Summary

Single unit infusions of a 10% soy bean emulsion (Intralipid) were evaluated in convalescing men and hypermetabolic thermally-injured patients. No significant thermogenic responses to the emulsions occurred in either group. Vital signs, CBC, and liver function studies remained unchanged. Fat clearance curves demonstrated an accelerated plasma disappearance of the emulsion in the acutely burned patients. ^{133}Xenon perfusion-diffusion studies were normal, and pulmonary diffusion capacity, using the carbon monoxide rebreathing technic, was also normal following the infusion. Blood gas levels did not change following infusion of single or multiple units of Intralipid.

An essential fatty acid deficiency of the red cell membrane was identified in five patients, with a marked decrease in linoleate, arachidonic, decosahexanoic acids, all members of the polyunsaturated fatty acid series which cannot be synthesized *de novo*. All patients had extensive burns, and most were on long term, fat free, parenteral diets before this essential fatty acid deficiency occurred. Infusing quantities of soy bean emulsion high in polyunsaturated fatty acids corrected the fatty acid deficiency in the red cell membranes. Administering an isocaloric fat-free diet to an individual for 2 months resulted in weight gain and wound healing but failed to correct the compositional fatty acid deficiency. Thus, the fatty acid deficiency in red cell membranes appears to be a combination of the stress of thermal injury and nutritional inadequacies, and can be successfully treated by the inclusion of polyunsaturated fatty acids in the diet.

Finally, fat emulsion was administered, along with other caloric support, to 10 critically injured individuals. The fat appeared to be utilized without complication, and the fat emulsion contributed 38% of the total caloric intake in this group of patients. The nitrogen and caloric support of these patients resulted in protein sparing in all, as manifested by varying degrees of nitrogen retention related to both extent of injury and the degree of nutritional support. The availability of this emulsion as an isotonic, high caloric, noncarbohydrate, energy source increases the flexibility of the surgeon's repertoire for nutritional support in the severely injured patient.

References

1. Ashcraft, K. W. and Leape, L. L.: Candida Sepsis Complicating Parenteral Feeding. JAMA, **212**:454, 1970.
2. Carson, L. A. and Liljedahl, S. O.: Lipid Metabolism and Trauma. Acta Chir. Scand., **137**:123, 1971.
3. Collins, F. D., Sinclair, A. J., Royle, J. P., Coats, D. A., Maynard, A. T. and Leonard, R. F.: Plasma Lipids in Linoleic Acid Deficiency. Nutr. Metab., **13**:150, 1971.
4. Dodge, J. T. and Phillips, G. D.: Composition of Phospholipids and of Phospholipid Fatty Acids and Aldehydes in Human Red Cells. J. Lipid Res., **8**:667, 1967.
5. Geyer, R. P.: Parenteral Emulsions—Formulation, Preparation, and Use in Animals. *In* Parenteral Nutrition, edited by H. C. Meng and D. H. Law, Charles C Thomas, Springfield, 1970, p. 339.
6. Greene, H., Hazlett, D., Demarre, R. and Dremesi, J.: Effect of Intralipid on Pulmonary Function in Normal Humans and on Electron Microscopy of Rabbit Lung and Liver. Presented at the International Congress of Nutrition, Mexico City, 1972.
7. Holman, R. T.: Essential Fatty Acid Deficiency (Progress in the Chemistry of Fats and Other Lipids), Pergamon Press, Limited, Elmsford, New York, 1971, p. 275.
8. Lewis, B. M., Lin, T-H., Noe, F. E. and Hayford-Welsing, E. J.: The Measurement of Pulmonary Diffusing Capacity for Carbon Monoxide by a Rebreathing Method. J. Clin. Invest., **38**:2073, 1959.
9. Loken, M. K., Medina, J. R., Lillehei, J. P., L'Heureux, P., Kush, G. S. and Ebert, R. V.: Regional Pulmonary Function Evaluation Using ^{133}Xenon, a Scintillation Camera, and Computer. Radiology, **93**:1261, 1969.
10. Monroe, H. N.: Carbohydrate and Fat as Factors in Protein Utilization and Metabolism. Phys. Rev., **31**:449, 1951.
11. Neerhout, R. C.: Disorders of the Red Cell Membrane. Clin. Pediat., **7**:451, 1968.
12. Paulsrud, J. R., Pensler, L., Whitten, C. F., Stewart, S. and Holman, R. T.: Essential Fatty Acid Deficiency in Infants Induced by Fat-free Intravenous Feedings. Am. J. Clin. Nutr., **25**:897, 1972.
13. Shohet, S.: Hemolysis and Changes in Erythrocyte Membrane Lipids. N. Engl. J. Med., **286**:577, 1972.
14. Soroff, H. S., Pearson, E. and Artz, C. P.: An Estimation of the Nitrogen Requirements for Equilibrium in Burned Patients. Surg. Gynecol. Obstet., **112**:159, 1961.
15. Warden, G. D., Wilmore, D. W. and Pruitt, B. A., Jr.: Central Venous Thrombosis: A Hazard of Medical Progress. In press, J. Trauma.
16. Ways, P. and Hanahan, D. J.: Characterization and Quantification of Red Cell Lipids in Normal Man. J. Lipid Res., **5**:318, 1964.
17. Westerman, M. P., Balcerzak, S. P. and Heinle, E. W., Jr.: Red Cell Lipids in Zieve's Syndrome: Their Relation to Hemolysis and to Red Cell Osmotic Fragility. J. Lab. Clin. Med., **72**:663, 1968.
18. Wilmore, D. W., Curreri, P. W., Spitzer, K. W., Spitzer, M. E. and Pruitt, B. A., Jr.: Supranormal Dietary Intake in Thermally Injured Hypermetabolic Patients. Surg. Gynecol. Obstet., **132**:881, 1971.
19. Wretlind, A.: Complete Intravenous Nutrition. Nutr. Metab., **14** (Supp. 1), 1972.
20. Wretlind, A.: The Pharmacological Basis for the Use of Fat Emulsion in Intravenous Nutrition. Acta Chir. Scand. (Suppl.), **325**:31, 1962.
21. Wyrick, W. J., Jr., Rea, W. J. and McClelland, R. N.: Rare Complications with Intravenous Hyperosmotic Alimentation. JAMA, **211**:1697, 1970.

Discussion

Dr. John M. Kinney (New York City): I think we are indebted to Dr. Wilmore and his associates for a contribution which is of both practical and immediate significance because surely fat emulsions will become commercially available soon and also for some potential questions which may open new avenues of therapy for the future.

First for the present advantages, it is as he has said a non-osmotic calorie source which means we can administer it by peripheral vein.

It is a non-carbohydrate source and as we see more and more problems in the occasional patient receiving large carbohydrate loads, use of this calorie source may minimize the hazards for the occasional patient who is at risk from non-ketotic hyperosmolar coma. I think the most important confirmatory evidence that this is safe is not only because it is promptly cleared from the blood and also because of this reassurance that the lipid is not providing damage to the pulmonary capillaries, something suggested by a report some 18 months ago which caused considerable concern.

It may provide other potential advantages in the future, but here I think we have to wait for more data. It all hinges on whether or not there is such a thing as a true essential fatty acid deficiency in adult man.

The lesion which the authors demonstrated in the red cell membrane, leads us to ask the next question—does this occur in other tissues and perhaps more importantly, is there a physiologic deficiency which goes with this biochemical defect? Probably there is. It is hard to believe that at some point it does not become important, but as yet we do not know.

Finally, I would like to emphasize the point which was touched upon in closing, namely the question of whether carbohydrates and fat are interchangeable. (Slide) Here, we look at the common biochemical pathways that link body protein, a tiny amount of carbohydrate and adipose tissue as the major organic constituents in the adult man. Both carbohydrate and fat can provide two carbon fragments to be burned in the circle representing the TCA or Kreb's Cycle. However, while they both can provide two carbon fragments, fatty acids cannot provide the synthetic role (*i.e.* synthesis of non-essential amino acids) which carbohydrate breakdown can.

In the future when intravenous fat emulsions do become commercially available, we have to remember that there still will be a need for some carbohydrate to go with it.

DR. STANLEY M. LEVENSON (Bronx): I would like to echo Dr. Kinney's remarks about enjoying the paper. I had the opportunity of reading the full manuscript last night, and thank Drs. Wilmore and Pruitt for this courtesy.

I think it is appropriate that this paper has come from a U.S. Army Laboratory because I'm sure many of you know that the great bulk of investigative work in this country dealing with intravenous fat emulsion which was carried out so long and so arduously some decades ago in the United States was supported largely by the U.S. Army Medical Research and Development Command. I think that it's appropriate that the testing of a product developed on the continent is being carried out with such success in an army laboratory.

I would like to point out that the specific basis for the toxicity which was noted previously with Lipomul (Upjohn Co.) the preparation in use in the United States in the 1950's has really never been established. I am referring particularly to the toxicity associated with repetitive large infusions of the fat emulsion. You will recall that this toxicity was characterized by fever, sore throat, hepatomegaly, splenomegaly, thrombocytopenia and hemolytic anemia; all of these were reversible.

Presumably the toxicity had some relationship to the materials that were being used, *e.g.*, the phosphatide stabilizer. The phosphatide stabilizer in Intralipid is different and seemingly the toxicity does not seem to be occurring, at least in the doses of Intralipid used (about 3-5 Gm. fat/Kg. body weight; no fat orally).

There has never really been a question as to whether or not an I.V. fat emulsion is desirable and needed. After all, that is the way we get most of our fat after every meal.

The problem has been how to make an I.V. fat preparation commercially that would simulate the physiologic fat emulsion that each of us makes every time we eat a meal containing fat (and for most of us, that is almost every time we eat) so that it can be metabolized without toxicity. Fortunately the Swedes, among others, have seemed to accomplish this.

The availability of Intralipid brings the challenge that Drs. Wilmore and Kinney mentioned, namely, to determine how and when to use I.V. fat and, more generally, how to improve parenteral nutrition in general.

It is clear that we have come a long way since the early days of Robert Elman and others who pioneered in the field of parenteral nutrition, but there are many questions that are still unanswered.

For example, what should the ratio of the essential and non-essential amino acids be in different clinical situations?

It certainly is sort of ridiculous—that's too strong a word—unrealistic is perhaps better—to think that the same pattern of amino acids is optimal for all patients of all ages of all sexes under all conditions—and yet our present preparations of protein hydrolysates and amino acids allow for minimal flexibility.

I'm sure the time will come when there will be a number of different amino acid preparations to be used in various clinical situations.

Dr. Wilmore and his associates have called attention to the usefulness of I.V. fat emulsion from at least 2 points of view, one unique to fat, the other shared by fat with other nutrients. The latter is as a source of calories; the former, unique to fat, is as a source of essential unsaturated fatty acids.

The report today by Dr. Wilmore and his associates of the rapid development of biochemical changes in the red blood cells consistent with a deficiency of essential fatty acids has come as a surprise to most of us. The thought that a deficiency of essential fatty acids would occur *in adults* in such a brief period of time as found by Wilmore was considered, but discounted by most nutritionists—in fact as recently as a year and a half ago at an international conference on parenteral nutrition, the workshop concerned with fat metabolism suggested this just would not happen, at least not for many months, even in the complete absence of intake of essential fatty acids. The fact that the biochemical changes found by Wilmore were reversed by the administration of fat, orally or intravenously, suggests that this does represent fatty acid deficiency, as stated by the authors. However, I would echo Dr. Kinney's point, namely, the necessity to determine the physiologic significance of these biochemical changes in the red blood cells, *e.g.*, in terms of red blood cell function and survival, and also how generalized the changes are in other cells and tissues.

One would like more detailed information about the specific patients to try to understand why some of the burned patients showed the changes in their red blood cells while others did not. The authors suggest that prior diet, associated disease, *e.g.*, alcoholism, and the increased metabolic rate characteristic of burn patients are involved, but these need documentation. Clearly this is critical in terms of trying to understand the mechanisms underlying the changes observed.

We hope that in future studies the possible physiologic consequences of the changes described will be sought—and exploration of how general the phenomenon described is for other cells in the body. Assuming these changes are physiologically significant the necessity for a certain amount of essential fatty acids in any long term parenteral regimen is evident. Obviously, this is much more critical for the very young—especially the new born infant whose brain is developing at a rapid rate—and in whom failure of appropriate brain development may be impossible to correct at a later date.

Dr. Wilmore, will you clarify the following?

I believe you said that although the clearance of the injected fat was faster than normal in the burn patients who received single infusions of 500 ml. of fat emulsion, clearance seemed delayed in those patients receiving I.V. fat for many days. I interpreted that to mean the clearance was actually slower in those patients than normal. Is that the case?

Also, was there any evidence of the liver pigment that had been found almost universally in patients who received the older fat emulsion preparations in any of your patients who died, Dr. Wilmore?

PROFESSOR LARS-ERIK GELIN (Goteborg, Sweden): Before I

make my comment, I would like to express my deep appreciation for being included as the Corresponding Member in this old and famous Association of distinguished surgeons and for the ideals it stands for in progress and ethics in the surgical profession.

I have truly enjoyed Dr. Wilmore's presentation. The problems related to forced feeding with fat both orally and parenterally, are both metabolic and hemodynamic in nature.

We studied the earlier available fat emulsions (Lipomal) and found that they induced heavy aggregation of red cells, platelets and produced the known damages both to liver, kidney and to lung in rats and rabbits.

When "Intralipid" came, we infused the same doses to healthy animals but could not observe the previous changes in blood.

One consequence though was still there, the risk for thrombi in ligated veins if the dose was increased to three times the dose of previously used fat emulsions. That risk I think still exists and is dose related.

We found that the most probable reason for the toxicity of previous fat emulsions was ascribable to the emulsifier which damaged the membranes of the red cells which produced the aggregation of the cells.

Intralipid has not that disadvantage and can, in our hands, be safely used up to an amount of a supply of 2,000 calories per day, but no more. Then come adverse effects, similar to those of previous fat emulsions.

I think Intralipid has come to stay as a help to force feed our patients in metabolic need of high caloric intake.

Drs. Wretlind, Schuberth and Hallberg are the ones to credit for the detection of the emulsifier which is less damaging than the previous ones.

DR. DOUGLAS W. WILMORE (Closing): Essential fatty acid deficiency has been described in newborn infants receiving fat-free nutrition, and one or two adult patients receiving long-term fat-free parenteral nutrition. Now, polyunsaturated fatty acid deficiency has been uncovered in patients following major injury. The deficiency has been described in five patients. Two of these individuals were alcoholics, and abnormalities in fat metabolism have been previously associated with this group of patients. The remaining three individuals were referred to our unit following an interval of long-term fat-free parenteral nutrition following major injury, sepsis, and other complications. Therefore, two patients revealed dietary alterations which may have contributed to the deficit, and the other three patients were maintained on long-term fat-free therapy and therefore acquired this deficiency state during their post-traumatic catabolic course. The development of the deficiency depends on the metabolic state of the patient, the requirements for essential fats for body growth or wound repair, and the availability of polyunsaturated fatty acids either in body stores or provided by food intake. When the need for essential fatty acid is increased and fat is not provided in the diet, the circumstances are optimal for a deficiency state to occur.

How widespread is this essential fatty acid deficiency? How is it expressed, and what physiologic significance is it? The deficiency may be first detected with the appearance of ecosatrianoeic acid in the serum, but in addition there will be marked deficiency of the polyunsaturated fatty acids in cell membranes. The essential fatty acid deficient red cells are abnormal cells. They have abnormal osmotic fragility characteristics, and in the one patient studied the cell half life was remarkably short and the individual demonstrated a mild hemolytic anemia. Essential fatty acid deficiency in the laboratory animal is expressed by a multitude of membrane abnormalities and is first seen in organs which have high cell turnover rates. In the rat, for example, deficiency may occur in the plasma and red cells and then defects are noted in the mitochondrial membranes of the cells taken from the gastrointestinal tract and liver. We have not been able to sample other tissue in our patients, but I suspect that in widespread deficiency, there are fatty acid alterations which affect many tissues and membranes, including skin.

All the discussants inquired about the amount of fat that could be present in the diet of the seriously injured patient. It is our impression that the trauma patient, with a high rate of hepatic glucose production, requires more carbohydrate to achieve protein sparing than does the patient who is simply in resting starvation. Carbohydrate is an essential component of the diet if protein sparing is to be optimal, but at some level fat may be interchanged with carbohydrate to achieve comparable nitrogen balance. However, administration of fat alone would simply achieve weight stabilization without positive gains in nitrogen metabolism. We are now determining the level of carbohydrate-fat interchange in order to use these dietary constituents available to us for optimal nutritional efficiency.

Clearance rates were demonstrated with one unit of intravenous fat, and these clearance rates remained accelerated following multiple unit infusions.

We appreciate Dr. Gelin's comments about his experience with the use of Intralipid. Indeed, the Europeans have used this and other emulsions for the past 10 or 15 years and we all certainly can profit from their experience and comments.

We have not seen red cell or platelet aggregation with this particular emulsion, and fat pigmentation has not occurred despite the fact that one patient received over seventy liters of ten per cent emulsion over a 2½ month period. At the present time, the emulsion appears safe and we are presently determining guidelines for optimal use of fat emulsion in critically injured trauma patients.