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The Effect of an Intravenous Fat Infusion on Blood Coagulation

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THE EFFECT of fat ingestion on blood coagulation in man has been the subject of rather intensive investigation, but the results have been conflicting and the effect of lipemia on coagulability of the blood *in vivo* has not been clearly defined. A decrease in the whole blood coagulation time and the Russell viper venom or "Stypven" time are most frequently observed as the result of lipemia, but the significance of these changes as an index of coagulability of the blood *in vivo* is open to question.[1] The importance of determining the effect of lipemia on blood coagulation is obvious, since increased coagulability of the blood could play an important role in initiating intravascular thromboses and is subject to control by restriction of dietary fat. The current status of the relationship of fat ingestion to blood coagulation has been recently reviewed.[2,3]

When a fat emulsion suitable for intravenous use became available, it seemed worthwhile to determine the effect of this preparation on blood coagulation. Previous studies on the effect of lipemia on blood coagulation have been performed in subjects with a normal coagulation mechanism. Since the effect of lipemia is assumed to be an increase in the coagulability of the blood, it was considered worthwhile to evaluate the effect of lipemia in subjects with coagulation disorders. The results of studies of blood coagulation, following the infusion of an intravenous fat preparation (Lipomul®)‡ in normal subjects and in subjects with coagulation disorders, constitutes the present report.

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MATERIAL AND METHODS

The subjects comprising this study were hospitalized on the wards of the Louisville General Hospital. The subjects utilized as normal controls had no evidence of a coagulation defect and were not acutely ill at the time of study.

The effect of the infusion of Lipomul was studied in three types of coagulation defects: hypoprothrombinemia, hemophilia and thrombocytopenia. The subjects with hypoprothrombinemia were selected on the basis of a prolonged one-stage prothrombin time. This group consisted primarily of subjects with liver disease.

Lipomul, the intravenous fat preparation utilized in these studies, has the following composition per 100 ml.: Cotton seed oil, 15 gm.; phosphotides (purified soya lecithin), 1.2 gm.; pluronic F-68, a synthetic coemulsifier, 0.3 gm.; and dextrose, 4.0 gm.[4] Lipomul, 500 cc., was given intravenously to the subjects in a fasting state, and the period of infusion ranged for from two to three hours.

The following coagulation studies were performed before and within thirty minutes after the infusion. The methods utilized are as described by Miale and the normal value for these procedures in our laboratory are indicated in parentheses.[5] The whole blood coagulation time by the Lee and White method (ten to fifteen minutes) and in siliconized glassware (twenty to forty minutes), the one-stage prothrombin time utilizing human brain as a source of thromboplastin (twelve to fourteen seconds), prothrombin consumption (more than twenty seconds), the Russell viper venom

TABLE I

Blood Coagulation Studies Before and After Infusion of Lipomul in Normal Subjects

Case No.	Coagulation Time: Lee and White (10–15 min.)		Coagulation Time: Silicone (20–40 min.)		Prothrombin Time (12–14 sec.)		Prothrombin Consumption (>20 sec.)		Russell Viper Venom Time (14–16 sec.)		Thromboplastin Generation Test (Maximal Activity) (min.)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	12	10	25	38	13	13	31	20	16	8	3	4
2	10	15	20	33	14	14	24	25	16	9	3	5
3	12	6	22	8	12	12	20	22	15	5	2	2
4	15	15	—	—	12	11	48	23	23*	17	—	—
5	13	17	24	22	14	14	22	22	27*	16	4	4
6	10	11	20	60	14	14	—	—	16	5	3	3
7	15	12	25	19	12	12	—	—	14	7	—	—
8	13	12	39	20	14	14	40	29	22	8	4	3
9	15	13	70	65	13	14	28	27	13	7	2	2
10	15	13	26	13	11	12	—	—	16	5	4	3
11	15	14	19	16	—	—	—	—	—	—	4	3
12	12	13	35	31	14	13	—	—	22*	8	4	3
13	10	15	—	—	11	12	—	—	14	8	6	5

* Venom time performed on platelet poor plasma.

(Stypven) time (fourteen to sixteen seconds) and the thromboplastin generation test. The results of the thromboplastin generation test are expressed as the time of maximal activity of the incubation mixture. In normal subjects, maximal activity generally occurs within the first three minutes of incubation. In several instances the venom time was performed on platelet poor plasma which resulted in a prolongation above the normal range for platelet rich plasma. These exceptions are indicated in the tables.

RESULTS

The results of the coagulation studies performed before and after the infusion of Lipomul in ten normal subjects are shown in Table I. The most consistent and significant change observed was a decrease in the Russell viper venom time. The whole blood coagulation time showed no consistent or significant change. The prothrombin time, prothrombin consumption and thromboplastin generation were not altered by the infusion.

The results of the coagulation studies in the patients with hypoprothrombinemia are shown in Table II. As in the normal subjects, the most consistent change observed was a decrease in the Russell viper venom time. A decrease in the whole blood coagulation time following the infusion was noted in some instances, but was not consistent or significant. The abnormal one-stage prothrombin time was not significantly changed.

The results of the coagulation studies performed in the subjects with hemophilia and thrombocytopenia are shown in Table III. In the subjects with hemophilia, coagulation times were not performed in siliconized glassware because they were greatly prolonged both before and after the infusion, and accurate determination was difficult. The thromboplastin generation test was not performed in two of the subjects with thrombocytopenia because of the low platelet yield of the plasma. The results of the studies in the subjects with hemophilia and thrombocytopenia were essentially similar to those in the normal control subjects and the group with hypoprothrombinemia; a decrease in the Russell viper venom time. The abnormal prothrombin consumption and thromboplastin generation were

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TABLE II

Blood Coagulation Studies Before and After Infusion of Lipomul in Subjects with Hypoprothrombinemia

Case No.	Coagulation Time: Lee and White (10–15 min.)		Coagulation Time: Silicone (20–40 min.)		Prothrombin Time (12–14 sec.)		Prothrombin Consumption (>20 sec.)		Russell Viper Venom Time (14–16 sec.)		Thromboplastin Generation Test (Maximal Activity) (min.)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	11	12	60	46	18	20	—	—	25	8	—	—
2	17	14	62	40	16	15	—	—	16	12	5	4
3	16	13	66	47	18	17	48	23	20	10	4	6
4	20	18	80	45	23	22	25	32	30	15	6	5
5	11	8	27	30	15	16	—	—	20	6	—	—
6	15	17	—	—	19	20	—	—	21	10	5	5
7	13	13	29	23	15	16	37	34	18	7	—	—
8	14	14	59	58	15	15	37	22	16	7	6	5
9	14	16	—	—	16	14	—	—	10	9	—	—
10	14	19	29	29	16	17	—	—	25	11	5	6
11	11	12	—	—	21	21	33	22	37	8	6	6
12	15	15	75	75	21	20	—	—	18	12	6	3
13*	18	17	—	—	30	32	65	56	28	10	—	—
14†	14	13	26	13	18	14	—	—	17	12	—	—

* Dicumarol induced hypoprothrombinemia.
† Congenital Factor VII deficiency.

TABLE III

Blood Coagulation Studies Before and After Infusion of Lipomul in Subjects with Thrombocytopenia and Hemophilia

Case No.	Coagulation Time: Lee and White (10–15 min.)		Coagulation Time: Silicone (20–40 min.)		Prothrombin Time (12–14 sec.)		Prothrombin Consumption (>20 sec.)		Russell Viper Venom Time (14–16 sec.)		Thromboplastin Generation Test (Maximal Activity) (min.)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
	Subjects with Thrombocytopenia											
1	11	9	70	42	13	13	13	12	—	—	—	—
2	11	11	23	30	12	13	13	15	21	9	—	—
3	13	12	16	14	14	15	19	18	18	6	2	2
4	15	15	—	—	12	12	14	14	20	7	2	2
5	14	19	29	29	16	17	21	20	25	11	5	5
	Subjects with Hemophilia											
1	31	24	—	—	13	13	10	12	10	8	6	6
2	90	105	—	—	14	14	12	12	*24	8	2	2
3	120+	120+	—	—	15	14	10	12	13	10	4	4
4	120+	120+	—	—	13	13	13	13	*21	12	6	6

* Venom time performed on platelet poor plasma.

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neither corrected nor made worse by the infusion of Lipomul. Platelet counts were performed before and following the infusion of Lipomul in the subjects with thrombocytopenia but no significant change was noted.

COMMENTS

The only significant and consistent change observed following the infusion of Lipomul was a decrease in the Russell viper venom time. This change was observed in both the normal subjects and those with coagulation defects and is in essential agreement with the findings following the ingestion of fat.[2,3] A decrease in the Russell viper venom time as a result of lipemia has been considered to represent hypercoagulability of the blood.

There are several ways in which lipemia could result in hypercoagulability of the blood. Increased coagulability of the blood could occur as a result of lipemia if lipids possessed inherent properties capable of initiating coagulation, e.g., thromboplastic activity. Studies with platelet derivatives have demonstrated that certain phospholipids possess thromboplastic activity and produce normal thromboplastin generation when substituted for platelets in the thromboplastin generation test. The platelet phospholipid associated with potent thromboplastic properties is phosphitidylserine.[6] The results of the studies described herein do not indicate that the phospholipid of Lipomul supplemented intrinsic thromboplastin generation since the abnormal prothrombin consumption and thromboplastin generation test observed in the subjects with thrombocytopenia and hemophilia were not corrected.

Lipemia could enhance coagulability of the blood by potentiating or accelerating the activity of the plasma factors necessary for normal blood coagulation. The failure of the induced lipemia to decrease the prothrombin time in hypoprothrombinemia, or to enhance intrinsic thromboplastin generation in hemophilia and thrombocytopenia, is not consistent with this hypothesis. It is abundantly clear, however, that lipemia can potentiate the activity of Russell viper venom, but the mechanism by which this potentiation occurs is obscure. Russell viper venom is a partial thromboplastin which has an action like certain antecedents of thromboplastin resembling a mixture of Christmas factor, antihemophilic globulin and factor VII.[7] Viper venom is a foreign substance in relation to human blood coagulation and potentiation of its activity by lipemia is of doubtful significance as an index of coagulability of the blood *in vivo*. Lipemia does not potentiate intrinsic thromboplastin generation as reflected by the thromboplastin generation test, but might potentiate the activity of thromboplastins derived from tissues similar to the potentiation of Russell viper venom. This potential mechanism of lipemia-induced hypercoagulability has not been adequately studied. Studies are in progress in our laboratory to determine whether or not lipemia potentiates the thromboplastic activity of material derived from the intima of normal and arteriosclerotic blood vessels.

Lipemia could also increase and enhance coagulability of the blood by inhibiting the effect of fibrinolysin. Greig has reported inhibition of fibrinolytic activity *in vitro* by lipemia following the ingestion of fat and the magnitude of the inhibition varied with the degree of lipemia.[8] This important mechanism by which lipemia might enhance coagulability of the blood requires further study.

The available evidence does not provide an adequate basis for attributing enhanced coagulability of the blood to lipemia *per se* and of the mechanisms outlined herein, the potentiation of the coagulant activity of Russell viper venom is the most consistent finding. The demonstration of an intermediate product in intrinsic thromboplastin generation or a tissue thromboplastin with properties similar to Russell viper venom would enhance the validity of the venom time as a measure of coagulability of the blood *in vivo*. The present technics available for the study of blood coagulation *in vitro* are inadequate to evaluate enhanced coagulability of the blood *in vivo*. The development of more adequate technics for determining the coagulability of blood *in vivo* is necessary, since a recent report of increased coagulability of the blood in patients with ischemic heart disease and its correction by restriction of dietary fat implies that dietary fat may have a role in the genesis

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of thrombosis other than in producing arteriosclerosis.[9,10]

A febrile reaction associated with thrombocytopenia has been observed in some patients who have received consecutive infusions of 10 or more units of Lipomul. We did not observe any untoward reaction or bleeding tendencies following the infusion of a single unit of Lipomul in either the normal subjects or those with coagulation disorders. There was no evidence from the coagulation studies described that abnormalities in coagulation were made worse by the infusion. Daily infusions of Lipomul were given for ten days to one subject with hemophilia and to one subject with hypoprothrombinemia without any clinical evidence of bleeding, thrombocytopenia or alteration in blood coagulation.

SUMMARY

The results of blood coagulation studies following intravenous fat infusion in normal subjects and patients with coagulation disorders are reported. The only consistent change noted was a decrease in the Russell viper venom time. The Russell viper venom time is considered to be a poor indicator of coagulability of the blood *in vivo*. It is suggested that there is no conclusive evidence that lipemia *per se* results in hypercoagulability of the blood.

REFERENCES

1. O'Brien, J. R. Fat ingestion, blood coagulation and atherosclerosis. *Am. J. M. Sc.*, 234: 373, 1957.
2. Hashim, S. A. and Clancy, R. E. Dietary fat and blood coagulation. *New England J. Med.*, 259: 1115, 1958.
3. Poole, J. C. F. Fats and blood coagulation. *Brit. M. Bull.*, 14: 253, 1958.
4. Meyer, C. E., Faucher, J. A., Schurr, P. E. and Webster, H. D. Composition, preparation and testing of an intravenous fat emulsion. *Metabolism*, 6: 591, 1957.
5. Miale, J. B. Laboratory Medicine—Hematology. pp. 691, 697, 705–718. St. Louis, 1958. C. V. Mosby Co.
6. Marcus, A. J. and Spaet, T. H. Platelet phosphotides—their separation, identification and clotting activity. *J. Clin. Invest.*, 37: 1836, 1958.
7. Hall, G. H. The coagulant action of Russell Viper Venom. *J. Clin. Path.*, 9: 237, 1956.
8. Greig, H. B. Inhibition of fibrinolysis by alimentary lipaemia. *Lancet*, 2: 16, 1956.
9. McDonald, L. and Edgill, M. Coagulability of the blood in ischemic heart disease. *Lancet*, 2: 457, 1957.
10. McDonald, L. and Edgill, M. Dietary restriction and coagulability of the blood in ischemic heart disease. *Lancet*, 1: 996, 1958.

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