The New England Journal of Medicine

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NOTICES should be received not later than noon on Monday, 24 days before date of publication.

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POST-TRANSFUSION VIRAL HEPATITIS AND THE TTVS

FROM the mid-1940s until the 1960s, studies of post-transfusion viral hepatitis focused on prevention by immune serum globulin. The value of globulin in transfusion hepatitis is still to be determined.[1] However, investigations of such prophylaxis provided an important source of information about the risk of post-transfusion hepatitis in the United States during that period. By the early 1970s, it was evident that a system of surveillance was needed for continued monitoring of the rate of post-transfusion disease. Recognition of the increased hazards associated with paid blood donors had led to a decreased use of commercial blood banks as a source of blood.[2] In addition, donor screening with the initial tests for hepatitis B surface antigen had reduced the incidence of transfusion-transmitted Type B hepatitis; a further reduction was anticipated when more sensitive methods to detect hepatitis B virus carriers among donors became available.[3]

In 1973, the Division of Blood Diseases and Resources of the National Heart, Lung, and Blood Institute sought to assess the incidence and cause of post-transfusion viral hepatitis and to evaluate additional means to decrease its risk. Their request for proposals led to the Transfusion-Transmitted Viruses Study (TTVS). This project prospectively monitored recipients of blood, as well as controls not receiving transfusions, at institutions in four cities during the period from July 1974 through November 1979. The foresight of establishing such a study is evident from the data presented so far.[4-6] A broad picture of the risks of viral hepatitis associated with hospitalization and with transfusions is now available for this five-year period. One wonders whether comparable surveillance will be performed in the 1980s.

An important additional goal of the TTVS was to evaluate laboratory methods for identifying carriers of viral hepatitis among blood donors. The study examined the usefulness of currently available tests and of tests just emerging from research laboratories. It had been anticipated that more sensitive assays to identify carriers of hepatitis B virus would have to be sought. The priorities changed, however, with the realization that non-A,non-B hepatitis was the most frequent cause of transfusion-associated hepatitis. Without specific markers of non-A,non-B hepatitis virus or viruses, the emphasis on carrier detection switched to nonspecific indicators of hepatic dysfunction.

In this issue of the *Journal*, members of the TTVS Group present the best evidence to date that blood donors with elevated serum alanine aminotransferase (ALT) levels have a significantly increased likelihood of transmitting non-A,non-B hepatitis. One of the primary conclusions of this study is that 40 per cent of the non-A,non-B post-transfusion hepatitis could have been prevented by discarding units with an ALT

value in the upper 3 per cent of the distribution (i.e., ALT ≥45 IU). This calculation presupposes that the unit with the elevated ALT level was the one that caused the hepatitis. In those who acquired hepatitis after receiving several units of blood of which one unit had an elevated ALT, the hepatitis might have been caused by a unit without an elevated ALT. Indeed, 7 per cent of the multi-transfused patients who received only blood with an ALT below 45 IU became infected with hepatitis.

Not all units with an elevated ALT were found to be infectious. Actually, 63 per cent of the patients (100 of 160) who received a unit of blood with an elevated ALT did not acquire hepatitis. Although we have no way of knowing the immunity of the recipient population to non-A,non-B hepatitis, it is clear that a variety of conditions other than a carrier state for non-A,non-B hepatitis can lead to moderately elevated ALT levels in blood donors.

Discarding donor blood with an ALT above 44 IU would require replacing it with units with ALTs of 44 IU or lower, which, despite their normal ALT, would have a 5.3 per cent chance of carrying hepatitis. Thus, the predicted efficacy of ALT screening in hepatitis prevention needs to be modified. Data on the patients who received single units of blood in the TTVS suggest that 21 per cent of the hepatitis would have been prevented by replacement of the elevated-ALT unit with one with an ALT below 45 IU. As shown in Table 3 of the paper, 12 recipients of single units received blood with an elevated ALT, and five contracted hepatitis. Since one recipient would probably have contracted the disease even if the blood had a "normal" ALT, exclusion of donors with elevated ALT levels would have prevented only four cases of hepatitis. This figure represents only 21 per cent of the 19 hepatitis cases in the group receiving single units.

Nonetheless, screening blood donors with the ALT test appears to be a promising way to decrease the risk of post-transfusion hepatitis: at least 21 per cent of the cases of transfusion-associated hepatitis might be prevented, with a loss of 3 per cent of the donor population. Another independently conducted, although smaller, study led to a similar conclusion.[7] The question is whether ALT testing of all blood donors should become routine. Is the expected benefit to the patient worth the drawbacks, especially to the donors and to the blood-service complex? In other words, what is the practicality of setting up ALT testing, and what is its impact? A number of questions have to be answered before adoption of the ALT test is to be recommended: How can the test be made uniform from one blood bank to the next? Above what level should donors be excluded? What should they be told when rejected, and should they be rejected permanently? Blood banks would have to add the cost of ALT testing to the cost of blood and recruit more donors to replace those rejected. Physicians would be asked to see patients with "transaminitis"; for most, the cause would not be evident, nor would a treatment be forthcoming; hence there would be no means available to allay the apprehensions of these rejected donors. When compared with the test of hepatitis B surface antigen to detect carriers of hepatitis B, the ALT test is nonspecific and would eliminate 10 to 20 times more blood donors. The manifold effects of ALT testing must be thoroughly considered before there is widespread adoption of such an interim measure (to be used until specific tests for non-A,non-B viruses become available).

A third aspect of the TTVS is worthy of note. It was recognized that delays are inevitable when "new" hepatitis tests are used to screen blood donors because of questions about benefit and cost. It was appreciated that the same situation would probably recur as each new hepatitis-screening test became available. The Division of Blood Disease and Resources stipulated, therefore, that the TTVS save aliquots of each serial blood sample from each patient as well as each donor. Over 1500 recipients and a comparable number of nontransfused controls are represented by an average of 11 specimens each; about 5000 donors are represented by an aliquot of the donated blood. These serums are stored in a repository and are available to the scientific community.

The TTVS ended before confirming the value of any of the recently described serologic techniques for identifying carriers of non-A,non-B viral agents.[8-10] The most immediate application of the well-documented TTVS samples, therefore, will be in evaluations of such potential tests for carriers of non-A, non-B virus. Valuable as this foreseeable use will be, attention should also be called to less obvious ones. There has been speculation about the transmission by transfusion of oncogenic viruses and of agents that are possibly responsible for chronic degenerative disorders. It was this long-term potential usefulness, beyond issues of viral hepatitis, that led the investigators involved to adopt the broad designation of the Transfusion-Transmitted Viruses Study.

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HUMORAL HEARTACHE — DO PLATELETS HAVE A ROLE?

THE possible causes of angina pectoris have intrigued physicians and their patients since the first descriptions of this disorder. Early investigators, including Sir William Osler,[1] postulated that contraction of coronary arteries ("spasm" in modern terminology) might cause an imbalance between myocardial oxygen supply and demand. The subsequent demonstration that most patients with angina pectoris had diseased, stenotic coronary arteries led to the alternative hypothesis that blood supply was fixed and that myocardial demand was the more important variable. Angina pectoris would then occur when the myocardial demand for oxygen exceeded that which could be delivered across a stenotic coronary artery. We may now have come full circle; evidence is accumulating that transient decreases in blood flow may be an important cause of myocardial ischemia and angina pectoris.

Decreased flow could result from obstruction of stenotic vessels by platelet plugs. Indeed, the work of Folts et al.[2] has demonstrated that platelet aggregates do form when the coronary artery is partly occluded in dogs, and that the buildup of platelet aggregates and their subsequent dissolution produces phasic changes in coronary blood flow. In addition, systemic infusion of catecholamines, adenosine diphosphate, or thrombin can induce platelet aggregation and myocardial ischemia in animals in which coronary anatomy is normal.[3] There is also some autopsy evidence that platelets are involved in cardiac events in human beings. Patients who have died suddenly, presumably from arrhythmias or myocardial ischemia, frequently have platelet emboli in the coronary microcirculation.[4] A more direct demonstration that platelets occlude the coronary arteries and thereby cause ischemia in patients is not yet available, although circulating platelet aggregates and increased concentrations of secreted platelet proteins have been noted in the blood of patients with ischemia or infarction.[5,6]

The possibility that platelets contribute to the ischemic complications of coronary heart disease is so appealing that a number of large clinical trials of antiplatelet therapy have been undertaken. In fact, the cardiologist has been forced to develop acronyms to help catalogue these studies, and the pages of the *Journal* have contained references to PARIS I (Persantine Aspirin Reinfarction Study), PARIS II, and AMIS (Anturane Myocardial Infarction Study). Although the data are not yet conclusive, cardiologists prescribe antiplatelet drugs for their patients and themselves in the hope that they may ameliorate myocardial ischemia and prevent infarction.

Vascular spasm, another potential cause of reduced coronary blood flow, could occur in normal or partially occluded vessels. The clinical syndrome of angina at rest, ST-segment elevation, and spasm of normal coronary arteries (often referred to as Prinzmetal's variant angina) represents only one end of a broad spectrum. Maseri and his colleagues have emphasized that angina at rest can be accompanied by variable ST-segment and T-wave changes and may be due to spasm that is superimposed on a fixed stenotic lesion.[7] These intriguing clinical observations have led to a resurgence of interest in the possible causes of spasm. An altered sensitivity of the coronary arteries to vasoconstrictor stimuli, an increased concentration of vasoconstrictor, or alternatively, a decrease in the concentration of vasodilators in the coronary circulation have all been considered as explanations of spasm.

Some relatively new information about the biochemistry and physiology of short-lived mediators produced by the metabolism of arachidonic acid within platelets and cells of the vessel wall has opened up an exciting new area for clinical investigation.[8] After activation, platelets release arachidonic acid from membrane phospholipids and convert it to an unstable derivative, thromboxane A_2, which then causes both vasoconstriction and platelet aggregation. Endothelial cells also convert arachidonic acid or an unstable endoperoxide precursor released by platelets into prostaglandin I_2 (prostacyclin), which is a potent vasodilator and inhibitor of platelet aggregation. The balanced production of these two compounds is thought to regulate blood fluidity and vascular tone in the microcirculation.

These compounds are known to have potent biologic effects in vitro, but their in vivo effects are hard to discern, since they are short-lived local regulators. After their release by the platelet or the vessel wall, they are rapidly transformed by nonenzymatic chemical rearrangements into stable but inactive derivatives. The advent of radioimmunoassays for the stable derivatives thromboxane B_2 and 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$), coupled with the elegant coronary-blood sampling techniques available in the cardiac catheterization laboratory, has permitted in-