MODERN CONCEPTIONS OF BLOOD CLOTTING.*

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Despite the large number of researches which have been made on blood coagulation, no single one of the many theories advanced satisfies the criterion of a tenable hypothesis in which all known facts should be correlated.

A better understanding of the fluidity and clotting of blood should lead to important results. On the practical side, we may hope for the elucidation of thrombosis—the formation of clots in the vessels—of the lack of coagulability in haemophilia, of the changes in plasma during shock, and of the fatal intravascular clotting caused by certain snake venoms. On the theoretical side, light should be thrown on the reactions of colloids, on the mechanisms of immunity and of susceptibility, and possibly on the problems of genetics, as haemophilia is transmitted from parent to offspring, and the existence of homologous bloods often depends on family relationship.

In this paper the current theories of blood coagulation will be reviewed briefly from the standpoint of investigations made in collaboration with my friends Drs Hewitt, de Souza, and Taylor,* and evidence for a simpler view will be presented.

The pioneers in this subject, Hewson and Lister, studied blood in excised veins. More recent inquirers have often formed their conclusions from reactions in test tubes. Much disagreement has thus arisen. Plasma changes so rapidly when shed that reactions in vitro may differ from those in vivo. Many attempts have been made to overcome this difficulty by experimenting with blood kept fluid by anti-coagulants, the substances commonly employed being "peptone," neutralised nucleic acids, soluble oxalates and citrates. Except in the cases of oxalated and citrated bloods, clotting ultimately occurs, and the blood so treated thus differs from normal circulating

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blood, which remains fluid during the life of the animal. It is generally accepted that the inhibition of coagulability of oxalated blood is due to the removal of ionised calcium. Such blood clots in vitro (Arthus and Pagès) and in vivo when sufficient calcium chloride is added to neutralise the oxalate. The difference of behaviour of blood after oxalation and recalcification from normal circulating blood cannot be attributed to the presence of crystals of calcium oxalate, as crystals of this salt, equal in size to erythrocytes, can be injected into the circulation of pithed cats without causing thrombosis. Disturbance of the plasma by the acts of oxalation and recalcification is thus indicated. The mixing of citrates with shed blood also inhibits clotting, and the subsequent addition of sufficient calcium chloride to neutralise the citrate causes rapid coagulation, as first shown by Sabbatani. The intravascular injection of citrates into pithed cats and into anesthetised rabbits suppresses coagulability. The subsequent intravascular injection of calcium chloride into the cat restores coagulability, but does not induce thrombosis; in the rabbit, however, extensive intravascular clotting may occur. These data show that deductions from experiments on blood kept fluid by anti-coagulants have only a limited meaning, and should not therefore be employed as the basis of generalisations on the fluidity and clotting of blood. It is noteworthy that the theories of Morawitz and of Howell, commonly taught in England and America, and that of Bordet, widely accepted in France and Belgium, are based on experiments on shed oxalated plasma, whilst the conclusions of Wooldridge and of Nolf are largely founded on observations on blood kept fluid by "peptone."

Some of the generally accepted facts may now be recalled. There exists in blood a substance called fibrinogen, which is converted into solid fibrin whenever clotting occurs. In shed blood a powerful coagulant is found called by the earlier workers fibrin ferment, by later observers thrombin or thrombase. Thrombin is absent from circulating blood, which contains its antecedent substance called pro-thrombin or thrombogen. Pro-thrombin is converted into thrombin prior to clotting. Thrombin rapidly coagulates fibrinogen.
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So far we are on sure ground, but theorists have assumed that a number of other substances exist in circulating plasma and play a part in its fluidity. I allude to anti-thrombin (Howell), pro-anti-thrombin (Howell and Holt), anti-pro-thrombin, and anti-thrombokinase (Collingwood and MacMahon), and to the fibrinolysin postulated by Nolf. Not one of these so-called substances has, however, been found in normal blood. Hirudin, the active principle of leech extract, is an anti-thrombin, but it is not a constituent of the plasma. Howell and Doyon have manufactured anti-thrombins, the former by heating oxalated plasma to 60°, the latter from cells and tissues subjected to the autoclave and to putrefactive processes. Such methods imply so drastic a disintegration of colloidal complexes that they afford no evidence of these or similar substances in blood. Employing less drastic methods, Mills, Raap, and Jackson obtained an anti-thrombin by the extraction of rapidly dried lungs with benzine; but these workers admit that the method they employed involves the removal of phospholipin from a protein-phospholipin complex, so that again there is only a product of cellular break-down. The existence of anti-pro-thrombin in the living organism is equally dubious. Howell and Holt obtained the anti-coagulant heparin from liver heated to 70°, by repeated extractions and precipitations in which ether, acetone, and hot absolute alcohol were employed. Heparin prevents clotting both in vivo and in vitro, but does not neutralise the coagulant action of thrombin. It is therefore not an anti-thrombin. Although these authors admit there is no direct evidence of the existence of heparin in blood, they maintain it is anti-pro-thrombin and plays a part in the maintenance of the fluidity of circulating blood. Pro-anti-thrombin is the name of the supposed mother substance of anti-thrombin; the belief in its existence in unaltered blood is solely based on the "evidence" for anti-thrombin. The other so-called substances (e.g. anti-thrombokinase and fibrinolysin) are mere suppositions devised to bridge gaps in current theories of fluidity and clotting.

In the hypotheses of Morawitz, of Fuld and Spiro, and of Howell, clotting is held to arise from the formation of
thrombin, which converts the fibrinogen of blood into the fibrin of clots. The fluidity of circulating blood is said to be maintained by the hepatic secretion of anti-thrombin. Wooldridge, however, demonstrated that massive amounts of thrombin can be injected into the circulation of carnivores without causing thrombosis. To explain this, it was suggested that thrombin stimulates the liver to produce an excess of anti-thrombin, which neutralises the injected thrombin (Howell, Gasser). But large amounts of thrombin can be injected into the circulation of cats deprived of hepatic activity without causing intravascular clotting, and attempts to cause the liver to secrete anti-thrombin by means of bile, bile salts, secretin, and by electrical stimuli have yielded negative results (Denny and Minot). There is an important difference in the blood of mammals and that of birds. At room temperatures the former clots rapidly on glass surfaces, the latter remains fluid for several hours. To explain this it was suggested that an exceptionally large amount of anti-thrombin exists in birds' plasma (Howell). We have, however, found that birds' blood shed into clean glass vessels clots rapidly at 37°. The fluidity at room temperatures is thus readily intelligible as due to birds' blood possessing greater thermostability than mammalian blood, and there is no need to postulate an anti-thrombin.

That moderate amounts of "peptone" restrain the coagulability of certain mammalian bloods in vivo and apparently fail to do so in vitro is commonly regarded as due to the hepatic secretion of an excess of anti-thrombin. Recent work, however, opposes this view. Employing Howell's test for anti-thrombin, Nolf found no difference in normal and "peptone" blood. We have observed that the intravascular injection of "peptone" into both cats and tortoises deprived of hepatic activity suppresses clotting, and Nolf subsequently noted that the anti-coagulant action of "peptone" on the blood of the domestic fowl with the liver extirpated is actually greater than in intact animals. We have also found that when adequate precautions are taken to preserve the surface conditions of shed blood, no greater concentrations of "peptone" are required to restrain clotting in vitro than in vivo. By similar experiments it was also demonstrated that the anti-
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coagulant action of neutralised nucleic acids is also independent of hepatic secretion, and that smaller quantities suffice for the restraint of clotting when added to blood immediately it is shed, than are required after blood has been in contact with glass for two or three minutes. Changes in the surface condition of blood, arising from contact with surfaces wetted by blood, account for the reduced anti-coagulant action in vitro, and there is no need to postulate specific antibodies in the control of coagulation.

Despite the experiments just cited, de Waele still regards the earlier observations of Nolf and of Doyon on the action of “peptone” on fasting dogs as crucial evidence of the hepatic secretion of anti-thrombin. The study of the protocols of a large number of experiments on the influence of “peptone” on the circulating blood of carnivores reveals that although inhibition of clotting may be evident in fasting animals it is frequently absent in those regularly fed. Further, it is well known that “peptone” has no anti-coagulant action on the blood of normal rabbits, and de Waele has demonstrated that although suppression of coagulability results from the stimulation of the depressor nerve of starving rabbits no such effect is produced in normal animals. Inhibition of clotting is thus largely determined by the processes of inanition, which involve the breaking down of tissue proteins and in starving animals acidosis. It has been shown that the disintegration of cells, tissues, and of protein-phospholipin complexes (Mills) yields anti-coagulants, and it seems probable that the suppression of clotting in fasting animals is due to the presence of substances formed by the autolysis (“autophagie”) of tissues and not to the liberation of normal products of secretion. It thus appears that experiments on fasting animals lend no support to the widely accepted view, first suggested by Spiro and Erlanger, that the normal fluidity of blood is maintained by a balance of coagulants and anti-coagulants. Recognising the difficulties in the opinion that the liver is the source of anti-thrombin, Popielski suggested its secretion by the vascular endothelium. Loeb, however, made careful extractions of the linings of blood vessels and found no anti-thrombic substance. Rettger gave serial intravascular injections of thrombin without producing
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an anti-coagulant. The following experiment is concordant with these findings. A living heart was isolated from the circulation by mass ligature. Threads were inserted into the ventricles. Massive clots were found round the threads but some fluid blood remained in the ventricles. This clotted very rapidly when shed and accelerated the coagulation of normal shed blood. If fluidity had been maintained by an anti-thrombin secreted by the cardiac endothelium, this blood should have been neither hypercoagulable nor an accelerator of clotting.

I have found that massive amounts of thrombin can be injected into the circulation of well-fed anaesthetised rabbits without causing thrombosis, and that the blood of these animals clots as rapidly when shed as does pure blood to which a similar amount of thrombin has been added in vitro. Protection against clotting by thrombin, therefore, exists in vivo when neither the injection of “peptone” nor the excitation of the depressor nerve affords evidence of the presence of anti-coagulants. Such protection ceases when the blood is shed.

From the experiments just described I deduce:—

(1) It is superfluous to assume that the fluidity of normal circulating blood is maintained by the secretion of anti-thrombin.

(2) That some plasma constituent inhibits the coagulant action of thrombin in vivo.

(3) This plasma constituent loses its protective power when in contact with glass, and thus differs from anti-thrombins which are stable in contact with surfaces wetted by blood.

Limitations of space prevent the discussion of the various modifications of the thrombin theories, which are mainly concerned in speculations as to how thrombin arises from its mother substance. Of these hypotheses that of Bordet has one outstanding feature—the recognition that the surface conditions of the blood are a factor in its fluidity. Bordet, however, conformed to the general belief that anti-thrombin exists in normal blood and preserves it from change.

In the theory of Wooldridge, supported by Mills, and in part by Nolf, clotting is held to arise from the interaction of
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two plasma constituents named respectively A and B fibrinogen. The fibrinogen of the laboratory is called C fibrinogen and is said to be almost absent in normal plasma, but to be formed from A fibrinogen in the process of clotting. Thrombin is regarded as a subsidiary reaction product.

The following are some of the objections to this hypothesis:

1. No place is provided for the coagulant thrombin, which undoubtedly exists in shed blood.
2. No rôle is assigned to calcium salts, which were subsequently found to be essential for clotting.
3. No explanation is offered as to how fluidity is preserved in vivo. Wooldridge largely based his conclusions on experiments on the precipitate formed by cooling blood shed after the intravascular injection of "peptone." This blood differs from normal blood, and Wooldridge was probably dealing with a combination of "peptone" and a plasma constituent and not with an unaltered component of the plasma.

The following experiments indicate that fibrinogen exists in plasma. Cat's blood, obtained from an anaesthetised animal, was shed through a paraffined cannula into paraffined tubes. It was centrifuged in an ice-box without clotting. The addition of appropriate amounts of neutral salt to the plasma so obtained yielded fibrinogen, and material which when treated with calcium chloride formed thrombin. These two substances appeared identical with fibrinogen and pro-thrombin prepared by the usual methods. In like manner, I have obtained fibrinogen and pro-thrombin from birds' plasma, which at laboratory temperatures shows no visible signs of clotting. One other substance is believed to be essential for the coagulation of blood. It is called thrombokinase or cytozyme and is said to convert pro-thrombin into thrombin. As disintegrated platelets yield a coagulant, it is held that the lysis of platelets inaugurates clotting. Support to this opinion was afforded by Ducceschi, who found that cocaine prevents both the lysis of platelets and the clotting of blood. I have confirmed Ducceschi's observation and also found that neutralised thymus nucleic acid, hirudin, and isotonic gum acacia inhibit the distintegration of platelets. But egg-white, which is anti-coagulant to shed blood, destroys platelets and the addition of isotonic gum acacia to shed blood does not prevent clotting. A general
correspondence between substances anti-lytic to platelets and anti-coagulants does not therefore appear to exist.

Other evidence opposes the opinion that the lysis of platelets inaugurates clotting. (a) Bürker observed that platelets are preserved on oiled or paraffined surfaces, yet under these conditions the first stage of clotting—the formation of a reversible gel—occurs.1,41 (β) Achard and Aynaud and also Sacerdotti found that platelets may be absent or present in "peptonised" blood without altering its coagulability, and the same has been observed in blood after the injection of neutralised nucleic acids.8 (γ) Gratia has shown that solutions of calcium chloride disintegrate platelets, and it has been demonstrated that the intravascular injection of this salt does not provoke clotting.

It is well known that neither red or white corpuscles nor contact with damaged tissues is essential for blood clotting. It follows that the plasma contains all the constituents required for that process.

The views of Nolf are a development of those of Wooldridge, modified by partial adherence to the hypothesis of Morawitz. In his earlier papers, blood coagulation is described as a mutual precipitation of colloids, involving a proteoclastic enzyme called leuco-thrombin, said to be secreted by both leucocytes and the vascular endothelium, and two plasma proteins hepato-thrombin and fibrinogen. In the presence of calcium salts, leuco-thrombin and hepato-thrombin unite to give thrombin, which precipitates the fibrinogen of blood as the fibrin of clots. The fluidity of both circulating and "peptone" blood is supposed to be due to the presence of an excess of hepato-thrombin, which is identified with the anti-thrombin of other writers. There is, however, no direct evidence of the secretion of leuco-thrombin, or of its combination with another plasma constituent to form thrombin; neither is there any experimental evidence that any precursor of thrombin is an anto-coagulant. Later, Nolf re-named hepato-thrombin thrombogen (pro-thrombin), and thus endeavoured to bring his views into line with those of Morawitz. He also altered his opinions respecting the fluidity of both "peptone" plasma and normal circulating blood.46 The former he ascribed to the
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presence of liver anti-thrombin, the latter to the deposition of a film of fibrin on the linings of blood vessels. Thrombin, he averred, acts only through the medium of thromboplastic substances, and that circulating blood remains fluid because such material is absent from the fibrin film. Unfortunately, no demonstration has been given of the supposed film, and no direct evidence is offered of the alleged protective properties of fibrin. Evidence will be presented later of the existence of protective material in plasmas which have not suffered surface change. No evidence is, however, forthcoming of the identity of this protective material with fibrin, or of its attachment to the vascular endothelium. Nolf explains the lack of coagulant action of thrombin in vivo by supposing its fixation by the vascular endothelium. Direct evidence of this supposition is wanting, and we have found that blood shed fifty minutes after the intravascular injection of thrombin coagulates with extreme rapidity. It thus behaves like blood to which thrombin has been added in vitro, and unlike blood from which thrombin has been removed. Recently, Nolf assigned the fluidity of "peptone" plasma to a deficiency of coagulable material. It is generally recognised that "peptone" plasma is clotted by dilution with water, by the passage of carbon dioxide, and by filtration through a clay cell. It is difficult to believe that any of these acts, particularly dilution, can remedy a deficiency of material.

The theory of Hekma marked a notable advance, as it endeavoured to explain blood clotting by reference to known physical processes. From the close similarity of the precipitation of fibrinogen and fibrin alkali hydrosol, Hekma concluded that fibrin exists in blood and is not formed from fibrinogen by enzyme action. Thrombin is regarded as an agglutinator of fibrin and not as a catalyst. Blood clotting is believed to occur in two stages: (1) A change from a state of emulsion to one of true suspension, coinciding in time with the appearance of the crystalline-like needles of fibrin described by Stübel; and (2) the apposition of these elements to form threads and films. Obviously, these conclusions do not embrace the pre-clot changes in coagulation in which thrombin is developed. Neither do they correlate many of the facts which experiments on living
animals have brought to light. For example, the inactivity of the coagulant thrombin in vivo, the fluidity of blood adjacent to clots in the excised jugular of the horse, and the suppression of clotting arising from the slow intravascular injection of tissue extracts remain unexplained.

There seem to be many unsurmountable objections to the various theories of coagulation hitherto devised, and that the whole subject may be readily explained on comparatively simple physico-chemical lines. From the evidence it appears probable that: (1) There exists in blood a protective colloid which is united to the clotting complex (fibrinogen-pro-thrombin complex) of the plasma whilst the blood remains fluid, but is disunited from that complex whenever clotting occurs. (2) Surface changes in the plasma cause disunion of the protective colloid and the clotting complex.

This view is concordant with the work of Henderson, which points to the plasma being a single physico-chemical system; and falls into line with the researches of Belgrave, which indicate that the preservation of the fluidity of rubber (Hevea) latex is due to the presence of a protective colloid and its coagulation to the disturbance of that colloid.

Mellanby has brought forward evidence that the fibrinogen of blood is closely associated with pro-thrombin. It will be seen that I accept that evidence and write of a fibrinogen-pro-thrombin complex instead of two disunited substances fibrinogen and pro-thrombin. The essential factors in fluidity and clotting are thus: (1) A fibrinogen-pro-thrombin complex; (2) a protective colloid; and (3) salts of calcium. During fluidity the protective colloid preserves the fibrinogen-pro-thrombin complex from change. The absence of the coagulant action of thrombin in vivo is thus accounted for, without postulating any anti-bodies. The coagulant action of thrombin on shed blood is equally intelligible, as surface changes, caused by shedding, have disunited the protective colloid from the fibrinogen on which thrombin acts.

The next step in clotting is the conversion of pro-thrombin into thrombin by ionised calcium salts and by other agencies, such as the detritus of cells and tissues. The thrombin thus formed converts fibrinogen into fibrin. The earlier stage of
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this process is reversible, as is so characteristic of many colloidal reactions, the later stage is irreversible. Thrombin thus acts both as a coagulant and as a fixer of coagulation. It is essential for complete clotting and is not a subsidiary reaction product. Whether it acts quantitatively, as maintained by Rettger, or as a catalyst I regard as undecided. The recent work of Kugelmass, however, supports the latter view. The final stage of clotting—the contraction of the clot—appears from the work of Howell to be a physical process due to ageing and condensation. We have shown that adhesion plays an important part in this process, so that both in the inauguration and completion of clotting the physical effects of contact with surfaces wetted by blood play an essential part. It is patent that in this view the inception of clotting is regarded as the lysis of a colloidal complex. Several substances such as “peptone,” neutralised nucleic acids, egg-white, and certain arsenobenzols restrain the clotting of freshly shed blood, but fail to inhibit the coagulation of fibrinogen by thrombin. We have shown that each of these substances suppresses the lysis of erythrocytes by various agencies. The parallelism of protection against haemolysis and protection against clotting is enhanced by the finding that both haemolysis and blood clotting are inhibited by soluble oxalates and citrates, and that both are restored when sufficient calcium chloride is added to neutralise these salts. Haemolysis is essentially the disintegration of the colloidal complexes of red blood corpuscles, and the identity of behaviour of protective substances in restraint of haemolysis and of the first stage of clotting indicates that both processes are examples of lysis.

Lethal intravascular injections of cobra venom do not haemolyse the blood of the frog while it remains in the vessels. If, however, the blood is shed into isotonic saline, which is non-haemolytic to frog’s corpuscles, lysis appears in a few minutes and is contemporaneous with clotting. Further, Nolf found that dog’s blood containing an auto-haemolysin—i.e. material lytic to the dog’s own erythrocytes—does not exhibit haemolysis whilst kept fluid by “peptone,” and that haemolysis sets in at the same time as clotting occurs. The existence of protective material in plasma and its loss of
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Protective power in the act of clotting is thus not a matter of conjecture but of fact.

It is not possible to deal fully here with the application of the theory just enunciated to the many aspects of blood coagulation; I will only allude to certain well-known phenomena which are explained by it. *In vivo* it may be assumed that the protective colloid of the plasma is not disturbed by the surface conditions of the vascular wall, so that the circulating blood remains fluid. The retardation of clotting on oiled or paraffined surfaces appears to be due to slowness of change in the protective colloid on unwetted surfaces.

The introduction of cotton threads into blood produces clotting both *in vivo* and *in vitro*; in the former case coagulation is localised, in the latter general. In both cases the electro-positive ions in the fluid adjacent to the threads (which are electro-negative) act as disturbants of the protective colloid and then of the fibrinogen-pro-thrombin complex, so that the thrombin formed converts fibrinogen into fibrin. The undisturbed protective colloid in circulating blood shields the fibrinogen from the action of thrombin; clotting is thus localised. That the clot formed when an artery is ligatured does not lead to general thrombosis may be explained similarly. The partial fluidity of the blood in the excised jugular of the horse is in like manner intelligible. Fredericq found that a small clot and thrombin are almost invariably present, though a considerable volume of plasma remains fluid. Lack of disturbance of the protective colloid of this plasma accounts for its fluidity. I have found that if blood in this condition is stirred with a glass rod immediate clotting occurs, but if the rod is oiled or paraffined fluidity remains. Howell found that the addition of small quantities of water to the blood of the terrapin induces clotting, but that the addition of isotonic saline had no such effect. The hypotonic fluid disturbs the protective colloid, the isotonic saline fails to do so.

Thrombosis is produced by the rapid intravascular injection of tissue extracts, of some snake venoms, and of certain synthesised substances (Pickering). This is intelligible as due to disturbance of the surface conditions of the protective colloid. In intravascular clotting by nucleo-protein direct union
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with the injected material appears probable, as Mills has shown that a quantitative relationship exists between the material injected and the clots formed. In clotting by snake venoms damage to the vascular wall is indicated by the presence of haemorrhages. Such damage substitutes surfaces wetted by blood for the unwetted endothelial linings of the vessels, and thus accounts for coagulation.

Relatively stable unions of neutral salts and the fibrinogen-pro-thrombin complex account for the continuance of fluidity in salted plasmas. This is concordant with the observation of Wooldridge that thrombin is absent from these plasmas.

The anti-coagulant action of "peptone" and of certain arsenobenzoins may be attributed to direct unions with the protective colloid. The products of these unions appear to be more stable than normal blood. "Peptonised" blood ultimately clots when exposed in glass vessels. Gradual dissolution of the union of the protective colloid and "peptone" explains this. "Peptone" plasma is clotted by filtration through a clay cell, by dilution with water, and by the passage of carbon dioxide, acts which may well disturb colloidal unions and effect the lysis of colloidal complexes.

Unlike "peptone," hirudin unites with plasma after change of surface conditions, but Gratia has shown it inhibits both the initial phases of clotting and the action of thrombin on fibrinogen. Its action and neutralisation by tissue extracts are explicable on the views stated.

In restraint of clotting, neutralised nucleic acids occupy a midway position between hirudin and "peptone." The potency of their anti-coagulant action is greatest in vivo, least when blood is shed on glass, their influence on blood shed on paraffined surface occupying an intermediate position. Further, the power to prevent clotting progressively decreases with the length of time shed blood has been in contact with glass. Each of these phenomena is consistent with the view that neutralised nucleic acids combine with that plasma constituent which undergoes change when in contact with surfaces wetted by blood. Suppression of clotting by anti-thrombins and by heparin is also intelligible. In the former case thrombin may be neutralised, in the latter, a stable union with the protective
colloid and/or the fibrinogen-pro-thrombin complex is indicated. Such reactions do not, however, imply that these anti-coagulants exist in the living animal.

A considerable number of substances which produce intravascular clotting when injected rapidly into the circulation not only retard coagulation when injected slowly, but render the blood temporarily immune to subsequent action of the coagulant. This is called the negative phase of coagulation, and appears to be a physical process akin to the fractional neutralisation of the toxic properties of arsenious acid by ferric hydroxide, and to the Dansyz reaction in the neutralisation of toxins by anti-toxins in vitro. But the serial or slow injection of all intravascular coagulants does not produce either tolerance or immunity to their subsequent action. When silica sols are employed, Gye and Purdy found that general thrombosis results. This they attribute to damage to the vascular wall. The alterations in the surface conditions of the damaged vascular wall disturb those of the protective colloid—hence the thrombosis.

It will be noticed that I have refrained from using in explanation of the phenomena of the fluidity and clotting of blood the many so-called substances postulated by advocates of the thrombin theories. I have endeavoured to conform to the precept of William of Occam—entia non sunt praeter necessitatem.

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