Fat emulsions for complete intravenous nutrition

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AN ADEQUATE amount of food is important in order to maintain a patient in the best possible condition to stand such strains as disease or trauma of different kinds (infections, burn, surgery, etc.). If oral feeding is impossible the nutrients have to be given in some other way. The two possibilities available are tube feeding and intravenous nutrition. The intravenous route is employed when tube feeding is impossible.

Complete intravenous nutrition means the administration of adequate amounts of all the essential nutrients: protein or amino acids, fats, carbohydrates, electrolytes, vitamins and water.

The intravenous supply of water, carbohydrates, electrolytes and vitamins has been employed for many years without difficulty. The supply of protein can be covered by blood, plasma and/or amino acid solutions. To utilize the supplied amino acids in the synthesis of proteins and, concomitantly, to maintain body weight and normal body composition, it is necessary to supply also the other nutrients and calories required. It is difficult or, in many cases, even impossible to give a sufficient amount of calories in the form of amino acids, carbohydrates or alcohol. This is because too large a volume of fluid has to be provided when isotonic solutions are used. When hypertonic solutions are administered, vascular complications such as thrombophlebitis arise, and a hyperosmotic diuresis may also occur.

When parenteral nutrition has to be used it is possible to cover the caloric needs by means of fat emulsions given intravenously. The high caloric content of fat emulsion, containing 10–20% of fat, makes it possible to avoid the disadvantages associated with the large volumes or high concentrations required to cover the caloric need by other nutrients. The fat in the emulsion does not change the tonicity of the water phase. It can be infused into peripheral veins without causing vascular complications. The infusions do not produce a diuresis. Further, no losses are observed in the urine or the faeces. It is also possible that the fats in the emulsion contribute to the maintenance of the normal lipid composition of the body.

Fat was apparently first administered parenterally in 1869 (Wentzel & Perco, 1869). After comprehensive animal experiments they gave subcutaneous injections of fat to a patient suffering from Pott's disease and in an emaciated condition. Hodder in Toronto used intravenous infusion of milk as a treatment for cholera in 1873 (Hodder, 1873). The first systematic attempts to administer artificial fat emulsion to man were carried out in Japan between 1920 and 1930. In the United States this subject was discussed, but nothing really useful was achieved, however, until 1950. In 1957 clinical and experimental results were published with a fat emulsion which, on administration, caused only a few acute side effects, and which seemed to be of great clinical value (*Metabolism*, 1957). This fat emulsion, Lipomul, was investigated extensively during the following years. As a result of certain side-effects, however, the manufacture of Lipomul was later discontinued.

Several reviews of intravenous fat emulsions have been published (Geyer, 1960; Schuberth & Wretlind, 1961; Schön & Zeller, 1962; Edgren & Wretlind, 1963; Wretlind, 1964a). Papers dealing with recent experimental and clinical research in the field of intravenous fat emulsions were published in the *American Journal of Clinical Nutrition* in 1965.

A fat emulsion for intravenous nutrition usually contains a vegetable oil in water and one or two emulsifiers to stabilize the emulsion. A large number of fats or triglycerides have been studied during recent years. The five commercial fat emulsions, Infonutrol, Intralipid, Lipofundin, Lipomul and Lipiphysan, contain either cottonseed oil or soybean oil. As emulsifiers, different phosphatides are used. To obtain isotonicity with the blood, the water phase contains glucose, sorbitol or glycerol. The fatty acid compositions of the two oils differ. Soybean oil contains more linoleic acid and less saturated fatty acids than cottonseed oil. Soybean oil also contains linolenic acid, which is not found in cottonseed oil (Edgren & Wretlind, 1963; Rose *et al.*, 1965).

This paper will treat mainly of the experiences gained with the soybean oil–egg-yolk phosphatide emulsion. These emulsions contain 100 g or 200 g of fat, 12 g of egg-yolk phosphatides, and 25 g of glycerol per litre. Comparisons will be made between this emulsion and some cottonseed oil emulsions.

Experimental studies

There are many questions that must be answered

before it is justifiable to use an artificial fat emulsion intravenously in man. Some of these questions are related to acute and chronic toxicity, utilization, dosage and comparison with chylomicrons of the chyle, which can be regarded as a physiological fat emulsion.

Toxicity

Emulsified low-molecular triglycerides, such as tributyrin and trinorvalerin affect the circulation and the respiration (Wretlind, 1957; Westerholm & Wretlind, 1960). Only fat emulsions without such pharmacological effects can be employed. The commercial emulsions at our disposal today do not affect circulation and respiration. Some emulsions may cause unfavourable effects on the microcirculation in capillaries by aggregation of erythrocytes and fat particles (Brown *et al.*, 1955; Bergentz, 1961; Bergentz, Gelin & Rudenstam, 1961). No such effects have been observed in connection with the soybean oil emulsion (Gigon, Enderlin & Scheidegger, 1966).

Before fat emulsions can be used for intravenous nutrition it is necessary to ensure that tolerance is sufficiently high. Investigations of acute toxicity by single infusions in rats and dogs have shown that emulsions can be given in amounts up to 15 g/kg body weight without lethal effects. This means that the acute toxicity of these emulsions is very low and of no clinical importance. Single intravenous injections of the soybean oil emulsion given to man in doses up to 0·6 g fat/kg during 2 min without causing any symptoms, have confirmed the very low acute toxicity (Hallberg, 1965b). Also single infusions of this emulsion given to man in doses of 3–4 g fat/kg during 3–4 hr do not cause any symptoms.

The chronic toxicity or tolerance during long-term administration is of importance because, as a rule, there is a clinical demand for prolonged administration of fat emulsions. For long-term intravenous administration of fat, it is necessary to know that quantities corresponding to the caloric requirement are without toxic effects. Long-term infusions of cottonseed oil emulsions in man and in the dog have been stated to cause anorexia with loss of weight, vomiting, gastro-intestinal bleeding, hyperlipaemia, anaemia, thrombocytopenia and prolonged coagulation and prothrombin times (Artz, 1959; Preston & Henegar, 1959; Werr & Preston, 1959; Cohn *et al.*, 1960). The anaemia is regarded as haemolytic (Loewy *et al.*, 1943; Levenson, Upjohn & Sheehy, 1957; Artz, 1959; Alexander & Zieve, 1961). Liver damage and spontaneous bleeding may also occur (Artz, 1959; Cohn *et al.*, 1960), consequently, these emulsions are not recommended for administration to man in doses exceeding 75 g fat/day for 14 consecutive days. Such effects, called 'long-term reactions' or 'overloading syndrome',

have not been described in connection with the soybean oil emulsion. However, changes in the coagulability of the blood during a single infusion have been observed (Amris, Brockner & Larsen, 1964). These changes, reversible with heparin, have never been known to cause clinical symptoms. Anaemia has been observed after repeated fat emulsion infusions in man and in the dog (Collins *et al.*, 1948; Mann *et al.*, 1949; Upjohn, Creditor & Levenson, 1957; Kaley, Meng & Bingham, 1959; Cohn *et al.*, 1960). There are great differences between the various emulsions.

Changes in the blood proteins and lipoproteins have been described. A decrease in the albumin concentration has been observed after prolonged infusions with cottonseed oil, whereas the concentration of lipoprotein was increased (Dohrman, Pezold & Weller, 1959). It is difficult to determine whether these findings are toxic influences and/or a physiological response to the administration of fluid (Holm, 1965). Increase in lipoprotein concentration is also observed in man after the administration of chylomicrons (Hallberg, 1965e).

The blood-plasma potassium concentration is stated to decrease after fat administration (Baba, 1931; Marble *et al.*, 1934). The other plasma electrolytes are not affected. The effect on potassium concentration has been considered favourable in the treatment of anuria, and is thought to depend on decreased cellular catabolism.

Dogs are well-suited for experimental studies on long-term tolerance for fat emulsions. With a moderate volume and amount of fat, the entire caloric requirement can be covered (corresponding to 9 g fat/kg/24 hr). Dogs have also the advantage that side effects, such as nausea, vomiting, diarrhoea, etc., are easily recorded.

Studies on the tolerance in dogs for Lipomul and SR-emulsion (15% cottonseed oil, stabilized with polyethylene glycolstearate and tartaric acid ester of monoglycerides) have been made (Cohn *et al.*, 1960). The dogs survived 4·5 g fat/kg 5 days a week during 6 weeks. If larger doses of Lipomul were given the dogs died. The SR-emulsion became lethal with 7·5 g fat/kg. Similar results have been reported by Elster (1962) with Lipofundin in doses of 6–7 g fat/kg/day given to ten dogs. All the dogs died in 7–8 days.

Edgren *et al.* studied Infonutrol and Intralipid in dogs, with a dosage of 9 g fat/kg/day for 4 weeks (Edgren *et al.*, 1964). All dogs that received the soybean oil emulsion, Intralipid, survived. Berg *et al.* found no differences in toxicity between Lipofundin and Intralipid in studies on dwarf pigs (Berg *et al.*, 1965).

The present study includes further tolerance investigations in dogs, which have been partly reported by Wretlind (Wretlind, 1964b) and

Hakansson (1965). Infonutrol, Intralipid, Lipo-fundin and Lipiphysan were given in a dosage of 9 g fat/kg/day over a planned experimental period of 28 days. The infusions were given during 4–5 hr with the dogs in a Pavlov stand. The effects on body weight, survival time and bleeding tendency are given in Fig. 1. All dogs receiving Intralipid survived in good condition and increased 14% in body weight. All the other dogs died before the end of the period. The survival time varied between 3 and 25 days. The last-mentioned dogs had marked symptoms from the overloading syndrome before

a greater increase in the plasma phosphatide concentration. With a reduction of the phosphatide concentration from 1·2% to 0·6% there was only a slight increase of the phosphatides and triglycerides in the blood. The number of white blood corpuscles increased when the cottonseed oil emulsions were administered, whereas the soybean oil emulsion caused only slight changes.

From this investigation it is obvious that the toxicity varies with the type of fat emulsion. The results show that dogs given the soybean oil emulsion survived in good condition, but all dogs receiving
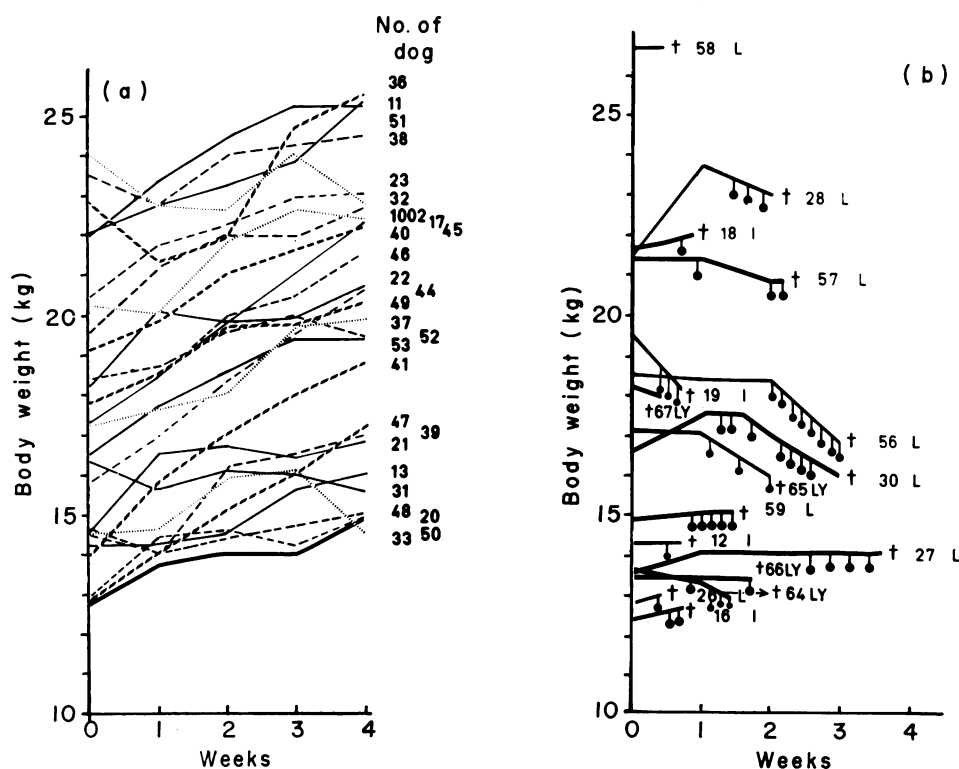

FIG. 1. Changes of body weight, bleeding and survival time in dogs given daily infusions of fat emulsions in amounts corresponding to 9 g fat/kg for planned 28 consecutive days. (a) The soybean oil emulsion, Intralipid (average weight increase, 14 ±0·4%). (b) The cottonseed oil emulsions, Infonutrol (I), Lipofundin (L) and Lipiphysan (LY); ●, bleeding; †, death.

death. 'Intravenous fat pigment' (see below) was found in the liver.

All animals receiving Intralipid were killed. The presence of the intravenous fat pigment in the liver, spleen and bone marrow was established. Signs of liver damage were not observed. In some cases, proliferation of reticulo-endothelial cells was found in the liver and spleen. The cottonseed oil emulsions caused more pronounced anaemia and a more elevated triglyceride and cholesterol content in the blood than did the soybean oil emulsion. On the other hand, the soybean oil emulsion brought about

the cottonseed oil emulsions died under our experimental conditions.

Morphological changes

After long-term infusions of cottonseed oil emulsions in man and in the dog, ulcers in the stomach and duodenum have been observed (Jordan, 1957; Levenson *et al.*, 1957; Artz, 1959; Werr & Preston, 1959; Cohn *et al.*, 1960; Hartwig *et al.*, 1961). Liver disturbances with jaundice and abnormal bromsulphthalein-retention, as well as increased thymol turbidity and cephalin flocculation,

were noted (Preston *et al.*, 1957; Watkin, 1957). So far no such side effects have been recorded in connection with soybean oil–egg-yolk phosphatide emulsions.

The appearance of pigment in the liver and spleen of both man and animals after long-term fat infusions is interesting from a pathological point of view. Meyer *et al.* (1957) observed a brown pigment in the reticulo-endothelial system of patients and dogs treated repeatedly with cottonseed oil infusions. According to Thompson *et al.* (1960) this 'intra-venous fat pigment' had not been described earlier. Intravenous fat pigment in the reticulo-endothelial cells has been observed also after soybean oil emulsions, but to a much less extent than with cottonseed oil emulsions (Thompson *et al.*, 1965).

Numerous liver-function tests were performed (Thompson *et al.*, 1965) in an attempt to assess the potential hazards which might be associated with large doses of emulsions, the deposition of intra-venous fat pigments in the liver, the development of proliferative lesions or the alterations produced within hepatocytes. These included bromsulphthalein retention, radioactive colloidal gold uptake, radio-active rose bengal uptake and excretion, total bili-rubin, direct bilirubin, serum alkaline phosphatase, micro-autoradiography of hepatocytes employing tritiated thymidine, serum lactic dehydrogenase, and serum glutamic pyruvic transaminase. It was not possible to demonstrate that large doses of emulsion, the intravenous fat pigment itself, proliferative lesions associated with its deposition or ultra-structural changes in hepatocytes, produced any impairment of liver function, either during the course of infusion or afterwards.

Elimination from the blood stream

Knowledge about the course of elimination of intravenous fat emulsions is of fundamental importance for two reasons. Firstly, in order to be able to give the correct amount of this nutrient, and, secondly and more theoretically, so as to understand the alimentary lipaemia and allied physiological and pathological problems. The latter statement is based on the fact that the artificial fat emulsion may have many similarities with chylomicrons, and can, for this reason, be used as a model in studies on chylomicron metabolism (Dole & Hamlin, 1962; Boberg & Carlson, 1964; Hallberg & Wersall, 1964; Hallberg, 1965d).

The elimination of the triglycerides of fat emulsions and chylomicrons has been previously described as following an exponential or complex course (Carlson & Hallberg, 1963). By means of studies in the dog and man, the kinetics of the elimination have been established in both (Hallberg, 1965d). No differences were observed either between the species or between the triglycerides in the soy-bean oil emulsion or the chyle isolated from the thoracic duct.

To demonstrate the elimination of fat particles from the blood, and the changes in the endogenous lipoproteins, it was necessary to separate the emulsion triglycerides from the endogenous plasma-triglycerides (Hallberg, 1964).

The changes in the endogenous plasma-trigly-cerides caused by the fat emulsion are interpreted as a recirculation of the infused triglycerides. This recirculation indicates that the fat emulsion is utilized by metabolic processes. The changes in the recirculating triglycerides are, with regard to magnitude and duration, dependent not only on the given dose of the fat emulsion (Hallberg, 1965a, b) but also on the nutritional and traumatic state (Hallberg, 1965c) of the patients.

The kinetics of the elimination of fat particles from the infused fat emulsion are as follows: Above a so-called 'critical concentration' there is a maximal elimination capacity. Below the 'critical concentra-tion' the elimination is dependent on the triglyceride concentration.

The mechanism for the removal of emulsion-triglycerides from the blood stream is unknown, but is assumed to depend on an enzyme (lipoprotein lipase), the amount of which determines the size of the maximal elimination capacity and the blood flow through the organ where that enzyme is located in the body. The size of the fraction of the total blood volume which passes the enzyme locations per unit of time determines the concentration-dependent elimination rate. The lipoprotein lipase activity has been investigated *in vitro* using different fat emulsions as substrates. There was no difference between Intralipid and chylomicrons but an obvious difference between all the other emulsions and the chylomicrons (Boberg & Carlson, 1964).

The following quantitative findings on the elimina-tion have been obtained for the soybean oil emulsion (Hallberg, 1965d).

(1) The elimination rate is independent of the dose.

(2) The maximal elimination capacity is signi-ficantly influenced by the nutritional state. The capacity increases during starvation.

(3) In the traumatic state in man, both rate con-stants are increased.

(4) The elimination of the fat emulsion from the blood stream causes changes in the endogenous lipoprotein concentrations, which are increased.

The rate constants, for the elimination of the fat emulsion from the blood stream in man, permitted calculation of the maximal dose per 24 hr. After an overnight fast (15 hr) this was 0·07 mM fat/l plasma/min with a standard deviation of ± 0.03 mM/l/min ($n = 22$). This value corresponds to 3·8 g $\pm$ 1·6 g (SD) fat/kg body weight/24 hr.

Utilization of intravenously supplied fat

Infusion of fat emulsion causes increased heat production, raised oxygen consumption, and lowered respiratory quotient, which indicate that the fat is metabolized (Baba, 1931; Meyer *et al.*, 1957; Mueller, 1957). After the supply of ^{14}C-marked fat, three-quarters of the ^{14}C can be found after a short time in the expired air (Geyer, Chipman & Stare, 1948; Geyer *et al.*, 1951). Weight and nitrogen balance can be obtained by giving an adequate nutritive supply together with intravenous fat emulsions (Mann *et al.*, 1948; Meng & Early, 1949; Krieger *et al.*, 1957; Levine *et al.*, 1957). A prolonged survival time, for starved dogs receiving intravenous fat emulsions, has been reported (Narat, 1937a, b). Our own experiments—reported below—with complete parenteral nutrition in the dog, where three-quarters of the caloric need were covered by intravenous fat, also demonstrate that fat is utilized after intravenous administration.

The above investigation and other studies provide strong evidence that intravenously supplied fat is utilized.

Complete parenteral nutrition in dogs

Tolerance studies of fat emulsions have been carried out in connection with complete parenteral nutrition in the dog using approximately the same method as that described by Meng & Early (1949). In the present study the different nutrients were administered in the amounts shown in Table 1

TABLE 1

Amount of calories and nutrients per day and kg body weight during complete parenteral nutrition in the dog

Amino acids as 10% Aminosol* with 10%		
glucose	2·25	g
Fat as Intralipid 20%	6·0	g
Glucose as 10% Aminosol solution with		
10% of glucose	2·25	g
Calories	78	calories
Water	47	g

Minerals			*Vitamins*		
Na$^+$	88	mg	Vitamin A	860	i.u.
K$^+$	30	mg	Vitamin D$_2$	50	i.u.
Ca^{2+}	5	mg	Tocopherol	6	mg
Mg^{2+}	1	mg	Thiamine hydrochloride	0·25	mg
Fe^3$^+$	1·4 mg		Riboflavine–phosphate		
			sodium	0·10	mg
Cu^{2+}	42	μg	Pyridoxine hydrochloride	0·10	mg
Mn^{2+}	28	μg	Niacinamide	1·00	mg
Zn^{2+}	28	μg	Pantothenol	0·15	mg
Co^{2+}	14	μg	Biotin	0·0125	mg
J$^-$	8	μg	Choline	49	mg
Cl$^-$	105	mg	Cobalamine	0·7	μg
P	47	mg			

Vitamin A and D, tocopherol and choline were included in the Intralipid emulsion. All other vitamins, minerals, and electrolytes were added to the Aminosol solution.

* Vitrum, Stockholm, Sweden.

(Hakansson, Holm & Wretlind, 1965). About three-quarters of the caloric requirement were given as fat. The infusions were given daily for about 6 hr with the dogs in Pavlov stands. Four dogs were given complete parenteral nutrition for a experimental period of 10 weeks. At the end of the period all the dogs were in excellent condition. The dogs gained weight during the experimental period. The haemoglobin content, haematocrit, red cell count and plasma proteins changed only slightly. The triglyceride, phosphatide and cholesterol content increased to a moderate extent (Hakansson *et al.*, 1965). The nitrogen, sodium, potassium and calcium balances were positive during the period. At autopsy, the day after the experiments had concluded, no macroscopic changes were observed in the organs, except for duodenal ulcers in one of the dogs. The microscopic investigation showed intravenous fat pigment, haemosiderin and fat particles in the reticulo-endothelial cells. In one dog some miliary necroses of liver cells were demonstrable. This dog was in a good condition and showed no signs of illness before being killed.

These investigations have thus demonstrated that dogs can be kept in good condition for a long time wholly by intravenous administration of nutrients.

Conclusions from experimental studies

A great number of different fat emulsions have been investigated. The available fat emulsions had very few acute side-effects. However, they showed great differences in long-term tolerance. Some of them produced lethal effects. The properties of soybean oil emulsion were such that the total caloric requirement could be covered in the dog for 4 weeks without side reactions. This fat emulsion was eliminated from the blood stream at the same rate as chylomicrons in dog and man. Intravenous fat pigment in the reticulo-endothelial cells was observed in connection with all the emulsions. Complete parenteral nutrition with the soybean oil emulsion could be given to dogs for a period of 10 weeks.

Clinical studies

A large number of different fat emulsions, which passed the acute toxicity tests, were used in clinical studies. Schuberth & Wretlind (1961) and Schuberth (1963a) reported on such clinical studies in man. It was later shown that only one of the emulsions, Intralipid, satisfied all the demands, including chronic toxicity tests. Since 1960 we have restricted our clinical investigations to this emulsion. In order to determine the incidence of acute side-effects and long-term reactions, a large number of infusions have been given in man. Clinical studies were also made to show the utilization of the infused fat and the possibility of using the intravenous fat emulsions for long-term, complete, parenteral nutrition in man.

Materials

In 1963 a study of 1086 infusions of the soybean oil emulsion was reported (Schuberth, 1963b). The present material is an extension of that study to 2781 infusions. The infusions have been given to surgical and geriatric patients, under strict control, by a special nurse.

Results

Acute side reactions. Most acute reactions were manifested as rise in temperature. No such reactions occurred in 97·3% of 2781 infusions. Chills were noted in about 1% of the infusions. Most of them occurred some hours after the end of the infusions. These reactions were never serious. The incidence of rise in temperature and chills seems to be independent of the amount of fat given.

Other acute side effects were a sensation of warmth, shivering without fever, vomiting, pain in chest and back, and thrombophlebitis. A sensation of warmth was the most frequent side effect (8%). This subjective sensation, however, was manifested only in a moderate degree, and never caused discomfort. The very low incidence (one case) of thrombophlebitis was impressive. We are under the impression that the relatively high incidence of thrombophlebitis in connection with highly concentrated amino acid or glucose solutions is eliminated when these infusions are given simultaneously with fat emulsion. This phenomenon may be regarded either as merely the result of dilution, or due to the protective influence of the emulsion on the vascular endothelium.

Long-term reactions. Most of the patients given more than fifteen infusions have been controlled by means of laboratory analyses, such as haemograms, liver function tests, electrolytes and coagulation tests. No evidence of any unfavourable effects was observed but a transitory prolongation of the retention of bromsulphthalein and a slight increase in transaminase values was noted in some cases. To summarize, it may be inferred that Intralipid can be infused in doses corresponding to 2 g fat/kg body weight/day over a long period with only slight risk of acute untoward reactions. Not a single case of overloading syndrome has been observed.

Utilization. It is difficult to estimate the clinical effect of supplying calories in the form of fat emulsion. One way is to assess the overall impression of the patient's general condition (Freuchen & Ostergaard, 1964). On the other hand, it is desirable to estimate to what extent patients will benefit from adequate intravenous nutritional therapy. Whether the caloric supply is adequate can be determined by its effect on the nitrogen balance. A positive or less-negative nitrogen balance means that the caloric source is utilized. In this test it is necessary to give a basal amount of 100–150 g of carbohydrate. A

substantially reduced nitrogen loss, by infusion of fat, glucose and casein hydrolysate, has been shown by many authors (Abbott & Albertsen, 1963; Krieger *et al.*, 1957; Larsen & Brockner, 1965; Wadström & Wiklund, 1964). Scharli (1964) had no difficulty in obtaining a positive nitrogen balance in man by using amino acids in combination with calories as dextrose (about 500 calories) and Intralipid (about 1200 calories).

The effect of Intralipid on nitrogen balance in the post-operative period after gastrectomy, was studied in twenty cases (Schuberth, unpublished). The patients were divided into three groups, which received various amounts of fat, carbohydrates and amino acids. The results are shown in Fig. 2. The
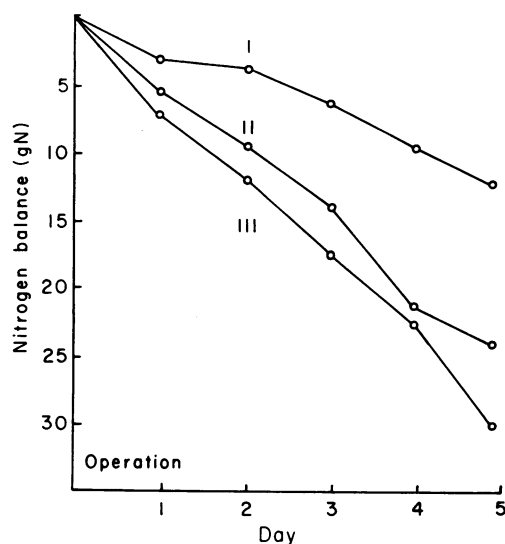

FIG. 2. Cumulative nitrogen loss during the 5 first post-operative days after partial gastrectomy in cases with duodenal ulcer. Group I consisted of eight patients receiving 36 calories, 1·5 g amino acids, 2 g fat and 3 g glucose/kg body weight/day: group II, eight patients with 15 calories, 1·5 g amino acids and 2·2 g glucose: group III, four patients with 16 calories and 4·0 g glucose.

nitrogen loss during the first five post-operative days was largest with an intravenous supply of only 16 cal/kg body weight, in the form of glucose, and no amino acids (III). With 15 calories and 1·5 g of amino acids the nitrogen loss was less (II). The smallest nitrogen loss occurred with 36 calories, 2 g of fat, 3 g of glucose and 1·5 g of amino acids per kg body weight and day (I). This indicates that the fat supplied had a nitrogen-sparing effect.

Long-term infusions. During recent years a number of long-term infusions of Intralipid have been given to clinical patients to maintain complete parenteral nutrition including glucose and amino acids as Aminosol. The longest period of parenteral nutrition was that given to a patient suffering from Crohn's disease, with several abdominal fistulae. He

received 2–2·5 g of fat, 0·4–6·2 g of glucose and up to 1·2 g of amino acids per kg body weight per day regularly for more than 5 months (Fig. 3). The total amount of fat administered was 15,040 g. The general condition of the patient improved although nutrition by mouth was impossible and in spite of the fluid losses through the fistulae of the small intestine. Control of the patient including all the above-mentioned tests, revealed no disturbances of any kind. Liver biopsy was performed after 4½ months

cases where caloric requirements cannot be covered by means of oral nutrition or tube feeding. In some instances there may be a need to supply fat parenterally as a supplement to an ordinary diet. The following aspects may be emphasized:

(1) *Pre-operative conditions.* As a result of prolonged nutritional disturbances the general condition of a patient may be affected to such an extent that an improvement is necessary before major surgical measures can be undertaken. In such cases it is
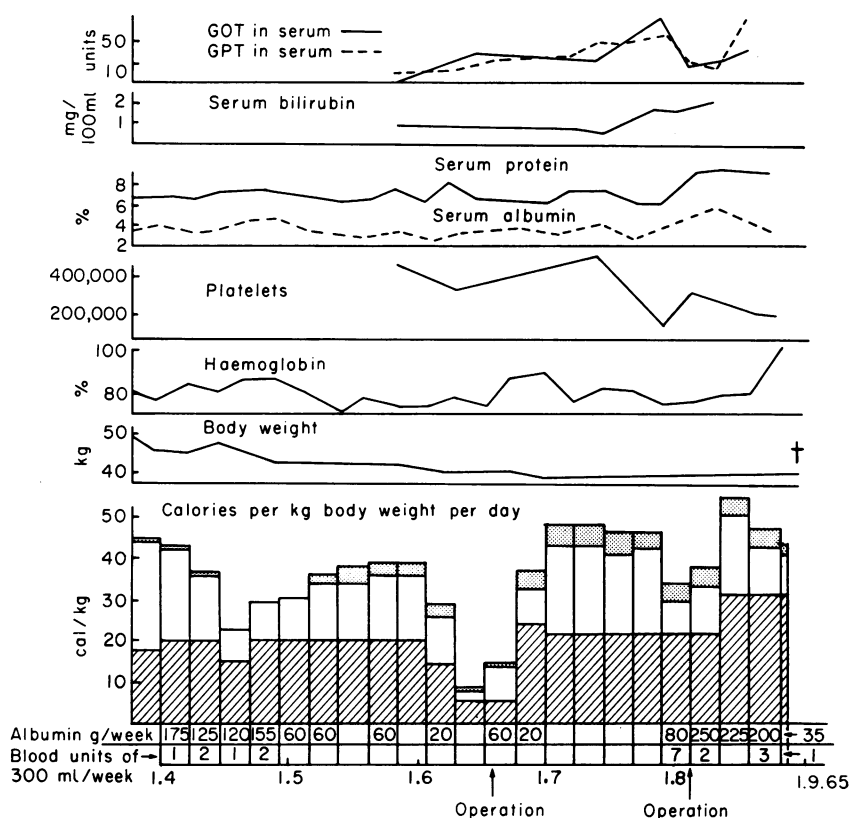

FIG. 3. Complete parenteral nutrition during 5 months in a 22-year-old patient suffering from Crohn's disease. The diagram shows the amount of fat (20% Intralipid) (cross-hatched columns), amino acids (10% Aminosol) (stippled columns) and glucose (unshaded columns) given. The changes in body weight, haemoglobin, platelets and concentration of protein, albumin, bilirubin and transaminases (GOT, GPT) in serum are also recorded in the chart.

of parenteral therapy. The histological examination showed no evidence of any abnormality. He died 1 month later of his primary disease. Without parenteral nutrition it would not have been possible to keep this patient alive for such a long time.

Conclusions

Indications

We consider infusion of fat emulsion, together with amino acids and carbohydrates, is indicated in

often of value to administer generous quantities of calories and nitrogen preoperatively.

(2) *Post-operative conditions.* Oral nutrition or tube-feeding is often difficult in the post-operative phase. In these conditions, including pre-operative nutritional disturbances, it is advisable to start parenteral nutrition on the 1st day after the operation by giving fat in doses up to 2 g/kg body weight in addition to carbohydrates and amino acids. Thus, the patient will be in a better condition, and the

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risk of complications in the post-operative phase
will be reduced. In less critical cases it is advisable
to use intravenous administration of fat emulsion,
together with carbohydrates and amino acids, if the
patient cannot take food by mouth on the 4th or
5th post-operative day.

(3) *Conditions with reduced or interrupted intestinal
absorption.* Serious enteritides and ulcerative colitis
may be favourably affected by large supplies of
calories at an early stage. In this context, cases with
intestinal fistulae, with low utilization of food taken
by mouth as a consequence, should be particularly
emphasized.

(4) *Burns.* The large caloric requirements of cases
with burns must be given due consideration. Even
if alimentation by mouth is possible, it appears that
parenteral therapy with fat as a supplement to
carbohydrates and amino acids is to be recom-
mended, especially in serious cases. The considerable
loss of fluid through evaporation from burned sur-
faces shown by Kinney (1960), increases the caloric
need. Each litre of water that evaporates means a
caloric requirement of 576 calories. The use of fat
emulsions is the only way to provide an appropriate
amount of calories to patients with burns.

(5) *Prolonged unconsciousness* may be an indica-
tion for complete parenteral nutrition when tube
feeding is contraindicated.

(6) *Various forms of cachexia*, e.g. anorexia ner-
vosa, may sometimes call for parenteral nutrition.
It is also conceivable that cachexia, due to general
carcinomatosis or comparable conditions, would, in
some cases, be an indication for parenteral nutrition,
and fat emulsion should then be used.

(7) *In anuria*, when it is important to limit the
supply of fluid, the administration of a large amount
of calories in small quantities of fluid may be
valuable (Alwall, 1964; Kille & Lawson, 1964) and
others have used fat emulsions in uraemic and
anuric patients with and without dialysis. In this
way it was possible to keep the patients in a fairly
good nutritional condition and to reduce the loss
of body weight and body protein.

Contra-indications

Pathological hyperlipaemia is a contra-indication
to the use of fat emulsion. Liver damage and blood
diseases with coagulation disturbances have been
discussed as contra-indications. The limited experi-
ence makes it difficult to give more precise recom-
mendations.

Recommendations

Fat emulsions are given as ordinary drip infusions.
We have developed a convenient method for simul-
taneous administration of the different solutions.
Separate drip chambers are used for fat emulsion
and for solutions containing 10% of carbohydrates

and 10% of amino acids. The two infusion sets are
connected by a Y-shaped joint piece, so that the
combination of fat emulsion and amino acids or
carbohydrates enters the venous bloodstream
through the same cannula.

Table 2 shows our schedule for complete paren-
teral nutrition to cover basal and high requirements
of calories, amino acids, carbohydrates, and fat.
The solutions and the amounts of these are given
in Table 3. The infusion rate should not exceed
0·5 g fat/kg body weight/hr.

TABLE 2

Recommended daily allowance of water, calories, amino
acids, carbohydrate and fat for complete parenteral nutrition

	Per kg body weight per day to cover:	
	Basal requirements	High requirements
Water	25–35 ml	50–60 ml
Calories	25–30 calories	50–60 calories
Amino acids	1 g	2 g
Glucose or fructose	2 g	5 g
Fat	2 g	3 g

TABLE 3

Amount of solutions for complete intravenous nutrition to
cover basal and high metabolic requirements

Solutions	Basal require- ments (ml) in a patient with a body weight of:		High require- ments (ml) in a patient with a body weight of:	
	50 kg	70 kg	50 kg	70 kg
20% fat emulsion	500	700	750	1050
20% glucose or fructose solution	500	700	1250	1750
10% amino acid solution	500	700	1000	1400

Summary

When using complete parenteral alimentation it
is necessary to give adequate amounts of water,
calories, amino acids, electrolytes and vitamins.
The practice is first to determine the amount of
fluid which should be given according to the cir-
cumstances in the particular case. Then the question
arises how to administer the different nutrients in
adequate amounts with the determined quantity of
fluid. If the patient can be given large amounts of
fluid, there are fewer problems. But when restricted
fluid supply is necessary, it is difficult to satisfy the
patient's calorie requirements. In most cases it will
be a question of giving the patient adequate amounts
of nutrients in a fairly small amount of fluid.

Recently, fat emulsions have been produced, and these have given more opportunities for providing adequate parenteral alimentation with moderate amounts of fluid, because of the higher caloric value of the fat.

The commercially available fat emulsions contain either cottonseed oil or soybean oil. Experimental studies show that the acute side-effects with these are few. There are great differences, however, in tolerance for repeated infusions of larger quantities. We found that all cottonseed oil emulsions examined in dogs gave lethal effects in quantities which correspond to the caloric needs, whereas the soybean oil emulsion, Intralipid, in an amount of 9 g fat/kg body weight/day, could be administered over a period of 4 weeks without serious side-effects. Moreover, experiments in dogs were carried out with complete intravenous nutrition during a period of 10 weeks. In these experiments three-quarters of the caloric requirement were covered by fat in the form of a soybean oil emulsion. Throughout this period the dogs were in good condition.

The kinetics of the elimination of soybean oil emulsion from the blood stream were investigated. No differences were observed for the elimination of triglycerides from chylomicrons and those from the artificial fat emulsion. The rate of elimination was independent of the dose. The maximal elimination capacity increased after fasting.

A large number of investigations in animals and man have shown that intravenous fat emulsions are well utilized in the body.

A report is given on 2781 infusions of Intralipid in man. In 97·3% no pyrogenic complications were recorded. In 1% of the infusions, chills were recorded. In a separate study on 235 selected patients chills were observed in 0·85%.

In twenty-eight patients more than fifteen consecutive infusions were given. A transitory increase of bromsulphthalein retention was noted in some cases, but no other side effects were observed.

The main indications for fat infusions are conditions when complete oral nutrition cannot be maintained, for example pre- and post-operative conditions, severe enteritides, ulcerative colitis, burns, prolonged unconsciousness, various forms of cachexia, and renal insufficiency.

The following recommendations are given for intravenous feeding: 1–2 g of amino acids, 2–3 g of fat as a soybean oil emulsion, and 2–5 g of glucose or fructose per kg body weight per day. According to the results of our investigations, these amounts can be given for long periods. One patient, who suffered from Crohn's disease, received daily infusions of 2–2·5 g of fat, 0·4–6·2 g of glucose and up to 1·2 g of amino acids per kg body weight for more than 5 months without any signs of side reactions.

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