Symposium on Intravenous Fat Emulsions

Preface

IN THIS day and age of research-oriented thought, scientific study may be approached by a myriad of avenues. Projects may be designed to answer one small seemingly insignificant question of a much larger unknown, or may be completely without obvious objective, or may be aimed specifically at what would appear to be a realistic goal. The latter is sometimes callously referred to as "contract" research or "product-oriented" research. Supposedly it is the easiest of the endeavors and presumably requires only hard work, lots of money and little originality. However, such research often turns out to be anything but easy, and, actually, in its course of evolution produces more questions than it answers. Its byproducts of valuable scientific information are many and it may catch the fancy of investigators who are intrigued by its elusiveness and captivated by its complexities. Such has been the case in the quest for a safe, practical and utilitarian fat emulsion for intravenous administration to human subjects.

Although the need for an intravenous solution high in calories which could be given in relatively small volumes has been recognized for years, it is not yet available to the practicing physician. One can recount multiple indications for such therapy in all areas of medical practice. Intravenous therapy with other nutrients—water, minerals, vitamins, carbohydrates and protein—has assumed sophisticated status in the armamentarium of most physicians. Yet, suitable and safe intravenous therapy with fat emulsions has not. The reason for this is clear: reaction rates are too high for a substance that in most instances is "supplemental" rather than "essential." We will return to this problem of untoward reactions in a moment.

The recognition of the need for such a product is not new. As early as 1895, Laube administered camphor oil to cardiac patients and suggested that it might be useful as a source of calories. In the early 1900's, studies on the metabolic effect of intravenously administered fat to animals was begun, and we are told that during World War I Germany used camphorated oil intravenously. However, major credit should go to the Japanese, Yomakawa and associates, who were really the first to attempt, in a systematized fashion, to provide nutrition to patients by using castor oil emulsions. In the 1930's, Holt and associates used fat emulsions in marasmic children, but it was not until after World War II that a concerted program to develop such a product was begun in this country.

Numerous investigators from various sources of scientific pursuit have contributed to this effort over the years. This symposium with its extensive bibliographies will attest to such a fact, and it is not the intent of this preface or the symposium to overlook the numerous and exciting contributions of all who have worked in this field. However, there is little doubt that the Surgeon General's Office, through its Research and Development Com-

mand, has been the prime mover in the search for an intravenous fat emulsion in this country. With the horrifying experiences of trauma indelibly imprinted in their minds, and armed with the knowledge of the importance of nutritional status in the traumatized patient, it is not surprising that the Army Medical Service would be interested in such a preparation. Largely through the efforts of Col. Tyrone Huber, a small group of investigators banded together with two or three interested pharmaceutical firms to form what has militantly, yet fondly, been called the Task Force on Intravenous Alimentation. Until the present time, the Army has continued to support the vast majority of the work in this area.

The group was small, meetings were informal and information readily disseminated between the members. However, the inevitable happened—the Task Force attracted new investigators and grew until finally the lines of communication became difficult, logistics more complicated and meetings so formal that true interchange of ideas was sacrificed. However, out of this rather impressive effort came worthwhile information and, more importantly to some, a product. At about this time, the first U. S. published symposium appeared in *Metabolism* (1957) which reported the proceedings of a conference held in Kalamazoo and sponsored by The Upjohn Co. During the early years, formulation of a stable emulsion and the elimination of acute adverse side effects were major problems that were overcome. Everyone was enthusiastic—the battle was won. Shortly thereafter, the roof fell in. At the Kalamazoo meeting appeared the first reports of a serious, delayed reaction occurring in patients receiving multiple infusions. Soon thereafter, confirmations came from various sources and the so-called long-term reaction or the "fat overloading syndrome" became the major problem facing the group. To this day it is unsolved. Restrictions were placed on the marketed product; enthusiasm dwindled as did the Task Force.

If is probably worth a short digression to reflect upon the "fat overloading syndrome" since its appearance has profoundly affected the entire course of investigation into intravenous fat therapy. This syndrome, although manifesting the vagaries of any clinical syndrome, is characterized by the abrupt onset of fever, anorexia and malaise, vague abdominal discomfort, bleeding phenomena, anemia, jaundice and hepatosplenamegaly. It occurs in patients who have received multiple, consecutive infusions. The minimal number of infusions required to initiate the reaction is not really known. It may occur some days after the last infusion and on several occasions has appeared to respond to treatment with adrenocortical steroids. The hemorrhagic complications are the most serious and have been life-threatening in several instances. What is known about its causation? Really very little. In many instances, the seriousness of the clinical situation precluded exhaustive study. Those studies that have been performed reveal a mixture of coagulation defects, liver dysfunction, varieties of anemia, and hyperlipemia and tissue lipidosis of varying amounts. Because of the latter, the term "fat overloading syndrome" came into usage, but the facts are that few patients with this reaction demonstrate significant hyperlipemia, and tissue biopsies have shown questionably significant lipid deposition. Thus, the preferred term is "long-term reaction." With the appreciation of the severity of this reaction, few investigators were willing to expose human subjects to its hazard for further study of its mechanism.

Thus, it was back to the drawing boards! Those of stout heart, however, picked up the pieces and continued their work. New formulations, both in the oils and the emulsifiers, were tried. Now, however, a new problem was at hand. How could one screen new emulsions for the long-term reaction without exposing human subjects to its obvious danger? Can animals be used for such screening? Are synthetic systems better than natural ones? What are the pathophysiologic expressions of the long-term reaction? What is their cause? These and many more questions have been approached over the succeeding years. There have been flashes of hopefulness, only to be dashed by the results of further experiments. Investigators abroad have become more active

in the quest and have stirred imaginations now and then. These are some of the areas to be touched upon by this symposium.

Through all of this, the Surgeon General's Office has continued to support investigators willing to try their hand. As one might surmise, a great deal of information has been accumulated. Some has been published, but the great majority of it is buried in data books or relatively unavailable in progress reports. The purpose of this, the second such U. S. symposium, is to make these data available to the general scientific community in the hope that it will spark interest in the uninitiated or furnish clues to the veteran. All investigators who are or had been under contract from the Surgeon General's Office were invited to contribute. The response was gratifying. It is our hope that a useful purpose will be served.

The papers have been grouped into areas of interest, for convenience to the reader. As one might expect, there are controversial issues among various investigators concerning many aspects of the problem. We regard this as "healthy" and have not made an effort to discourage active disagreement, as will be evidenced by several papers in the symposium. However, we have encouraged objectivity.

JOHN F. MUELLER, M.D.
Brooklyn-Cumberland Medical Center
Brooklyn, New York
AND LT. COL. JOHN E. CANHAM
U.S. Army Medical Research and Nutrition Laboratory
Fitzsimons General Hospital
Denver, Colorado

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