COAGULATION TIME OF THE BLOOD IN LOBAR PNEUMONIA.*

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Observation of the variation in time within which the blood coagulates when removed from its normal surroundings is of importance in the study of certain diseases, and accurate determination of the factors involved in producing any variation in the normal coagulation time of the blood would, no doubt, throw some light upon the nature of the pathological processes concerned. A large number of methods designed to estimate the time of coagulation under normal and pathological conditions have been devised. Many of these methods give fairly accurate results in the hands of their originators, but the time of normal coagulation differs considerably when determined by different methods, so that comparison of one observer’s results with those of another is unsatisfactory.

Morowitz¹ has devoted much study to the relation of different elements and to the sequence of events in the process of blood coagulation. The most satisfactory and adequate explanation of the phenomenon, however, has recently been offered by Howell,² who has carefully traced the various stages in the reaction, which finally results in the conversion of fibrinogen into fibrin. All the elements necessary for coagulation are present in the circulating blood. The inception of the process is prevented, however, by the presence of a substance, antithrombin, which binds the prothrombin, thus preventing its activation within the vessels by the calcium salts present. When shed blood is exposed to tissue juices or foreign surfaces, a body designated thromboplastin, originating either from tissue juices or the disintegration of certain cellular elements in the blood, develops. Thromboplastin, by its ability to combine with antithrombin, frees the previously bound prothrombin. This immediately reacts with the calcium salts of the blood with the liberation of active thrombin, which then precipitates the fibrinogen as fibrin. This explanation emphasizes the probability that failure of the coagulative power, or changes in the coagulation time of the

* Received for publication, August 1, 1912.
¹ Morowitz, P., Handbuch der biochemischen Arbeitsmethoden, 1911, v, 223.
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blood, are dependent upon variation in some one or more of the factors described. Quantitative estimation of the substances concerned is possible and would yield more valuable results than simple determination of the coagulation time, even were the methods for the latter observation uniform. Whipple\(^1\) has recently applied such a procedure to the study of certain diseases and urges a classification of conditions associated with hemorrhage upon the basis of the specific element responsible for the change in coagulative power.

In the present paper are given the results obtained from a study of the coagulation time of the blood in a number of cases of lobar pneumonia. On account of the large amount of time required, quantitative estimations of the thrombin, antithrombin, and fibrinogen were not made, so that it is possible to explain only by inference the prolongation of the coagulation time observed during the acute stage of pneumonia.

METHOD.

The method used for determination of the coagulation time was a comparatively simple one. An attempt was made to guard against certain obvious sources of error. A fairly large quantity of blood, about seven cubic centimeters, was used for each determination in order that the proportion of volume to the surface exposed to contact with foreign substances might be as great as possible.

The blood was obtained by rapidly filling an all glass syringe, having a needle of large calibre, with blood directly from the median basilic vein of the patient. A stoppered glass tube was then filled from the syringe to within about two centimeters of the top. The tube had previously been inserted through a rubber stopper into a large glass cylinder containing water kept at 38°C. The average time for the complete operation was about forty-five seconds. The apparatus was then carried to a room kept constantly at 38°C, and after the lapse of some minutes the tube was carefully rotated every thirty seconds. The time of coagulation was measured from the period at which half the quantity of blood had been withdrawn from the vein to the point at which the blood failed upon rotation to flow from one end of the tube to the other. Great care was taken to prevent the presence of air bubbles upon the upper surface of the blood, as these accelerate the formation of a clot at this point. All glassware with which the blood came in contact was maintained as nearly as possible at body temperature and was kept scrupulously clean. The specimen of blood was taken by venous puncture in order to prevent contact with lacerated tissue.

It had been assumed, that if prolongation of the coagulation time occurred, such a condition would probably be dependent upon an

excess of antithrombin. If such were the case, the ordinary method of obtaining drops of blood from a skin puncture would expose it to contamination with thromboplastin, and inasmuch as the excess of antithrombin might be very slight, a sufficient quantity of thromboplastic substances might be absorbed during the formation of a small drop to mask entirely the presence of a slight excess of antithrombin. It is a well known fact that successive drops from the same skin puncture clot with increasing rapidity. This can hardly be looked upon as comparable to the shortening of coagulation time which occurs during hemorrhage. The blood while in the vessels shows no tendency to clot, and the time within which it coagulates when removed depends upon the variety and nature of external conditions, so that different methods in the main give variable results.

No special advantages are claimed for the method used in this study. It is possible for the same individual to obtain comparable results if variations in technique are carefully guarded against.

The idea has become current that the coagulation time of the blood is shortened during the acute stage of lobar pneumonia. This opinion has developed in spite of the observations of Hayem, Pye-Smith, and Coleman, that the clotting time is prolonged in pneumonia. Cohen, in a study of six pneumonia patients, found the average time slightly shortened. The formation of white clots in the heart and vessels of patients dying of lobar pneumonia is a common observation at autopsy. In this hospital a marked sedimentation of the red cells, with the formation of a buff coat, occurred when tubes of blood obtained from pneumonia patients were allowed to stand. Such observations are infrequent in the case of normal blood and suggest that the coagulation time of the blood in pneumonia is sufficiently delayed to allow a settling of the heavier cellular elements.

In the course of some recent experiments in which rabbits were infected with massive doses of pneumococcus, the fact was noted that when the animals died, after the lapse of only a few hours, the blood had already become practically incoagulable. These ob-

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* Hayem, G., Du sang et de ses altérations anatomiques, Paris, 1889, 323.
* Pye-Smith, P. H., Allbutt and Rolleston, System of Medicine, 1898, v, 91.
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Observations seemed to indicate the probability of a prolongation of coagulation time during lobar pneumonia. The following cases demonstrate in most instances a definite increase in the clotting time of the blood during the acute stage of lobar pneumonia with a gradual return to normal during the period of convalescence.

Case 1.—411. Severe infection. Recovered. Lysis on the ninth day of disease.
Coagulation time:  10 min.  11 min., 10 sec.  6 min., 30 sec.

Case 2.—418. Mild infection. Recovered. Lysis on the fourth day of disease.
Dec. 24, 1911, two days before lysis.  Dec. 29, 1911, one day after lysis.  Jan. 8, 1912, temperature normal.
Coagulation time:  16 min.  10 min.  7 min.

Case 3.—409. Severe infection. Died on the fourth day of disease.
Jan. 4, 1912, second day of disease.
Coagulation time:  17 min., 10 sec.

Case 4.—413. Severe infection. Died on the fourth day of disease.
Jan. 7, 1912, third day of disease.
Coagulation time:  13 min.

Case 5.—423. Severe infection. Died on the seventh day of disease.
Coagulation time:  15 min.  18 min.

Case 7.—454. Mild infection. Recovered. Crisis on the third day of disease.
Jan. 21, 1912, day of crisis.  Jan. 28, 1912, seven days after crisis.
Coagulation time:  12 min.  10 min., 30 sec.

Case 8.—430. Severe infection. Died on the tenth day of disease.
Coagulation time:  11 min.  12 min.
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Case 9.—438. Severe infection. Died on the fourth day of disease.
Jan. 24, 1912, second day of disease.
Coagulation time:
9 min.

Case 10.—503. Moderately severe infection. Crisis on the seventh day of disease.
Jan. 25, 1912, four days before crisis.
Jan. 29, 1912, one day before crisis.
Jan. 30, 1912, day of crisis.
Feb. 14, 1912, two weeks after crisis.
Coagulation time:
11 min., 45 sec. 12 min. 9 min. 9 min.

Case 11.—460. Severe infection. Died on the fifth day of disease.
Feb. 2, 1912, third day of disease.
Feb. 4, 1912, fifth day of disease.
Coagulation time:
8 min., 45 sec. 11 min., 30 sec.

Case 12.—472. Severe infection. Died on the fifth day of disease.
Feb. 12, 1912, third day of disease.
Feb. 14, 1912, fifth day of disease.
Coagulation time:
13 min., 30 sec. 12 min., 45 sec.

Case 13.—497. Moderately severe infection. Recovered. Crisis on the seventh day of disease.
Feb. 13, 1912, two days before crisis.
Feb. 15, 1912, day of crisis.
Feb. 18, 1912, three days after crisis.
Coagulation time:
14 min., 15 sec. 11 min., 30 sec. 8 min., 30 sec.

Case 14.—484. Severe infection. Died on the eighth day of disease.
Feb. 19, 1912, third day of disease.
Feb. 23, 1912, seventh day of disease.
Coagulation time:
9 min., 15 sec. 13 min., 30 sec.

Case 15.—502. Severe infection. Recovered. Crisis on the eighth day of disease.
Feb. 19, 1912, seven days before crisis.
Feb. 21, 1912, five days before crisis.
Feb. 27, 1912, day of crisis.
March 11, 1912, thirteen days after crisis.
Coagulation time:
11 min. 9 min., 15 sec. 7 min., 30 sec. 7 min., 30 sec.

Case 16.—501. Moderately severe infection. Recovered. Crisis on sixth day of disease.
Feb. 19, 1912, four days before crisis.
Feb. 21, 1912, two days before crisis.
Feb. 23, 1912, one day after crisis.
March 11, 1912, seventeen days after crisis.
Coagulation time:
8 min., 15 sec. 10 min., 15 sec. 11 min. 6 min., 45 sec.
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Case 17.—480. Severe infection. Died on the seventh day of disease.
Feb. 21, 1912, sixth day of disease.
Coagulation time: 13 min., 45 sec.

Case 18.—553. Moderately severe infection. Recovered. Pseudocrisis on fifth day of disease. Crisis on eighth day of disease.
March 5, 1912, five days before crisis. March 7, 1912, day of pseudocrisis. March 11, 1912, one day after crisis. March 26, 1912, sixteen days after crisis.
Coagulation time: 11 min., 30 sec. 9 min., 30 sec. 11 min., 45 sec. 8 min.

Case 19.—405. Mild infection. Recovered. Crisis on eighth day of disease.
Coagulation time: 6 min., 15 sec. 6 min., 40 sec. 7 min. 8 min., 30 sec.

Case 20.—401. Severe infection followed by empyema.
Dec. 21, 1911, fourth day of disease.
Coagulation time: 12 min., 30 sec.

In seven instances the coagulation time of the blood in approximately normal individuals was determined by the method described. The specimens of blood were obtained from treated cases of syphilis in whom there was no evidence of syphilitic disease of the liver. The average coagulation time of the blood of these individuals was seven minutes and thirty-nine seconds. The shortest time observed was five minutes and fifteen seconds, and the longest time nine minutes. The average coagulation time of patients with pneumonia during the acute stage of the disease was twelve minutes and twenty-seven seconds. The shortest time was six minutes and fifteen seconds, and the longest time eighteen minutes. The average coagulation time at the time of discharge in patients who recovered was seven minutes and thirty-two seconds. The shortest time observed was six minutes and thirty seconds, and the longest, excepting one patient whose blood had last been tested some days before discharge, was nine minutes.

From these examples it is seen that the coagulation time of the blood is definitely prolonged during the acute stage of pneumonia. In one instance, case 20, a very mild infection involving part of one
lobe, the coagulation time during the height of the disease was possibly slightly less than normally. The degree of prolongation of the coagulation time seems to have no definite relationship to the severity of the pneumonic process. The coagulation time tends to become shorter at about the time of the crisis, but probably does not return to normal for some time afterward. At the time of discharge all patients show a coagulation time that is within normal limits, and the average coagulation time at this period corresponds very closely to that observed in approximately normal individuals.

The factor which causes the lengthening of coagulation time in pneumonia was not decisively determined because quantitative estimations of the various elements entering into the coagulation of the blood could not be made. For the following reasons, however, it was believed probable that the long coagulation time was caused by an increase in the antithrombin of the blood. In rough estimations made by centrifugalization, the proportion of the solid element of the clot to the serum has been found to be markedly increased during lobar pneumonia. This striking increase, of course, cannot be accounted for by an increase in the cellular elements and must be due to an increased amount of fibrinogen in the circulating blood. That an increase in the amount of fibrinogen occurs during pneumonia is known and has received experimental confirmation in pneumococcus infections of animals. It is not unlikely that the characteristically large fibrin content of pneumonic exudates depends upon the increased fibrinogen of the blood. Dr. Peabody, in this hospital, has shown that the decrease in calcium content is very slight and is inadequate to explain the changes in coagulation time. Howell has determined that the formation of fibrin from fibrinogen is not a fermentative process but is a quantitative reaction between thrombin and fibrinogen. Inasmuch as a large firm clot always forms in pneumonic blood, it would seem unlikely that there is a deficiency of thrombin, but that the delay is caused by the presence of some inhibitory substance such as antithrombin. In addition, Whipple has recently demonstrated by accurate methods, that in an analogous infection the delay in coagulation time is occasioned by an increase in antithrombin.

* Whipple, G. H., *loc. cit.*
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The liver is generally accepted as the principal source of the antithrombin of the blood. Meek\(^9\) has recently confirmed the results of other observers in showing that the liver is most important in the regeneration of circulating fibrinogen. The increase in both of these elements of the blood during lobar pneumonia would seem to be due to a common stimulus affecting principally the liver. It is well known that injection into the circulation of animals of certain degradation products of protein induces a prolongation of the coagulation time of the blood. In lobar pneumonia opportunity is afforded for absorption from the lung of large quantities of such substances. Inasmuch as it is shown in the present paper that at the time of the crisis, when probably the greatest quantity of these substances reach the circulation, the coagulation time tends to decrease, it is unlikely that they are the chief factors concerned in the lengthening of coagulation time. The result is more probably produced by some specific effect upon the liver of intoxicating substances originating from the infecting organism.

SUMMARY.

The coagulation time of the blood is generally prolonged during the acute stage of lobar pneumonia, returning to normal during the period of convalescence.

There seems to be a simultaneous increase in the quantity of circulating fibrinogen. The lengthening of the coagulation time is probably due to an increased formation of antithrombin. The source of the increased antithrombin and fibrinogen is probably the liver, and the stimulus to increased production of these two substances is due to the nature of the infecting organism.