Effects of Meals of Different Fats on Blood Coagulation

By Ancel Keys, Ratko Buzina, Francisco Grande, and Joseph T. Anderson

Previous work has shown that a high-fat meal produces an increased coagulability of the blood. This fact is of interest in view of the effects of dietary fat on the serum cholesterol and its association with coronary disease. Since fats containing large amounts of unsaturated fatty acid tend to reduce the serum cholesterol rather than increase it, it is important to examine the effects of fats with different fatty acid composition on blood coagulation. Comparisons are presented of the effect on blood coagulability of feeding butterfat, corn oil, hydrogenated coconut oil, and a marine fish oil.

RECENTLY we reported on the increased coagulability of blood after a fat meal. That the effect was due to the ingested fat was shown by the fact that no shortening of the coagulation time occurred in the same individuals after eating a nonfat meal of equal caloric content or after continuing fasting. In fact, in both these conditions the coagulation time tended to be slightly prolonged in comparison with the control (pre-meal) blood sample.

MATERIALS AND METHODS

Fats. In previous experiments we used butterfat and the question arose as to whether other fats provoke a similar response. The present paper presents the findings from a new series of experiments with corn oil, hydrogenated coconut “oil” (actually a soft solid), and sardine oil as well as with butterfat. These oils were selected to represent great diversity in the constituent fatty acids. In terms of degree of saturation of the fatty acids, the experimental fats and oils range from hydrogenated coconut oil (Hydrol*) with an iodine number (Hanus) of 2.5 to sardine oil with a value of 185. The iodine numbers of butterfat and of corn oil are 38 and 120 respectively.

Subjects. Twelve schizophrenic men aged 35 to 60 years were subjects in 5 experiments, 1 each of the 4 fats and 1 with a carbohydrate meal. They were long-time patients in the Hastings State Hospital but were physically healthy and considered to be metabolically “normal.” All of them were cooperative, stabilized in their mental illness, and were accustomed to venepunctures. Four of the men had been subjects in the previously reported studies with butterfat. Before and between experiments they subsisted on the standard diet of the hospital, which provides, on the average, about 40 per cent of the calories in the form of fats and is in other respects similar to average “good” American diets.

Procedure. The experiments were started in the morning. The men had their usual meals the night before and they arose and made their toilets but breakfast was withheld. They walked slowly to the metabolic laboratory where they spent the next 6 or 7 hours sitting or standing about, neither indulging in exercise nor showing any excitement. The venepunctures were made in a vein in the antecubital fossa with the subjects quietly seated. After the pre-meal venepuncture, each subject rapidly (within 2 to 8 minutes) “ate” the meal comprising 120 Gm. of the fat emulsified in a half homogenizer with skim milk to make a volume of 300 ml. The carbohydrate meal consisted of about 1080 calories of boiled rice and sugar with about 200 ml. of skim milk. All of the men readily took the meals except for 2 who could not be persuaded to swallow the sardine oil emulsion.

Venepunctures were made before and at 4 and 5 hours after the meal with siliconized syringes and needles treated with Arquad,† which is a cationic agent that inhibits clotting on the surface so treated. In the few cases where a clean puncture of the vein was not achieved rapidly, a new puncture was made with a new needle. Coagulation was measured from the moment blood started to enter the syringe.

The method for determining whole blood coagulation time at 37 C. in siliconized tubes has already been described.† The times referred to in this paper are the averages for the 2 final tubes in the series of 4 tubes of 1 ml. of blood for each sample.

Lipemia was estimated from the optical density of the exalted plasma as estimated in the Evelyn photoelectric colorimeter with the 620 ma filter.

RESULTS

The results are summarized in table 1, which gives the averages for the 5 pre-meal samples

* Manufactured by Durkee Famous Foods, Chicago, Ill.

† Manufactured by Armour and Co., Chicago, Ill.
TABLE 1.—Changes in Coagulation Times (Minutes) after Various Fat and Carbohydrate Meals

<table>
<thead>
<tr>
<th>Subject</th>
<th>Mean pre-meal</th>
<th>Butterfat</th>
<th>Corn oil</th>
<th>Coconut oil</th>
<th>Fish oil</th>
<th>Carbohydrate meal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 hrs.</td>
<td>5 hrs.</td>
<td>4 hrs.</td>
<td>5 hrs.</td>
<td>4 hrs.</td>
<td>5 hrs.</td>
</tr>
<tr>
<td>Ha</td>
<td>39</td>
<td>-7</td>
<td>-4</td>
<td>-1</td>
<td>-5</td>
<td>-6</td>
</tr>
<tr>
<td>Pe</td>
<td>43</td>
<td>-9</td>
<td>-9</td>
<td>-5</td>
<td>-7</td>
<td>-8</td>
</tr>
<tr>
<td>Mu</td>
<td>36</td>
<td>-8</td>
<td>-7</td>
<td>-2</td>
<td>-3</td>
<td>-7</td>
</tr>
<tr>
<td>Cr</td>
<td>37</td>
<td>-5</td>
<td>-6</td>
<td>-3</td>
<td>-4</td>
<td>-7</td>
</tr>
<tr>
<td>Fr</td>
<td>42</td>
<td>-8</td>
<td>-7</td>
<td>-10</td>
<td>-10</td>
<td>-5</td>
</tr>
<tr>
<td>Ki</td>
<td>44</td>
<td>-11</td>
<td>-8</td>
<td>-5</td>
<td>-6</td>
<td>-6</td>
</tr>
<tr>
<td>Wy</td>
<td>43</td>
<td>-7</td>
<td>-6</td>
<td>-9</td>
<td>-9</td>
<td>-9</td>
</tr>
<tr>
<td>Ha</td>
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<td>+1</td>
<td>-9</td>
<td>-1</td>
<td>-2</td>
<td>-3</td>
</tr>
<tr>
<td>Ke</td>
<td>49</td>
<td>-7</td>
<td>-7</td>
<td>-12</td>
<td>-5</td>
<td>-9</td>
</tr>
<tr>
<td>Gl</td>
<td>42</td>
<td>-8</td>
<td>-2</td>
<td>-4</td>
<td>-2</td>
<td>-12</td>
</tr>
<tr>
<td>La</td>
<td>40</td>
<td>-9</td>
<td>-5</td>
<td>-6</td>
<td>-4</td>
<td>-2</td>
</tr>
<tr>
<td>Mean</td>
<td>41.4</td>
<td>-7.0</td>
<td>-6.5</td>
<td>-5.1</td>
<td>-5.1</td>
<td>-7.0</td>
</tr>
</tbody>
</table>

The differences presented are between each postmeal coagulation time (on 1 day) and the mean of all 5 premeal coagulation times for the same subject.

TABLE 2.—Summary of Differences between Mean Clotting Times (Minutes) at Four and Five Hours after a Fat Meal and at Same Times after a Carbohydrate Meal

<table>
<thead>
<tr>
<th></th>
<th>Butterfat</th>
<th>Corn oil</th>
<th>Coconut oil</th>
<th>Fish oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean, fat meal</td>
<td>-9.00</td>
<td>-7.33</td>
<td>-9.21</td>
<td>-4.00</td>
</tr>
<tr>
<td>Carbohydrate...</td>
<td>19.64</td>
<td>11.06</td>
<td>21.34</td>
<td>29.50</td>
</tr>
<tr>
<td>Variance...</td>
<td>±1.28</td>
<td>±0.96</td>
<td>±1.33</td>
<td>±1.72</td>
</tr>
<tr>
<td>S.E...</td>
<td>7.03</td>
<td>7.64</td>
<td>6.92</td>
<td>2.33</td>
</tr>
</tbody>
</table>

* N = 12, t is 4.32 at p = 0.001 † N = 10, t is 2.23 at p = 0.05.

for each man and the differences between these values and those observed at 4 and at 5 hours after the meal. Shortening of the coagulation time was observed in all blood samples drawn after corn oil and coconut "oil" and in all but 1 sample after butterfat. After fish oil there was a similar tendency but the result was less uniform. After the carbohydrate meal there was, as previously observed, a tendency for the coagulation time to be prolonged.

A statistical analysis of the coagulation times is given in table 2. The effect of each fat is compared with that of the carbohydrate meal. For this purpose the values at 4 and at 5 hours after the meal for each man were averaged. It is clear that butterfat, corn oil, and coconut oil all shorten the coagulation time by some 7 ½ to 10 minutes as compared with the carbohydrate meal control and that the differences are highly significant. The effect of fish oil is much more variable and the average shortening is only about half as great as with the other oils. The effect of the fish oil is significant at about the 4 per cent probability level.

The various oils behave entirely differently in regard to the production of visible lipemia. The optical density data are summarized in table 3. Butterfat and corn oil uniformly produce an intense lipemia while coconut oil is remarkable in that the plasma after ingestion remains almost as clear as before. Fish oil produced intense lipemia in 2 men, moderate lipemia in 4 others, and very slight lipemia in 4 men; and these differences were not correlated with the changes in coagulation time observed in these men. Obviously, whatever may be responsible for the effects on blood coagulation is not closely correlated with the gross degree of lipemia. This confirms the previous conclusion reached from our studies on butterfat meals' and agrees with O'Brien's findings.²

These studies provoke consideration of the coagulation time as an individual characteristic. Within the accepted "normal" range of blood coagulability, do individuals tend to differ even
when they are on the same diet and pursuing the same mode of life? Compared with mentally normal men, schizophrenic men may tend to be more variable from time to time in blood coagulability just as they are in some other characteristics. Further, the particular subjects in these 5 experiments are, in general, rather homogeneous in regard to their individual average coagulation times so the inter-individual variability in the group in these experiments may be an unusually small fraction of the total variability (intra- plus inter-individual variability). Accordingly, an analysis of variance with the 150 coagulation measurements on these 10 subjects should give a low estimate for the consistency of individual differences in respect to blood coagulability.

Table 4 summarizes the analysis of variance with the data from these 150 observations. For the pre-meal observations, 37 per cent of the total composite variance is accounted for by the differences between individuals and almost none of the variance was attributable to between-day trends. For the postmeal values, the variance from occasion to occasion is significant, of course, but even so 29 per cent of the total variance is attributable to consistent differences between individuals. In other words, in this series the different individuals show consistent individual differences in spite of the fact they were all subsisting on exactly the same diets and were maintaining the same mode of life in general. Finally, the analysis of variance shows, as we would expect, that there was no significant difference between days for the pre-meal measurements. For the postmeal values, variance due to differences between occasions is highly significant statistically.

**Discussion**

Most of the previous studies on blood coagulation after fat meals have involved butterfat, either as the only fat or as a major constituent in a fatty meal. As we have pointed out, the evidence, independent from our own, is overwhelmingly in agreement that butterfat does indeed increase the coagulability of the blood. The data in the literature on the effects of other food fats are very few. Duncan and Waldron reported shortening after meals of olive oil and of corn oil as well as of butterfat and later they provided data indicating that corn oil and butterfat were essentially the same in their effects. Finally, on the basis of experiments with oleomargarine and a single trial of a hydrogenated fat (Crisco) the same workers concluded that "apparently the more saturated the fat, the less effect it has on coagulation."

Our results do not agree with this last conclusion; if anything they indicate that all
food fats tend to shorten the coagulation time but that the more saturated the fatty acids in the fat, the greater is the effect. The least saturated oil we used, sardine oil, had less effect than the others and there was a slight trend for the effects of the other fats to decrease in the order of decreasing saturation. However, the differences between corn oil, butterfat, and coconut oil are statistically not significant in spite of the great range in saturation they represent.

After re-analysis of the data of Waldron and Duncan we believe their suggested conclusion about the effect of fatty acid saturation is not supported by their own data. Firstly, in most cases they used different patients to test the different fats and no serious emphasis can be given to differences in the coagulation response in such group comparisons. More particularly, we note that in all of their studies corn oil and butterfat were not significantly different, though corn oil is one of the least and butterfat one of the most saturated of the common food fats. Their single result on 1 patient fed hydrogenated shortening is not significant, of course. Only in the experiments with oleomargarine is there a significant difference between fats in the experiments of Waldron and Duncan. But we have no information about the fatty acid composition of the oleomargarine they used and it is idle to speculate about its degree of saturation. Oleomargarine is by no means a uniform substance, and different oleomargarines, or even the same brand bought at different times, have widely variable compositions and degrees of hydrogenation.

The duration and time of maximum effect of the fatty meal is of interest. Waldron and Duncan reported a maximum shortening of clotting time 1 hour after the fatty meal, with considerably smaller changes at 2 and at 3 hours. However, we found only a small effect at 1 hour and the maximum effect was in the period from 4 to 6 hours after a fat meal rather than at 2 hours or at 6 hours. Presumably, technical differences in the methods used account for the variable appearance of the time of greatest coagulability.

In any case, the effect on coagulation seems to be limited to a few hours after a fatty meal. We have not demonstrated the total duration of a significant effect but it is less than 15 hours and does not appear to be cumulative from day to day.

Evidence for the latter statement was obtained in studies on 2 groups of men who were studied on low- and high-fat diets. Fourteen schizophrenic men, different individuals but like those studied with the special fat meal reported above, were maintained on a diet high in ordinary mixed food fats (40 per cent of calories from fats) and then were changed to a low-fat diet (12 per cent of calories from fats) that provided the same amount of calories, proteins and vitamins. After 2 weeks on the low-fat diet the average before-breakfast coagulation time was 41.36 minutes as compared with an average of 40.23 minutes for the before-breakfast value on the high-fat diet. This small difference is statistically not significant and an equally insignificant difference, in the opposite direction, was obtained with 14 obese university students who were controlled on 2 reducing diets of constant calories but differing in fat content (20 per cent and 60 per cent fat calories). Half of the students had the high-fat diet for several weeks and then changed to the low-fat diet while the other students made the reverse order of change. The average before-breakfast coagulation time was 49.07 minutes on the high-fat diet and 46.64 minutes on the low-fat diet.

It is not clear what stage (or stages) in the events in coagulation is altered after a fat meal. The experiments of O'Brien indicate that the effect on coagulability of a fatty meal is prevented by platelet action. We found a reduction in the prothrombin time but this effect was smaller and less significant than the effect on the whole blood coagulation time. Salvini and Sordi observed a small increase in prothrombin activity as well as a shortening of the coagulation time of recalciﬁed plasma but their most striking result was a marked decrease, averaging 40 per cent, in the “heparinoid substances” as estimated by the method of Gibson and co-workers. Fullerton, Davie, and Anastosopoulos observed shortening of the coagulation time of recalciﬁed plasma in the presence of snake venom. Finally, it has
been claimed that the effect of the fat meal is inhibited to some extent by the simultaneous ingestion of sugar.

**Summary**

Twelve men were studied on 5 occasions before and at 4 and 5 hours after isocaloric meals of butterfat, corn oil, coconut oil, and sardine oil, emulsified with skim milk, and of boiled rice and sugar with a similar amount of skim milk.

After the carbohydrate meal the average coagulation time of whole blood in siliconized tubes was slightly lengthened, but all of the fatty meals produced a significant shortening of the coagulation time. Compared with after the carbohydrate meal, the average coagulation times were 4 minutes shorter after the fish oil and from 7.3 to 9.2 minutes shorter after the other fat meals.

Visible lipemia was marked after butterfat and corn oil, almost nil after coconut oil, and variable from individual to individual after the fish oil. There was no correlation between visible lipemia and the coagulation time.

The effect of the fatty meal seems to be limited to a few hours after the meal and is not cumulative. Measurements of before-breakfast coagulation time on 2 groups of men on controlled low-fat and high-fat diets disclosed no effects of the different character of the diets eaten during the preceding days.

* An analysis of inter- and intrindividual variability showed that coagulation time tends to be an individual characteristic, even when all of the individuals are well within the extremes of accepted "normality," but that a fat meal tends to change the bloods of all individuals in the same direction.

**Acknowledgment**

Dr. F. W. Sheeley, Superintendent of the Hastings State Hospital, made it possible to do the work at his hospital. We are grateful to Mrs. Helen Williams, to Mrs. Rose Marie Keidel, to Dr. B. Bronte-Stewart, and to Dr. Josef Brozek for help in one or another aspect of the work. The faithful assistance of the young men volunteer aides from the Church of the Brethren is especially appreciated.

**Summario in Intereiungua**

Dece-duo homines esseva studiato a 5 occasione ant ante 4 e 5 horas post isocaloric repastos de grassia butyric, oleo de mais, oleo de coco, oleo de sardina—omne istos emulsifcate con lacte discremate—e ris bullite e sucro con un simile quantitate de leacte discremate.

Post le repasto a hydratos de carbon, le tempore medie de coagulation de sanguine intreg in tubos revestite de silicium esseva levemente prolongate, sed omne le repastos grasse produceva un significative reduction del tempore de coagulation. In comparation con le valores obtenite post le repasto a hydratos de carbon, le tempore medie de coagulation post le repasto a oleo de pisce esseva 4 minutas plus breve; post le altere grassias, illo esseva 7,3 e 9,2 minutas plus breve.

Lipemia visible esseva marcate post grassia butyric e oleo de mais; illo esseva quasi absent post oleo de coco; e illo variava ab un individuo al altere post grassia de pisce. Nulle correlation existeva inter le lipemia visible e le tempore de coagulation.

Le effecto del repasto grasse es apparentemente limitate a alicun horas post le repasto individual; illo non es cumulative. Mesurations del tempore de coagulation ante le prime repasto del die esseva executeate in 2 gruppos de homines mantenite super dietas a basse e a alte contento de grassia, respectivemente. Le resultatos reflecteva nulle effectos correlationate con le differente dietas ingerite durante le dies precedentee.

Un analyse del variabilitates inter- e intra-individual monstrava que le tempore de coagulation tende a constituer un caracteristica individual, mesmo quando omne le individualos se trova intra le limites del extremos de lo que es acceptate como "normal," sed que un repasto grasse tende a alterar le sanguine de omne individuos in le mesme direction.

**References**


Although rheumatic heart disease, coronary atherosclerosis, and hypertension are the most frequent causes, thyrotoxicosis, constrictive pericarditis, pulmonary embolism, malignant disease in the mediastinum, accidental electric shock, and digitalis administration are other causes. The last factor was referred to by Mackenzie in 1911. Benign "idiopathic" atrial fibrillation is not uncommon in healthy adults with excesses of work, tobacco, and emotion.

Of 500 consecutive cases, 30 per cent had rheumatic heart disease. Relative advantages of atrial fibrillation include (1) ease of control of ventricular rate, (2) decreased incidence of subacute bacterial endocarditis, (3) freedom from paroxysmal attacks. A clot was found in the left atrium of 43 of 106 patients (40 per cent) with atrial fibrillation and 3 of 144 patients (2 per cent) with sinus rhythm.

Of 32 patients with systemic embolism preoperatively, 22 had atrial clot at operation and 5 of these 22 suffered operative embolism. "So far not one of the 32 patients with a past history of systemic embolism has experienced further embolism in the years following operation."

The authors introduce their article with the following well-turned phrases of Hay and Jones: "The auricles pipe and the ventricles must dance... a dance that sometimes leads to death."

McKusick
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