Recent Advances in Intravenous Fat Alimentation

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THE INCREASING advances in medical and surgical technics available today make the search for intravenous fluids capable of providing complete parenteral alimentation to the patient over a given period of time, ever critical. Those solutions presently available to the clinician for intravenous feeding fall short of the ideal goal. By complete alimentation is meant a regimen which provides adequate calories, carbohydrate, protein, fat, minerals, and vitamins. At the present time, caloric needs afforded best by fat, are most difficult to furnish. Numerous studies have shown quite well that amino acids, for example, will not appreciably contribute to protein synthesis unless adequate calories are given. Apparently, the protein precursors will be used for energy purposes in the absence of adequate calories. Thus intravenous solutions supplying calorigenically rich fat would be ideal for such purposes. These realizations have been the basis for numerous investigations over the years into the development of a utilizable intravenous fat emulsion.

The contributions to the development of such a preparation are multitudinous and cannot be adequately acknowledged in this report. Freeman has detailed much of the early developments in his excellent monograph on the subject.[1] The problems of composition, stability, animal studies, etc., are monuments to the diligence and ingeniousness of many experimentors. Literally hundreds of oils and emulsifiers have been mixed in varying combinations searching for a safe and practical product. Certainly Stare and his co-workers at the Harvard School of Public Health deserve credit for their exhaustive efforts in this regard. Finally cottonseed oil emulsified with soybean phosphatide in a high pressure homogenizer, stabilized with a synthetic polymer, pluronic F68, and rendered isotonic with 4 per cent dextrose was found most satisfactory. Then followed literally thousands of clinical trials in human beings. It soon became obvious that this preparation, although superior to previously tested emulsions, was still accompanied by an incidence of adverse side reactions too great to allow for general practical usefulness. Thus in our series of 229 infusions in 110 patients there was an over-all reaction rate of approximately 50 per cent per patient.[2] The reactions consisted of severe back pain, fever, chills, dyspnea, cyanosis, and rarely, acute shock. Fever alone occurred in approximately 30 per cent of the subjects.

Several observations suggested that the soybean phosphatide which was used might be responsible for the high reaction rate. This fraction has since been purified and in January 1956 the presently available emulsion was ready for clinical testing. Our original studies with the improved emulsion were performed on 129 patients receiving 298 infusions and have been recently extended by us as well as many others. These observations have shown that with the prominent exception of

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fever, all other adverse reactions have been virtually eliminated from the single infusion.[2,3] Fever, albeit mild, still appears in approximately 30 per cent of patients receiving intravenous fat emulsions.

The persistence of fever as an untoward reaction, even though all other side effects had been eliminated with the purification of the phosphatide, led us into a study of the nature of the delayed, usually mild, and clinically unimpressive febrile reaction. Early studies by our group had failed to incriminate pyrogens, particle size or *in vivo* hemolysis as a cause of the fever.[4] During the course of observations on the manner in which individuals cleared the infused fat emulsion from their blood, it became apparent that a highly significant correlation existed between the rate of clearance and the febrile reaction.[5] Those patients in whom the infused fat was removed from the blood very slowly did not develop fever, whereas in those subjects in whom fever did occur the fat disappeared rapidly. It was an interesting clinical observation that the "sicker" the patient, the more likely it was that fever would occur and that rapid clearance would be found. Not all patients who were "fast clearers" necessarily developed fever, however. These data were interpreted as suggesting that fever results in susceptible persons from endogenous heat produced by rapidly cleared and metabolized fat. The alternate hypothesis that there is a "pyrogenic substance" associated with the fat which is more rapidly released during the process of fast clearing cannot be denied. Further efforts at "cleaning up" the oil may finally resolve this problem.

In an effort to establish the assumption that rapid clearing is evidence of rapid oxidation, blood ketone levels were measured in a group of hospitalized subjects and correlated with clearing rates.[6] Much to our surprise, only minor rises occurred in blood ketones following the infusion of 600 ml of a 15 per cent cottonseed oil emulsion. These rises were so small that no significant correlation between them and clearing could be made. Since other evidence indicates that the fat is metabolized, the two-carbon fragment released by oxidation of the fatty acid chain presumably moves immediately into the citric acid cycle and the opportunity for condensation into acetoacetate is not afforded.

The variation in the manner in which the fat is removed from the blood, noted between individuals, as well as within the same individual under varying conditions, is an interesting phenomenon. The physiologic mechanism for clearing is poorly understood at the moment. Studies from our laboratory have shown that clearing-factor enzyme or lipoprotein lipase does not play a major role intravascularly.[7] There is reason to believe that a major portion of the infused fat actually leaves the blood stream as particulate fat—the chylomicron. Its ultimate fate thereafter remains to be elucidated, but it is probable that it is handled in much the same manner as is ingested fat.

It would seem, therefore, that there is available a fat emulsion readily acceptable to the majority of patients who need it, provided it is administered for a short period of time. However, the question of its safety and utility after many repeated infusions remained. Several cases[8,9] have been reported of patients receiving multiple fat emulsions in whom a rather characteristic moderately severe, clinical syndrome appeared. These unfortunate subjects developed a febrile illness associated with hepatosplenomegaly, anemia, jaundice, abdominal discomfort and bleeding tendencies. The nature or cause of this illness has not been adequately explained.

We have had the opportunity of observing two such long-term reactions to intravenous fat emulsion therapy. One such patient was a 44-year-old white woman admitted to the Psychosomatic Ward of the Cincinnati General Hospital because of a long history of functional gastrointestinal symptoms, severe psychoneurosis, hysterical syncope, weight loss, and diarrhea. After an intensive diagnostic workup failed to reveal any significant organic disease, she was given 600 ml of Lipomul®* intravenously each day for 24 days. After 22

* Lipomul, Upjohn, is a 15 per cent cottonseed oil emulsion, containing 1.2 g per cent soybean phosphatide, 3 per cent Pluronic F68 and 4 per cent dextrose and was kindly furnished by Dr. E. A. Hawk, The Upjohn Company, Kalamazoo, Michigan.

uneventful infusions the patient began to complain of vague abdominal pain anorexia. She developed low grade afternoon fever. By the 24th infusion vomiting began which was rapidly followed by progressive fever, hepatomegaly, and lethargy. The intravenous fat therapy was discontinued. The fever progressively rose until it reached 105° F (Fig. 1). At this point intravenous hydrocortisone was instituted which was followed by a lysis of the fever and a rapid restoration toward normal in all clinical manifestations. The various clinical and laboratory data are shown in Figures 1 to 4. These, along with observations from other patients receiving multiple fat infusions can be summarized as follows:

Hemogram (Fig. 2): Mild, progressive anemia occurred. There was an associated reticulocytosis; however, studies of fecal urobilinogen and red cell survival with Cr^{51} failed to demonstrate a hemolytic process. Bone marrow studies before and after the fat were essentially normal as was red cell uptake of Fe^{59}. Blood loss except from venipuncture could not be established. There was no change in the leukocytes nor was there a significant drop in the circulating thrombocytes.

Liver Function (Fig. 3): No change occurred in any liver function test except for the BSP retention which progressively increased. This has been noted frequently by others but is always reversible with discontinuation of the fat. This may represent "clogging" of the reticulo-endothelial cells by the particulate fat, a well-recognized occurrence following fat emulsions. Biopsy of the liver in one patient with this syndrome failed to demonstrate excessive fat deposition in the liver parenchyma but did show small nonspecific microgranulomas unassociated with fatty material or pigment.

Lipid Studies (Fig. 4): There is no evidence that persistent hyperlipemia occurred during the daily administration of the lipomul. Although a very slight increase in total fatty acids was noted, there was no change in the fasting optical density of the serum. There was some decrease in fat tolerance as measured by the clearing test, but this did not progress after the first week. The rather marked rise in esterified cholesterol has not been a routine finding in other patients, and may well be related to the low pre-infusion cholesterol values in this patient. Our experience with multiple infusions to date shows that the cholesterol changes may be quite variable.

Coagulation Studies: As will be noted from Table I there are two important changes noticeable. One is the hypercoagulability which accompanies each individual infusion. The other is the hypocoagulability noted at the time of the acute febrile illness. Although this patient

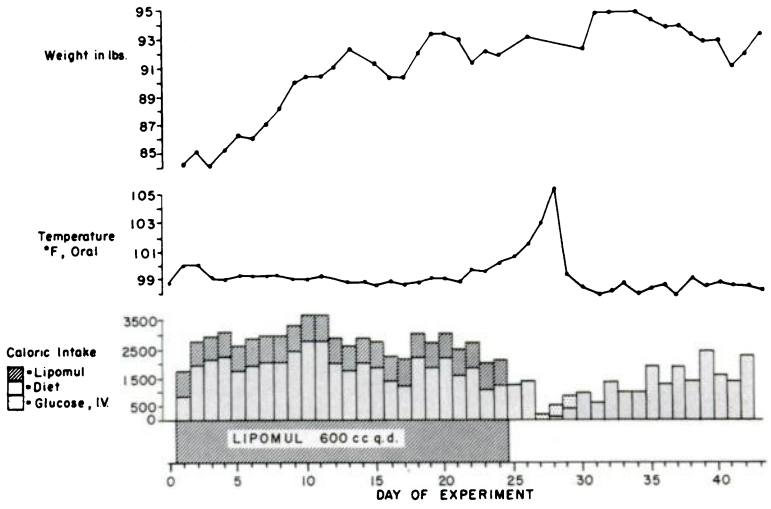

Fig. 1. Effects of daily administration of fat emulsion on weight and dietary intake.

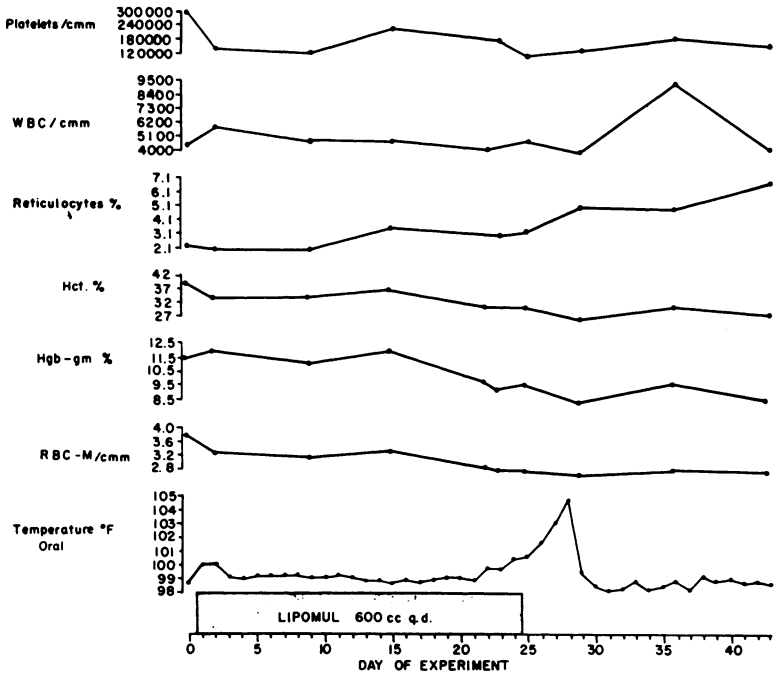

Fig. 2. Effects of daily administration of fat emulsion on the blood count.

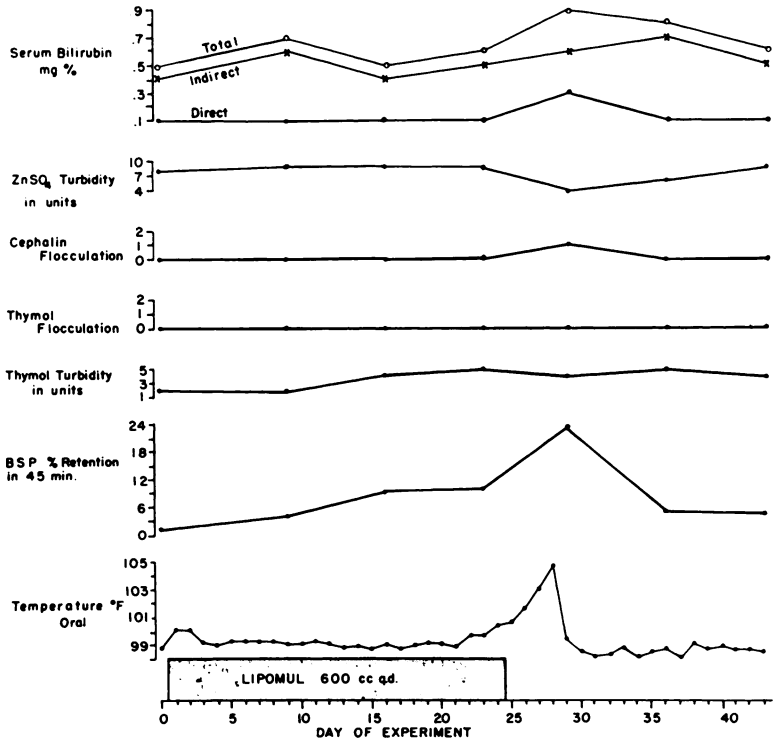

Fig. 3. Effects of daily administration of fat emulsion on liver function tests.

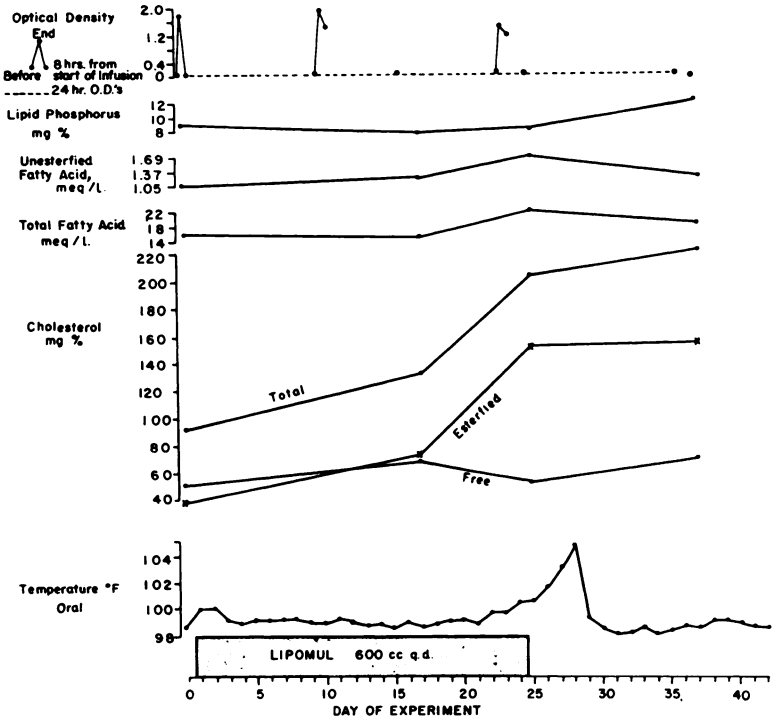

Fig. 4. Effects of daily administration of fat emulsion on serum lipids.

did not bleed, it was the clinical impression from observations of needle punctures that a definite bleeding tendency existed. This was borne out by the prolonged clotting time and markedly depressed prothrombin as measured by the TAMe assay.[10] This combination of hypercoagulability associated with individual infusions and a gradually decreasing concentration of prothrombin after repeated infusions has been a constant finding in our patients. Further work is being pursued along these lines in collaboration with Dr. Helen Glueck, but at the present the hypothesis is offered that the soybean phosphatide in the emulsion acts as

TABLE I

EFFECTS OF INTRAVENOUS FAT ON COAGULATION MECHANISMS

Date	7-31-57	8-6-57		8-12-57		8-20-57		8-23-57		9-3-57	9-6-57	9-17-57
		Before	After	Before	After	Before	After	Before	After			
Siliconized Lee White Clotting Time												
1st Tube	4 min.	14 min.	6min.	9 min.	——	——	6min.	9 min.	6 min.	22 min.	8 min.	6 min.
2nd Tube	——	19 min.	8min.	14 min.	——	——	12 min.	14 min.	——	41 min.	12 min.	12 min.
3rd Tube	26 min.	25 min.	——	20 min.	——	——	12 min.	18 min.	——	60 min.	16 min.	17 min.
Plasma Prothrombin Time												
Control	11.4 sec.	——	13 sec.	13.0 sec.	——	——	13.0 sec.	12.7 sec.	——	11.6 sec.	11.1 sec.	10.5 sec.
Patient	11.9 sec. (95%	——	11.5 sec. (100%	11.5 sec (100%	——	——	12.5 sec (100%	11.2 sec. (100%	12.6 sec. (100%	16.0 sec. (57%	13.7 sec. (70%	11.2 sec. (97%
Serum Prothrombin Time												
28° Serum												
20 min. inc.	11.3 sec.	——	<60 sec.	8.8 sec	——	——	8.5 sec	8.7 sec.	10.9 sec.	10.5 sec.	10.2 sec.	9.5 sec.
40 min. inc.	13.2 sec.	——	<60 sec.	9.9 sec	——	——	9.5 sec.	11.0 sec.	10.9 sec.	11.9 sec.	12.1 sec.	9.8 sec.
60 min. inc.	60.2 sec.	——	<60 sec.	22.4 sec	——	——	17 sec.	13.6 sec.	48.8 sec.	11.6 sec.	13.4 sec.	15.2 sec.
Plasma TAMe Assays	35 u/ml	——	38 u/ml	32 u/ml	——	——	28 u/ml	32 u/ml	39 u/ml	10 u/ml	28 u/ml	49 u/ml
Serum TAMe Assays												
20 min	27 u/ml	——	1 u/ml	20 u/ml	——	——	5.0 u/ml	34 u/ml	7 u/ml	4 u/ml	0	36 u/ml
40 min	12 u/ml	——	1 u/ml	11 u/ml	——	——	5.0 u/ml	5 u/ml	7 u/ml	0	0	13 u/ml
60 min	8 u/ml	——	2 u/ml	6 u/ml	——	——	8.2 u/ml	6 u/ml	6 u/ml	0	0	7 u/ml
Factor V	normal		normal	normal			normal	normal	normal	slight fall	normal	normal
Factor VII	normal		normal	normal			normal	normal	normal	normal	normal	normal

a thromboplastic material which promotes the increased coagulability. Repeated episodes of the hypercoagulability state gradually deplete the body of prothrombin which cannot be adequately replenished. Whether or not this theory will prove to be true, only future work will disclose. It would seem, however, that the effect of repeated infusions of fat on the coagulation processes is a fertile area for further research.

As yet there is no adequate explanation of the severe clinical syndrome precipitated by repeated administration of intravenous fat emulsions. There is not enough experience as yet to predict how many patients or which ones will develop the reaction, nor how many infusions would be required to produce it. It should be mentioned that in most instances in which the syndrome has developed, a large caloric intake has been provided the patients. The latter have been, for the most part, experimental or volunteer subjects who were not particularly ill. This has led to the hypothesis that the syndrome may represent an "overloading phenomenon" with fat. Our studies of the serum failed to demonstrate hyperlipemia nor did the liver biopsy reveal excessive lipid in the liver, thus there is no proof of this attractive hypothesis. The obvious clinical similarity between this reaction and idiopathic hyperlipemia gave impetus to the above suggestion.

The prompt response to hydrocortisone in the patient herein described suggests that hypersensitivity should be an etiologic consideration. At this moment there is nothing to prove or disprove such a possibility. Our findings related to the clotting abnormalities certainly do not explain the entire picture, but may give some insight into one of the more important clinical manifestations. Further experience will be necessary before more definitive statements can be made and steps taken to prevent this important reaction to repeated infusions of fat emulsions.

SUMMARY

It would appear that the presently available fat emulsion is a safe and practical product for short-term administration. However, if it is to be used for repeated and long-term therapy, the possibility of the development of the described febrile syndrome should be appreciated. As yet no test is known which will alert the clinician to its imminence. The advisability of intermittent rather than persistent therapy is suggested.

There are many problems yet to be met in the general field. The present phosphatide-stabilized emulsion is unstable to electrolytes or amino acids so that a "complete" emulsion is not feasible. Non-phosphatide emulsions prepared with synthetic emulsifiers are stable to these supplements but as yet are attended with high reaction rates in humans.[11] In addition, lipomul is "broken" by freezing so that emulsions resistant to environmental extremes would be desirable. Dehydrated preparations have been studied and their development will be watched with interest.

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