The Need of Fat in Intravenous Feeding[1, 2]

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OF the six broad classes of nutrients—protein, fat, carbohydrate, minerals, vitamins, and water—all have been given intravenously, at least on occasion. The intravenous administration of water, saline, and glucose are commonplace. More recently the water-soluble vitamins and various protein preparations (casein hydrolysates, plasma, albumin, mixtures of amino acids, etc.) have been used intravenously. Preparations of the fat-soluble vitamins A and D suitable for intravenous administration are available though are not widely used. As far as we know, mineral mixtures other than saline or Ringer's solution, designed to supply the body with the many inorganic elements needed in normal nutrition are not available, though recent research has dealt with fluids containing also phosphorus and potassium. While fat has been given intravenously, its administration by this means is quite unusual, and it is generally not considered in parenteral therapy.

One might comment briefly on specific indications for parenteral nutrition. Actually this is desirable whenever the gastrointestinal tract cannot or should not be used, either completely or partially. Such conditions include the following:

1. Patients unable to take any food or fluid by mouth because of vomiting or obstruction.

2. Patients in whom utilization of orally ingested food is unsatisfactory, as for example, those with a severe diarrhea as in ulcerative colitis, sprue, or infant diarrhea, or patients with various types of intestinal fistula.

3. Patients in whom oral ingestion of food is deleterious, as for example, in peritonitis or in those in whom complete rest of the gastrointestinal tract is desirable.

4. Patients with severe anorexia and in whom tube feeding results in further psychic trauma or vomiting, diarrhea, or distention.

5. Patients in whom the time available for correction of nutritional depletion is limited, as for example, in the pre- and post-operative treatment of extremely malnourished individuals, such as those with many types of carcinoma.

6. Patients in whom caloric intake is particularly important to prevent destruction of body protein and the accumulation of nitrogenous waste products, as for example, in uremia.

Thus there are many significant reasons for parenteral nutrition, and the nutritional adequacy of such nutrition depends on the individual patient and the length of time that parenteral feeding is required. The use of fat emulsions administered intravenously to infants and children should be particularly important because of the increased caloric requirements for growth and the present difficulties of supplying a sick child with anywhere near adequate calories by vein. Likewise, intravenous fat may be of particular importance in combating the emaciation accompanying many types of carcinoma.

Work on the preparation of fat emulsions suitable for intravenous administration and on some of the metabolic aspects of the intravenous administration of fat has been under way in this laboratory for the last six years. The first study (1) was quite heroic in that an attempt was made to make up two mixtures, one an aqueous solution and the second a fat emulsion, which together would furnish all the nutrients thought at that time (1942) to be essential for the oral nutrition of the dog. Adult dogs receiving only water orally were infused with these mixtures, and they did not do very well. Nausea and vomiting were frequent, a severe anemia developed, and the dogs all lost weight rapidly. It was thought that the basic difficulty in this work probably involved the infusion of fat, hence it was decided to concentrate on the preparation of fat emulsions for intravenous use.

The chief advantage of the use of fat in parenteral nutrition resides in its contribution to the energy intake. Since oil-in-water emulsions do not exert osmotic effects, any convenient concentration of fat may be used. This, coupled with the high energy content of fat, makes it possible to introduce considerable quantities of energy into relatively small volumes of infusion mixture. Fat is not irritating to the vein wall and hence sclerosis of the vein does not result. Furthermore, fat is not excreted by the kidney and hence calories from fat given intravenously are not lost in the urine as is the case with much of the glucose and protein hydrolysates given by this route. With a sufficiently high caloric intake the utilization of protein from parenteral or oral sources would be maximal, the destruction of body protein would be minimal, and it ought to be possible to improve considerably the nutritional status of a severely emaciated child or adult, or to prevent such an emaciated condition from developing.

Emulsions have been prepared with various types of homogenizers and with sonation. The high pressure dairy homogenizer has given the best emulsions in reasonable quantity. The homogenizer is used at pressures of 4,000 to 5,000 pounds per square inch and produces emulsions of particle size comparable to that of chylomicra.

The problem of stabilization of emulsions is an extremely difficult one under ordinary conditions, and the extra "breaking" impetus of sterilization by autoclaving adds to the problem. The stabilizer 1. must maintain the status quo of the emulsion from preparation through autoclaving and standing; 2. must itself be relatively nontoxic; and 3. its emulsions must be nontoxic. A great number of common "stabilizers," "emulsifiers," and "wetting agents" do not efficiently fulfill the first requirements. A soybean phosphatide preparation known as Asolectin * has been the best source of an emulsion stabilizer; however, it was found to be the cause of certain histopathologic lesions occurring following fat infusions (2). By a series of fractionations with various organic solvents it was possible to remove the components of this preparation that caused these lesions (3). More recently this phosphatide preparation has been further purified.

With regard to fat, we have usually worked with emulsions containing 15 or 30% fat and have used

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as a source of fat corn oil, coconut oil, or butter oil. The difficulties of preparing a stable and sterile emulsion increase as the concentration of fat is increased. The emulsions are made isotonic with dextrose and are generally buffered with Na_2HPO_4 to bring the pH to near neutral. The composition of a typical emulsion is as follows: fat at 15 or 30%; dextrose at 4%; stabilizer at 1 to 3%; water to make up to 100% and Na_2HPO_4 to adjust the hydrogen ion concentration to approximately pH 7.0. The caloric content of such an emulsion is approximately 1,600 for a liter of the 15% emulsion and 3,200 for the 30% emulsion. Either concentration is a considerable increase over the 400 calories provided by a liter of 10% dextrose and of which the kidney will excrete about one-fourth of the calories. It has been found possible to sterilize the emulsion by autoclaving at 15 pounds' pressure for 15 minutes without any deleterious effect.

Normal adult dogs were used in most of the experimental work. They were infused from a drip bottle into a leg vein in the usual fashion. The early work with these emulsions may be summarized by saying that only those emulsions prepared with the soybean phosphatides proved satisfactory (4). Such emulsions were infused into dogs daily for periods of approximately one month. At the end of this time the dog appeared perfectly normal as judged by his general appearance, weight, and bromsulfalein liver function test. Usually there was a slight drop in the hemoglobin and hematocrit. Post-mortem examination of dogs infused with these emulsions showed no great abnormalities. Microscopically, stainable fat was present in occasional phagocytes in the lungs and in the liver Kupffer cells. In these organs and in the kidneys a cellular reaction had occurred, giving rise to scattered, discrete, occasionally partially necrotic granulomatous lesions. These consisted of central lipid-laden macrophages and occasional giant cells with surrounding collars of lymphocytes. In addition, there was evidence of moderate but widespread deposition of blood pigment in reticulo-endothelial phagocytes. However, as previously stated, most of this histologic reaction was found to be due to the phosphatide stabilizer, not the fat, and this can be prevented by purifying the phosphatide.

The next general study was to observe the utilization of emulsified fat given intravenously (5). In general, it was found that the daily intravenous administration of coconut oil emulsions to dogs receiving an oral ration adequate in all nutritional factors but inadequate in calories prevented further weight loss and produced an increase in nitrogen retention. The infused fat is not lost in the urine or feces, nor is it deposited as such in the tissues to any marked extent. In two dogs, in which total carcass analysis of fat was performed, it was found that the body lipids were only slightly displaced in their characteristics toward those of coconut oil. A minimum of 0.72 and 1.56 kilograms of coconut oil could not be accounted for in the tissues of these dogs and hence must have been metabolized during the experimental period. Thus fat given intravenously to the dog is utilized for energy.

The emulsions used in the preliminary studies generally contained 15% fat and were infused at a rather slow rate. Because of the potential clinical use of fat emulsions it was desirable to have some information on the rate of administration and also to know whether emulsions containing more than 15% fat were feasible. A study was designed for this purpose (2) and it was found that an emulsion containing 30% fat could be given with the same ease as the 15% fat emulsions. Furthermore, it was found that suitable fat emulsions could be given as rapidly as any of the ordinary parenteral fluids. The technical job of preparing and stabilizing a 30% fat emulsion is greater, and a larger concentration of stabilizer is required. An emulsion of 30% fat may be near the upper limit of practicability because of the viscosity of the emulsion and ready flow through a No. 19 or No. 20 needle.

Recently a study has been concluded (6), the results of which are now being prepared for publication, which shows that young, rapidly growing animals, with a consequently high caloric requirement, can utilize fat given intravenously as a source of energy. A total of 16 puppies was used in this study. They were able to receive up to 5 gm. of fat per kilogram of body weight per day and show normal growth and a positive nitrogen balance. Chemical data revealed no disturbance of plasma proteins, non-protein nitrogen, bilirubin, or liver function (bromsulfalein clearance) during the fat infusions. The puppies that were infused, either with the fat emulsion or just the phosphatide stabilizer, did show a moderate, self-limited, normocytic or slightly microcytic anemia. The anemia promptly improved when the infusions were terminated. In many respects this anemia seemed to simulate the anemia of infection. At the conclusion of the experiment histologic examination of the various visceral organs revealed no abnormal lipid retention, and this finding was supported by lipid analysis of the organs.

Attempts have been made to purify further the phosphatide stabilizer in the hope of removing whatever materials are responsible for the moderate anemia. Likewise, the possibilities of various co-stabilizers having a synergistic effect on the stability of the emulsion are being investigated. These studies are still in progress, but they have resulted in an improved emulsion and one that has been satisfactory for limited clinical trials. At the time of this writing fat emulsions have been given intravenously with reasonable success to seven adults and one child. The first two patients to receive fat emulsions intravenously were elderly women, both of whom had had extensive cerebral hemorrhages. They were completely paralyzed and unable to swallow. Each patient was given 300 ml. of a 15% coconut oil emulsion per day without any effect on temperature, pulse, respiration, or blood pressure. One of these patients received this amount of fat daily for eight days. Two weeks following the last fat infusion the patient expired. Gross and microscopic examination of the organs at autopsy revealed no abnormalities.

Of the next four patients to receive intravenous fat, two were severely emaciated as a result of carcinoma and two were uremic. At this writing they have each received daily from 300 to 600 ml. of a 15% emulsion (contributing from 450 to 900 calories) over periods varying from three to ten days with marked and prompt clinical improvement.

The seventh adult to receive intravenous fat was a woman with a chronic intractable steatorrhea. She was extremely emaciated, and the principal sup-

portive problem with her was one of supplying nutrition, particularly calories.

The one child to whom fat has been given was a four-year-old boy in whom the maintenance of an adequate caloric intake was the major supportive problem.

As is quite obvious, the clinical studies with intravenous fat are just beginning and at this time it is not possible to evaluate the results. It can be said, however, that fat emulsions have been prepared which can be given safely to man and which do not give rise to changes in temperature, pulse, blood pressure, or respiration.

Summary

Fat emulsions satisfactory for intravenous administration have an important role to play in parenteral nutrition. They offer an opportunity to provide adequate calories in a limited fluid volume. Fat emulsions given intravenously are utilized for energy requirements for growth and maintenance and are helpful in maintaining a positive nitrogen balance. They have been given successfully to man. They should play an important role in supportive and preventive therapy in pre- and post-operative care and in any disease characterized by serious weight loss or emaciation.

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Viscosity of Cottonseed Protein Dispersions[1]

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Introduction

IN a previous publication (1) a method for dispersing cottonseed proteins in concentrations as high as 25% protein to produce dispersions which were viscous, tacky, and did not gel was described. The preparation of the dispersions was accomplished by the inclusion of trichloracetate ion in the alkaline dispersing mixture, thereby preventing gel formation. The viscosity of the cottonseed protein dispersions was found to decrease on aging the dispersion and to be dependent upon the concentration of alkali used in its preparation and upon the concentration of protein. The instability of viscosity of the dispersions made it difficult to utilize such dispersions for manufacture of fibers, films, adhesives, sizes, and related products because the "working life" was too short for industrial operations.

This publication describes the results of an investigation of the effect of various methods of preparing the meal and of preparing the cottonseed protein dispersions upon their viscosity characteristics.

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EXPERIMENTAL

Materials and Methods

Isolation of Protein. Cottonseed protein was isolated from oil-free meals which were obtained by three methods of solvent extraction: 1. removal of the oil by means of n-hexane (6), 2. removal of the oil by means of the mixed solvent flotation process (deglanding process) followed by a second extraction with n-hexane (2, 7), and 3. removal of the oil by means of isopropanol.[3] The maximum solvent temperature reached during the preparation of the cottonseed meals was less than the boiling point of hexane. Cottonseed meal, prepared as described, was suspended in a 0.2 N sodium sulfite solution at pH 7.5 in the ratio of 10 liters of solution to 1 kilogram of meal. The suspension was stirred for 2 hours at room temperature, after which the extract was separated from the insoluble residue by centrifugation, in a solid basket centrifuge, and the protein was precipitated by the addition of gaseous sulfur dioxide to the extract, lowering the pH to 4.0. The protein curd was washed several times with water and twice with acetone, after which it was air-dried at room tem-

[3] Meal supplied through the courtesy of W. D. Harris, Agricultural and Mechanical College of Texas, College Station, Tex.