PLASMA FIBRINOLYSIS IN MAN: THE EFFECT OF CHYLOMICRONS DERIVED FROM DIFFERENT DIETARY FATS* †

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In 1955 Fearnley and Lackner (2) demonstrated the presence in human plasma of "spontaneous fibrinolysis." They reported that this activity was thermodilable, that dilution of the plasma increased its degree, and that either exogenous epinephrine or mild exercise resulted in increased activity (1, 2). A previous study from this laboratory reported significant inhibition of such fibrinolysis after ingestion of liquid meals containing large amounts of butterfat (3). These observations were in agreement with the data of Greig which showed that ingestion of meals containing certain mixed animal fats inhibited fibrinolysis (4). Subsequent reports by Nitzberg and coworkers (5), Billimoria and coworkers (6), and Buckell and Elliott (7) supported these conclusions. Although our observations were restricted to a single dietary fat, the results indicated that the chylomicrons of human plasma were solely responsible for the observed inhibition.

The purposes of the present study were to quantify more completely the observations of our initial study, to observe the effects of two additional natural fats on plasma clot lysis using a modification of our original system, and to examine the fatty acid composition of the dietary fats and of the chylomicrons that appear in the blood stream after ingestion of these fats. The dietary lipids used (butterfat, egg yolk, and safflower oil) were distinctly different in fatty acid composition and in many other respects, including iodine number (40, 76, 141), sterol (2.8, 4.0, 0.2 per cent), and phospholipid (11, 26, <0.1 per cent), and served as representative samples of commonly ingested fats. In addition, their great divergence in composition allowed a broader test of the possibility

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† This term was suggested by Fearnley in his latest publication (1) to designate the "natural" fibrinolytic activity of the plasma of normal subjects in contrast to the fibrinolysis which may be induced by agents such as streptokinase or urokinase.

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that dietary fats differ in their effect on fibrinolysis. Indeed, the report of Greig and Runde (8) suggested that the nature of the ingested fat influences the type of response. These authors reported that butterfat or egg yolk usually inhibited fibrinolysis, whereas sunflower seed oil, Arachis (peanut) oil, and coconut oil usually increased fibrinolysis. In their studies, however, these fats were fed in different amounts and their effects were not correlated with changes in serum lipids. Reasons for the differences in the effect of these fats were therefore not clearly evident from their experiments.

As a first step in the extension of these studies, the experiments reported in our first communication (3) were repeated and expanded to include observations on the effect of safflower oil (see part A under Experimental Procedure). Additionally, in order to study the inhibitory phenomenon more completely, the ultracentrifugal procedure used in part A was modified, permitting isolation of the chylomicron fraction largely free of other lipoprotein constituents of plasma. Varying amounts of these "washed" chylomicrons were added to plasma drawn shortly after its fibrinolytic activity had been stimulated in vivo by prior administration of epinephrine to a subject, and the fibrinolytic activity of the plasma was then measured (part B under Experimental Procedure). This method allowed us to reproduce in vitro a range of concentrations of chylomicrons encompassing that expected during all phases of alimentary lipemia.

Also, the fatty acids of both the triglycerides and the phospholipids of the chylomicron were analyzed by gas-liquid chromatography in order to examine some of the many factors which might be responsible for their inhibitory action (see part C).

EXPERIMENTAL PROCEDURE

A. Comparison of the Effect of Ingestion of Butterfat and Safflower Oil on "Spontaneous" Fibrinolysis.—Twenty-five experiments were performed on plasma from 8 healthy young males; blood was drawn from these subjects both following a 12 hour fast and 4 hours after ingestion of their designated formula. The ingested meals (either butterfat or safflower oil) contained 1.5 gm. of triglyceride/kg. of body weight. All formula feedings were equated in volume and in content of protein, carbohydrate, and fat. Protinex® was the protein supplement added to the safflower formula, and sucrose was used to supplement both the egg yolk (see part B) and the safflower oil formulas.

The formulas were ingested between 3 and 4 a.m., and venesection performed 4 hours later. The blood was drawn into sterile siliconized precooled syringes and immediately transferred to an ice-cooled Erlenmeyer flask for 2 to 3 minutes, then centrifuged for 5 minutes at 27,500 r.p.m. (50,000 G) in the No. 40 rotor of a Spinco model L refrigerated ultracentrifuge. This step separated the plasma into a clear bottom fraction and a turbid top fraction containing chylomicrons. Immediately after centrifugation the lower one-half of the plasma (fraction II) was removed by aspiration with a needle and syringe. The residual turbid plasma

© National Drug Company, Philadelphia; composition, 61.25 per cent protein and 30 per cent carbohydrate.
(fraction I) was then removed, and the turbid material homogeneously dispersed by ejecting the plasma through a No. 24 hypodermic needle. A series of 40 siliconized tubes (15 X 100 mm.) were partly filled with 2.4 ml. of solution of 0.04 M veronal buffer (pH 7.4) containing 0.04 M CaCl₂. 0.1 ml. of fraction I was added to 20 of the tubes, and 0.1 ml. of fraction II to the remaining 20. The contents of each tube were mixed with individual roughened glass stirring rods. The tubes (with rods in place) were transferred to a 38° water bath, where clotting occurred on the rods within 20 minutes. After a total of 40 minutes of incubation, duplicate or triplicate measurements of fibrinolytic activity were made at timed intervals.

Fibrinolytic activity was measured by the method of Fearley and Lackner (2), and residual clot protein was measured by the method of Folin and Ciocalteu (9). The end point of clot lysis was defined as the time when clot fragmentation first begins in tubes of either fraction I or II. The percentage of the original clot lysed was calculated by comparison of amount of protein remaining on the glass stirring rod at the final incubation time with the protein content of the initial (40 minute) sample.

Lipid determinations were performed as follows: total cholesterol was measured by the method of Abell et al. (10), phospholipids by the method of Stewart and Hendry (11), and total lipids by the method of Bragdon (12). Plasma triglycerides were calculated by the method of Bragdon (12); in these calculations a free cholesterol/total cholesterol ratio of 0.27 was assumed, and lipid phosphorus was converted to phospholipid by use of the factor 25.

Fraction II, the “chylomicron-poor” fraction, was considered a control because it allowed comparison of lysis rates (during both dietary states of fasting and postprandial lipemia) of two plasma fractions which differed only in their content of chylomicrons. This control was necessary because individuals vary considerably in the fibrinolytic activity of their plasma when this is measured at different times (2, 6, 13), and since variations can be expected as a result of physical exercise (2, 6).

B. Comparison of the Action of Aqueous Suspensions of Purified Chylomicrons on the Fibrinolytic Activity of the Plasma of a Single Individual.—Eight studies were performed. All steps from time of venesection to the beginning of the fibrinolysis assay were completed within 90 minutes, and during this period, glassware and solutions (including blood and plasma) were kept between 0° and 4°C. Chylomicrons were isolated from the lipemic blood of 6 normal young male students following ingestion of butterfat, safflower oil, or egg yolk formulas (see part A). The chylomicrons were obtained by a method which differs from the technique used in part A. Whole blood (13.5 ml.) was first centrifuged for 30 minutes at 40,000 G in a No. 40 rotor of a Spinco model L ultracentrifuge. The visibly turbid top 2 ml. of plasma was then aspirated from the lusteroid tubes, layered under 0.04 M veronal buffer,² and re-centrifuged in the No. 40 rotor for 20 minutes at 20,000 G. The top 2 ml. from each tube was aspirated and suspended (after forceful ejection through a No. 24 needle to insure emulsification) in the veronal buffer. An aliquot was removed and saved for subsequent analysis of total lipid (12), total cholesterol (10), and phospholipid content (11).

Simultaneously with the preparation of the purified chylomicrons of the fed subject (the “donor”), plasma from a second normal subject (the “recipient,” a 30 year old male) was prepared. The recipient was given 0.5 mg. of epinephrine hydrochloride subcutaneously 30 minutes before venesection to increase plasma fibrinolytic activity (2).

A 0.1 ml. aliquot of the recipient plasma was pipetted in triplicate into each of a series of 15 X 100 ml. siliconized glass test tubes. Then 2.4 ml. of a suspension of chylomicrons in veronal buffer was added and mixed with the plasma. The amounts of chylomicron lipid added ranged in final concentration from 0 to 750 mg. total lipid per 100 ml. of recipient plasma.

² Containing 0.04 M CaCl₂.
Assays of plasma fibrinolytic activity were then performed as in part A.

C. Determination of the Fatty Acid Composition of the Chylomicrons.—After the studies on fibrinolysis were completed, one of the “donors” was refed the three formulas on 3 separate days; the chylomicrons were isolated by the method described in part B. The fatty acids of the chylomicrons were then analyzed by gas-liquid chromatography (14).

The lipids of the chylomicrons were first extracted and freed of non-lipid contaminants by the technique of Folch and associates (15). The lipid extract was brought to dryness under reduced pressure in a rotary evaporator, reextracted in petroleum ether (b.p. 60 to 70°F.), and separated into a non-phospholipid fraction (A) and a phospholipid fraction (B) by adsorption onto 10 g. of silicic acid, followed by extraction with three 25 ml. volumes of redistilled ethyl ether (A), then by three 25 ml. volumes of redistilled absolute methanol (B). The technique followed the principles outlined for column chromatography by Hirsch and Ahrens (16) but was adapted to the needs of this study in the above simplified fashion.

### TABLE I

*Average Percentage Clot Lysis of Plasma Fractions I and II of Normal Subjects*

Measurements after fasting and after high fat meals.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>Percentage of clot lysis</th>
<th>Difference (Fr. II − Fr. I)</th>
<th>Percentage inhibition of lysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Fr. I*</td>
<td>Fr. II</td>
<td></td>
</tr>
<tr>
<td>I. Fasted 12 hrs.</td>
<td>8</td>
<td>20.1</td>
<td>20.3</td>
<td>0.2</td>
</tr>
<tr>
<td>II. 4 hr. postprandial (1.5 gm. butterfat per kg. body weight)</td>
<td>8</td>
<td>10.5</td>
<td>31.0</td>
<td>20.5‡</td>
</tr>
<tr>
<td>III. 4 hr. postprandial (1.5 gm. safflower oil per kg. body weight)</td>
<td>9</td>
<td>10.0</td>
<td>24.5</td>
<td>14.5‡</td>
</tr>
</tbody>
</table>

* Top fraction of plasma after ultracentrifugation (“chylomicron-rich” fraction).
‡ Difference significant at p < 0.001.

Separation of the major lipid classes was, however, identical with that achieved with the column method. The fatty acids of these two fractions were then interesterified with methanol and the resultant methyl esters identified and their relative amounts calculated by gas-liquid chromatography (14). Aliquots of the three dietary lipids were similarly analyzed.

### RESULTS

**A. Comparison of the Fibrinolytic Activity of Plasma Following Ingestion of Safflower Oil and Butterfat.—** As can be noted in Table I, the rate of clot lysis of fraction I (containing chylomicrons) was consistently less than that of

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4 When derived from a lipid extract of chylomicrons, this fraction contains primarily triglyceride (see Results); however, the small amounts of free cholesterol and cholesterol esters present in chylomicrons are included in this fraction.

4 Activated by oven heating for 6 hours at 100°F. See reference 16 for data on type of silicic acid used.
fraction II (optically clear) in both the butterfat and safflower oil experiments. The differences between fraction I and fraction II were highly significant ($p < 0.001$). In contrast with this result, the plasmas of fasting subjects showed no significant differences in the rates of lysis of fractions I and II (Table I). Usually both fractions I and II were optically clear in the fasted subjects; in a few cases a slight turbidity was seen in fraction I.

The lipids of fraction I and II were also determined (Table II). With fasted subjects no significant difference in lipid composition was found. However,

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>Plasma fraction</th>
<th>Total lipid*</th>
<th>Total cholesterol*</th>
<th>Phospholipid*</th>
<th>Calculated triglyceride*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Fasted 12 hrs.</td>
<td>8</td>
<td>I</td>
<td>626</td>
<td>209</td>
<td>254</td>
<td>69</td>
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<tr>
<td></td>
<td></td>
<td>II</td>
<td>614</td>
<td>212</td>
<td>251</td>
<td>50</td>
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<tr>
<td></td>
<td></td>
<td>Difference</td>
<td>12</td>
<td>-3</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>II. 4 hr. postprandial (1.5 gm. butterfat per kg. body weight)</td>
<td>8</td>
<td>I</td>
<td>875</td>
<td>222</td>
<td>305</td>
<td>275</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II</td>
<td>744</td>
<td>222</td>
<td>290</td>
<td>165</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference</td>
<td>131</td>
<td>0</td>
<td>15</td>
<td>110</td>
</tr>
<tr>
<td>III. 4 hr. postprandial (1.5 gm. safflower oil per kg. body weight)</td>
<td>9</td>
<td>I</td>
<td>778</td>
<td>218</td>
<td>265</td>
<td>256</td>
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<tr>
<td></td>
<td></td>
<td>II</td>
<td>653</td>
<td>215</td>
<td>255</td>
<td>148</td>
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<tr>
<td></td>
<td></td>
<td>Difference</td>
<td>125</td>
<td>3</td>
<td>10</td>
<td>108</td>
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</tbody>
</table>

* Values in mg./100 ml.

after feeding either butterfat or safflower oil the concentration of total lipid and of triglycerides was significantly higher in fraction I ($p < 0.001$). The increased amount of total lipid in fraction I over that of fraction II consisted of 84 per cent triglyceride in the butterfat group, and 86 per cent in the safflower group; these data are consistent with the percentage triglyceride composition of chylomicrons as determined by Bragdon et al. (17) and by Laurell (18) and supported our assumption that fractions I and II differed in lipoprotein content mainly by the presence of chylomicrons in fraction I.

B. Comparison of the Effect of Purified Chylomicrons from Three Different Dietary Sources on Plasma Fibrinolysis.—The results of the eight experiments are summarized in Fig. 1, for butterfat (three experiments), Fig. 2, for safflower oil (two experiments), and Fig. 3, for egg yolk (three experiments). A com-
Fig. 1. Effect of the *in vitro* addition of chylomicrons derived from butterfat on the fibrinolytic activity of epinephrine-stimulated plasma.

Each solid point on the graph represents the result of a single experiment. The percentage lysis which occurred between added lipid levels of 0 to 75 mg./100 ml., 75 to 200 mg./100 ml., and 400 to 700 mg./100 ml. were averaged and plotted as open circles.

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Fig. 2. Effect of the *in vitro* addition of chylomicrons derived from safflower oil on the fibrinolytic activity of epinephrine-stimulated plasma.

Each solid point on the graph represents the result of a single experiment. The percentage lysis which occurred between added lipid levels of 0 to 75 mg./100 ml., 75 to 200 mg./100 ml., and 400 to 700 mg./100 ml. were averaged and plotted as open circles.

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Composite of the data in the three figures is presented in Fig. 4. In each of these figures the percentage of inhibition of lysis is plotted against the mg./100 ml. of added chylomicron total lipid. The percentage lysis which occurred between added lipid levels of 0 to 75 mg./100 ml., 75 to 200 mg./100 ml., and 400 to
Fig. 3. Effect of the in vitro addition of chylomicrons derived from egg yolk on the fibrinolytic activity of epinephrine-stimulated plasma.

Each solid point on the graph represents the result of a single experiment. The percentage lysis which occurred between added lipid levels of 0 to 75 mg./100 ml., 75 to 200 mg./100 ml., and 400 to 700 mg./100 ml. were averaged and plotted as open circles.

700 mg./100 ml. were averaged and plotted. In each instance the percentage inhibition of fibrinolysis was calculated by comparison with the rate of lysis of an aliquot of "recipient" plasma which contained no added chylomicrons, but which was diluted to the same extent with veronal buffer.

The lipid composition of the "donor" chylomicrons was similar for each
of the three types of dietary fat and the average of all the experiments was as follows: total cholesterol, 8.7 per cent (range 2.6 to 11.8), phospholipid, 15.7 per cent (range 12.8 to 18.1), and triglyceride, 75.6 per cent (range 70.1 to 84.6).

TABLE III
Fatty Acid Composition of Chylomicrons and of the Dietary Fats

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>10:0</th>
<th>12:0</th>
<th>14:0</th>
<th>14:1</th>
<th>15:0</th>
<th>15:0 br</th>
<th>16:0</th>
<th>16:1</th>
<th>17:0 br</th>
<th>18:0</th>
<th>18:1</th>
<th>18:1 iso</th>
<th>18:2</th>
<th>18:3</th>
<th>20:2 to 22 unsaturated</th>
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<tr>
<td>Butterfat</td>
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<td>&quot;Donor&quot; chylomicrons</td>
<td>1.6</td>
<td>1.7</td>
<td>7.0</td>
<td>1.2</td>
<td>1.3</td>
<td>1.2</td>
<td>31.9</td>
<td>5.2</td>
<td>1.0</td>
<td>11.2</td>
<td>31.3</td>
<td>3.2</td>
<td>4.1</td>
<td>1.1</td>
<td>1.2</td>
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<tr>
<td>Ingested fat</td>
<td>4.3</td>
<td>2.2</td>
<td>9.6</td>
<td>1.0</td>
<td>1.4</td>
<td>1.0</td>
<td>30.9</td>
<td>1.9</td>
<td>1.8</td>
<td>9.6</td>
<td>14.4</td>
<td>1.5</td>
<td>2.1</td>
<td>1.0</td>
<td>0.0</td>
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<td>&quot;Donor&quot; chylomicrons</td>
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<td>Egg yolk</td>
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<td>Ingested fat</td>
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</table>

* Components which comprise less than 1.0 per cent of the total were omitted.

† The number preceding the colon is the number of carbons of the molecule; that following the colon indicates the number of double bonds of unsaturated acids; br refers to branching of the aliphatic chain. iso refers to positional or geometric isomers of the common unsaturated acids; for example, 18:1 is oleic acid, 18:1 iso is elaidic acid.

§ Fraction A from silicic acid, containing primarily triglycerides.
¶ Fraction B from silicic acid, containing phospholipids.
¶¶ The phospholipid content of safflower oil was <0.1 per cent.

The data of part B (Figs. 1 to 3) reveal that chylomicrons of the three types all inhibit fibrinolytic activity to a comparable degree, and that the inhibition is well correlated with the concentrations of chylomicrons. Comparison of the composite data (Fig. 4) by the method of least squares similarly indicated that the slopes of the lines obtained by plotting percentage lysis inhibition against the amount of added lipid were statistically indistinguishable at the 5 per cent confidence level. On substitution of the amounts of added phospholipid, triglyceride, or cholesterol for total lipid, a similar, approximately linear relation-
ship was obtained. Again, no difference in these slopes could be detected by the method of least squares when the butterfat, safflower oil, and egg yolk data were compared.

C. Comparison of the Fatty Acids of the Chylomicrons with those of Fed Fat.—Although the dietary fats differed widely from each other (Table III), fractions A and B of a single fat were virtually identical in composition. The phospholipid content of safflower oil was too low (<0.1 per cent) to allow isolation of a fraction B. Table III demonstrates that the fatty acid composition of the triglycerides and sterol esters (fraction A) of the chylomicrons closely resembled the composition of the fatty acids of the fed fat.

The close correspondence of chylomicron fraction A fatty acids to dietary fatty acids are in accord with the data recently reported by Bragdon and Karmen (19). Their report, however, did not include the step of preliminary separation of lipid classes by silicic acid.

Fraction B (phospholipids) of the chylomicrons contained a different pattern of fatty acids after each dietary feeding, and in each instance the difference reflected the composition of the fed fat. However, the similarity of composition was less striking than that present between fraction A chylomicrons and dietary fats.

DISCUSSION

The in vitro inhibition of fibrinolysis after ingestion of fat reported in these experiments raises the questions of whether this phenomenon occurs in vivo, and whether the inhibition of this activity disturbs the equilibrium between deposition and lysis of fibrin on vascular intima. Both questions are relevant to the possibility that “abnormal” deposition of fibrin is an early and prerequisite step in atheroma formation (20–22). Our data permit some comments only in regard to the first question.

The likelihood of a significant effect of fat ingestion on fibrinolysis in vivo cannot be estimated without evaluating the conditions of measurement. Many methods have been designed to assay certain limited aspects of the complex reactions that comprise the entire phenomenon of fibrinolysis. Some are designed to measure either the fibrinolytic enzyme of plasma (plasmin or fibrinolysin) (23) or some of its known plasma protein inhibitors (24). Other methods have been devised to assay either the amount of the inactive form of plasmin (plasminogen) (25) or of activators of this proenzyme (25). In addition, either casein (26) or synthetic esters (27) have been used successfully to replace the usual substrate of plasmin (fibrin), partly to increase precision of analysis. Unfortunately, since timing the exact beginning of clot fragmentation is difficult, our methods do not allow as precise an endpoint as do some others. Although the plasma is diluted in buffer, all the components of plasma which influence fibrinolysis in vivo are present in our system in vitro. In addition, our use of low temperatures in all steps preceding clot incubation prevented the loss of activity that Fearnley and Lackner noted when these steps were per-
formed at room temperature (2). It seems probable then that systems such as ours are likely to include all of the many factors of the fibrinolytic system which participate in vivo.

It is interesting to speculate how chylomicrons inhibit fibrinolysis. Our studies demonstrate that each of the three types of chylomicrons inhibit fibrinolysis to a similar degree despite profound differences in the triglyceride fatty acids and despite less striking but considerable differences in phospholipid fatty acids. If current concepts of chylomicron structure are correct, however, the fatty acids of both the phospholipids and triglycerides are primarily in the inner lipid "core" and are covered by a thin coating of protein and by the polar moieties of the phospholipids. If the chylomicron interferes with clot lysis, further studies should logically be devoted to the properties of these latter substances.

CONCLUSION

The plasma fibrinolytic activity, measured in vitro, of 17 healthy normal young males was consistently and equally inhibited by prior ingestion of equal amounts of either a relatively saturated animal fat (butterfat) or a highly unsaturated vegetable fat (safflower oil).

This effect was further studied by the addition of purified chylomicrons derived from ingestion of either butterfat, safflower oil, or egg yolk to an in vitro system. The inhibitory effect was quantitatively similar in all experiments despite wide variations in composition of the fed fat and pronounced differences in fatty acid composition of the lipids of the chylomicrons.

It seems reasonable to suggest from our data that the proteins and the non-fatty acid portions of the chylomicron phospholipids may be important determinants of the inhibitory effect of chylomicrons on fibrinolysis.

BIBLIOGRAPHY