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# THE COAGULATION OF THE BLOOD.

By FREDERICK P. HENRY, M.D., PHILADELPHIA.

THE coagulation of the blood, although invariably treated of in physiological text-books, is in no sense of the term a physiological process, being a product of abnormal conditions. The blood circulating in the living, healthy vessels, never coagulates, but no sooner is the vessel-wall injured, however slightly, by a needle puncture or an escharotic, than a thrombus begins to form at the site of injury. This local coagulation may be regarded as a conservative effort to repair the lesion, but, if so, the remedy is frequently worse than the disease, for the thrombus may be swept away by the blood-current, and if finally arrested in a terminal artery—such, for example, as the arteria centralis retinæ—may work irreparable mischief. The coagulation of albuminous fluids, whether it take place within or without a cell-body, is a necrosis, the importance of which in pathological processes is just beginning to be recognized, and the time is probably not far distant when the recently introduced term, *coagulation necrosis*, will be considered tautological. Hayem speaks of the coagulation of the blood as a kind of rigor mortis—*une espèce de rigidité cadavérique*,—and this manner of regarding it is justified not only by the change in its physical properties, but also by the fact that coagulation never occurs without the destruction of some of the morphological elements of the blood. Nevertheless, the act of coagulation furnishes most important data for the study of the physiology of the blood, for it is a spontaneous analysis, the thoroughness of which de-

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pends upon the slowness with which it takes place. For this reason, horses' blood, which coagulates very slowly, is much employed in physiological researches. In such blood, before the clot has begun to form, the red corpuscles have gravitated to the bottom of the vessel, while the white remain at the top and form the buffy coat, and it has always been a matter of observation that, in such blood, the clot becomes gradually firmer as its upper layers are approached ; and, further, that a relation exists between the density and color of coagula. In the upper layers, where the color is lightest, the density is greatest, and *vice versa*. In other words, coagulation is most perfect where the white corpuscles are most abundant.

It would serve no practical purpose to give a history of the rise and progress of the various theories that have been upheld with regard to the coagulation of the blood, and their subsequent decline and fall ; but no paper on the subject can be regarded as complete, that does not contain some reference to the experiments made by Dr. Andrew Buchanan, of Glasgow, in 1831. This observer found that certain animal fluids, such as lymph—liquor pericardii—and non-inflammatory effusions, such as the fluids of hydrocele, hydrothorax, and ascites, which do not coagulate spontaneously, may be made to coagulate by the addition of the fluid obtained by squeezing a blood-clot in a linen cloth. He subsequently found, that the most effective method of causing the above-named liquids to coagulate was by adding to them what he called *washed blood-clot*. This he made by mixing blood with from six to ten parts of water and stirring for five minutes. The mixture was allowed to stand for from twelve to twenty-four hours, and then filtered through a coarse linen cloth ; the residue left upon the filter was then washed with water. This substance, mixed with a little spirit of wine to prevent putrefaction, retained its coagulative power for many months. This washed clot is a mixture of fibrin and white corpuscles, the red corpuscles having been dissolved in water and removed by filtration, and the question that presented itself to the mind of Buchanan was : Upon which of these ingredients does this coagulative power depend ?

He concluded that it was due to the white corpuscles, from the facts, that the upper layers of a clot, in which these bodies are most numerous, possessed a much greater coagulative power than portions taken from the lower layers, and that this coagulative property was unusually powerful in the buffy coat of horses' blood, which is almost entirely composed of white corpuscles. From these researches Buchanan concluded that fibrin exists in solution in serous fluids and in the liquor sanguinis, and that it has no spontaneous tendency to coagulate, but does so when brought in contact with a substance derived from the white corpuscles, which substance he considered to be of the nature of a ferment, for he compared its action to that of rennet upon milk.

These facts attracted little attention, and were almost entirely forgotten when Prof. A. Schmidt, of Dorpat, re-discovered them in 1861. He endeavored to isolate from blood the substance on which its coagulative power depends, and believed that he had identified it with serum-globulin, which he accordingly called the fibrinoplastic substance. He precipitated serum-globulin from serum by diluting it with water and passing through it a stream of $CO_2$, and demonstrated that serum from which the so-called fibrinoplastic substance had been thus precipitated had lost its coagulative power. Schmidt considers that there is little or no serum-globulin in the circulating blood, but that it is the product of the white corpuscles, which, according to him, undergo rapid destruction when the blood is withdrawn from the vessels. He found that plasma, from which the white corpuscles had been separated by filtration, was very poor in serum-globulin ; while the white corpuscles remaining on the filter yielded a large percentage of this substance.

He next endeavored to ascertain upon what the coagulating property of transudates depends, and identified it with a substance belonging also to the class of globulins, to which he gave the name of fibrinogen. Transudates from which this substance had been precipitated no longer coagulated on the addition of the fibrinoplastic substance, and, on the other hand, when these two substances were isolated and mingled in alkaline solution con-

taining a certain proportion of salts, the result was the formation of fibrin. Coagulation, Schmidt then supposed, was due to the interaction of these two bodies in saline solutions. He subsequently ascertained that the two bodies may be present in a fluid —that of hydrocele, for instance, which may contain considerable quantities of serum-globulin—without coagulating, but that a clot will form on the addition of blood or blood serum. It then appeared evident that a third factor was necessary to the act of coagulation, and this he named fibrin ferment. He obtained this substance from blood, or, preferably, serum, by mixing it with twenty times its volume of alcohol, and setting it aside for a considerable period of time—two weeks to three months. The alcohol coagulates all the proteids of the serum, which are collected on a filter, dried and pulverized, and the powder dissolved in water. Such a solution, when added to a mixture of fibrinogen and fibrinoplastin, that does not coagulate spontaneously, will often cause the prompt formation of a clot. Schmidt derives the ferment, as well as the serum-globulin (fibrinoplastin), from the white corpuscles; for he found that plasma, from which these bodies had been separated by filtration, when subjected to the process for obtaining ferment, yielded a very inactive solution of this substance, and that blood received directly from a vessel into absolute alcohol—by which means the destruction of the white corpuscles is supposed to be prevented—yielded no ferment whatever. He also demonstrated, by actual counts of the white corpuscles, that a large number of these bodies disappear in the act of coagulation, presumably partly in the formation of fibrin ferment. He counted the leucocytes in the plasma of horses' blood, and found that they numbered 14,909 per cubic millimetre in an average of eleven counts; he then allowed the plasma to coagulate and counted the leucocytes of the serum, and found that they numbered, in an average of nine counts, but 4,222 per cubic millimetre, 71.7 per cent. having disappeared in the coagulum. He also counted the red corpuscles before and after its defibrination, and found the difference to be only thirty per cent. He therefore argues that the disappearance of the leucocytes is not a mechanical entanglement

in the meshes of the fibrin, for, were this the case, there would be no such difference in the percentage of disappearance between the red and white corpuscles. Besides, on examining a clot with the microscope, the red corpuscles may be seen entangled in the meshes of the fibrin, while of the white, not a trace remains but a few greatly altered cells, the majority having entirely disappeared in the formation of the clot.

Schmidt's theory of coagulation, therefore, is that it is due to the union of two substances, fibrinogen and serum-globulin, under the influence of a ferment, and that the fibrinogen exists as such in the circulating blood, while the serum-globulin and ferment are formed after the blood is withdrawn from the vessels.

The researches of Hammarsten tend to prove that serum-globulin is an unnecessary factor in the formation of fibrin, which, according to him, is derived solely from fibrinogen under the influence of the ferment. He has prepared fibrinogen free from all traces of serum-globulin, and has caused the formation of a clot by the addition of the ferment only. He admits that coagulation may be produced by the addition of serum-globulin to a transudation that will not coagulate in the presence of the ferment alone, but he has shown that other substances, such as calcium chloride and casein, have the same effect. He has also shown that, from fluids which do not coagulate on the addition of ferment, fibrinogen may be obtained which does coagulate when the ferment is added. In such a case the fluid evidently contained substances that prevent coagulation. Such substances are free alkalies, alkaline carbonates, and certain salts. For example, in a hydrocele fluid containing very little fibrinogen, that does not coagulate on the addition of the ferment and does coagulate on the further addition of calcium chloride, it is possible that this salt may decompose an alkaline carbonate that held the fibrin in solution. He claims also that when coagulation is produced by adding serum-globulin to a non-coagulating mixture of fibrinogen and ferment, the effect is due to impurities mingled with the serum-globulin, for when he repeated the same experiment with pure serum-globulin, coagulation did not take place.

Hammarsten, therefore, attributes the formation of fibrin to one substance, fibrinogen, which exists as such in the blood, under the influence of a ferment derived from the white blood corpuscles

The above-named observers agree in regarding fibrin as a precipitate caused by the union of soluble substances in the liquor sanguinis.

Later observations by Wooldridge, Norris, Hayem, and Bizzozero attribute the formation of fibrin, in great part, to a direct transformation of morphological elements of the blood.

In the Proceedings of the Royal Society for June 18, 1881, is an important contribution to the subject by Mr. L. C. Wooldridge. He obtained leucocytes from lymphatic glands, by a process described in his paper, and washed them thoroughly with a half-per-cent. solution of common salt, after which he found that their normal microscopic appearance was unaltered. He then found that if to one volume of suspended cells an equal volume of ten-per-cent. solution of common salt were added, the whole was immediately converted into a "peculiar semi-transparent jelly" which behaved chemically precisely like fibrin, while, under the microscope, he found that the cells, as such, had entirely disappeared. "Only nuclei imbedded in a distinctly fibrous ground-substance" were visible. Similar results were obtained on adding distilled water or a solution of magnesium sulphate. He then studied the behavior of leucocytes toward plasma. The most convenient way of obtaining plasma is by injecting peptone into the blood of an animal. If the animal be bled a few minutes after the injection, the blood does not coagulate, and by means of the centrifugal machine the corpuscles may be entirely separated from the plasma. Wooldridge obtained a specimen of this peptone plasma which presented the following characters :

It was totally uncoagulable : 1. On dilution with water. 2. On passing a current of $CO_2$ through it. 3. On addition of Schmidt's fibrin ferment. 4. On addition of serum-globulin. 5. On addition of normal serum. 6. On standing till it was foul.

Nevertheless, on adding leucocytes to such plasma, coagulation promptly followed, of which the completeness was in direct ratio

to the number of leucocytes added. As additional facts in favor of his view that the plasma changes the leucocytes directly into fibrin, he gives:

1. The weight of the coagulum is, as near as may be, in such observations, identical with that of the cells that have been added.

2. The percentage of albumins in peptone plasma before coagulation is identical with the percentage after coagulation with cells.

3. The protoplasm of the cells has completely disappeared and has been converted into a partly fibrous, partly granular, ground-substance; the nuclei remain.

4. If to a very large quantity of suspended cells (say 50 cubic centims.) a very small quantity (1 cubic centim.) of peptone plasma be added, the whole clots firmly.

Wooldridge does not deny that Hammarsten's theory of coagulation is partly true, for he concludes his paper with the statement that there are "two essential processes in the coagulation of the blood, one of which has been hitherto entirely wrongly appreciated or overlooked." This latter process is that the "dead" plasma converts the white corpuscles directly into fibrin. At the same time, however, that this occurs, a substance is liberated from the cells which converts the fibrinogen also into fibrin. This is the other process. The substance which is liberated from the cells is fibrin ferment.

Later observations by Norris, Hayem, and Bizzozero associate the formation of fibrin with changes in certain morphological elements of the blood: by the first, to changes in what he terms the invisible corpuscle or advanced lymph disc; by the two latter, to similar changes in bodies termed by Hayem *hæmatoblasts*, from their supposed share in the formation of the red corpuscle, by Bizzozero, *Blutplättchen*. At the present time, the subject has assumed such a controversial aspect that it is somewhat difficult to arrive at an exact understanding of it. Thus Norris claims that the blood-plates[1] are nothing but products of disintegration

[1] This term is used for both the "hæmatoblasts" of Hayem and the "blutplättchen of Bizzozero, which are identical.

of his colorless corpuscle, while Hayem and Bizzozero maintain that the corpuscle of Norris is nothing but a red corpuscle decolorized by manipulation. Certain it is, however, that the blood-plates may be seen in the circulating blood. These bodies (as shown by Osler) are the component constituents of Schultze's granule masses seen in blood by all microscopists. They are the elementary corpuscles of Zimmermann, the *globulins* of Donné, the *grains sarcodiques* of Vulpian, and the *granulations libres* of Ranvier. The latter regarded them as particles of fibrin which serve as centres of coagulation, just as a crystal of sodium sulphate, dropped into a solution of the same, will serve as a centre of crystallization.

If a cover glass be firmly fastened to a slide with parafine, as directed by Hayem, and blood dropped at its edge, it will run beneath by capillarity, and in the islets free from red corpuscles may be readily seen, with a power of from 400 to 500 diams., the bodies described as blood-plates. They are exceedingly delicate, colorless bodies, with a diameter from two to three times less than that of the red corpuscles, and, according to Hayem, exist in the blood in health, to the number of 255,000 per cubic millimetre. They are scarcely under observation than they begin to alter in shape in a variety of ways, but in each instance a division of the blood-plate into two portions may be detected—namely, the one central, vitreous-like, and strongly refractive ; the other peripheral, granular, and of a gray color. The latter is extremely viscous, and causes the formation of groups of blood-plates, from the borders of which may be seen to proceed a number of exceedingly fine filaments that cross each other in every direction, thus forming an irregular network. These changes are exactly coincident with the formation of a coagulum, and the agents which prevent these alterations in the blood-plates are precisely the ones that prevent the formation of fibrin. Among these may be mentioned a temperature of O° C., certain saline solutions, liquor amnii, and dropsical effusions.

Hayem does not absolutely claim that fibrin is derived directly from his " hæmatoblasts, " for, in referring to the viscous matter

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