ALANINE AMINOTRANSFERASE (ALT) TESTING OF BLOOD DONORS IN THE U.S.

Report of a meeting held on January 9, 1981

Present: Drs. Barker, Sandler, O'Malley, Dodd, Becker, Katz, and Miller (American Red Cross), Pindyck and Szmuness (New York Blood Center, CCBC), Bove and Zuck (AABB), Donohue and Gerety (BoB) and Alter (NIH)

Observing: Dr. Sherman, Ms. Anderson, Ms. Ni, and Dr. Tabor

INTRODUCTION:

Dr. Barker opened the meeting at 10:30 a.m. He defined the purpose of the meeting which was to:

(1) review current data relating donor ALT levels to the transmission of non-A, non-B hepatitis, and data on the distribution of ALT levels among blood donors;

(2) determine what action, if any, should be taken on the basis of these data;

(3) develop guidelines for communications and further actions based upon the results of tne meeting.

PRESENTATION OF DATA:

A considerable amount of original data was distributed and discussed in detail. For the purposes of this report, the salient points will be summarized briefly.

The TTV Study:

Dr. Szmuness outlined the structure and function of the TTV (Tranfusion Transmitted Virus Study). Twelve hundred and fifty two blood recipients were entered into the study and were carefully evaluated for post-transfusion hepatitis for a period of fourteen weeks following transfusion. Hepatitis was defined on the basis of two consecutive enzyme elevations not more than 17 days apart. At least one of those elevations had to be greater than 90 international units/liter (IU/L). During the

study, a total of 134 non-A, non-B hepatitis cases were observed with an overall attack rate of 10.7%. This attack rate was strongly associated with donor ALT levels, reaching 50% among recipients of at least one blood unit with an ALT level greater than 60 IU/L. This relationship also held amongst recipients of single unit transfusions. Finally, of the eleven recipients of more than one unit with elevated ALT, ten developed non-A, non-B hepatitis. Overall, the study concluded that elimination of donations with ALT levels greater than 45 IU/L would result in a 40% reduction in non-A, non-B post-transfusion hepatitis. The proportion of donors with ALT greater than 45 IU/L was 3% overall. This proportion varied widely from region to region with a low of 1.4% in St. Louis and a high of 5.8% in Houston.

NIH Study:

Dr. Alter presented the results of a continuing post-transfusion hepatitis study, carried out in the clinical center at NIH. In his study, the non-A, non-B hepatitis attack rate was approximately 12.7%. There was a very clear increase in attack rate among recipients of at least one unit of blood with ALT levels greater than 2.25 standard deviations above the mean.

The mean and standard deviation were defined on the basis of a log-normal distribution of ALT levels, reflecting the known distribution of such values in normal populations. The data were also normalized for transfusion volume, and it was similarly concluded that rejection of donors with elevated ALT levels would result in a significant reduction in the incidence of post-transfusion non-A, non-B hepatitis. In contrast to the fixed value of 45 IU/L used by the TTV group, Dr. Alter recommended a statistical cutoff, selecting the value of 2.25 standard deviations from the mean. On the basis of his studies, this limit would exclude about 1.6% of donations and would be expected to reduce post-transfusion

hepatitis non-A, non-B by 42%.

Red Cross Study:

Dr. Dodd presented preliminary data on a study designed to evaluate the distribution and significance of ALT levels in geographically representative Red Cross Blood Services' regions. The population distribution of ALT levels was log-normal. Values obtained in this study were not strictly comparable to those found by the TTV gouup, since a different test methodology was used. However, for the purposes of analysis, an elevated ALT was defined as one greater than 45 IU/L (approximately equivalent to 41 IU/L in the TTV study). It was clear that there was considerable variation from region to region with a range of 2.48% (Madison, WI) to 5.63% (Birmingham, AL) of donors with elevated ALT levels. An alternate way of looking at these data is that the upper limit of normal is variable from region to region. Data were also presented to show significant variation between males and females and a peak of ALT elevation in the 25-35 year age group. Certain ethnic minorities were more frequent among donors with elevated ALT. An analysis of post-transfusion reporting to individual Red Cross centers indicated that approximately 600-700 post-transfusion cases are recognized and reported to the Red Coss each year. Of these, 27% were diagnosed as hepatitis B.

St. Louis Donor Study:

Dr. Miller presented data on 12,000 consecutive donors to the St. Louis region. The distribution of ALT levels was substantially similar to that described by Dr. Dodd, as were the significant risk factors associated with ALT elevations. A point of specific interest was the high frequency of chronicity of these elevations: approximately 60% of donors with ALT levels greater than 60 IU/L were also found to have elevated levels on subsequent occasions.

Finally, Dr. Zuck presented data indicating the extreme variation of test results between different methodologies.

DESIRABILITY OF DONOR TESTING:

Dr. Barker summarized the post-transfusion data by pointing out that it appeared that the introduction of donor screening would be likely to reduce the attack rate for post-transfusion non-A, non-B hepatitis by at least one-third. The participants agreed to reject the possibility of ignoring the data and to discuss the alternative positions that: a policy of testing ALT levels for all donor bloods be introduced or, that there was insufficient data at present and further studies were necessary to evaluate the consequences of universal testing.

Discussion first focused on the severity of the disease in question. It was recognized that the data presented at this point had related only to transaminase elevations in blood recipients. Participants in the post-transfusion studies indicated that approximately 25% of all such cases were defined as clinical and furthermore that 50-60% of all post-transfusion ALT elevations were chronic, lasting at least six months. A proportion of chronic post-transfusion non-A, non-B hepatitis cases involved significant liver pathology reflecting chronic active hepatitis and in a small number of cases, cirrhosis. On the basis of the post-transfusion data presented, it appeared that there could be as many as 300,000 cases of post-transfusion hepatitis annually in the United States.

Of these, it was felt that perhaps 15,000 might be sufficiently ill to be hospitalized. Thus, introduction of donor screening migh be expected to prevent 5,000 serious cases of hepatitis annually. It was not clear to what extent a reduction in chronic sequelae such as cirrhosis might be achieved. The other aspect of this argument was the relatively small number of clinical cases reported to Red Cross regions each year. It was, however, widely recognized that post-transfusion hepatitis is seriously

under-reported.

At this point, the discussion turned to the broader implications of introducting ALT testing of blood donors. The first issue was the advisability of introducing a non-specific test when a specific serologic test might shortly become available. Overall, the perception of the meeting was that, even if a specific marker for carriers of non-A, non-B hepatitis were recognized, it could take as long as two years to bring it to the marketplace.

Discussion then turned to donors who will be found to have elevated ALT levels. It was recognized that not only was it hard to define a level of abnormality appropriate to the rejection of unsuitable blood units, but is was also extremely difficult to define a level of abnormality which would reflect a potential health problem to the donor. Furthermore, at this time, it was not possible to decide whether to defer a donor from future donations on the basis of a single elevated ALT level. The consensus of the meeting was that a great deal more information needed to be developed before policies relating to the handling of ALT elevated donors could be resolved.

There was some discussion of the cost of performing ALT testing in the blood center environment. Dr. Pindyck had arrived at an overall figure of $1.50-2.00 per test, including equipment, supplies, staff, loss of blood, recordkeeping and disposal costs. It was agreed that other hidden costs would emerge. An example of such a hidden cost would be the need to recruit additional donors. Dr. Dodd presented data that the overall cost of performing such testing within the Red Cross would also be $1.50-2.00 per unit. With the preliminary information available, the costs of preventing one serious case of post-transfusion non-A, non-B hepatitis was estimated to be roughly $3000-4000 (5000 prevented into $15-20 x 10^6).

POLICY ON TESTING

Although it was felt that many issues remained to be resolved, the meeting returned to discussion of whether ALT testing of blood donors should be adopted or whether more data was required before making such a decision. It was first of all agreed that the data which had been presented could not be questioned. Furthermore, it was agreed that it would no longer be ethical to perform controlled studies on the effects of exclusion of donor blood with elevated ALT. There was a certain amount of concern about the effect of ALT testing upon the ability to provide an adequate blood resource and of the effects on the cost of health care. Dr. Szmuness expressed the opinion that it would be wise to perform more studies on the effects of introducing ALT testing, particularly with respect to the donor population and further, that additional risk factors possibly associated with the transmission of non-A, non-B hepatitis remained to be analyzed. Despite these concerns, the participants agreed that there was evidence that the introduction of ALT testing would reduce the incidence of post-transfusion non-A, non-B hepatitis.

GUIDELINES FOR TESTING

Dr. Zuck felt that it was extremely important to provide the blood banking community with appropriate guidelines for performing testing. Furthermore, considerable guidance would be necessary to establish cutoff limits for rejection of blood units. A working group was recommended to provide such guidelines (Drs. Zuck, Alter, Szmuness, Pindyck, Kahn (St. Louis), and Dodd, plus a statistician to be named).

JOINT STATEMENT

It was agreed that a statement of the consensus of the meeting should be developed along the following lines:

"A solid body of evidence indicates that recipients of blood with significantly elevated ALT levels are at increased risk of developing post-transfusion hepatitis. Blood collection agencies in the U.S. should prepare to test ALT levels of all blood units, and to avoid transfusion of those with significantly elevated levels of this enzyme. The agencies should inform and advise donors with elevated ALT levels on a selective basis, the criteria for which are yet to be developed. A working group will provide guidance on standardization of test methodologies and cutoff levels."

Finally, it was agreed that it would be desirable to prepare a sounding board article to be submitted to the New England Journal of Medicine. This article would relate to the published TTV data and would deal with the implications of ALT testing and would address many of the concerns which have been raised at this meeting.

Dr. Barker thanked the participants and closed the meeting at 3:30 p.m.

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