Serum Transfusion as a Hemostatic Procedure

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Serum transfusion of 15 to 55 ml was done in 30 cases, and prothrombin time, thrombo-test, and plasma clot time were measured at various intervals. A marked shortening of clotting time was seen in 13 of 17 cases with normal coagulability and 11 of 13 cases of abnormal blood clotting. Favorable clinical effects were seen in 5 of 8 cases of leukemia including a case with oozing from the tongue, and also in cases of anemia, gastric ulcer, and essential hematuria. The prolonged plasma clot time was markedly shortened in two cases of hemophilia A, and in each of the cases of liver damage and stomach cancer, and a case under Warfarin treatment.

Only negligible side-effect was seen in a few cases, and the serum transfusion was considered to be a useful hemostatic procedure in various hemorrhagic conditions.

In the last decade much progress has been made in the study of blood coagulation and hemostasis. In company with the progress of anticoagulant therapy, the mechanism of blood coagulation has been greatly elucidated, and the factors of blood coagulation were defined by the International Committee on Blood Coagulation in 1962. Apart from some controversies on the theoretical model and definition, the factors are generally accepted.

Certain factors of blood coagulation were made clear by the studies of the cases of hemorrhagic diathesis. Patek (1937) had first recognized in the classical hemophilia a defect in the plasma globulin which is now called antihemophilic globulin (AHG). Then, the deficiencies of plasma thromboplastin component (PTC) and plasma thromboplastin antecedent (PTA) were discovered by Aggeler (1952) and Rosenthal (1953).

Furthermore, not only the congenital or familial coagulation defects such as Hageman traits and Stuart factor deficiency, but also the acquired coagulation defects in liver damage, leukemia, aplastic anemia and others have been confirmed. Thus, the pathophysiology of hemorrhage in hemophiliacs or hemophiloids and in acquired hemorrhagic diathesis has been clarified to a great extent along with the progress in the analysis of physiochemistry of the blood coagulation. Therefore, reasonable treatments have been clinically attempted with new hemostatics such as vitamin K, adrenochromes, steroid hormones, tissue extracts and trans-4-aminomethyl cyclohexane-carboxylic acid.

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However, these modern hemostatics are still within the scope of 'passive' management, and blood or plasma transfusion is the 'active' and best treatment for hemorrhagic disorders even today. But, repeated or massive blood transfusion is apt to produce untoward complication and side-effects, and a better procedure for hemostsis is still required.

It has been known that serum accelerates blood coagulation in vitro. And, Yoshida recently made an extensive study on the clot promoting serum factor(s) (CPSF), and found that serum was approximately 50 times as effective as plasma in clot promotion of normal plasma and 12 times of Warfarin-treated plasma, and concluded that serum transfusion would be a useful hemostatic procedure. The effectiveness of serum transfusion in a PTA deficient patient reported by Campbell et al. encouraged us to attempt a clinical investigation. From our previous work and from the work of others, we have evidence enough to assert that serum transfusion is a better hemostatic procedure than plasma transfusion in general hemorrhagic disorders, since hemostasis is initiated by the coagulation of blood.

There are some different opinions concerning the clinical effect of serum transfusion, but to my knowledge, there is no report on serum transfusion in acquired hemorrhagic disorders. The purpose of this paper is, therefore, to study and clarify the hemostatic effect of serum transfusion on blood coagulability in various hemorrhagic disorders.

**Review of Literature**

Hayem first reported the serum transfusion in 1923. Feissly demonstrated that serum could induce a clot promotion in vivo. Wessler and his associates recently carried out extensive studies on serum induced thrombosis in animals and contributed much to the study of intravascular coagulation and of the serum factor(s). In the early reports they ascribed the inducer of thrombosis to factor VII, but later they concluded that the inducing factors might be factors IX, XI and XII rather than factor VII. Thus the factor VII was thought to be responsible only for the transient hypercoagulability. According to Wessler and his associate, the serum thrombotic accelerator (STA) was completely adsorbed by barium sulfate, and for its activation Hageman factor, PTA, and PTC were necessary. Thrombus formation expressed by score was quantitatively related to the amount of serum infused. Serum infusion induced an immediate shortening of clotting time in the recipient animal, resulting in impaired thromboplastin generation test. Otherwise, there was no significant general side-effect by the serum infusion in the animal experiments. Wessler suggested that the thrombotic activity of serum acted upon a specific pathway in the coagulation mechanism of the recipient animal rather than through other physiologic alterations.

In 1964, Colman and Alexander reported a serum factor different from STA. With administration of lanthanides or actinides a marked impairment in thromboplastin generation occurred promptly owing to the formation of a reversible complex of the compounds with serum protein, which he named thorium vulnerable factor (TVF). This was adsorbed by barium sulfate and precipitated at 50 to 60% (NH₄)₂SO₄ saturation. Poller demonstrated the presence of a powerful heparin antagonist in serum and suggested that this might play an important role in the heparin 'resistance' in fresh thrombosis. This may be explained by the assumption that the presence of such substance
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as heparin antagonist in serum accelerates the clot promoting activity of serum.

There is abundant evidence supporting that serum factors are activated forms of plasma factors, and the former shows higher activity of coagulation and higher efficacy than the latter at least in the correction of serum factor(s) deficient hemorrhagic disorders. So, up to the present the serum transfusion has been undertaken mainly in PTC or PTA deficient patients or animals.

As for the clinical effectiveness of serum transfusion as a hemostatic procedure, several clinical reports have appeared in the literature, but the results are conflicting. In 1956 Heni and Krauss carried out serum transfusion of 150 to 250 ml as often as 9 times in a 41-year-old hemophilia B patient with definite favorable results. Shortening of clotting time was more remarkable with 200 ml serum than with 350 ml fresh blood. It was said that the effectiveness of serum transfusion seemed to decrease with repeated infusion. Campbell et al. reported that in a PTA deficient patient complete in vivo correction of clotting time was seen by infusion of 200 ml of normal 24-hour-old barium sulfate treated serum, whereas the same amount of fresh plasma showed only 50% correction, and that the serum transfusion was a more potent therapeutic measure in PTA deficiency and worthy of consideration especially in emergency. In two cases of hemophilia B, serum transfusion of 100 to 150 ml was repeatedly attempted by Welsh with interesting results. The effect of serum in correcting prolonged clotting time was stronger and longer (at least 17 days) than that of plasma (less than 24 hours). He observed that in both patients a more prompt clinical improvement was achieved by serum therapy than by plasma therapy.

Contrary to the above reports, Nour-Eldin and Wilkinson reported in 1958 that in 3 cases of hemophilia B serum transfusion of 150 to 400 ml could not definitely increase the production of plasma thromboplastin. They stated that extraneous serum might be quickly destroyed and that the beneficial effect of serum on the blood clotting time might be due to the component(s) other than Christmas factor or unknown factors contributing to these processes.

Quick and Hussey preferred fresh or fresh-frozen plasma to serum in correcting abnormal coagulability in PTC deficiency, because hemophilia B plasma contained thromboplastinogen in a normal concentration which could be activated by normal plasma and hemolysate containing "Erythrocin", a new potent clotting factor in erythrocytes. According to the results of Mustard et al., both serum and plasma transfusions were effective in correcting the clotting defect in three canine hemophilia B. The increased factor IX activity in the transfused animals was proportional to the activity of the transfused materials.

Recently Fantl and Sawers performed the serum transfusion of 1,100 ml in cases of hemophilia A and von Willebrand's disease with the factor VIII in 10% and 1% respectively, and compared the result with that of plasma transfusion. Serum as well as plasma caused some shortening of the clotting time, but no shortening of bleeding time in the latter case. A component stimulating factor VIII activity in vivo was considered to be present both in citrated plasma and in serum.

As mentioned above, the results of serum transfusion in the literature are conflicting.

**Materials and Methods**

1) **Materials**

a) Seventeen cases with normal clotting time consisting of 12 cases without bleeding evidence, and 5 cases with bleeding evidence (including each one case of gastric ulcer, gastrointestinal hemorrhage of unknown origin, pulmonary tuberculosis, lung cancer and essential hematuria).

b) Thirteen cases with abnormally prolonged clotting time consisting of two cases of hemophilia A, which was verified by the modified thromboplastin generation test (TGT),
one case of aplastic anemia with marked thrombocytopenia and increased capillary fragility, one case under anticoagulant therapy of Warfarin for femoral thromboangitis, in which the coagulability had to be reversed to normal in a few hours because of acute appendicitis, one case of stomach cancer with prolonged clotting time, and 8 cases of leukemia of various types.

2) Fresh plasma used for transfusion was prepared by drawing nine volumes of blood from apparently normal subjects with the same ABO blood group as the recipient into a syringe containing one volume of 3.8% sodium citrate solution and by centrifugation at 2,000 rpm for 15 minutes.

3) The serum for transfusion prepared from fresh plasma was used in 15 cases, and stored bank blood plasma containing ACD solution was used in 12 cases. The plasma was allowed to clot by adding 1/4 volume of 2% calcium chloride solution in a bottle and to stand at 20°C for 15 minutes. The clot was compressed by glass rod to accelerate clot retraction. The serum was transferred into a syringe and diluted with an equal volume of normal saline before infusion.

4) Antihemophilic plasma of Hyland Lab., U.S.A.

5) Calcium: 1/40 M CaCl$_2$ solution.

B) Methods

1) All plasma was prepared by adding one volume of 1/10 M sodium oxalate to ten volumes of whole blood and by centrifugation at 2,000 rpm for 5 minutes.


3) Thrombo-test (TT) (partly modified Owren's method): 2.2 ml of calcium solution were added to each vial, and 0.1 ml of the solution was blown into 0.1 ml of plasma in a test tube at 37°C and clotting time was determined. Normal range: 40 to 60 sec.

4) Plasma clot time of plasma recalcification time (PCT). Normal range: 86 to 110 sec.

5) Clotting time and plasmin activities were measured 10 to 15 minutes before and 1/4, 1, 2 and/or 3,6 and 12 hours after the transfusion.

6) Studies of plasmin activity were carried out as follows:

a) Fibrin plate method by Astrup-Muellertz. Normal range: 100 to 200 mm$^2$ in standard plate.

b) Fibrinogen tyrosine method after Ratnoff and Menzie. Normal range: 250 to 350 mg/100 ml.

c) Total plasmin: Maki's modification of Kunitz's method. Normal range: 8 to 12 × 10$^{-3}$ units/ml.

d) Immediate inhibitor: Maki et al.'s modification of Norman's method. Normal range: 3 to 7 × 10$^{-2}$ units/ml.

e) Fibrinolysis: Maki's modification of von Kaulla's method. Normal range: 40 to 60 γ/100 ml.

f) Caseinolysis: Maki's modification of Kunitz's method. Normal range: 0 to 20 γ/100 ml.
Casein, trypsin thrombin, fibrinogen and streptokinase used in this study were commercial products of casein nach Hemmarsten (Merck, Germany); trypsin, Mochida; thrombin, Mochida (Mochida Pharm. Co., Tokyo, Japan); bovine fibrinogen, Armour Co., Kankakee, Illinois, U.S.A.; and varidase, Lederle Co., New York, U.S.A.

Results

A) Cases with normal PCT

Fifteen to 48 ml of serum were transfused in 17 cases with normal PCT. The results are shown in Tables 1 and 2. There was no difference in response according to different procedures in serum preparation, nor was there any clear relation between the amount of transfused serum and the effectiveness or side-effects.

In 2 of 5 cases with bleeding evidence a marked clinical effect was obtained by the serum transfusion. In Case 1 of a 47-year-old male with gastric ulcer the

<table>
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<tr>
<th>No.</th>
<th>Diagnosis</th>
<th>Sex</th>
<th>Age</th>
<th>Body weight</th>
<th>Serum amount</th>
<th>Original PCT</th>
<th>Effect on PCT</th>
<th>Side-effect</th>
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<tbody>
<tr>
<td>1</td>
<td>Bleeding gastric ulcer</td>
<td>M</td>
<td>47</td>
<td>49 kg</td>
<td>48 ml</td>
<td>107 sec</td>
<td>Effective</td>
<td>No</td>
</tr>
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<td>2</td>
<td>GI hemorrhage</td>
<td>F</td>
<td>21</td>
<td>40</td>
<td>45</td>
<td>118†</td>
<td>Effective</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Pulm. tbc. with bloody sputum</td>
<td>M</td>
<td>64</td>
<td>51</td>
<td>40</td>
<td>108</td>
<td>Effective</td>
<td>Headache</td>
</tr>
<tr>
<td>4</td>
<td>Lung cancer with bloody sputum</td>
<td>M</td>
<td>48</td>
<td>48</td>
<td>15</td>
<td>104</td>
<td>Effective</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Essential hematuria</td>
<td>F</td>
<td>48</td>
<td>47</td>
<td>15</td>
<td>99</td>
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<td>No</td>
</tr>
<tr>
<td>5*</td>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>98</td>
<td>Effective</td>
<td>Mild headache</td>
<td></td>
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<tr>
<td>6</td>
<td>Gastric ulcer</td>
<td>F</td>
<td>39</td>
<td>50</td>
<td>20</td>
<td>66</td>
<td>Ineffective</td>
<td>No</td>
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<tr>
<td>7</td>
<td>Gastric ulcer</td>
<td>M</td>
<td>87</td>
<td>60</td>
<td>20</td>
<td>70</td>
<td>Ineffective</td>
<td>No</td>
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<tr>
<td>8</td>
<td>Aplastic anemia</td>
<td>M</td>
<td>19</td>
<td>56</td>
<td>20</td>
<td>69</td>
<td>Effective</td>
<td>No</td>
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<tr>
<td>9</td>
<td>Sarcoïdosis</td>
<td>M</td>
<td>25</td>
<td>67</td>
<td>20</td>
<td>82</td>
<td>Effective</td>
<td>No</td>
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<tr>
<td>10</td>
<td>Duodenal ulcer</td>
<td>F</td>
<td>32</td>
<td>47</td>
<td>20</td>
<td>99</td>
<td>Effective</td>
<td>No</td>
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<td>11</td>
<td>Stomach cancer</td>
<td>M</td>
<td>45</td>
<td>41</td>
<td>20</td>
<td>98</td>
<td>Effective</td>
<td>Palpitation</td>
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<td>12</td>
<td>Peritonitis tbc.</td>
<td>F</td>
<td>34</td>
<td>36</td>
<td>20</td>
<td>81</td>
<td>Ineffective</td>
<td>Palpitation</td>
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<td>13</td>
<td>Familial tremor</td>
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<td>48</td>
<td>20</td>
<td>87</td>
<td>Effective</td>
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<td>14</td>
<td>Xanthoma</td>
<td>F</td>
<td>32</td>
<td>40</td>
<td>25</td>
<td>100</td>
<td>Effective</td>
<td>No</td>
</tr>
<tr>
<td>15</td>
<td>Splanchnophtosis</td>
<td>F</td>
<td>51</td>
<td>39</td>
<td>20</td>
<td>101</td>
<td>Ineffective</td>
<td>Mild headache</td>
</tr>
<tr>
<td>16</td>
<td>Chronic hepatitis</td>
<td>M</td>
<td>36</td>
<td>60</td>
<td>20</td>
<td>134†</td>
<td>Effective</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>Cholecystopathy</td>
<td>F</td>
<td>36</td>
<td>42</td>
<td>15</td>
<td>90</td>
<td>Effective</td>
<td>No</td>
</tr>
</tbody>
</table>

* Transfusion was repeated in case No. 5 on different occasions.
† In these cases PCT was slightly prolonged.
transfusion of 48 ml of fresh serum shortened the clotting time to a 'hypercoagulable state' (Fig. 1). Clotting time, however, returned to normal range within 17 hours. Fecal occult blood disappeared thereafter. In Case 5 of a 48-year-old female suffering from essential hematuria, who had been treated with various hemostatics in vain, urinary red cells decreased definitely following the serum transfusion and the clotting time shortened, although a complete management of hematuria was not attained. To the latter patient serum transfusion was performed twice. Apart from temporary mild headache at the second transfusion, no other side-reaction was observed.

In Case 2 of a 21-year-old female with gastrointestinal hemorrhage of unknown origin, transfusion of 45 ml of fresh serum caused a significant shortening of PCT and PT (Fig. 2), although clinically no noticeable hemostatic effect was seen. In Cases 3 and 4, shortening of the clotting time was seen, but bloody sputum persisted.

To sum up, the clotting time was shortened by serum transfusion in all the cases with hemorrhagic evidence, and in 8 of the 12 cases without hemorrhagic
Fig. 2. Infusion of 45 ml fresh serum to a 21-year-old case of gastrointestinal hemorrhage of unknown origin.

Fig. 3. Effect of serum transfusion on PCT of 13 accelerated cases in normal coagulation group.
Fig. 4. Effect of serum transfusion on PCT; original and maximal acceleration time in normal group.

Fig. 5. Effect of serum transfusion on PCT of 4 unchanged or prolonged cases in normal group.
Fig. 6. Effect of serum transfusion on PT & TT; shortened cases in normal group.

Fig. 7. Infusion of 20 ml of fresh serum and the same amount of fresh plasma to a 45-year-old case of stomach cancer.

Fresh serum:  
Fresh plasma: ---
evidence. There was no conspicuous change in PT and TT as in PCT. The results of these tests are summarized in Table 2:

Fig. 3 illustrates the course of PCT in 13 cases with shortening of PCT after serum transfusion. The thick line represents the mean value. The maximum shortening of clotting time was attained within 15 minutes after transfusion in 6 cases, after 1 hour in 3 cases and after 2 or 3 hours in 4 cases. In Cases 9–11 W-shaped curves were observed. It is obvious from the mean value that in most cases the maximum shortening was attained immediately after transfusion, the clotting time then gradually returning to the original value. The duration of effectiveness of serum transfusion in the normal group is estimated for about 6 hours. Fig. 4 illustrates the maximum shortening of the PCT in these cases in comparison with the original clotting time. The thick line represents the mean value which shows shortening of the maximum clotting time by 25 seconds.

Fig. 5 shows the course of coagulability in cases where PCT was unchanged or prolonged after the transfusion. It is of interest that most of the patients had originally a rather short clotting time. As for PT and TT, there was no difference in effectiveness between hemorrhagic and non-hemorrhagic cases as shown in Table 2. The changes in both tests in the accelerated cases are shown in Fig. 6. The clotting time shortened gradually, and the maximum shortening was attained in 2 hours, but some effectiveness was observed over 6 hours.

In the comparative study of the effect of serum transfusion and that of fresh plasma, there was a clear difference, as shown in Fig. 7. It was obvious that, unlike the serum transfusion, the plasma transfusion did not cause any change in the clotting time in cases of normal PCT.

B) Cases with abnormal PCT

1) Hemophilia A. Two cases of hemophilia A, which was proved by TGT, were subjected to the study.

Case 1. H.A., 21-year-old male: This patient had had bleeding tendency since childhood, such as hematuria, tarry stool, subcutaneous hematoma and epistaxis. He was admitted to our department because of uncontrollable bleeding after extraction of the left inferior first great molar tooth. 25 ml of serum, antihemophilic plasma (Hyland lab.) and fresh plasma were transfused at 48-hour intervals. Figs. 8–10 give the result of each infusion, which indicates that fresh serum can correct the clotting time of hemophilia A as effectively as fresh plasma. The duration of effectiveness of serum was 6 hours, which was the same as that of fresh plasma. Serum was superior to antihemophilic plasma, the effect of which lasted for less than 6 hours.

Case 2. H.O., 30-year-old male: This patient also had a bleeding tendency with family history since 19 years of age. He was hospitalized because of subcutaneous hematoma in the gluteal region. He was transfused 25 ml of serum and 48 hours later the same amount of fresh plasma. As shown in Fig. 11, the plasma
Fig. 8. Infusion of 25 ml fresh serum to a 21-year-old case of hemophilia A.

Fig. 9. Infusion of 25 ml antihemophilic plasma (Hyland Lab. USA) to the same case in Fig. 8.
Fig. 10. Infusion of 25 ml fresh plasma to the same case in Fig. 8.

Fig. 11. Infusion of 25 ml of fresh serum and the same amount of fresh plasma to a 30-year-old case of hemophilia A.

Fresh serum: ————  Fresh plasma: ——-
showed practically no effect in correcting the clotting time, whereas the serum showed an obvious effect. The duration of the effect was approximately 6 hours. In both cases there was no conspicuous change in PT and TT, which were originally normal. In Case 2, there was no significant change in plasmin activity after the transfusion.

2) **Aplastic anemia.** A 42-year-old male suffering from aplastic anemia for 3 years and 3 months, with 4.9 g/100 ml hemoglobin, $173 \times 10^4$ red blood cells and 3,700 white blood cells. The thrombocytes were extremely reduced to 43,000/comm, and petechiae were found on the arms and loins. A significant shortening of the clotting time was observed following intravenous instillation of 50 ml of fresh serum (Fig. 12). Abnormal bleeding time of 9.5 minutes was corrected to 4.5 minutes, and purpura on Rumpel-Leede's capillary fragility test was less marked after the transfusion, when the test was done on the right arm before and on the left after the transfusion.

3) **Patient under anticoagulant therapy.** A 35-year-old male had suffered from thromboangitis obliterans of the femoral artery for 2 years. His clotting time indicated a 'hypercoagulable state' before anticoagulant therapy. Warfarin had been administered for 40 days with a maintenance dose of 7.5 mg/day. Twenty ml of serum transfusion for an emergency operation shortened the clotting time immediately, but only temporarily, as shown in Fig. 13. The patient showed no side-effect and tolerated the serum transfusion and operation very well.

4) **Stomach cancer.** A 47-year-old male had abdominal swelling and large tumor at the greater curvature of stomach with severe anemia of hemoglobin 8.0
Fig. 13. Infusion of 20 ml fresh serum to a 35-year-old case under Warfarin treatment due to thromboangitis obliterans.

Fig. 14. Infusion of 18 ml fresh serum to a 47-year-old case of stomach cancer.
g/100 ml and hypoproteinemia 4.4 g/100 ml. There was no evidence of hepatic lesion, but the coagulation time was prolonged. Transfusion of 18 ml of fresh serum resulted in shortening of PCT from abnormal range to normal, and it was still in the normal range after 6 hours. A slight shortening of PT and TT was observed (Fig. 14).

5) Hepatitis chronica. Case 16 of a 36-year-old male (Table 1) exhibited a slight prolongation in clotting time (PT 18.0 sec, TT 61 sec and PCT 134 sec). This patient was admitted to the hospital because of long-lasting severe icterus with total serum bilirubin of 12 mg/100 ml on admission, which after the treatment of 1-year duration decreased to 2.5 mg/100 ml (direct 2.0 mg/100 ml; indirect 0.5 mg/100 ml). Other laboratory data were as follows: Z.S.T. 17.1 K.U., T.T.T. 3.9 M.U., T.P. 6.4 g/100 ml, A/G 0.6, GOT 11.0 K.U., and GPT 20.0 K.U. There were no esophageal varices, but slightly hard liver edge was palpable. The transfusion of 20 ml of serum shortened PT to 17.6 sec, TT to 47 sec, and PCT to 101 sec.

6) Leukemia. Serum transfusion was done in 8 cases of leukemia: a case of chronic myelocytic leukemia, 2 of monocytic leukemia and 5 of acute myelocytic leukemia, including one of promyelocytic leukemia. In Table 3 the amount of transfused serum and the result are summarized. In all the cases PCT was abnormal before serum transfusion. As shown in Fig. 15, shortening of PCT within 15 minutes after transfusion was seen in 6 cases, and prolongation in 2 cases, in which the clotting time, however, returned to normal after one hour and was still shortened by 20% of the original after 12 hours.

The mean value of shortening of the clotting time was about 15% of the original value. The clotting time was shortened in 15 minutes to 3 hours after transfusion, and then gradually prolonged even to 25% in 6 to 24 hours. PT and TT showed a temporary prolongation in 2 and 3 cases respectively. In both tests, however, the mean value showed no significant change (Fig. 16).

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Type of leukemia</th>
<th>Serum amount</th>
<th>Plasma clot time</th>
<th>Clinical effect</th>
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<tr>
<td>1</td>
<td>Mon. L</td>
<td>25 ml</td>
<td>Initial 182 sec</td>
<td>Petechiae,</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>15 min after 172 sec</td>
<td>prolonged bleeding</td>
</tr>
<tr>
<td>2</td>
<td>CML</td>
<td>25</td>
<td>130</td>
<td>Petechiae</td>
</tr>
<tr>
<td>3</td>
<td>AML</td>
<td>30</td>
<td>156</td>
<td>Petechiae</td>
</tr>
<tr>
<td>4</td>
<td>Mon. L</td>
<td>55</td>
<td>230</td>
<td>Oozing from</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>the tongue</td>
</tr>
<tr>
<td>5</td>
<td>AML</td>
<td>45</td>
<td>223</td>
<td>Petechiae,</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>prolonged bleeding</td>
</tr>
<tr>
<td>6</td>
<td>AML</td>
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<td>7</td>
<td>AML</td>
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<td>170</td>
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<td>8</td>
<td>APromyL</td>
<td>55</td>
<td>152</td>
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<td></td>
<td></td>
<td></td>
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<td>prolonged bleeding</td>
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TABLE 3. Serum transfusion in leukemia
Fig. 15. Effect of serum transfusion on PCT in 8 cases of leukemia.

Fig. 16. Effect of serum transfusion on PT & TT in 8 cases of leukemia.

Five of 8 cases were considered clinically to be improved. There were seen decrease of purpura, stopping of oozing from the tongue, reduction of capillary fragility, shortening of bleeding time and improvement from malaise. Clinically ineffective cases were the following three. In a case complicated with bleeding gastric ulcer, the autopsy revealed a naked arterial vessel in the center of the ulcer. A second case of acute promyelocytic leukemia with hypofibrinogenemia
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fell into a state of afibrinogenemia with marked prolongation of clotting time, and the genital bleeding and petechiae were not improved. A third case with acute myelocytic leukemia in a terminal state showed no effective response.

C) Plasmin activity

Plasmin activity was measured in 3 cases. A 57-year-old female (Case 4 in Table 3) with monocytic leukemia and gingival bleeding had been treated with various hemostatics including ε-aminocapric acid, steroids, adrenochromes and others before admission. Eight weeks after admission a newly developed oozing from the surface of the tongue became severe and continued for 4 days in spite of the administration of various hemostatics. Thrombocytes were $9.4 \times 10^4$, RBC $392 \times 10^4$, WBC 1500/cmm, and bleeding time 4.5 min. On the 4th day of oozing a 55 ml serum transfusion was performed. Dramatic effect was seen and the oozing ceased completely 6 hours after transfusion. As shown in Fig. 17, a marked shortening of PCT occurred soon after transfusion, but it returned once to the original value. However, the shortening appeared again after 3 hours. PT and TT were shortened soon after transfusion, but not so markedly as PCT. The study of plasmin activity in this case revealed that the lysed area of the heated fibrin plate decreased gradually with time. The lysed area by euglobulin plus streptokinase was $25 \text{ mm}^2$ initially, and then decreased to $13 \text{ mm}^2$ in 3 hours and disappeared 6 to 24 hours after transfusion. Measurement of the lysed area by serum plus streptokinase revealed a similar tendency. On the standard plate there was no marked decrease of the lysed area till 6 hours after transfusion, but the area

![Fig. 17. Infusion of 55 ml fresh serum to a 57-year-old case of monocytic leukemia.](image)
decreased almost to zero in 24 to 36 hours. The amount of fibrinogen was originally normal and no significant change occurred. Oozing from the tongue has not occurred thereafter.

A 16-year-old female (Case 8 in Table 3) had acute promyelocytic leukemia. She was suffering from genital bleeding, petechiae and malaise, which were refractory to every treatment. Thrombocytes were $1.2 \times 10^4$, RBC $224 \times 10^4$, WBC 1800/cmm, and bleeding time 8.5 minutes. The result of a 55 ml serum transfusion is shown in Fig. 18. There occurred a marked prolongation of PCT and PT 15 minutes after transfusion. TT was unchanged in 15 minutes, but prolonged in 2 hours. The clotting time returned to the initial value after 6 hours. There occurred a marked change in fibrinogen and fibrinolysis. Initial hypofibrinogenemia of 84 mg/100 ml turned to afibrinogenemia in 15 minutes to 2 hours after transfusion. The course of fibrinolysis was parallel to that of fibrinogen decrease. Total plasmin also decreased after 15 minutes, but soon returned to normal. There occurred no change in her hemorrhagic diathesis. The patient died 2 weeks later and a micro-angiopathy was found at autopsy in the bone marrow and glomeruli of the kidney.

In Case 2 of hemophilia A (Fig. 19), the changes in plasmin activity after serum transfusion were not so remarkable as in the cases mentioned above, though changes of fibrinolysis were slightly noticed.

**D) Side-effects**

Palpitation, flushing of the face and headache were complained of by some patients 3 to 5 minutes after transfusion, which subsided spontaneously within 5 to 10 minutes. These side-effects were seen in 5 of 17 cases with normal PCT and
Fig. 19. Plasmin activity after serum transfusion in a 30-year-old case of hemophilia A (the same case as in Fig. 11).

6 of 13 cases of abnormal PCT. Two cases complained of a rather severe headache which also subsided spontaneously. There was no relation between the side-effect and the amount of transfused serum. In 3 cases with intravenous drop instillation, however, no such unpleasant reaction occurred.

DISCUSSION

The shortening of PCT following serum transfusion occurred in 13 of 17 cases with normal PCT. This result suggests that serum transfusion is certainly a useful hemostatic procedure in hemorrhagic disorders with coagulation defects. In 2 of 5 cases with normal PCT and in 7 of 9 cases with abnormal PCT hemorrhagic symptoms were definitely improved by serum transfusion.

As shown in the in vitro experiment by Yoshida, shortening of the clotting time was seen not only in PCT but also in PT and TT even in cases with normal PCT. This finding agrees with his assumption that serum promotes blood coagulation probably by its enzymatic factor(s), acting on more than one phase of the coagulation steps.

In 4 cases rather short original clotting times were unchanged or prolonged after serum transfusion. It may be assumed that serum induces a vital reaction in the system of blood coagulation and actuates the homeostatic mechanism properly in vivo. Shortening of the clotting time occurred most strongly immediately after the transfusion in most of the cases with normal coagulability and in hemo-
philia A, but in leukemia and in some cases with normal coagulability the shortening gradually progressed with time, the maximum appearing after 6 to 8 hours. If the serum shortened the clotting time only by correcting the deficiency in the coagulation system, the response would have appeared at the maximum immediately after serum transfusion. Therefore, it may be speculated that serum transfusion would induce a continuous reaction in vivo. However, the question still remains whether the shortening of clotting time was brought about by formation of intravascular clotting, thereby producing serum factor(s), or by other unknown mechanism.

The maximum shortening of PT and TT was attained approximately 2 hours after serum transfusion. However, it is difficult to find a plausible explanation as to why the maximum effect appears at different times in these tests and PCT. In contrast with serum, plasma transfusion in patients with normal coagulability does not induce a change in the clotting time. This can be well interpreted by the fact that normal cases have originally ample coagulation factors. The question why serum, not plasma, can induce shortening of the clotting time may be comprehended by Yoshida's hypothesis that the transfused serum shortens the clotting time enzymatically by enhancing the 'chain' reaction of coagulation steps. In hemophilia A the hypothesis was clinically supported by the fact that serum, supposedly lacking AHG, was just as effective as normal plasma and antihemophilia plasma in shortening the clotting time of AHG deficient plasma.

In the report of serum transfusion in von Willebrand's disease by Fantl and Sawers, it was described that factor VIII in 10% in original increased to above 80% 4 to 8 hours after serum transfusion. In hemophilia B and C, therefore, it may be expected that serum transfusion would correct prolonged clotting time both by supplying the lacking factor and by installing the clot promoting factor(s). The controversial report by Nour-Eldin and Wilkinson was concerned with only the results of TGT, which does not represent the coagulability of blood as a whole. It is interesting, however, that they also affirmed the favorable effect of serum on the clotting time.

Serum transfusion in aplastic anemia exerted a marked favorable effect not only by correcting the clotting time but also by shortening the bleeding time. This result certainly suggests that serum may contain some unknown components concerning capillary fragility or platelet function other than shortening of clotting time. As in aplastic anemia, the hemorrhagic diathesis may represent mainly increased capillary fragility and hypofunction of platelets. It is not known whether or not the serum reacts with platelets and/or vessels, but the following reports may give a clue to this problem. Jackson et al. and James et al. described that many factors such as thrombin, factors VIII and IX and fibrinogen were involved in platelet aggregation, progress of metamorphosis, clot formation and retraction. This suggests that substances concomitantly produced abundantly in the course of coagulation may promote the reaction of platelets. The transfused serum may also react directly against heparin in the vessel wall as reported by
Mustard et al. The author did not study the changes in the platelet counts. However, Wessler and Morris reported in his animal experiments of thrombus formation that serum infusion resulted in marked thrombocytopenia and impairment of thromboplastin generation in accordance with decreased whole blood clotting time. At any rate, treatment of hemorrhagic diathesis in aplastic anemia is still difficult today, and serum transfusion would be one of the recommendable procedures.

As for anticoagulant therapy it was reported that hemorrhage was recognized as a major complication in 5% of the patients treated on a short time basis. Sometimes surgical operation may be needed in patients under anticoagulant treatment. On such occasion, acute correction of prolonged coagulation time is possible by serum transfusion.

As mentioned by Alexander, plasma or plasma fraction rich in pertinent clotting factors should be immediately infused together with vitamin K, because the effect of vitamin K might be attained within 24 hours. Although ordinary ACD bank plasma is fully potent in the factors in spite of anticoagulants, patients with impaired cardiac activity may not tolerate the infusion of three units of stored blood, which is required to normalize the clotting time. As the coumarin congeners act in depressing the factors II, VII, IX, all of which are in activated form in serum, serum rather than plasma is expected to be more effective with a less amount of transfusion. In one of the author’s cases, an infusion of 20 ml serum to a patient under Warfarin therapy showed a definite shortening of the clotting time.

In cases with acquired coagulation defect seen in liver damage, choledochus stasis or malabsorption syndrome, the deficient factors are usually those of the serum. So, serum transfusion may be well effective. In a case of stomach cancer with prolonged coagulation time, serum transfusion resulted in a marked correction as expected. Serum transfusion of 20 ml was quite effective also in Case 16 in Table 1, whose liver function was severely impaired. Therefore, in hemorrhagic diathesis with hepatocellular damage, the treatment of choice is the serum transfusion.

The fact that serum transfusion showed a marked clinical hemostatic effect in 5 of 8 cases of leukemia brings about a new aspect in the treatment of troublesome hemorrhagic diathesis in the disease. As the causes of hemorrhagic diathesis in leukemia the followings are generally referred to; 1) thrombocytopenia or non-functioning thrombocytes, 2) increased capillary fragility, 3) lack of coagulation factors, 4) increase of circulating anticoagulants and 5) elevated plasmin activity. The most important cause is said to be a lack of or defect in thrombocytes and increased capillary fragility. Therefore, the mechanism of effectiveness of serum transfusion may be explained as an acceleration in blood coagulation in the first place, but the decrease of purpura, reduction of capillary fragility, shortening of bleeding time, etc., suggest that the infused serum produces or stimulates a component which may be concerned with platelet function, vessel wall, and
plasmin activity. Even so, the author believes that the favorable result of serum transfusion is initially ruled by the acceleration of blood coagulation. The reason why the maximum shortening of clotting time was gradually attained in some cases was already discussed.

Studies of 3 cases, in which serum transfusion was clinically ineffective, revealed that in one case hemorrhage was from a macroscopically visible blood vessel. In another case the patient was in a collapsed state. This kind of hemorrhage is, without question, beyond the reach of ordinary medical treatment. The last case was that of acute promyelocytic leukemia. In such a case a combination of hypofibrinogenemia with elevated plasmin activity had been reported.31 We learned from this case that in acute promyelocytic leukemia serum transfusion should be done very carefully perhaps after preliminary administration of fibrinogen, antiplasmin and heparin.32 In our case fibrinogen rather acutely decreased to the level of afibrinogenemia following the transfusion. It was difficult to ascertain whether intravascular clotting was induced by the serum transfusion and whether microangiopathy belonged to the natural course of promyelocytic leukemia. However, from the fact that the original low level of fibrinogen was further lowered, it was assumed that the transfusion accelerated the microangiopathy with thrombosis which preceded such treatment.

It seems that serum transfusion in leukemia does not always induce an elevation of plasmin activity, for in a case with monocytic leukemia oozing from the tongue dramatically stopped with a decrease of plasmin activity after the serum transfusion. It was suspected that a strong inactivation of plasmin occurred as shown in the fibrin plate. It is reported that oozing may occur in cases of elevated plasmin activity. The administration of anti-fibrinolysin or EACA is naturally expected to stop the activation of fibrinolysis and widely used in the hemorrhagic diathesis in leukemia. In the author’s case, however, oozing from the tongue occurred during the treatment with EACA, and this suggests that serum supplies some factors to inactivate fibrinolysin which cannot be inactivated by EACA.

Serum transfusion in hemophilia A did not induce a marked change in plasmin activity, though a slight decrease of fibrinogen was temporarily recognized. In general, it can be said that serum transfusion induces changes in plasmin activities, although not consistently.

Side-effects of serum transfusion reported as ‘nitride reaction’ by Kato33 in 1951 are a sense of tightness in the chest, lumbago, nausea, vomiting and headache. These symptoms are said usually to subside spontaneously in a few minutes without sequelae. On the other hand, there are reports5–8,21 that serum from 100 to 1,100 ml was infused in hemophiliacs without any side-effect. Here, one might suspect that serum would give no more conspicuous side-effect than plasma, for transfusion of whole blood or plasma itself gives side-effects such as hemolysis, fever, toxic effect of potassium and/or serum hepatitis.34 Therefore, instead of large volume of blood transfusion a small amount of serum transfusion is highly
recommended for hemostatic purpose. There occurred no side-effects in the cases where serum transfusion was done by way of intravenous drip.

After all these considerations it is concluded that the serum transfusion is an effective hemostatic procedure without serious side-effect, although the method of infusion and the instruments for preparing the serum await further improvement.

**Summary**

1) Serum transfusion from 15 to 55 ml was done in 30 cases, and PT, TT and PCT were examined at various intervals. A marked shortening of clotting time was seen in 13 of 17 cases with normal coagulability and 11 of 13 cases with abnormal one.

2) In 17 cases with hemorrhagic diathesis a marked clinical effectiveness was seen in 10 cases as follows:
   a) Hemorrhage was lessened in bleeding gastric ulcer and essential hematuria in which the PCT was originally within normal range.
   b) In 5 of 8 cases of leukemia such favorable effects were seen as decrease of purpura, ease of oozing from the tongue, reduction of capillary fragility, shortening of bleeding time and improvement in general malaise. The same effects were seen in a case of severe aplastic anemia.
   c) In cases with liver damage and stomach cancer, the prolonged PCT was shortened. In a case under Warfarin treatment, a temporary shortening of clotting time was induced. In two cases of hemophilia A a marked shortening of PCT was induced by serum transfusion of 25 ml.

3) The question why the maximum shortening of the clotting time was not attained immediately after transfusion in some cases and the effect on plasmin activity were discussed.

4) It is concluded that serum transfusion is a useful hemostatic procedure in various hemorrhagic conditions.

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**References**


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