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A SURVEY OF RECENT DEVELOPMENTS IN BLOOD TRANSFUSION

PART I

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At the outbreak of the recent world war, the study of blood transfusion passed from the clinician to the laboratory worker. Since that time bacteriologists, pathologists, serologists, geneticists, physicists, biochemists, statisticians and engineers have all played a part in covering a vast field of study. The developments resulting from their work have been such that it is no easy matter for even the full-time laboratory worker to keep abreast of the times. These two articles can therefore survey only some of the advances, as seen by the author, which are of common interest to the laboratory worker and to the clinician.

Developments will be considered under the following headings :—

1. Collection, storage, preservation and handling of blood. The *in vivo* survival of transfused red cells.
2. Plasma. The recognition of homologous serum jaundice.
3. Blood grouping and compatibility tests. Blood group antigens and their practical importance, especially the Rh factor.

4. The diagnosis and treatment of haemolytic transfusion reactions, including incompatible transfusion.

5. The study of disease with the aid of transfusion.

1. Collection, Storage, Preservation and Handling of Blood. Study of the Survival of Transfused Red Cells.

Selection of Donors

The past ten years has seen greatly improved standards with regard to blood donation. The National Transfusion Service permits only healthy persons who have not suffered from certain diseases to be bled. This is essential since the assurance must be given that blood donation is harmless. Such an assurance, presumably, has always been given, but cannot always have been justifiable since persons suffering from certain diseases, for instance high blood pressure, were often used as donors, and such persons may suffer serious harm when bled, especially repeatedly, the standard amount (420 cc.). Rigid precautions must be taken to see that donors are in fact

healthy and, so far as can be foreseen, will suffer no harm from blood donation.

Donors may be of either sex, the age limits being 18 to 65 years. Consent of parents is necessary for minors. A haemoglobin test* must be done before each blood donation, however often the donor is bled, and the result recorded on the donor's record card. Before each proposed donation, a donor should read through a questionnaire asking whether he or she has suffered from any of the following diseases:—tuberculosis, epilepsy (fits), cancer, diabetes, goitre, blood disease (e.g. polycythaemia, etc.), rheumatic fever (within the last ten years), heart disease, kidney disease, high blood pressure, stroke, jaundice (within the last 12 months—see below) or malaria.

A person who has had any of these diseases is not acceptable as a blood donor. The donor, having read the questionnaire and been accepted, should sign or initial his or her record card.

Exceptionally, certain persons affected with a moderately raised blood pressure may donate blood provided they are able, without any inconvenience, to do a full day's normal work. Persons suffering from high blood pressure must never be used as donors because of the liability to such complications as stroke, cardiac failure, or even death after blood donation, as shown by experience during the recent war. A person who has had cerebral seizures, stroke, hemiplegia or a heart attack should never be a donor. With older persons palpation of the pulse, auscultation of the heart and estimation of the blood pressure may be necessary. Palpation of the pulse may reveal unsuspected cardiac disease—e.g. auricular fibrillation. A person suffering from, or recently affected with tonsillitis, influenza, other infectious illness or boils, should not be bled until recovery is complete. Persons giving a history of mental breakdown, neurosis, etc., should not be used as donors. A donor who has had hepatitis and jaundice must not donate blood until six months have elapsed from the time of recovery from the jaundice. This is to ensure that the agent (? virus) responsible for homologous serum jaundice shall not be transmitted to the recipient by blood transfusion.

It is the responsibility of the doctor who uses fresh blood to ensure that the donor has not had syphilis or other transmissible disease such as malaria. Complete reliance cannot be placed on a negative serological test for syphilis done some time previously, since the donor may subsequently have acquired infection. Ideally, if fresh blood is used, a serological test for syphilis should be done immediately before *each* blood donation. Only blood which gives a negative serological test for

syphilis is issued by the National Transfusion Services, i.e. a test for syphilis is done each time a donor is bled. In recently-acquired syphilis, a serological test for syphilis may be negative but the person's blood may, nevertheless, be highly infective at this stage. Hence, if fresh blood is to be used, discreet enquiry should be made of the prospective donor as to possible infection. In stored blood in cold storage, the spirochaete survives about four days and the malarial parasite not longer than ten days.

A person who has had malaria should never be used as a donor for blood transfusion no matter how many years have elapsed since the last malarial attack, lest the parasite be transmitted to the recipient. Ex-malarial subjects are used as donors for plasma manufacture, the red cells being discarded. Complete medical examination of prospective donors, generally, is not necessary. Suitability to donate blood should be assessed on the general condition. Persons of frail and small physique are generally not suitable. Robust health is essential. Females may be bled during the menstrual flow. Blood donation during pregnancy is not desirable, and a mother should preferably not donate blood until two years have elapsed from the date of her last confinement.

Collection of Blood. Records

Collection of blood must be by venepuncture only and local anaesthesia must be used. Under no circumstances should a donor's vein be cut down upon. The volume of blood taken must not exceed 440 cc. A donor should not be bled oftener than twice a year, and preferably only once. Six months should elapse between donations. A donor should rest recumbent for at least 20 minutes after donation. Thereafter the donor should sit up for 5 or 10 minutes before being allowed to depart. Light refreshment should be given during the rest period. Before departure the site of venepuncture should be inspected and a light dressing applied and instructions as to 'self-care' given the donor. Complaints by donors should receive careful attention. The donor's record card must show the date of donation, the result of haemoglobin tests, amount of blood taken, the initials of the donor (see above) and the name of the doctor responsible for venepuncture. Un- toward sequelae, e.g. haematoma, syncope, etc., which may complicate blood donation should be recorded on the donor's record card. Donors who faint after each donation should be rejected.

The Donor and the Community

These regulations are designed to protect the donor, though they obviously protect the doctor responsible for blood collection as well as the

* The minimum acceptable haemoglobin level is 85%

recipient. They apply also to donors selected from friends or relatives of patients. A Transfusion Service cannot exist without donors and the community owes them a considerable debt. Every consideration should, therefore, be given to the donors' welfare. The regulations governing the bleeding of donors, drawn up since the war by the National Transfusion Service, are an important step forward. The general availability of donors and blood banks today is in striking contrast to the state of affairs which existed before the outbreak of the recent war. Donors of all ABO groups are now regularly utilized and utilization of group O donors only is now largely obsolete. The organization of donor panels on a national scale is a really great advance. In general, each area of population meets the blood and plasma needs of its own hospitals. Rh-negative blood, a commodity unheard of ten years ago, is now (with care) generally available and has proved an inestimable boon, especially in maternity practice. Blood donation is a most important social service and is of incalculable value to the nation.

Storage and Handling of Blood

An understanding of the principles involved in blood storage is essential. Many disasters have occurred in consequence of faulty management of blood banks simply because those in charge had little or no knowledge of the principles involved. Hospital blood banks have been, and are still, a constant source of anxiety to the Regional Transfusion Officer. Blood banks should always be the responsibility of a medical officer, preferably a pathologist. Knowledge of the principles underlying storage of blood has advanced considerably in the past few years and its application in practice is important.

Blood, when taken from the donor, should within 30 minutes go into refrigeration and be stored at a temperature of 2° to 6° C. Food, or pathological samples such as excreta, pus, etc., should never be put in a blood bank refrigerator. A responsible person, e.g. a laboratory technician or hospital pharmacist, should check and record, each morning and evening, the temperature of the refrigerator. A maximum-minimum recording thermometer, or a thermograph, should be used. Freezing must not occur, and the temperature must not rise unduly. A Transfusion Officer may justifiably decline to stock a bank unless these precautions are taken. The temperature records should be kept for periodic inspection and an engineer should examine the refrigerator regularly, at least every three months, to ensure that the machinery is in working order, since faulty refrigeration may cost lives. Transfusion

of blood which has been frozen, and therefore haemolyzed, may prove fatal. Blood should not be left longer than 30 minutes out of refrigeration. Blood left unduly long out of refrigeration may become unsafe to use because of bacterial growth, etc., and should be labelled 'Dangerous for Transfusion' or discarded. For a discussion on the effect of temperature on blood storage and its *in vivo* survival, see Gibson, *et al.* (1947). Blood should not be warmed before transfusion; transfusion of overheated blood may prove fatal (Baker, 1937). It is quite safe to transfuse blood cold from refrigeration. Unauthorised persons should not have access to blood banks. A bottle of blood should show on its label(s) the blood group (ABO and Rh), date of collection, serial number of the donor, expiry date, temperature for storage (2° to 6° C.) and the preservative solution. A special register should show the fate of all bottles of blood put in the blood bank. A knowledge of the preservative solution used, as will be seen, is of very great practical importance. The labels on blood bottles exist for a purpose, namely, to state precisely what is in the bottle and to act as a guide to the doctor who transfuses the blood. Hence blood bottle labels are of medico-legal importance. Many transfusion disasters are attributable to failure to examine blood bottle labels before transfusion, with the consequence that time-expired or incompatible blood has been transfused.

Differential Agglutination

Before dealing with glucose-preservation of blood, differential agglutination must be considered, as it will be frequently alluded to and is of immense practical importance in elucidating the fate of transfused blood. The routine application, in recent years, of differential agglutination to the study of the fate of transfused blood constitutes a notable advance, ranking in importance with the general introduction of stored blood preserved with glucose. With the aid of differential agglutination, it is possible to state with considerable precision the fate of the transfused blood in the recipient's circulation. Differential agglutination, like glucose-preservation of blood, is not new. As long ago as 1919 it was described by Ashby, who pointed out that after transfusion of O blood to an A recipient, the blood of the recipient was a mixture of O and A cells. Accordingly, if a sample of the patient's blood taken after transfusion was mixed with anti-A serum, the A cells would be agglutinated and the free unagglutinated group O cells of the donor could be counted in a red cell counting chamber. Wiener (1934) used the MN groups. If the recipient was M and the donor N, the survival of the donor's red

cells could be directly followed simply by using an anti-N serum, and vice versa. Differential agglutination until 1939 was sporadically used by very few workers. Mollison and Young (1940) suggested the combined use of sera of the ABO and MN systems. Hitherto the method had given only approximate results. Dacie and Mollison (1943) pointed out that much more accurate results with the Ashby technique could be obtained by using potent agglutinating sera and intensifying agglutination by centrifugation. The technique is not difficult but requires practice. Some highly potent ABO grouping sera may exhibit the phenomenon of 'zoning.' It is important to find (by experiment) at what dilution such sera will cause maximum agglutination. Such 'zoning' sera, appropriately diluted, may cause intense agglutination and are very suitable for differential agglutination work. Diluted high titre 'zoning' ABO grouping sera were used by Mollison (1944 M.D. Thesis, cited by Loutit, 1945; Mollison, 1947). Loutit (1945) used high titre zoning sera diluted as much as 1:32. When a mixture of agglutinable cells and agglutinating serum is made, e.g. B cells and anti-B serum, some cells may not be agglutinated despite centrifugation. These unagglutinated cells constitute the inagglutinable or blank count, and with good sera may be less than 10,000 and should certainly not be more than 50,000 per c.mm. In differential agglutination studies, the blank count must be determined by experiment before transfusion and due allowance made for it in subsequent counts. A wide range of antigens and their anti-sera may be used in differential agglutination. This is a great advantage when blood homologous in the ABO system has been transfused, because differences in MN or Rh groups, etc., can be exploited. The following is a list of some of the antigen-antibody systems which can be used in differential agglutination:—(1) ABO system; anti-A, anti-B. (2) MN system; anti-M, anti-N, anti-S. (3) Factor P; anti-P. (4) Rh Factor; anti-C, anti-C^w, anti-D, anti-D^u, anti-E, anti-c, anti-d, anti-e. Other antigen antibody systems which could be used are Kell, Lewis, Lutheran, etc. Several of the sera are very rare. It may be of great importance, in a particular transfusion, to know the fate of the transfused red cells and their *in vivo* survival can be followed by the use of differential agglutination.

With the aid of transfusion and differential agglutination studies, Ashby (1919), Wiener (1934), Mollison and Young (1940) and others subsequently showed that fresh red cells normally survived in the circulation of the recipient for 100 to 120 days which, presumably, is the normal life span of the erythrocyte. It is something of a

paradox, therefore, that standard textbooks of recent printing give the life of the red cell as 30 days.

Radio-Active Red Cells in in vivo Survival Studies

An interesting recent advance in the study of the fate of transfused blood is the use of transfused red cells tagged with isotopes of radio-active iron (see Gibson, Aub, *et al.*, 1947, and Gibson, Evans, *et al.*, 1947). The donor is dosed with an iron salt such as ferrous sulphate which has incorporated in it the radio-active isotope of iron. New erythrocytes of the donor take up the radio-active iron and such tagged cells can be detected after transfusion in the circulation of the recipient. The test is exceedingly sensitive and very accurate, but is of limited value since radio-active iron released from destroyed donor red cells becomes rapidly incorporated in new erythrocytes made by the recipient. Accordingly, the test is not reliable after 48 hours. The method is of use in that it will detect only intact donor cells containing radio-active iron in the blood of the recipient. If most of the donor blood is destroyed within a few hours of transfusion, it follows that few, if any, tagged red cells of the donor will be detected in the patient's blood, say, 24 hours after transfusion. The test can only be done by skilled workers with special apparatus.

Blood Preservation

Considerable advances have been made in recent years in our understanding of blood preservation. An important advance is the proof, with the aid of differential agglutination, that glucose is essential to the preservation (*in vitro*) of stored red cells and to their survival (*in vivo*) in the circulation of the recipient. In any given transfusion, the oldest or effete red cells of the donor will be the first to be eliminated. An anticoagulant is not a blood preservative. For instance, sodium citrate, heparin or defibrination will prevent coagulation but will not preserve blood. A preservative solution must contain, of course, an anticoagulant but it must also contain glucose. Without glucose the red cells will undergo rapid deterioration. Blood should never be stored without glucose.

Glucose-preservation of blood is no new discovery. In 1916, Rous and Turner published their experimental observations on using a mixture of three parts of blood, two parts of isotonic sodium citrate and five parts of isotonic dextrose solution for red cell preservation. Erythrocytes would keep for a month in this mixture, whereas with citrate alone haemolysis was marked in less than two weeks. In the Great War of 1914-1918, Captain O. H. Robertson (1918) made use of this experimental work and used a mixture consisting of 500 cc. blood, 350

cc. isotonic sodium citrate and 850 cc. isotonic glucose solution. Red cells preserved well in this solution and could be safely transfused, even after 26 days, with good results. Moreover, the blood mixture could be transported without harm to the red cells. Before transfusion, the supernatant fluid was syphoned off and the sedimented red cells then suspended in dilute gelatin solution, the final volume being 1,000 cc. It is remarkable that this important work was allowed to lie dormant until about the time of the outbreak of the recent world war. Despite this work, early in the recent war many blood banks were, in fact, operated using simply citrated blood (i.e. without glucose), and many transfusion disasters were directly attributable to this. The general adoption of glucose-preservation of blood during and since the war constitutes a very notable and important advance. Stored glucose-preserved blood is a great advance, since it ensures that blood can be procured from banks at any time and secondly, as will be seen, the results of transfusion are about as good as the transfusion of absolutely fresh blood. Since concentrated red cells must be prepared from stored blood, its preservation with glucose is very important. The tremendous advantage of having grouped and tested blood on hand for immediate use, especially of homologous group in the ABO and Rh systems, needs no elaboration here. Blood banks are now generally available throughout Great Britain and have been of incalculable benefit to the community. It is, apparently, not generally appreciated that the safe and successful use of preserved blood is dependent on the fact that the erythrocyte cannot survive without glucose. All concerned with the transfusion of blood should be conversant with the importance of glucose in the preservation of blood.

Our knowledge of the principles underlying blood preservation has improved considerably in the past ten years. Transfused fresh blood normally survives *in vivo* for 100 to 120 days, so that its rate of elimination is about 1 per cent. per diem. Wiener and Schaefer (1940) showed that the longer citrated blood *without glucose* was stored, the less good was its *in vivo* survival. Patients receiving blood stored seven days or less did not develop hyperbilirubinaemia. With blood older than ten days, jaundice and haemoglobinuria might complicate transfusion. Blood aged 21 days was eliminated from the recipient's circulation within 24 hours. Blood stored seven days or less survived in the recipient almost as well as fresh blood. Therefore seven days was set as the time limit for storage of citrated blood. However, Mollison and Young (1940) pointed out that the *in vivo* survival of citrated blood *stored with glucose* was little inferior to that of fresh blood.

They confirmed the observations of Rous and Turner (1916). Mollison and Young (1942) confirmed that citrated blood stored without glucose up to six days survived *in vivo* almost as well as fresh blood, and that when storage was longer the donor erythrocytes were rapidly destroyed in the recipient's circulation. Thus 14-day old blood stored without glucose survived poorly *in vivo* since 75 per cent. of the red cells were eliminated in 24 hours, and in three weeks all were eliminated. On the other hand the *in vivo* survival of glucose-preserved blood aged 16 to 18 days was little inferior to that of fresh blood. It should be noted here that transfusion of blood stored without glucose for more than ten days may be dangerous, especially if large amounts be given, since destruction of the donor erythrocytes in the recipient's circulation may be sufficient to result in jaundice, haemoglobinuria and suppression of urine, as the writer has observed. The importance to the clinician of having stored red cells preserved so that they will survive normally *in vivo* is obvious. While glucose effectively prolongs *in vivo* survival of stored red cells, other sugars such as dextrin and sucrose, do not have this effect.

A very important advance was the establishment, by the aid of differential agglutination studies on the *in vivo* survival of transfused blood, that the value or effectiveness of a preservative solution could not be assessed on *in vitro* tests, which in fact might be of little value (Mollison and Young, 1941). Such *in vitro* tests as spontaneous haemolysis, osmotic fragility in saline and resistance of red cells to trauma such as shaking (mechanical fragility) may, in fact, be quite misleading. Thus, red cells stored in certain preservative solutions, e.g. Rous-Turner solution, may become very fragile as judged by osmotic fragility tests but, nevertheless, the *in vivo* survival of such preserved red cells may be excellent, even when stored up to 21 days (Mollison and Young, 1942). A solution causing much haemolysis *in vitro* would, obviously, be contraindicated. A solution giving slight haemolysis *in vitro* might not be contraindicated if the *in vivo* survival of the red cells was satisfactory. On the other hand, certain substances, e.g. dextrin and sucrose, will in the same way as glucose delay the onset of haemolysis *in vitro*, but have little effect in prolonging *in vivo* survival.

When stored blood is transfused there is an immediate rise in the recipient's serum bilirubin (Mollison and Young, 1940), and this rise is maximal four to five hours after transfusion. The six hours following transfusion are a period of rapid destruction of effete erythrocytes. Initially, with stored glucose-preserved blood, there will be some destruction of the transfused erythrocytes

(dependent on length of storage), though the ultimate survival of the bulk of the red cells will be good (about 80 per cent.) when storage is as long as 21 days.

The most important advance yet made with preservative solutions* is the introduction of citric acid-sodium citrate-glucose (acid-citrate-dextrose or, briefly, A.C.D.) blood preservative mixtures. Hitherto the best preservative solution was the Rous-Turner mixture which was objectionable because it was bulky and caused over-dilution of the plasma. Consequently the plasma was not suitable for drying. Loutit and Mollison (1943), and Loutit, *et al.* (1943), showed that blood preserved in citric acid-sodium citrate-glucose preservative solution was safe to transfuse, caused no untoward reactions, and the *in vivo* survival of the transfused red cells was better than with any other preservative solution yet tested. Moreover the citrate and glucose solutions could be autoclaved together without caramelization, a most important technical advance which has eased the work of transfusion laboratories considerably. With trisodium citrate-glucose solutions, the two components must be autoclaved separately to avoid caramelization. The fact that acid citrate and glucose solutions can be autoclaved together means that sterility can be guaranteed, which was not absolutely possible when glucose had to be added to the trisodium-citrate solution after autoclaving, however careful the technique. Caramelization produces a brown or coffee colour of varying degree, but a clear solution is essential to permit of easy examination before use. Further, caramelization means some reduction of glucose content which must be avoided since this may adversely affect the *in vivo* survival of the transfused preserved red cells. The final concentration of glucose in the mixture of blood and preservative solution should be about 0.6 per cent. Of the various A.C.D. preservative mixtures yet devised, the best appears to be disodium citrate-glucose (Loutit and Mollison, 1943); this is now in general use in this country. Standard British blood mixtures contain 120 cc. citrate-glucose and 420 cc. blood, and this yields excellent plasma for processing. The biochemical and biophysical changes occurring in the stored and transfused red cell are not likely to be of interest to the clinician, but for a discussion of this subject see Loutit (1945) and a Symposium by various workers (1947).

2. Plasma. The Recognition of homologous serum jaundice.

The widespread availability of plasma is one of the great boons of modern Transfusion Services and is one of the important developments made in

transfusion therapy in recent years. Plasma may be issued in dried or liquid state. Dried plasma will, apparently, keep indefinitely, but the time-expiry date is provisionally set at five years from the date of preparation. Plasma has saved thousands of lives. It is first and last a blood substitute and, lacking red cells, it can never be as efficient as whole blood in the treatment of oligæmic shock. Nevertheless, it has been repeatedly shown that it can effectively tide over grave emergencies many patients who have bled severely. Whenever possible, homologous blood should be used in the treatment of oligæmic shock. When homologous blood is not available for the emergency treatment of hæmorrhage in childbirth, the hazards of the Rh factor must particularly be kept in mind and plasma is then of especial value; homologous blood can be given later. Excessive plasma transfusion may cause a forced dilution of the patient's hæmoglobin. However, on occasion, large volumes must be given as in the treatment of burns. Dried plasma, when reconstituted, should be used within an hour or discarded lest it become contaminated by bacterial growth. It has been used in concentrated form in acute hypoproteinaemia. If transfused concentrated, e.g. double strength, the dangers of circulatory overloading in diseased subjects should be borne in mind. Brown, *et al.* (1942), found that concentrated serum was of little value in the treatment of the nephrotic syndrome and might have adverse effects. However Golden and Fraser (1947) recommend its use for the oedema of toxæmia of pregnancy. Convalescent plasma or serum has, apparently, been used with success in both the prophylaxis and treatment of infectious diseases such as whooping cough, measles, mumps and scarlet fever.

One of the great advances of recent years is the successful fractionation of the plasma proteins. It would be out of place here to discuss these various fractions, fibrinogen, fibrin, the globulins, etc., since they are used for purposes other than transfusion. Serum albumin has been isolated almost pure. It is mainly responsible for the osmotic pressure of the plasma and maintenance of blood volume is in large part dependent on it. It is, therefore, effective in the treatment of oligæmic shock. Its use in states of protein deficiency such as occur in renal or hepatic disease is still in the experimental stage.

Plasma transfusion is not without complications. Embolism due to fibrin particles in liquid plasma has been reported. Angio-neurotic oedema and urticaria are occasional complications, but seem

* Solutions must be made up in pyrogen-free distilled water to avoid febrile reactions.

to cause no serious harm. Plasma is prepared by pooling plasma of different ABO groups so as to cross-absorb the anti-A and anti-B isoagglutinins on the A or B agglutininogen present in plasma of corresponding group. This reduces the titre of the anti-A and anti-B isoagglutinins so that they can cause no harm to a recipient's red cells when transfused. Circulatory overloading and heart failure may complicate transfusion of excessive amounts of plasma.

Homologous Serum Jaundice

This is a late and serious complication of transfusion of plasma and, rarely, of blood. The approximate incidence (Lehane, 1949) of homologous serum jaundice after transfusion is:—(1) Large pool plasma, 10 per cent. (2) Small pool plasma, 1.5 per cent. (3) Blood, 0.8 per cent. The recognition during the recent war of homologous serum jaundice, probably a virus infection of the liver, as a late complication of transfusion was a notable advance. The virus can apparently survive indefinitely in liquid, frozen, or dried plasma. The disease was first recognized just before the recent war following the use of convalescent measles serum. It has complicated the use of human serum in yellow fever vaccination and the injection of plasma from a person convalescent from mumps. Only a minute amount of infected plasma or serum injected intravenously or subcutaneously is necessary to transmit the disease. Scrupulous sterilization of syringes and needles has eliminated this disease as a complication of intravenous injections in diabetic or venereal disease clinics and in hospital wards. The disease can be transmitted experimentally to human volunteers, but not to animals, by injection of blood or serum from patients in the icteric or pre-icteric stage of the disease. The diagnosis is made on clinical grounds. A history of transfusion is essential. The disease becomes manifest 40 to 120 days after transfusion or inoculation of human plasma, serum, or blood. Joint pains, erythematous rashes, urticaria, ano-

rexia, malaise and vomiting may occur, followed by jaundice (see Ministry of Health Memorandum, 1943). It seems that some persons may carry the virus but not develop the disease. The mortality rate is not less than 1 per cent., and may be much higher. Death is due to liver necrosis. The disease is, apparently, not identical with infective hepatitis (catarrhal jaundice) and it may be that it is never transmissible naturally, but only by inoculation of blood, plasma or serum. Transmission of the disease by naso-pharyngeal washings has not been successful (Bradley, *et al.*, 1946). During the war, plasma was made in pools from the donations of many donors, and Spurling, *et al.* (1946), found an incidence of jaundice of 7.3 per cent. in patients who received such pooled plasma. It is now made in small pools from the donations of not more than ten donors. This has appreciably reduced the incidence of the disease. A single infected donor will contaminate an entire pool. This disease will continue to occur since there is as yet no test which will detect the icterogenic agent other than inoculation of human volunteers. Moreover, not all volunteers inoculated will develop the disease. The virus resists heat and disinfectants (Bradley, *et al.*, 1946); recent work, however, suggests that it may be destroyed by ultra-violet light. It is regrettable that there is still considerable laxity among clinicians in recording serial numbers of bottles of plasma or blood transfused; such recording is essential and should be compulsory. When the serial number of a bottle of plasma (or blood) which has caused the disease is known, it at once becomes feasible to withdraw all bottles of plasma of the same batch, and to track down and eliminate infected donors from the donor panel. It is too early yet to state what the late results of this disease may be. Cirrhosis is a possibility. Patients apparently dying of the disease have been successfully treated by intravenous injections of protein hydrolysate (Bradley, *et al.*, 1946).

(To be continued)