HYPOPROTHROMBINEMIA: STUDIES OF A CASE OF THE IDIOPATHIC TYPE AND THE EFFECT OF SERUM ADMINISTRATION

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HEMORRHAGIC diathesis due to idiopathic hypoprothrombinemia was reported first in 1941 by Rhoads and Fitz-Hugh. A case of this type has been admitted to the Pediatric Service of the University of Virginia Hospital five times between 1945 and 1948. In the first portion of this report an account of this case is presented and other similar reports in the literature are reviewed. The second portion of the paper deals with special studies made on our patient which have suggested a new approach to the therapeutic problem presented by patients of this type.

PART I. CASE REPORT

A 5 year old white female was admitted to the Pediatric Service of the University of Virginia Hospital first in November, 1945, for study of abnormal bleeding which had occurred intermittently since the age of two weeks. Prior to admission episodes of severe epistaxis, hematemesis, and melena had occurred, but there was no history of hemarthrosis. On admission hematuria was present.

Developmental history revealed that the patient received an essentially adequate diet but developed somewhat slower than the average child. She experienced no illnesses other than whooping cough and chickenpox, and received no salicylates or other toxic medications. A thorough investigation of other members of this family was not possible. No history of hemorrhagic phenomena in other members of previous generations could be elicited from the mother. The prothrombin conversion time of the mother's plasma was normal.

Physical Examination. On admission the patient's temperature, pulse and respirations were normal. There were many old hematomata of varying size over both lower extremities but there were no recent hemorrhages. There was no jaundice, adenopathy, or hepatosplenomegaly.

Laboratory Data. Hematologic studies: red count 3.7 millions, hemoglobin 11 Gm., white count 7,200. Blood and bone marrow differential counts normal. Reticulocytes 1.3 per cent, hematocrit 39, sedimentation rate 6 mm. at the end of one hour. Platelets were 388,000, bleeding time was 2.3 minutes (Duke), tourniquet test was negative, and clot retraction was normal. The prothrombin time (Quick) ranged from 61 to 92 seconds and the clotting time (Lee-White) 11 to 48 minutes on various admissions.

Admission urinalysis showed 3 plus albumin, innumerable red cells, no casts and specific gravity was high. Subsequent examinations were negative. Stool examination revealed ascaris lumbricoides ova on the first admission but none on subsequent observations. Blood urea was 2.0, calcium 9.4. The Schick, tuberculin, Wassermann and plasma salicylate tests were negative.

Liver Function Studies (1945-1948 inclusive). Bromsulfalein, hippuric acid excretion, cephalin flocculation, thymol turbidity, proteins and A/G ratio, alkaline phosphatase, cholesterol and esters, icterus index, bilirubin, urobilinogen quantitative 24 hour urine, and urobilinogen quantitative fecal were all within normal limits.

Other Studies (1945-1948 inclusive). Electrophoretic study of the patient's blood revealed a normal protein pattern with no fibrinogen deficiency. Direct examination of nailbed capillaries revealed normal appearance and normal response to traumatic rupture. Roentgenograms of the chest, skull, and long bones were normal.

Deficiency of vitamin K, liver dysfunction and depression of prothrombin by certain substances such as dicoumarol or salicylates were considered as possible causes of the prothrombin deficiency. The lack of
response to large doses of synthetic vitamin K preparations given by oral and parenteral routes seemed to exclude vitamin K deficiency. A careful history, examination, and numerous tests of liver function failed to indicate liver disease or the presence of any agent known to depress prothrombin formation. Therefore it appeared that this patient had idiopathic hypoprothrombinemia. The absence of any change in either the subjective or objective clinical manifestations, including signs of liver disease, over a three year period of repeated observations has substantiated this interpretation.

In reviewing the literature on idiopathic hypoprothrombinemia, and the various cases reported therein, one is impressed with the definite disease pattern they seem to form. The onset is during infancy or childhood without any sexual predilection. The family history is frequently bisexually positive for hypoprothrombinemia of a subclinical degree. These patients run a similar chronic course, characterized by cutaneous hemorrhages, epistaxis, hematemesis, hematuria, hemorrhathrosis, and uterine bleeding severe enough to necessitate hysterectomy. The results of the hemorrhagic tests in these patients are nearly uniform. Besides the prolonged prothrombin times, the clotting time was prolonged in all but the case of Murphy and Clark,\(^2\) which presented more the picture of pseudohemophilia with prolonged and variable bleeding time and abnormal nailbed capillaries, but normal platelets and coagulation time. Though the cases of Rhoads and Fitz-Hugh,\(^1\) and Hagen and Watson\(^1\) showed prolonged bleeding times, these were noted to be only slightly or infrequently abnormal. In general the capillaries, platelets, and other factors have shown no abnormality. The prolonged coagulation time is presumably a reflection of the prothrombin defect, since no increase in circulating anticoagulants, antithrombin or similar substances have been demonstrated.

Successful therapeutic efforts in these cases have been limited to the administration of some effective factor, or factors, present in whole blood, plasma, or, as in the authors’ case, serum. These patients have been uniformly refractory to various forms of vitamin K administration.

Idiopathic hypoprothrombinemia is not always of a degree sufficient to produce clinical bleeding and several such subclinical cases have been reported. Many of these occurred in families who were studied when one member suffered clinical bleeding, as reported by Giordano,\(^4\) Murphy and Clark,\(^2\) Hauser,\(^5\) and Hagen and Watson.\(^3\) Other cases have been discovered by Plum\(^6\) and Quick\(^7\) and have led the latter to speculate on the prevalence of this state. The prothrombin estimations of these patients ranged from three seconds above the controls\(^8\) to as little as 2.4 per cent of normal,\(^4\) and in a few the coagulation times were slightly prolonged, but not of the order which those with an hemorrhagic disorder exhibited. The other hemorrhagic tests failed to indicate abnormalities in the other factors concerned in hemostasis, except for a few isolated observations unassociated with any abnormal bleeding.

The single cases reported by Lewis and Bennett,\(^10\)\(^,\)\(^11\) and Austin and Quastler\(^11\) of acute and subacute idiopathic hypoprothrombinemia respectively, would seem to be somewhat different in nature from the above described group of chronic cases. That of the former ran an acute course with a normal prothrombin time after three days therapy with vitamin K, blood and plasma. Austin and Quastler’s patient showed a fluctuating prothrombin “clotting power” over a six month
### Table 1.

**Cases with Chronic Hemorrhagic Disease and Prolonged Prothrombin Time**

*All cases of unknown etiology and all vitamin K refractory*

<table>
<thead>
<tr>
<th>Authors and year of report</th>
<th>Patient</th>
<th>Age of onset</th>
<th>Family history</th>
<th>Hematologic studies</th>
<th>Prothrombin time and response to therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhoads and Fitzhugh 1941</td>
<td>18 yr. male</td>
<td>9 mos.</td>
<td>Negative</td>
<td>CT 8-360'; BT 2-25'; CR variable; PC normal; TT negative and positive; qualitative F defect?</td>
<td>Quick, 70-120%; control 20-24%; blood had hemostatic effect</td>
</tr>
<tr>
<td>Giordano 1943</td>
<td>22 yr. male</td>
<td>5 yrs.</td>
<td>Positive</td>
<td>BT 4'; TT positive; CT, CR, PC, F normal</td>
<td>Quick, 210%; Control 25%; blood and plasma effective</td>
</tr>
<tr>
<td>Murphy and Clark 1944</td>
<td>18 yr. male</td>
<td>4 yrs.</td>
<td>Positive</td>
<td>BT 14-15'; CT, CR, PC, TT normal; qualitative F defect?; nail bed capillaries abnormal</td>
<td>Quick, 60-100%; control 10%; blood apparently had hemostatic effect</td>
</tr>
<tr>
<td>deMarval and Borchelt 1944</td>
<td>14 yr. female</td>
<td>8 yrs.</td>
<td>Negative</td>
<td>CT 12-43'; BT, CR, PC, F normal; TT negative and slightly positive</td>
<td>Quick, 25-53%; of normal</td>
</tr>
<tr>
<td>deMarval 1945</td>
<td>23 yr. female</td>
<td>3 yrs.</td>
<td>Positive</td>
<td>CT 10-12' (abnormal according to author); BT, CR, PC, TT normal</td>
<td>Quick, 20-25%; of normal</td>
</tr>
<tr>
<td>Hauser 1945</td>
<td>3 yr. male</td>
<td>3 mos.</td>
<td>Positive</td>
<td>CT (Bürker) 3'-11'; 20', usually prolonged; BT, CR, PC, TT, F normal</td>
<td>Index, 21-80%;</td>
</tr>
<tr>
<td>Owren 1947</td>
<td>29 yr. female</td>
<td>3½ yrs.</td>
<td>Negative</td>
<td>CT 25' (also prolonged by two other methods); BT 45-5'; PC, F normal; &quot;Parahemophilia&quot;</td>
<td>Quick, 70-80%; control 15-20%; blood and &quot;factor V&quot; (isolated from plasma) effective</td>
</tr>
<tr>
<td>Quick 1947</td>
<td>1 yr. male</td>
<td>Soon after birth</td>
<td>Positive</td>
<td>CT 12'; BT, CR, PC, F normal; &quot;Pseudohypoprotrombinemia&quot;</td>
<td>Quick, 10%; control 11-12.5%; blood effective</td>
</tr>
<tr>
<td>Quick 1947</td>
<td>5½ yr. male</td>
<td>1 wk.</td>
<td>Positive</td>
<td>Bro. of 8</td>
<td>Quick, 10%; control 11-12.5%; blood effective</td>
</tr>
<tr>
<td>Hagen and Watson 1948</td>
<td>31 yr. female</td>
<td>2 yrs.</td>
<td>Positive</td>
<td>CT, 69'; of tests prolonged; BT, 43'; of tests prolonged mildly; CR 49'; abnormal; TT usually negative; PC, F, nail bed capillaries normal</td>
<td>Quick, 47-81%; controls 11-12.5%; plasma effective</td>
</tr>
<tr>
<td>Authors</td>
<td>8 yr. female</td>
<td>2 wks.</td>
<td>Negative</td>
<td>CT 11-48'; BT, CR, TT, PC, F, nail bed capillaries normal</td>
<td>Quick, 35-80%; controls 12-15%; blood and serum effective</td>
</tr>
</tbody>
</table>

* In this table the following symbols are used: BT, bleeding time; CT, clotting time; CR, clot retraction; PC, platelet count; TT, tourniquet test; F, fibrinogen. Quick refers to the one-stage prothrombin method.

Period of treatment with vitamin K and blood. Autopsy showed a granulomatous process, possibly Hodgkin's sarcoma, and probably hematogenous tuberculosis in the lungs, liver and nodes.
In table 1 we have grouped the cases thus far reported in which there is a chronic hemorrhagic disorder associated with a defect in the prothrombin mechanism of undetermined etiology. Thus it can be seen that these cases present a very similar clinical picture and essentially the same laboratory abnormalities if the Quick method of prothrombin determination is used. The various studies indicate that hypoprothrombinemia may not be a single simple defect and that perhaps more than one factor may be involved in deficient prothrombin conversion. Owren concluded that his patient was lacking in what he termed factor V, and chose to designate the resulting hemorrhagic state "parahemophilia." Quick studied two brothers with abnormal bleeding and concluded that there was no deficiency of prothrombin component B or the labile factor, but instead, a deficiency of a "new coagulation constituent." He felt that pseudo-hypoprothrombinemia was a more fitting designation for this condition. Of course, the implication is that some of these reports are dealing with similar pathologic processes to which different terms or interpretations have been applied.

**Table 2.**—Prothrombin Determinations on Mixtures of Different Types of Plasma in Equal Volumes (1945).

<table>
<thead>
<tr>
<th>Types of plasma added and prothrombin times</th>
<th>Patient</th>
<th>Control</th>
<th>Dicoumarinized</th>
<th>Stored</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>66.0</td>
<td>14.0</td>
<td>87.0</td>
<td>600</td>
</tr>
<tr>
<td>Control (14.0)</td>
<td>18.0</td>
<td>14.0</td>
<td>19.0</td>
<td>2.00</td>
</tr>
<tr>
<td>Dicoumarinized (87.0)*</td>
<td>45.0</td>
<td>14.0</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>Stored (Over 600)</td>
<td>25</td>
<td>17</td>
<td>10.0</td>
<td></td>
</tr>
</tbody>
</table>

* Prothrombin time of dog’s plasma before dicoumarinization eight (8) seconds.

**PART II. SPECIAL STUDIES**

At the time of the first admission of our patient in 1945 certain preliminary observations were carried out in an attempt to determine the nature of the prothrombin defect. Because of the concept of Quick and others at that time that the prothrombin complex was composed of two factors, prothrombin "A," which was labile and disappeared from stored plasma, and prothrombin "B," which was depressed by dicoumarol, various mixtures of the patient’s plasma with normal and old human and dicoumarinized dog plasma (human not available) were set up to determine which component was reduced in this patient. The results are shown in table 2. It will be noted that when stored plasma and dicoumarinized plasma, each with a long prothrombin time, were mixed in equal parts there was a marked reduction in the prothrombin time to a level far below that of either plasma alone. This could be interpreted as indicative of a different type of prothrombin deficiency in each type of plasma and that mixing the two restored the deficient parts of the prothrombin complex more nearly to normal. It was also apparent that the addition of either prothrombin deficient stored plasma or dicoumarinized plasma to the patient’s plasma lowered the prothrombin time below that of either plasma alone. This might indicate that the patient was deficient in both of these factors.
An infusion of old plasma brought no appreciable change in the patient's prothrombin time. These data could be interpreted to mean that the patient's plasma was deficient in both prothrombin "A" and "B."

At the time of the admission in 1948 the patient's coagulation defect was felt to be the same as that found on the previous admissions. Possible deficiency of vitamin K was again excluded by the intravenous administration of 75 mg. of synthetic vitamin K. The prothrombin time was not affected by this substance, being 65 seconds before injection and 65 seconds 6-12 hours after injection.

The patient's prothrombin time was consistently elevated, ranging from 50 to 80 seconds. These values varied from day to day, despite fair uniformity of activity of the thromboplastin as tested against normal controls. No apparent reason for the wide variations could be found.

In the light of certain recent advances in the knowledge of factors concerned in coagulation, especially in regard to prothrombin conversion, it was felt that some preliminary investigations were indicated to determine the nature of the defect exhibited by this patient. The procedures previously carried out (table 1) involving mixing of various types of human plasma with the patient's plasma in equal volumes were repeated. The results are shown in table 3.

It was found, as previously, that normal plasma mixed with the patient's plasma in equal amounts substantially lowered the prothrombin time of the patient's plasma, but not to normal levels. Normal plasma mixed with either old plasma or dicoumarinized plasma gave about the same result. Both old plasma and dicoumarinized plasma, each with a prolonged prothrombin time, substantially lowered the patient's prothrombin time, but not as markedly as did normal plasma. Furthermore, it will be noted that a mixture of all three of these abnormal plasmas yielded a lower prothrombin time than any two.

These data could be interpreted as previously to indicate that the lower prothrombin times resulting from mixtures of the various prothrombin deficient plasmas was due to an elevation of the prothrombin concentration of the plasma mixture as a result of different portions of the prothrombin complex being supplied by the various individual plasmas. However, this interpretation, which is according to the concepts of Quick, is open to some objections. Against it is the fact that the addition of purified prothrombin* to the patient's plasma failed to bring

* Supplied through the courtesy of Dr. Walter H. Seegers, Wayne University College of Medicine, Detroit, Mich.
the prothrombin time to normal. Bringing the concentration of added prothrombin to 100 mg. per 100 cc. lowered the prothrombin time from 67 to 37 seconds. The additions of increasing amounts failed further to reduce the time of prothrombin conversion. This result would indicate a deficiency of some other factor necessary for the rapid conversion of prothrombin to thrombin as well as a deficiency of prothrombin per se. Mixing the various types of prothrombin-deficient plasmas may have altered the concentration of this factor and hence caused more rapid conversion of prothrombin, even though the latter was still in low concentration.

The existence of a factor in normal blood which is necessary for the rapid conversion of prothrombin seems to be beyond dispute. The disagreement as to the nature of the factor and its mechanism of action will not be discussed here. We have chosen to use the term accelerator or activator globulin (Ac-globulin) after Ware, Guest, and Seegers, but are cognizant of the unsettled similarity of the substance so named to the "labile factor" of Quick, factor V and factor VI of Owren, and the prothrombokinase of Milstone.

Because of the importance of this Ac-globulin in the rate of prothrombin conversion it is apparent that the Quick one-stage prothrombin technic is not an accurate measure of prothrombin concentration in the plasma, since the variable factor of accelerator globulin activity is not controlled. The two stage determination of prothrombin concentration would appear to be less affected by variations in accelerator globulin since the rate of conversion of prothrombin is not measured, but rather the actual amount of thrombin produced during a definite incubation period. However, this test may be criticized as a measure of prothrombin concentration since the activity of Ac-globulin apparently also influences the amount of thrombin produced. Seegers, et al. have recently modified the two stage method to measure the concentration of prothrombin by adding known amounts of Ac-globulin to a reaction mixture containing specified amounts of thromboplastin, calcium ions and the plasma to be tested, and incubating for varying periods of time before adding fibrinogen. Although the Quick one stage method does not measure actual prothrombin concentration, it does serve as an accurate measure of the speed of prothrombin conversion to thrombin, a reaction in which all of these factors take part. It will be noted that in the protocols presented, prothrombin is expressed in terms of prothrombin time rather than per cent concentration of normal. This terminology was used because it is evident that a measure of prothrombin time cannot be accurately interpolated to prothrombin concentration by the usual graphic method unless the activity of Ac-globulin is controlled.

Ware and Seegers have demonstrated that accelerator globulin is in a highly active state as it exists in serum after clotting. They believe that it is in a less active state in the plasma where it exists as a proenzyme. According to these authors it is activated by the formation of small amounts of thrombin in the first stage of clotting, amounts too small to cause clotting of fibrinogen. The activation of plasma Ac-globulin is then followed by increased thrombin formation and the reactions proceed by co-autocatalysis. After the concentration of thrombin has been built up to the point where clotting occurs, the reaction is spent. The thrombin formed is destroyed, as is thromboplastin, but Ac-globulin was found to survive in the serum in a highly active state.
It was therefore felt that some estimation of the activity of accelerator globulin might be ascertained by studying the influence of small amounts of the various sera on the speed of prothrombin conversion of the various plasmas. It was considered that the small amounts of other factors pertaining to clotting in thrombin-free serum, such as antihemophilic globulin, platelet breakdown products, and prothrombin would not interfere with the use of serum as a rich source of this material. Platelet breakdown products and antihemophilic globulin appear to participate in the initiation of coagulation and furnish active thromboplastic effect. They have no influence on the rate of prothrombin conversion when an excess of artificial tissue thromboplastin is used, as shown by Ferguson and Lewis.21 The prothrombin content of fresh serum immediately after clotting is normally less than 10 per cent of that of normal plasma. Barium carbonate adsorption of the residual prothrombin was carried out in some instances but difficulty was encountered in avoiding an excess of the material which inhibits the activity of prothrombin in the plasma to which the barium carbonate-treated serum was added. It was not felt that the small amount of prothrombin in the serum would be sufficient to bring about the striking changes noted.

<table>
<thead>
<tr>
<th>Types of sera added</th>
<th>Patient</th>
<th>Dicoumarinized</th>
<th>Stored</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>60.5</td>
<td>24.8</td>
<td>23.3</td>
</tr>
<tr>
<td>Normal serum</td>
<td>15.7</td>
<td>14.5</td>
<td>17.0</td>
</tr>
<tr>
<td>Patient's serum</td>
<td>48.5</td>
<td>19.5</td>
<td>16.5</td>
</tr>
<tr>
<td>Dicoumarinized serum</td>
<td>28.5</td>
<td>24.0</td>
<td>23.3</td>
</tr>
<tr>
<td>Stored serum</td>
<td>24.0</td>
<td>18.5</td>
<td>21.0</td>
</tr>
</tbody>
</table>

It will be seen from table 4 that one part of normal serum in three parts of the patient's plasma brought about a marked reduction in the prothrombin time from a value of 60.5 to 15.7 seconds (normal control 15.0 seconds). Normal serum also brought about a striking reduction in the prothrombin time of dicoumarinized and old plasma, particularly the former. On the other hand, the patient's serum did not bring about nearly so marked a reduction in the prothrombin time of either the patient's or dicoumarinized plasma, but did reduce that of old plasma, the reason for which is not apparent. Neither serum from dicoumarinized nor stored blood possessed as much accelerating effect as did normal serum. There seemed little doubt that normal serum possessed a factor which was capable of accelerating prothrombin conversion in the patient's plasma. It is apparent that any alteration in prothrombin concentration by the addition of serum could not account for this remarkable reduction in prothrombin time (table 3). This acceleratory effect of normal serum on prothrombin conversion is also demonstrated by the use of purified prothrombin. A clotting mixture consisting of purified prothrombin 0.1 cc., human fibrinogen 0.2 cc., and thromboplastin 0.05 cc. was used. Upon recalcification with 0.1 cc. calcium chloride (0.024 M) at 37 C it was observed that purified prothrombin was converted to yield sufficient thrombin to clot human fibrinogen in an average
time of 2.86 seconds. This is in accord with previous findings that thrombin is produced slowly, in the absence of Ac-globulin by the interaction of thromboplastin, calcium and purified prothrombin. However, if 0.05 cc. normal serum (thrombin-free) was added to the mixture at the time of recalcification with 0.05 cc. calcium chloride, clotting occurred in 45 seconds. Also it was noted that fresh normal serum possessed a more marked acceleratory effect than did normal serum which was 2.4 to 48 hours old, the latter bringing about clotting in 74 seconds. In contrast, using the same technic, fresh serum from the patient produced clotting in 90 seconds and 2.4 hour old serum in 110 seconds.

The data in table 5 show the relative potency of fresh normal serum in accelerating the conversion of prothrombin in the patient's plasma. These findings would be in accord with the concept of the enzymic or catalytic action of this substance.

A modification of the two stage method of prothrombin determination was performed in order to evaluate further the concentration of prothrombin in this patient's blood. The results of this test seemed to indicate an actual deficiency of prothrombin, as well as delay in its convertibility to thrombin, as previously demonstrated. A 1:11 dilution of control defibrinated plasma yielded a prothrombin time of 13 seconds whereas the same dilution of the patient's defibrinated plasma yielded a prothrombin time of 68.5 seconds. However, since adequate control of accelerator globulin activity was not possible, interpretation of the results was difficult. Dr. Walter Seegers kindly performed determinations of both prothrombin and Ac-globulin of a sample of the patient's plasma. He reported a prothrombin concentration of 41 per cent by the original two stage technic and 60 per cent by the modified technic in which the amount of accelerator globulin was controlled. He concluded that the Ac-globulin concentration was in the neighborhood of 50 to 60 per cent of normal. It is interesting to note that neither the prothrombin concentration nor that of Ac-globulin, as determined by Dr. Seegers, was as low as might have been anticipated. Perhaps the moderate depression of both these factors simultaneously was sufficient to bring about the marked retardation of prothrombin conversion noted, whereas a deficiency of either factor alone would have to be more extreme before a comparable delay in prothrombin conversion time would be noted. Although Dr. Seegers' prothrombin value was somewhat higher than our tests would seem to indicate, his general conclusions, that a deficiency of both factors was present, are in agreement with the results we obtained.

The marked acceleration of prothrombin conversion in the patient's plasma by the addition of normal serum in vitro prompted the administration of fresh normal serum to the patient in the hope of lowering the prothrombin time of the circulating blood. Accordingly a normal donor of the same blood type was bled. The

| Proportions of serum to plasma | 1:1 | 1:3 | 1:6 | 1:12 | 1:20 | 1:40 | 1:80 | 0:1 |
| Prothrombin time in seconds | 16 | 16.5 | 18 | 22 | 25.5 | 31.5 | 39 | 57 |
blood was allowed to clot and the serum removed under sterile precautions. Fifteen cc. of this serum was injected intravenously 2 hours after collection, at which time it was free of thrombic activity. There was a slow decline in the patient’s prothrombin time from a level of 67 seconds to 37 seconds in 16½ hours. At this time 45 cc. more of the serum (which was by this time 18 hours old) was given and the prothrombin time fell from 34 seconds to 25 seconds in one hour. Three hours after the second injection the patient’s prothrombin time was 22 seconds. This was the lowest prothrombin time yet recorded for this patient. Twenty-four hours later the patient’s prothrombin time was 32 seconds. It is of interest that as little as 15 cc. of serum given intravenously had a significant effect. These results are shown graphically in figure 1.

Fig. 1. The effects of intravenous administration of fresh serum on the prothrombin time of patient H. H.

It is interesting to note that the patient’s coagulation time, which was 19 minutes on admission, was now 12 minutes, suggesting an improved state of coagulability of the patient’s blood. It is also of some interest that the patient’s serum became more active in accelerating prothrombin conversion when added to her own plasma after the above treatment. Thus, one part of the patient’s serum obtained after treatment, with three parts of the patient’s plasma collected before the intravenous administration of serum, lowered the prothrombin time from 64 seconds to 27 seconds, whereas previously the patient’s serum had reduced the prothrombin time from 60.5 seconds to 48.5 seconds.

The patient was seen March 15, 1949 on a return visit after the preceding data had been completed. She was admitted to the hospital because of bleeding from her gums for three weeks. Examination revealed six carious deciduous teeth. The
gingival tissue around some of these was hypertrophied and irritated and bleeding occurred with mastication. Prothrombin time (Quick) was 72 seconds with a control of 12, and the clotting time (Lee-White) was 23 minutes. There were no other significant changes from the previous studies.

In figure 2 are shown the effects of giving the patient fresh whole blood and fresh serum, both separately and, later, together. After each administration it will be noted that the prothrombin and clotting times were markedly reduced within an hour’s time; and further, that the most marked reduction was obtained when the two were given close together, near the end of her stay. These results are interpreted as further evidence in support of the hypothesis that she is deficient in two factors, prothrombin and accelerator globulin, which were presumably supplied by the blood and serum respectively.

The extraction of the six carious teeth was done under a general anesthetic and bleeding was minimal both in amount and duration. Her course remained uneventful and it was felt that she had been carried through a potentially dangerous procedure by the use of the blood and serum.

Discussion

These studies support the concept that serum contains an active substance which is capable of accelerating prothrombin conversion to thrombin. It is likely that deficiency of this substance may play a role in many types of hemorrhagic states, as suggested by Alexander and co-workers. It is probable that alterations in
Ac-globulin are of particular importance in various types of prothrombin deficiency. Further investigation is needed to delineate clearly the different types of hypoprothrombinemia and to evaluate the use of serum in treating certain cases of this type.

Our observations also suggest, as do those of Owen and Bollman24 in dogs, that depression of Ac-globulin activity is a major factor in the hypoprothrombinemia produced by dicoumarol. It is obvious that if such be the case, serum or some fraction of the serum such as Ac-globulin may be of potential value in quickly reducing the prothrombin time to safe levels in cases of dicoumarol intoxication. We have carried out preliminary observations on the effect of intravenous normal serum from compatible blood on the prothrombin time of three patients receiving dicoumarol. The pattern of response in all has been the same. In the most recent patient the prothrombin time before giving 175 cc. of serum was 49 seconds. An hour after administration of the serum it was 30 seconds, rising to 38 seconds at the sixth hour, with controls of 15. Twenty-four hours later it had risen to 40 against a control of 12 seconds.

From the evidence that both prothrombin and Ac-globulin are depressed in hypoprothrombinemia following dicoumarol and with liver diseasei. 25 control of the coagulation defect will depend upon the correction of both deficiencies. An apparently effective and simple means of so doing is to give whole blood, thus supplying prothrombin and fresh, thrombin-free serum rich in Ac-globulin in a highly active form.

SUMMARY AND CONCLUSIONS

1. The reported cases of idiopathic hypoprothrombinemia are reviewed briefly, and a case observed for over three years is presented. Particular attention is called to the similar clinical pattern presented by the chronic cases.

2. Studies are presented indicating that in this patient the delay in prothrombin time was due, at least in part, to a deficiency of a factor necessary for rapid conversion of prothrombin. This factor, or factors, which we have called Ac-globulin, is contained in a highly active state in fresh normal serum.

3. After the in vitro demonstration of a deficiency of Ac-globulin in the patient’s blood, it was possible to bring about a marked reduction in the patient’s prothrombin time by the intravenous administration of relatively small amounts (15 to 45 cc.) of fresh normal (thrombin-free) serum. A further reduction of the prothrombin time to near normal values was brought about by combined whole blood and serum administration. The evidence suggests that partial correction of both prothrombin and Ac-globulin deficiency respectively resulted from such therapy.

4. The possible effects of serum and whole blood upon the delayed prothrombin conversion rate of dicoumarolization and liver disease are discussed and preliminary observations in the former type suggest that such therapy may be useful.

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REFERENCES


11. ———: Personal communication to Hagen and Watson.


HYPOPROTHROMBINEMIA: STUDIES OF A CASE OF THE IDIOPATHIC TYPE AND THE EFFECT OF SERUM ADMINISTRATION

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