CLINICAL SECTION

Discussion on
TRANSFUSION OF PLATELETS AND PLATELET SUBSTITUTES

Participants:
William J. Harrington, Washington University School of Medicine,
St. Louis, Missouri.
Carl H. Smith, Cornell University Medical College, New York, New York.
Eugene P. Cronkite, Brookhaven National Laboratory,
Upton, Long Island, New York.
C. Lockhard Conley, Johns Hopkins University Medical School,
Baltimore, Maryland.
Frank H. Gardner, Peter Bent Brigham Hospital, Boston, Massachusetts.

Moderator:
Leandro M. Tocantins, Jefferson Medical College,

Tocantins: Blood transfusions directly from donor to the thrombocytopenic patient earned the reputation of being effective as a hemostatic measure even before citrated blood was introduced in the early twenties. Later, it was discovered that when blood was stored it lost some of this property. In the last few years, it has even been shown that platelet-poor stored blood, if given in large amounts, may indeed help to disrupt hemostasis and maintain bleeding by replacing or diluting the platelet-bearing patient's blood. This has driven some workers to return to the direct methods of transfusing blood, made easier today by plastic and silicone surfaces.

There is little doubt that much of the hemostatic effect of unmodified blood is due to its content of fresh intact platelets. It was logical, therefore, that attempts should be made to: (a) prepare concentrates of such platelets and thereby avoid the necessity of injecting large amounts of whole blood, (b) preserve such concentrates and have them available at once when needed and (c) develop substitutes obtained from animal, vegetable or synthetic sources, capable of duplicating the action of platelets.

How far we have succeeded in these objectives and where any of the now available technics fit in the control of excessive hemorrhage are still matters of dispute. A group of workers active in this field has been asked to discuss these and other points. We shall begin by asking: In which situations do you feel that transfusion of platelets is useful?

Harrington: By "platelet transfusion" we understand the administration of viable platelets capable of recirculation for six to eight days in the absence of adverse environmental factors. Platelet transfusions are most commonly useful when impaired platelet production determines the thrombocytopenia,
the projected duration of need is less than two months, the candidate's direct platelet count is less than 20,000/mm.³ and abnormal bleeding uncontrollable by steroids is in evidence. Examples within this framework are some instances of leukemia, marrow injury from radiotherapy or other antimitotic agents and acute aplasia of the marrow due to any cause.

In addition are cases of autoimmune thrombocytopenia due to certain drugs or chemicals wherein even prompt recognition and discontinuance of exposure to the causative agent leaves a period of four to seven days for regeneration of platelet levels. Only in this interval of recovery would infusion of viable platelets be warranted. A final and increasingly recognized example is thrombocytopenia associated with massive blood transfusions of bank blood.

Platelet transfusions have very limited value in most instances of idiopathic thrombocytopenia, in thrombotic thrombocytopenia and in cases wherein iso-immunization to platelets has resulted from prior transfusions. They may or may not be beneficial when splenomegaly is a factor.

Smith: In our laboratory, transfusions of platelet concentrates or extracts have not been used. In situations where the administration of whole, viable platelets has been desired, fresh whole blood collected in plastic bags or in siliconized apparatus has been employed. In those situations where the administration of the erythrocytes has not been necessary or desirable, the platelet-rich plasma from a bottle of fresh blood, collected as above and centrifuged at low speed, has been employed.

The use of “platelet-rich” transfusions has been reserved for thrombocytopenic hemorrhage in which there is significant external blood loss (epistaxis, hematuria, melena) or where the general bleeding tendency appears so active that intracranial hemorrhage is threatened. Purpura alone has not been considered an indication for platelet-rich transfusion.

Cronkite: I feel that transfusion of separated platelets, platelet-rich plasma or fresh blood is useful in the thrombopenias due to temporary hypoplasia of the bone marrow.

Conley: Transfusion of platelets may be useful as a temporary measure in critical emergencies in which serious bleeding is the result of thrombocytopenia. When large numbers of fresh platelets are administered the platelet count may be transiently elevated to levels at which abnormal bleeding is lessened, provided that there is no abnormal mechanism producing rapid elimination of platelets in the recipient. The enormous numbers of platelets required, their relatively short survival time and the likelihood of the development of refractoriness to transfused platelets limit the usefulness of platelet transfusions for the prolonged treatment of thrombocytopenic states.

When blood transfusions are required to correct anemia in patients who have severe thrombocytopenia, it is wise to use fresh blood containing viable platelets. If stored blood containing nonviable platelets is administered to thrombocytopenic patients, the recipient’s platelets are further diluted, with the result that bleeding may be enhanced. This is particularly likely to occur if several transfusions of stored blood are given.

Gardner: We have used platelet transfusions only to control bleeding resulting from thrombocytopenia: (1) as preparation for surgery. Thrombocy-
topenia associated with congestive splenomegaly may be controlled prior to porto-caval shunting procedures. (2) Control of thrombocytopenia in patients with I.T.P. who have not responded to corticoid therapy prior to splenectomy. (3) Elective surgery in any patient with thrombocytopenia. Platelet transfusions are helpful to terminate menorrhagia in thrombocytopenic women until hormonal control of uterine bleeding can be initiated.

Tocantins: Since there is general agreement regarding the usefulness of transfusion of platelets to control excessive bleeding of the thrombocytopenic type, what, in your judgment, is the most practical and effective method of transfusing platelets?

Harrington: Donors are selected in advance by routine determination of compatibility with the prospective recipient. Whole blood is collected rapidly through a free-flowing venepuncture into nonwettable equipment containing disodium ethylenediamine tetraacetic acid, with care to assure adequate mixing in the process. The donation is then promptly infused through a #18-gauge needle. Less satisfactory but usable are uncoated glass bottles containing other anticoagulants. In all collections, foaming must be avoided; therefore, vacuum bottles are undesirable. Donors with thrombocytosis are most suitable. If normal subjects are employed, two or three units of blood may be necessary to provide an adequate platelet yield. Venections may then be required coincident with the transfusions to avert circulatory overload in the recipient.

Smith: The most practical method has been the collection of fresh blood into plastic or siliconized containers. Blood so collected is ordinarily administered immediately after collection. To obtain platelet-rich plasma, the bottle or bag is centrifuged slowly and the platelet-rich plasma transferred via siliconized tubing to a second plastic bag or siliconized bottle.

Cronkite: As long as red cells are also needed, fresh whole EDTA or ACD blood is the best. When platelets only are needed, the best and most practical method is the preparation of platelet-rich plasma with the plastic bag technic (the Fenwal bags and technic are satisfactory), using 1 per cent Na₂ EDTA in 0.7 per cent NaCl as the anticoagulant. In the International refrigerated centrifuge #PR2, approximately one hour centrifugation at 50 x g gives a good yield of platelet-rich plasma. The plasma is squeezed out into another bag by the Fenwal device in a closed system and the platelet-rich plasma immediately administered.

Conley: The simplest and most economical means of transfusing platelets is by giving whole blood immediately following its withdrawal from the donor and without intervening refrigeration. Platelets are rapidly eliminated if even a small amount of clotting occurs during the collection of the blood. The use of plastic or silicone-treated equipment lessens the likelihood of this occurrence. The volume of blood required to produce the desired increase in the platelet count may be roughly calculated from an estimation of the recipient's blood volume and platelet count and the platelet count of the donor blood. In practice, the theoretical value is rarely achieved, presumably because of the rapid utilization or elimination of some of the transfused platelets. Blood obtained from donors with unusually high platelet counts, as from patients with polycythemia vera, can be used to advantage. In situations in
which it is undesirable to administer large amounts of red cells, platelet-rich plasma may be separated from the fresh blood by differential centrifugation. This procedure is readily and simply accomplished, with no hazard of contamination, if plastic bags and a centrifuge large enough to accommodate them are employed. Any attempt to separate platelets inevitably results in a considerable loss so that the net yield is substantially less than if whole blood is transfused. Furthermore, manipulation of the platelets tends to shorten their survival time and thus to lessen their therapeutic efficacy. It is possible by centrifugation technics to produce platelet preparations of very high concentration. There appears to be no advantage of such preparations at present, however, because of the loss of platelets in preparation and the decrease in their viability as a result of this procedure.

Gardner: When thrombocytopenia is associated with massive blood loss, whole blood collected in ACD is adequate to provide viable platelets. If blood volume replacement does not require whole blood, collections are obtained using sodium versenate as the anticoagulant. Platelet-rich plasma and platelet concentrates are prepared by differential centrifugation at 4°C. Platelets tend to go into irreversible clumping in citrate-dextrose solution and cannot be resuspended after centrifugation. For maximum yield in the recipient, platelets should be handled in plastic bag equipment and reinfused within four to six hours after collection from the donor.

Tocantins: Stickiness, agglutinability and rapidity of disintegration are properties of platelets which we all have come to regard as inseparable from their ability to behave as efficient hemostatic agents. They are, however, the very properties which are difficult to preserve intact so that they may be exerted in the bleeding area. Most of the members of the panel stress the importance of having fresh blood swiftly collected, on neutral surfaces, and promptly given to the patient. The logistics obstacles that this creates make us all wonder how much of these desirable properties are lost by storage and methods of preservation. Do you believe aged (greater than one day) platelets preserve their ability to induce hemostasis? If so, which functions of platelets do you consider are preserved and what methods are best for maintaining them? Please describe briefly the methods and solutions which you consider most suitable to preserve platelets.

Cronkite: I believe platelets lose their capacity to induce hemostasis within a few hours and that platelets greater than one day of age are essentially useless for effective therapy.

Gardner: Platelets maintained at 4°C. in ACD for 24 to 48 hours have clot-retracting ability. Such stored platelets will have an abbreviated life span in the recipient. Clot retraction is the most physiologic measurement to follow in any preservation technic. At the present time, our laboratory has no suitable procedure to store platelets, since the yield of viable platelets in the recipient is markedly diminished.

Conley: When blood is stored, as in a blood bank, there is rapid and progressive loss of the viability of the platelets as measured by their ability to raise the platelet count of the thrombocytopenic recipient and by their effectiveness in improving hemostasis. Extensive studies of this phenomenon by Jack-
son and Krevans at The Johns Hopkins Hospital have shown that in dogs and man there is an easily measurable loss of platelet viability after blood has been stored in plastic bags under blood bank conditions for 24 hours. This loss is increased at 48 hours, and by the end of one week, few viable platelets remain. At a time when stored blood is ineffective in even momentarily raising the platelet count of thrombocytopenic recipients, such blood may have a normal platelet count, the platelets may enhance thromboplastin generation and prothrombin utilization at a normal rate, and even clot retraction may be preserved. It is clear that these in vitro platelet activities do not correlate well with the viability of platelets as measured by their ability to circulate when transfused. In blood stored for a relatively brief period, i.e., 48 hours, the platelet count, clot-accelerating function and clot-retracting activity are not appreciably lessened. When such blood is transfused the platelet count of the recipient may be transiently increased, but the concentration of circulating platelets falls over a period of hours. Thus, the platelets are viable, but their life span is greatly shortened by this brief period of storage. There is confusion concerning the term “preservation” of platelets because of the different criteria employed by investigators to determine whether stored platelets have “survived.” At this time there appears to be no method suitable for clinical use for preserving platelets, so that, when transfused, the platelets will have a normal or near normal life span in the circulation of the recipient. The problem is one which is currently being studied by a number of investigators.

Smith: A small experience indicates that aged platelets have the ability to induce hemostasis in certain cases of bleeding but not in others. Clot retraction properties are lost rapidly, but thromboplastic function, thrombin-fibrinogen accelerator function and some labile factor-like and antiheparin functions appear to be relatively stable in the aged platelets and platelet fragments (in vitro). The effectiveness of these aged platelets, we believe, will be analogous to the effectiveness of lipid preparations, and it is necessary to know the sites and degree of hemorrhage as well as the amounts of “aged platelets” or cephalin given, frequency of administration, etc.

Harrington: Platelets stored more than one day are regularly nonviable and exert hemostatic effects only during their infusion. Improvement of vascular integrity and coagulability of the blood are possible. For the preservation of platelet viability, nonwettable equipment containing ethylenediamine tetraacetic acid, as noted above, has proved best in our hands but still limits storage to one day. I have had no experience with devices or manipulations purported to decrease storage lability of other properties of platelets.

Tocantins: Even though most of us will agree that certain platelet preparations are effective as hemostatic agents, we have difficulty in quantitating this effect to our satisfaction. There has been much uncritical work on this point, and we are anxious to know how the members of the panel feel about it. What criteria do you employ for judging the effectiveness of platelet preparations?

Conley: Consideration of this question requires a definition of the term “effectiveness.” Platelet preparations and platelet extracts prepared and stored
in a variety of ways maintain their effectiveness in the thromboplastin generation test for long periods of time. If one employs ability to produce clot retraction as a measure of effectiveness, then the conditions of preparation must be much less harsh and the time of storage shortened. If one is interested in the therapeutic effectiveness of platelet preparations, the only simple, objective and reliable measurement is the extent and duration of the increase in platelet count produced by the preparation. In the study of a single patient or of small groups of patients, apparent alterations in hemostasis cannot be used as a measure of the therapeutic effectiveness of a platelet preparation, since variations in degree of bleeding and capillary fragility occur so unpredictably without relation to therapy. The hemostatic effects of such preparations can be studied statistically in a large group of patients provided that appropriate controls are used. Demonstration that the administration of a platelet preparation enhances "prothrombin consumption" does not mean a priori that hemostasis is necessarily improved.

Gardner: Platelet preparations are of value if they will show improvement of the bleeding time and clot retraction in the recipient. Measurements of thromboplastic activity do not necessarily indicate hemostatic function.

Cronkite: The effectiveness of platelet preparations is best assayed in animals by a combination of: (a) the ability of the platelets to circulate in the irradiated thrombopenic recipient; (b) their effectiveness in reducing the outflow of red cells in the thoracic duct of the irradiated thrombopenic dog; (c) their effectiveness in preventing bleeding of the irradiated dog or rat as demonstrated by comparison of the histologic appearance of the lymph nodes of irradiated control animals, animals irradiated and given fresh blood transfusions and those irradiated and given transfusion of the preparation for evaluation; (d) their effectiveness in preventing decrease in hematocrit; (e) their effectiveness in preventing hematomata at site of minor trauma in animals with aplastic marrow.

In patients one can use items a, d and e, capillary fragility and apparent clinical cessation of bleeding. Coagulation tests often improve after transfusion of platelets and platelet fractions that are ineffective when compared to fresh platelets, using the above criteria.

Harrington: A significant elevation of the platelet count is the desired and most unequivocal criterion of effectiveness. Other indices must also be employed but are more capricious: amelioration of purpura, shortening of the bleeding time (Ivy) and decrease in capillary fragility. Spontaneous fluctuation in severity of the hemorrhagic manifestations, unaccompanied by parallel changes in platelet level, are well recognized.

Smith: To date we have judged the effectiveness of platelet-rich blood or cephalin by their ability to halt obvious hemorrhage (epistaxis, melena, hematuria). With platelet-rich blood we expect to see evidence of improvement in six hours; with cephalin which is administered by steady drip usually within twelve hours. We have not been impressed with the usefulness of laboratory determinations in evaluating the effectiveness of a "platelet" preparation. In certain instances we have noted marked improvement in gross bleeding with no evidence of improved prothrombin consumption or clot retraction.
By contrast we have also noted apparent failure to obtain lessening of bleeding, while the laboratory tests have been markedly improved. We have been led to postulate that platelets or platelet substitutes may leave the circulation at the site of hemorrhage, thus causing improvement in bleeding with no change in in vitro tests. Dosage is a major consideration here.

Tocantins: When using platelet preparations, one important complication to avoid is the production of a systemic reaction. This may often have adverse effects on a patient who is already bleeding. There have been reports of severe local and constitutional reactions following the administration of such preparations, and reports of the development of antibodies against platelets through continued use of them. What is the experience of this group regarding these two points, namely, the occurrence of adverse reactions, immediate or delayed, and the development of platelet antibodies after repeated platelet transfusions?

Gardner: No serious reactions have been encountered with platelet preparations. In two instances transient flushing has been noted in recipients who destroyed all the transfused platelets. The vasodilatation was attributed to rapid platelet lysis, for in both instances the recipients had been "immunized" with multiple platelet transfusions. No platelet antibodies have been found in any patient with a rapid destruction of transfused platelets. Platelet antibodies have not been found in recipients who have demonstrated progressive shortening of Cr\textsuperscript{51}-labelled platelets after multiple transfusions. The frequent onset of a shortened life span after multiple transfusions emphasizes the need for limitation of platelet infusions.

Harrington: In recipients with auto- or isoantibodies for platelets, the transfusions are occasionally followed by low grade febrile reactions and rarely by shaking chills and high fever. With repeated, spaced transfusions of viable platelets isoantibodies regularly develop. When nonviable platelets are administered, isoimmunization develops more slowly.

Conley: Our experience has been limited to the use of fresh whole blood or fresh platelet-rich plasma and no reactions have been encountered. Some patients who have received transfusions are refractory in that the platelet count cannot be elevated by the infusion of even enormous quantities of platelets. Several investigators have demonstrated that small amounts of the plasma of these patients will produce severe thrombocytopenia when injected into normal recipients. It seems likely that the antiplatelet substance in the plasma of these patients is in the nature of an antibody. In view of the possibility of development of such a refractory state, it is apparent that thrombocytopenic patients should not be transfused without real indication. Many patients with "idiopathic" thrombocytopenic purpura are refractory to the administration of platelets even though they have not been transfused, and in these cases the presence of the antiplatelet substance is presumably the cause of the thrombocytopenia. Platelet transfusions are of no value in cases of this type.

Smith: We have not studied the development of platelet antibodies.

Tocantins: Since we are still far from having even a suitable plasma protein substitute, we cannot of course speak of platelet substitutes, though we may
aspire to develop substances which duplicate some of the functions of platelets. A few of these have been proposed. What do the members of the panel think is the area of usefulness of such partial platelet substitutes as brain extracts and soya bean phospholipids? Are you impressed with their value in controlling bleeding?

Smith: We believe that lipid platelet substitutes will have a definite place in therapy of thrombocytopenic bleeding. In our own studies with soybean phosphatide we have seen several striking examples of unquestioned benefit. Factors of dosage and frequency of administration require much further study.

Cronkite: I have never used platelet substitutes. I am not impressed by the published investigations of their effects in experimental animals.

Gardner: Our group has had no experience with these agents.

Harrington: Unless preservation of platelets can be improved, the need for partial platelet substitutes will continue. My own experience with these preparations has been too limited to justify comment on their efficacy. On theoretical grounds, however, I suspect that the most critical hemostatic factor(s) in platelets are concerned with maintenance of vascular integrity and are unrelated to clot-promoting properties. Substitutes for only the latter have been extensively studied to the present time.

Conley: Certain preparations containing phospholipids and derived from sources other than platelets have been shown to be effective substitutes for platelets in the thromboplastin generation test. The intravenous injection of such preparations into thrombocytopenic recipients has been reported to improve the impaired prothrombin consumption of the recipient's blood. Lyophilized platelets and platelet extracts apparently have similar effects. None of these preparations enhance clot retraction. Several investigators have reported that such preparations temporarily improve hemostasis in patients with thrombocytopenic bleeding. Much more critical study is necessary before these claims can be accepted. In a recent experimental study of this problem, Jackson and his associates (J. Clin. Invest. 37:904, 1958) observed that the transfusion of fresh platelets to dogs rendered thrombocytopenic by irradiation resulted in elevation of the platelet count and prompt cessation of bleeding into the lymph. In contrast, lyophilized platelets did not circulate and had no hemostatic effect. At this time there is no convincing clinical or experimental evidence that "partial platelet" substitutes are effective in controlling bleeding, but much more study of this problem is needed.

CLINICAL AND FUNDAMENTAL ASPECTS OF TRANSPLANTATION OF BONE MARROW

Abstract of an exchange of views of interested workers at a conference held in Philadelphia, Pennsylvania, on April 14, 1958, during the meeting of the Federation of Societies of Experimental Biology. Arranged by A. Hollaender, Oak Ridge, Tenn.

Participants

Observations on the foreign marrow reaction: Tocantins stated that one of the major obstacles to clinical research on marrow transplantation, now that procurement and preservation of bone marrow are somewhat better understood, is the reaction of the host to the foreign bone marrow. Congdon reported that more detailed experimentation showed less benefit from delaying the injection of foreign bone marrow on long-term survival after irradiation than originally thought. Uphoff said that if acquired tolerance embryonic liver is not equally good in all genetic combinations as a method of precluding the reaction; in most cases there is increased survival following the gross evidences of the reaction. She felt that young embryonic liver (14 days) was better than older stages of gestation. Trentin reported that he had tried six homologous genetic combinations using fetal material to circumvent the foreign bone marrow reaction. He found no benefit from fetal liver compared to adult homologous bone marrow.

(Note after the Conference: In spite of the variation in the early reports on the superiority, or lack of it, of fetal blood-forming tissues for treatment of lethal total body irradiation, there is now substantial evidence in some homologous experiments to show the decided advantage of homologous fetal liver over adult homologous bone marrow. Long-term survival is better with fetal liver; histologic recovery of the lymphatic tissues approaches that of isologous bone marrow, and donor blood-forming cells stay in the host without evidence of reversion. Until better methods are devised, we probably should look upon homologous fetal blood-forming tissues as the most desirable material for transplantation [Congdon].)

Trentin cited evidence that, he thinks, favors the idea that the injected foreign bone marrow contains or gives rise to donor-type, antibody-forming cells in the irradiated host. He said: (1) that he finds no evidence of destruction of the grafted marrow; (2) skin grafts from the marrow donor stay on the foreign host; (3) genetic theory and experimental results in parent to F1 bone marrow studies prove to his satisfaction that bone marrow gives rise to antibody cells (graft against host reaction).

Owen pointed out that he had been unable to confer actively acquired tolerance to a subsequent injection of homologous bone marrow in one strain of
irradiated mice. In his experiment there was evidence of actual pre-immunization by this treatment. He also was unable to get enhancement of homologous bone marrow therapy. Owen commented on the theory of transplantation genetics as it was used by Trentin. He felt that some sort of reservation should be retained in considering how much the genetic theory actually applied to the problems of foreign bone marrow disease. He suggested that this might not be entirely a transplantation antigen reaction, but that foreign bone marrow disease might be a hypersensitivity reaction involving combinations between antigen and antibody in the host and, among them, antigens that are under a somewhat different type of genetic control. Kaliss agreed in general with Owen's remarks on genetic theory. He felt, however, that the enhancement phenomenon required exacting experimental conditions, not all of which are understood. Cole reported on the killing effect of adult C57L spleen on irradiated LAF1 mice. Bone marrow, thymus and newborn spleen would not replace the adult spleen in the effect. With adult spleen there was also some killing of unirradiated LAF1 mice. Living cells were required.

Ambrus said that in bone marrow experiments on Swiss mice, cortisone and HN2 therapy given to the donor animals gave some increase in long-term survival. Very little benefit was seen with A mice as donors and C57L as irradiated recipient. Ambrus also reported that monkeys could be treated after HN2 injury with bone marrow. Autologously, $10^8$ cells were effective in monkeys, but homologously hundreds of millions were required. Pooled homologous monkey marrow was less satisfactory than unpooled marrow. Ambrus thinks that in pooled material one kind of marrow could produce antibodies against another as well as the host. Very large doses of cells seemed to overcome the harmful effect of pooled marrow.

Dammin presented the histologic findings in irradiated rabbits surviving for different periods after homologous bone marrow therapy. Extreme atrophy of lymphatic tissues was usually present. Very rarely a long-term survivor showed normal lymphatic tissue.

Santos reported that pretreatment with heterologous red blood cells prevented "take" of heterologous bone marrow in irradiated mice. In LAF1 mice he could not show a detrimental effect of the heterologous bone marrow when the radiation dose was reduced to midlethal levels. He said this was contrary to reports by others who found detrimental effects in their experimental situations.

Cameron referred to a stunting phenomenon that occurs in 35 to 45 percent of parabiotic animals, a phenomenon which may be related to the foreign marrow reaction. Congdon commented on the need for finding drugs that influence the immune system, since none of the technics used to circumvent the foreign bone marrow reaction are entirely satisfactory.

Makinodan discussed the chemical nature of the antigens in tissues responsible for graft rejection. A material very resistant to enzymatic degradation, possibly a polysaccharide, has been obtained. Santos pointed out that he could get hemoglobin or an antiserum to red blood cells to function like a tissue antigen in his test system. Kaliss thought that some of the genetic work at
his institution indicated different kinds of antigens in the transplanted tissues demonstrable in different systems.

Treatment of experimental and human leukemia: Trentin introduced the subject of treatment of experimental mouse leukemia by irradiation and/or bone marrow injections. He had many mice carrying a transplanted Gardner C3H lymphosarcoma surviving 280 days after 880 roentgens and bone marrow therapy. The treatment has to be given soon after transplantation of the tumor. With a myeloid tumor this treatment was not effective. He also tried to treat a spontaneous leukemia in mice without success. Djerassi had studied treatment of three transplantable leukemias and two solid tumors. Radiation and bone marrow therapy had little or no effect in his mice. About one thousand mice were used in this work. Ambrus stated that he had seen a few mice apparently cured of their leukemia by radiation and bone marrow therapy in connection with triiodothyronin pretreatment and hypoxia during radiation, but in most leukemia experiments he had little success with this method.

Kirschbaum pointed out that the Gardner Lymphosarcoma was more radiosensitive than other leukemias. Uphoff said that she had tried experimental therapy in 10 to 12 transplantable leukemias. The animals died as a result of the radiation therapy. Those that lived 3 to 5 months appeared to be cured, but after autopsy showed small islands of tumor cells in tissue sections.

Dameshek commented on the desirability of getting the leukemia under control in the patient even though the treatment did not destroy the very last leukemia cells. McFarland reported on clinical cases treated with supradosage chemotherapy in five terminal cases of leukemia. The disease was not eradicated. Thomas discussed the severity of the infections occurring in patients after total body irradiation. In one young girl with leukemia, there had been an extended remission after 300 r and bone marrow donated by her sister.

Kay reported on clinical work in England with bone marrow therapy. Aplasias had not responded to bone-marrow-type therapy. Loeb reported work by Hill on use of radioisotopes and marrow transplantation in patients with leukemia. No significant remissions were seen; all of the patients, however, were terminal.

Transplantation after chemotherapy: Dameshek discussed the use of autologous marrow after supradosage chemotherapy in Hodgkins' disease. Remissions were seen in most cases and blood counts returned to normal in 10 to 14 days. Homologous bone marrow was used in terminal cases.

Schwartz (Boston) presented work on 6-mercaptopurine (6MP) in rabbits given crystalline bovine serum albumin. The antibody titer could be markedly depressed with this compound. Three mg./Kg. of 6MP was used in the rabbits. Kirschbaum used thiotepa to injure mice, followed by isologous or homologous bone marrow. Excellent survival was obtained without "late disease." The survivors after homologous bone marrow therapy did not accept skin grafts from the homologous type donor. Odell discussed chemical (Myleran) injury to bone marrow treated by bone marrow therapy. He found the same results in Sprague-Dawley rats as reported by Weston, but much less success in another type of rat whose individuals were genetically more diverse than
the Sprague-Dawley. Talbot had a similar experience in England. The August rat could recover from Myleran damage with isologous bone marrow but not with homologous marrow therapy.

**Antibody response:** Stoloff reported on response of irradiated patients to diphtheria toxoid. A normal response occurred at 250 r, but no response in a single patient receiving 800 r. It is known that leukemics make antibody nicely. Schwartz reported on an identical twin with leukemia given 300 r and 3 billion bone marrow cells from the normal twin. An 8-week remission was observed followed by a relapse of the leukemia. He also reported a new case of leukemia given 275 r followed by 3 billion cells from the mother. No “take” of the maternal cells was observed. The child went into a short remission followed by a sudden leukemic crisis.

Frei reviewed some work indicating a nearly normal antibody response in leukemic patients. Klein also commented on the known ability of leukemics to produce antibody in a nearly normal manner. Ferrebee commented on the extreme difficulty of treating the infections that occur in irradiated dogs surviving after homologous marrow transplantation.

**Aplastic states:** Dameshek discussed the use of aspirated marrow therapy in aplastic anemia. In 12 patients, 4 showed some improvement possibly related to the marrow treatment. Tocantins mentioned 5 aplastic anemia cases given marrow from excised bones with some transient (about 2 weeks) improvement in reticulocyte and platelet counts.

**Experiments in primates:** Rothberg referred to 3 chimpanzees given 900 r and homologous marrow therapy. One animal survived. No marker system was available to determine if transplantation occurred in this animal. McAlpine reviewed the bone marrow experiments in 150 monkeys carried out by Weston. Half of the animals were gamma ray controls. Multiple injections of pooled homologous marrow were used. No definite benefit from marrow therapy in respect to marrow recovery was seen after lethal exposures.
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