BLOOD SUBSTITUTE SOLUTIONS

BY

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This is the second of two articles by Dr. Bogomolova. Her first, on "Medical Blood Preparations," appeared last week (August 4, p. 294).

The problem of blood substitutes has attracted considerable attention. Thousands of papers on the subject have been published, but so far no substitute solution has been found which fully satisfies the clinicians.

I. E. Gagen-Torn (1895) states that "intravenous injections were suggested for the first time by Guerman in Russia in 1830." In 1832, Latta first injected a saline solution into the vein, in a case of cholera. Since then blood-substitute solutions have been frequently used, but it is only since the second world war that the attention of scientists throughout the world has been attracted to the problem. In the past few years laboratories have been set up in many countries with the object of studying blood substitutes, and extensive clinical tests have been carried out.

Types of Substitute

It is impossible to arrive at an understanding of the vast number of suggested blood substitutes unless they are correctly classified (Amberson, 1937). Of the great number of classifications suggested the following division into three groups seems to be the most acceptable: (1) saline crystalloid solutions; (2) colloidal solutions; (3) combined solutions (Bagdassarov, 1955).

Saline solutions are subdivided into three subgroups: ordinary saline or glucose-saline; anti-shock solutions containing narcotics to act on the nervous system; and complex saline solutions, used in the treatment of sepsis and other conditions.

Colloidal solutions are subdivided into five subgroups: those containing elements of human blood; those containing carbohydrate colloids of high molecular weight; those of a chemical nature; those acting on the capillaries (pharmacodynamic); and those consisting of albumin.

Combined solutions are obtained by mixing solutions with different properties and adding drugs to them. These include anti-shock saline solutions with blood added to them, and hydrolysates with human plasma.

Clinical Requirements

Blood substitutes should meet the following requirements (Gropper *et al.*, 1952; Petrov, 1954): They should (1) replace fluid lost from the circulation after haemorrhage; (2) combat shock by improving the blood circulation; (3) reduce dehydration and prevent rapid clotting of the blood; (4) combat intoxication; (5) correct hypoproteinaemia and cachexia; and (6) raise the protective capacity of the body.

In accordance with these requirements, the following factors should be assessed when appraising blood-substitute solutions:

(1) *Substitution Action*.—This can be judged by the rise in the blood pressure and the duration of its maintenance at a high level, the elimination of haemodynamic disorders, and the restoration of the blood circulation.

(2) *Antishock Action*.—Elimination of shock should be speedy and lasting.

(3) *Hydrating Action*.—In many diseased states water balance is disturbed and the tissues are dehydrated. In

such cases thrombosis is frequent and the circulation is impaired. The hydrating effect of the solutions should lead to the rapid cessation of blood clotting.

(4) *Detoxicating Action*.—Detoxication is necessary in cases of intoxication due to endogenous poisons formed in the course of various diseases (burns, obstructions, sepsis, etc.).

(5) *Alimentary Effect*.—In a great number of cases the carbohydrate and protein balance is disturbed. Parenteral injection of appropriate nutrient solutions helps to eliminate hypoproteinaemia and improve the exchange.

(6) *Stimulative Effect*.—This manifests itself in the stimulation of various organs and systems. Metabolism improves, the functioning of the endocrine glands is enhanced, and the processes of regeneration are accelerated. It is most important that the blood substitute solution should stimulate blood formation: this is particularly valuable in cases of anaemia.

However, no solution fully satisfies all these requirements. It is for this reason that a number of different types of solution are needed in clinical practice, and it is our firm belief that modern clinics should have a variety of blood substitutes at their disposal.

The blood substitute should, above all, be isotonic or slightly hypertonic in relation to blood, its osmotic pressure approximating to that of blood plasma.

Undesirable Properties.—A blood substitute solution should be free of the following undesirable properties: (a) It should not be pyrogenic. Its injection into the vein of a rabbit should not raise the body temperature by more than 0.6° C. (b) It should not possess primary toxicity—that is, it should not cause any toxic manifestations during injection either in normal or in exsanguinated animals. (c) No toxic effects should result from repeated injections, and histological examination of the organs of experimental animals should show no pathological changes. (d) The solution should not be anaphylactogenic. It should not produce any signs of anaphylaxis even when injected repeatedly after periods of maximum sensitization. (e) Transfusion of the solution should not affect the recipient's blood coagulation, neither should it cause wound-bleeding. (f) When mixed with blood the solution should not cause agglutination or clumping of erythrocytes, nor should it interfere with the blood-grouping of the patient after transfusion. (g) It should be capable of being completely eliminated from the body in the first few days after its injection or should be utilized by the body; it should not remain in the tissues or organs for any length of time. (h) When injected intravenously the solution should not cause nausea, vomiting, or vascular reactions, which have hitherto been characteristic of solutions containing amino-acids.

Other Desirable Properties

The method of manufacture, and the conditions and duration of storage, should allow of the widest use of the solution. Therefore the solution should be capable of being manufactured from readily available raw materials; its preparation should be as simple as possible; when manufactured on a large scale it should be of standard quality and, if a colloid solution, of constant molecular weight; it should not vary under different conditions of storage in a liquid state (low or high temperatures); it is an advantage if it can be dried for prolonged storage; and it should stand repeated sterilization without any change in its properties.

Preparations Used in the Soviet Union

Now let me describe the blood substitutes in use in the Soviet Union.

Of the saline solutions hypertonic sodium chloride is preferred; we firmly believe that such solutions are more beneficial, since they remain longer in the blood stream (Petrov, 1945). As in other countries, such ordinary saline solutions have recently been replaced by improved colloidal solutions.

We also use glucose-saline anti-shock solutions containing alcohol and various narcotic drugs (Filatov, 1944, 1948). The Leningrad Institute of Blood Transfusion has developed, and is widely applying, two solutions in particular: No. 28, containing morphine as a narcotic, and No. 43, containing alcohol and barbiturates.

Of the substitutes containing elements of human blood, Petrov's liquid, a saline solution containing 10% of stored blood, was widely used during the second world war (Petrov *et al.*, 1954). It was given in 1,500,000 cases, and was highly beneficial in the treatment of the wounded.

Of solutions prepared from elements of human blood, we attach particular importance to-day to a new solution called "aminokrovin" (Tschapligina, 1955). It is obtained by oxygen hydrolysis of the residual blood clot after the extraction of serum, of the erythrocytic mass obtained after skimming plasma, of the blood of corpses, or of retroplacental blood. This solution fully meets clinical requirements, and conforms to most of the criteria of a satisfactory blood substitute. Therapeutically it is an effective replacement, anti-shock, hydrating, and detoxicating fluid, and its nourishing and stimulating properties are excellent. It has no harmful effects. Accordingly transfusion of this solution is indicated in cases of blood loss, shock, burns, sepsis, intestinal obstruction, cachexia, hypoproteinaemia, and delayed healing as well as in various surgical conditions.

Carbohydrate colloidal blood substitutes are used all over the world and merit the keenest attention. Foremost among these solutions are undoubtedly those of the dextran type (Maycock, 1952; Bell, 1954). Two such solutions have been made in the U.S.S.R.—polyglukin and syncol. The latter has some admirable properties: it relieves shock safely, and compensates blood loss satisfactorily (Goschkina, 1954; Kulagin, 1954). But it has some minor drawbacks, in that it causes slight bleeding from wounds and affects the coagulability of the blood. The latter drawback has, however, very little practical importance. These disadvantages, found in every colloidal solution of the dextran type, are in the case of syncol fully compensated by its effectiveness in cases of shock and blood loss of moderate gravity. In addition, the solution is of great value in preparing leucocyte suspensions and certain types of stored blood, as well as in other fields of medicine.

Recently we have succeeded in obtaining a high-molecular colloidal carbohydrate solution without the use of bacterial synthesis. The solution, named "AP," is a colloidal polysaccharide (Bogomolova *et al.*, 1954). Some progress has also been made in the preparation of pectine solutions. The Leningrad Institute of Blood Transfusion has now completed its research on this.

With regard to colloidal solutions of a chemical nature, our attention has now turned to various polyvinyl derivatives. One of these solutions has been tested at the Leningrad Institute of Blood Transfusion. This is a blood-substituting solution of the polyvinylpyrrolidone type (Ouschakov *et al.*, 1954; Schostakowski and Wassilief, 1954). Experimental investigations have proved the excellent qualities of the solution both for blood replacement and for combating shock.

Albumin and Other Solutions

A large group of blood substitutes are made from albumin. Their importance is unquestionable, above all in cases of cachexia.

The results of the work of many investigators studying the preparation of solutions of modified heteroproteins suggest that this problem is nearing solution (Bellenki, 1950). However, even now we cannot claim to have protein solutions that fully satisfy the clinician. Their main deficiency lies in the incomplete elimination of anaphylactogenic properties (Fedorof *et al.*, 1953).

Leontiev, in 1934, was working on this problem, and the "napprin" solution he suggested was the first preparation of this kind (Tschurcina and Leontiev, 1945).

A heterogenous serum, prepared according to Professor N. G. Belenky's prescription, has been widely used in the U.S.S.R. in recent years. By means of special treatment its antigenic properties have been considerably reduced. This serum may be given in amounts of from 2 to 4 litres, and it is useful in cases of serious blood loss, traumatic shock, and hypoproteinaemia. Efforts are continuing to find a new heterogenous protein serum completely devoid of any antigenic properties (Filatov, 1943, 1948; Petrov *et al.*, 1952).

Such a preparation has been produced by scientists in L'vov and named VK-8. The injection of this solution does not produce any anaphylactic reactions. It has been found to be a highly effective blood substitute (Petrov, 1954; Grosdof, 1955).

Great attention has lately been given to protein hydrolysates (Romanova, 1954). Many such solutions are in use in a number of countries. A casein hydrolysate has been produced at the Central Institute of Blood Transfusion in Moscow. Other solutions are being prepared at the Leningrad Institute of Blood Transfusion. Solution L 103 is an incomplete acid hydrolysate of animal blood. The ingenious use of ion-exchange resins in its production makes possible its large-scale manufacture. Experimental and clinical investigations have proved its high qualities as a nutriment and as a blood substitute (Petrov *et al.*, 1954).

Another protein hydrolysate—"aminol"—has also been produced at the Leningrad Institute. It is obtained by fermentative hydrolysis of animal blood.

Combined Solutions

Several combined solutions have been suggested in the Soviet Union. The most promising is the amino-protein solution consisting of the L 103 solution with 1% of human plasma added. The addition of plasma increases the solution's colloidal properties and makes it more easily assimilated by the body.

UBP, another combined solution, is a carbohydrate and protein plasma-substitute. It is composed of syncol and human blood plasma. Yet another solution of the same type is a combination of syncol and protein hydrolysate. These solutions have been shown to have a high therapeutic value. These combined solutions can be prepared immediately before transfusion; hence it is important to have at hand the basic solutions needed.

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