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Hyperalimentation in infants

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With 12 figures and 7 tables

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The first demonstration of normal growth and development in Beagle puppies fed all nutrients entirely by vein was presented before the International Society of Parenteral Nutrition in Hamburg in 1966 (1). The crystalline solution contained approximately 20 to 25 percent dextrose, four to five percent amino acids, and five percent solute in the form of minerals, vitamins, and trace elements. The solution was propelled continuously through a 0.22 micron membrane filter and an indwelling catheter into the superior vena cava. The proximal end of the catheter was tunneled sub-

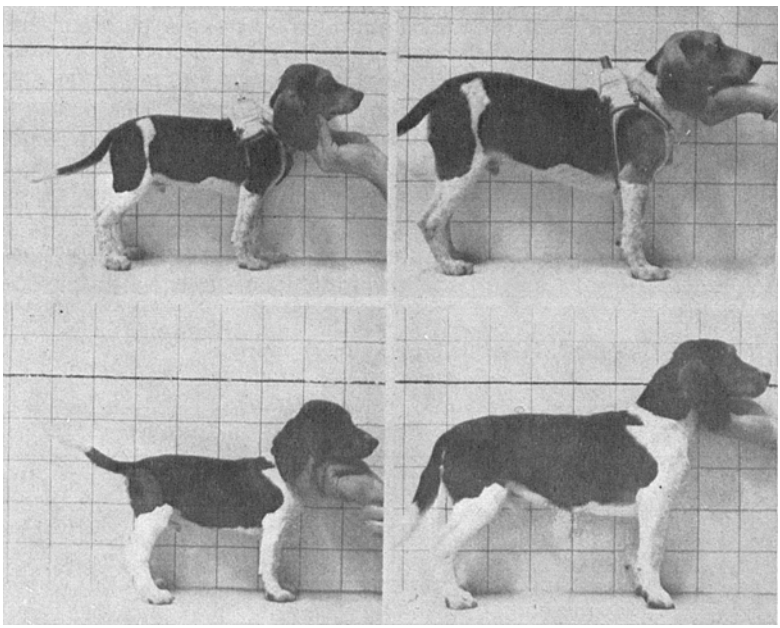

Fig. 1. Two litter mate male Beagle puppies at six weeks of age are demonstrated in the left hand frames. The same animals are demonstrated 100 days later in the right hand frames. The upper animal was maintained entirely on intravenous hyperalimentation. The lower animal was maintained on an oral diet recommended for Beagle puppies. Each animal developed normally and comparably.

Tab. 1. Nutrients (kg/day) puppy

		Oral diets	
		Recommended	Control
Protein	gm	8.8	10.5
Carbohydrate	gm	15.9	18.0
Fat	gm	2.6	3.3
Calories	Kcal	140–200	140
Water	ml	–	100–140

		Intravenous diets		
		"Balanced"	"Essential"	"Fat-free"
Protein	gm	4.0	4.0	4.0
Carbohydrate	gm	25.0	30.0	31.0
Fat	gm	2.6	0.6	0.0
Calories	Kcal	140	140	140
Water	ml	130–190	130–160	130–160

cutaneously from its insertion site in an external jugular vein to exit through the skin on the back and was attached to a counterbalanced, swivel apparatus that allowed the animal full range of motion in any direction within the cage (2). Litter mate male Beagle puppies weighing approximately 3 kg at twelve weeks of age were selected for comparison. One animal of each pair was fed entirely by central vein. The control animal was fed an oral diet for the same study period. Each of the twelve animals grew and developed normally and comparably. Figure 1 demonstrates the results obtained in one pair of animals studied for 100 days.

The basic nutrients required for growth in Beagle puppies fed by mouth were given to control animals in somewhat greater than the recommended doses (Tab. 1). In formulating the intravenous diets used by *Dudrick* et al. (1), only half of the recommended nitrogen ration could be

Tab. 2. Minerals-MG (kg/day) puppy

	Oral	
	Recommended	Intravenous
Sodium	210	100
Potassium	440	115
Chloride	315	225
Calcium	530	72
Phosphorus	440	58
Magnesium	22	4
Iron	1.3	0.058
Copper	0.16	0.065
Cobalt	0.055	0.041
Manganese	0.22	0.14
Zinc	0.22	0.14
Iodine	0.066	0.046

Tab. 3. Vitamins (kg/day) puppy

	Oral Recommended	Intravenous
A	200 IU	100 IU
D	20 IU	10 IU
E	2.2 IU	0.05 IU
Thiamine	0.03 mg	0.5 mg
Riboflavin	0.09 mg	0.1 mg
Pyridoxine	0.05 mg	0.15 mg
Niacin	0.4 mg	0.1 mg
Pantothenic Acid	0.1 mg	0.25 mg
C	–	5.0
B_{12}	0.0013 mg	0.003 mg
K	–	0.1 mg
Folic Acid	0.009 mg	0.015 mg
Choline	60 mg	25 mg
Biotin	–	0.007 mg
PABA	–	2.0 mg

given by vein because amino acid toxicity occurred whenever the daily dose exceeded 4 gm/kg/day. Therefore, additional carbohydrate was given in the intravenous diet in order to induce maximum protein sparing and utilization of amino acids for protein synthesis rather than for energy. In the initial intravenous diet, the recommended fat allowance was given intravenously as a fat emulsion. When the Food and Drug Administration abruptly withdrew the cottonseed oil emulsion, Lipomul, from the United States Formulary, the remaining intravenous fat available in the laboratory was rationed. It was thought that the essential fatty acid requirements could be met in the animals by infusing doses of 0.6 gm/kg/day.

Tab. 4. Comparison of daily average pediatric nutrient requirements per kilogram

	Oral Recommended	Intravenous
Protein	2.5 gm	4 gm
Calorie	115 Kcal	125 Kcal
Water	150 ml	125 ml
Sodium	46 mg	100 mg (4–5 mEq)
Potassium	58 mg	156-195 mg (4–5 mEq)
Chloride	150 mg	150 mg (4 mEq)
Calcium	218 mg	72 mg (3–4 mEq)
Phosphorus	218 mg	58 mg (5–6 mEq)
Magnesium	60 mg	25 mg (2 mEq)
Iron	6 mg	0.02 mg
Copper	0.07 mg	0.022 mg
Cobalt	–	0.014 mg
Manganese	0.2 mg	0.04 mg
Zinc	0.3 mg	0.04 mg
Iodine	0.07 mg	0.015 mg

In order to keep the diet isocaloric, additional carbohydrate was added. After the supply of intravenous fat was exhausted, fat was necessarily omitted from the diet, and additional carbohydrate was added to the crystalline solution. Serendipitously, administration of this solution was the anlage of the intravenous hyperalimentation technique as it is now practiced (Tab. 1). The animals grew and developed just as well on a fat free diet for periods of up to eight months as they had on the two diets containing fat for similar periods of time.

The differences between the dosages used for the intravenous and oral minerals were derived from initial reasonable estimates coupled with serial measurements of serum levels and urinary output of the various elements (Tab. 2). Calcium was given as organically-bound calcium gluconate, and phosphorus was given as organically-bound sodium glycerophosphate to avoid precipitation.

Vitamin A, D, E, C, thiamin, riboflavin, pyridoxine, niacin, and pantothenic acid were given as the commercially available vitamin preparation, MVI. Vitamins B_{12}, K and folic acid were given parenterally in the recommended dosages once weekly. In the dog, choline, biotin and paraaminobenzoic acid serve as vitamins and must be added in the recommended doses to produce normal growth and development. When using the commercially available product MVI, the fat soluble vitamins were given in lower than the oral recommended dosages because of their tendency to accumulate in the liver. The water soluble vitamins were given in higher than recommended dosages because they are readily excreted via the kidneys (Tab. 3).

Successful achievement of normal growth and development in animals as well as positive nitrogen balance in adult surgical patients attested to the probable safety of providing all nutrients entirely by vein to the newborn human infant. Based on knowledge of the daily average pediatric nutritional requirements, the information obtained in producing normal growth and development in Beagle puppies, and serial serum and urine measurements of administered minerals and electrolytes, a solution

Tab. 5. Comparison of daily average pediatric vitamin requirements

	Oral	
	Recommended	Intravenous
Vitamin A	1,500 IU	3,000–4,000 IU
Vitamin C	30 mg	150–200 mg
Vitamin D	400 IU	300–400 IU
Vitamin E	–	1.5–2.0 IU
Thiamine	0.4 mg	15–20 mg
Riboflavin	0.6 mg	3–4 mg
Pyridoxine	0.25 mg	4.5–6.0 mg
Niacin	6 mg	30–40 mg
Pantothenic Acid	–	7.5–10.0 mg
Vitamin K	1.5 mg	1.0–1.5 mg
Folic Acid	0.35 mg	0.5 mg
Vitamin B_{12}	1 mcg	1 mcg

providing adequate intravenous requirements of the major nutrients for newborn infants was developed (3, 4, 5) (Tab. 4). Initially, 4 gm of protein in the form of fibrin hydrolysate were given per kilogram daily. Subsequently, normal growth and development have been achieved in infants receiving 2½ to 3 gm of intravenous amino acids/kg/day. Historically, the higher dose of nitrogen substrates was given to insure delivery of maximum quantities of protein moieties for tissue synthesis.

Tab. 5 compares the intravenous dosages of vitamins administered in the pediatric hyperalimentation solution with the oral recommendations. Vitamins A through pantothenic acid were given in the fixed ratios which were present in the commercially available parenteral vitamin mixture, MVI. The limiting vitamin in this mixture for infants is vitamin D. This vitamin is given in a dose of 300 to 400 international units per day in order to prevent the development of rickets. Of necessity, the remainder of the vitamins are given in somewhat excessive quantities. To date, hypervitaminosis has not been reported. Vitamin K, folic acid, and vitamin B_{12} are given individually in approximately the daily recommended doses. During the initial stages of pediatric hyperalimentation, it was assumed that the intravenous dose of vitamin D would be somewhat less than the oral recommended dose because a major function of vitamin D is to aid in the absorption of calcium and phosphorus across the gastrointestinal tract mucosa. A reduction in the intravenous dose of vitamin D to 100 to 200 international units produced decalcification, particularly of the tibial plateau, and the development of a rachitic rosary at the costochondral junctions within a three week period. Reestablishment of vitamin D administration at a dosage level of 400 international units quickly produced regression of the rachitic clinical manifestations.

A unit of pediatric hyperalimentation solution capable of providing the daily nutrient requirements for the average newborn infant, can be formulated easily in the United States from commercially available products in any hospital. The combination of 400 ml of protein hydrolysate or crystalline amino acids with 250 ml of 50 % dextrose produces a solution which contains approximately one calorie per ml (Tab. 6). In order to complete the solution, however, 75 ml of additives are made to the base

Tab. 6. Unit preparation of pediatric solution

Base Solution			
400 ml	5% Glucose 5% Protein Hydrolysate	160 Kcal	20 gm Glucose 20 gm Hydrolysate
+			
250 ml	50% Glucose	500 Kcal	
650 ml		660 Kcal	
+			
75 ml	Additives		
725 ml	Final Solution		

Infusion rate: 145 ml/kg/day = 130 Kcal/kg/day

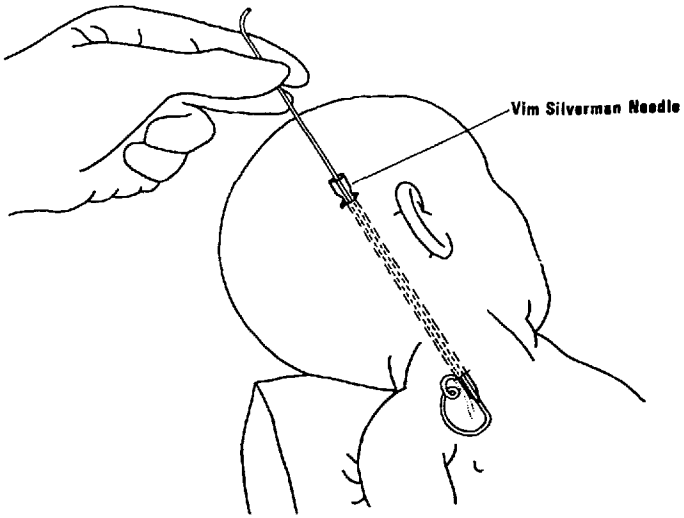

Fig. 3. The catheter is directed subcutaneously through a *Vim Silverman* needle to emerge through a small incision in the parietal scalp behind the ear. With minimum trauma to the infant, the needle may be removed, thus leaving the catheter in place in a long subcutaneous tunnel.

contemplated, the infant should be maintained on a metabolic bed for accurate collection of all external secretions (Fig. 4).

In order to insure maximum safety to the patient, our group strongly recommends that any institution in which hyperalimentation is practiced should have a designated and qualified hyperalimentation team. The minimum team should consist of an attending physician, well versed in

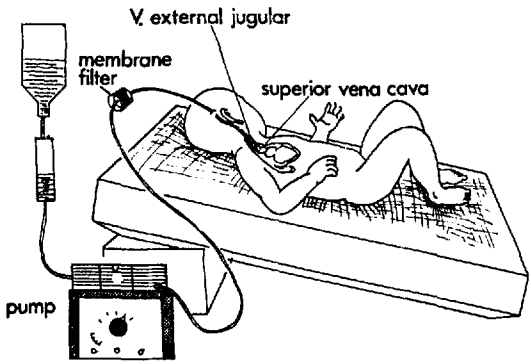

Fig. 4. Hyperalimentation solution is delivered to the infant continuously and accurately by means of a constant infusion pump. A 0.22 micron membrane filter is inserted between the catheter and the intravenous administration tubing. The infant is maintained on a metabolic bed in order to provide accurate collection of all urine and other wastes.

nutrition and metabolism, a conscientious interested resident or research fellow, a pharmacist trained in solution formulation, and a research technician or nurse. Other members of a truly complete team would include a nutritionist, physical therapist, social worker, and psychiatrist. It has been demonstrated all too often in the literature (9, 10, 11) that failure to comply with the standard procedures outlined by our team for the execution of safe and effective intervenous hyperalimentation will result in an inordinately high rate of metabolic, mechanical and infectious complications. In order to minimize the development of inflammation and infection at the catheter-skin exit site, the dressing is changed at least three times a week; the skin around the catheter is treated with iodine or other antiseptic solution; and fresh antimicrobial ointment is applied. A new sterile dressing is fixed to the skin by tincture of benzoin and adhesive tape, and the intravenous delivery tubing is changed. All connections are secured with tape to prevent accidental disengagement. The importance of conscientious, meticulous and regular catheter care cannot be overemphasized.

The indwelling central venous catheter should be maintained as an intravenous life-line. That the catheter should be used exclusively for delivery of the intravenous hyperalimentation solution is inherent in this philosophy. The temptation to withdraw blood via the catheter, to use the catheter for frequent central venous pressure monitoring, to inject bolus medication via the catheter, or to use the catheter for blood constituent administration must be repressed. Three-way stopcocks within the delivery system must be condemned, for maintenance of the sterility of any system containing a three-way stopcock is virtually impossible.

Should the infant develop fever or other signs of infection or sepsis, the physician should promptly and thoroughly evaluate the fever of unknown origin. Therefore, the chest, urinary tract, and wound must be completely examined. If no source of systemic infection can be detected, the intravenous tubing and bottle or bag of fluid should be changed and cultured. If the patient does not improve in one to two hours, the catheter should be incriminated empirically as the source of sepsis, and the catheter should be immediately removed and its distal tip cultured. Usually 24 to 48 hours are allowed to elapse prior to insertion of another central venous catheter on the contralateral side. In the interim, a needle should be placed into a peripheral vein, and isotonic or slightly hypertonic dextrose is infused in order to prevent "rebound" hypoglycemia. In some patients, it may be necessary to insert another central venous catheter immediately after its removal because of the desperate nature of the patient's illness.

One hundred and fifty infants have been given total intravenous nutritional support by our group. Eighteen of these patients have had either a ruptured omphalocele or gastroschisis. Using intravenous hyperalimentation as an adjunct to their surgical management, the mortality rate in these 18 infants has been zero. Previous experience in managing these congenital defects in our institutions prior to hyperalimentation yielded a 60 to 80 percent infant mortality rate. Hence, the value of adequate parenteral nutritional support and bowel rest in the treatment of these conditions is obvious.

Clinical example no. 1

The initial physical examination of a 2780 gm female infant, following a normal pregnancy and spontaneous delivery, revealed intrauterine rupture of an omphalocele. The extruded small bowel and right colon were covered with a fibrinopurulent exudate and were markedly dilated (Fig. 5). No other congenital abnormalities were apparent on physical examination. The child was taken to the operating room where the abdominal wall defect was covered with a patch of silastic-impregnated dacron cloth, sutured to the fascial ring of the abdominal wall defect.

Fifteen hours following the surgical procedure, a polyvinyl catheter was inserted into the superior vena cava via the right external jugular vein. Hyperalimentation was instituted in order to rest the inflamed bowel and to provide nutrients for growth of the infant with the hope that the bowel would soon regain its "right of domain" within the peritoneal cavity. By the fifteenth postoperative day, all of the bowel was within the peritoneal cavity, and on day 16, the infant had a spontaneous bowel movement per rectum. Accordingly, the infant was begun on oral feedings in addition to the hyperalimentation solution. On the twenty-eighth postoperative day, she underwent a second operation in which the plastic sheet was excised from the abdominal wall, and the central venous feeding catheter was removed to minimize the risk of infection. For three days she was fed by peripheral veins with standard pediatric intravenous solutions. On day 30, she experienced another spontaneous bowel movement, and the following day, she was begun on oral feedings exclusively.

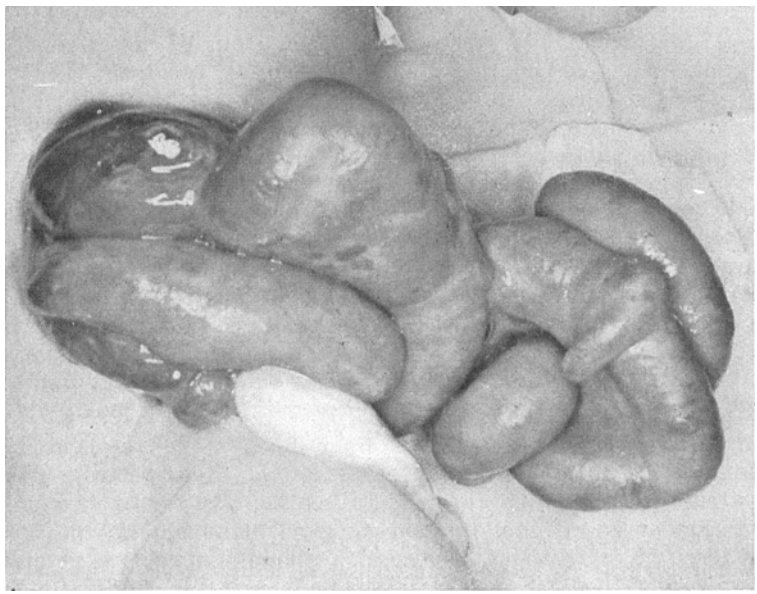

Fig. 5. The small bowel and proximal right colon are extruded through a ruptured omphalocele. A fibrinopurulent exudate covers the bowel, which is inflamed, thickened and dilated.

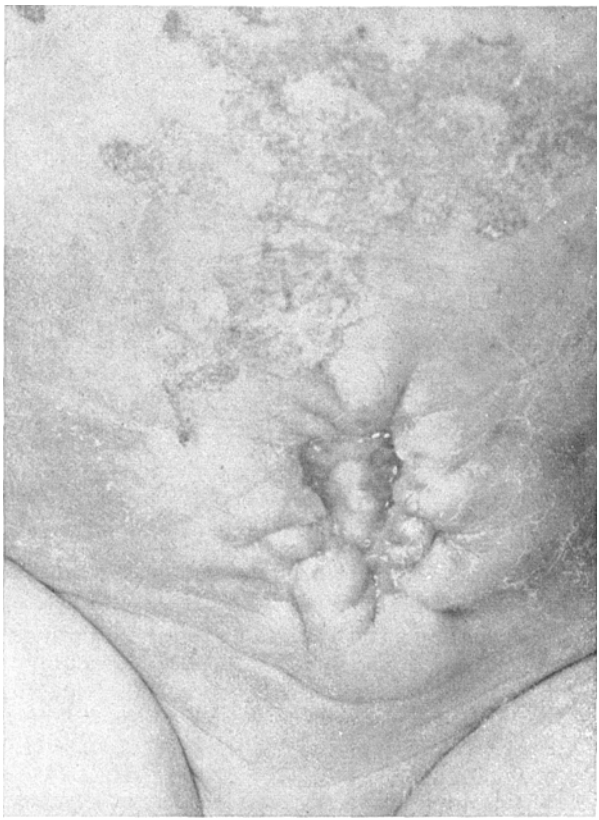

Fig. 6. Complete healing of the omphalocele defect occurred during the period of parenteral hyperalimentation.

By the fortieth postoperative day, the base of the wound was completely filled with granulation tissue and epithelialization was progressing spontaneously (Fig. 6). By the forty-ninth postoperative day, the wound was completely healed by secondary intention. The child is now five years of age with no residual health problems.

After an initial weight loss common to all newborn infants as they mobilize excessive total body water, this infant gained weight normally at a rate of approximately 30 gm/day (Fig. 7). The ability to metabolize an intravenously administered glucose load differs somewhat in each infant. We recommended that initial nutritional efforts after birth be carried out with standard pediatric 5 % dextrose and 0.25 % saline solutions. Following insertion of the superior vena caval catheter, the concentration of glucose should be gradually increased over the ensuing few days until full strength hyperalimentation solution is tolerated. Acceptable metabolism of the glucose load is determined by serial measurements of serum and urine glucose levels. If hyperglycemia and glycosuria occur, an osmotic diuresis will ensue, and the infant may become rapidly and severely

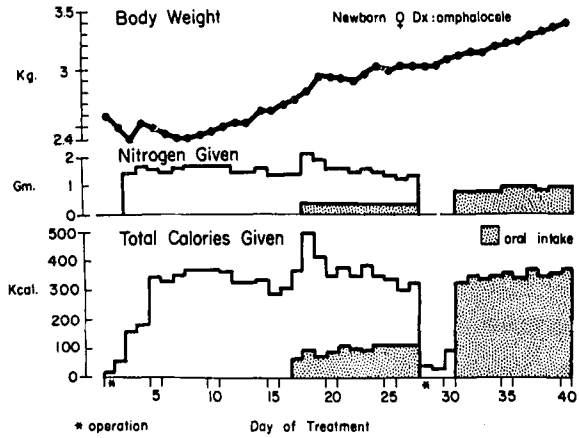

Fig. 7. The number of calories supplied by intravenous glucose was gradually increased over a period of five days to provide caloric balance and normal weight gain during the 27 days of parenteral hyperalimentation. When oral feedings were begun, the infant spontaneously ingested a similar caloric ration to that which had been provided by intravenous hyperalimentation.

dehydrated. The adaptation of the infant's metabolic pathways to tolerate the ever increasing glucose load has not been convincingly identified. In one infant in whom serum insulin levels have been recorded, a marked rise in the plasma insulin level was initially noted when 20% dextrose solution was infused. The plasma insulin level, however, regressed to

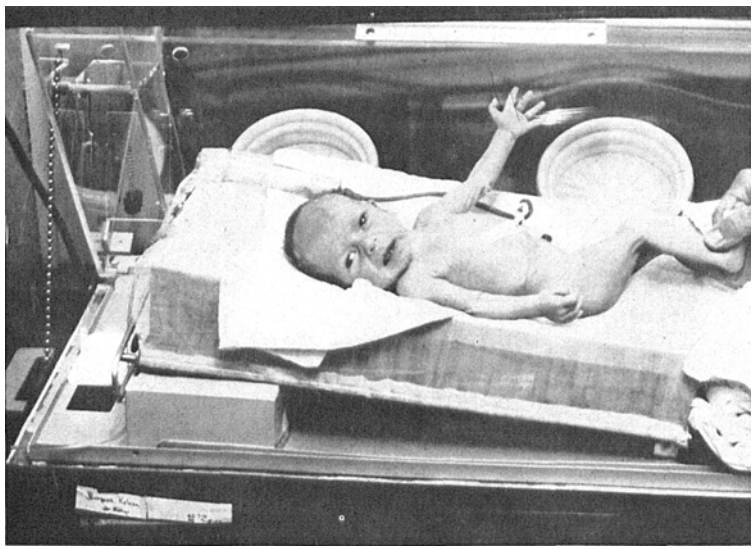

Fig. 8. A newborn infant 18 days following massive small bowel resection for small bowel atresia but prior to treatment with intravenous hyperalimentation.

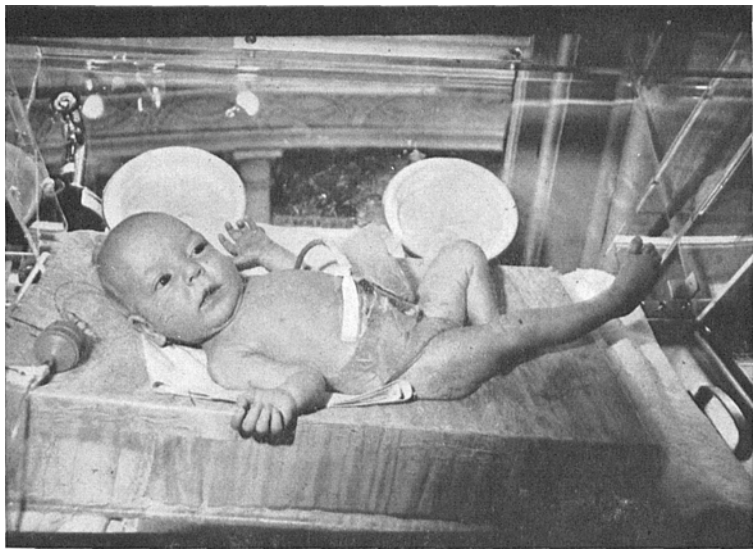

Fig. 9. The same infant after 45 days of intravenous hyperalimentation.

normal after five days of infusion, and the infant remained normoglycemic (12).

After intravenous hyperalimentation was discontinued and oral feedings begun in the infant herein described, she spontaneously ingested a similar caloric load to that which had been provided by vein (Fig. 7).

Clinical example no. 2

Following an uneventful pregnancy and normal spontaneous delivery, a female infant weighing 2300 gm was born on July 16, 1967. Severe protracted vomiting developed on the second day of life. Roentgenographic examination with barium contrast enema revealed an obstruction at the sigmoid colon. A dilated fluid-filled stomach and duodenum with an absent gas pattern distal to the ligament of *Treitz* was also noted. Initial nutrition was provided with standard pediatric 5 % dextrose and 0.25 % saline solutions peripherally. Exploratory laparotomy revealed massive small bowel atresia from the ligament of *Treitz* extending to the terminal 3 cm of ileum. There was an atretic segment 2 cm in length in the mid-transverse colon, as well as a high rectal stricture. The atretic small bowel was resected and the bulbous end of the duodenum was anastomosed end-to-side to the distal 3 cm of ileum. The splenic flexure was anastomosed to the hepatic flexure, and a loop colostomy was performed to bypass the rectal obstruction. A decompression gastrostomy tube was inserted. The infant was then fed by peripheral vein with plasma, blood, and a 10 % dextrose and amino acid solution containing vitamins and minerals. On this regimen, however, her weight dropped from 2300 gm at birth to 1816 gm in 18 days. She became extremely hypometabolic manifested by a pulse rate of 60 to 80 per minute, respirations of 12 to 14 per minute and

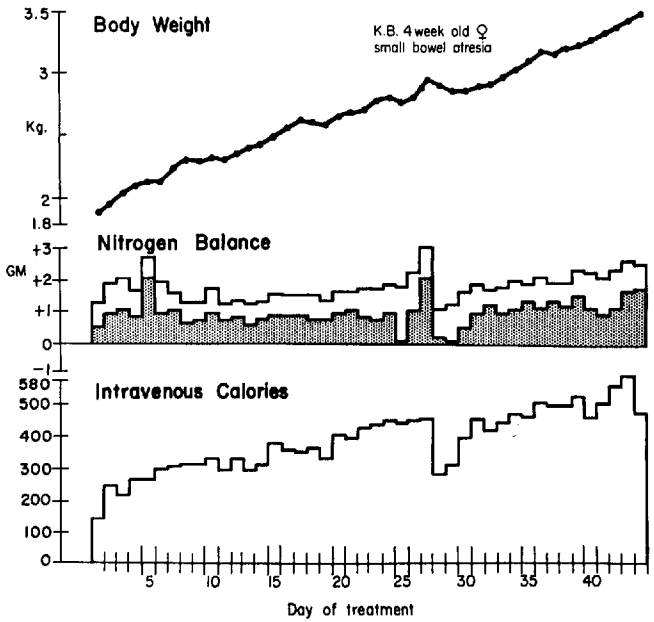

Fig. 10. Weight gain, nitrogen balance, and intravenous calories delivered by intravenous hyperalimentation in the infant with small bowel atresia. The stippled area represents the difference between the nitrogen ingested and the nitrogen excreted.

temperature of 96° F even while in a 101° F isolette (Fig. 8). A polyvinyl catheter was inserted into her superior vena cava via the external jugular vein, and pediatric hyperalimentation solution was begun.

Forty-five days after the institution of intravenous hyperalimentation, the patient had gained weight from 1816 gm to 3405 gm. She had also increased in length by 5.5 cm, head circumference by 6.5 cm and chest circumference by 8.5 cm (Fig. 9). The infant was maintained on positive nitrogen, sodium, and potassium balances throughout this period of time (Figs. 10 and 11). The importance of balance studies is indicated by the calcium and phosphorus metabolism in this infant. Insufficient calcium and phosphorus were provided to produce positive balances until day 20 (Fig. 11). Hypophosphatemia and hypocalcemia will regularly result if phosphorus and calcium are not provided in adequate amounts in the nutritional solution daily (13).

This infant was maintained on intravenous hyperalimentation for 21 months. An upper gastrointestinal series performed at one year of age revealed marked dilatation of the duodenum with increased mucosal folds of the duodenal remnant. The length of bowel had not increased any more than one would expect from natural growth, but the circumferential increase was marked (Fig. 12).

In an attempt to determine the prognosis of this infant and subsequent infants with short gut syndrome, an experiment was designed utilizing Beagle puppies (14). Three groups of puppies were studied. Ninety percent

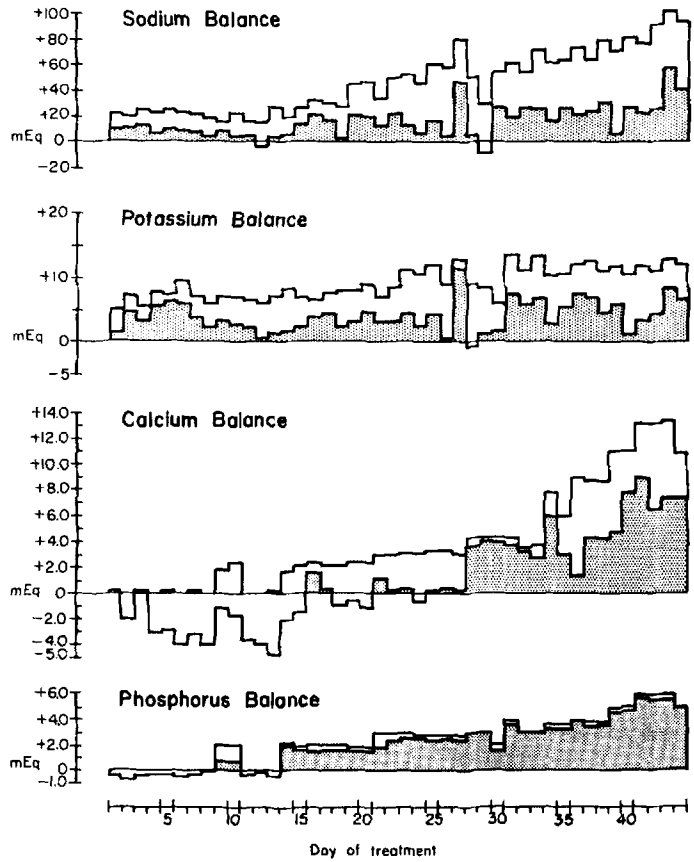

Fig. 11. Sodium, potassium, calcium, and phosphorus balances during the first 45 days of intravenous hyperalimentation in the infant with small bowel atresia. The bottom line in each graph represents the difference between the intake and output of each element.

of the small bowel was excised in two of the groups, with the third group serving as non-operated controls. Arbitrarily, one set of the resected animals was fed for one month with parenteral hyperalimentation and given nothing by mouth. The other set of resected animals was allowed to eat ad lib by mouth following three days of postoperative intravenous support. After the 30-day experimental period, the hyperalimented animals as well as the resected and non-resected controls were allowed to eat ad lib horse meat, cereal and water for the first year of life. Near-normal growth and development was achieved in all of the resected puppies, who were fed with intravenous hyperalimentation for the first 30 postoperative days. In contrast, the initially orally-fed resected litter mates failed to thrive, had an increased mortality rate, and achieved only half-normal size at the end of the year. In the animals fed for 30 days with parenteral hyperalimentation, the duodenal villus height, mucosal thickness, and total

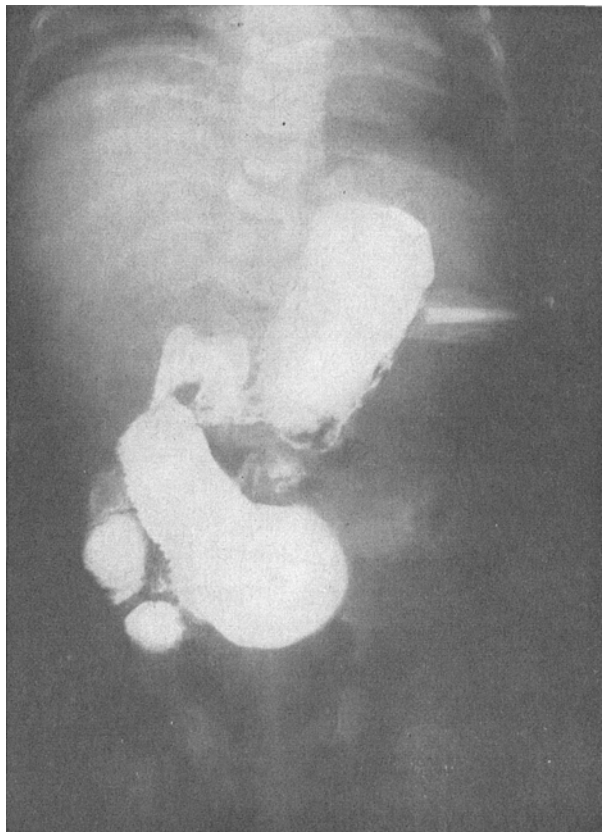

Fig. 12. Upper gastrointestinal radiograph of the infant with massive small bowel resection for small bowel atresia following 21 months of intravenous hyperalimentation. The dilated structure in the midabdomen is the duodenum.

bowel wall thickness were twice that of the control animals and significantly greater than that of the animals resected but fed initially by mouth. These data strongly support the hypothesis that bowel adaptation is secondary to increased mucosal absorptive surface area rather than to increased transport across the individual cells (15).

In summary, the technique of intravenous hyperalimentation is the first parenteral feeding technique that has promoted normal growth and development for prolonged periods of time in animals and man, and remains the only means by which to provide such support in countries like the United States of America where intravenous fat emulsions are not uniformly available for clinical use. It is not only life-saving in the management of many pediatric congenital catastrophies, bowel dysfunctional syndromes, and, as recently reported, extreme prematurity, but also offers the scientist a unique opportunity to study in the laboratory and in man many aspects of nutrition, metabolism, pathophysiology, and applied biochemistry in a manner heretofore impossible to achieve.

Summary

Experiences gained in 150 newborns and infants receiving a complete parenteral nutrition are summarized. An infusion pattern for the complete parenteral nutrition of newborns is presented. Technical questions of parenteral nutrition are discussed. Finally the treatment of 2 newborns with inborn errors of the gastrointestinal tract is reported.

Zusammenfassung

Erfahrungen aus der kompletten parenteralen Ernährung von bisher über 150 Säuglingen und Kleinkindern werden zusammengefaßt. Ein für die komplette parenterale Ernährung Neugeborener ausgearbeitetes Infusionsschema wird vorgestellt. Technische Fragen der parenteralen Ernährung werden erörtert. Abschließend wird über die Behandlung zweier Neugeborener mit angeborener Mißbildung des Gastrointestinaltraktes berichtet.

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