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Parenteral Nutrition—Thirty-Five Years of Research on Nutrient Solutions

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栄養輸液の研究に従事して

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The reminiscences of my life of research start with fond memories of the late RINNOSUKE SHOJI, Professor of Physiology in the Faculty of Medicine at Kyoto University, and later President of Hyogo Prefectural College of Medicine (now Kobe University School of Medicine).

Under his direction I was engaged in research on "Gas Exchange in Pulmonary Alveoli".

The food situation at the end of World War II was in such a serious state that in the student restaurants corn or acorn powder was added to the rice, and side dishes of the stems of sweet potatoes were also served as a means of allowing the students to fill themselves up. One day, busy obtaining a supply of experimental instruments, I missed my dinner, and the professor, taking pity on me, sent me a lunch box packed with polished white rice, called "silver rice" at the time, along with tasty side dishes made by his wife. Actually being in a state of near malnutrition, and in no mood at all for any experiments, I devoured the lunch as soon as the professor left—a fine thing up to this point. With a full stomach I returned home and, as I recall, slept soundly—the lunch box left unwashed in the laboratory and, needless to say, no experiments completed that day. When I reached the laboratory the next morning, I could not find the wooden lunch box anywhere. Professor SHOJI, usually very strict, gave me a good scolding for my irresponsible behavior and told me to search for it. I desperately looked for it everywhere, even to the point of crawling under the floor boards. But in those days the rats too were hungry, and they had not only dragged it away, but had gnawed it until it was no longer of any use.

This shameful experience was one of the first steps in my long life of research.

Key words: Fatgen-D-Venolipid (Fat emulsion), Fat metabolism, Essential fatty acid, Hyperalimentation, One pack method.
索引語：ファトゲンD-ベノリピッド(脂肪乳剤)，脂肪代謝，必須脂酸，高カロリー輸液，ワンパック方式.
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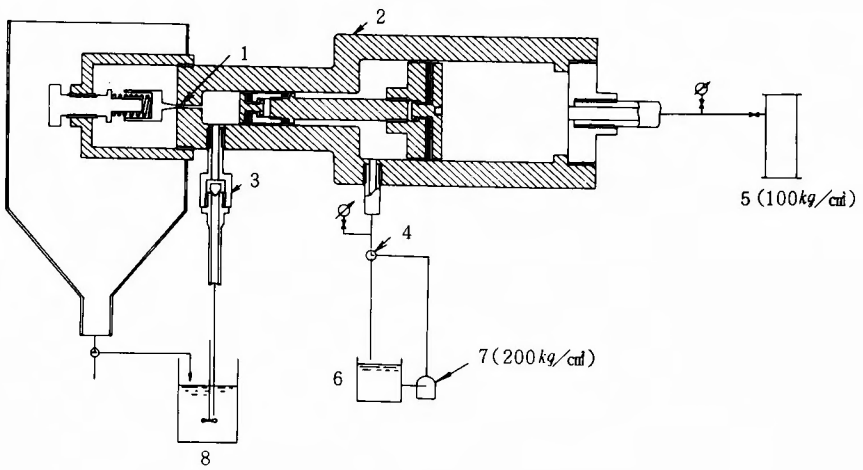
Because of the scarcity of food, all the Japanese were suffering from fatigue, weight loss, anemia and edema. Therefore, these were the kind of patients I had to treat as my earliest clinical subjects. (And nowadays one's first patients are apt to have diabetes!)

Leaving the department of physiology in September, 1946, I entered the department of surgery, and studied under the cordial but strict professor YASUMASA AOYAGI. One day as I walked into his office, he suddenly called me and told me that since I had now finished my M.D. thesis, I might be interested in doing some work on intravenous lipid infusions and ways into the production of a supply of lipid parenteral nutrition. True research, he pointed out, is just this kind of dealing into problems that may, actually, never become solved.

I started out by collecting all possible references to the subject of my study. In those days foreign literature was not available, and so we were limited to Japanese reports. Fortunately, as I'll describe later, the first approach to this subject originated, almost certainly, in Japan.

One of the first references I could get my hands on was one by the late MAKOTO SAITO, professor of the department of surgery in the school of medicine at Nagoya University, in which he reported that Lombre, a fat emulsion he had produced by emulsifying Lipiodol (an iodine oil) was successfully used in angiography, however, I could obtain no information about the preparation of Lombre. Another report, by SHOTARO YAMAKAWA, professor of internal medicine in the school of medicine at Tohoku University, and his students, described basic and clinical experiments with an intravenous nutritional fat emulsion; the results which had been presented in a special lecture at the general meeting of the Japanese Society of Internal Medicine. The fat emulsion, "Yanol", had been prepared by Professor YAMAKAWA in 1928, who used cod liver oil and butter oil as the raw materials and lecithin as an emulsifier.

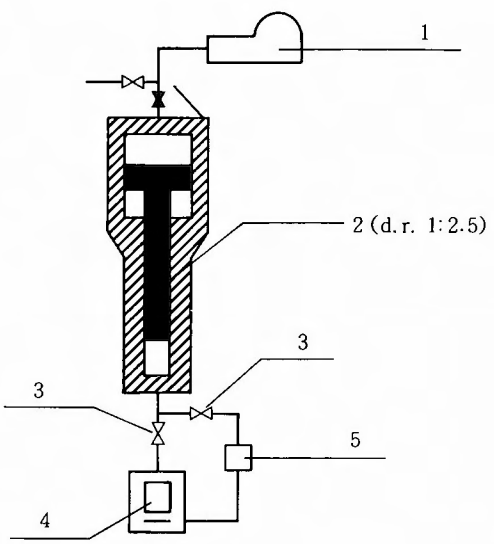


1. Ejection nozzle 2. Liquid-compressing cylinder
3. Check valve 4. Three-way cock
5. Compressed-gas storage 6. Water tank
7. Hydraulic press 8. Liquid tank

Fig. 1. High-pressure apparatus for preparing fat emulsions

Although the details of the preparation of Yanol were not described, I learned that it had been provided by Sankyo Pharmaceutical Co., Ltd. By the time I started my studies, however, the production of Yanol had been discontinued. Hearing that it had been used in a military hospital, I was able to obtain several samples. Chemical analysis proved that it contained only lecithin as an emulsifier, but no triglycerides. This was to be expected because the only colloid mills available then in Japan were those used to prepare emulsions of butter oil or creams for cosmetics. of butter oil or creams for cosmetics. In these mills, it is absolutely impossible to prepare fat emulsions composed of triglyceride particles, which is the lipid that is tolerated intravenously. Although Professor YAMAKAWA reported that large particles of lipids were well removed by centrifugation, it became clear that all particles of triglyceride were completely removed, and only a little lecithin remained in the fat emulsion. Actually, when infused into the veins of animals, the fat emulsion prepared by us could be histochemically stained in organs and tissues, although the lipid particles were less than 0.7 μ in diameter. On the other hand, the reports of the students who studied under Professor YAMAKAWA showed that the lipids which were infused into animal veins were changed into such small particles that they could not be histochemically stained at all. This finding, however, shows only that Yanol contains no triglycerides. Consequently, my next step was to go to the late SHINKICHI HORIBA and RYO KIYAMA, the greatest scientists in the field of colloid chemistry, who were professors of physical chemistry in the Faculty of Science at Kyoto University, and I received their kind instruction in colloid chemistry and high pressure chemistry.

In those days, methods in the formation of an emulsion, using ultrasonic equipment, had been



1. Air compressor 2. Piston
3. High pressure valve 4. Nozzle
5. Circulation pump

Fig. 2. Outlines of a homogenizer employed for preparing fat emulsions in the early stage of my basic study

studied by Dr. WOOD and others. My aim too, of course, was, by using such equipment, to emulsify lipids so that they could be used in intravenous infusions. However, the ultrasonic apparatus available at that time was not adequate, and our attempts ended in failure. After much trouble we finally constructed a homogenizer which was able to withstand 200 to 500 atmospheric pressures. (It is diagrammed in Figs. 1 and 2.) We examined the best conditions for preparing fat emulsions from all angles; i.e., rough emulsions were ejected through a nozzle 0.2 to 1.0 mm in diameter, etc. Our results were presented at the general meeting of the Japan Surgical Society in 1950. This was the first time that I reported my research at a general meeting.

In those days, although gelatin, Knox-20, and Demal-14, in addition to lecithin, were available as emulsifiers meeting our requirements, organic solvents were in short supply. Then, when our small ration of ethyl alcohol suddenly vanished into someone's mouth, my grief was too deep for tears.

At last, with extraordinary efforts, we succeeded in manufacturing a homogenizer for preparing fat emulsions which could withstand high pressures. By now we could receive foreign literature, and I knew that studies in this field, at the same time as ours, had been reported by many excellent workers in America: HOLT, MYERS, CLARK, DUNHAM, MCKIBBIN, MENG,

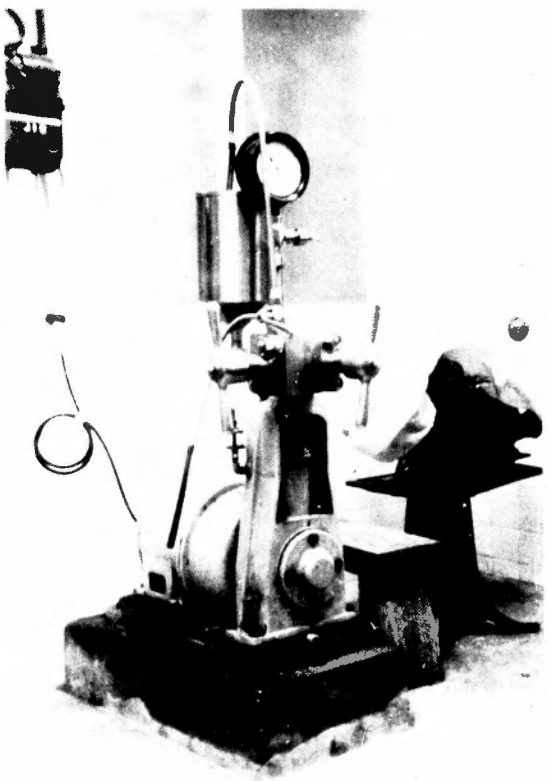


Fig. 3. Homogenizer

Table 1. Side effects due to cotton seed oil emulsions

Acute Toxicities	Chronic Toxicities (Overloading Syndrome)
1) Hypotension	1) Anemia
2) Tachypnea	2) Splenomegaly
3) Chest discomfort	3) Deposit of Thompson's pigment
4) Facial flushing	
5) Chill	
6) Pyrexia	
7) Low back pain	

SHAFIROFF, GEYER, and MOORE, who had done basic and clinical tests on fat emulsions for intravenous infusions prepared by an excellent high-pressure apparatus, diagrammed in Fig. 3. Thereafter, I changed my goal from the perfection of a homogenizer capable of withstanding high pressures (which wasn't my specialty), over to trying to discover the most suitable raw fat, and to this aim I devoted my best efforts.

In Japan I was the only one who had been studying in this field, but in America, excellent workers and technical equipment had enabled the research to progress to the point of clinical application. It was clear from the literature that the side effects of the fat emulsions were of great concern—acute toxicities such as hypotension, tachypnea, low back pain, chest discomfort, facial flushing, chills, and pyrexia; and chronic toxicities such as anemia, splenomegaly, and the appearance of Thompson's pigment in overload syndromes, as listed in Table 1.

As shown in Fig. 4, several kinds of saturated, mono-unsaturated, and, needless to say, poly-unsaturated fatty acids are present in the organs and tissues of the human body. So I prepared various single triglycerides containing a saturated or mono-unsaturated fatty acid, and compared their general nutritive effects. Triolein was the best, and undesirable damage of liver function or hemolysis occurred as the carbon chains of saturated fatty acids became shorter.

On the basis of theories current at the time, I compared the possibility of formation of aceto-acetic acid resulting from the β-oxidation of saturated, monounsaturated and poly-unsaturated fatty acids. For example, among C_{18} fatty acids, it was confirmed that such saturated fatty acids

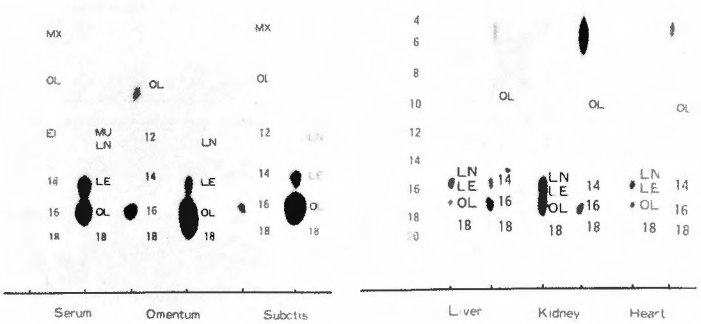


Fig. 4. Fatty acids in human tissues

as stearic acid were more ketogenic than unsaturated fatty acids such as oleic acid and linoleic acid, while linolenic acid was anti-ketogenic. Later it became clear that any saturated fatty acid greatly enhances the activity of HMG-CoA reductase which participates in cholesterol biosynthesis, while poly-unsaturated fatty acids may contribute to better nutrition (Fig. 5).

Furthermore, in cases of lipidosis due to diabetes or fatty liver, it has become clear that when saturated and mono-unsaturated fatty acids increase and combine with glyceride, not only at the α- and α'-positions, but also at the β-position where poly-unsaturated fatty acids combine in healthy subjects, then the turn-over rate of glyceride becomes slower and probably falls, causing lipid deposits in the body.

Therefore, I prepared various fat emulsions from natural fats or single triglyceridds synthesized chemically. The natural fats were butter oil, coconut oil, olive oil, camelia oill, sesame oil, soybean oil, cod liver oil, etc., each of which has a different kind and quantity of fatty acids. Their lipid-metabolism or lipid-utilizing activity was tested in the liver and other organs by histochemical methods or by the determination of tissue respiration by using Warburg's manometer. The results of these experiments showed that fat emulsions for intravenous feeding must be prepared from raw fats, the main components of which are mono- and poly-unsaturated fatty acid (essential fatty acids) and as little saturated fatty acid as possible. The natural fats which satisfy these requirements proved to be sesame oil and soybean oil. We reported these conclusions earlier than did any other workers in the world.

In those days in America, cotton seed oil was the most commonly used fat, and butter oil, apricot oil, cocoa oil, peanut oil, olive oil, and various chemically synthesized triglycerides were sometimes used. However, as noted above, the problem of side effects was yet to be solved.

Moreover, it was not yet well known how lipids were digested and through what route absorbed even after oral ingestion. We next examined fatty acids in the thoracic duct lymph and in portal blood by paper chromatography. Fortunately, the thoracic duct lymph and portal

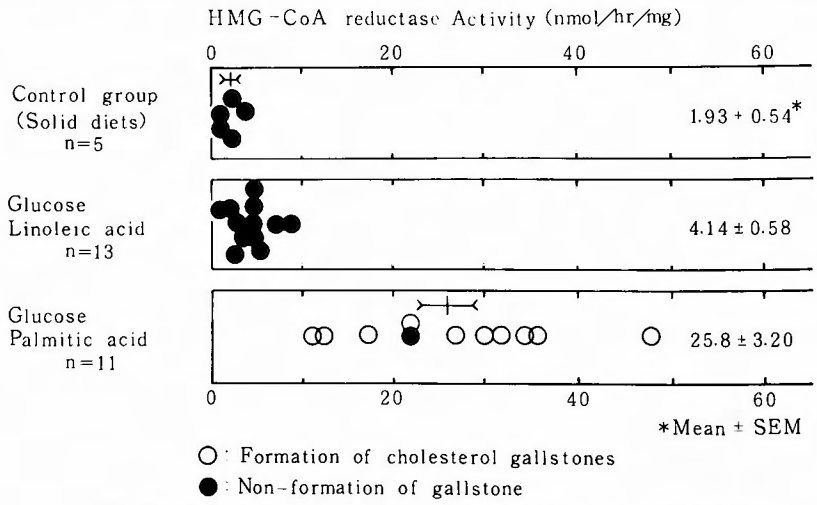


Fig. 5. Influence of dietary lipids on HMG-CoA reductase activity

blood do not contain fatty acids lower than lauric acid in the post-absorptive state. Therefore, we synthesized single triglycerides, such as trilaurin, tricaprin, tricaprylin, and tricaproin, and examined the fatty acids in the thoracic duct lymph and portal blood by paper chromatography, after the oral administration, to test on animals both an isomolar mixture and each fatty acid separately. We found that lower and intermediate fatty acids are transported mainly into the portal blood, and the higher ones into the thoracic duct lymph. Based on these findings, we decided that lipids which do not contain lower or intermediate fatty acids should be chosen for intravenous use.

In addition, we proved that when unsaturated fatty acids were erroneously treated or stored, auto-oxidation formed peroxides which induced fatty liver, liver necrosis, disappearance and necrosis of lymph nodules in the spleen, granular degeneration of renal epithelial cells, inhibition of enzymes and vitamins, etc.

It also became clear that fish oils, such as cod liver oil, with many highly unsaturated fatty acids, when made into emulsoids and infused intravenously, were apt to cause fatty liver.

For these reasons, we could not regard Yanol as the best fat emulsion for intravenous use, although we admired the ideas and zeal of the students of the late Professor SHOTARO YAMAKAWA.

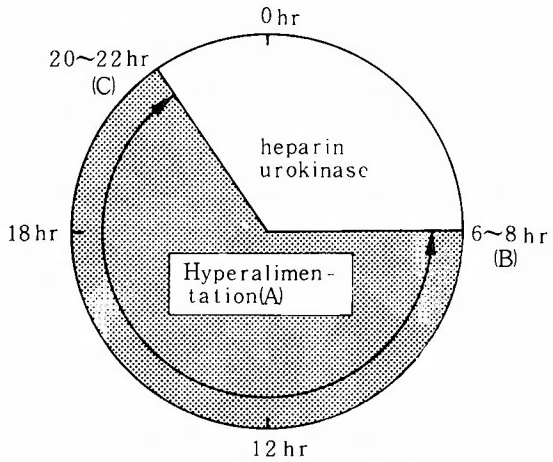
When these studies started, the only harm at all which people attributed to lipids was in relation to an outbreak of ketosis, an effect on the liver function, fatty liver, atherosclerosis, etc., and it was thought at the time that lipids could be actively synthesized from sugars in the body, which would provide equivalent calories; therefore the daily caloric requirement of lipids need not be determined. As a result, our earnest research often became the butt of ridicule and abusive language.

It is now generally considered that the rate of intravenous infusion of glucose must be kept at 0.5 g/kg/hour (Table 2). When biorhythm is totally ignored, and glucose solution is infused over 24 hours, 2400 calories can theoretically be supplied with only 600 g intravenous infusion of glucose. However, when the present concepts of biorhythm are taken into consideration, it becomes necessary to complete the infusion in 12–14 hours (Fig. 6). When excessive glucose is infused, hypertonic diuresis and hypertonic ketonemia with coma is induced. Even if an infusion is given in such a way that there is a corresponding rise in secretion of insulin in response to a gradual increase in the dose of glucose, an abnormal burden is placed on the pancreas, and its function may be affected. Now that the concept of individual biorhythm is established, we know

Table 2. Sugars employed for nutrient solutions

	Glucose	Fructose	Sorbitol	Xylitol	Maltose
Isotonic Solution	5%	5%	5%	4.56%	10%
Safe Infusion Rates g/kg/hr.	0.5	0.2～0.3	0.15	0.1～0.2	0.25～0.3

(Exp.) Glucose: 0.5 g × 50 kg (body weight) × 24 hrs. = 600 g/day



(A) Ono pack 2800 Cal/1950 ml
(B) Start of infusion
(C) End of infusion

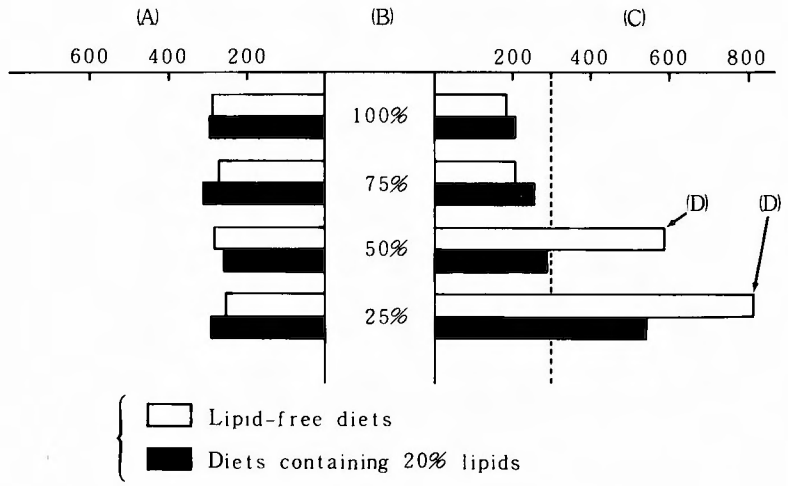
Fig. 6. Intermittent hyperalimentation

that we cannot depend on intravenous infusions of glucose alone, but need other nutrients also to cover up the faults. Nowadays we know that in traumatic or postoperative states, glycogenic amino acids such as alanine are mobilized to participate in glyconeogenesis, and on such occasions the tissues which receive their energy from glucose alone are limited to the central nervous systems, red blood cells, and white blood cells, and the other organs and tissues utilize fatty acids which are released from adipose tissues or ketone bodies.

Moreover, as the particular nutritional significance of essential fatty acids has been elucidated (i.e. a daily intake of about 8 g of linoleic acid), essential fatty acids also should be administered intravenously when all the calories needed must be supplied entirely by infusions.

The results previously reported by SWANSON show the protein-sparing action of lipids. On the left-side of Fig. 7, the basal values of nitrogen excretion represent, in nitrogen balance, the urinary nitrogen excretion in animals which are fed protein. On the right is shown the urinary nitrogen excretion of animals on protein-free diets. This figure shows that in animals receiving 75% or more of their required caloric intake, the measured values of nitrogen excretion are smaller than the basal values, whereas in those receiving less than 75% of the required calories, protein breakdown occurs in the body to supplement the shortage of energy, so that the measured values of nitrogen excretion exceeds the basal value. This figure also shows that animals on diets containing 20% lipids excrete less nitrogen than do those fed glucose as required calories only. Thus, lipids cannot be completely replaced by glucose. SWANSON's findings gave us the greatest possible support, since our studies on fat emulsions had been severely critisized until then.

At that time, various intermediates in the tricarboxylic acid cycle were being greatly emphasized as sparkers for fatty acid oxidation, and of course we also noted that glycerol might satisfy the need for the concomitant administration of glucose and vitamins, as well as providing



(A) Basal values of nitrogen excretion
(B) Caloric supplement (%)
(C) Measured values of nitrogen excretion (protein-free diets)
(D) Breakdown of body protein

Fig. 7. Protein-sparing actions of lipids

isoosmolarity. So we tried to prepare a fat emulsion with the same composition as that of the present Intralipid®, except that we used soybean lecithin as an emulsifier. There were no good methods of sterilization without boiling in those days. Boiling immediately destroys fat emulsions by enlarging lipid particles, so they are of no use in intravenous infusions. Therefore, a way to increase the stability of fat emulsions had to be found. These situations caused a dosage restriction and a high frequency of side effects in intravenous infusions of 20% sesame oil emulsion, "Fatgen-D®", which was prepared by us. It is really sad to realize that if excellent sterilization had been available in those days, fat emulsions similar to Intralipid® could easily have been produced in Japan, for I was the only one in those days to insist that fats for clinical use must be purified sesame oil or soybean oil, which do not contain any peroxides.

Soybean oils have the advantage of containing more linolenic acids that do sesame oils, which are more antiketogenic than oleic acid and linolic acid, and they do not contain sesamine and sesamol, which are present in sesame oils. However, at that time there was no way to avoid the use of purified sesame oils as raw materials, since other materials were scarce in Japan soon after World War II. Therefore, we prepared a fat emulsion of 20% sesame oil, Fatgen-D, which could be used clinically, at any rate, although its dose was limited (Fig. 8).

New techniques of sterilization now make it possible to prepare fat emulsions which can be infused in large quantities without any side effects. Therefore, it is now possible to prepare fat emulsions of the same composition as Intralipid®, except for the use of soybean lecithin which was always prescribed as an emulsifier prior to the preparation of Fatgen-D, A new soybean fat emulsion, Venolipid®, has already been on the market, kindly prepared with soybean lecithin as an emulsifier by Morishita Pharmaceutical Co., Ltd (Fig. 9). Scanning electron microscopy of

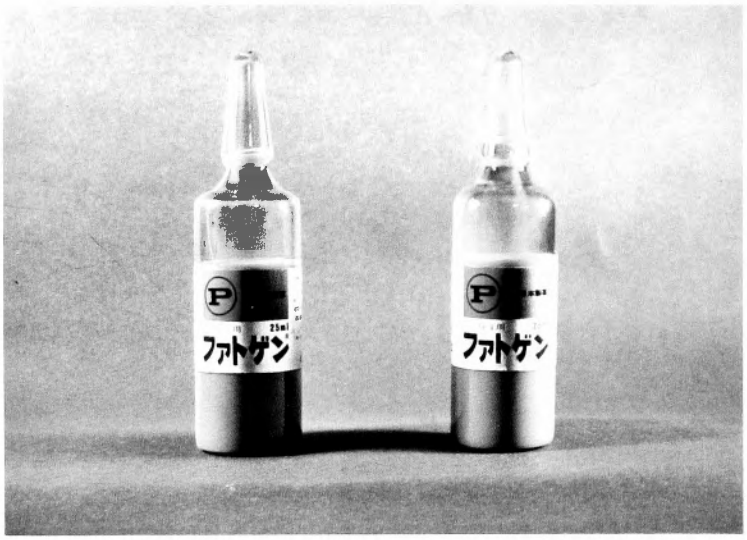


Fig. 8. Photograph of Fatgen-D Amples

this product simultaneously fixed with osmic acid and glutaraldehyde in combination with malachite green, as recently devised by us, shows the lipid particles in the fat emulsion to be so geneous that it can be safely used for intravenous infusion even after complete sterilization (Fig. 10).

So I can say that my life-work has reached its final stage, at last.

On the other hand, the progress in these studies has made it more necessary to elucidate the metabolism and physiological significance of poly-unsaturated fatty acids, e.g., essential fatty acids. In the early days, only the findings reported by BURR and DEUEL were well known in relation to the physiological significance of essential fatty acids: i.e., fatty acid deficiency can

Fig. 9. Photograph of Venolipid vials

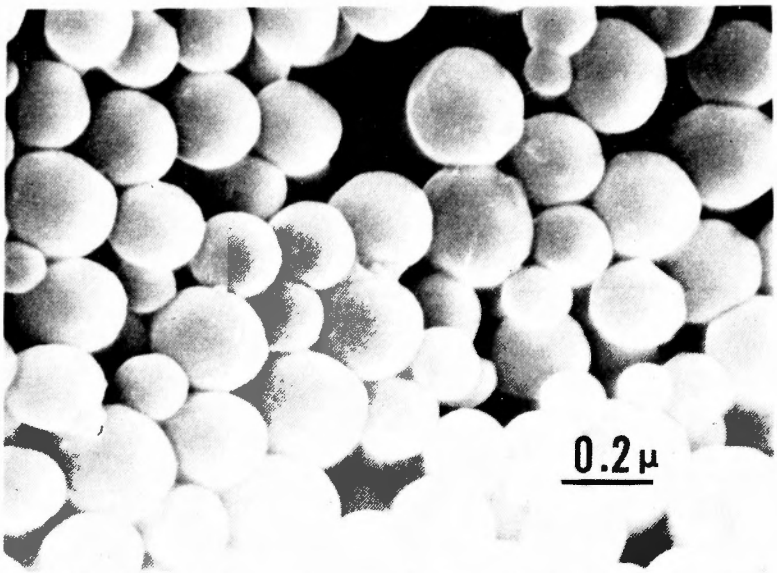


Fig. 10. Scanning electronmicroscopic findings of lipid particles in Venolipid

delay growth and cause tail necrosis, kidney damage with hematuria and death in mammals such as rats. In regard to the determination of fatty acids, there was only the alkaline isomerizing method devised by HOLMAN and HAYES, which had a large error in the determination. We tried to clarify the cause of this error, and ascertained that it resulted from a background absorption curve (Fig. 11). Next, we devised a modified method that resulted in few errors in fatty acid determination. This method enabled us to elucidate many physiological characteristics of essential fatty acids and led to remarkable progress in our studies especially with the use of thin layer chromatography, which was developed soon after, and gaschromatography, which Assistant Professor KISAKU SATOMURA studied under the late Professor HANSEN. Some important by-products of these studies are: a hypothermic anesthesia technique which has become popular throughout the world as an aid in open heart surgery in infants (BARRATT-BOYES named this the "Kyoto technique"), elucidation of the pathophysiology of cholesterol gallstone formation, etc.

My story goes back to about 1946, when I entered the department of surgery of Kyoto University. At that time, we had only actisol to prevent wound infections, blood transfusions were limited to 50 ml at most, and 40 ml of 20% glucose solution was the standard intravenous infusion, while subcutaneous solutions were a combination of 500 ml of 5% glucose and 500 ml of Ringer's solution. Under these conditions, which from the beginning we had to treat on patients who were also badly underfed, one can imagine what the results of surgery were like.

The Commercial availability of Politamin in 1950, advances in blood transfusion, the development of antibiotics beginning with penicillin, and the introduction of endotracheal anesthesia made advances in surgery more and more possible.

In our laboratory in 1963 or so, taking a hint from cardiac catheterization, we started hyperalimentation mainly with 50% hypertonic glucose solution and the concomitant infusion of fat emulsions through a catheter placed in the rapid blood stream of the central vein. The main

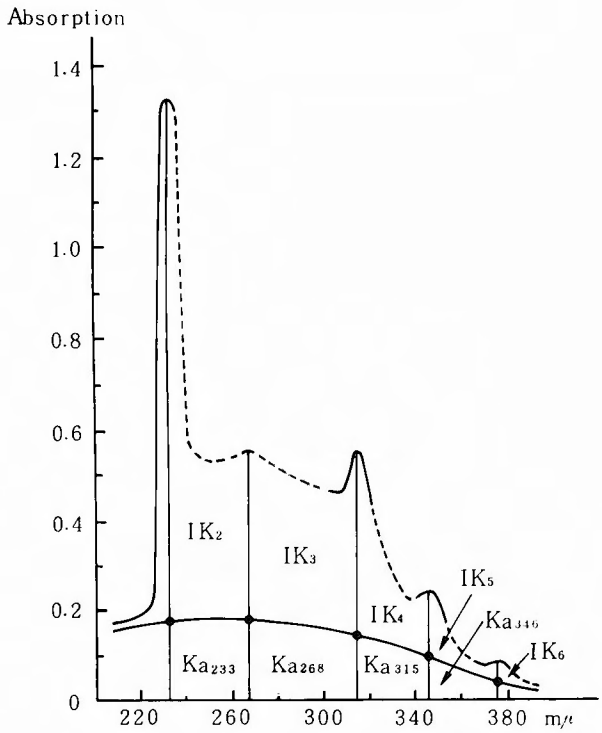


Fig. 11. Background absorption curve

points, including a discussion of some problems in the concomitant use of insulin, were presented in a chapter "Metabolic Care before and after Operations", of a book entitled "New Surgical Managements", which was published in 1964 by Igaku Shoin Co., Ltd. Although not published in European language, this preceded the report presented by Dr. DUDRICK in 1967. Because of worries about infections and thrombosis and occasional actual experiences with them, we were compelled to discontinue hyperalimentation.

Fat emulsions with similar compositions such as Lipomul® and Lipofundin®, were commercially available and clinically used in Europe in those days, made chiefly from cotton seed oil as a raw material (Table 3). However, there, too, those who used fat emulsions were worried about several side effects, as I mentioned before. In 1961, WRETLIND, HALLBERG, and SCHUBERTH in Sweden began to use clinically a 10% soybean oil emulsion, Intralipid®. It is well known that Europeans began to use this for total parenteral nutrition via peripheral veins, noting that it had fewer side effects and a high calorie potential.

On the other hand, in America where the sale of fat emulsions for parenteral use was not permitted, DUDRICK proposed in 1967 that hyperalimentation of calories exceeding basal metabolic rates could be supplied by hypertonic glucose solution through a catheter in the central vein instead of by peripheral veins, in the same way that we had already done. Because of our bitter experiences, described earlier, we discontinued parenteral fat infusions before DUDRICK proposed them, but have always struggled to find ways to use them safely and also with respect to the

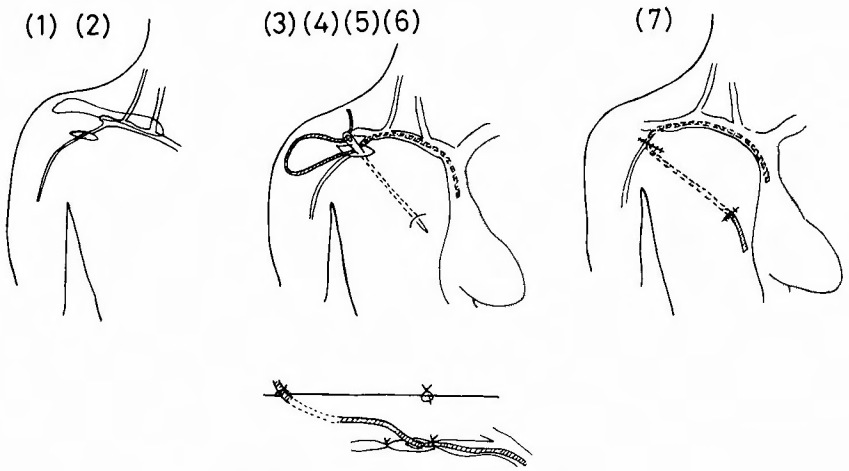
Table 3. Compositions of fat emulsions for intravenous injections (g/100 ml)

	Fatgen-D (Japan)	Intralipid (Intrafat) (Sweden, Japan)	Venolipid (Japan)	Lipiphysan (France)	Lipofundin (Germany)	Lipofundin S (Germany)
Plant oils	Sesame oil	Soybean oil	Soybean oil	Cotton seed oil	Cotton seed oil	Soybean oil
	20	10~20	10	15	10	10~20
Phospholipids (P. L.)	Soybean Lecithin	Yolk P. L.	Soybean Lecithin	Soybean Lecithin	Soybean P.L.	Soybean P.L.
	0.2	1.2	1.2	2.0	0.75	0.75–1.5
Sugars	Glucose	Glycerol	Glycerol	Glucose	Sorbitol	Xylitol
	8.0	2.5	2.5	5.0	5.0	5.0
Vitamin E	0.4	—	—	0.5	0.858	—
Amino acids	Methionine					
	400 mg	—	—	—	—	—
Distilled water	ad.	ad.	ad.	ad.	ad.	ad.
	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml

concepts of biorhythm.

Consequently, we used a silicone or heparinized catheter to prevent thrombosis, exposed the subclavian or cephalic vein, and fixed the catheter securely so that patients could walk and move their arms and hands soon after the start of hyperalimentation. (Fig. 12).

The routine method in which several bottles of nutrient solutions were set side by side and air needles inserted during intravenous infusion, inevitably allowed prolonged contact with the



(1) Incision of Trigonum omoclaviculare
(2) Exposure of cephalic vein
(3) Long subcutaneous tunnel constructed
(4) Silastic tube pulled out through the tunnel
(5) Skin fixation
(6) Insertion of the tube into the vein
(7) Tip of the tube inserted into the superior vena cava

Fig. 12. Insertion of silastic tube into the central vein

contaminated air in the sickroom. We tested countermeasures against such severe complications as infection and sepsis and hit on the use of soft bags. There could be filled and mixed within a laminar flow area, and several nutrient solutions could be infused together through a catheter in the central vein, as shown in Fig. 13. A subcutaneous tunnel was constructed so that part of the catheter could be buried as far as possible (Fig. 12). Moreover, to avoid the use of soft bags of vinyl-chloride which can release a plasticizer, we ordered new soft bags of a copolymer of ethylene and vinyl acetate from Terumo Co., Ltd., and Nipro Co., Ltd., which were free of this danger (Fig. 14).

Thus, a milipore filter, which we had had to set in the intravenous drip instillator circuit before, was not needed in the hyperalimentation system to prevent sepsis. Because fine lipid particles cannot pass through milipore filters, fat emulsions had to be infused separately into peripheral veins, when they were infused simultaneously with other solutions. The introduction of the one-pack method with the use of soft bags has eliminated such complications and made it possible for hyperalimentation, in which the concept of biorhythm are fully incorporated, to be performed with no fear of hyperosmotic diuresis, because a 50% hypertonic glucose solution can be diluted with an amino acid solution and a fat emulsion to achieve lower viscosity (Fig. 15). Consequently, the problems of overloading individuals and organs, and of various side effects due to 24-hour continuous infusion, have been solved.

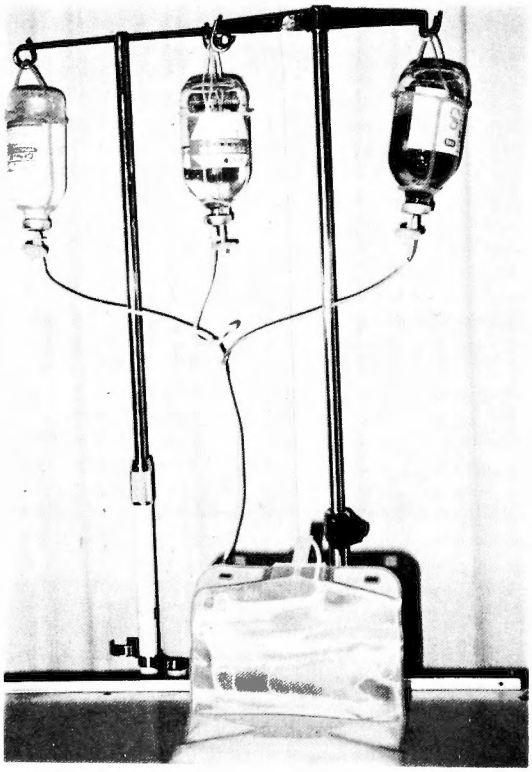


Fig. 13. Preparation of a pack filled with hyperalimentation solutions

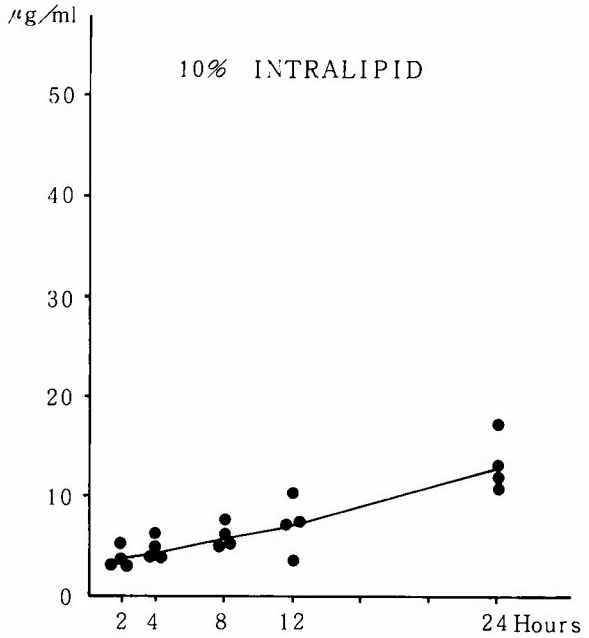


Fig. 14. DEHP released from polyvinyl chloride bag packed with fat emulsion

Of the patients who received hyperalimentation by the one-pack method for more than one month (we had performed liver function tests for GOT, GPT and alkali-phosphatase before, during and after treatment), only one had any abnormalities, a patient with cancer of bile duct. Complete prevention of red blood cell deformities in the blood stream might depend mainly on the use of the one-pack method, although such deformities have been until now considered to be due to the intravenous infusion of a large quantity of a colloid solution such as fat emulsion, as shown in Fig. 16. The more severe deformities of red blood cells, echinocytes or acanthocytes, occur in the blood stream of patients with severe hypoproteinemia.

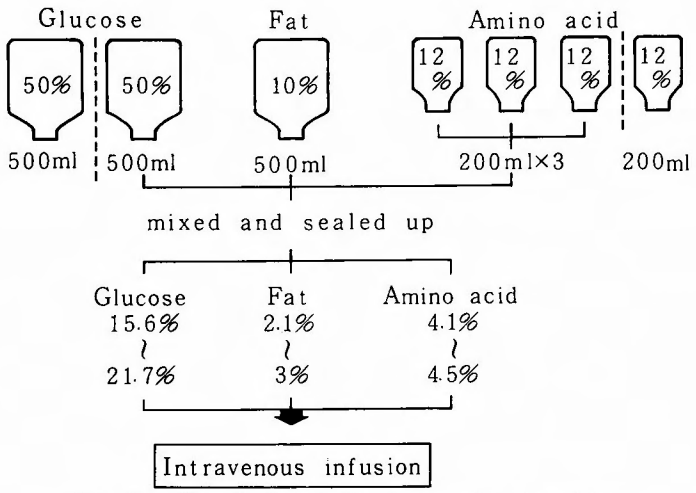


Fig. 15. Mutual dilution of various nutrients by mixing

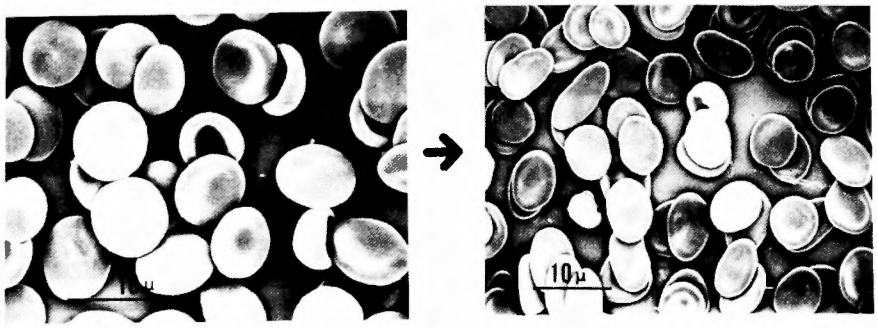


Fig. 16. Change in RBC caused by intravenous infusion of fat emulsion

The one-pack method of hyperalimentation involves the mixture of glucose, amino acids and fats in soft bags prior to infusion, so it is necessary to test the stability of the lipid particles to see whether or not the size of the fine particles increases in the mixed solution. As shown in Fig. 17, it became clear that the lipid particles remained unchanged for 48 hours after mixing, as long as the mixture was stored at 2 to 8°C.

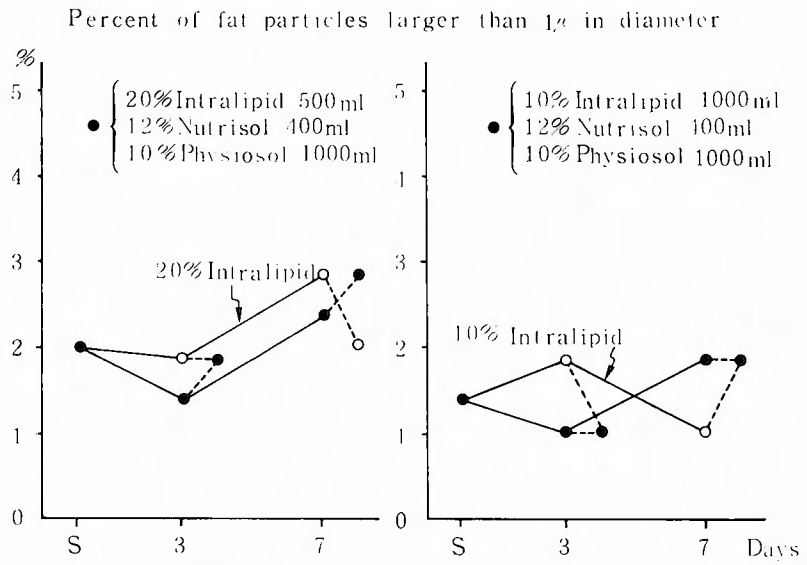


Fig. 17. Stability of fat emulsion in mixed solutions.

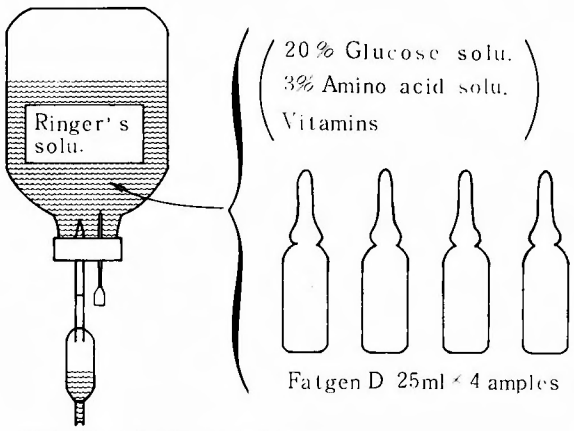


Fig. 18. Nutrient solutions
1955 to 1960 (Kyoto Univ. Surg. II)

My decision to try the one-pack method of hyperalimentation was probably due much to my past experience with the clinical application of 20% sesame oil emulsion, Fatgen-D, with added amino acid and glucose solution, which was then diluted 5 to 10 fold with Ringer's solution and infused into a peripheral vein (Fig. 18).

Prescriptions and merits of the one-pack method of hyperalimentation are summarized in Table 4. The method makes it possible to avoid trouble in changing bottles, and patients, too, are set free from the heavy bottles weighing 1.5 to 1.7 kg, so they can leave their beds, walk as far as they wish and chat with their friends in a visiting room even during hyperalimentation (Fig. 19). Thus, they can lead a more normal life soon after surgery, and their social rehabilitation is

Table 4. Characteristics of hyperalimentation solutions by one-pack method

	One-pack method	Conventional method of *Dudrick*
Contents of solutions	50% Glucose solution 500–1000 ml	50% Glucose solution 1500 ml
	12% Amino acid solution 600 ml	12% Amino acid solution 600 ml
	10% Fat emulsion 500 ml	—
	Electrolyte·Vitamin solutions 100 ml	Electrolyte·Vitamin solutions 100 ml
Concentration of sugars	14.7–22.3%	34.1%
Calories	2000–3000 Cal.	3400 Cal.
Osmotic diuresis	none	probably some
Exchange of bottles	unnecessary	2–4 times a day
Infusion pump	unnecessary	used every time
Degree of patient freedom	Both hands free Walking is possible Entirely free at night	Limitations are present Impossible to walk Surveillance needed at night
Filters	unnecessary	exchanged every three days
Sepsis	very rare	great posibility
Nursing care	almost unnecessary	indispensable

greatly accelerated. The method also makes it possible for an infusion to be carried out without the metabolic imbalance that may result from the conventional way of infusing intravenously 1000 ml of glucose solution, next 600 ml of amino acid solution, and finally 500 ml of fat emulsion in succession. Consequently, our one-pack method of hyperalimentation provides a more natural metabolism in line with cyclic hyperalimentation (Fig. 20), as was latter proposed by BLACKBURN.

Infusions, needless to say, are discontinued at night, and the catheter is flushed with an anticoagulant solution such as heparin or urokinase. Thus, the one-pack method of hyperalimentation, which we devised, may be called an "artificial gut", by which energy of 30 to 60 Cal per kg of body weight can be supplied daily (Table 4).

The results of these studies were presented at the symposium, "Infusion Therapy—its advances and problems", at the 19th general assembly of the Japan Medical Congress, which was held in Kyoto in 1975. Later, we learned that SOLASSOL et al. had devised a similar method almost concurrently with us. They used expensive soft bags of silicone. However, our cheaper disposable soft bags are more convenient and safer, and avoid problems of production and contamination.

Hyperalimentation has so far been used satisfactorily for the indications listed in Table 5

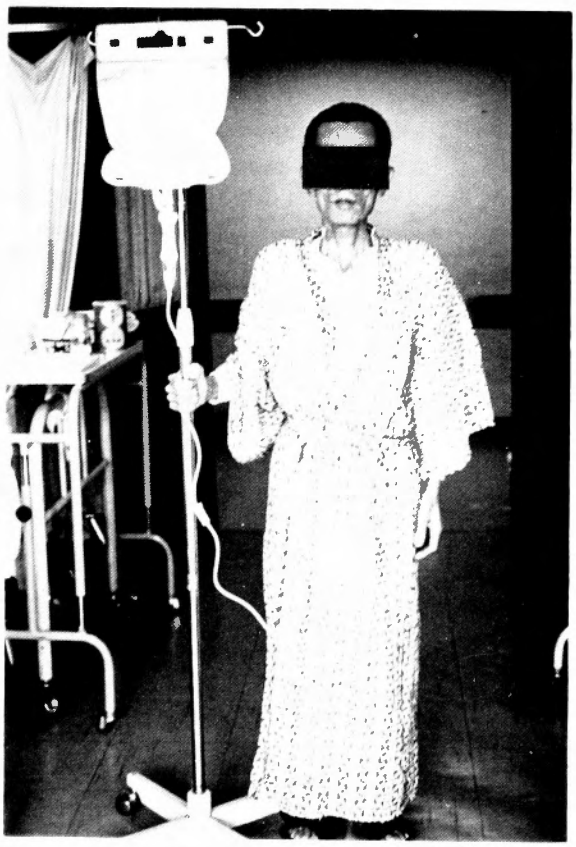


Fig. 19. Photograph of a patient receiving hyperalimentation by one-pack method.

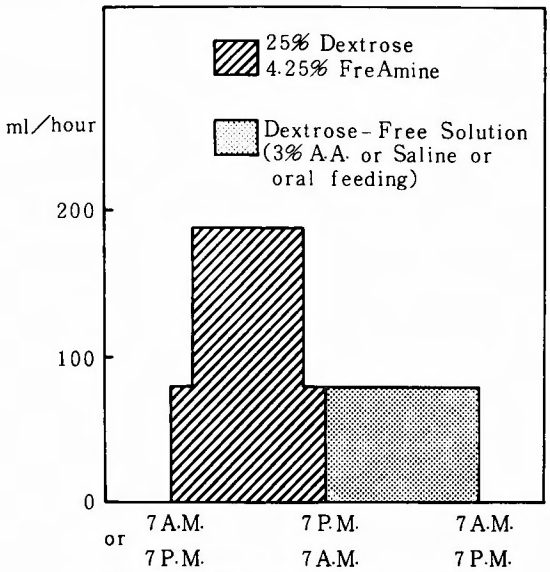


Fig. 20. Cyclic hyperalimentation

and 6, as compiled in 1976 by a lecturer in our department, HIROSHI TANIMURA.

The hyperalimentation solutions in the one-pack method are easy to prepare and safe to use, so that even home parenteral nutrition can be carried out. Patients can receive hyperalimentation at home after hospitalization, and instruction of the family for about a week in the method of exchanging soft bags, controlling infusion rates, and care of the intravenous catheter is given.

As an example, home parenteral nutrition was carried out in a patient incapable of oral food intake, an 80-year-old woman with a marked desire to live. During surgery inoperable eso-

Table 5. Indications for intravenous hyperalimentation

A.	Failure of enteral nutrition
	Severe malformation of digestive tract
	Functional insufficiency of digestive tract in premature and newborn infants
	Massive intestinal resection
	Obstruction of upper digestive tract
	Long-term intestinal paralysis
	Some neurosurgical problems
	Some otorhinological problems
	Anorexia nervosa
	Tetanus
B.	Temporary discontinuance of enteral nutrition
	Regional enteritis, Ulcerative colitis
	Acute pancreatitis
	Esophagus perforation
	Intestinal fistula, Pancreatic fistula
	Leakage of digestive tracts
C.	Nutritional improvement before and after operation
D.	Massive burns
E.	Renal failure

Table 6. Commercial preparations of hyperalimentation solutions (one-pack method) (Kyoto Univ. Surgery II, *Tanimura* 1976)

Sugar	50% Glucose solution 500 ml×2		500 g	2000 Cal
Amino acids	12% Proteamin 12X		30 g	120 Cal
	containing 5% xylitol 200 ml×3		72 g	288 Cal
Fat	10% Soybean fat emulsion 500 ml		50 g	550 Cal
Electrolytes				
Na, Cl	contained in Proteamin-12X			90 mEq, 90 mEq
K	Aspara K	40 ml		40 mEq
Ca	Calcicol	20 ml		9 mEq
Mg	Magnesol	10 ml		4 mEq
P	(Lecithin in fat emulsion)			216 mEq
Vitamins (B_1, B_2, B_6, B_{12}, C, K)				10 ml

Water content, 2282 ml; Calories, 2958 Cal (1.3 Cal/ml)

phageal carcinoma was found (Table 7). Soft bags packed with various solutions as prescribed for outpatients (Table 8) were sealed and given to her family. She maintained a daily caloric intake of 2358 Cal for over four months under the care of her family without any need for a trained nurse (fortunately one of her family was a doctor). Weekly urine tests were done for sugar and ketone bodies with Labsticks and her temperature was recorded three times every day. Thus, medical and nursing care was satisfactory with only one visit a month by a doctor.

The nutritional state of this patient improved greatly, and her family began to hope that the primary disease might be treated somehow, although she was very old and her carcinoma was not resectable.

We were persuaded to treat the patient with chemotherapy along with hyperalimentation. More than one month later, however, the patient died from advanced carcinoma.

Our longest experience with home parenteral nutrition has proceeded without trouble for more than one year.

Table 7. Patient on home parenteral nutrition

Subject:	K. G. (80-year-old woman)
Diagnosis:	Abdominal esophageal carcinoma (before operation)
Catheter:	Anthron I type
Insertion methods and sites of catheter:	
	from cephalic vein to superior vena cava by cut-down method
	7 cm subcutaneous tunnel
	anterior chest fixation
Infusion method:	
	Gravitation infusion by one-peack method
Duration:	About four months
Complications:	none

Table 8. Contents of hyperalimentation solutions (One-pack)

50% Glucose solution	500 ml	1000 Cal
12% Amino acid solution	600	408
10% Fat emulsion	500	550
Electrolytes	1000	400
Potassium preparation	40	—
Vitamins	14	—
	2654 ml	2358 Cal
		N·P Cal/N=198.3
Trace elements	1 ample (in pack)	once every 2 days
Folic acid	2 amples (intramuscular)	once a month
Iron preparation	2 amples (intravenous)	once a month

Thus, parenteral nutrition has made very great progress. We could not possibly have foreseen its success when I started my research in this field. In conclusion it would not be too much to say that it is as a result of the depleted food supply and the nutritional state of patients at the end of World War II, that I was inevitably destined to pursue this subject "Surgery and Lipid Metabolism" throughout my life. For more than thirty years, my studies have progressed one after the other as described in this paper, as I received hints or stimuli from the data obtained: Study on Fluids, Elucidation of Special Physiological Significance of Essential Fatty Acids, Study on a Factor Causing Pulmonary Edema, Study on the Surfactants of the Lung, Development of Hypothermic Anesthesia and its Application to Open Heart Corrective Surgery of Infants, and Elucidation of the Origin of Cholesterol Gallstones and Black Stones.

Ultimately these studies are all part of a single web, although the relationship among them sometimes seemed obscure. Solutions to the problems of lipid metabolism in surgery has been my goal throughout my active life.