SUMMARY AND CONCLUSIONS

1. Intravenous infusions of citrated whole blood, citrated plasma, serum, physiological saline and glucose solution were given by the gravity-drip method and the rate of flow under various conditions was measured.

2. The following factors were found to have an important influence on the rate of flow of these infusions: (1) the size of the vein at the site of the infusion, (2) the temperature of the fluid as it enters the vein, (3) the nature of the fluid (some fluids induce venoconstriction) and (4) the pressure of the fluid.

3. Infusions *given into large veins,* such as the median cubital, always flowed rapidly; the temperature and nature of the fluid had little effect on the rate of flow.

4. When infusions were given into small veins, however, such as the long saphenous vein at the ankle, the temperature of the fluid, as it entered the vein, had a pronounced effect on the rate of flow. Cooling the fluid caused contraction of the vein and marked slowing of the rate. Increase in temperature gave rise to venodilatation and increase of flow.

5. Similarly, the nature of the fluid had a striking effect on the rate of flow into small veins. Human serum and reconstituted dried plasma were found to contain a factor which caused strong sustained contraction of the vein with resultant slowing of the flow. Such a factor was not demonstrated in fresh citrated whole blood, fresh citrated plasma, physiological saline or 5% dextrose solution.

The nature of this venoconstrictor substance was not determined. It could be demonstrated at once in serum obtained by coagulation of fresh whole blood or plasma. It seemed to develop gradually in citrated whole blood or plasma on prolonged storage. It was not related to the blood group of the donor or to the pH of the fluid.

6. Increasing the pressure resulted in a marked increase in the rate of flow when the vein offered little resistance to the flow of the infusion. When, on the other hand, there was strong contraction of the vein resulting in a very slow flow, increase in the pressure failed to induce a rapid flow and often caused pain near the site of the infusion.

7. In shocked patients with cold extremities, the small peripheral veins commonly used in giving infusions, may be strongly contracted. Since such patients are in urgent need of rapid replacement of a depleted blood volume, *a large vein should be selected for the infusion.* This is more important if the replacement fluid is serum or stored plasma. If the infusion must be given into a small vein and application of pressure fails to induce a rapid flow, warming the fluid will lead to dilatation of the vein and a marked increase in rate.

The authors wish to express their indebtedness to Dr. Albert Fisher of the Connaught Laboratories, Toronto, for the measurement of the pH of infusion fluids, the preparation of citric acid solution and other assistance.

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STUDIES ON INCREASED COAGULABILITY OF THE BLOOD*

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SINCE the discovery of a physiological anticoagulant by Howell and Holt[1] in 1916, interest has developed in the subject of thrombosis from a therapeutic standpoint and has been increased greatly by the purification[2, 3] of the substance in the form of heparin. Murray, Jacques, Perrett and Best[4] demonstrated in 1937 the effect of heparin as a preventive in experimental thrombosis, and a year later[5] Murray and Best described the clinical use of this substance and in a subsequent report[6] pre-

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sented statistical evidence of the efficacy of heparin in the prevention of postoperative thrombosis.

As early as 1929[7, 8] Dam published his first paper on vitamin K and subsequent work by him and others[9, 10, 11, 12] demonstrated the relationship between vitamin K and the prothrombin concentration of the blood. This work coincided with that of H. P. Smith[13, 14] on the effect of jaundice and injuries to the liver on the prothrombin concentration. At an even earlier date Schofield[15] and Roderick[16] were investigating the hæmorrhagic diseases in cattle arising from eating improperly cured hay and sweet clover. Some 10 years later Campbell and Link[17] isolated hæmorrhagic concentrates from spoiled sweet clover and subsequently synthesized the responsible agent[18] which they called dicoumarin.

On demonstrating the effect of dicoumarin on prothrombin concentrations new enthusiasm concerning the question of therapy in thrombosis was born. As a result, numerous papers have been published concerning the effect of dicoumarin on the incidence of thrombosis and pulmonary embolism.[19, 20, 21, 22] In each paper a large series of cases was followed and on no occasion, in any paper concerning heparin or dicoumarin, has mention been made of a test which would help to indicate the necessity of such therapy by demonstrating an increased coagulability of the blood. While such an abnormality is undoubtedly only one of several factors concerned in thrombosis, there would appear to be great need, particularly at this time, for a method that would allow the clinician to recognize at least those cases in which this tendency to an acceleration of the process of clotting is present. Apparently a finer analysis of any shortening of the time of coagulation is essential before this desired result can be obtained.

In a discussion on the congealing process we may ask "On what factors concerned in coagulation would an acceleration depend?" If one employs the time-honoured theory as a working basis, it would appear to lie in the concentration of one substance and one substance alone. Starting with the various factors and their relation to one another, we have:

Prothrombin + Calcium + Thromboplastin
↓
Thrombin + Fibrinogen
↓
Fibrin

The amount of fibrin is dependent upon the fibrinogen concentration and affects only the solidity of the resulting clot. No relation exists between the fibrinogen concentration and the velocity of the congealing reaction except in rare cases of fibrinopenia.[23] Nygaard[24] has demonstrated the effect of varying thrombin concentrations. His results are identical with those of Quick[25] and show that reduction of the percentage of the solution of thrombin has little or no effect on the velocity of the reaction except when the concentration becomes as low as 20% of normal. A reduction of 80% of the thrombin concentration retards the velocity of coagulation by only some 8 seconds. From this he concludes that "In the coagulation system it appears to be a general rule that the velocity of the entire process is governed by the processes leading to the thrombin formation".

If we consider these processes leading to thrombin formation, three factors, prothrombin, calcium and thromboplastin must be discussed. As regards prothrombin Quick[26] has confirmed Eagle's[27] observation that a constant amount of prothrombin yields a constant amount of thrombin; but there is no evidence to show that under natural conditions the prothrombin concentration of the blood ever rises above the normal or optimum level, and in fact under therapeutic conditions where excessive amounts of vitamin K are given, the prothrombin concentration is not increased beyond the physiological limit, but rather storage of the vitamin results.

While it is well recognized in recalcification experiments, *in vitro,* that the velocity of thrombin formation is influenced by the concentration of added calcium, it has never been demonstrated that the variations in the level of calcium in the blood under normal or even pathological conditions are sufficient to affect appreciably the speed of this process.

It would appear, therefore, that an increase in the only remaining factor, namely thromboplastin, is the cause of an accelerated coagulability and as a matter of fact there is considerable evidence to support this view. Quick[28, 29] has demonstrated that as the amount of this agent is increased the clotting time becomes progressively shorter, until a minimum value is reached after which no further shortening of the time occurs, irrespective of how great the excess of thromboplastin. Moreover Nygaard[30]

concludes that other factors being normal the concentration of thromboplastin governs the velocity of conversion of prothrombin to thrombin. Since therefore an acceleration of the process of coagulation is due to an increase in the concentration of thromboplastin the question arises how may this increase be brought about.

Thromboplastin can be derived from all tissues[31 to 33] and hence is essentially a tissue extract. In the circulating blood it exists principally as potential thromboplastin in the platelets but also to an appreciable extent in active form in the plasma.[34 to 37] The content in the platelets may be estimated relatively by an enumeration of these morphological elements of the blood and it is recognized that when such an increase occurs a tendency to thrombosis develops. However we have no method of measuring the thromboplastin content of plasma, though it would appear that it would be increased in all probability wherever a drainage of tissue fluids into the circulation occurs, as for example, following hæmorrhage to replace the lost blood volume, in the resolution of inflammatory exudates by the lymphatics, etc.

The question of a protective mechanism against an increase in active thromboplastin is answered by heparin. Heparin has been isolated from the circulating blood by various workers[38 to 40] and later Jorpes[41 to 43] gave some suggestions as to its chemical nature. Subsequently Holmgren and Wilander[44] demonstrated that mast cells are particularly rich in material considered to be heparin. These mast cells are most prominent in the vascular wall and the tissues surrounding the vessels. Brinkhous, Smith, Waren and Seegers[45, 46] have demonstrated that heparin along with its serum complement is antagonistic to thromboplastin.

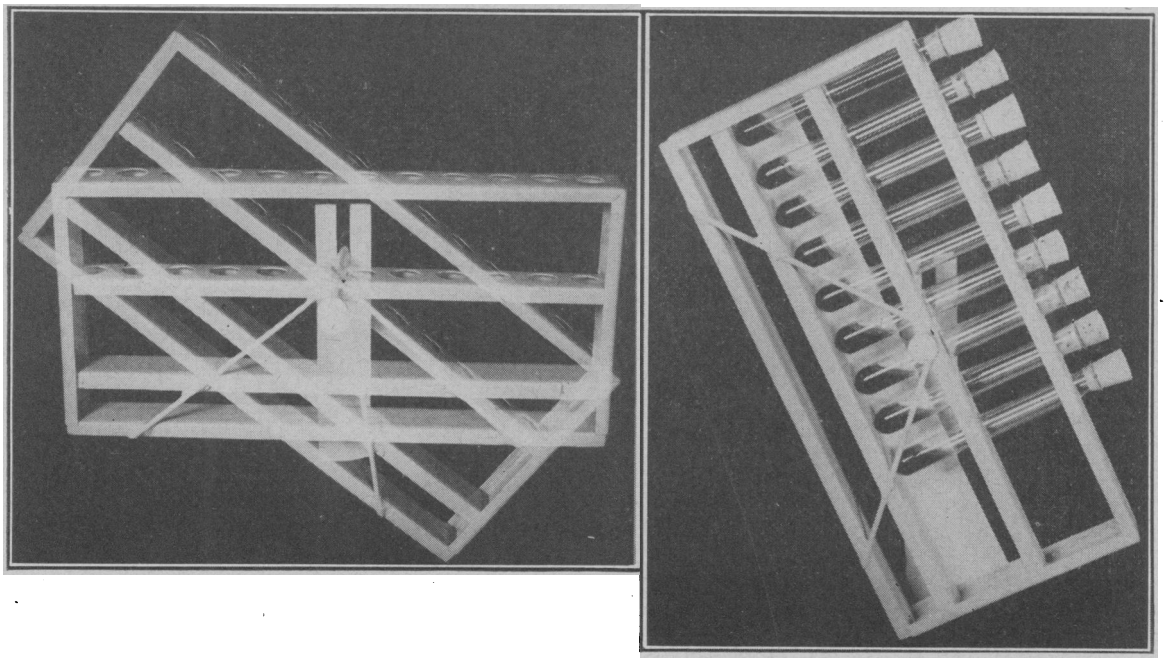

Fig. 1 **Fig. 2**

Fig. 1.—Empty rack showing construction for rotation on central axis (double exposure).
Fig. 2.—Rack with tubes in rotated position. Congealing has occurred in tubes 1 to 5, but blood is still fluid in tubes 6 to 9.

From the evidence presented, although there are many controversial points it would appear that in the circulating blood heparin and thromboplastin are in a state of dynamic equilibrium. Thus cases demonstrating a tendency towards increased coagulability may have this equilibrium upset in that there is an uncompensated increase in the thromboplastin content.

Recently we have devised a test, based on the theoretical considerations presented above, that allows for a recognition of an accelerated coagulation and apparently gives an indirect measurement of the thromboplastin present. This is accomplished by a controlled deceleration of the process, by the use of heparin. The coagulation is put into "slow motion", as it

were; and finer changes are magnified and thus more accurately measured. The detailed technique has been published in this Journal,[47] so will be presented here in only very brief form.

TECHNIQUE

Increasing concentrations of heparin are made up in physiological (0.9%) saline so that ½ c.c. saline contains 1/10, 2/10, 3/10 up to 7/10 units of heparin. Nine Wassermann tubes are placed in a special test tube rack which can be rotated about a central axis and the tubes are prepared for the test by the addition of the heparin saline solutions as indicated below (Fig. 1).

Tube No.	*Contents*
1.	empty
2.	½ c.c. normal saline
3.	½ c.c. normal saline + 1/10 unit heparin
4.	½ c.c. normal saline + 2/10 units heparin
5.	½ c.c. normal saline + 3/10 units heparin
6.	½ c.c. normal saline + 4/10 units heparin
7.	½ c.c. normal saline + 5/10 units heparin
8.	½ c.c. normal saline + 6/10 units heparin
9.	½ c.c. normal saline + 7/10 units heparin

One c.c. of whole blood, freshly withdrawn from the arm vein of the individual, is placed in each tube which is then corked. The whole rack and tubes are then gently agitated to insure the mixing of the blood and the fluid in the tubes. The time is then recorded and the actual test, which is conducted at room temperature, begins. The test tube rack is gently rotated in a clockwise direction every two minutes to an angle of 70 to 80° and the fluidity of the blood in each tube is noted. The end point for each tube (congealing) is that point at which the blood no longer flows along the side of the tube (modified Lee and White method) (Fig. 2). The time taken for each tube to congeal is recorded on graph paper plotting 1/10 units of heparin against time in minutes.

Using this method it was demonstrated, by carrying out the test on a series of 50 normal adults, that while there is a certain amount of variation in different individuals, the graphs fall within quite well defined limits and these were therefore established as the bounds of normalcy (Fig. 3).

In consideration of the evidence presented that heparin along with its serum complement is antagonistic to thromboplastin, we endeavoured to demonstrate this fact with the use of the test described. The range for two normal individuals was established over a period of two weeks. Comparing day to day results there were minor fluctuations of the curve of the graph which may be credited to error in technique or reading, but these did not exceed plus or minus 4 minutes (Fig. 4). Three experi-

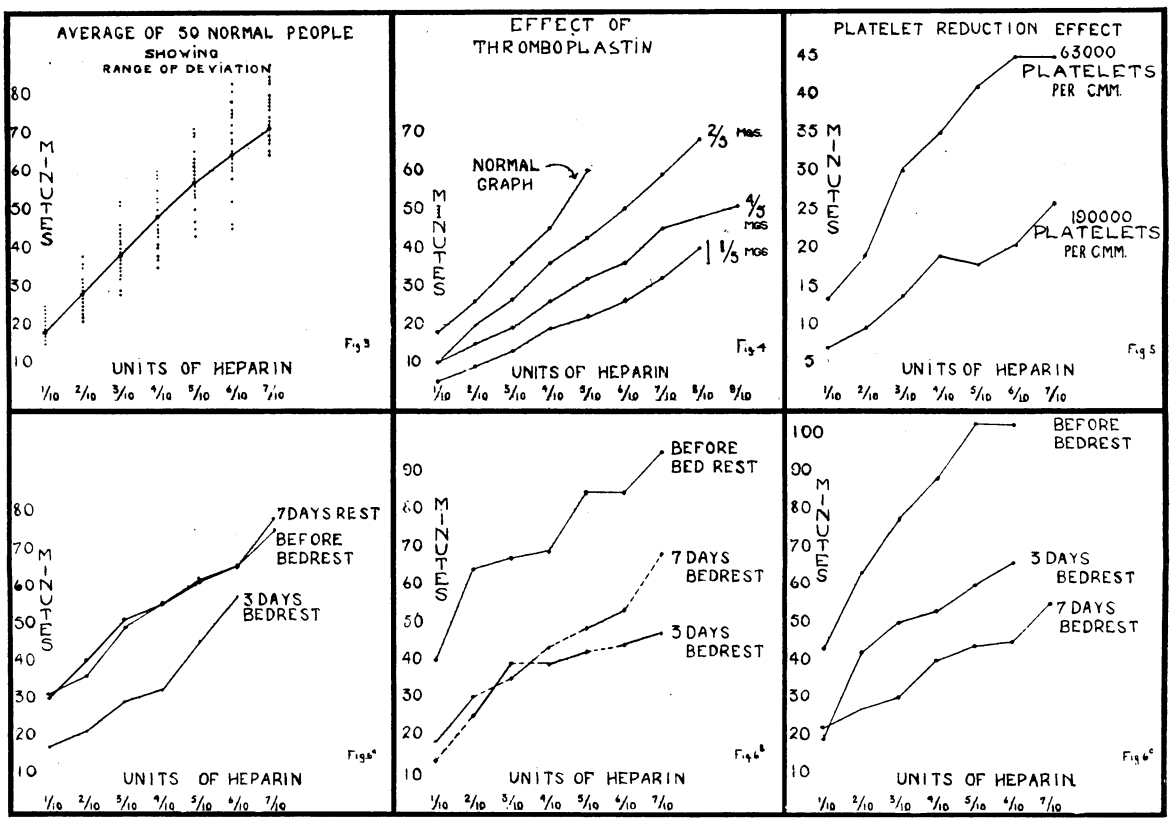

Fig. 3.—Results of test on 50 normal individuals demonstrating amount of variation. Continuous dark line represents mathematical average of these graphs. **Fig. 4.**—Demonstrating clockwise rotation of curve of graph on addition of increasing quantities of thromboplastin. **Fig. 5.** — Demonstrates effect of platelet reduction by centrifugalization—producing a deceleration of congealing process. **Figs. 6a, 6b and 6c.**—Results of test on three men during bed rest. The increase in coagulability varies with the thoroughness with which this condition was maintained.

mental tests were conducted on each individual as follows: two-fifths of a milligram of dry thromboplastin[48] was added to each tube and the test conducted in the usual manner. The quantity of thromboplastin was increased to 4/5 mgm. and the procedure repeated on another specimen of blood. The thromboplastin concentration was then increased to 1 1/5 mgm. and the test performed once again. The three resulting graphs (Fig. 4) for each subject indicate that there is a clockwise shift of the curve corresponding in all cases to the amount of thromboplastin added.

The thromboplastin concentration was then altered in an indirect manner. Two specimens of blood were withdrawn from a normal subject, one from each arm. Control platelet counts were done (235,000 per c.mm.) on the whole blood. Each specimen was citrated, using 9 volumes of blood to one volume of citrate solution (3.8%). One specimen was centrifuged for 15 minutes at 1,500 revolutions per minute. The supernatant plasma was decanted off and the platelets in this plasma per c.mm. enumerated and found to be 190,000 per c.mm. One c.c. of this plasma was added to each of the previously prepared test tubes and recalcified. Then the test was performed in the usual manner.

The second specimen was centrifuged at 3,000 r.p.m. for 15 minutes and the supernatant plasma decanted off and the platelet count found to be 63,000 per c.mm. The same procedure was repeated for this specimen and the results of the two compared (Fig. 5). It will be noted that with the reduction in platelets there has occurred a counterclockwise shift of the curves, indicating a prolongation of the coagulation time.

RESULTS

The results of these two experiments would appear to support the view that our test is a method of indirectly measuring the relative amount of thromboplastin in specimens of blood.

Having established the varied range of coagulability in the normal individual (Fig. 3) when this method is used, the test was carried out on a large number of patients under various circumstances. The results showed some interesting changes, the more important of which

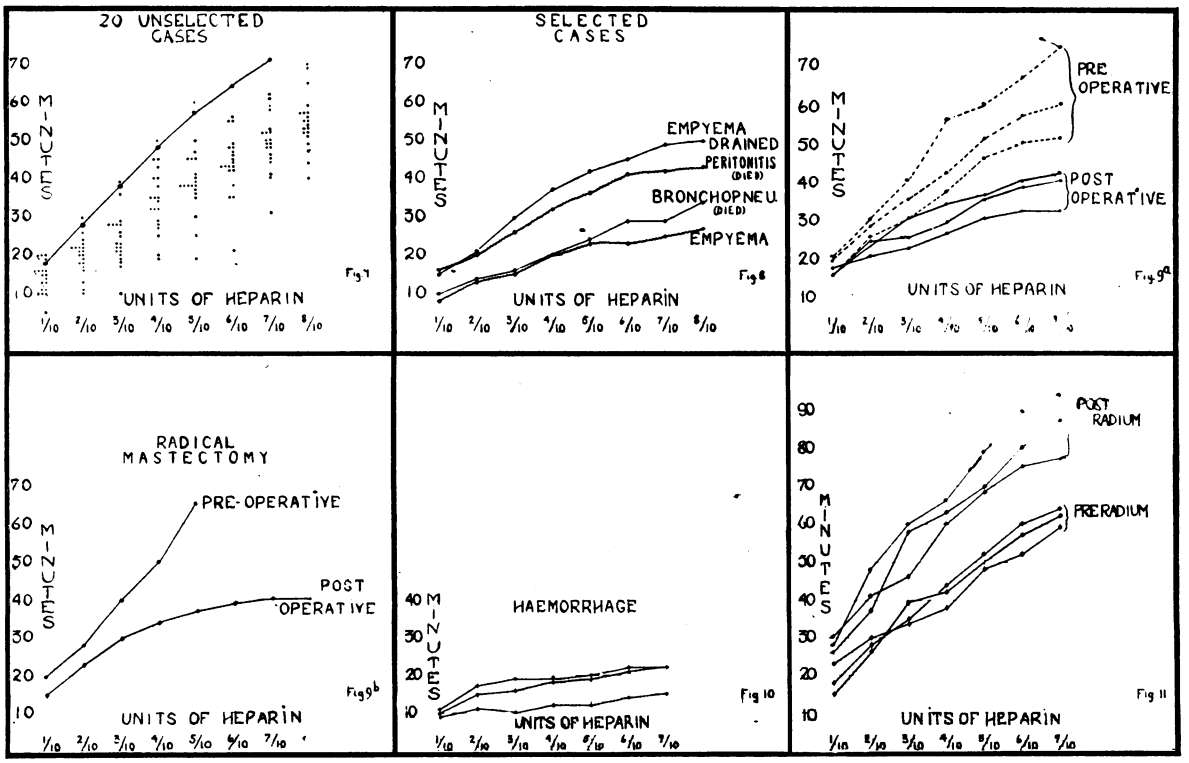

Fig. 7.—Composite results of test on twenty unselected patients confined to bed. Dark line is average of normal individuals. **Fig. 8.**—Acceleration of coagulation as results of infective processes. **Fig. 9a.**—Demonstrating marked clockwise postoperative rotation of graph. **Fig. 9b.**—Demonstrating clockwise postoperative rotation in an individual case. **Fig. 10.**—Marked rotation of graph as result of hæmorrhage. **Fig. 11.**—Counter clockwise rotation as a result of radium therapy—thus slowing of the coagulation rate.

we shall attempt to summarize here under the following headings: (1) bed rest; (2) acute infections; (3) postoperative cases; (4) hæmorrhage; (5) radiation therapy.

While it is well recognized that bed rest predisposes to thrombosis there has been no definite proof that this may be referable to an increased coagulability of the blood under these circumstances. In order to investigate this question three young men under observation for mental disorders (dementia præcox) were chosen for these studies. Tests were performed on each patient after a period of moderate exercise. These compared favourably with those of the normal group and fell within the bounds of normalcy. Then the patients were confined to bed, during which period all privileges were denied, bed trays being supplied for all meals, etc. At the end of three days tests were again performed (Fig. 6) which demonstrated an accelerated coagulation. On the fourth day one individual (Fig. 6a) could be kept in bed no longer and the second (Fig. 6b) became moderately active; the third (Fig. 6c) slept throughout the week. At the end of seven days the tests were repeated (Fig. 6) after which the patients were released for ward routine and outdoor exercise. The blood was examined on the 8th day and this demonstrated a return of the curve of the graph in each case to within normal limits. It will be noted that the rotation of the curves varies somewhat in the different cases and is most marked and persistent in the third patient who maintained complete inactivity throughout the whole period.

Moreover this tendency towards increased coagulability was demonstrable in a large number of patients confined to bed, who were not seriously ill but were admitted to hospital for investigation or previous to minor operations (Fig. 7). The majority of these patients showed a marked clockwise rotation of the curve but in others this rotation was not so pronounced.

It is of course impossible to determine how great a rôle this increased coagulability of the blood during bed rest plays in the associated well recognized tendency to thrombosis, as other factors such as slowing of the blood current may well be equally if not more important. However it is indeed interesting to know that such an accelerated coagulation does occur under these circumstances.

Several individuals suffering from acute localized or generalized infections were examined. They all showed a high degree of clockwise rotation of the curve of their graph indicating acceleration of the coagulation process (Fig. 8). This group includes cases of pneumonia, empyema, peritonitis, abscesses, etc.

In a number of patients in which subsequent operation could be anticipated preoperative and postoperative studies were carried out. Some of these patients were not confined to bed when first examined. Tests were carried out 24 hours after operation and all showed a marked clockwise rotation of the curve of the graph from the previous normal or a slightly accelerated position (Fig. 9a).

In a few cases tests were carried out up to a period of one week postoperatively, during which the marked degree of rotation appeared to be maintained. It would be interesting if finer analysis of this change were studied in order to demonstrate the exact time at which the rotation occurs. As it has been shown that a rise in the platelets occurs after operation it may be that this increase in thrombocytes is a factor in producing this accelerated coagulability.

Three cases suffering from acute exsanguinating hæmorrhage were examined. In all of these the acceleration of coagulation as demonstrated by the curve of the graph was very marked, in fact it was the greatest of any of the patients examined (Fig. 10). This agrees with the generally accepted view that the blood clots more rapidly under such circumstances and may well be due to the fact that the rapid entrance of tissue fluids into the circulating blood in an attempt to maintain volume raises the content of thromboplastin in the plasma to an extremely high level.

An opposite effect apparently occurs during radium therapy. Three patients suffering from carcinoma of the cervix were tested during their course of therapy and each demonstrated a counterclockwise rotation of the curve of the graph, indicating a slowing of the coagulation process (Fig. 11). It would be interesting to know whether a similar change takes place following x-ray therapy but up to the present time such cases have not been examined. Again, the question of how great a rôle the

changes in the number of platelets play in this alteration remains to be settled.

SUMMARY

By means of a specific test whereby finer analysis of the velocity of coagulation is possible it is shown that an acceleration occurs during uncomplicated bed rest, in acute inflammatory conditions, following operation and in the presence of severe hæmorrhage.

Evidence is presented to support the view that the test gives an indirect means of measuring the thromboplastin factor of the process of coagulation and that it is upon an increase of this factor that acceleration depends.

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A SIMPLE OFFICE TEST FOR UTERINE CANCER DIAGNOSIS*

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AN office procedure to enable early diagnosis of uterine cancer is now available. Such a test has been made possible largely by the work of Papanicolaou and Traut,[1] in which the vaginal smear technique is employed. Their results would appear to indicate a fairly high degree of accuracy. This conclusion has recently been corroborated by the work of Meigs *et al.*[2] It has been found in our clinic, and the above-mentioned investigators have also stated, that in many cases intensive study of several slides is required to arrive at the correct diagnosis when the smears are taken directly from the vagina. A simple modification of this technique would appear to render the test more rapid and more efficient. This modification consists in taking the smear directly from the external os of the cervix. Here the concentration of cancer cells is greater. In our series of cases, smears from the vagina were compared with smears from the external os, and in both cervical and fundal carcinoma a much greater concentration of cancer cells was consistently present in the latter group.

The statement that uterine cancer may be accurately diagnosed by the vaginal or cervical os smear probably arouses an initial skepticism in the minds of many. The idea at first glance perhaps appears somewhat far-fetched. It may be the impression of some that the vaginal smears consist only of vaginal epithelial cells scraped off from the vaginal mucosa, and that the diagnosis of cancer is attempted from the morphological and staining characteristics of the vaginal cells themselves. It is difficult to conceive how any diagnosis of uterine cancer could be made from a study of these cells alone. When one considers, however, that the vaginal secretions contain not only vaginal cells but also cells thrown off from the cervix, the endometrium, and the tubal epithelium, the horizon of the diagnostic possibilities might appear to be broadened. Consider, further, that, while the epithelium of the genital tract is normally exfoliated at a certain rate, the cells from a

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