DICUMAROL THERAPY CONTROLLED BY THE STABILIZED THROMBIN
METHOD FOR DETERMINATION OF PROTHROMBIN

By L. A. Sternberger, M.D.

A N ADEQUATE method of control for the anticoagulant effect of dicumarol is an essential condition for the evaluation of effectiveness and danger of this therapy. Such a method should control the action of dicumarol only; it should be independent of accidental variations in clotting factors due to other causes. As long as these requirements are not fulfilled, the optimal dosage of dicumarol cannot be determined: with too large doses hemorrhage results, while too small doses make it impossible to obtain the full therapeutic effect of the drug.

Hitherto the one-stage method of Quick1 or modifications of it have been used exclusively in clinical work. It rests upon the principle that if in the coagulation of blood-plasma thromboplastin, calcium and fibrinogen concentration are kept constant, the clotting time depends only on prothrombin, provided that these four factors are the only coagulation factors existing. Thromboplastin is controlled by addition of excess of this factor. The activity of thromboplastin has to be determined by standardization with a relatively large number of normal control plasmas. Since the normal controls are to be used for standardization of a reagent for the method, the absolute value of prothrombin in normals cannot be established. Calcium concentration is to remain at its constant optimum. But it was pointed out by Jacques and Dunlop3 and by Quick4 that the prothrombin time of hypoprothrombinemic oxalated plasma is very sensitive to changes in calcium concentration so that in such plasmas this requirement becomes very hard to fulfill. The prothrombin clotting time of hypoprothrombinemic undiluted plasma is compared with that of diluted normal plasma: dilution with normal saline changes the fibrinogen concentration significantly, and although Nitsche and co-workers5 have attempted to avoid this by using fibrinogen as diluent and Rosenfield and Tuft6 by employing deprothrombinized plasma, the results have not been uniform.

The one-stage method does not take into account any of the following coagulation factors, which are capable of influencing the prothrombin time: (1) Antithrombic substances described by Astrup7 and by Glazko and Ferguson8 which destroy thrombin immediately after its formation. (2) Owen's fifth coagulation factor,9 which is required in addition to thromboplastin and calcium to convert prothrombin to thrombin, and variations of which may increase or decrease the prothrombin time. (3) Autocatalytic factors described by Astrup7 and Owen.9 Because of such factors the rate of conversion of prothrombin to thrombin is not constant. The principle of the one-stage method is that the rate of conversion of prothrombin to thrombin is dependent on the concentration of prothrombin by a definite relationship. (4) Inhibition factors postulated by Ferguson and Glazko10 and by Tocantins11 which slow down the conversion rate of prothrombin to thrombin. Moreover, normal plasma may contain any number of unknown factors,7 which affect the thromboplastin used in the one-stage method, so that, as pointed out by Conley and Morse,11 results obtained with different thromboplastins are not comparable. In fact, serious doubts arise as to whether the one-stage method gives more than a rough estimate of plasma prothrombin. On the other hand, the evaluation of the effectiveness and safety of dicumarol therapy can be made only if a strictly reliable control method is available and practical, giving absolute results, so that reports from one laboratory can be compared with those obtained in another.

The stabilized thrombin two-stage method12 is independent of any of the above factors of inaccuracy and, in addition, gives results in absolute units. With the use...
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of the modification to be described in this paper (related particularly to the preparation of a stable thrombin reagent and to different quantities of materials used in the test) it does not take more time of performance than the one-stage procedure. The method is based on our observation that alcohol suppresses the antithrombic activity of plasma, so that it becomes possible to keep constant the amount of thrombin obtained after quantitatively converting prothrombin to thrombin.

METHOD FOR DETERMINATION OF PROTHROMBIN

Principle

The oxalated plasma used contains the prothrombin to be examined, as well as antithrombin and fibrinogen. First, the fibrinogen is removed by adding thrombin. Fibrinogen becomes thus converted to fibrin, and is rolled out with a stirring rod. The resulting fluid contains all the prothrombin, antithrombin, and the added thrombin (but not fibrinogen). However, within ten minutes the added thrombin will have been inactivated by the antithrombin present. Now the antithrombin activity will be suppressed by the addition of alcohol, and prothrombin converted to thrombin with human milk (thromboplastin) and calcium. The resulting fluid contains all the thrombin obtained quantitatively from the prothrombin originally present (but does not contain active antithrombin). It does not clot as such, because fibrinogen has been removed previously. The amount of prothrombin is now determined by adding various dilutions of the thrombin thus obtained to constant amounts of normal plasma and recording the thrombin-fibrinogen clotting times. This method is independent of the activity of the reagents used. Thus, prothrombin concentration can be directly read from the thrombin-fibrinogen clotting times, and no comparison with normal controls is necessary.

Reagents

25 per cent by volume of ethyl alcohol in normal saline solution.
50 per cent by volume of ethyl alcohol in normal saline solution.
0.1 M sodium oxalate solution.
0.2 M calcium chloride solution.
Thrombin solution.
Fresh normal oxalate plasma.
Human milk.

Preparation of Thrombin Solution

A temperature between 16 and 18 C. is maintained while the following ingredients are placed successively into a flask and stirred after each addition:

380 parts of 25 per cent by volume of ethyl alcohol in normal saline solution.
145 parts of normal saline solution.
25 parts of 0.2 M calcium chloride solution.
210 parts of human blood (whole blood: 9 parts of blood obtained by venepuncture and rendered incoagulable by addition to 1 part of 0.1 M sodium oxalate solution).
75 parts of human milk.
75 parts of 50 per cent by volume of ethyl alcohol in normal saline solution.

The material obtained after the lapse of about 5 to 10 minutes (crude thrombin) will clot an equal volume of human plasma in 6 to 8 seconds. It is very stable. It may be processed immediately or may be kept in the refrigerator without loss of activity for at least eight months.

To 32 parts of "crude thrombin" (shaken well to obtain a uniform suspension) are added 18 parts of
95 per cent ethyl alcohol by volume. The whole is shaken violently and centrifuged immediately in an angle centrifuge. The sediment obtained is resuspended in 16 parts of oxalated merthiolate saline solution (prepared by placing 2 parts of 0.1 M sodium oxalate solution and 10 parts of 1 per cent merthiolate [sodium ethyl-mercurithiosalicylate] into a volumetric flask and making up to 100 with normal saline solution). The suspension is stirred to break up the sediment as completely as possible, whereafter it is centrifuged, and the sediment discarded. The supernatant thrombin solution will clot an equal volume of fresh oxalate plasma in 4 seconds. It is stable for at least six months' storage in the ice box.

_Fresh human plasma:_ Nine ml. of blood are drawn by venepuncture from a normal subject with as little trauma as possible, and added immediately to 1 ml. of 0.1 M sodium oxalate solution contained in a centrifuge tube. The plasma is obtained by centrifugation.

_Human milk:_ It may be used fresh or it may be stored in the ice box for at least one month. If milk has been stored it should be well shaken to obtain a uniform suspension.

**Procedure for the Determination of Prothrombin**

Four and five-tenths ml. of blood are drawn by venepuncture and added as rapidly as possible to a centrifuge tube containing 0.5 ml. of 0.1 M sodium oxalate solution. The tube is shaken immediately by inverting it three times. The plasma is obtained by centrifugation.

The procedure to follow is done at a temperature range between 16 and 22 degrees centigrade.

_Step one, defibrination:_ 0.5 ml. of thrombin are added to 1.0 ml. of the plasma. After 10 minutes the liquid is expressed from the clot by wrapping the latter around a glass rod (using best a pipet with a broken, rough end).

_Step two, thrombinization:_ To 0.75 ml. of defibrinated plasma there are added successively:
- 1.75 ml. of 2.5 per cent by volume of ethyl alcohol in normal saline solution.
- 1.125 ml. of 50 per cent by volume of ethyl alcohol in normal saline solution.
- 0.3 ml. of human milk.
- 0.075 ml. of 0.2 M calcium chloride solution, shaking after each alcohol addition and after the addition of the calcium.

_Step three, dilution:_ Serial dilutions of the thrombinized, stabilized plasma obtained in step two should be set up not earlier than 10 minutes after thrombinization, and preferably not later than 1½ hours thereafter. If stored, rather than fresh milk is used for thrombinization, dilutions should be set up only after the lapse of 20 minutes after thrombinization. For dilution, a 25 per cent (by volume) solution of ethyl alcohol in normal saline is used.

_Step four, clotting:_ With a pipet graduated to the tip, 0.2 ml. of various dilutions of thrombinized plasma are drawn into Wassermann tubes containing 0.2 ml. of fresh human plasma. At the moment of contact with the plasma a stop-watch is started. The tube is held—after brief shaking—against a screened source of light (an electric bulb screened by placing filter paper in front of it proves satisfactory). The test tube is tilted in a way that the fluid contained in it is allowed to flow in turn along its walls from the bottom of the tube towards its top, and back to the bottom again, and the moment of appearance of granularity is recorded by stopping the stop-watch. (The fibrin appears in the form of granules, rather than of threads, because of the presence of alcohol. Therefore, the tube should not be rotated but tilted. End points are very sharp, if this procedure is followed.)
Evaluation of the Amount of Prothrombin by the Stabilized Thrombin Method

Results with this method are obtained in absolute values, and no comparison with a normal standard is necessary. In order to obtain comparable results with the one-stage method, we fix the normal value of prothrombin arbitrarily as 100. This corresponds (see table 1) to a clotting time of 18 seconds obtained when adding to 0.2 ml. of normal plasma 0.2 ml. of a 1:10 dilution of thrombinized plasma (i.e., a 1:80 dilution of the original plasma). In hypoprothrombinemic plasma this value will be obtained at a correspondingly lower dilution.

We usually set up dilutions of 40, 20, and 10 per cent for samples presumably normoprothrombinemic, and dilutions of 80, 40, and 20 per cent for hypoprothrombinemic thrombinized plasmas. Occasionally also dilutions of 60 and 30 per cent are set up, particularly in cases in which the clotting time of 18 seconds seems to occur in between 80 and 40 per cent. If the values recorded as normal in table 1 do not coincide exactly with any one of the dilutions actually set up, but happen to lie in between them, the significance of this can be evaluated by comparing the values obtained at the various dilutions tested and observing whether corresponding deviations of the clotting times occur at all these dilutions. With this procedure the following values of prothrombin can be determined with accuracy; (more definite recording would be within the limits of experimental error): 100, 150, 100, 75, 50, 35, 25, 20, 17, 14, 12.5, 11, 10, 8.5, 7, 6, 5.5 and 5. Standard error and standard deviation of the clotting times recorded in table 1 have been computed in a previous publication.12

Dicumarol Treatment

In this series, 43 cases were given dicumarol for a period of seven to forty-five days. These include 27 cases of pulmonary embolism, 7 cases of thrombophlebitis, 4 cases of arterial embolism, and 5 postoperative cases treated prophylactically. All cases of arterial embolism and the more severe cases of pulmonary embolism were also given heparin for the first one or two days of treatment, usually until the prothrombin reached a level of 50. Heparin was always given by continuous intravenous drop infusion, and the venous blood coagulation time kept between 15
and 21 minutes. It is noteworthy, that the determination of prothrombin with our method is not influenced by the amount of heparin in the blood, since it excludes the effect of antithrombin and is not dependent upon the conversion time of prothrombin to thrombin. Thus, unlike with the one-stage method, continuous administration of heparin does not disturb the determination of prothrombin.

The Prothrombin Level before Treatment

Frequently patients showed a hyperprothrombinemia of 150 to 200 before treatment. This was particularly marked in patients with long standing thrombosis before institution of treatment, or in cases of pulmonary embolism, especially in recurrent pulmonary embolism. On the other hand, among 78 postoperative determinations of prothrombin, there were also 11 cases of hyperprothrombinemia, yet none of them did develop postoperative thrombosis or embolism. It is our impression that the presence of hyperprothrombinemia cannot be used to predict whether a patient is predisposed to thromboembolic disease. It seems, however, that some patients, if having already contracted a thrombosis, may, after a certain lapse of time, develop an occasional hyperprothrombinemia.

Determination of Dosage

In all our patients we endeavored to keep the level of prothrombin between 17 and 50. Dicumarol is a slow acting and very cumulative drug. In attempting to keep the patient at a certain maintenance level, it is necessary to determine the dose to be given on a certain day not only by the prothrombin level for that particular day, but also by the previous response of the patient. Such maintenance was accomplished by the following program of dosage:

First day: Always 300 mg. are given.
Second day: In patients with thromboembolic disease, 200 mg. are given; in all prophylactic cases and in every weak or emaciated patient, 100 mg.
Third day: If the prothrombin for that day is 100 or above, 200 mg. are given. If it is 75-100 mg. or less, no dicumarol is given.
Fourth and each subsequent day: If the prothrombin is above 50, 200 mg. are given. If it is 50, and was on the preceding day above 50, 100 mg. are given. If it is 50 and was on the preceding day 50 or less, 200 mg. are given. If the prothrombin is 35, and was on the preceding day more than 35, no dicumarol is given. If it is 35 and was on the preceding day also 35, 100 mg. are given. If it is 35, and was on the preceding day less than 35, 200 mg. are given. If the prothrombin is less than 35, no dicumarol is given.

Using this program of administration of dicumarol in the stabilized thrombin method for the determination of prothrombin, it is easy to keep the prothrombin level between 17 and 50. During a total of 513 determinations of prothrombin in the hypoprothrombinemic maintenance period of dicumarol in this series, only in 11 determinations (2.3 per cent) was the prothrombin more than 50, and only in three instances (0.6 per cent) was it less than 17. Daily variations of prothrombin were smaller with this method of control than with the one-stage method. This becomes obvious, if it is borne in mind that the one-stage method is dependent also
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on other factors besides the quantity of prothrombin (as outlined above), while the stabilized thrombin method is a direct measure of the amount of prothrombin after it has been converted to thrombin.

Comparison with the One-Stage Method

In a number of cases we have been running parallel determinations with the one-stage method of Quick. An example is given in figure 1. The dosage of dicumarol was determined by the results of the stabilized thrombin method. It will be seen that in the beginning of treatment prothrombin values fell off more rapidly and after stoppage of dicumarol returned more quickly to normal with the one-stage than with the stabilized thrombin method. This discrepancy is explained if consideration is taken of the fact that the one-stage method is dependent on both, the quantity of prothrombin as well as the speed of conversion of prothrombin to thrombin, while the stabilized thrombin method is dependent only upon the quantity of prothrombin. It may well be that fresh circulating prothrombin is more active in its rapidity of conversion to thrombin than less recently formed prothrombin, while both, new and old prothrombin, still form the same amount of thrombin from a given amount of prothrombin. It was pointed out by Overman and co-workers and by Witters that dicumarol probably acts by inhibiting the formation of prothrombin in the liver through competition with vitamin K. Dicumarol hypoprothrombinemia is induced by slowing down the formation of new prothrombin. Therefore, in the beginning of the treatment, the relative amount of old prothrombin in circulation will predominate over that of newly formed prothrombin, and a lower value is obtained with the one-stage method than does correspond to the total amount of

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![Graph](image-url)
prothrombin present. Upon stopping dicumarol new prothrombin is formed again, while the reserve of prothrombin in the circulating blood is relatively small. As a result the relative amount of newly formed prothrombin will predominate over that of old prothrombin, and a higher value of prothrombin is obtained with the one-stage method that does correspond to the quantity of prothrombin actually present. Similar results have been obtained by Hum and Mann in comparing the one-stage method with the two-stage method of Warner, Brinkhous, and Smith.

Treatment of Pulmonary Embolism

Twenty-seven patients were treated. Thirteen of them had multiple emboli and were first seen only after a recurrent embolization. In none of these patients did dyspnea or cyanosis last for more than two days after the start of treatment, although 9 of the cases with recurrent pulmonary emboli were continually cyanotic and dyspneic from the time of occurrence of the first embolus till the second day after the start of treatment, i.e., for a period varying from 5 to 16 days (average: 7 days). In only 1 of the 27 cases did a further infarction occur during treatment. It took place on the eighth day, and symptoms were mild. All patients recovered. They were allowed out of bed 3 to 7 days after all of the following conditions had been fulfilled: (1) absence of fever; (2) absence of blood in the sputum; (3) absence of large amounts of pleural exudate (but a patient was never kept in bed because of the presence of a few friction rales); (4) absence of continuous pain (few patients had still some slight pain on deep inspiration when first out of bed). Dicumarol therapy was continued for 1 to 2 days after the patient had been ambulatory. With this program the period of treatment in these 27 cases was minimum 5 days and maximum 30 days, average 16 days. The average daily dose of dicumarol was 121 mg. The time of recumbency of the patients had no relation to the initial severity of symptoms. The shortness of the period of morbidity is outstanding, particularly if it is considered that there was an exceptionally large proportion of severe cases in this series.

Case Report: A 54 year old man was admitted because of a repeated pulmonary embolus complicating thrombophlebitis. He was in a state of severe cyanosis and dulled consciousness. Respiration was of the Cheyne-Stokes type; the pulse was too weak to be felt. Big rales could be heard from a distance. The patient had a generalized purpuric rash which was reported to have developed about three days before admission. The thrombocyte count was 180,000 per cu. mm.

The patient was given immediately 0.110 Gm. papaverine hydrochloride intravenously and was started upon a continuous intravenous drip infusion of heparin in glucose (100 mg. of heparin per 300 cc. of 5 per cent glucose solution). At the same time blood was withdrawn by venesection (300 ml.). Because of the severity of the condition, the purpura was ignored, and dicumarol was started. Heparin was discontinued after twenty-four hours of treatment.

The patient's condition improved rapidly. Twelve hours after the treatment had been started, he began to respond to words, the cyanosis became less and the respiration regular. The pulse, although still weak, was improving.

After forty-eight hours the patient started to cough out a small amount of bloody, nummular sputum, consciousness had fully returned, dyspnea had disappeared, cyanosis was fading. On the fourth day the patient wanted to get out of bed, and on the fifth day there was no more blood in the sputum. On the eighth day the patient was allowed out of bed and on the ninth day treatment was stopped.
In this case anticoagulant treatment was considered a matter of last resource, and dicumarol was given, although the patient was having a purpuric rash on admission. Within twelve hours of treatment, while heparin was being given, the rosy purpuric spots became deep red in color. At this time the prothrombin was still 100. After interruption of heparin the purpura started to disappear, while prothrombin was falling to be maintained at a level of 35. No erythrocytes were found in the urine at any time during the treatment.

**Thrombophlebitis**

Seven cases, including 2 patients with thrombophlebitis during typhoid fever, were treated. In all but one patient did local pain disappear within three days of treatment. Some patients were seen first after having been suffering from the disease for weeks. In all patients there was a regression of the extent of local tenderness from the start of treatment on. In no case did pulmonary embolism develop. The period of treatment was minimum 4 days, maximum 45 days, average 19 days. The average daily dose of dicumarol was 119 mg.

**Arterial Embolism**

There were only 4 cases of arterial embolism in this series. Three patients suffered from myocardial infarction and contracted emboli in the popliteal artery. They were given dicumarol and heparin (the latter was discontinued when the prothrombin level had reached 50) and in all of them the circulation had become restored within 4 days. All patients recovered from the myocardial infarction. One case of embolism of the retinal artery came to treatment only after vision had been lost for two days, and no improvement was observed during treatment.

**Prophylactic Treatment**

Five cases were given dicumarol prophylactically after surgical intervention. Treatment was started on the second postoperative day and continued until the patient was out of bed. In none of these cases did thrombosis develop. The period of treatment was minimum 3 days, maximum 8 days, average 7 days. The average daily dose of dicumarol was 115 mg.

**Relation of Dosage of Dicumarol to Clinical Condition**

The average daily dose of dicumarol was similar in all clinical conditions treated, although there were large individual variations. The most sensitive patient (pure prophylactic treatment) received a total of 400 mg. during 8 days of treatment (average: 50 mg. daily), while the least sensitive patient (pulmonary embolism) received a total of 2400 mg. during 12 days of treatment (average: 200 mg. daily).

**Complications**

The only complication of dicumarol treatment is hemorrhage due to excessive hypoprothrombinemia. In this series there was only one case of bleeding (2 per cent). This was a wound hemorrhage in a cachetic patient receiving prophylactic treatment. As we desired, in this series, to establish the usefulness of our method of control, we have never hesitated to give dicumarol to patients with relative contraindications to the use of anticoagulant therapy (see the case of purpura described...
above). We believe that the hemorrhage did occur only because of disregard of such contraindications.

Case Report: A two-stage Lahey's abdominoperineal resection of a reticulosarcoma of the rectum was performed by Dr. Joseph on a 60 year old emaciated man. After the second operation he was rather dehydrated and was lying in bed listlessly without making any spontaneous movement. Prophylactic dicumarol treatment was instituted on the fourth postoperative day and continued until the eleventh postoperative day, as shown in the following table:

<table>
<thead>
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<th>Date</th>
<th>Prothrombin</th>
<th>Dicumarol (Gm.)</th>
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<tbody>
<tr>
<td>August 11</td>
<td>100</td>
<td>0.3</td>
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<tr>
<td>August 12</td>
<td>50</td>
<td>0.1</td>
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<td>August 17</td>
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<tr>
<td>August 18</td>
<td>11.5</td>
<td></td>
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<tr>
<td></td>
<td>9 a.m.</td>
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</table>

The patient was very sensitive to small doses of dicumarol. The blood-tinged discharge from the perineal wound was present before and during the whole course of treatment, but the amount of blood did not increase until August 17. On this day prothrombin was still falling. Because of the anemia and general weakness the patient was given a transfusion of 800 ml. of "banked" blood. Fresh blood was not used, because this transfusion was not given for hypoprothrombinemia. At 1 a.m. the following morning (August 18), 8 hours after this transfusion, blood started to ooze from the operative wound. At this time prothrombin was 11.5. Immediately, thrombin was injected into the wound cavity and cessation of bleeding was instantaneous. The patient was also given Hykinone (menadione bisulfite, Abbott), 0.072 Gm. by slow intravenous injection. Eight hours thereafter the prothrombin was 17 and bleeding did not recur. The patient made an uneventful recovery.

It may be possible that administration of "banked" blood diluted the patient's circulating prothrombin and thus initiated the bleeding. Also any of the following contraindications to the use of dicumarol may have predisposed to the bleeding: (1) an extensive, infected, operative wound, (2) surgery of the gastro-intestinal tract, (3) dehydration and cachexia.

In all our patients repeated urinalyses for a search of erythrocytes were made. In none did microscopic hematuria appear during treatment, while in those patients who were treated after surgery of the urinary tract, hematuria never became more marked and often disappeared during dicumarol administration.

With the stabilized thrombin method it is possible to keep the patient well within the boundaries of the therapeutic zone and variations of prothrombin from day to day are relatively small. There were only three hyper-reactors (7 per cent) in this series, out of which only one (2 per cent) had a hemorrhage, and this would have been prevented, had we excluded cases with contraindications to dicumarol. With the use of the one-stage method 16.6 to 27 per cent of hyper-reactors are encountered, and hemorrhagic complications occur in 4.7 to 40 per cent, average: 8.3 per cent.
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Conclusions

The stabilized thrombin method for the determination of prothrombin is the only procedure which determines prothrombin quantitatively and is independent of other coagulation factors. Since it is independent of the activity of the reagents used, no normal controls are necessary.

In using the stabilized thrombin method for control of the clinical administration of dicumarol rather constant hypoprothrombinemic levels could be attained, and daily variations of prothrombin were relatively small. There were less hyper-reactors and less hemorrhages than would be expected with the use of the one-stage method. Rarely did a patient's prothrombin rise above the therapeutic range during treatment.

The ease with which such safe and effective therapeutic levels can be maintained is explained by the fact that, while the one-stage method is dependent upon a number of coagulation factors, the stabilized thrombin method is a direct quantitative estimation of only prothrombin.

Acknowledgments

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References

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