Idiopathic Hypoprothrombinemia Associated with Hemorrhagic Diathesis, and the Effect of Vitamin K

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PROLONGATION OF THE PROTHROMBIN TIME as measured by the one-stage method described by Quick is usually associated with one of three conditions: (1) a deficient absorption of vitamin K, (2) the administration of anticoagulants or (3) liver disease. However, 17 cases have been reported, some with a hemorrhagic diathesis, associated with a prolongation of the prothrombin time in which these three usual conditions were lacking. Likewise, circulating anticoagulants and fibrinogen deficiency were not demonstrable. Most of these cases were classified as idiopathic hypoprothrombinemia. However, it is now recognized that a deficiency of accessory factors (factor V, Ac-globulin) may prolong the prothrombin conversion rate, thereby prolonging the prothrombin time without direct relation to the prothrombin content.

Few of the above cases have been completely studied in regard to the accessory factors and thus it is impossible to evaluate the exact factor or factors responsible for the observed prolonged prothrombin time. Although 2 of the cases were recognized as not being due to hypoprothrombinemia and some of the others may not have been, it is important to consider them all in order to emphasize the difference in factors in cases with prolonged prothrombin times. It is the purpose of this report to record 2 cases of idiopathic hypoprothrombinemia associated with a hemorrhagic tendency and to present observations on the treatment of the condition, particularly on the use of synthetic water soluble and oil soluble vitamin K preparations. In addition, a classification of the previously reported cases is suggested.

Case 1 (fig. 1). P. D., a 29 year old, married truck driver of Italian parentage, was admitted to the New York Hospital in December 1947, complaining of bloody urine for three months.

Present Illness: He was in apparent good health when examined for selective service in 1943 but was rejected for military duty after repeated urinalyses. In 1946, curious about the urinary findings but feeling entirely well, he consulted a local physician whose urinalyses revealed albumin, white and red blood cells, and casts. A spice-free, low-protein, low-salt diet caused no improvement of his urine, which was found to be abnormal on repeated examination.

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Nine months before admission a tooth extraction was followed by profuse bleeding requiring suture. For the next six months he remained asymptomatic but then began to notice red urine, nocturia three to four times each night, frequency during the day, and occasionally aching right flank pain.

Three weeks before admission he was cystoscoped and retrograde pyelograms were done. This examination indicated that the bladder was normal but that blood could be seen issuing from the right ureteral orifice and that a slight right hydronephrosis was present. During the next four days he received "sulfa" tablets and two injections of penicillin. At about this time he first noted periorbital swelling.

Two weeks before admission he developed aching pain, swelling, and tenderness of the right calf. These symptoms progressed, and he was seen by another physician who made a diagnosis of phlebitis and advised bed rest. He remained in bed for the next week with subsidence of his leg symptoms, but during this time began having transient arthralgias in all of his joints and noted definite though transient swelling of the finger and wrist joints. He had neither chills nor fever and lost no weight. In recent weeks his gums had bled when he brushed his teeth, and about two weeks before admission he noted an apparently spontaneous large ecchymosis on his right hip.

Because of the persistence of the hematuria and the occasional passage of clots in his urine, he was admitted to The New York Hospital on the Urology Service.

Family History: The parents were Italian. There was no history of any abnormal bleeding tendency in any member of the family.

Past History: This was unremarkable save for an episode of "walking pneumonia" of three weeks duration in 1942 and occasional migraine-like headaches from age 18 to 26. In the course of his work he had slight exposure to various aniline dye dusts through handling containers of these materials.

Physical Examination: The patient was a muscular and well-nourished young adult male who did not appear particularly ill. He was sallow but not pale. There was a fading ecchymosis about 4 cm. in diameter over the right hip and there were traces of dried blood about the gums. There were no conjunctival hemorrhages and the fundi were not remarkable. A mild generalized lymphadenopathy was present with rubbery, freely movable, non-
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tender nodes about 2 cm. in diameter in each axilla and smaller but similar nodes in the anterior and posterior cervical chains and in the epitrochlear, inguinal and femoral regions.
The lungs and the heart were normal. The blood pressure was 130/75. The abdomen was soft and no organs nor masses were felt. There was slight tenderness and limitation of motion in the left wrist and all the fingers with slight fusiform swelling of the proximal interphalangeal joints. He complained of discomfort on movement of the elbows and shoulders. There was deep tenderness in the right calf.

After four days on the Urology Service, during which time he had several mild epistaxes, he was transferred to the Medical Service.

Laboratory Findings: Repeated urinalyses showed red blood cells varying from 15 per high power field to gross blood, 10 to 25 white blood cells per high power field, occasional fine and coarsely granular casts and 3 to 4 plus albumin. The blood urea nitrogen was 22 mg. The urea clearance test was 21.6 and 18.3 per cent of normal. Urine examination for malignant cells and acid-fast bacilli was negative.

Serologic studies by the New York City Department of Health were as follows: Mazzini 2+, Kahn 2+, Kolmer anti-complementary. These were considered to be inconclusive in regard to the diagnosis of syphilis.

Stool guaiac tests were positive throughout his hospital course.

Serum proteins totaled 5.5 Gm. per cent with an albumin/globulin ratio of 3.2/2.3. Serum bilirubin was 0.2 mg. per cent; thymol turbidity 4.5 units (normal up to 5 units); cephalin flocculation 15 units (normal up to 5 units); and bromsulfalein retention 2.9 per cent (normal 0 to 5 per cent). These tests were considered to indicate normal hepatic function.

Serum calcium was 7.7 mg. per cent; serum phosphorus 4.2 mg. per cent. The blood vitamin C level was 0.83 mg. per cent. Plasma fibrinogen was 0.328 Gm. per cent. No cryoglobulin was found.

Hematologic Data: Hemoglobin was 11.6 Gm., red blood count 3.3 M., hematocrit 29 per cent, and white blood count 5,200 with the following differential; lymphocytes 12 per cent, monocytes 7 per cent, eosinophils 4 per cent, mature polymorphonuclear 44 per cent, band forms 32 per cent and unclassified cells 1 per cent. The reticulocyte count was 2.4 per cent. The platelet count was 150,000 and the platelets appeared slightly reduced and swollen on smear. The clotting time (Lee-White, 3-tube method) was over 65 minutes (normal 5 to 10 minutes); on standing eighteen hours, the blood formed a tough, retracted clot. The tourniquet test was negative. The erythrocyte fragility test showed hemolysis beginning at 0.40 per cent (control 0.40 per cent) and not complete at 0.25 per cent (control complete at 0.25 per cent). Sternal marrow aspiration yielded a total count of 78,000 cells per cu.mm. (normal 50,000 to 150,000) and 20 megakaryocytes per chamber (normal 5 to 20).

The marrow differential count was as follows: lymphocytes 5 per cent, eosinophils 2 per cent, mature polymorphonuclears 9 per cent, band forms 22 per cent, metamyelocytes 19 per cent, myelocytes 13 per cent, promyelocytes 8 per cent, blast forms 1 per cent, erythroblasts 5 per cent, normoblasts 15 per cent and reticuloendothelial cells 1 per cent.

The prothrombin time (modification of the Quick method) was 30.4 seconds undiluted (normal 15 seconds) and over 3 minutes on a 12.5 per cent saline dilution (normal 42.2 seconds).

Course: The patient’s hospital course was marked by persistent generalized bleeding as evidenced by bleeding from the gums and nose, into the conjunctivae, reti ne, and skin, and into the stools and urine. His transient arthralgias continued, lasting from a few hours to a day or two, involving the elbows, the ankles and the interphalangeal joints of the hands and accompanied by heat, redness and swelling. Prothrombin determinations (undilute, 100 per cent plasma) ranged from 29.0 seconds to over 180 seconds during the first five weeks of hospitalization. There was no demonstrable effect on the prothrombin time from parenteral menadione in doses up to 288 mg. per day. The effect of still larger doses of menadione is clouded by further therapeutic efforts as noted below. Frequent transfusions of fresh blood in amounts up to 1500 ml. per day had no appreciable effect on the prothrombin time.

On the twenty-sixth hospital day an enlarged lymph node was removed from the left axilla. Meticulous hemostasis, topical thrombin, and transfusions of fresh whole blood were used during the operation. Pathologic examination of the sections of the node showed com-
plete obliteration of its architecture with areas of hemorrhage. Occasional large phagocytes and numerous eosinophils were present. There were no Reed-Sternberg giant cells. The findings were considered to be those of atypical chronic lymphadenitis.

In spite of the precautions taken there was considerable oozing from the biopsy wound. For the first time the patient began to run a fever of between 38 and 39 C. Repeated blood and throat cultures and repeated examinations revealed no cause for the fever.

On the thirty-seventh hospital day and again the following day, the patient received 32 mg. of medrolone intravenously. On the thirty-eight hospital day he suddenly complained of severe generalized abdominal pain and quickly went into shock with a fall in blood pressure to 85/40. Within two hours the abdomen became rigid and a fluid wave and shifting dullness were detected. Transfusions of whole blood and plasma were given with subsequent improvement in his general condition.

About midnight the same day, oil-soluble vitamin K, oxide* was obtained and 1,000 mg. were given intravenously according to the method described by MacDonald and Davidson. A prothrombin time done one and one-half hours after the completion of the treatment was 17.0 seconds and daily prothrombin times for the next five days varied from 16.0 to 19.5 seconds. The clotting time also fell to and remained within normal limits. There were no further evidences of bleeding except for microscopic hematuria.

During the thirty-eighth day, however, the patient passed no urine. In spite of intravenous fluids of 4,000 ml. each day his output the following day was 350 ml. He was then given 900 ml. of sodium sulfate intravenously in a 4.07 per cent solution and thereafter his daily output was over 2000 ml. His blood urea nitrogen which was 120 mg. per cent on the fortieth day fell to 96 mg. per cent two days later. He developed a generalized edema and marked edema of the upper respiratory tract with consequent respiratory distress. The latter was substantially relieved by epinephrine and an infusion of 20 per cent glucose. During this time, however, the patient became confused, stuporous, disoriented, and his speech became slurred but there were no localizing neurologic signs. On the morning of the forty-second day he became comatose and died.

Autopsy Findings—Gross: The right and left pleural spaces contained respectively 300 and 350 ml. of bloody fluid. The peritoneal cavity contained 3,000 ml. of dark unclotted blood.

The spleen weighed 550 Gm., was congested and hyperplastic and showed several infarcts. In association with one of these on the surface of the organ, there was a large laminated clot which appeared to be the site of the massive intraperitoneal hemorrhage. The liver weighed 1,930 Gm. and was moderately firm and congested. The right kidney weighed 225 Gm.; the left 240 Gm. The cortical surfaces were flecked with petechiae. On cut surface the entire parenchyma, but particularly the cortex, was both diffusely and focally infiltrated with yellowish-white tissue. The calyces and pelvis were blood stained and there was clotted blood in the left pelvis. The lymph nodes in general were two to four times enlarged, firm, and red-brown in color. The cut surfaces appeared yellowish-white. The lungs were moderately congested and edematous, and together weighed 925 Gm. The heart weighed 415 Gm. and there was moderate hypertrophy of the left ventricle. In the anterior portion of the hypophysis there was a small necrotic infarct. There was a hemorrhagic infarct in the posterior portion of the right cerebellar hemisphere running into the white matter at the level of the middle cerebellar peduncle. There was also a smaller hemorrhagic infarct in the left cerebellar hemisphere.

Microscopic: There was an extensive fibrinoid degeneration of the collagens of the glomerular lobules of the kidney indistinguishable in places from the "wire loop" lesions of disseminated lupus erythematosus. This fibrinoid degeneration was also noted to a much less extensive degree in arterioles of the liver, the spleen and the heart. In addition there was a rather marked plasma cell infiltration in the kidneys, the lymph nodes, the spleen and the bone marrow. The bone marrow also contained many abnormally swollen megakaryocytes with pale cytoplasm and pyknotic nuclei.

Case # (Fig. 2). G. K., a 40 year old Jewish female bookkeeper was admitted to the New

* Vitamin K, oxide was kindly supplied by Mr. William J. Reilly of Merck and Company.
York Hospital for the eighth time in January 1949 complaining of severe rectal bleeding of ten days' duration.

Present Illness: She was first admitted to the hospital in 1934 for the repair of a ventral hernia. An incidental complaint was that she had had hemorrhoids with occasional bleeding for about three years. External and internal hemorrhoids were present. Her hemoglobin was 75 per cent, red blood count 3.5 M., white blood count 6,100 with a normal differential. No abnormal bleeding tendency was noted at operation.

In 1937 she was admitted because of joint pains in the feet, knees and right arm and shoulder. Transient small red spots had appeared intermittently on her arms and legs for two or three years and there had been some increase in her rectal bleeding. Her hemoglobin was 10.7 Gm., R.B.C. 3.4 M., W.B.C. 10,600 with a normal differential. The platelet count was 42,000. The bleeding time (Duke) was 8 minutes; (normal 1 to 5 minutes); the clotting time (Lee-White) 34 minutes (normal 5 to 10 minutes). After 24 hours there was poor retraction of an abnormally fragile clot. The tourniquet test was positive. Prothrombin activity and fibrinogen concentrations were reported as normal although the methods in use then were not as accurate as those used today. The stools were grossly bloody. A diag-

![Graph](image.png)

**Fig. 2.**—Undiluted (100 per cent plasma) prothrombin times and treatment of Case 2.

nosis of idiopathic thrombocytopenic purpura was made and a splenectomy was done. The spleen appeared normal on histologic examination. The platelet count postoperatively ranged from 350,000 to 490,000 and the tourniquet test became negative. The bleeding from the hemorrhoids appeared to subside, and with transfusions the red blood count rose to 4.2 M. with 84 per cent hemoglobin.

Two weeks after this discharge she was readmitted for incision and drainage of a small abscess in the splenectomy wound. Bleeding time, clotting time and platelet count were normal and there was good clot retraction although the clot was slightly fragile.

The patient was irregular in her clinic visits thereafter, but in 1938 she was seen complaining of occasional pain in her ankles and on one visit had pitting ankle edema.

In April 1940 she complained of pains in her arms and legs and of intolerance to cold. She noted occasional bleeding from the rectum. Her hemoglobin was 13.4 Gm., R.B.C. 2.9 M., W.B.C. 10,500 with the following differential count: mature polymorphonuclears 15 per cent, band forms 13 per cent, lymphocytes 57 per cent, monocytes 11 per cent and eosinophils 4 per cent. The smear showed macrocytosis. Volume index was 1.44. The platelet count was 240,000, the bleeding time was 3 minutes and the tourniquet test was positive. The clotting time was slightly prolonged; clot retraction was good with a firm clot. Gastric analysis yielded no free acid after histamine. Pernicious anemia was suspected. The patient...
refused to take parenteral liver extract although she did take ferrous sulfate and an unknown amount of liver by mouth.

During this period the patient had an erythematous rash on her face which was diagnosed as chronic urticaria. Skin tests with ragweed, oak, timothy, dog epithelium and dust were positive and she received a series of desensitizing injections.

She was admitted again in September 1940 for an acute sinusitis which subsided quickly on conservative treatment; no sulfonamides were used.

Her anemia continued, the R.B.C. ranging between 3.0 and 4.3 M., the hemoglobin between 9.0 and 11.4 Gm.

In 1943 the rectal bleeding increased, her R.B.C. dropped to 1.7 M. with 3.8 Gm. of hemoglobin and she was readmitted for a hemorrhoidectomy. She had no further significant rectal bleeding and her R.B.C. returned to the previous levels of 3.0 to 4.0 M. She continued to take ferrous sulfate but was inconstant in her clinic visits. Blood counts at intervals, however, showed approximately the same mild anemia for the next five years.

Ten days before the admission in January 1949 the patient began to pass considerable amounts of blood by rectum several times a day. She became very fatigued and pale. On the day of admission she had a nosebleed lasting all day. She had noted no ecchymoses nor hematuria.

Family History: There was no history of any abnormal bleeding tendency in any member of the family.

Past History: The patient was never robust. All of her life she had had frequent colds complicated by sinusitis and otitis media. She had an incision and drainage of a cervical node at age 9, an appendectomy at age 12 and a cholecystectomy for cholesterosis of the gall bladder at age 20. A tonsillectomy at age 22 was said to have been followed by excessive bleeding. There was no history of contact with chemicals. The dietary history was not abnormal and alcohol was taken rarely.

Physical Examination: The patient was a slender, underdeveloped, poorly nourished woman who appeared chronically and moderately acutely ill. The skin and mucous membranes were pale. There were no ecchymoses nor petechiae. The nares were encrusted with blood. There were several nodes 2 cm. in size in the right posterior cervical chain and a few shotty axillary and inguinal nodes. The lungs were clear. The heart was not enlarged; there was a moderately loud blowing apical systolic murmur. A firm, nontender liver was palpable 5 cm. below the right costal margin. There were no other abdominal masses. There was a ring of bleeding prolapsed hemorrhoids.

Laboratory Findings: An uncatheterized urine specimen obtained on admission showed a trace of albumin and a few red blood cells and white blood cells, but subsequent specimens were normal.

Serologic tests for syphilis were negative.

Total serum protein was 5.3 Gm. per cent with an albumin/globulin ratio of 3.9/1.4. thymol turbidity, bromsulfalein retention, cholesterol, cholesterol esters, bilirubin and alkaline phosphatase determinations were normal. The cephalin flocculation was 12 units on admission (normal up to 5 units), but gradually fell to 3 units.

Serum calcium was 7.7 mg. per cent; serum phosphorus 4.0 mg. per cent. The blood vitamin C level was 0.58 mg. per cent. Plasma fibrinogen was 0.308 Gm. per cent. No cryoglobulin was found.

Hematologic Data: Hemoglobin was 5.5 Gm., R.B.C. 1.4 M., hematocrit 17, W.B.C. 4,900 with the following differential: lymphocytes 45 per cent, monocytes 8 per cent, mature polymorphonuclears 21 per cent, band forms 22 per cent, metamyelocytes 1 per cent and normoblasts 4 per cent. The reticulocyte count was 2 per cent. The platelet count was 300,000 and the platelets appeared adequate on smear. The bleeding time (Duke) was 3 minutes; clotting time (Lee-White 3 tube) 30 minutes; and the clot retraction normal. The tourniquet test was negative. Sternal marrow aspiration showed the following: total count 17,000 cells per cu. mm.; one megakaryocyte per chamber; lymphocytes 20 per cent, eosinophils 3 per cent, mature polymorphonuclears 7 per cent, band forms 14 per cent, metamyelocytes 11 per cent, myelocytes 10 per cent, promyelocytes 5 per cent, proerythroblasts 2 per cent, erythroblasts 3 per cent and normoblasts 24 per cent.
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The prothrombin time was 188 seconds undiluted (control 16.5 seconds) and over 5 minutes on the 12.5 per cent saline dilution (control 41.5 seconds).

Course: In the four days following admission, the patient received 1,900 ml. of blood, but continued to pass grossly bloody stools and although the prothrombin time appeared to decrease, it remained markedly prolonged. The intravenous administration of 648 mg. of menadione in divided doses over the next seventy-two hours produced no decrease in the prothrombin time. A single intravenous dose of 1,000 mg. of menadione was then given with no change in the prothrombin time within forty-eight hours. Because of the urgency of the situation, 1,000 mg. of vitamin K$_1$ oxide was then administered intravenously and forty-eight hours later the prothrombin time had definitely decreased. This dose was then repeated and over the next five days there was a gradual decrease in the prothrombin time to the normal range, where it remained without further therapy. The rectal bleeding stopped and there were no other hemorrhagic manifestations.

One of the axillary lymph nodes was biopsied and the pathologic diagnosis was chronic lymphadenitis. No eosinophils nor Reed-Sternberg cells were seen. The wound healed uneventfully. The patient was discharged improved on the sixty-eighth hospital day.

Four days after discharge the patient noted the onset of periorbital and dependent ankle edema. Therefore, one week after discharge, she was readmitted for evaluation. She had had no more rectal bleeding. Except for slight edema about the eyes and in the ankles there was no significant change in her physical examination. Her urine was normal. Her hemoglobin was 11 Gm. R.B.C. 3.2 M. and W.B.C. 9,000 with normal differential. The total serum protein was 7.3 Gm. per cent with an A/G ratio of 4.5/2.8. Liver function studies were otherwise essentially unchanged from those on her previous admission. Her prothrombin times were normal.

She continued to have slight puffiness of her face and ankles. No additional information pertinent to the elucidation of her case was obtained. She was discharged after four weeks.

Special Studies

As previously noted, the Quick one-stage prothrombin time is a summation of the effect of several factors in addition to the prothrombin concentration. Whether the prolongation of the prothrombin time in these 2 cases was due to a hypoprothrombinemia or to one or more of these other factors was determined by the following studies:

Case 1

1. Effect of Serum: To rule out a defect in the second phase of coagulation, fresh normal serum containing thrombin but no fibrinogen was added to the patient's blood. The results are shown in table 1. These results, together with the fibrinogen determination of 0.328 Gm. per cent, indicate no defect in fibrinogen.

2. Effect of Normal Blood on Patient's Plasma: The patient's plasma was mixed with normal blood and clotting times were determined. The results obtained are shown in table 2. No anticoagulant effect was demonstrated under these conditions.

3. Effect of Normal Plasma on the Prothrombin Time of Patient's Plasma: The effect of normal plasma on the prothrombin time of the patient's plasma was determined. The results obtained are shown in table 3.

The determination on January 26, 1948 did show the patient's plasma to prolong the prothrombin time of the normal plasma beyond that expected from dilution. However, January 29, 1948 there was no such effect. These data suggest a transient anticoagulant effect of the patient's plasma, although no clear
interpretation seems justified on the basis of only two determinations. It is of interest that Conley, et al. 22 have recently found a transient anticoagulant action of the plasma in some cases of hypoprothrombinemia due to dicumarol or severe liver disease.

**Table 1.—(Case 1)**

<table>
<thead>
<tr>
<th>Patient's Blood</th>
<th>Normal Blood</th>
<th>Normal Serum</th>
<th>Clotting Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. ml.</td>
<td>0.0 ml.</td>
<td>0.5 ml.</td>
<td>9 min.</td>
</tr>
<tr>
<td>2. ml.</td>
<td>0.0 ml.</td>
<td>0.5 ml.</td>
<td>2 min.</td>
</tr>
<tr>
<td>2.0 ml.</td>
<td>0.0 ml.</td>
<td>0.5 ml.</td>
<td>Over 90 min.</td>
</tr>
</tbody>
</table>

**Table 2.—(Case 1)**

<table>
<thead>
<tr>
<th>Normal Blood</th>
<th>Patient's Plasma</th>
<th>Clotting Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0 ml.</td>
<td>0.0 ml.</td>
<td>5½ min.</td>
</tr>
<tr>
<td>1.0 ml.</td>
<td>0.01 ml.</td>
<td>6½ min.</td>
</tr>
<tr>
<td>1.0 ml.</td>
<td>0.05 ml.</td>
<td>9 min.</td>
</tr>
<tr>
<td>1.0 ml.</td>
<td>0.1 ml.</td>
<td>5 min.</td>
</tr>
<tr>
<td>1.0 ml.</td>
<td>0.2 ml.</td>
<td>6½ min.</td>
</tr>
<tr>
<td>1.5 ml.</td>
<td>0.5 ml.</td>
<td>4 min.</td>
</tr>
</tbody>
</table>

**Table 3.—(Case 1)**

<table>
<thead>
<tr>
<th>Date</th>
<th>Normal Plasma</th>
<th>Patient's Plasma</th>
<th>Proth. Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-26-48</td>
<td>0</td>
<td>100%</td>
<td>48 sec.</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>0</td>
<td>15 sec.</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>50%</td>
<td>26 sec.</td>
</tr>
<tr>
<td>1-29-48</td>
<td>0</td>
<td>100%</td>
<td>29 sec.</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>50%</td>
<td>13.4 sec.</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>50%</td>
<td>16.0 sec.</td>
</tr>
</tbody>
</table>

**Table 4.—(Case 1)**

<table>
<thead>
<tr>
<th>BaSO4 Plasma</th>
<th>Patient's Plasma</th>
<th>Saline</th>
<th>Prothrombin Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100%</td>
<td>0</td>
<td>29 sec.</td>
</tr>
<tr>
<td>100%</td>
<td>0</td>
<td>0</td>
<td>No clot in 2½ hrs.</td>
</tr>
<tr>
<td>50%</td>
<td>50%</td>
<td>0</td>
<td>53 sec.</td>
</tr>
<tr>
<td>0</td>
<td>50%</td>
<td>50%</td>
<td>50 sec.</td>
</tr>
</tbody>
</table>

4. Test for Accessory Factor: It has been shown that barium sulfate will remove prothrombin from oxalated normal plasma, but has little effect on the accessory factors (Ac-globulin, factor V). 17 Therefore, barium sulfate-treated normal plasma contains essentially normal amounts of accessory factors, but no prothrombin. Addition of such plasma to the patient's plasma would correct the prothrombin time prolongation if it were due to accessory factor deficiency. However, if due to prothrombin deficiency, the addition of the barium sulfate-
treated normal plasma would have no appreciable effect on the prothrombin time. The results of such tests are recorded in table 4.

These results show that the addition of the plasma containing accessory factors had no more effect on the prothrombin time than the addition of a corresponding amount of saline. This indicates that the defect in the patient’s plasma was not due to an accessory factor deficiency.

5. Two-stage Prothrombin Determination: Prothrombin determination by a modification of the two-stage method (Warner, Brinkhous and Smith) was done by Dr. Joseph E. Flynn (Department of Pathology, Columbia University, College of Physicians and Surgeons). No prothrombin units were obtained (normal: 300 units per ml.). No evidence of factor V deficiency was obtained.

6. Prothrombin Times on Patient’s Family: The prothrombin time determinations on 5 members (mother, brother, 2 sisters and a paternal uncle) of the patient’s family were within the normal range.

Case 2

1. Effect of Thrombin: In this case thrombin solution (Topical Thrombin, Parke, Davis & Co.) was added to the patient’s plasma with the results as recorded in table 5.

These results, together with the fibrinogen determination of 0.308 Gm. per cent, indicated no defect in fibrinogen nor evidence of an anticoagulant inhibiting the effect of thrombin.

2. Effect of Normal Plasma on the Prothrombin Time of Patient’s Plasma: The results obtained are shown in table 6.

These data indicate that the patient’s plasma did not prolong the prothrombin time of normal plasma.
3. Effect of Normal Recalciﬁed Plasma on the Clotting Time of Patient’s Plasma: The results are shown in table 7.
These results show no signiﬁcant prolongation of the clotting time of recalciﬁed normal plasma by the patient’s plasma.

4. Test for Accessory Factor Deﬁciency: The effect of barium sulfate-treated normal plasma on the patient’s plasma was determined. The results obtained are recorded in table 8.
The addition of plasma containing accessory factors did not affect the prothrombin time any more than the addition of saline, indicating that there was no deﬁciency of accessory factors.

5. Two-stage Prothrombin Determination: The two-stage prothrombin determination done by Dr. Flynn showed less than 10 units of prothrombin per ml. (normal: 300 units per ml.). Addition of factor V (Ac-globulin) produced no increase in prothrombin. Therefore, there appeared to be no defect in the amount of factor V (Ac-globulin) in the patient’s plasma.

6. Prothrombin Times on Patient’s Family: The prothrombin times on 3 members (mother, father and brother) of the patient’s family were within the normal range.

**TABLE 7.—(Case 2)**

<table>
<thead>
<tr>
<th>Normal Plasma</th>
<th>Patient’s Plasma</th>
<th>Saline</th>
<th>Clotting Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>0</td>
<td>0</td>
<td>56.5 sec.</td>
</tr>
<tr>
<td>50%</td>
<td>0</td>
<td>50%</td>
<td>60.0 sec.</td>
</tr>
<tr>
<td>50%</td>
<td>50%</td>
<td>0</td>
<td>65.0 sec.</td>
</tr>
</tbody>
</table>

**TABLE 8.—(Case 2)**

<table>
<thead>
<tr>
<th>BaSO₄ Plasma</th>
<th>Patient’s Plasma</th>
<th>Saline</th>
<th>Prothrombin Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100%</td>
<td>0</td>
<td>30.7 sec.</td>
</tr>
<tr>
<td>100%</td>
<td>0</td>
<td>0</td>
<td>No clot in 2½ hours</td>
</tr>
<tr>
<td>50%</td>
<td>50%</td>
<td>0</td>
<td>50.6 sec.</td>
</tr>
<tr>
<td>0</td>
<td>50%</td>
<td>50%</td>
<td>51.4 sec.</td>
</tr>
</tbody>
</table>

**DISCUSSION**

In neither of these 2 patients was there evidence of deﬁcient absorption of vitamin K, of dicumarol or other drug poisoning, or of liver dysfunction of sufﬁcient magnitude to account for the hypoprothrombinemia. Furthermore, it is believed that the possible presence of circulating anticoagulants was excluded. Therefore, it is believed that each of these 2 cases had a hypoprothrombinemia without evident cause associated with a hemorrhagic tendency. Neither of them had a history of unusual bleeding in childhood and thus there is no indication that the defect was on a congenital basis. Therefore, the experimental results indicate that these 2 cases should be classiﬁed as idiopathic hypoprothrombinemia.
<table>
<thead>
<tr>
<th>Author</th>
<th>Sex</th>
<th>Age at Onset</th>
<th>Familial Incidence</th>
<th>Component Study</th>
<th>Response to Vitamin K</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhoads &amp; Fitz-Hugh</td>
<td>M</td>
<td>9 mos.</td>
<td>Neg.</td>
<td>Not done</td>
<td>Uncertain</td>
<td>None</td>
</tr>
<tr>
<td>Giordano, 1943</td>
<td>M</td>
<td>5 yrs.</td>
<td>Pos.</td>
<td>Pos.</td>
<td>Uncertain</td>
<td>None</td>
</tr>
<tr>
<td>Murphy &amp; Clark, 1944</td>
<td>M</td>
<td>4 yrs.</td>
<td>Pos.</td>
<td>Equiv.</td>
<td>Prothrombin deficiency</td>
<td>None</td>
</tr>
<tr>
<td>de Marval &amp; Bonehill, 1944</td>
<td>F</td>
<td>8 yrs.</td>
<td>Neg.</td>
<td>Not done</td>
<td>Not done</td>
<td>None</td>
</tr>
<tr>
<td>de Marval, 1945</td>
<td>F</td>
<td>3 yrs.</td>
<td>Pos.</td>
<td>Not done</td>
<td>Not done</td>
<td>None</td>
</tr>
<tr>
<td>Hauser, 1945</td>
<td>M</td>
<td>3 mos.</td>
<td>Pos.</td>
<td>Not done</td>
<td>Not done</td>
<td>None</td>
</tr>
<tr>
<td>Hauser, 1945</td>
<td>M</td>
<td>Childhood</td>
<td>Pos.</td>
<td>Not done</td>
<td>Not done</td>
<td>None</td>
</tr>
<tr>
<td>Austin &amp; Quastler, 1945</td>
<td>M</td>
<td>56 yrs.</td>
<td>Neg.</td>
<td>Not done</td>
<td>Not done</td>
<td>None</td>
</tr>
<tr>
<td>Owren, 1947</td>
<td>F</td>
<td>3½ yrs.</td>
<td>Neg.</td>
<td>Not done</td>
<td>Accessory factor deficiency (factor V)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>Age</td>
<td>Family History</td>
<td>Lab Results</td>
<td>Treatment</td>
<td>Response</td>
</tr>
<tr>
<td>------------</td>
<td>-----</td>
<td>-----</td>
<td>----------------</td>
<td>-------------</td>
<td>-----------</td>
<td>----------</td>
</tr>
<tr>
<td>Quick, 1947</td>
<td>M</td>
<td>birth</td>
<td>Pos.</td>
<td>Accessory factor deficiency</td>
<td>None</td>
<td>Congen., accessory factor deficiency</td>
</tr>
<tr>
<td>Quick, 1947</td>
<td>M</td>
<td>1 wk.</td>
<td>Pos.</td>
<td>Accessory factor deficiency</td>
<td>None</td>
<td>Congen., accessory factor deficiency</td>
</tr>
<tr>
<td>Lewis &amp; Bennett, 1947</td>
<td>F</td>
<td>29 yrs.</td>
<td>Uncert.</td>
<td>Not done</td>
<td>Uncertain</td>
<td>Effective</td>
</tr>
<tr>
<td>Heindl et al., 1948</td>
<td>F</td>
<td>43 yrs.</td>
<td>Neg.</td>
<td>Not done</td>
<td>Not done</td>
<td>Effective</td>
</tr>
<tr>
<td>Crockett et al., 1949</td>
<td>F</td>
<td>2 wks.</td>
<td>Neg.</td>
<td>Prothrombin deficiency</td>
<td>None</td>
<td>Congen. combined prothrombin Aeglobulin deficiency</td>
</tr>
<tr>
<td>Landwehr et al., 1950</td>
<td>M</td>
<td>3 wks.</td>
<td>Pos.</td>
<td>Prothrombin deficiency</td>
<td>None</td>
<td>Congen.</td>
</tr>
<tr>
<td>Covey et al., 1950</td>
<td>F</td>
<td>Childhood</td>
<td>Pos.</td>
<td>Prothrombin</td>
<td>None</td>
<td>Congen.</td>
</tr>
<tr>
<td>Case 1</td>
<td>M</td>
<td>29 yrs.</td>
<td>Neg.</td>
<td>Prothrombin deficiency</td>
<td>None</td>
<td>Effective</td>
</tr>
<tr>
<td>Case 2</td>
<td>F</td>
<td>43 yrs.</td>
<td>Neg.</td>
<td>Prothrombin deficiency</td>
<td>None</td>
<td>Effective</td>
</tr>
</tbody>
</table>
To classify accurately the previously reported cases of “idiopathic hypoprothrombinemia,” it is essential to know whether the defect could be ascribed to a prothrombin deficiency or to a deficiency of accessory clotting factors. Such information is not available in the majority of the cases in the literature. The familial incidence of prothrombin time abnormalities appears to be a differential characteristic of value, but again the majority of the reports do not include laboratory data on the relatives of the patients with hypoprothrombinemia.

Review of the previously reported cases (table 9) does suggest, however, that “idiopathic hypoprothrombinemia” may be divided into two groups: (1) a congenital form, in which the bleeding tendency becomes manifest in the early years of life and in which in most instances other members of the family demonstrate either a bleeding tendency or a prolongation of the prothrombin time, and (2) an acquired form, in which the bleeding tendency becomes apparent only in adult years and in which there is no evidence of familial hemorrhagic manifestations or abnormal prothrombin times. The cases of Owren and Quick, although appearing to fall into the first group, should be further separated since the defects in each of them were clearly concerned with an accessory clotting factor rather than with prothrombin. The 2 cases of the present report, possess the characteristics of the “acquired” group.

There would seem to be considerable doubt whether the “acquired” group truly represents an “idiopathic” hypoprothrombinemia or even a single or definite disease entity. Of the 3 cases previously reported 7, 10, 12 2 were found to have no other significant abnormality. In the third case, autopsy disclosed a widespread granulomatous disease, the precise nature of which was not apparent. In Case 1 of this report, the autopsy also revealed generalized lesions of an obscure and unrecognizable pattern, which, however, were quite distinct from that found in the case of Austin and Quastler. The possibility that the lesions in Case 1 could have arisen as an abnormal hypersensitivity response to the blood or medications he received during his final illness seems most unlikely, particularly in view of the evidence of renal disease which preceded his hospitalization by at least four years. In Case 2, it also appears that the prothrombin deficiency is but a part of a generalized, though obscure, disease. The bleeding tendency and anemia, in the presence of normal prothrombin activity in 1937, and the persistence of the anemia, the joint symptoms, skin lesions and edema indicate a generalized disease process of which the hypoprothrombinemia is probably only another manifestation.

What the pathogenesis of the prothrombin defect may be and what relation the defect bears to the apparently varied pathologic states presented by these 2 patients, by the patient of Austin and Quastler and perhaps by other cases of “acquired idiopathic hypoprothrombinemia” must await more complete understanding of the nature and metabolism of prothrombin. It does seem significant, however, that of the 5 cases reported (including the two of this report) 4, 10, 12 have responded to massive doses of vitamin K1 oxide. The fifth case was given only relatively small amounts of a water soluble preparation (Synkamin). Whether the response to massive vitamin K therapy is an additional point of differentiation between the “congenital” and the “acquired” form of
hypoprothrombinemia is not known. Of the "congenital" cases, only the case of Hagen and Watson, who was given 800 mg. of vitamin K$_1$ oxide over a three day period, received anything approaching the dosage used in the cases of Heindl, et al., Lewis and Bennett, and those presented in this report.

The data on these 2 patients indicates that vitamin K$_1$ oxide was effective whereas the synthetic water soluble vitamin K preparation (menadione) was not. Lewis and Bennett observed this difference in therapeutic response to these substances in a case of idiopathic hypoprothrombinemia. In Case 1 it should be noted that the patient was given his largest doses of menadione during the thirty-six hours before he received the vitamin K$_1$ oxide and that the shortening of the prothrombin time could have been due to either or both agents rather than to the vitamin K$_1$ oxide alone. In Case 2, however, the difference in action appears more evident. She was given large intermittent doses of menadione intravenously without effect over a period of seventy-two hours. She then received 1,000 mg. of menadione by infusion without response over the next forty-eight hours. One thousand mg. of vitamin K$_1$ oxide produced a definite effect in forty-eight hours, and a second dose at this time produced a normal prothrombin time within five days.

The difference between the effectiveness of the vitamin K$_1$ oxide and the water soluble methylnaphthoquinone derivatives cannot be explained. It is not known how these essential compounds exert their characteristic biologic effects. The inactivation of enzyme systems by certain compounds structurally related to their substrates is well recognized. The structural similarities of the anticoagulant 4-hydroxycoumarin derivatives to substances possessing vitamin K activity, and the antagonistic action of compounds with vitamin K activity toward these anticoagulants lend support to the suggestion that these anticoagulants and vitamin K act through a common system. Since vitamin K$_1$ oxide was effective in restoring normal prothrombin activity in these cases the presence of a vitamin K inhibitor should not be excluded. The possibility that these 2 patients inactivate the water soluble vitamin K more rapidly than the vitamin K$_1$ oxide might explain the difference in their actions. However, no definite conclusions can be made from the available data.

**Summary**

Two cases of hypoprothrombinemia of unknown cause are presented. In each case there was a marked hemorrhagic diathesis which, in Case 1, led to death. In each there were additional findings (clinical or necropsy) which suggested that the prothrombin deficiency was only one manifestation of a generalized disease.

The pertinent literature is reviewed and a classification of the previously reported cases of "idiopathic hypoprothrombinemia" into "congenital" and "acquired" types is offered. Both of our cases fall into the "acquired" group. The treatment of the condition is discussed and it is pointed out that vitamin K$_1$ oxide in large doses restored the prothrombin time to normal after the apparent failure of large doses of water soluble menadione. A rationale for this difference in response is suggested.
IDIOPATHIC HYPOPROTHROMBINEMIA

Conclusions

1. Idiopathic hypoprothrombinemia may be congenital or acquired.
2. The acquired type may be only a manifestation of certain poorly understood pathologic states.
3. In the presence of a prothrombin deficiency which is resistant to the administration of water soluble methylnapthoquinone compounds, large doses of the more potent vitamin K₁ oxide should be used.
4. While large doses of vitamin K₁ oxide produced a return of the prothrombin time to normal in 2 cases no tendency to produce an overswing to abnormally short times was observed.

REFERENCES

LEY, READER, SORENSON AND OVERMAN 755


—, — and Link, K. P.: Studies on the hemorrhagic sweet clover disease. VIII. The effect of 2-methyl-1,4-naphthoquinone and 1-ascorbic acid upon the action of 3,3'-methylenebis (4-hydroxycoumarin) on the prothrombin time of rabbits. J. Biol. Chem. 145: 155, 1942.
Idiopathic Hypoprothrombinemia Associated with Hemorrhagic Diathesis, and the Effect of Vitamin K

ALLYN B. LEY, GEORGE G. READER, C. W. SORENSON and RALPH S. OVERMAN