Clotting Compass *)

Department of Biochemistry Marquette University School of Medicine Milwaukee, Wisconsin

Armand J. Quick

A simple diagrammatic presentation of the clotting defect in a hemorrhagic state has an advantage of easy comprehension and ready comparison with other bleeding conditions. G e r e n d á s (1) has developed such a visual scheme which he has named a coagulogram. We have had the opportunity to investigate a variety of bleeding diseases with a battery of tests, many of which are not included in the coagulogram of G e r e n d á s . A somewhat different clotting chart was therefore designed for which the name "clotting compass" seems appropriate. The tests selected for the cardinal points are the clotting, bleeding, prothrombin and prothrombin consumption times. Eight other procedures constitute the auxiliary points (Fig. 1). The lines representing the tests radiate from an inner circle corresponding to the normal values of the various methods, and have as the maximum abnormal values the distal points in the periphery.

Tests

Clotting time (CT): One ml of blood collected with a silicone-coated syringe and needle is directly transferred to a clean glass test tube (13 × 100 mm) and placed in a water bath at 37° C. It is gently tilted every 30 seconds until a solid clot forms. The normal range is 5 to 8 minutes.

Bleeding time (BT): A carefully sterilized spring lancet with a blade 2 to 3 mm long is employed. The lobe of the ear is selected for the test. The normal range is 1½ to 3½ minutes.

Prothrombin time (PT): Acetone-dehydrated rabbit brain is the source of the thromboplastin reagent. The procedure is carried out according to the author's directions (2). The normal value is 12 seconds.

Prothrombin consumption time (PCT): The method of the author is followed precisely (2). One ml of blood is clotted in a standard size test tube at 37° C. Exactly 15 minutes after a solid clot forms, the tube is centrifuged for 1 minute to separate the serum from the clot, and then reincubated at 37° C for 45 minutes. The prothrombin time of the serum is determined by forcefully blowing 0.1 ml of serum into the following mixture:

<div style="margin-left:4em">

Thromboplastin reagent   0.1 ml
Calcium chloride 0.02 M   0.1 ml
Deprothrombinized fresh rabbit plasma   0.1 ml.

</div>

The time for a solid clot to form is carefully determined. The normal range is usually 15 to 35 seconds. The lowest abnormal value is 8 seconds which indicates almost complete lack of prothrombin consumption.

Prothrombin consumption time with hemolysate (PCT H): The test is carried out exactly as the basic prothrombin consumption time except that 0.1 ml of human erythrocyte extract is added to the blood before it is clotted. The normal value given in the chart is 60 seconds but the usual range is 45 to 60 seconds. The lowest pathological value obtainable is 8 seconds.

Prothrombin consumption time with serum (PCT S): To 1 ml of the blood to be tested, 0.025 ml of pooled aged normal serum is added before clotting. The procedure from this point is the same as the basic prothrombin consumption time. Although the normal value in the chart is given as 20 seconds, occasionally healthy subjects may have values as low as 16 seconds.

Thromboplastinogen activity time (TAT): Acetone-dehydrated rabbit brain extract is heated to 60° C for 20 minutes to destroy its holothromboplastic activity. To 1 ml of blood, 0.025 ml of the heated thromboplastin reagent is added and the test carried out as the basic prothrombin consumption time. The normal range is 15 to 35 seconds and as in the basic test, the lowest obtainable value is 8 seconds.
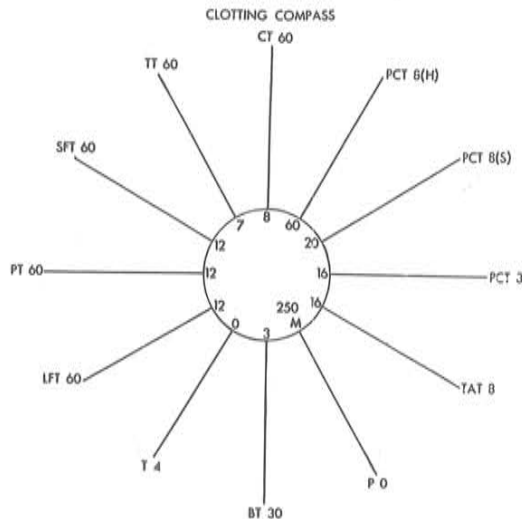

Fig. 1: The clotting compass

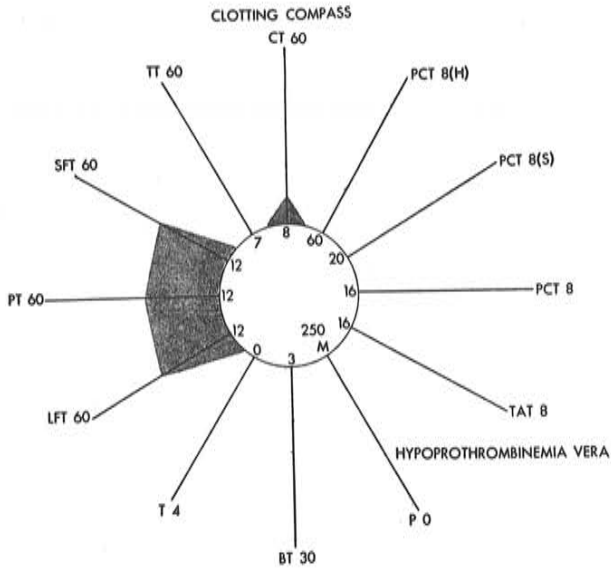|					
CT	=	clotting time	P	=	platelet count
PCT (H)	=	prothrombin consumption time with hemolysate	BT	=	bleeding time
			T	=	tourniquet test
PCT (S)	=	prothrombin consumption time with serum	LFT	=	labile factor time
			PT	=	prothrombin time
PCT	=	prothrombin consumption time	SFT	=	stable factor time
TAT	=	thromboplastinogen activity time	TT	=	thrombin time

F i g . 2 : Hypoprothrombinemia vera. The prothrombin time is prolonged and is not corrected by either labile factor (deprothrombinized rabbit plasma) or stable factor (aged serum). The clotting time is prolonged and is proportional to the prothrombin time.
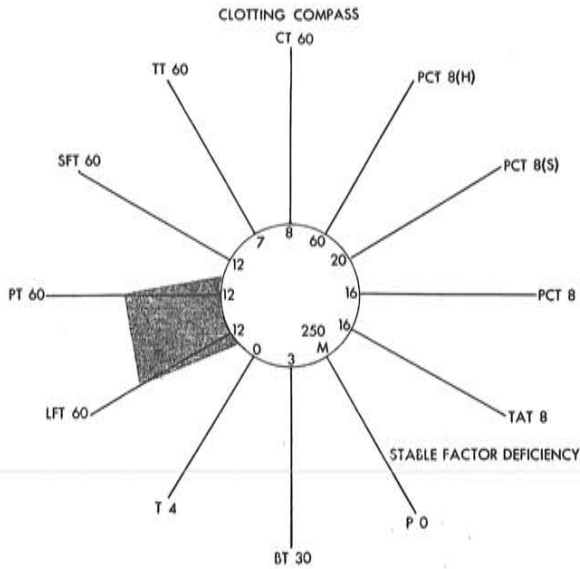

F i g . 3 : Stable factor deficiency. The prothrombin time is prolonged and is not corrected by labile factor but is normalized by aged normal serum. The clotting time, characteristically, is entirely normal.
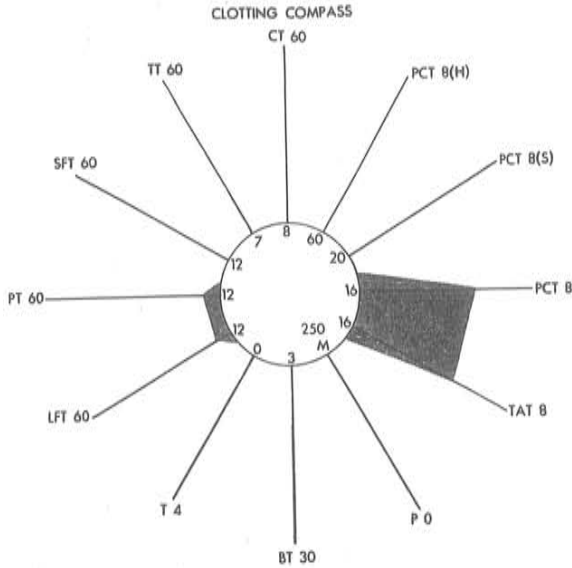
Fig. 4: Hypoprothrombinemic state with defective prothrombin consumption. The exact classification of this condition is uncertain. It has similarity to the cases reported as the Stuart-Prower defect.
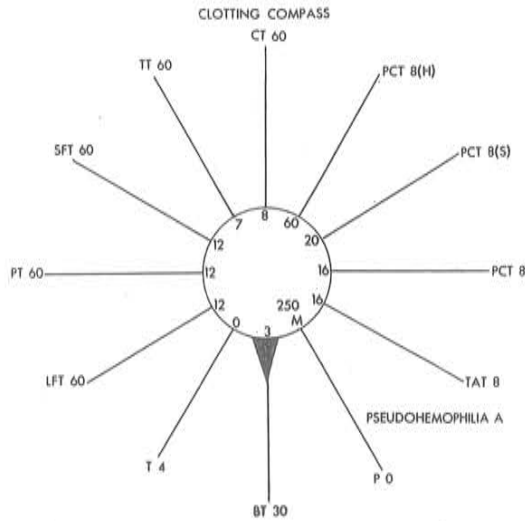

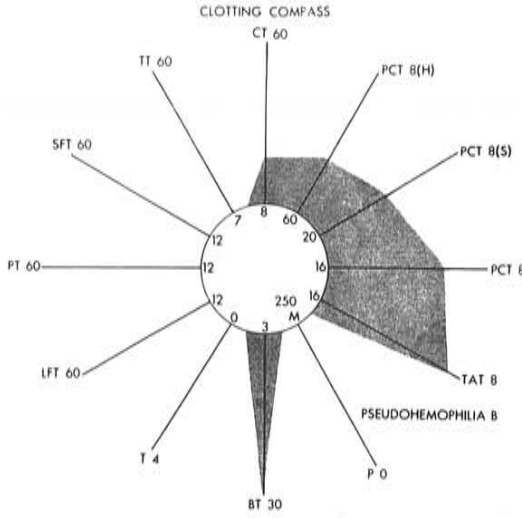Fig. 5: Pseudohemophilia A (von Willebrand's disease). All findings are normal except the bleeding time.

Fig. 6 : Pseudohemophilia B (vascular hemophilia). The pattern is similar to classical hemophilia
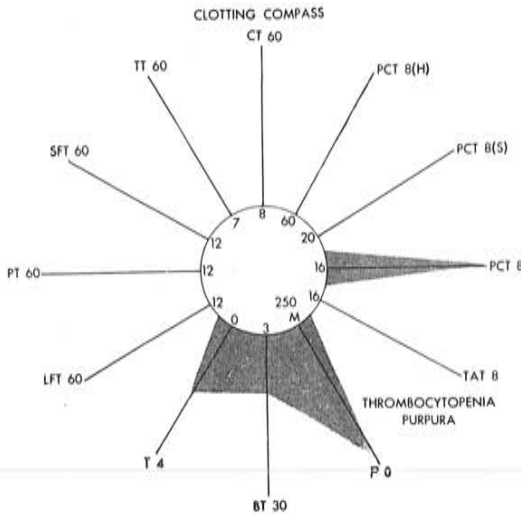except that the bleeding time is strikingly prolonged.

Fig. 7 : Thrombocytopenic purpura. The tourniquet test is often strongly positive, the bleeding time
prolonged and the platelet count low. The defective prothrombin consumption time is corrected by
platelets and platelet substitutes, such as hemolysate and TAT reagent. In the severe case, no correction
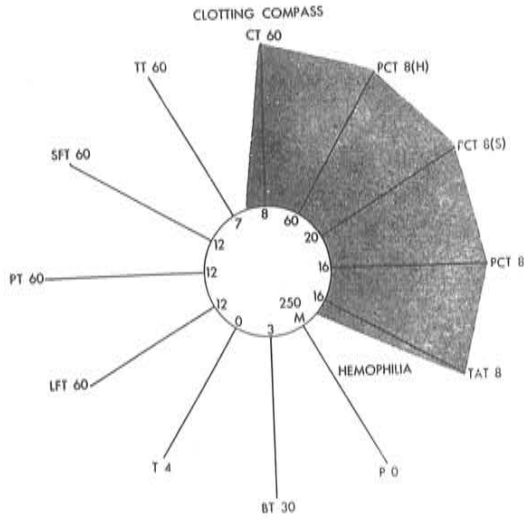is effected by aged serum.

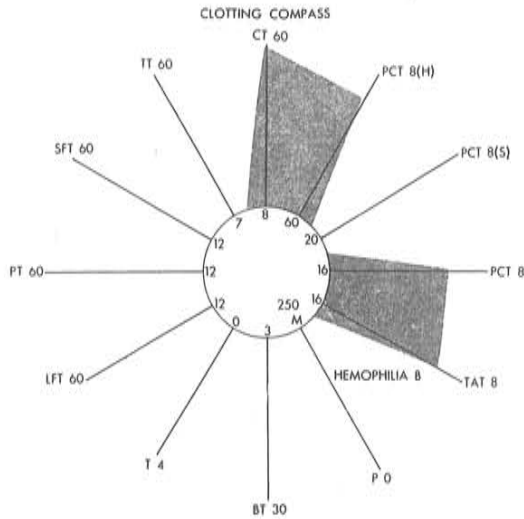Fig. 8 : Hemophilia. The characteristic pattern of the severe form.

Fig. 9 : Hemophilia B (PTC deficiency or Christmas disease). The marked correction with stored pooled plasma characterizes the disease.

Labile factor time (LFT): The determination is the same as in the basic prothrombin time except that to 0.09 ml of the oxalated plasma to be tested, 0.01 ml of fresh deprothrombinized rabbit plasma is added. If the prolonged prothrombin time is due to a deficiency of either prothrombin or stable factor, no correction occurs; whereas if labile factor is lacking, complete correction of the prothrombin time to 12 seconds occurs.

Stable factor time (SFT): To 0.09 ml of the oxalated plasma to be tested, 0.01 ml of pooled normal aged serum is added before the prothrombin time is determined by the standard procedure. A correction to 12 seconds is obtained if plasma lacks stable factor but the prothrombin time will remain unchanged if either prothrombin or labile factor is deficient.

Thrombin time (TT): The thrombin reagent is prepared by the author's adaptation (3) of the Eagle method (4). The product obtained is diluted 1 to 5 with distilled water. When 0.1 ml is added to 0.2 ml of oxalated plasma, a clotting time of 7 seconds is obtained.

Platelet count (P): The platelet count is made in the usual manner by direct count in a counting chamber using sodium citrate as diluent with one important modification (2). The blood is collected with a silicone-coated syringe and needle, and 1 ml mixed directly with 0.5 ml of 3.8% sodium citrate in a small siliconized test tube. The citrated blood is used for the final dilution in a red blood cell pipette. The normal platelet count with this method is 200 000 to 400 000.

Tourniquet test (T): A blood pressure cuff is placed on the upper arm and inflated to a pressure midway between the diastolic and systolic. After 5 minutes the antecubital space below the cuff is examined for petechiae. Normally, a circle 2.5 cm in diameter will contain less than 2 pin point hemorrhages. The results are empirically graded from 0 to 4.

The Clotting Compass of Various Bleeding States

The diagrams (Fig. 2—9) are based on the actual data obtained on individual patients. Whenever possible, the patient with the most severe form of the disease was selected.

Discussion

The clotting compass is intended to present graphically the coagulation defect of various hemorrhagic diseases using a battery of standardized tests. It should not be regarded as an automatic device for diagnosis. While it is helpful in differentiating the various bleeding states, other procedures which are not included are often required to make a definitive diagnosis. In devising the chart, only tests which we routinely employ and for which we have established the normal and pathologic range of values were selected. The tourniquet test is perhaps the least important since it has little diagnostic value, but it is at times of clinical value. Although the importance of the thromboplastin generation test of B i g g s and D o u g l a s (5), especially in the differentiation of hemophilia from hemophilia B, is well recognized, it was not included in the chart because the results of this procedure run somewhat parallel with those obtained by means of the prothrombin consumption tests.

It is both interesting and significant that the clotting time is prolonged only in some hemorrhagic diseases. In hemophilia and in hemophilia B, it is markedly

prolonged in the severe form; likewise, in true hypoprothrombinemia, it is abnormally long and appears to be proportional to the prothrombin time. In a severe case with a prothrombin time of 60 seconds, the clotting time was over 1 hour. This contrasted strikingly with the findings of a patient with stable factor deficiency. Her prothrombin time, likewise, was approximately 60 seconds, but her clotting time was normal. In fact, in none of the cases of stable factor deficiency which we studied was the clotting time found to be significantly prolonged.

The bleeding time also presents some puzzling aspects. It is usually prolonged in moderately severe thrombocytopenia. It is strikingly prolonged in one type of hemophilia-like disease in which a true deficiency of thromboplastinogen or antihemophilic globulin is found. The abnormal bleeding time is probably not directly caused by this lack since the concentration of thromboplastinogen in true hemophilia is exceedingly low, but the bleeding time is normal. No agreement has been reached concerning the name for this disease. S i n g e r and R a m o t (6) proposed the term pseudohemophilia B, while others favor the name vascular or angio-hemophilia. The selection of the name actually is contingent on the interpretation of the term hemophilia. If the name carries with it the connotation of a specific hereditary pattern, pseudohemophilia B should be the more suitable; whereas, if the lack of a definite clotting factor is regarded as the dominant characteristic, vascular hemophilia is the more justifiable name. In von Willebrand's disease or pseudohemophilia A, the bleeding time in the 12 cases that have been studied has been the only abnormal finding. This is in agreement with the observations of many other investigators.

Several important diseases have not been charted. Hyperheparinemia presents a rather involved pattern (7). The clotting and thrombin times are very prolonged in the severe case. The prothrombin times, including LFT and SFT tests, are moderately prolonged. The tourniquet test, bleeding time, and platelet count are not altered. The prothrombin consumption tests are difficult to carry out and the interpretation of the results is unsatisfactory.

It would be desirable to have the pattern of congenital labile factor deficiency but there has been no opportunity to study a patient with this disease. If one assumes that the results obtained on normal stored plasma are similar to those from a patient with the deficiency, one can expect to find that the prothrombin time and SFT tests are abnormal and that the prothrombin consumption time is low, as well as the associated tests (TAT, hemolysate and serum). It is difficult to ascertain whether the clotting time is normal or prolonged. O w r e n (8) found it to be prolonged, while B r i n k and K i n g s l e y (9) reported the clotting time to be normal.

Summary

A diagram has been devised based on a battery of tests, the results of which are recorded as points on a compass. The tests employed are described. The clotting pattern of various hemorrhagic diseases are presented and discussed.

Résumé

Un diagramme a été conçu de telle façon que les résultats d'une batterie de tests sont notés comme points sur un compas. Les tests employés sont décrits sommairement et les troubles de coagulation dans les différentes diathèses hemorragiques sont presentés et discutés brièvement.

Zusammenfassung

Es wurde ein Diagramm entwickelt, das auf einer Serie von Tests beruht, deren Resultate als Punkte in den Kompaß eingetragen werden. Die angewandten Tests werden beschrieben. Die charakteristischen Veränderungen der Nutzanwendung bei verschiedenen hämorrhagischen Diathesen werden dargestellt und besprochen.

References

(1) Gerendás, M.: The coagulogram. An aid in the evaluation of disorders in blood clotting. Therap. Hungarica 1: 3 (1956).

(2) Quick, A. J.: Hemorrhagic Diseases. Philadelphia, Lea & Febiger, 1957.

(3) Quick, A. J.: On the action of heparin and its relation to thromboplastin. Am. J. Physiol. 115: 317 (1936).

(4) Eagle, H.: Studies on blood coagulation. I. The role of prothrombin and platelets in the formation of thrombin. J. Gen. Physiol. 18: 531 (1935).

(5) Biggs, R. and Douglas, A. S.: The thromboplastin generation test. J. Clin. Path. 6: 23 (1953).

(6) Singer, K. and Ramot, B.: Pseudohemophilia type B. A.M.A. Arch. Int. Med. 97: 715 (1956).

(7) Quick, A. J. and Hussey, C. V.: Hyperheparinemia: Report of a case. Am. J. Med. Sci. 234: 251 (1957).

(8) Owren, P. A.: Parahaemophilia: Haemorrhagic diathesis due to absence of a previously unknown clotting factor. Lancet 1: 446 (1947).

(9) Brink, A. J. and Kingsley, C. S.: A familial disorder of blood coagulation due to deficiency of the labile factor. Quart. J. Med., New Series 21: 19 (1952).