The Use of Orally-fed Liquid Formulas *in Metabolic Studies*

By Edward H. Ahrens, Jr., M.D.,* Vincent P. Dole, M.D.,† and David H. Blankenhorn, M.D.‡

The performance of exact metabolic studies in human subjects frequently is complicated by problems arising from the use of assorted natural foods. Strict adherence to dietary prescriptions demands elaborate calculations by dietitions and considerable reliance on the average values published in standard food tables. In order to achieve better definition of intake and to minimize analyses of dummy diets, many workers have resorted to the feeding of the same menu every day, or to the use of two- or three-day alternate menus. Kinsell and co-workers[1] have solved many of the problems inherent in the use of natural foodstuffs by preparing formula diets stabilized with Tween 80®. Designed for certain specialized metabolic studies, these formulas represented unusual proportions of fat, protein, and carbohydrate, and were for the most part administered through a polyethylene tube kept for weeks at a time in the stomach or duodenum. In the nutritional management of surgical patients, Barron[2] has tube-fed a regular hospital diet ground into a watery suspension in a colloid mill. Other workers[3–10] have used orally administered fat emulsions as defined sources of fat in metabolic studies.

On the premise that balanced liquid formulas fed by mouth would be acceptable to adult subjects for prolonged periods, we have compounded a number of mixtures and put them to trial during the past year. The present report is based on experiences with 30 adult patients given oral formula feedings as their sole nutriment for periods of 2 to 16 weeks. The formulas proved entirely acceptable, economical, and simple to use.

Ingredients

Three basic formulas are given in Table I. These, with minor variations, have met the needs of four different types of metabolic study: (1) Variation in the amount of formula fed determined the caloric intake of obese subjects, without disturbing the composition of their diets. (2) Caloric levels remained constant while the proportions of protein, carbohydrate, and fat were varied. (3) Both the caloric value and the relative proportions of protein, fat, and carbohydrate were fixed in studies of a qualitative variable—the substitution of one type of fat for another. (4) Formula feedings have been used as a simple and effective means of limiting dietary sodium in the study of patients with hypertension, and of dietary copper in the study of patients with Wilson's disease.

The more elaborate experiments, such as the comparison of different dietary fats, show best the advantages of formula feeding. In these experiments protein was supplied by Lesofac®,* a commercial milk product very low

From the Hospital of The Rockefeller Institute for Medical Research.

* Associate, The Rockefeller Institute for Medical Research, and Associate Physician to the Hospital.

† Member, The Rockefeller Institute for Medical Research, and Physician to the Hospital.

‡ Assistant, The Rockefeller Institute for Medical Research, and Assistant Physician to the Hospital.

* Lesofac (Wyeth), manufacturer's analysis as follows: Protein 50.0%, carbohydrate 39.2%, fat 1.0%, cholesterol 25 mg. %, ash 5.8% (including sodium 0.02, calcium 0.80, potassium 0.85, magnesium 0.10), moisture 4.0%, vitamin B_1 2 mg. %, vitamin B_2 4 mg. %, niacinamide 20 mg. %.

in fat and sodium. Carbohydrate, above the amount included in Lesofac®, was added as dextrose. Fat in the different formulas was provided by cream or butter fat, egg yolk, prime steam lard, corn oil, cottonseed oil, coconut oil, cocoa bean oil, or synthetic triolein. Some of these formulas were analyzed for homogeneity of fat content by countercurrent distribution—a labor that was economical in relation to the study because it defined the dietary fat for many days of intake.

Evaporated milk is a convenient source of protein, but it introduces a poorly-defined mixture of proteins, fats, minerals, and vitamins. Lesofac® meets the needs of studies requiring control of fat or sodium and forms exceptionally smooth and durable emulsions. Ideally, one would like to have a single, defined protein, which is both nutritionally complete and free from accessory foods. Purified casein was used in trial emulsions, but proved a failure because the heavy denatured granules could not be ground and dispersed into a stable emulsion.

Dextrose has been used because it is less sweet than sucrose. Lactose caused gas and loose stools, and after a week had crystallized out of stored formulas. Starch produced an indigestible gluelike pudding, even after partial hydrolysis by autoclaving.

TABLE I

Basic Formulas

Quantities given make one unit of 500 calories as calculated from the conventional values: protein and carbohydrate = 4 cal./Gm.; fat = 9 cal./Gm.

	Weight	P	F	C	Na	Cholesterol	Cal.
	(Gm.)	(Gm.)	(Gm.)	(Gm.)	(mg.)	(mg.)	
(1) *Defined fat, low cholesterol, low sodium* (1.25 cal./Gm.)							
Oil (corn oil, cottonseed oil, coconut oil)	22.0	—	22.0	—	—	—	198
Lesofac®	37.5	18.8	0.4	14.7	7.5	9.4	136
Dextrose	41.5	—	—	41.5	—	—	166
Water, to make	400.0						
		18.8	22.4	56.2	7.5	9.4	500
Distribution of calories		15%	40%	45%			
(2) *Mixed animal fat, high cholesterol, low sodium* (1.25 cal./Gm.)							
Frozen egg yolk	25.0	3.5	7.5	2.5	6.5	318.0	91
Butter (unsalted)	18.0	0.2	14.6	—	3.2	50.3	133
Lesofac®	30.0	15.0	0.3	11.7	5.8	7.5	110
Dextrose	41.5	—	—	41.5	—	—	166
Water, to make	400.0						
		18.7	22.4	55.7	15.5	375.8	500
Distribution of calories		15%	40%	45%			
(3) *Evaporated milk formula with the same caloric distribution as human milk* (1.50 cal./Gm.)							
Corn oil (Mazola)	12.5	—	12.5	—	—	—	116
Evaporated milk (Borden)	175.0	12.0	14.0	17.5	175	47.6	243
Dextrose	34.5	—	—	34.5	—	—	141
Water, to make	333.3						
		12.0	26.5	52.0	175	47.6	500
Distribution of calories		10%	48%	42%			

Corn oil (Mazola*) proved to be a convenient source of fat. It is well defined in terms of fatty acid composition and is readily digested; although highly unsaturated it does not deteriorate rapidly at room temperature. Homogenates made with a refined fat are more stable than those that include milk or cream: corn oil formulas, for example, remained homogeneous after 12 weeks of storage at −15° C., while fat globules separated from milk or cream formulas during a single week of cold storage. Butter, on the other hand, makes durable formulas. Apparently the natural emulsion of fat in milk is broken much more easily during cold storage than the artificial emulsions produced by a high pressure homogenizer; limitation of storage time of milk formulas must be reckoned against their economy and ease of preparation.

It is desirable to set the caloric value of formulas at a fairly high level, since reduction in the volume of liquid simplifies storage and consumption. Caloric concentrations in the range of 1.25 to 1.50 cal./Gm. proved satisfactory for oral use. More concentrated formulas are too rich to be palatable but are suitable for tube feeding: a mixture of Lesofac®, corn oil, and dextrose, similar to No. 1 in Table I but containing relatively less protein and water (2.0 cal./Gm., P 10%, F 40%, C 50%), flowed by gravity through a polyethylene tube 30 inches long and 2.1 mm. outer diameter (size 8 French) at a rate of 5 ml./min. This formula was administered by tube to one undernourished patient with cirrhosis who was unable to take adequate food by mouth. She received 57 cal./Kg., given in six equal doses each day, without gastrointestinal distress.

Mineral intake presented no problem with milk formulas, except for the need of an iron supplement when the experiment lasted a month or more. Sodium was restricted in certain studies by substitution of Lesofac® for milk, but otherwise the mineral contents of the two formulas were similar. A capsule of mixed vitamins* given as a daily supplement brought the intake of known essentials above minimum requirements.

Bland formulas have proved to be more acceptable than flavored. Our initial use of coffee or chocolate syrup has been discontinued. Chromic oxide has been suspended in some formulas as an inert marker (1 mg. per ml. formula); it remained well mixed after freezing and thawing. Methyl cellulose (4 mg. per ml. formula) was added in some cases to provide residue.

Preparation

A Waring blendor suffices for the preparation of formula for one or two patients, but, if studies are to be carried out on a larger scale, it is more efficient to homogenize formulas in larger lots and to store the bottled formulas in the frozen state. Moreover, formulas made with a high-pressure homogenizer are much less viscous than those made with a Waring blendor; the viscosity of oral formulas is of relatively little importance, but is critical if the formula is to be fed by tube. At the present time we prepare formulas in 40-Kg. batches; two people can process at least 6 batches in one day—enough to feed about fifteen patients for a week. The cost of these operations (materials and salaries of personnel) is less than one-tenth of that required to run a conventional metabolic kitchen.

Equipment (total cost about $1000): (1) a Toledo scale of 45-Kg. capacity with double-beam counterbalance, Model 2081; (2) two aluminum tanks of 10-gallon capacity with outflow spigot, one in which to premix the ingredients on the scale and the other to receive the emulsion from the homogenizer; (3)

* Mazola (Corn Products Refining Co.), manufacturer's analysis as follows: Glycerides 98.1%, nonsaponifiable matter 1.9%, free fatty acids 0.03%, phospholipids—trace; iodine number 125; component fatty acids—linoleic 56.2%, oleic 30.1%, palmitic 9.9%, stearic 2.9%, hexadecenoic 0.5%, myristic 0.2%, above C_{18} 0.2%; component glycerides: mono-oleo-dilinolein 49.2%, mono-saturated-dilinolein 34.2%.

* Unicap (Upjohn), manufacturer's analysis as follows: vitamin A—5000 U.S.P. units, vitamin D—500 U.S.P. units, ascorbic acid—37.5 mg., thiamine hydrochloride—2.5 mg., riboflavin—2.5 mg., pyridoxine hydrochloride—0.5 mg., calcium pantothenate—5.0 mg., nicotinamide—20 mg., folic acid—0.25 mg., vitamin B_{12}—1 μg.

Fig. 1. Equipment used for homogenization of formula in 40-Kg. batches. Ingredients are added by weight to container on scale and premixed with food whipper. Mixture flows into homogenizer bowl, and homogenate is forced through tubing into container on right. Cartons are filled and stored in deep freeze until thawed for use.

a Logeman homogenizer, Model A40, with special outflow nozzles, Model 40; (4) paraffin-coated conical containers, pint or quart sizes (Sealright Kones), with flat, heavy paper disc stopper. Figure 1 pictures the homogenizing equipment in our formula kitchen.

One of the aluminum tanks and a large food whipper with a pan to hold it are counterbalanced on the scale to zero weight. Most of the water to be used in the formula is run into the tank, and then the various ingredients are measured in by weight—first the water-soluble ingredients and last the oil—with vigorous stirring after each addition. Finally, the batch is made up to weight with water. Fats with a high melting point, such as lard (35° to 38° C.) or butter, are warmed until liquid and stirred into the mixture. If the water temperature in the pre-mixing container is held between 30° and 37° C., water-miscible ingredients can be incorporated easily and the oil subsequently added does not separate spontaneously.

After thorough manual mixing in the first tank, the batch is run by gravity into the homogenizer and from there is discharged through the homogenizing orifices into Tygon tubing and up into the second tank. The entire batch is allowed to accumulate, then is stirred to assure uniformity and is poured out into paraffined containers. While one worker fills and caps the containers, the other weighs out a new batch into the first tank. It is advantageous to stamp each cap with formula number and date before inserting into the containers. The containers are stored at —15° C. until required. They are then thawed at room temperature for 4 to 6 hours and held in the ward refrigerator until weighed out for serving that day. The emulsion of thawed formulas is broken on refreezing; unused thawed containers are discarded at the end of each day.

Bacteriological studies of each batch have been made. Loopfuls of undiluted formula taken immediately after preparation and samples of the basic ingredients were streaked on blood agar and eosin-methylene blue pour plates. In all cases the processed formulas showed an increased growth of air-borne organisms as compared to the ingredients, but in no instance have any pathogens been recovered. Storage at —15° C. and subsequent thawing had no significant effect on the colony counts, which always were far below the number allowed in pasteurized milk.

Clinical Use

Thirty patients have been fed completely on a formula basis for periods up to 16 weeks. Nausea, vomiting, diarrhea, flatulence, and bloating were absent except as rare episodes which disappeared during continued formula feeding. One patient with cholelithiasis had suffered from post-prandial gas and fullness for three years while on a solid diet, and remained free of these complaints over a period of four months when fed solely on a formula containing 40% of calories as corn oil. Bowel movements have been formed, but less frequent and copious on these residue-free diets than on solid foods. With the formula divided into five or six feedings during the day, the patients reported an almost constant feeling of satiety, even when the total intake was reduced to 600 calories per day.

Dogs did well when fed solely on formulas in an experiment on the effect of dietary sodium. The low sodium formula (No. 1, Table I) was used as a simple means of limiting intake, the same formula with added sodium chloride (2.1 Gm./L.) being used as a control. Twelve dogs took the feedings well for periods of 2 to 10 weeks, held steady weights or gained, had no diarrhea, and seemed in good general health.

Since it is possible by this technique to eliminate daily variation of the diet, fluctuations of body weight from day to day are minimized. As examples, the daily weight records of four hospitalized patients can be cited in terms of means and standard deviations: 47.9 ± 0.15 Kg. (30 days), 44.9 ± 0.20 Kg. (23 days), 58.1 ± 0.20 Kg. (42 days), and 64.0 ± 0.10 Kg. (24 days). We have not been able to achieve this degree of stability with conventional diets, even when these were served from a metabolic kitchen.

Great demands are put upon the staff of a metabolic kitchen, as well as upon the patient, in any experiment needing exact and simul-

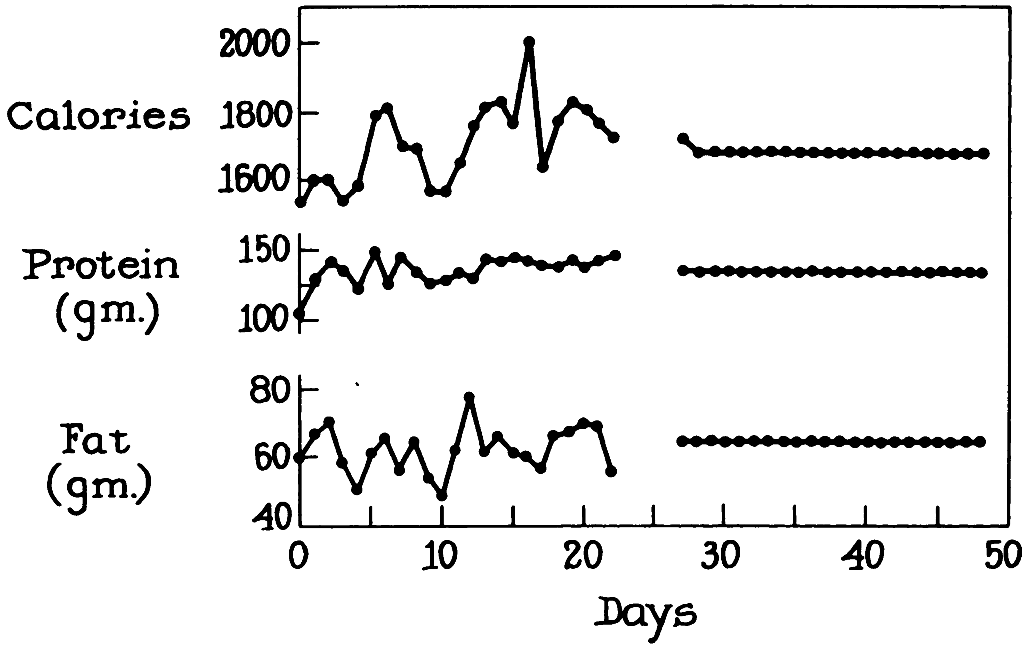

Fig. 2. Dietary intake of a patient fed mixed natural foods (day 0 to day 22) contrasted to liquid formula (day 27 to day 48).

taneous control of several different dietary variables: calories, fat, carbohydrate, protein, minerals, vitamins, and possibly other factors. Figure 2 contrasts the variations encountered in one experiment which started with the feeding of mixed natural foods and ended with the use of formulas.

The digestibility and high caloric value of liquid formulas suggest that they might be useful in the treatment of malnourished patients. To date, however, our main experience has been limited to the feeding of patients who were either normal or overnourished.

Summary

Oral formulas as a sole source of nutriment proved to be valuable in a variety of metabolic studies. Patients had no difficulty in taking liquid feedings for periods up to 16 weeks. Dogs, in one experiment lasting 10 weeks, maintained weight or gained. As compared to mixed natural foods, formulas have the advantages of constant and defined composition, economy, and ease of preparation. A few basic formulas can meet the needs of various metabolic studies. The three most useful in our experience are described.

References

1. Olson, F. Michaels, G., Partridge, J. W., Boling, L., Margen S., and Kinsell, L. W.: The use of formula diets administered via polyethylene tube or orally for constant intake (balance) studies. J. Clin. Nutrition 1: 134, 1953.
2. Barron, J.: Tube feeding with liquefied natural foods. *Henry Ford Hosp. Med. Bull.* 1: 13, 1953.
3. Geyer, R. P.: Fat absorption and the experimental basis of oral fat emulsions. *Ann. New York Acad. Sc.* 56: 16, 1952.
4. Shoshkes, M.: Clinical studies on the use of an oral fat emulsion. *Ibid.* 56: 22, 1952.
5. Van Itallie, T. B., Moore, F. D., and Stare, F. J.: Oral fat emulsions in the study of calorie-nitrogen relationships in man. *Ibid.* 56: 28, 1952.
6. Levenson, S. M., Lounds, E. A., and Morris, R.: Oral fat emulsions in the feeding of patients with severe burns. *Ibid.* 56: 37, 1952.
7. Albanese, A. A.: The use of oral fat in hyperalimentation and parental alimentation. *Ibid.* 56: 55, 1952.
8. Grollman, A.: The use of oral fat emulsions in experimental and clinical medicine. *Ibid.* 56: 65, 1952.

9. Stein, I. F., Jr., Kuhl, W. J., Goldberg, E. M., Grossman, M. I., and Meyer, K. A.: The use of oral fat emulsions in surgical patients, by mouth, gastrostomy, and jejunostomy—clinical and metabolic studies. *Ibid.* 56: 69, 1952.

10. Lowe, C. U., and May, D. D.: Absorption of orally administered emulsified lipid in pancreatic insufficiency in infants and children. *Ibid.* 56: 93, 1952.

Resumen

El uso de fórmulas líquidas administradas por vía oral en los estudios metabólicos

Las fórmulas orales como fuente alimenticia única han demostrado su valor en una variedad de estudios metabólicos. Los pacientes aceptaron sin dificultad alguna la alimentación líquida durante períodos de hasta 16 semanas. Perros, en un experimento continuado por un período de 10 semanas, mantuvieron o aumentaron su peso. En comparacíon con los alimentos mixtos naturales, las fórmulas ofrecen las ventajas de su composición constante y defenida, economía, y facilidad de preparación. Unas pocas fórmulas básicas pueden satisfacer los requerimientos de diversos estudios metabólicos. Se describen las tres fórmulas que han sido las más útiles en la experiencia de los autores.