Further Experiences with Blood Coagulation after Fat Meals and Carbohydrate Meals

By JAIME BORRERO, M.D., ERWIN SHEPPARD, PH.D., AND IRVING S. WRIGHT, M.D.

There have been conflicting reports as to whether the ingestion of fat increases the tendency for the blood to clot, and hence, by implication, the risk of thromboembolic complications in man. In this study the effect of a single meal containing a large amount of fat was compared with that of a practically purely carbohydrate isocaloric meal. Under carefully controlled conditions the clotting time varied widely under fasting conditions, and after both fat and carbohydrate meals the clotting time became longer, shorter, or remain unchanged. The results were unpredictable and although a slight trend toward shortened clotting times was evidenced after the fat meals, the results did not reach accepted statistical standards of probability.

In 1949 Duncan and Waldron\(^1\) reported an acceleration of blood clotting time after the oral administration of fat. An original report from this department\(^2\) casts doubt on this finding and it was suggested that the acceleration of clotting may well have been due to deposition of thrombin on the surface of glass syringes when they were reused for successive venipunctures. Then Waldron and Duncan published data that they believed substantiated their original claims.\(^3\)

Buzina and Keys,\(^4\) working with physically healthy men, aged 35 to 60, and using a larger amount of fat, reported a significant shortening of the whole blood coagulation time but no alterations after the ingestion of isocaloric, nonfatty meals. English workers\(^5-12\) have reported on different aspects of this problem.

Hall\(^5\) related clotting variations after a fat meal to platelet preservation and stated that there was no change in blood coagulation when adequate platelet activity was present.

Barkhan, Newlands, and Wild\(^6\) have isolated from human brain tissue a phosphatidylethanolamine that they found to be an accelerator of coagulation. O'Brien\(^9\) believes that behavior of phosphatidylethanolamine and platelets is similar. Studying further the effects of eggs and different fats on blood coagulation,\(^11\) he found a shortening of Stypven clotting times 1\(\frac{1}{2}\) to 2\(\frac{1}{2}\) hours after a meal. There were considerable differences among individuals but no significant differences among different types of fat meals. There is some question whether the Stypven clotting time may actually be measuring the fat in the blood rather than an actual change in the clotting mechanism.

MacLagan and Billimoria\(^12\) reported definite shortening of the clotting time after feeding 2 ounces of fat food, the maximal effects taking place 4 to 6 hours after a test meal.

Because of the opposing conclusions reached by different investigators and because Buzina and Keys\(^4\) believed they found statistically significant support of acceleration of clotting times with a fat meal after re-analysis of the data of Tulloch, Overman, and Wright,\(^2\) it was decided to try to reproduce as closely as possible the work of Buzina and Keys and to evaluate the results.

METHODS

Blood was withdrawn from an arm vein with siliconized syringes and 20-gage needles. If there was any difficulty in obtaining blood, a new venipuncture was done in the opposite arm with a new needle and a new syringe. A stopwatch was started as soon as blood entered the syringe. The tourniquet was kept in place no more than 60 seconds. One milliliter of blood was added to

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From the Vascular Section of the Department of Medicine, Cornell University Medical College-New York Hospital, New York, N. Y.

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BLOOD COAGULATION AFTER FAT AND CARBOHYDRATE MEALS

Fig. 1. Variation of clotting times under fasting conditions.

For the whole-blood clotting time, 1 of the siliconized tubes was tilted every 60 seconds starting at the end of 9 minutes from the time of blood withdrawal until clotting occurred, at which time tilting of the second tube was similarly started. When clotting occurred in the second tube, tilting of the third and fourth tubes was started simultaneously, and the average clotting time for the third and fourth tubes (computed from the time of blood drawing) was taken as the final clotting time.

The studies were conducted in 3 separate series. 1. Three healthy males, aged 27, 28, and 29 years, were tested in the fasting state. Blood was drawn and clotting time determined according to the above technic, and repeated twice in the same morning at hourly intervals. Nothing was taken orally throughout the experiment. This test was repeated twice on different days for each individual. The object of this series of tests was to determine the variations of clotting times in the same individual from test to test on the same day without food and also on different days. 2. Nineteen healthy individuals, aged 19 to 30 (13 men and 6 women) were then tested. The subjects ingested a test meal of 300 ml. of 40 per cent butterfat cream totaling 1,080 calories after the control blood samples were withdrawn. Blood samples were drawn at 1.0, 2.0, 3.5, 4.5, and 5.5 hours after the meal. According to Buzina and Keys’ routine, the experiments were repeated with the same subjects, after a meal that provided 964 calories but only 0.15 Gm. of fat. This low-fat, high-carbohydrate meal consisted of cooked rice, table syrup, grape juice, lactose, and marshmallows. 3. Finally, 10 individuals, aged 35 to 70, were tested in the same manner with the fat meal and the carbohydrate meal.

RESULTS

Recorded in figure 1 are the clotting times measured under fasting conditions. The variation for clotting times in the same individual during the same day ranged from 7 minutes to 31 minutes between the first and the third sample. Variations in the same individual for different days ranged from 20 minutes to 33 minutes. In contrast with the report of Buzina and Keys, our clotting times during continued fasting were either longer or shorter than the initial one.

Table 1.—General Statistical Analysis

<table>
<thead>
<tr>
<th>Hours</th>
<th>1</th>
<th>2</th>
<th>3.5</th>
<th>4.5</th>
<th>5.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>+0.310</td>
<td>+5.414</td>
<td>+0.828</td>
<td>-2.378</td>
<td>+3.621</td>
</tr>
<tr>
<td>Fat-carbohydrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.E.</td>
<td>2.748</td>
<td>3.221</td>
<td>2.814</td>
<td>3.038</td>
<td>2.507</td>
</tr>
<tr>
<td>t</td>
<td>0.113</td>
<td>1.681</td>
<td>0.294</td>
<td>0.783</td>
<td>1.444</td>
</tr>
<tr>
<td>p</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

tp 0.1 = 1.70, tp 0.05 = 2.05, tp 0.01 = 2.76. N.S. = No significance.

The variation of clotting times of samples from each individual were calculated first after fat meals and then after carbohydrate meals, by subtracting the values found at the 1, 2, 3.5, 4.5, and 5.5 hours from the corresponding fasting value. Plus (+) signs indicate shortening and minus (−) signs lengthening. When the + or − variations were calculated for the whole group, the mean was found for the values at the 1, 2, 3.5, 4.5, and 5.5 hour levels after the test meals and the difference between the fat and carbohydrate values was calculated.

Because no appreciable difference was found in the age groups of 19 to 30 and 35 to 70, the experiments were analyzed to include a total of 29 patients. Statistically significant acceleration of the clotting times after a high-fat meal was not found. The maximal effect was at the end of the second
hour but this did not reach the 10 per cent level of statistical probability.

Our next step was to analyze the data by means of a paired contingency table. For the contingency table the responses were classified as positive, negative, or unchanged. The designation "unchanged" did not mean that the readings were identical but rather that they fell within the limits of variation inherent in the technic. The inherent variation, determined from the differences between duplicates, was found to be approximately plus or minus 4 minutes.

Table 2 shows the results with the average responses at 3.5, 4.5, and 5.5 hours after meals. After a fat meal the blood of 14 individuals showed a positive response, i.e., a decrease in clotting times, and 5 an increase or negative response. After the isocaloric carbohydrate meal, a total of 12 individuals had a positive response (shortening) and 6 a negative one (lengthening). A sign test was applied to the results, for both fat and carbohydrate, those individuals being disregarded whose clotting times were unchanged by their test meals when compared to their fasting times.

Here again there was no statistically significant difference between the changes induced by fat and those produced by carbohydrate. As in our original statistical presentation (table 1), the sample that showed the nearest approach to statistical significance was at the second hour. The results with a paired contingency table were also analyzed (table 3). A total of 16 patients showed a decrease in clotting times following a fat meal. Four showed an increase.

### Table 2.—Fat Action on Blood Clotting: Average Response at 3½-4½-5½ Hours

<table>
<thead>
<tr>
<th>Change</th>
<th>Fat</th>
<th>Positive</th>
<th>Unchanged</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Unchanged</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>10</td>
<td>5</td>
<td>29</td>
<td></td>
</tr>
</tbody>
</table>

Sign test for fat action, +3.36; sign test for carbohydrate action, +1.36.

### Table 3.—Fat Action on Blood Clotting—Second Hour

<table>
<thead>
<tr>
<th>Change</th>
<th>Fat</th>
<th>Positive</th>
<th>Unchanged</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Unchanged</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>9</td>
<td>4</td>
<td>29</td>
<td></td>
</tr>
</tbody>
</table>

Sign test for fat action, +6.05; sign test for carbohydrate, +0.36.

Following carbohydrate meals, 10 showed a decrease compared with their fasting clotting times and 11 an increase. In this experiment the sign test showed a statistical significance between the 5 per cent and the 1 per cent level after the fat meal. The apparent discrepancy between the statistical data in table 1 and table 3 is a function of the characteristics of the different tests employed. Table 1 presents the results of analysis by means of the t test, a measure of degree of change. In table 3 the data presented are the result of application of the nonparametric sign test, a measure of direction of change only. Thus table 1 represents a slightly more efficient evaluation and while the values at the end of 2 hours approach significance, the criteria of significance are not achieved. When the first series of individuals, 19 to 30 years old, were tested, heparin tolerance tests, Stypven clotting times, prothrombin times, and thrombin generation tests were done in the first 10 individuals but abandoned thereafter because no changes were found.

### Discussion

Because of the important and controversial issue involved, special care was taken in the conduction of the present study. Subjects were selected for their willingness to cooperate and the presence of good veins suitable for adequate venipuncture.

The small group of 10 subjects aged 35 to 70 were ambulatory hospital cases, without evidence of metabolic disturbances, liver disease, gastrointestinal pathology, or renal
disease. They were included in the general group because it was found that they showed the same response after fat and carbohydrate tests meals as that of the younger group composed of medical and nursing students.

There was a great variability in the fasting clotting times among subjects and also in the same subject for different samples in the same day and for different days.

We agree with O'Brien,10 that there is considerable difference among individual responses to a fat meal just as there is in responses to a carbohydrate meal.

The maximal shortening of coagulation time after a meal was found to occur at the end of 2 hours after the test meal. Comprehensive statistical analysis demonstrated that this showed only a 10 per cent rate of probability. This is below the limits of statistical standards and cannot be accepted as a demonstration of significant response.

SUMMARY

The results of studies of changes in the coagulation time after a fat and a carbohydrate test meal ingested by 29 subjects are presented. It was found that the whole blood clotting times in siliconized tubes following the Lee-White method as modified by Buzina and Keys varied from individual to individual and in the same subject during the course of one day and from one day to another. Although there seems to be a slight trend toward shortening of clotting times following a standard fat meal, the results do not reach accepted statistical standards of probability. These experiments fail to confirm or deny the claim that fat ingestion accelerates to a significant or consistent degree the whole blood clotting time. A similar inconclusive trend toward shortening of the clotting time was observed following the ingestion of a carbohydrate meal in a substantial proportion of the tested individuals. Additional studies including the Stypven clotting time, heparin tolerance, prothrombin time, and thrombin generation, failed to show any trend toward increased speed of clotting. While these studies fail to demonstrate that the ingestion of a meal containing a large amount of fat encourages intravascular clotting, it is recognized that all existing methods of investigation of this mechanism are relatively crude and that such a possibility exists through a system not yet discovered.

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SUMMARIO IN INTERLINGUA

Es presentate le resultatos de studios relative al alterationes del tempores de coagulation post repastos experimental de grassia e de hydratos de carbon ingerite per un serie de 29 subjectos. Esseva constataque le tempores del coagulation de sanguine integre in tubos a revestimento de silicona, determinate secundo le metodo de Lee-White in un modification per Buzina e Keys, variava ab un individuo al altore e in le mesme individuo ab un die al altere e in le curso del mesme die. Ben que il pare exister un leve tendentia verso acelerate tempores de coagulation post repastos standard a grassia, le resultatos non satisface le acceptate standards statistic de probabilitate. Iste experimentos non confirma e non denega le assertion que le ingestion de grassia accelerara a grados significative e de manera uniforme le coagulation de sanguine integre. In un proportion considerabile del individuos studiate, un simile tendentia inconclusive esseva observate in le acceleration del coagulation post le ingestion de repastos a hydratos de carbon. Studios additional—incluse le tempore coagulatori de Stypven, le tolerancia de heparina, le tempore prothrombinic, e le generation de thrombina—non revelava ulle tendentia verso un acceleration del processo coagulatori. Durante que iste studios non demonstra que le ingestion de repastos a alte contento de grassia promove le coagulation intravascular, il debe esser recognoscite que omne le exist-
ente methodos pro le investigation de iste mechanismo es relativemente crude. Il remane possibile que le phenomeno in question va esser demonstrate per medio de un systema non ancora discoperite.

REFERENCES


Borrero, Sheppard, AND Wright


The diagnostic features of myxoma of the left atrium are discussed and illustrated by the histories of 2 patients recognized during life and confirmed by surgery and autopsy. Characteristic findings include a past history of variable signs and symptoms, readily influenced by changes in posture and rapid progression of heart failure not responding to the usual therapy. Fluoroscopically forceful esophageal pulsations may be observed at the level of the left atrium. If the atrial tumor is large enough, cardiac catheterization reveals pressure elevation in the right ventricle and in the pulmonary artery. In the pulmonary wedge-pressure curve an early positive deflection replaces the normal dip during ventricular systole. Finally angioecardiography reveals a filling defect within the shadow of the atrium.

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