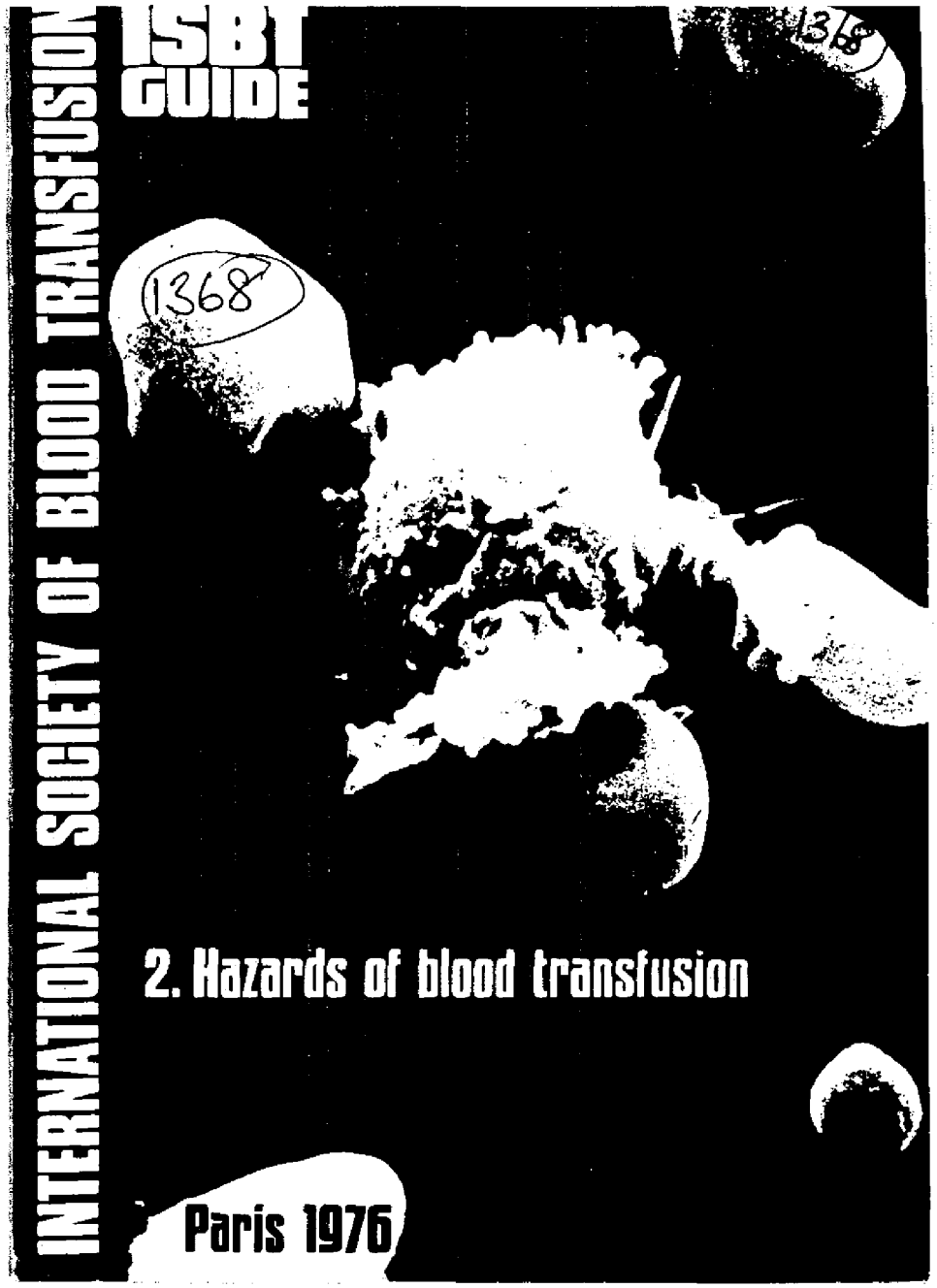
INTERNATIONAL SOCIETY OF BLOOD TRANSFUSION
ISBT GUIDE
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2. Hazards of blood transfusion
Paris 1976

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2. Hazards of blood transfusion

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The electron micrograph of the cover was made by Professor Peter Biberfeldt, Stockholm, and shows a monocyte phagocytosing antibody-coated red cells; layout by Suzanne Öhman.

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Blood replacement therapy should now be regarded as an applied paraclinical discipline—one that demands a considerable degree of expertise if the appropriate products and product volumes are to be selected for clinical use. For maximum recipient protection, a working knowledge of all possible undesirable effects of blood transfusion is obligatory. Such hazards may conveniently be classified under the following headings: cellular and protein incompatibilities; transmission of infection; metabolic effects; hemostatic defects; pharmaceutical incompatibilities; and miscellaneous, often iatrogenic, dangers.

This brochure is intended to be a brief review. No attempt has been made to cover all possibilities, because circumstances differ from country to country. We are aware, for example, that some subjects of importance in tropical countries have not been covered in detail.

CELLULAR AND PROTEIN INCOMPATIBILITIES

All transfusions carry a risk of immunization either by red cells, platelets, or white cells. It should be borne in mind that such immunization may have delayed consequences such as haemolytic disease of the newborn, problems in transplantation, etc.

Red Cells

Routine laboratory pre-transfusion tests [recipient blood-typing and antibody-screening; compatibility testing of recipient versus donor; donor blood-typing and antibody screening] are designed to reduce the chance of incompatibility causing destruction of either the donor's or recipient's red cells. Presently available manual tests have a certain threshold of sensitivity which is significantly above, for anti-D at least, the minimal concentration that can bring about red-cell destruction. "Compatible blood" may not, therefore, always survive normally in the recipient and has been known to lead to "*delayed haemolytic transfusion reactions*" characterized by partial or complete removal of the donor red cells from the recipient's circulation, starting several days after the transfusion. Red cells that are incompatible *in vitro* at temperatures above 28°C may be expected to have a shortened sur-

vival time in the recipient and should, therefore, be avoided under all ordinary circumstances.

The possibility of a clerical error, mislabelled tubes or blood containers, or of a misidentified patient must be guarded against. The numerous necessary precautions and control measures to avoid such errors cannot be described here. The donor sample should be taken from a segment of tubing integral with the plastic pack or from a labelled tube firmly attached to the parent container. The compatibility test or "crossmatch", i.e. a direct test of the recipient's serum against red cells from a sample of the donation, should include the indirect antiglobulin test to minimize the chance of transfusing red cells that are serologically incompatible at 30–37°C, since such cells can be expected to have a shortened survival time in the recipient.

Other possibilities are:

(i) Donor red-cell antigens may provoke formation of specific antibodies which, in turn, shorten the life-span of the remaining donor cells. [Donor and recipient are "matched" only for the major antigens A, B and D, and not for the many other immunogens in Rh and other blood-group systems.]

(ii) Donor alloagglutinins or alloantibodies passively transferred to the recipient may interact with the red cells of another donor and cause their rapid elimination from the recipient's circulation.

Acute symptoms of hypotension, chills, fever, or jaundice without reasonable explanation, haemoglobinaemia, haemoglobinuria or oliguria, appearing within a few hours following a transfusion should be thoroughly investigated.

White cells and platelets

The major leucocyte and platelet antigens are the expression of a highly complex genetic system, the HLA system. Other antigenic systems specific for either platelets or leucocytes also exist.

Anti-leucocyte antibodies are considered to be the principal cause of non-haemolytic transfusion reactions. The majority of these are febrile in nature and may be quite severe. Typical symptoms are: flushing, tachycardia, and cough shortly after the start of the transfusion, followed by a headache, rigor, and fever.

Normo-volaemic pulmonary oedema has been reported as an additional complication of a febrile reaction; immunization of the recipient against leucocyte antigens was thought to be the cause.

Post-transfusion purpura is a rare syndrome characterized by the sudden onset of severe thrombocytopenia about one week following blood transfu-

sion. The thrombocytopenia appears to be due to a specific platelet antigen provoking the formation of the corresponding antibody. In the subsequent reaction the patient's platelets also participate.

Methods for preparing buffy-coat-poor red cells, that is to say, red cells with a minimum of leucocytes and platelets, are described in most standards texts. Use of such blood, or of washed cells, or of red cells reconstituted from the frozen state will prevent most of the reactions described under this heading.

Plasma Proteins

Mild allergic reactions are quite common and are usually characterized by urticaria or other allergic skin manifestations. The expected reconstitution of a bleeding-induced hypovolaemia may not be obtained in such cases. Although probably often of an immunological nature, the exact mechanism of such reactions has not been fully explained.

Severe reactions of an anaphylactoid type are rare. The commonest cause of such reactions is now thought to be specific reaction between IgA and anti-IgA. Transfusion of a patient with class-specific anti-IgA may cause considerable problems; very carefully washed red cells may be tolerated in some cases, but in others the use of blood from donors with a proven deficiency of IgA is necessary. Autotransfusion, if feasible, is another solution.

Graft-versus-host (GVH) reaction

In intrauterine transfusions, mitotically-active donor lymphocytes may, very rarely, establish a graft in the foetus before it has achieved full immunological competence. Since mitotically-active lymphocytes may survive for 17 to 21 days in stored blood, transfusion of such blood to patients whose immunological responses are impaired as a result of disease or immunosuppressive therapy may lead to temporary engraftment of the recipient's bone marrow by immunologically competent lymphocytes. A GVH reaction may develop in consequence, and persist until the transplanted cells have been eliminated. Some authors have recommended that X-irradiation should be given to all random-donor blood-component transfusions if the patients are receiving immunosuppressive therapy, or are immunodeficient from other causes.

Other Allergic Phenomena including Passive Transfer of Allergy

Very occasionally a normal recipient may acquire sensitivity to atopens by being transfused with plasma containing reaginic antibody. Patients sen-

sitive to penicillin have been reported as reacting to donor blood when the donor is receiving large doses of that antibiotic; a case of a patient receiving penicillin reacting with donor anti-penicillin antibody has also been reported.

INFECTED BLOOD

The predominant symptoms due to gross bacterial contamination of transfused blood are: fever, severe shock with flushed skin, and pain appearing after a latent period of perhaps thirty minutes or less. A severe bleeding tendency may also be noted.

Bacteria may be introduced into a unit of blood directly from the donor's blood stream, from the collection needle when it comes in contact with the bacterial flora of the donor's skin, during the preparation of components, by opening the "closed" system, or at the time of administration. It is, of course, always possible that the containers—whether plastic or glass—may be contaminated through inadequate sterilization or through minute flaws in the wall. When several sample tubes have to be filled from a multiple pack, it is possible for the container to become contaminated through backflow of blood if a non-sterile, evacuated blood-collection tube is used.

Constant refrigeration at +4°C ±1°C is important from a few hours after the donation is collected until the time of administration; interruptions may give bacteria a chance to multiply. Rules should be made to govern the maximum length of time (i) that blood may safely be left out of the refrigerator, and (ii) that blood may be used after the system has been "opened". Such rules are important, not only with a view to reducing the chance of bacterial infections, but because storage at elevated temperatures involves the risk of a decrease in red-cell survival, particularly of red-cell concentrates.

Treponema pallidum

Treponema pallidum may be transmitted by the donor. It should be remembered that donors with primary syphilis may have negative serology; this creates a definite hazard when blood less than 24 hours old is administered, but blood stored at 4°C for four days or more is unlikely to transmit syphilis. The incubation period for transfusion-transmitted syphilis is between one and four months.

Post-transfusion syndrome

This syndrome has also been called the post-infusion syndrome or post-transfusion mononucleosis. The main features are: fever, splenomegaly,

and lymphocytosis. The onset occurs three to five weeks after the administration of blood, usually fresh and in large quantities. The cause is thought to be infection with cytomegalovirus (CMV), a member of the Herpes group, or more rarely with the Epstein-Barr virus (EBV). The syndrome has not, apparently, been reported after the use of blood more than 24—48 hours old. On the whole, the syndrome is usually benign and self-limiting; vulnerability to establishment of these viruses may be due to depressed immunological competence following surgery or immunosuppressive therapy.

Malaria

Malaria parasites may be transmitted from donor to recipient and occasionally such infections are fatal. The problem is compounded by the number of people who nowadays spend some time in areas where malaria is endemic and by the fact that asymptomatic parasitaemia may persist for as long as 32 months. The screening of donors is dealt with in the brochure, *Selection of Blood Donors*. However, such steps may not provide a solution in "developing" countries. "The generally accepted procedure in areas where non-immune persons may receive blood that may possibly contain scanty malaria parasites is the prophylactic administration of anti-malarial drugs to the recipients"*.

Toxoplasmosis

Post-transfusion toxoplasmosis has been reported occasionally in the recipients of leucocyte transfusions collected from donors with chronic myelogenous leukaemia. *Toxoplasma gondii* is an obligate intracellular parasite which can live and multiply in virtually all nucleated cells.

Trypanosomiasis and Leishmaniasis

Post-transfusion Chagas' disease may be a major problem in the selection of blood donors in endemic areas such as South and Central America. Exclusion of donor carriers of *T. Cruzi* can be accomplished by a complement-fixation test; such a test is mandatory in some Latin American countries. Routine tests for Kala-azar (visceral leishmaniasis) in endemic areas are not at present recommended.

* Editorial comment: "Transfusion malaria in developing countries". Brit. med. J. 1: 542, 1976.

Other diseases transmissible by blood transfusion

Brucellosis, yaws, typhus, measles, salmonellosis, and *Colorado tick* fever, may all be transmitted to the recipient by donor blood. Such occasions are, however, extremely rare.

Filariasis is not a danger to the recipient if present in donor blood, as the mosquito vector is essential for the development of the organism.

Viral Hepatitis

Jaundice appearing between about 15 and 180 days after transfusion of blood or blood derivatives may be caused by viral hepatitis. Hepatitis A has an incubation period of between about 15 and 50 days: spread is usually by the faecal-oral route. Hepatitis B infection has a longer incubation period of from about 40 to 180 days or more: spread is normally by parenteral injection, but other, non-parenteral, means of transmission occur. It is known, for example, that HB_sAg (an antigen on the surface of the virus) is present in saliva, sweat, breast milk, and vaginal secretions. "Non-A, non-B" infection is thought by some to be the commonest form of post-transfusion hepatitis.

The incidence of post-transfusion hepatitis is not known with any certainty, and doubtless varies widely from one area to another, as it will be much influenced by the prevalence of hepatitis virus carriers among blood donors and the level of immunity to hepatitis infection among blood recipients.

Tests for HB_sAg (previously called the hepatitis-associated or Australia antigen) are now available. Although these will detect no more than about 50% of hepatitis B virus carriers, no blood or blood product should be transfused unless the donor is known to have been negative for HB_sAg. It is recommended that each blood donation should be tested by such a method as counter-immunoelectrophoresis or, preferably, radioimmunoassay (RIA) or reverse passive haemagglutination (RPHA). If fresh blood has to be transfused before the results of such tests are known, a donor who has been tested previously for HB_sAg, and found negative should be used.

METABOLIC EFFECTS

In order to maintain a normal concentration of protons during storage of blood at 4°C, the pH must be acid when measured at 37°C. During storage, lactate is produced which further lowers the pH. When one considers the non-physiologic *milieu* in which red cells are preserved, it is surprising that symptoms due to lowered pH, citrate, potassium, and metabolic by-products of red-cell metabolism are usually only noticed when massive transfusions are given. Citrate-induced cardiac depression is the best known. Leakage of potassium from red cells to plasma during storage may cause a dangerous hyperkalaemia followed by hypokalaemia in the recipient of massive, rapid transfusions.

HEMOSTATIC DEFECTS

Bleeding after massive, compatible transfusions may be attributed to replacement of the patient's blood with stored blood deficient in platelets, or labile plasma coagulation factors, or both. Excessive bleeding or oozing, or both, may also be caused by incompatible or infected blood. When massive volumes of blood (more than 10 units) are transfused during a relatively short period of time, the supply of platelets and plasma coagulation factors may have to be considered. This may be done either by using relatively fresh whole blood (<4 days old) or older red-cell concentrates combined with other blood components such as fresh-frozen plasma and platelet concentrates.

OTHER UNTOWARD EFFECTS

Cardiac arrest resulting from the very rapid administration (a rate of from 50 to 100 ml per minute) of cold blood has been described. It seems clear that administration of large volumes of cold, acid, blood with increased plasma potassium, a relatively high citrate level, and decreased clotting factors may give rise to untoward effects such as hypothermia associated with metabolic acidosis. At rapid transfusion rates, warmed blood and the infusion of buffers greatly reduce the mortality from cardiac arrest following rapid, massive transfusions. It should be noted, however, that electronic blood warmers are not foolproof.

CIRCULATORY OVERLOAD

Overloading the circulation is most likely to occur in patients with chronic anaemia and in elderly or debilitated patients, especially those with chronic heart-disease. In the latter cases, overestimation of blood loss at surgical operation is frequently the cause. Symptoms of a rise in systemic venous pressure include distension of the veins of the neck, a feeling of fullness in the head, tightness in the chest and dyspnoea. These are warning signs of incipient pulmonary oedema.

PHARMACEUTICAL INCOMPATIBILITIES

Despite the temptation of convenience, a transfusion of blood or blood products should be that and nothing more; dilution of blood with isotonic saline immediately before transfusion is not, however, harmful. Any other substances mixed with donor blood or injected into the tubing of the administration set should be regarded as a potential hazard to the recipient. There are many examples; some of these are listed below:

(i) 5% aqueous solutions of glucose cause sludging of red cells and must therefore not be added to the actual unit.

(ii) Glucose in 0.2% saline may cause intravascular haemolysis when mixed with whole blood.

(iii) Calcium, which is found in Ringer's solution, may cause ACD or CPD blood to clot.

(iv) Certain drugs have been listed as potential hazards when added to units of blood, e.g. ethacrynic acid, hydrocortisone, and diphenylhydantoin.

(v) Drugs in the donor's circulation may be transferred to the recipient and may have ill-effects on the patient. If donors are questioned carefully about the drugs that they are taking, and only donors taking medicaments that would be harmless to the recipient are accepted, this danger will be obviated.

FILTER-PASSING DEBRIS

Filters in administration sets vary in the overall filter area, the diameter of the pores, and in the material used to create the mesh. There is a growing

literature on the danger of microaggregates of platelets and leucocytes plugging the pulmonary microvasculature and causing or contributing to what has been called the "adult respiratory distress syndrome". Special filters are available which will remove virtually all such debris, but these also remove platelets and leucocytes.

DELETERIOUS EFFECTS OF PLASTICS ON CELLULAR COMPONENTS OF BLOOD

The material used in plastics containers is not chemically inert; the polyvinyl-chloride is mixed with substances called plasticizers and stabilizers. There is evidence that the choice of plastics has a bearing on platelet yields. Numerous articles have mentioned the possible danger of toxic phthalate-ester plasticizers which may leach from the plastics during storage of blood; however, their biological significance has not yet been fully elucidated at the present time. It seems probable that the harmful effects are minimal in practical blood transfusion therapy, provided that carefully controlled plastics material is used.

G-6-PD DEFICIENCY IN BLOOD DONORS

Glucose-6-phosphate dehydrogenase deficient cells may be rapidly destroyed in the circulation of the recipient who has received certain common drugs, such as vitamin E, phenacetin or sulphonamides. In areas where G-6-PD deficiency is common, a screening test for potential donors is recommended.

EXOGENOUS HAEMOCHROMATOSIS

Patients who receive large quantities or volumes of red cells over a period of time may develop signs of iron-overloading, e.g. hepatic fibrosis.

AIR EMBOLISM

On the whole, collapsible plastics containers which are not vented prevent the dangers of air embolism. However, if there are leaks in the transfusion set or in the connection between this and the container, air might be sucked into the system. The procedure of pumping air into a vented container to increase the speed of transfusion should not be used.

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