened blood.

I consider that without undertaking thorough studies along these lines, the potential and actual scale of the 'benefit' side of the cost benefit calculation is unknown and therefore no rational decisions can be taken. Furthermore, the premature widespread introduction of routine ALT screening (or indeed any other form of screening procedure for known or putative non-A, non-B hepatitis agents) may make it exceedingly difficult to carry out evaluation of effectiveness of such a screening programme at any time in the future. There will obviously be profound reluctance to transfuse unscreened blood as part of a trial when screened blood is available.

I would therefore recommend that we are careful to establish the benefits *before* we become committed to the costs. We must know what improvement in the quality of our blood and blood products we are asking the community to pay for.

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R. Mitchell. At the moment there is no diagnostic test for either the alleged aetiological agent(s) or the alleged disorders of liver function associated with non-A, non-B hepatitis. We have been searching for a serological marker for non-A, non-B hepatitis for almost 3 years. Part of this study [1] included determining the percentage of blood donors with elevated SGPT levels. So far, 1,402 blood donors have been tested with 48 (3.4%) having levels above 35 SF U/ml. However, only 4 (0.3%) of these donors had levels in excess of 125 SF U/ml and all 4 were found to be prisoners.

In the USA, the TTV study [2] and the independent study of *Alter* et al. [3] showed retrospectively that if ALT screening had been performed routinely around 1.6–3.0% of donations would be excluded, with the benefit of preventing 29–40% of non-A, non-B post-transfusion hepatitis cases. However, although the ad hoc committee of the American Association of Blood Banks recently decided against recommending routine ALT testing, the New York Blood Centre plans to implement ALT testing soon [4].

As SGPT-ALT testing has obviously high false-positive and also high false-negative rates, we have no intention of suspending 3% of our volunteer blood donors on the basis of an SGPT-ALT test when they may have only transient elevations. Furthermore, such a policy would discourage donor

recruitment among the few willing to donate for the good of the community and would cause some anxiety in donors and their families when we cannot offer anything more than the argument that non-A, non-B hepatitis may exist. We have been most disturbed by the treatment or lack of treatment for unrelated diseases available to HBsAg positive blood donors and fear that donors with elevated SGPT/ALT levels may suffer the same problems.

We await the development of a specific serological test for non-A, non-B hepatitis. The use of nonspecific tests such as SGPT-ALT can have deep sociological and psychological effects on established blood donors and would necessitate the recruitment of voluntary nonremunerated replacements.

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R. Müller. Test systems aiming at reduction of post-transfusion non-A, non-B hepatitis by routine blood donor screening should comply with two prerequisites: specificity and sensitivity. In the case of ALT screening reason to hope for benefit was based on a test system lacking agent specificity but comprising extremly high sensitivity for parenchymal liver damage, which appears not unreasonable to assume in non-A, non-B hepatitis carriers. ALT testing is a highly sensitive indicator of parenchymal liver damage to various sources, among them non-A, non-B hepatitis agent(s). If every liver cell loses 1/1,000 of its contents the normal plasma ALT level will be doubled. In Germany, the main reasons for elevated ALT activity today, however, are alcohol consumption and obesity. Slightly elevated ALT activities in blood donors therefore are observed so frequently that blood bank services could not cover all the requirements were they to apply a strict upper normal range ALT limit of 22 IU/l.

Lack of agent specificity and reduction of sensitivity for practical purposes are strong arguments against routine ALT screening in blood donors. This comprehension was supported by several previous studies which failed to provide conclusive evidence for a justification of routine donor ALT screening [1, 2]. Two more recent reports, however, have clearly shown a significant association of an elevated ALT level in donor blood and the development of recipient non-A, non-B post-transfusion hepatitis. In both studies the incidence of hepatitis was directly related to the ALT level in blood donors [3, 4].

Of course, ALT screening does not completely prevent transmission of non-A, non-B post-transfusion hepatitis. To some extent

the disease is transmitted by healthy carriers revealing normal ALT activity [5]. The proportion of transfusion associated non-A, non-B hepatits according to case history in 566 serologically proven non-A, non-B hepatitis cases recognized in the Hannover area between 1975 through 1980 rose steadily from 5% in 1975 to 19.2% in 1980 despite the fact that all donors are regularly tested for ALT [6].

Since ALT testing identifies some asymptomatic carriers and a small minority of patients with anicteric acute and chronic non-A, non-B hepatitis who can transmit the agent(s), I feel that screening for ALT in blood donors should not be abandoned. Moreover, transfusion of blood and blood products in Germany is subject to the same regulations applied to the administration of drugs, which appoint a maximum of safety with regard to toxicity and infectivity. Considerering the costs of ALT screening on each unit of blood is therefore minimal compared with the total cost amount which may arise from one case of non-A, non-B post-transfusion hepatitis running a chronic course.

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H.W. Reesink, E.E. Reerink-Brongers. Since all donor blood is screened for HBsAg, post-transfusion hepatitis B (PTH-B) has decreased all over the world. However in the USA an appreciable proportion (1–20%) of recipients of blood or blood products still develop PTH which in 90% of the cases is of the non-A, non-B (NANB) type. This high incidence of PTH-NANB is partly explained by the fact that in the USA blood from paid donors is still widely used; blood from this source is associated with a 4 to 8-fold higher incidence of both PTH-B and PTH-NANB in recipients, than blood from volunteers [1]. Also plasma products notably factor VIII and factor IX concentrates, prepared either from plasma of paid donors or from plasma of unknown origin, possibly collected in countries where viral hepatitis is highly endemic, are associated with a high incidence of PTH-NANB in recipients. In Sweden, a commercial factor VIII concentrate caused hepatitis NANB in 40% of patients, receiving replacement therapy for the first time [2]. However, not only blood may

cause hepatitis NANB. An incidence of 2.2% was found in the USA in hospitalized patients undergoing surgery without blood transfusion [1].

About 20–40% of acute NANB-hepatitis patients show clinical symptoms of the disease. Although the clinical features of acute NANB-hepatitis are relatively mild, as compared to hepatitis B, it is estimated that about 25% of all NANB patients will develop chronic hepatitis or cirrhosis [1, 3, 4].

At present there is no specific test available to detect the infectious NANB virus carrier, but two prospective studies in the USA have shown that donor blood with an increased level of ALT is associated with a statistically higher risk of transmitting PTH-NANB. Exclusion of donors with elevated ALT levels (>2–2.25×SD) would have reduced the incidence of PTH-NANB in those studies with 30–40%. On the other hand 70% of the recipients of blood with an increased ALT level did not develop PTH-NANB, which is not surprising since elevated ALT values may be due to both inflammatory and toxic (alcohol) liver damage. Thus, the price which would have to be paid for such a reduction in PTH is considerable: the increase of costs per donation would be 2–3 US dollars, and moreover 1.5–3% of the donor population would have to be rejected as donor, although the majority of them would probably not transmit PTH-NANB. The resulting 'stigmatization' of these rejected donors is a problem in itself. Because it is not known how many donors, with normal ALT levels at the first screening, will later develop elevated ALT values, the loss of donors in the long run might be even higher and what to do with a donor whose ALT has become normal again? Should he still be considered as a possible NANB carrier?

In the Netherlands PTH is rare. Symptomatic PTH-B as well as PTH-non-B are estimated to occur with an incidence of 0.05–0.1 per 1,000 units of transfused blood. These figures are comparable with those in Sweden [5]. To establish the incidence of PTH-NANB in the Netherlands, a prospective study in 380 recipients of blood was set up [6]. This study showed that 13 (3.4%) recipients developed PTH-NANB with elevated ALT levels but without clinical features of hepatitis. Only 1 recipient had abnormal transaminases longer than 4 months and only 1 of the 38 donors who donated their blood to these 13 patients had a borderline increased ALT level. In another follow-up study of 540 open heart surgery patients, each receiving blood products from about 20 different donors, only four cases of symptomatic non-B hepatitis were found [*Coutinho*, personal commun., 1981].

Apparently in the Netherlands PTH-NANB is less frequent and its course is possibly milder than in the USA.

Which recommendations may now be given for the prevention of PTH-NANB? For practical purposes it is useful to distinguish betweeen areas with a high and with a low incidence of PTH-NANB.

Where the incidence is high the following measures may be considered to reduce PTH-NANB: (1) The usage of blood from paid donors, known to have an increased risk for transmitting PTH, poth for the transfusion of whole blood and the preparation of blood products (notably cellular components and coagulation factor concentrates) should be reduced as much as possible and be replaced by blood from unpaid donors. (2) ALT screening of donor blood, notably from paid

donors, may be introduced until a specific test for diagnosing NANB-hepatitis is available. (3) Standard immunoglobulin (SIG) could be added to the earlier (see 1) mentioned blood products. Some studies have shown the efficacy of this measure; however, more data are required to establish the real value of SIG for the prophylaxis of PTH-NANB.

In areas were the incidence of PTH-NANB is low, the following may be recommended: (1) A national blood transfusion program to provide plasma products (especially coagulation factor concentrates) from local, unpaid donors, known to have a low risk for transmitting PTH, should be instituted and if already present further supported. Once this program is able to meet the requirements, in terms of both quality and quantity, it should include the prohibition of importing, distributing and using products prepared from plasma of donors with an increased risk of transmitting PTH or from plasma of unknown origin, because this has possibly been collected in countries with a high incidence of viral hepatitis. It may be expected that in countries where PTH-NANB is rare, the majority of the population has no immunity against NANB-hepatitis and thus is highly susceptible to infection transmitted by products prepared from 'high risk' plasma. (2) The introduction of ALT screening we do not advocate, when the overall incidence of PTH-NANB is low. It might however be advisable to start prospective trials with the aim to learn the incidence of symptomatic as well as asymptomatic PTH-NANB, and its possible relationship with donor ALT levels. (3) We would not advise either that SIG be added to blood products from local donors as described in '1, the reasion being that the incidence of PTH-NANB is too low to justify this measure and further that SIG prepared from a population with a low attack rate of NANB infections, may not protect against PTH-NANB.

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B. Chataing, J. Ducos, Smilovici C. Trepo. Because of the sources of transfused blood (volunteer but also commercial or community) the incidence of post-transfusion hepatitis (PTH) has always been higher in the USA than in France where only volunteer blood is used.

The magnitude of the problem in the 1950s triggered studies which evaluated the attack rate, the morbidity and long-term sequelae of the disease. Incidence of PTH for example after cardiac surgery ranged from 2 to 20% with 7% of the cases affecting future health [1].

When the wave of enthusiasm associated with the successive breakthroughs following the discovery of Australia antigen passed, it became apparent that the hope of eradicating PTH through increasingly more sensitive and costly screening for HBs Ag would remain in vain. Again this prompted new prospective studies for precise evaluation of the magnitude of the PTH problem, its nature and possible preventive strategy [2]. These investigations provided priceless information of universal value on the existence, natural history and incidence of NANB hepatitis and its overwhelming importance for PTH as well as for public health.

One o the most impressive practical results of the multicenter transfusion transmitted viruses study was to show that blood donors with elevated ALT values carry an excess risk of transmitting NANB hepatitis [2]. Others [3, 4] confirmed this result which had already been suspected more than 20 years ago, thus leading to widespread transaminase screening in Germany.

It was calculated by Alter that 30–40% of PTH cases could be avoided by the rejection of 1.6–3% of units with the higher ALT values.

ALT screening is perfectly standardized and can be tested automatically at a reasonable cost. Furthermore, since there are at least two distinct blood-borne NANB viruses, a nonspecific test might detect both agents as well as some of the few HBs-negative HBV in infection carriers.

The present state of development of specific markers for NANB viruses is still at the research level with all the expected pitfalls [5]. Despite hopes, it will certainly take a minimum of 2–4 more years before the full evaluation and licensing process of future tests will be completed. These future potential screening tests will be more or less sensitive for one or more NANB agent, hopefully for the most common ones. No doubt such tests will then become the method of choice in hepatitis prevention.

One additional merit of PTH studies is that one may no longer comfortably avoid the question of PTH prevention without guilt. We are forced to ask: how should we be using the information that ALT screening can prevent at least half of PTH cases *now?* The answer may well depend on to whom it will be asked to. If asked to the potential blood recipients, they will certainly choose ALT tested blood as long as there is enough of it.

If asked to the budget computer of the national health service the latter will ask for a cost benefit analysis. Blood donors may wonder about the value of their worry without a clear answer on the significance of the finding for their future health. Finally, lawyers may advise potential clients that it is anyway worth a suit. The answers of medical and blood bank experts will certainly not be unanimous as proved in the literature and as this *Vox Sanguinis* forum may confirm.

In fact, it is not evident to decide who has

the ability to judge and take the responsibility. Carefully selected ethics comitees may well have their word to say about it. Meanwhile one may ask what the technical and the financial alternatives of ALT screening are? Is there any better way in the long run for patients and public health to use funds and efforts that one may be ready to devote to ALT screening? Would the money spent be more fruitful if invested in research to speed identification of the etiologic agents of PTH and development of specific serologies?

Post-transfusion studies have also shown [2, 6] that besides ALT elevation the presence of anti-HBc with or without anti-HBs was also associated with an increased attack rate of NANB PTH in recipients.

Cossart et al. [6] estimated that elimination of units positive for markers of postexposure to HBV might reduce the incidence of PTH by up to one-half. One does not know at present whether units of blood with raised ALT are the same as those containing anti-HBc. The task of testing all units of blood for HBs Ag and anti-HBc may appear both overcostly as well as impractical to all blood banks lacking radioimmunoassay facilities (to use the only commercially available anti-HBc test).

Such a policy will undoubtly suggest the replacement of screening for HBs Ag by anti-HBc. A cost benefit analysis of this has been done at the Toulouse Transfusion Service [7], where 51,990 blood donors were tested for both HBs Ag and anti-HBc.

HBs Ag was detected in 0.12% and anti-HBc in 5,38% of the donors.

All 60 HBs Ag-positive units were also detected by anti-HBc. In addition, 0.72% of the donors were found to be positive for anti-HBc alone and (4,54%) for both anti-HBc and anti-HBs. It was calculated that the benefit derived from processing 1.24% of all plasma units with anti-HBs titers $\geq$3 IU would pay for the extra cost of retesting anti-HBc-positive units for anti-HBs.

It remains to be shown whether prevention of additional hepatitis B cases related to 0.72% of anti-HBc-positive units and of up to half of NANB PTH cases is worth the value of 4% of the blood units which would have to be rejected. Preliminary data in screening for anti-HBc in Lyon revealed that the overall prevalence of anti-HBs 4,3% and anti-HBc 0.45% was lower than in Toulouse. At the Lyon Transfusion Service Systematic screening for ALT of 2,000 blood donors revealed elevated values $\geq$45 IU in 3.5% of cases.

Among donors positive for anti-HBc without HBs Ag or anti-HBs we found in 47% of those with normal ALT and 66% of those with elevated values a new antibody by indirect immunofluorescence reacting specifically with liver nuclei of NANB hepatitis patients [8] (presumably similar to anti-HBc for an HB-like form of NANB hepatitis). By contrast in the absence of HBV marker anti-NANBc was detected in 6 and 28% of those with normal and elevated ALT values, respectively.

Key parameters in the decision evaluation process will have to be (1) the epidemiology of PTH (attack rates, prevalence of ALT elevations versus that of anti-HBc with or without anti-HBs; (2) relative needs of blood; (3) cost benefit analysis of ALT versus anti-HBc screening and respective efficiency in reducing PTH; and (4) comparative difficulties necessary to turn each method into practice.

Because major variation of these parameters may be anticipated in different centers

of the world, no rigid policy can be envisioned at the moment without proper information. A major effort should be undertaken in various representative geographic and socioeconomic areas to quickly answer those questions since extrapolation from the USA figures should not be made without a minimum of clinicoserological studies.

Failure to undertake such needed studies should not be considered as a valid alternative to ALT screening.

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Erratum

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