Feb. 2, 1971 M. B. MITTLEMAN 3,560,162

DIAGNOSTIC DEVICE

Filed Nov. 27, 1968

Fig - 1

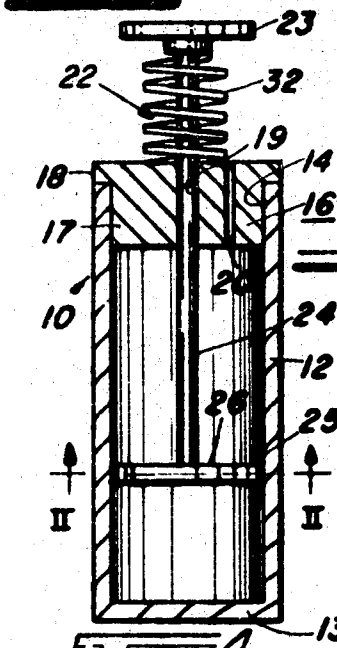


Fig - 2

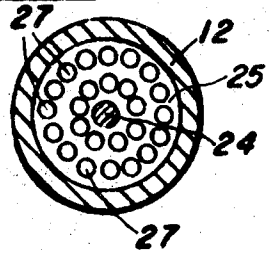


Fig - 3

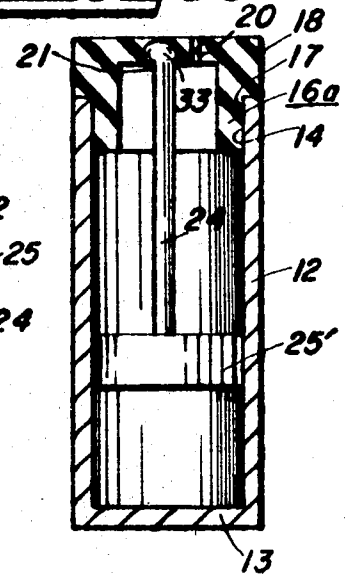


Fig - 4

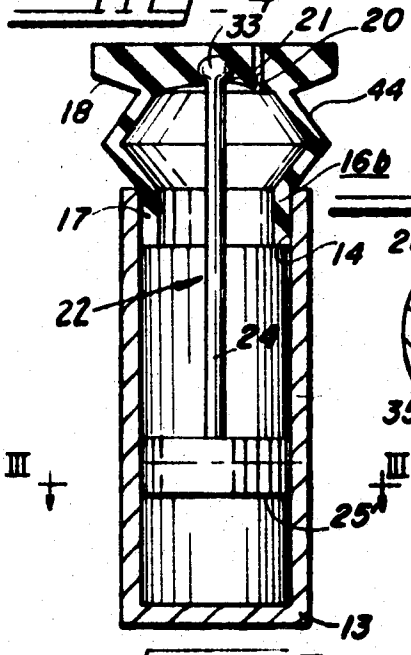


Fig - 5

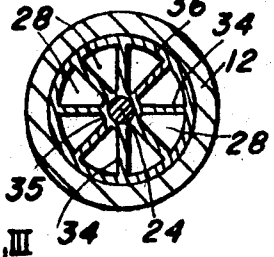


Fig - 6

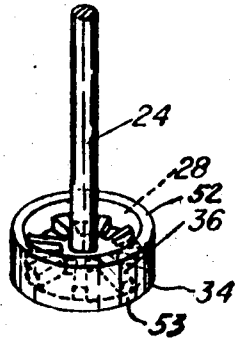


Fig - 7

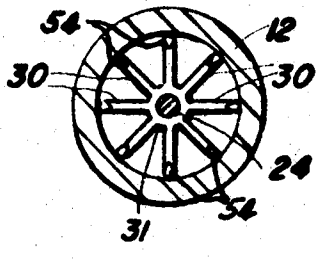
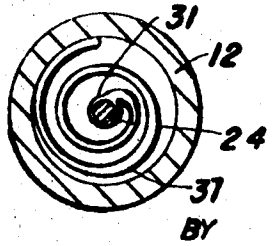


Fig - 8



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DIAGNOSTIC DEVICE

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U.S. Cl. 23—253 10 Claims

ABSTRACT OF THE DISCLOSURE

A manually operable diagnostic device useful in measring prothrombin time comprising a cylindrical member having recoilable agitator means disposed therewithin for operative engagement with a sample of blood or blood plasma contained thereby and capable in operation to provide a clearly discernible, and hence readily determined measure of the prothrombin time of the whole blood or blood plasma.

This invention relates generally to the determination of 1-stage prothrombin time, partial thromboplastin time and thrombin time for whole blood or blood plasma and more particularly to means and methods for making such determinations on relatively small samples of whole blood without requiring sophisticated laboratory or clinical facilities.

As background for the present invention, it appears desirable to devote some attention to blood coagulation properties so that the relationship of prothrombin to the hemostatic mechanisms of anticoagulant therapy is appreciated.

Thus, while it is well known that blood clotting or coagulation is the transformation of liquid blood into a semi-solid gel-like state of consistency, it should be further noted that clotting involves whole blood with functions assigned to plasma and blood platelets. These components, functioning as a unit, are essential in the conversion of one of the plasma proteins, fibrinogen from sol (liquid) to gel (solid) state. This change in consistency is brought about by the formation of fibrinmonomer and the subsequent polymerization of the fibrinmonomer to fibrin in the presence of calcium and fibrin stabilizing factor or plasma factor XIII.

The clotting process may be initiated by the action of tissue juices (thromboplastin) that are released from tissues upon injury. The clotting process may also be initiated as a result of the disruption of blood platelets with subsequent release of pro-coagulant substances such as adenosine di-phosphate and platelet factor III. In the presence of vascular injury the clotting response occurs quite automatically. When blood escapes from an injured vessel the clotting mechanism is activated as a result of the action of tissue thromboplastin and the additional procoagulate derived from the disintegration of platelets. The ultimate factor in the clotting mechanism is thrombin, because it acts to convert fibrinogen into fibrin. Thrombin exists in the blood in an inactive form, prothrombin, which is converted to thrombin by means of activators such as thromboplastin, platelet factor III acting in conjunction with plasma accelerators such as factors V, VII, VIII, X, XI and XII and calcium. As a consequence of thrombin formation, fibrinogen is converted to fibrinmonomer, and this latter substance forms the insoluble fibrin in the presence of plasma factor XIII and calcium.

While in the clotting of blood a number of reactions occur, the clotting mechanism can, for practical purposes, be divided into three major phases.

Phase I constitutes the generation of intrinsic thromboplastin. Certain components of the platelets such as platelets factor III and adenosine di-phosphate, as well as the pro-coagulant components of plasma, e.g., plasma factors V, VII, IX, X, XI, XII, and calcium, are essential for maximum generation of thromboplastin.

Phase II of the clotting mechanism is the production of thrombin. The thromboplastin generated in Phase I interacts with prothrombin and plasma factors V, VII and X and calcium. These several agents comprise collectively the prothrombin complex, whose degree of action is expressed as "prothrombin activity."

Phase III is the conversion of fibrinogen to fibrin by the enzymatic action of thrombin. The speed of this reaction is determined by the rate of thrombin generation and the temperature at which the reaction is conducted. The polymerization of the fibrinmonomer to fibrin polymer is related to factor XIII activity. Calcium is an essential component of both processes.

A number of anti-coagulants, namely, heparin and dicumarol, as well as others, have been proposed in anti-coagulant therapy. The administration of these compounds, as well as those conventionally employed, are generally dependent upon and their use controlled primarily by prothrombin time determinations. Thus, the need for quick and accurate means and methods of making such determinations becomes manifest. In this connection it should be observed that certain authorities believe that such tests do not measure the level of activity of the prothrombin in the blood, but rather measure the total potential coagulability of the blood. Pragmatically, it is necessary for the physician to know whether the amount of anti-coagulant given to a particular patient is adequate to maintain the total coagulability of the blood at such a level that neither spontaneous thrombosis nor hemorrhage will occur. For this purpose the generally-utilized measurement is "prothrombin time."

"Prothrombin time" as used herein, defines the period in which thrombin is formed by the interaction of platelet and plasma components and terminates in the conversion of fibrinogen to fibrin.

Prothrombin time in normal man is remarkably constant, being approximately 12–14 seconds. Thus, deviations, even of one second, may be indicative either of faulty techniques or of a significant abnormality in the patient's blood or hemostatic mechanism.

Hematologically, determination of prothrombin time is useful in characterizing the bleeding states due to coagulation defects into two major classes: (a) those with normal prothrombin activity and (b) those with decreased prothrombin activity. The first class comprises the diseases in which, although prothrombin time is entirely normal the generation of thromboplastin is defective, for example, hemophilia A, hemophilia B, thrombocytopenia, thrombobasthenia and pseudohemophilia B. The second class may be designated as the hypoprothrombinemic states, for example, hereditary hypoprothrombinemia vera, hereditary deficiencies of labile and stable factors, and other defective conditions.

Heretofore, in such time determinations, fresh blood was initially drawn from the patient and centrifuged to separate the blood plasma. A small amount of the plasma was added to an appropriate amount of thromboplastin and calcium chloride, and the time of clotting determined.

Among the specific prior art methods practiced in the management of those conditions for which anti-coagulant therapy was indicated, an early approach was provided by Quick. Quick's methodology was based on the determination of control values with Normal Plasma, such as Diagnostic Plasma (Warner-Chilcott Laboratories), and the determination of values with the unknown plasma

and then correlating the two to define the unknown conditions associated with the second values. The Quick test, however, possessed numerous limitations (see: "Comparison of a Micro Method and the Quick Method for Prothrombin Time," A. C. De Graff and S. Fisch, 5 Western Medicine No. 7, pp. 215–219, July 1964) and was not practical as an office procedure because it required special equipment and highly trained personnel and its results were not immediately available (see: "Laboratory Control of Coumarin Therapy," J. J. Seide, 57 Ann. Int. Med. 57, p. 572, 1962).

Briefly stated, Quick taught placing a measured quantity of blood or plasma and thromboplastin in tubes heated to about 37.5° C. The thromboplastin should also contain calcium ions preferably as calcium chloride to facilitate clotting. The amount of reagent added with the blood or plasma is selected to obtain the expected time readings for the control plasma. To obtain accurate clotting indications, the technician draws a wire loop repeatedly through the mixture until clot formation is sensed.

The major disadvantage of the foregoing procedure is that it requires centrifuging large samples of blood to obtain a plasma specimen and it requires equipment for the rigid regulation of the temperature. The nature of the test precludes the results from being immediately available.

To help overcome this difficulty, a method commonly referred to as the "Manchester Method" was developed. The Manchester Method is described in Manchester, B., "The Prevention of Myocardial Infraction," A.M.A. Arch. Int. Med., vol. 100, pp. 959–964 (December 1967), and Manchester, B., and Rabkin, B., "The Control of Dicumarol Therapy in Myocardial Infraction by Simple Blood Prothrombin Tests," Circulation, vol. 10, p. 691 (1954) and need not be elaborated here. In Manchester's method relatively small amounts of capillary blood can be used to obtain the desired readings and therefore it was capable of being practiced in a doctor's office and at the bedside as well as in conventional hospital situations. Manchester's method suffered, however, from the need for relatively expensive equipment for controlling environmental factors, e.g., the temperature of the reacting substances, and therefore still left a need for a rapid, accurate and reproducible procedure requiring minimized scientific equipment.

Next came Charles R. Kuzell who, in U.S. Pat. No. 3,041,146, Jan. 26, 1962, described special apparatus for maintaining environmental temperature and accurately determining time, namely, an electrically heated block of aluminum having a plurality of spheroid dimples defined in the top surface thereof. Kuzell's block is further provided with plurality of horizontal wells extending therethrough which hold and heat pipettes. In operation, a measured amount of blood and reagent are deposited in one of the heated dimples and intermixed therein. Simultaneously with the starting of a timer when the technician detects that the blood has coagulated, the timer is stopped and read for prothrombin time.

A different approach to the detection of coagulation is described in U.S. Pat. No. 3,158,445, Carl Huff, Nov. 24, 1964, wherein means are provided for detecting a change of light transmissivity of a light source passing through a blood and reagent mixture as the mixture coagulates.

While each of these prior approaches represented some advance over that which had been previously available, all required elaborate and expensive equipment and auxiliary energy supplies in order to be useful.

Further, all use a common technique for obtaining the end point, viz, agitating the blood-reagent mix with a wire loop repeatedly drawn therethrough until a definite solid clot appears. With such a technique, a human parameter is inevitable because each technician has his own method of manipulating the wire loop and the detection of the end point, i.e., the start of coagulation forming is essentially a subjective perception and requires a great deal of experience before uniformity can be assured.

Thus, in spite of the advances made, a need still exists in the art for a device which can measure prothrombin time without requiring hospital or clinical environments for its use but which also can be of great value to such institutions for different reasons; which can function accurately and well in the absence of gas, electricity or other forms of commercial energy; and which avoids to a maximal degree the variations inherent in the subjective manipulation of specimens by diverse technicians.

As will become apparent hereinafter, the present invention provides a diagnostic device which is capable of filling those needs by obtaining a standardized test which is amazingly reproducible.

Specifically, the present invention is predicated upon my development of a simple diagnostic device for assisting in the measurement of prothrombin times which comprises a cylindrical member biased reciprocating piston associated in the cylindrical member in substantially sealed engagement therewith, and self-sealing means in a surface thereof through which a blood or blood plasma sample can be quickly and easily introduced. Agitation of the sample by action of the reciprocating piston may be essentially uniform and the termination of the enzymatic reaction is readily observed as the fibrin clot forms. By conducting my prothrombin assay at room temperature and associating the blood or plasma with adequate amounts of thromboplastin and calcium, I am able to standardize the test and obtain good reproducible results.

Accordingly, it is a prime object of the present invention to provide a diagnostic device for use in the measurement of prothrombin time which is inexpensive to manufacture, easy to operate, readily moved and provides reproducible results.

Another object of the present invention is to provide a diagnostic device of the type indicated which permits the measurement of prothrombin time away from hospital and clinical environs, without the need for ancillary equipment such as centrifuges, constant temperature water baths or other environmental control.

A further object of the present invention is to provide a diagnostic device of the type indicated which is readily operable even in the absence of gas, electricity and other forms of commercial energy.

A still further object of the present invention is to provide a device of the type indicated which may be used in conjunction with the one of several available temperature charts which corresponds to the temperature at which it is used.

Still a further object of the present invention is to provide a device of the type indicated which avoids to a significant degree the variations inherent in the subjective manipulation of specimens by technicians which characterized prior devices and is sufficiently quick and easy to operate that results may be obtained concurrently to patient's visit with his physician.

These and still further objects, as shall hereinafter appear, are readily fulfilled by the present invention in a remarkably unexpected manner as shall be readily discerned from a careful reading of the following description of embodiments exemplifying the invention, especially when read in conjunction with the accompanying drawing in which:

FIG. 1 is a side elevation, partially in cross-section, of a diagnostic device embodying the present invention;

FIG. 2 is a cross-section taken along line II—II of FIG. 1;

FIG. 3 is a side elevation, partially in cross-section of another diagnostic device embodying the present invention;

FIG. 4 is a side elevation, partially in cross-section, of still another embodiment of the invention; and

FIGS. 5, 7 and 8 are cross-sections taken at the situs of

line III—III of FIG. 4 showing various configurations of plates which may be employed with the present invention; and

FIG. 6 is an isometric showing of a portion of the plunger of FIGS. 3 and 4 having a plate according to FIG. 5.

Referring to the drawing, in which like parts bear like reference numerals throughout the several views, my device is indicated by general reference number **10** and comprises a housing **12** having closed bottom **13** and an open mouth **14**. Housing **12** is preferably formed of a transparent material such as plastic, glass or the like and of cylindrical shape. When assembled, mouth **14** receives a stopper member **16** having a lower portion **17** and an upper portion **18**. Portion **17** is complementary to mouth **14** and fits snugly therewithin. Stopper member **16** is further provided with a shank-receiving opening **19** and a smaller self-sealing aperture **20**, the function of each to be hereinafter described.

A plunger **22**, comprising main shank **24**, an actuator plate **23** disposed at the upper end of the shank **24** and a commingler plate **25** disposed at the lower end of shank **24**, is operatively disposed within housing **12**. Plate **25** is provided with a plurality of strategically disposed openings **26** which are suitably defined in a variety of ways as will appear.

Actuator plate **23** and commingler **25** are integrally formed at and with the ends of shank **24** by any suitable means such as by gluing, forcefitting or the like.

In the embodiment of FIG. 1, a suitable spring **32** is operatively interposed between the upper surface of stopper member **16** and actuator **23** and functions to bias plunger **22** into a position in which commingler **25** is disposed in spaced relationship to bottom **13** of housing **12** when the device is at-rest.

Referring to FIGS. 3 and 4, an alternative embodiment is shown in which the bias of plunger **22** is provided by the resiliency of the stopper member. Thus, as shown by FIG. 3, stopper member **16*a*** includes a pressure responsive flexible upper portion **18** which bears against an enlarged end **33** of shank **24**. Enlarged end **33** is preferably bulbous and is attached to stopper member **16*a*** by means of shank holding means **21** defined therein. In this manner, shank **24** is rendered reciprocative, extending in response to the flexion of stopper member **16*a*** by the application of external force thereto and retractable in response to the bias provided by its own elasticity.

FIG. 3 also depicts a variant of the commingler designated as **25'**.

Referring to the drawing, commingler **25'** is cup-shaped and comprises a hollow cylindrical portion **52** having a bottom portion **53** which is provided with one of the various plate opening patterns to be hereafter described.

In the embodiments utilizing member **25'**, the member not only commingles the reagents deposited in housing **12**, the upstanding **52** creates a piston-like action with the inner wall of the housing **12** to maintain the reagents in their desired location and to guide plunger **22** in its reciprocative movement.

In the further embodiment shown in FIG. 4, stopper member **16*b*** is provided with an angularly shaped accordion-like side wall **44** which biases shank **24** in a spaced relationship to bottom **13** while permitting it to respond to an externally applied downward pressure on portion **18**. By pressing and releasing portion **18**, an operator imparts reciprocative action to plunger **22**. Shank **24** is seated into stopper **16*b*** by fitting bulbous portion **33** into seating portion **21** as described relative to FIG. 3.

Referring now to FIGS. 2, 5, 7 and 8, commingler members **25**, **25'** may be provided with diverse foraminous constructions within the scope of this disclosure.

As shown in FIG. 2, commingler plate **25** contains a plurality of small openings **27** disposed therethrough to maximize the passage area therethrough without significantly impairing its structural integrity. Alternatively, commingler plate **25** may contain a plurality of segmental or pie-shaped openings **28** defined by a plurality of radially extending spokes **34** operatively interposed between an inner sleeve **35** and outer annulus **36** as shown in FIG. 5. Annulus **36** may either be coplanar with spokes **34** or may comprise an upstanding cylindrical member as shown in FIG. 6 and designated **52**. For clarity, the bottom plate of the cup-shaped embodiment of FIG. 6 has been identified as **53** although it is to be understood that where the cylindrical annulus **52** is omitted, member **53** is substantially identical to plate **25** of FIG. 1.

Another commingler pattern is shown in FIG. 7 and comprises a plurality of arm members **30** which extend from annular ring **31** which is mounted in circumscription to the lower end of shank **24**. Each arm **30** carries an upwardly extending hook **54** at the outer end thereof. Finally, in FIG. 8, another commingler pattern comprises a continuous volute **37** extending from inner annular ring **31** in which shank **24** is secured. Volute **37** may be disposed in a common plane or as an upwardly reaching helix.

As is apparent, each of the several embodiments herein disclosed operates in substantially the same fashion. Therefore, in describing the operation in terms of a single embodiment, it should be understood that the description is applicable in principal to all. Further, reference to the biasing action which retracts shank **24** encompasses the action of the spring of FIG. 1, the memory of the elastic stopper of FIGS. 3 and 4, or any other mechanically suitable biasing means.

To utilize my device for the purposes stated, the housing member thereof is charged with a measured amount of a suitable reagent, such as thromboplastin with calcium chloride. The blood or plasma specimen to be measured is then introduced through self-sealing aperture **20** by any convenient means, although the use of a hypodermic syringe has been found to be satisfactory. Both the specimen and the reagents are deposited on the floor of the housing **12**.

If desired, the selected reagents may be charged with the specimen at the moment of use or they may be previously charged and lyophilized in the device substantially prior to use.

Immediately upon introducing the blood or plasma specimen into the chamber the device, and effecting an encounter between the specimen and the reagent, a suitable timer, such as a stop watch, is actuated. Thereafter, reciprocation of the plunger is commenced by the action of the operator applying a downward force to the upper end of shank and thereafter releasing such pressure sufficiently to enable the biasing means to return the plunger to its original position. This action is repeated continuously and with regularity until a coagulum is observed in the bottom of the transparent housing. Upon detection of the coagulum, the timer is stopped and the lapsed time determined.

The procedure described is, of course equally useful to measure the prothrombin time of normal control blood or plasma as well as the blood or plasma specimens from a patient on anti-coagulant therapy.

While accurate comparative control data can be obtained contemporaneously with the determination of the patient, I prefer to further assist the physician in his work by providing a plurality of calibrated readings obtained with my device. Thus, I provide a reading for each room temperature condition which is likely to be encountered in the physician's office. Each of the readings reports actual data obtained with my device at different room temperatures. I therefore provide a standard of comparison from which any deviation of the patient's readings from the norm can be readily detected.

From the foregoing, it becomes apparent that a new and highly useful diagnostic device has been herein described and illustrated which fulfills all of the aforestated objectives in a remarkably unexpected fashion. It is, of course,

understood that the embodiments herein described and illustrated are presented to exemplify my invention rather than limit it and that such modifications, applications and alterations as may readily occur to the artisan confronted with this disclosure, are intended within the spirit of the present invention, especially as it is defined by the scope of the claims appended hereto.

What is claimed is:

1. A diagnostic device for use in determining prothrombin time of a sample of whole blood or plasma comprising: a housing for receiving and containing the sample, said housing comprising a body portion having a mouth at one end thereof and stopper means sealingly engaged within said mouth, said stopper means having a self-sealing aperture defined therethrough for introducing the sample into said housing; a reciprocative plunger operatively assembled with said housing and actuatable therein for engagement with the sample; and means biasing said plunger into a non-engaging relationship with said blood sample.

2. A device according to claim **1** in which said body portion comprises a cylindrical tube.

3. A device according to claim **2** in which a portion of said plunger extends through said stopper in sealed sliding engagement therewith and has an actuator plate mounted to the end thereof in superposed relationship to said stopper and said biasing means is disposed externally of said housing in operative interposition between said actuator and said stopper and in circumscription to said plunger.

4. A device according to claim **1** in which said plunger comprises a shank portion and a commingle member, said commingler member being mounted to the lower end of said shank portion in substantially normal relationship thereto within said housing.

5. A device according to claim **4** in which said commingler member comprises an annular collar secured to said shaft and a continuous volute extending outwardly therefrom.

6. A device according to claim **4** in which said commingler member comprises a foraminous circular disc having a peripheral annulus defining the outer limits thereof and an inner collar engaging said shank.

7. A device according to claim **6** in which said foramini are defined between a plurality of arms extending radially between said shank and said peripheral annulus.

8. A device according to claim **6** in which said peripheral annulus comprises an upwardly extending hollow cylinder.

9. A diagnostic device for use in determining prothrombin time of a sample of whole blood or plasma comprising a housing for receiving and containing a sample, said housing comprising a cylindrical tube having a mouth at one end thereof and elastic stopper means sealingly engaged within said mouth, a reciprocative plunger operatively assembled with said housing and actuatable therein for engagement with the sample, said plunger being secured relative to said elastic stopper means and biased by the elastic memory thereof into a non-engaging relationship with said blood sample.

10. A device according to claim **9** in which said stopper means includes an accordion-like side wall which is in an extended position when in an at-rest condition.

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U.S. Cl. X.R.

23—230, 259; 259—113