MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

October 4, 1973

TOTAL PARENTERAL NUTRITION

Charles Walker, M.D.

A.S., a 63 year old white male was in an automobile accident September 1972. He sustained multiple compression fractures of the spine and pelvis and had a cerebral contusion. On conservative management he did well for twelve days, at which time abdominal pain appeared. It became much worse and two days later, he underwent an exploratory laparotomy. He was found to have a gangrenous small bowel secondary to venous thromboses. After resection, he had two to three inches of jejunum distal to the Ligament of Treitz, and the terminal three inches of ileum. Postoperatively when refeeding was attempted he developed massive diarrhea, a fistula and an abdominal wall abscess. On October 18, 1972, he was transferred to the Dallas Veterans Administration Hospital.

He was a chronically-ill appearing white male who was stable, slightly jaundiced with recent surgical scar and a fistula of the left upper abdomen. On admission his hemoglobin was 8.9 gms%, SGOT was 60, alkaline phosphatase 205, bilirubin 5.6, Ca^{++} 8.8, phosphorus 3.5, serum iron 15, TIBC 265, albumin 2.4 with the remainder of his lab tests being normal. His weight prior to surgery was 155 pounds.

Upper gastrointestinal series revealed approximately ten inches of small bowel distal to the Ligament of Treitz and a fistulogram revealed a fistula from small bowel (probably at jejunoileal anastomosis) to the abdominal wall. There was no evidence of distal obstruction.

On October 24, he weighed 142 pounds and he was started on total parenteral nutrition (TPN). He continued to gradually lose weight, falling to 132 pounds by October 30. He then gradually regained to 140 pounds by November 20, and remained in the 139-143 pound range until TPN was discontinued on January 24, 1973. He had a subclavian line during the first month and an internal A-V shunt was utilized during his last month of alimentation.

His fistula stopped draining soon after alimentation was begun. By early November, the patient felt much better, and from then until the completion of alimentation he spent a large part of each day roaming the halls. During these forays, a Holter pump was used to infuse the solutions. Oral intake was resumed December 20 and, except for 3-4 bowel movements per day, he tolerated the feedings and the fistula remained sealed. During the course of TPN, his liver function tests normalized.

Parenteral alimentation was discontinued on January 24 and oral intake increased to 2500 Kcal. He currently has 7-8 semi-formed bowel movements per day and his weight remains 143 pounds. Medications consist of Lomotil, medium-chain triglycerides 120 cc per day and six feedings per day. He puts out approximately 80 grams of fat per day.

The major goal of hyperalimentation is to provide energy and nitrogen to an individual who is unable to meet his current needs. To critically evaluate this treatment modality, we must first review energy and nitrogen metabolism.

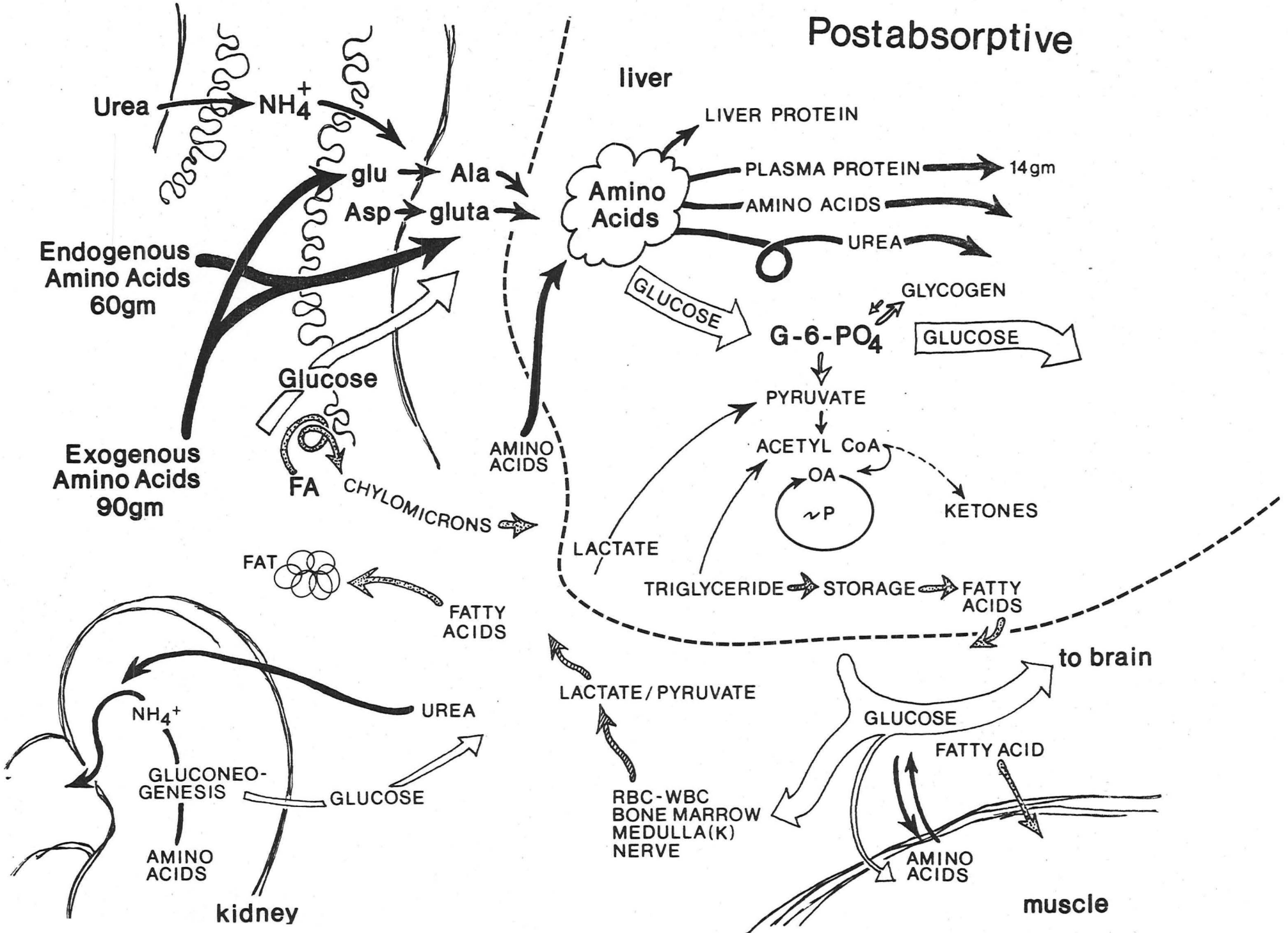
Fed State

A broad outline of nutrient flow is illustrated in Figure 1. After absorption, amino acids (except for glutamic and aspartic acid which are transaminated to alanine and glutathione in the intestinal mucosa) are transported to the liver via the portal blood.

These amino acids plus amino acids that are continuously arriving from the carcass have several destinations (Figure 1). A significant proportion are converted to liver proteins and plasma proteins; others (particularly the branched-chain amino acids and methionine which are not degraded in the liver) pass on into the systemic circulation, and the remainder are deaminated forming urea and alpha keto acids (1,2). The latter can then be metabolized to glucose or ketones and possibly reutilized in amino acid synthesis (3). Less urea will be formed when the ingested protein contains a high proportion of essential amino acids and excess nitrogen is not given (4).

During the fed state, glucose is the energy substrate for the central nervous system (CNS), red blood cells, white blood cells, bone marrow, renal medulla and peripheral nerve and to a limited extent muscle. In the CNS, glucose is completely oxidized to CO_2 and H_2O, but in the other sites it is only metabolized to lactate and pyruvate. The lactate and pyruvate are then returned to the liver where they can be remade into glucose (5).

Absorbed fat may be burned for energy, stored, or released to the periphery as fatty acids. Skeletal muscle utilizes the fatty acids as its major fuel source.


Postabsorptive
liver
Urea
NH_4^+
glu
Ala
Asp
gluta
Endogenous Amino Acids 60gm
Exogenous Amino Acids 90gm
Glucose
FA
CHYLOMICRONS
AMINO ACIDS
Amino Acids
LIVER PROTEIN
PLASMA PROTEIN
14gm
AMINO ACIDS
UREA
GLUCOSE
GLYCOGEN
G-6-PO_4
GLUCOSE
PYRUVATE
ACETYL CoA
OA
~P
KETONES
LACTATE
TRIGLYCERIDE
STORAGE
FATTY ACIDS
FAT
FATTY ACIDS
to brain
LACTATE/PYRUVATE
GLUCOSE
FATTY ACID
RBC-WBC
BONE MARROW
MEDULLA(K)
NERVE
AMINO ACIDS
muscle
NH_4^+
UREA
GLUCONEO-GENESIS
GLUCOSE
AMINO ACIDS
kidney

This metabolic schema seen in an individual who is eating at regular intervals is significantly altered when fasting occurs. To understand the changes that occur with fasting, several basic concepts are listed:

(1) Red blood cells, white blood cells, bone marrow and renal medulla must have glucose.

(2) After several days of starvation, ketone body oxidation can start displacing glucose oxidation in the brain, but initially glucose must be provided (6).

(3) During starvation, the only sources of glucose are:

(a) liver glycogen

(b) glucogenic amino acids

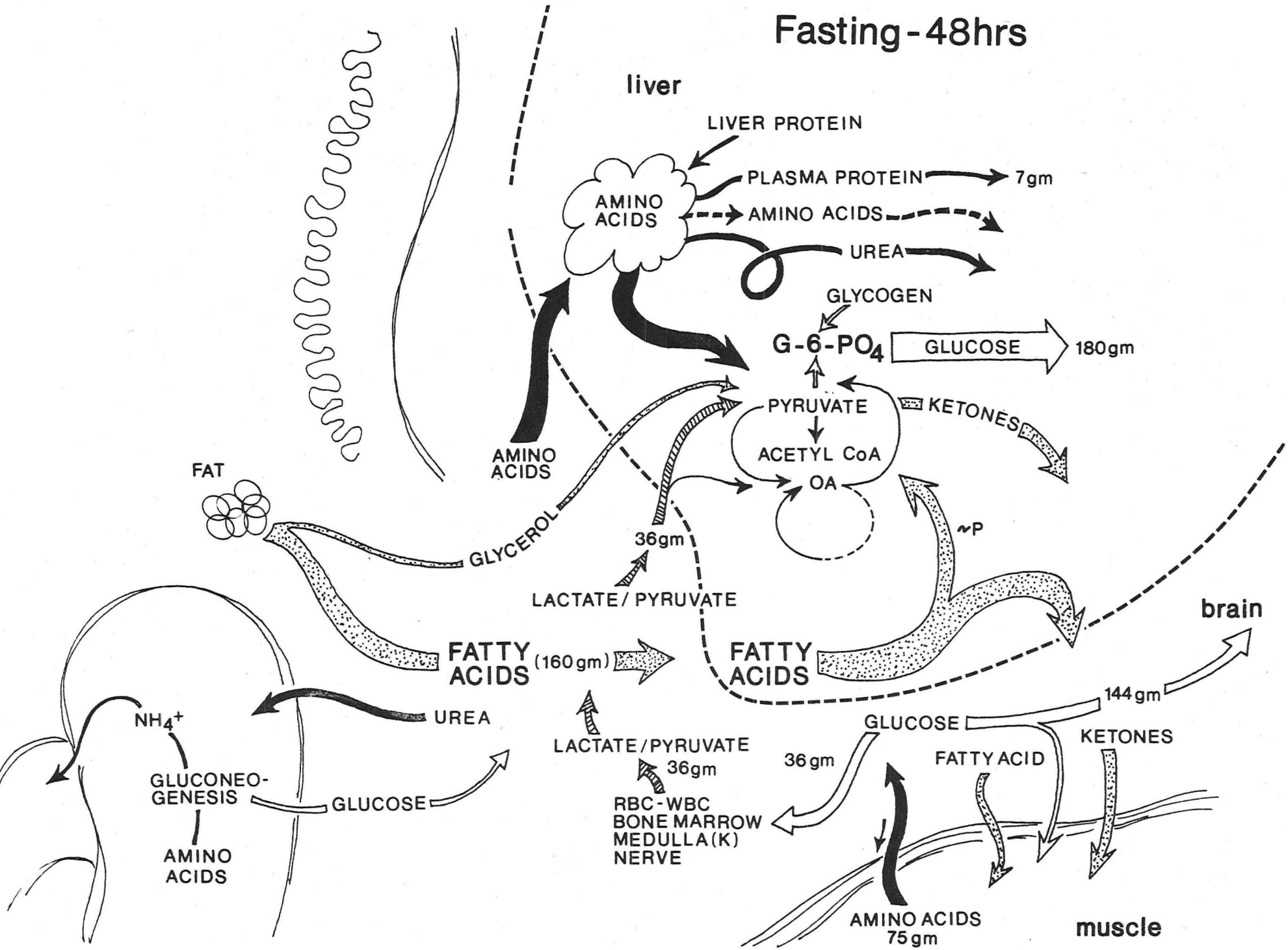
(c) glycerol, lactate, pyruvate.

(4) Fat is the most important source of stored energy, although amino acids are important as precursors of glucose.

(5) Glycogen is spared for an acute emergency such as anoxia or vigorous exercise.

Forty-eight hours after the onset of fasting, the following metabolic changes (Figure 2) are present. Glucose needs are now largely being met by gluconeogenesis. Liver proteins are being catabolized, plasma protein production has fallen and amino acid release to the periphery has fallen (4). Urea production remains high, reflecting the high rate of protein breakdown.

The substrates for gluconeogenesis are amino acids from skeletal muscle (75+ grams/day) and lactate/pyruvate shunted back to the liver from the periphery after partial glucose oxidation (36 gm/day). This consumption of protein to form glucose yields 75-150 gms of glucose per day.


Fasting - 48hrs
liver
LIVER PROTEIN
AMINO ACIDS
PLASMA PROTEIN
7gm
AMINO ACIDS
UREA
GLYCOGEN
G-6-PO4
GLUCOSE
180gm
PYRUVATE
KETONES
ACETYL CoA
OA
AMINO ACIDS
FAT
GLYCEROL
36gm
LACTATE/ PYRUVATE
~P
brain
FATTY ACIDS
(160gm)
FATTY ACIDS
144gm
GLUCOSE
KETONES
FATTY ACID
36gm
LACTATE/PYRUVATE
36gm
RBC-WBC
BONE MARROW
MEDULLA(K)
NERVE
NH4+
UREA
GLUCONEO-GENESIS
GLUCOSE
AMINO ACIDS
AMINO ACIDS
75gm
muscle

Fatty acids or ketones are now the major energy source for heart, kidney cortex and skeletal muscle. When starvation is prolonged for several weeks, additional adaptations (diagrammed in Figure 3) occur. The most significant change is the adaptation of the brain to ketone metabolism (6). Glucose needs are thereby reduced by 100 gm/day. Gluconeogenesis from amino acids is greatly reduced and most of the glucose released by the kidney and liver is from lactate, pyruvate and glycerol. Total nitrogen losses are reduced to 3-5 gms per day as reflected by reduced urea excretion. The kidney generates several grams per day of ammonia needed for titration of fixed acid, and the generation of this ammonia by the kidney necessitates utilization of amino acids and production of glucose. In fact, the kidney produces 45% of all glucose formed during starvation (7).

The end results of the adaptation to starvation are:

(1) The brain is supplied with energy

(2) There is relative sparing of body protein

(3) There is relative sparing of glycogen

(4) Fat, the most efficient storage form of energy, is utilized for energy needs.

(5) Much less urea is excreted, thus obligatory water needs are greatly reduced.

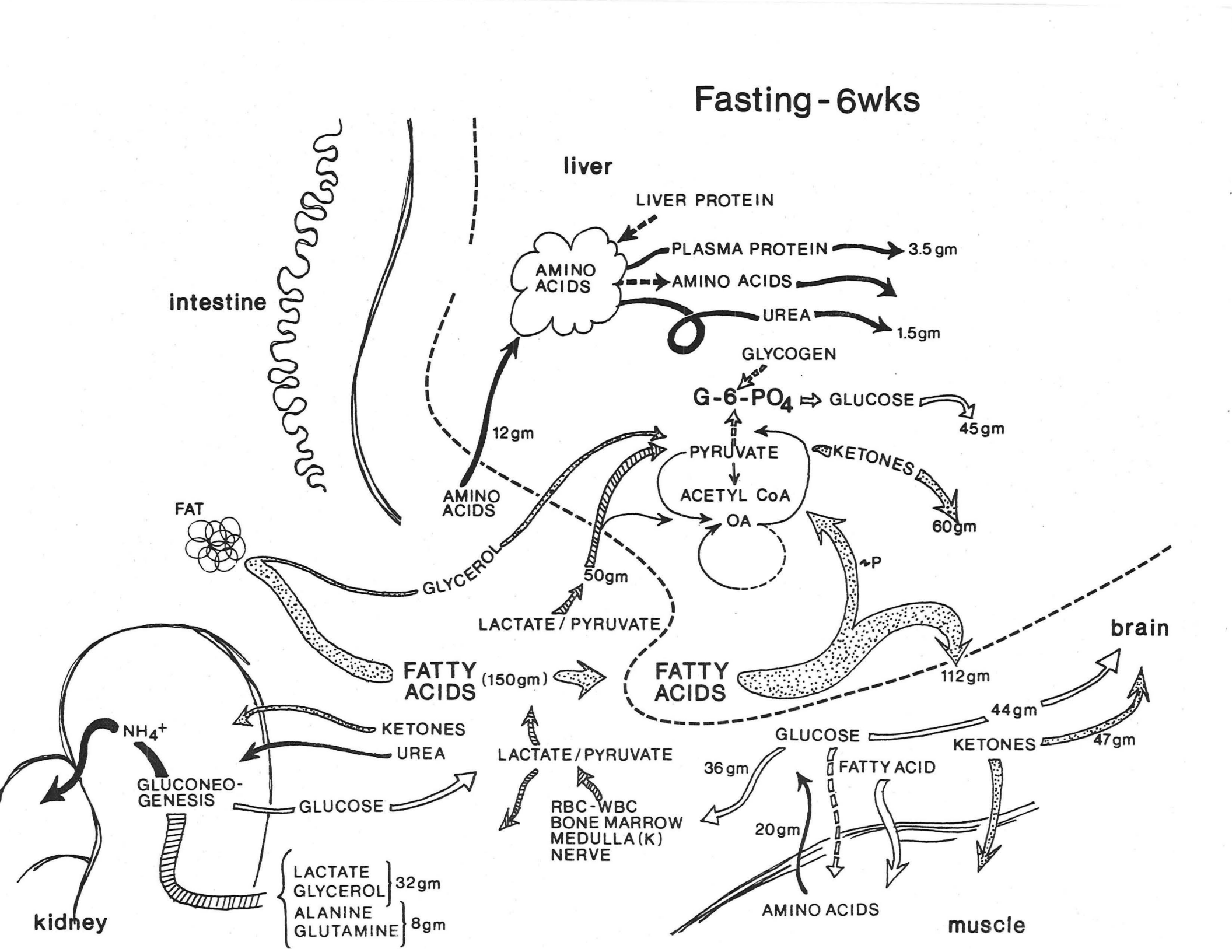
Controls

Before we can consider an artificial diet such as intravenous alimentation in starved individuals, we must first decide what triggers and limits the body's reaction to starvation. The following changes can be identified as important, and although listed independently, they obviously interact:

(1) Decrease intake of amino acids

(2) Decreased amino acid release from peripheral protein stores

(3) Availability of exogenous glucose or fat (endogenous or exogenous)


Fasting - 6wks
liver
LIVER PROTEIN
PLASMA PROTEIN
3.5 gm
AMINO ACIDS
AMINO ACIDS
UREA
1.5gm
intestine
GLYCOGEN
G-6-PO4 ⇨ GLUCOSE
45gm
12gm
PYRUVATE
KETONES
ACETYL CoA
OA
60gm
AMINO ACIDS
FAT
GLYCEROL
50gm
~P
LACTATE / PYRUVATE
brain
FATTY ACIDS (150gm)
FATTY ACIDS
112gm
44gm
GLUCOSE
KETONES
47gm
NH4+
KETONES
UREA
LACTATE / PYRUVATE
36 gm
FATTY ACID
GLUCONEO-GENESIS
GLUCOSE
RBC - WBC
BONE MARROW
MEDULLA (K)
NERVE
20gm
LACTATE
GLYCEROL
32gm
ALANINE
GLUTAMINE
8gm
AMINO ACIDS
kidney
muscle

(4) Hormonal changes:

Insulin

Glucagon

Catachols

Glucocorticoids

(1) Amino acid absorption - The presentation of exogenous amino acids to the liver fluctuates even during the fed state. These minor fluctuations (i.e., supper to breakfast) as well as protein deprivation of a few days cause prompt alterations in liver metabolism (4). Decreased synthesis of plasma proteins, catabolism of liver protein, and a reduction of amino acids released to the systemic circulation can often be appreciated in hours. RNA synthesis, liver enzyme levels and electron microscopic changes are also quickly appreciated (8,9,10).

(2) Peripheral protein - As starvation progresses, there is a progressive decrease of amino acid release from peripheral protein stores, which results in diminished substrate availability (11,12).

(3) Availability of glucose and fat -

Glucose: - An adult on a protein-deficient diet which contains adequate glucose and/or fat for caloric expenditures will eventually go into negative nitrogen balance, but the magnitude of the loss will be less than in the absence of fat and glucose. The explanation is obvious: protein is conserved because it does not need to be broken down to provide glucose. Most individuals have enough fat stores to handle the majority of their energy needs for a reasonable length of time. However, to handle the needs of the CNS and other glucose-dependent tissues during both the early and late phases of starvation requires either exogenous glucose or the breakdown of gluconeogenic amino acids.

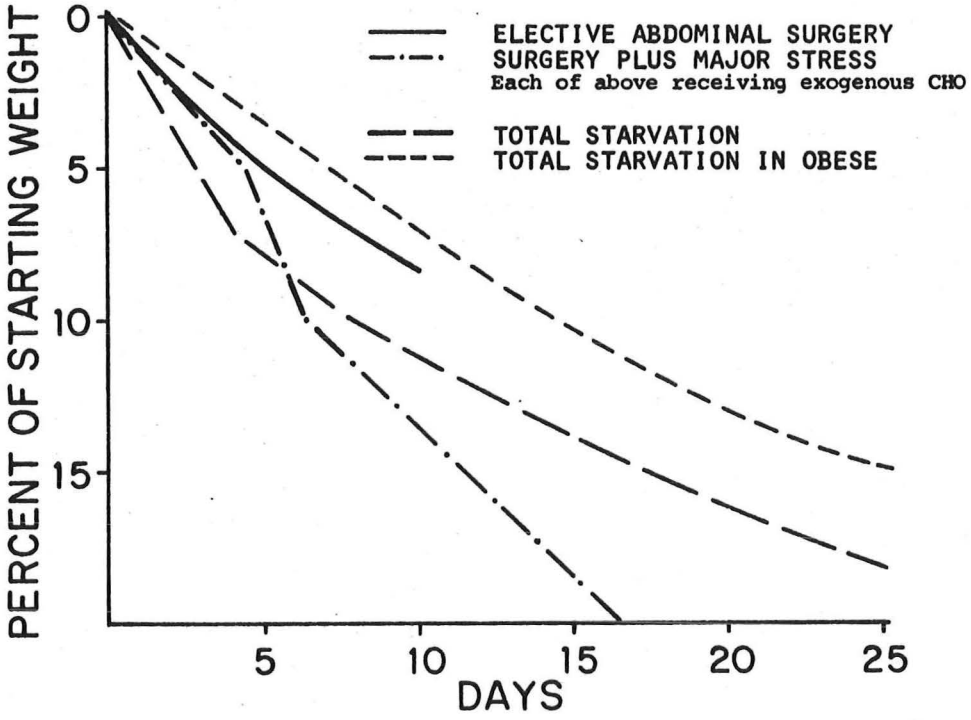
Fat: - It has been suggested that an individual on a protein-free diet, who is receiving exogenous glucose, will suffer no ill effects from his protein lack unless his edema-free weight falls 10% below his ideal body weight (13). Presumably this would occur because weight loss was largely fat. In fact, in all but the markedly obese, weight loss can be subdivided as 10% protein, 70% water and 20% fat. Most of the water is from tissues (largely muscle) that have released their nitrogen. Although the obese individual may lose proportionately more fat than the lean man, approximately 8 - 14 per cent of each man's weight loss, except for initial diuresis and edema fluid fluctuations, will be protein (14,15,16,17). When weight loss stops, protein loss has stopped and visa-versa. Rapid weight loss implies rapid catabolism.

The protein content of the average human body is estimated to be 15% of body weight. However, only 50% of this is lean tissue with an active turnover (i.e., muscle) such that it contributes most of the nitrogen during active weight loss. This 6 kg of muscle (the GI tract is the second most important source) is the major source of gluconeogenic amino acids. Its continued rapid loss which occurs in early starvation and stress (100 gms/day early starvation to 180 gms/day severe stress) is obviously a major factor in survival.

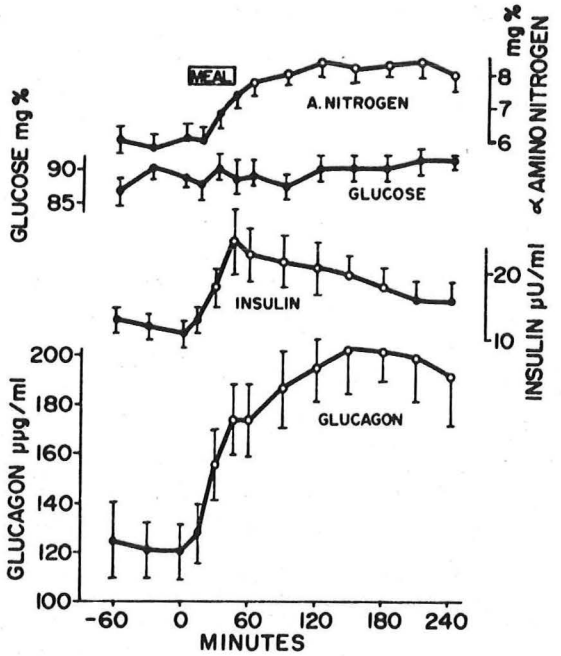
Figure 4 diagrams typical weight losses as seen in the total starvation of obese and lean individuals. Also shown are patients following uncomplicated abdominal surgery or surgery plus major stress who are receiving exogenous glucose. The surgical patients who received exogenous glucose lost weight much more slowly than the lean patient on total starvation presumably because gluconeogenesis was inhibited by the glucose. The severely-stressed patients lost much more weight in spite of exogenous glucose because of the stress reaction.

Fig 4

PATTERNS OF WEIGHT LOSS IN MAN



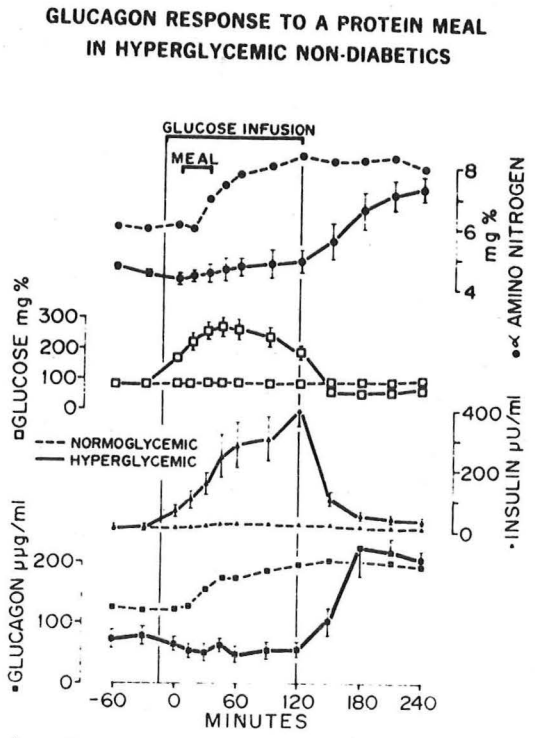
GLUCAGON RESPONSE TO A PROTEIN MEAL IN 14 NORMAL SUBJECTS



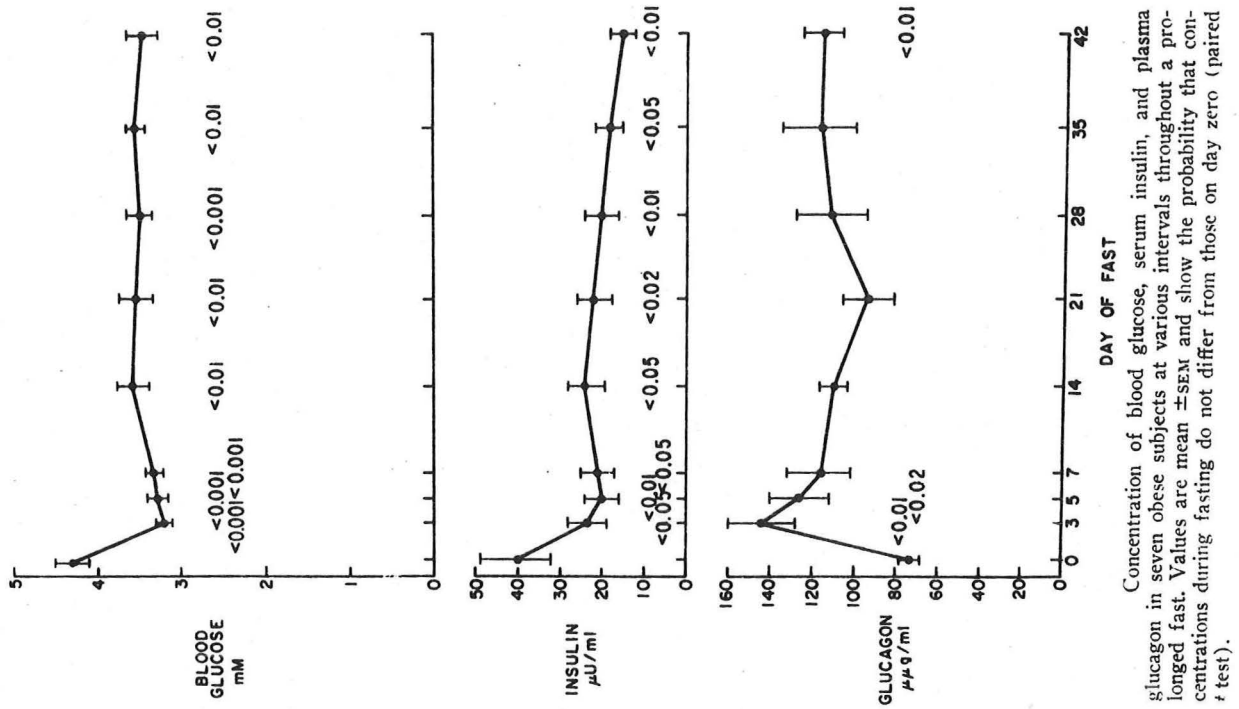
The effect of a large protein meal on the peripheral venous levels of pancreatic glucagon, insulin, glucose, and amino nitrogen in fourteen normal human volunteers. (Reprinted with permission of the *New England Journal of Medicine*.)

Fig 5

Fig 6



Prevention of the glucagon response to a protein meal by glucose infusion in non-diabetic human volunteers. (Reprinted with permission of the *New England Journal of Medicine*.)



Concentration of blood glucose, serum insulin, and plasma glucagon in seven obese subjects at various intervals throughout a prolonged fast. Values are mean ±SEM and show the probability that concentrations during fasting do not differ from those on day zero (paired *t* test).

Fig 7

(4) Hormonal changes: - Hormonal changes alter amino acid metabolism.

Insulin causes a rapid reduction in the plasma levels of all amino acids by enhancing their deposition and/or reducing their release from muscle. Amino acid uptake by the liver may be stimulated by insulin, but this probably contributes little to amino acid flux from the plasma (18,19).

Glucagon secretion in response to elevation of plasma amino acids (Figure 5) is felt to prevent the hypoglycemia that would occur if the hypoglycemic action of insulin was not opposed (20). Figure 6 illustrates the response of normal human volunteers to a beef meal with and without a concomitant glucose infusion. Glucose, by elevating blood sugar, prevents the glucagon rise and (via insulin release) lowers amino nitrogen. A similar situation exists with hyperalimentation, and we would expect to find high insulin and normal glucagon levels during hyperalimentation.

During starvation (Figure 7), blood glucose and blood insulin fall and glucagon rises (21). Glucagon is highest during the first week (at the time of maximum gluconeogenesis in the liver) and then gradually decreases but remains moderately elevated throughout the fast. Such a hormonal set would appear to encourage amino acid release from musculature and stimulate hepatic gluconeogenesis. This bi-hormonal action can be expressed as the molar insulin:glucagon ratio. This ratio is high during anabolism and its reduction enhances catabolism.

The action of the glucocorticoids is complicated, depending upon the dose of corticoid, nutritional status of the animal and the organ system being evaluated. They inhibit muscle protein synthesis and promote a flux of amino acids to the liver and other visceral organs (18). Cortisol stimulates glucagon which may mediate much of its gluconeogenic action. Epinephrine releases glucagon and both stimulate cAMP, which in turn stimulates glucose production by the liver (19).

They are both released in fasting, muscular exercise and stress. Catachols decrease insulin release from Beta cells.

Stress Reaction

Many of the patients who will be considered for hyperalimentation have diseases which elicit a response loosely referred to as stress reaction. Various events such as trauma, myocardial infarction or bacterial septicemia will produce this reaction. The nutritional and hormonal changes such events incur are inexorably tied to the need for and success of hyperalimentation. The changes seen are similar to the adaptation of starvation but more profound and at times apparently detrimental to the animal.

Carbohydrate Metabolism

The fasting blood sugar is elevated and tolerance to a glucose load is decreased. At times, this glucose intolerance can become so severe as to produce an overt diabetic state (22-25). Some recent studies indicate that the hyperglycemia associated with injury is probably a result of a greater synthesis of glucose relative to its utilization rate which is also increased. Glucose oxidation is probably not impaired by injury and sepsis (26).

Nitrogen Metabolism

During stress, there is a marked increase in nitrogen loss manifested by weight loss and elevated urea nitrogen. In severe trauma, huge nitrogen losses may be seen. Up to 20 grams of nitrogen (equivalent to 124 grams of protein) may be lost daily (17). This increased nitrogen utilization is accompanied by a 10-15 per cent increase in the resting metabolic expenditure (RME). This increase of RME is equivalent to the elevated nitrogen loss (27).

During stress, there is a modest decrease in liver nitrogen, reduced albumin synthesis and increased albumin catabolism.

All is not catabolic, however, for during infection leukocytes release factors which stimulate the flow of amino acids from muscles to the liver to produce acute phase reactants (glycoproteins) (28). It is not entirely clear why the body accelerates the catabolism of its muscle mass during stress. Amino acids are needed for synthesis of proteins but most of the accelerated release ends up in glucose. Glucose is needed for brain, kidney medulla, bone marrow, peripheral nerves, red blood cells and white blood cells. During shock an elevated glucose helps to insure that these glucose-dependent tissues receive energy. The fight against infection and repair of damaged tissue requires adequate glucose levels. Teleologically, the stress reaction must have conferred some protective value but injury and sickness of the severity routinely seen today would likely produce death in a primitive society. Thus, one could speculate that the stress reaction, helpful in moderately severe injury, might be harmful in the severely injured.

Fat Metabolism

During chronic stress, as during starvation, most of the body's energy needs are met by fat (14). Free fatty acids and triglycerides are elevated in varying proportions in different diseases and are inconsistently elevated in a given stress setting (29). The clearance of an intravenously injected fat (Intra-lipid) was normal after stress (30).

Hormone Metabolism

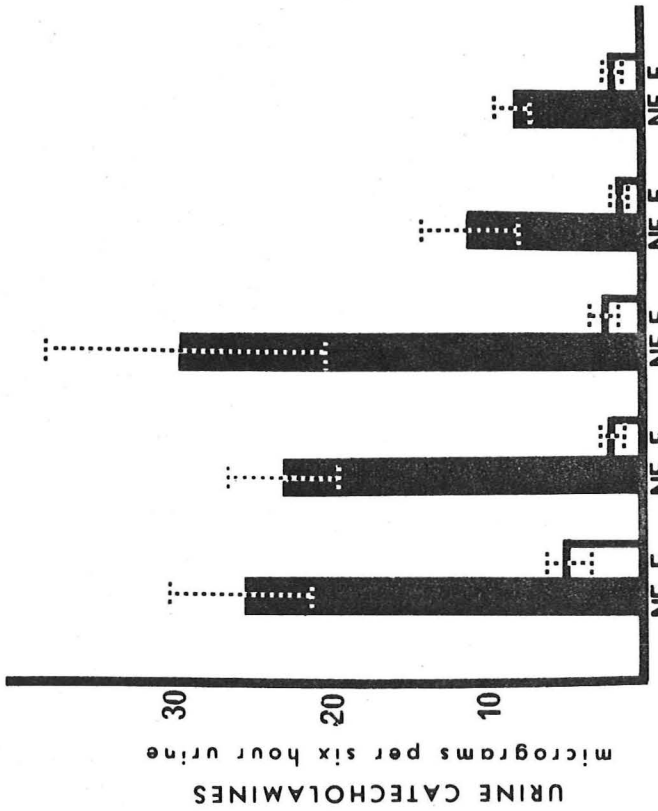
Various hormonal changes are seen during the stress reaction and may represent the major impetus to the metabolic changes that occur. Catachols, glucocorticoids and growth hormone have all been found to be elevated and their influence

plus the depression of immuno-reactive insulin are usually designated as being responsible for the glucose intolerance seen during the stress reaction (27,31). Certainly catachols and glucocorticoids can elevate the blood sugar. However, these hormones are not uniformly elevated and rises may be transient.

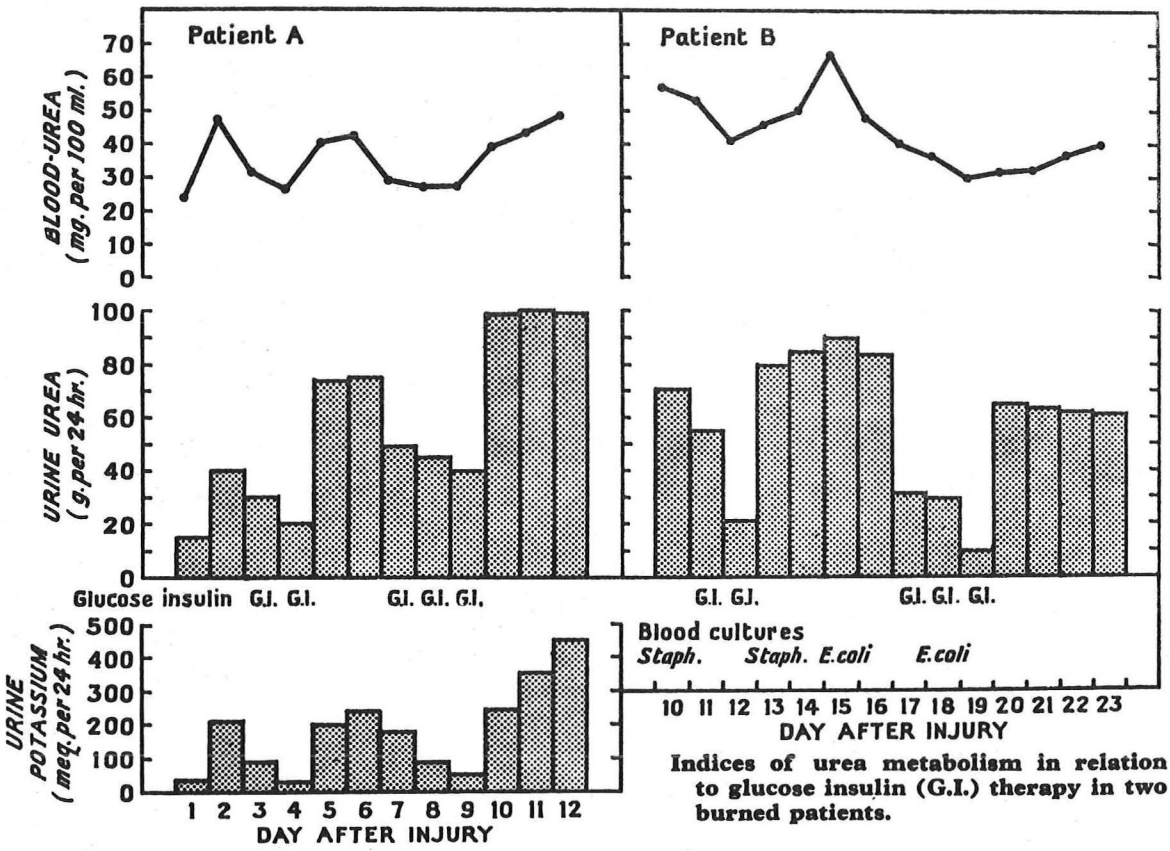
Figure 8 shows catachol excretion in ten patients after myocardial infarction (32). Catachols were elevated in the first three days but had returned to normal by day seven. Serum cortisol and growth hormone were normal throughout the 21 days, but glucose intolerance had improved only slightly by the 21st day. If glucagon were elevated, it could account for the glucose intolerance, accelerated protein breakdown and gluconeogenesis, and contribute to the elevation of serum-free fatty acids and triglycerides. In patients with severe trauma, diabetic ketoacidosis, severe bacterial infections and thermal burns, hyperglucagonemia is found (33,36). Upon recovery, glucagon is normal but data is not yet detailed enough to tell how closely the stress reaction correlates with the glucagon levels. The molar insulin:glucagon ratio may prove even a more sensitive index than glucagon alone (2). British investigators were able to reverse the massive nitrogen losses in two burn patients by infusing huge doses of insulin plus glucose. Figure 9, taken from their paper, shows the marked fall in blood urea, urine urea and urine potassium during such therapy. Although the authors did not measure glucagon, there is little doubt that it would fall, elevating the insulin:glucagon ratio (36).

Figure 10, based on partial data, illustrates what probably happens to glucagon, insulin and nitrogen balance during a stress reaction. Although other hormones are undoubtedly important, insulin and glucagon are probably the hormones that set the balance of anabolism versus catabolism.

Fig 8



Urinary catcholamine excretion following acute myocardial infarction: Six-hour urine collections on serial study days are described under methods, with normal range for norepinephrine being 5.5 ± 2.4 μg percent per six-hour urine.



Indices of urea metabolism in relation to glucose insulin (G.I.) therapy in two burned patients.

Fig 9

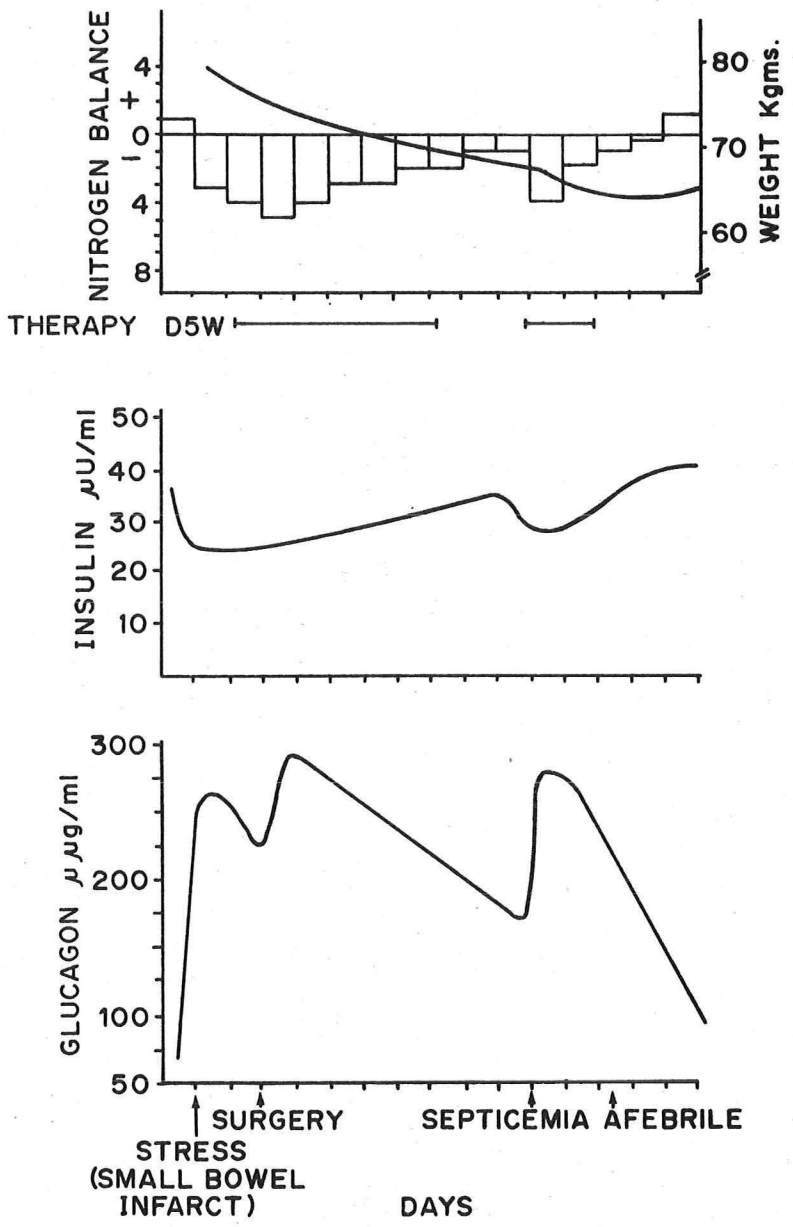

NITROGEN BALANCE
+
4
0
4
8
80
70
60
WEIGHT Kgms.
THERAPY D5W
INSULIN μU/ml
50
40
30
20
10
GLUCAGON μμg/ml
300
200
100
50
SURGERY
SEPTICEMIA AFEBRILE
STRESS
(SMALL BOWEL
INFARCT)
DAYS

Fig 10

Intravenous alimentation is an attempt to provide all the nutrients needed by the body for maintenance and repair, frequently in the face of elevated requirements. In simple terms energy, protein, water, minerals and vitamins must be provided in such a way that they may be effectively utilized without upsetting the homostasis of the body.

ENERGY

Energy needs can be met by carbohydrate or fat. A number of carbohydrates have been proposed as alternatives to glucose including fructose, sorbitol and xylitol.

Fructose:

Advantages (38)

a. Rapidly cleared from bloodstream - insulin not needed.
b. Rapidly converted to glucose and glycogen.
c. Less urinary loss than glucose.
d. Veins tolerate fructose solution better than a similar concentration of glucose
e. Uptake into liver and adipose tissue independent of insulin.

Disadvantages

a. The part of fructose which is transformed into glucose requires insulin for its further metabolism.
b. Rapid infusions may produce a lactic acid acidosis (39).
c. Rapid infusion may produce hyperuricemia.

Sorbitol:

Advantages:

a. More calories per gram.
b. Converted to fructose and would thus share advantages of fructose.

Disadvantages:

a. High urine losses.
b. Poor presursor of glycogen (38)
c. Same as fructose

Xylitol:

Advantages

a. Quickly converted to glucose
b. Liver utilization independent of insulin

Disadvantages

a. Poor precursor of glycogen
b. Most of utilization requires insulin
c. Increased incidence of liver function abnormalities.
d. Causes hyperuricemia

Glucose: Remains the carbohydrate of choice for intravenous nutrition.

Advantages:

a. Immediately available for use by the brain.
b. Stimulates insulin and inhibits glucagon, therefore anabolic.
c. Can infuse at 1.5 gm/kg/hr and reach steady state with neglibible urine losses.

Disadvantages:

a. Hypertonic at the concentrations needed to supply adequate calories.
b. In stress situations catachols and glucagon secretion reduce circulating insulin, thereby reducing utilization of glucose (probably true of other carbohydrates also).

Energy Needs - Adults 18 - 75 (38)

Although energy needs decrease slightly with age, 30 Kcal/kg/day is needed during modest physical activity (sitting for 8 hours plus one hour of walking) in men and women. Thus a 56/kg woman would require 1700 Kcal and a 66 kg man 2000 Kcal. If the individual is inactive subtract 400 Kcal. Metabolic energy requirements rise dramatically with stress as illustrated in Figure 11 taken from Dudrick and Rhoades (41).

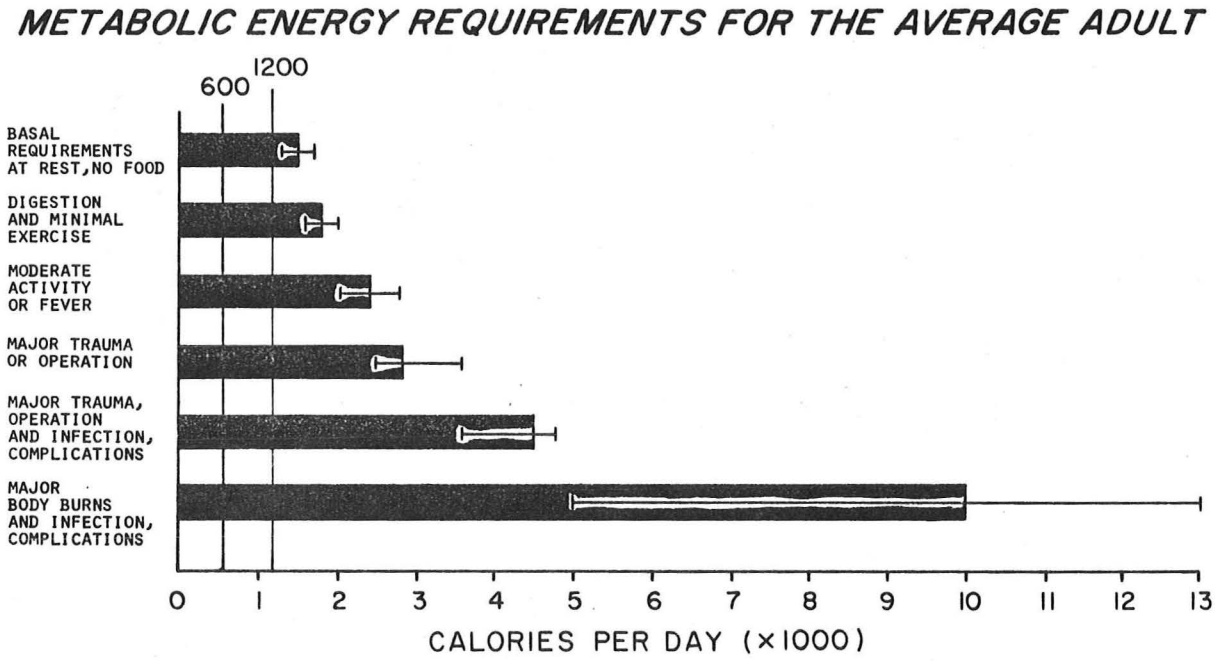
The calorie to nitrogen ratio, in an active individual, is between 200 and 300 calories per gram of nitrogen in an average diet. With no physical activity 125 to 200 calories per gram of nitrogen are utilized. During stress this apparently falls to 75-150 calories per gram of nitrogen (14, 17, 42). However, in practical application during stress, 120 to 250 calories per gram of nitrogen must be used or patients feel bad and develop elevations of blood urea nitrogen (4 , 44).

CALORIC NITROGEN RATIOS

Normal Diet

Physically active -	200 - 300 Kcal/gram N
Inactive	125 - 200 Kcal/gram N
Stress (Utilization)	75 - 150 Kcal/Gram N
Intravenous Nutrition	150 - 250 Kcal/gram N

Fig 11


METABOLIC ENERGY REQUIREMENTS FOR THE AVERAGE ADULT
600
1200
BASAL REQUIREMENTS AT REST, NO FOOD
DIGESTION AND MINIMAL EXERCISE
MODERATE ACTIVITY OR FEVER
MAJOR TRAUMA OR OPERATION
MAJOR TRAUMA, OPERATION AND INFECTION, COMPLICATIONS
MAJOR BODY BURNS AND INFECTION, COMPLICATIONS
0 1 2 3 4 5 6 7 8 9 10 11 12 13
CALORIES PER DAY (×1000)

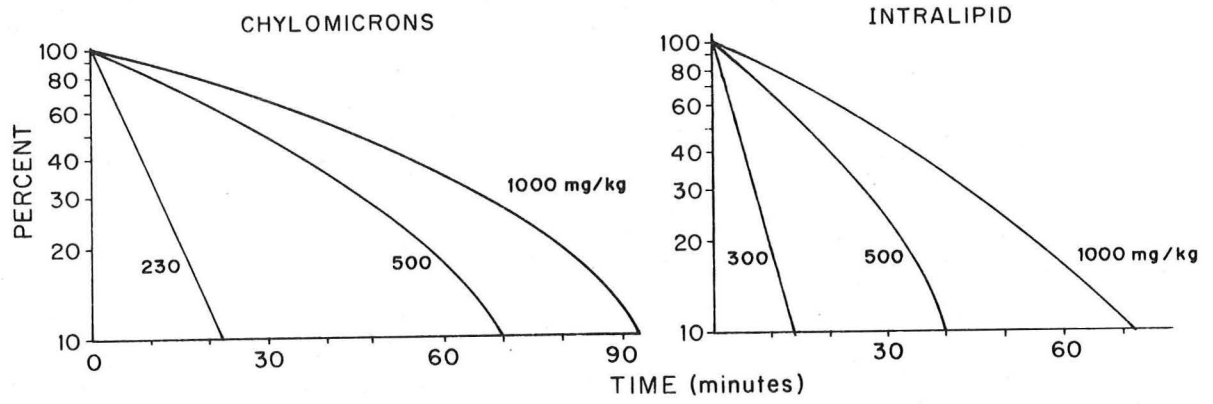

REMOVAL OF FATS FROM RAT BLOOD
CHYLOMICRONS
INTRALIPID
PERCENT
100
80
60
40
30
20
10
230
500
1000 mg/kg
300
500
1000 mg/kg
0
30
60
90
TIME (minutes)

Fig 12

Good information as to ideal calorie to nitrogen ratios does not exist. The fact that IV nutrition can maintain growth,indicates that the currently used ratio is adequate but it is quite possible that different ratios will be found that are better under different clinical settings (41).

Fat:

Fat emulsions can supply many of the calories needed during alimentation. In the past fats have caused many problems and are no longer available for clinical use in the United States. Wertland has emphasized that "because of the pronounced differences between the various fat emulsions regarding tolerance and toxicity it is not correct to speak of fat emulsions for IV nutrition in general terms. The name of the product and its exact composition must always be given" (8). One emulsion, Intralipid, appears to be clearly superior to other emulsions. It is soybean oil emulsified with purified egg yolk phospholipid, and also contains some glycerol.

Advantages of IV Fat

a. It is a concentrated source of energy (9 cal/gram) and can be given as an isotonic fluid. Thus it can be perfused in peripheral veins (at least in short-term studies) and it seldom causes thrombophlebitis.

b. Does not cause diuresis.

c. No losses in urine or stool.

d. It is not only well cleared from plasma but is biologically utilized (45). Studies have shown that Intralipid and chylomicron have similar chemical and physical properties (46). As seen in Figure 12 the clearance of a standard dose of chylomicron and Intralipid are quite similar (47). The fat is metabolized and is used as a source of energy to improve nitrogen balance (48).

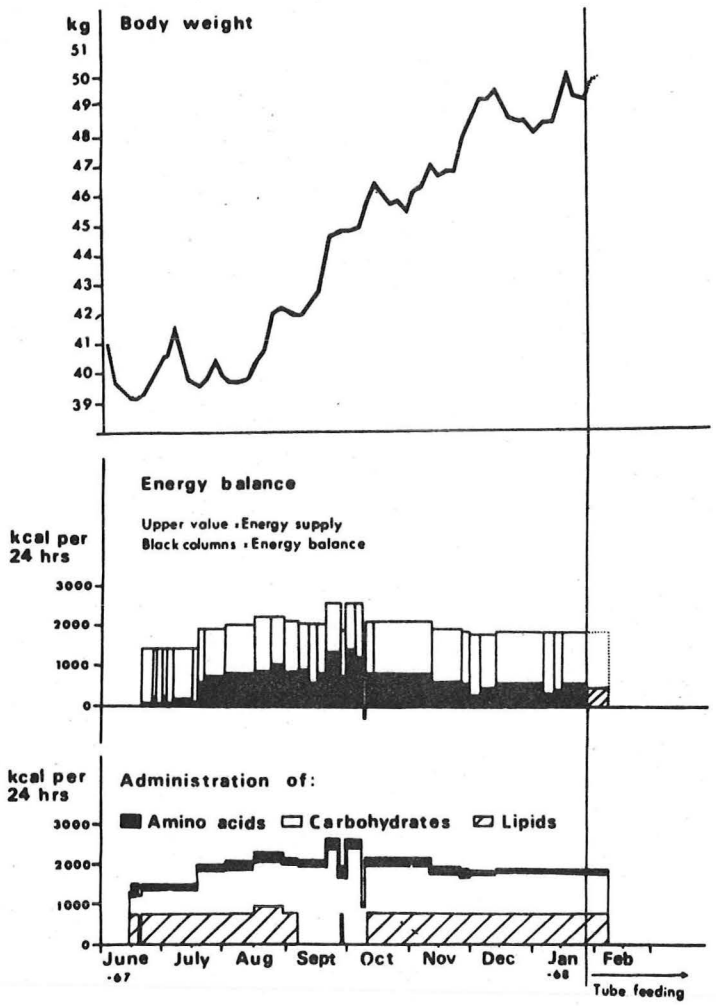
e. Supplies essential fatty acids and triglycerides ordinarily absent from parenteral programs (49).

f. Can be used for long periods without difficulty - Figure 13 (50). This figure illustrates seven months of therapy - no complications.

g. May be infused twelve hours per day instead of twenty-four.

Disadvantages of IV Fat

a. A number of problems which occurred with Lipomul, a cottonseed oil emulsion, are not seen with Intralipid. These include anemia, reduced platelets, coagulopathy, elevation of BSP and



- Changes in body weight and energy balance of a patient during complete intravenous nutrition for 7 months and 13 days

Fig 13

the overloading syndrome. This syndrome consisted of fever, abdominal pain, vomiting, hepatosplenomegaly, impaired liver function and severe coagulopathy.

b. Fat pigment and microgranulomas may form in the liver and spleen (51). Concomitant administration of Vitamin E will prevent much of the pigment and granuloma formation.

c. Low blood insulin may inhibit utilization.

d. May be contraindicated in individuals with certain hyperlipidemias.

e. Should be administered cautiously to patients with liver disease.

f. Studies in rabbits after Intralipid administration have demonstrated deposition of fat in the alveolar-capillary membrane and an inhibition of oxygen diffusion. However, studies in human burn patients reveal no change in diffusion capacity, blood gases or respiratory function after Intralipid (53).

In conclusion, fat emulsions have great promise and Intralipid which apparently behaves much like chylomicron will hopefully soon be made available for clinical trial.

Protein (Nitrogen)

Dietary Protein Requirements

The minimum requirement for protein in an adult is 0.42-0.50 grams per kilogram per day (8,54, 55). Since the coefficient of variation is approximately 15% if 0.55-0.65 grams of protein are given, then basal nitrogen requirements should be met in almost all adults. At least 10% of parenterally administered amino acids are excreted intact into the urine. If the remaining parenterally administered amino acids are effectively utilized basal requirements would be 0.61-0.71 grams of protein per kilogram per day. Thus basal requirements for a non-stressed adult would be 50 grams of protein per day.

TABLE I

ESSENTIAL AMINO ACID AND PROTEIN REQUIREMENTS IN MG/KG BODY WEIGHT OF HUMAN SUBJECTS OF VARIOUS AGES

Requirement	Infants	Child, 10-12 yrs.	Adult Man	Adult Woman
Histidine	25			
Isoleucine	111	28	11	10
Leucine	153	49	14	13
Lysine	96	59	12	10
Met. & Cys.	50*	27	11	13
Phe. & Tyr.	90*	27	14	13
Threonine	66	34	6	7
Trypophan	19	4	3	3
Valine	95	33	14	11
Total EAA (Excl.Histidine)	680	261	87	80
Total Protein Needs (Avg.)	1700	700	425	425
EAA as % Total	40%	36%	20%	19%

*Adding 50% to the mean requirement for methionine (39 mg/kg) and for phenylalanine (68mg/kg) to include cystine and tyrosine needs respectively.

In adults there are eight essential amino acids (Table I from Munro).[56] Infants need histidine and premature infants require cysteine-cystine.

A higher proportion of the total amino acid intake must be essential amino acids in growing infants and children.

Two facets of amino acid metabolism that could be important in designing an alimentation solution are first (Figure 1) that glutamic and aspartic acids are almost entirely transaminated to alanine and glutathione in the intestinal mucosa and thus normally are present in low concentration in plasma, and second, although most amino acids are efficiently extracted from the portal blood,

the branched chain amino acids, leucine, isoleucine and valine, are cleared by the carcass (4).

PARENTERAL VS ORAL NITROGEN REQUIREMENTS

Various opinions exist as to whether intravenously administered amino acids are as effectively utilized as the same amino acids ingested orally. Nitrogen balance studies have not given a consistent picture, but urea production appears to be higher when AA are given orally (57,58).

^{15}N was incorporated faster into serum globulin by the intravenous administration of ^{15}N ammonium acetate to healthy subjects and faster into serum albumin by oral administration (59). Since globulins are synthesized in the periphery and as albumin is made in the liver, this indicates that orally administered ammonia is preferentially utilized in the liver and intravenously infused ammonia in peripheral organs. Similar studies have shown that, following intravenous administration of essential amino acids to uremic patients who have been given ^{15}N urea intravenously, the incorporation of ^{15}N in muscle protein was higher than in plasma protein, but that oral administration of the essential amino acids produced the opposite result (60).

PARENTERAL AMINO ACIDS - PRACTICAL CONSIDERATIONS

(1) Several, rather than one or two, non-essential amino acids should furnish the non-essential nitrogen for optimum utilization (61).

(2) When essential amino acids are given in excess, then the proportion of essential to non-essential has little effect on nitrogen balance.

(3) Since the branched-chain AA are normally present in higher concentration in the peripheral circulation, possibly their concentration should be proportionately higher in the AA infusate.

(4) Two per cent of the population is heterozygote for phenylketonuria, thus part of the phenylalanine requirement should be met with tyrosine.

(5) Glycine inhibits anabolism if given in high concentrations (62).

(6) Since alanine is the main form of transport for amino-nitrogen between tissues, possibly it should be a major part of non-essential nitrogen.

PEPTIDE UTILIZATION

Approximately 30% of casein hydrolysate is peptides. In normal individuals of these peptides
20%/will be found in the urine but in post-traumatic patients up to 80% may be lost in the urine (64).

AMINO ACID COMPOSITION FOR VARIOUS DISEASE STATES

(1) Stress: The clinical setting in which amino acids are usually given to adults is such that you are attempting to promote tissue regeneration. Amino acid requirements for tissue repletion resemble those of the infant more than adult, therefore the proportion of essential AA should be high. (62)

(2) Renal Disease: The essential amino acids plus histidine are given and non-essential nitrogen is supplied from the expanded urea pool.

(3) Liver Disease: The essential AA plus restricted non-essential nitrogen.

Table 2 classifies and summarizes the use of amino acids and lists some other sources of nitrogen.

TABLE 2

INTRAVENOUS AMINO ACIDS

Isoleucine Leucine Lysine Methionine Phenylalanine Threonine Tryptophan Valine	Essential Amino Acids	Chronic Uremia; Liver Disease
Histidine	Essential for infants & in uremia	Chronic Uremia
Cysteine-Cystine	Essential for immature humans	
Arginine	For optimal utilization of amino acid mixtures & for detoxification	
Alanine Glutamic acid Proline	For optimal utilization of amino acid mixtures	Liver Disease
Aspartic Acid Glycine Serine Tyrosine Urea Ammonia	Sources of non-specific nitrogen	
Leucine Isoleucine Valine	Branched chain amino acids	
Glutamic Acid Aspartic Acid	Transaminated in gut wall	

WATER

Minimum water needs (no fever or abnormal losses):

1.0 ml per Kcal - Adults
1.5 ml per Kcal - Infants

120-150 ml water/kg - neonates
120-130 ml water/kg - children

The final mixture of the usual alimentation fluid contains 1.0 ml per Kcal.

When extra losses are present (nasogastric suction, etc.) extra water must be provided.

SODIUM

Under basal conditions sodium losses in the stool and from perspiration range from 10 to 25 mmol per day (38,65). Moderate perspiration can double the above range. Urinary losses flux over a wide range with losses as low as 1 mmol per liter in a sodium-depleted patient. Dudrick routinely puts 50 mmol of sodium in each liter and has not had a problem with sodium retention. Obviously patients with renal, liver or cardiac disease may require sodium restriction, and in such instances intake can be reduced to zero if necessary.

Sodium chloride is usually added to the protein hydrolysates while sodium bicarbonate is added to crystalline amino acid solutions. This is because the amino acids in the latter solution are precipitated as the hydrochloride salt and thus they have a tendency, particularly in infants, to cause an acidosis.

POTASSIUM

Potassium losses in the urine and feces will average 10 mmol per day. Urinary losses of potassium are higher than sodium as the kidney cannot conserve potassium to the extent it can sodium. One patient who was alimented intravenously for seven months average daily loss was 40 mmol (38). But generally much more potassium is provided since the type of patient needing intravenous alimentation is often potassium-depleted. Any time fluids are lost from the GI tract (vomiting, NG suction, fistulae or diarrhea) K^+ will quickly be depleted. Likewise, starvation (decreased K^+ intake and accelerating losses from protein breakdown) accompanies many of the problems necessitating parenteral food. When therapy begins adequate K^+ must be present as K^+ moves intracellularly with glucose. Also optimal amino acid uptake is unlikely to occur in the presence of hypokalemia (66).

Forty mEq of potassium is usually given with each 1000 Kcal. This means that most patients receive $\cong$ 120 mEq per 24 hours, but depending on losses as much as 250 mEq may be given in one day.

Severe metabolic alkalosis and/or hypokalemia may be seen with gastric outlet obstruction, diarrhea, fistula or rapid tissue losses. Large potassium deficits (400 mEq) are often present under such circumstances and a sudden glucose load will drive potassium intracellularly. The resulting hypokalemia could be fatal.

Not until the alkalosis and potassium deficit are corrected should alimentation be started.

CALCIUM AND PHOSPHORUS

Calcium is present in adequate amounts in the skeleton, and if the kidneys and skeleton are normal, parathyroid hormone will release adequate calcium to prevent hypocalcemia. If the serum calcium is normal at the start of intravenous nutrition some investigators have not given supplemental calcium but are content to monitor serum calcium. Balance studies during IV nutrition reveal a need for 200 to 500 mg of calcium to meet losses which are frequently increased because of immobilization. Since the infusion of phosphorus may precipitate hypocalcemia and as phosphorus is present or added to the various alimentation solutions, the addition of modest amounts of calcium (300 mg/day) is reasonable (67).

TABLE 3

AVERAGE COMPOSITION OF SOLUTIONS PER LITER

Solution	Amino-Sol	Amigen	Neo-Amino-sol	Cutter 8%	Freamine	McGraw Essential Amino Acid
Protein(gms)	46	42	50	80	85	53
Na (mEq)	2.5	33	14	40	10	5
Cl (mEq)	10	17	47	50	45	45
K (mEq)	17	19	-	30	-	-
Ca (mg)	20	115	-	-	-	-
Phosphate(mg)	10	220	-	-	-	-
Mg (mEq)	2.2	2.2	-	-	-	-

Phosphorus is abundant in casein hydrolysates (Amigen), present in trace amounts in fibrin hydrolysates (Aminosol) and absent in amino acid solutions. (Table 3). The administration of phosphate-free solutions has resulted in significant hypophosphatemia manifested clinically by paresthesias, weakness, seizure, reduction in erythrocyte 2,3-diphosphoglyceric acid and adenosine phosphate, and a shift in the hemoglobin disociation curve to the left. (68,69). Ten to 15 mEq of phosphate as KPO_4 should be added to each liter of amino acid solutions. Amigen, a casein hydrolysate, contains sufficient phosphorus and unless hypophosphatemia develops no additional KPO_4 needs to be added.

MAGNESIUM

If a patient is on a magnesium-free diet, magnesium deficiency can develop in less than one month. (70). As with most other minerals, requirements are a little hazy, but long-term balance studies indicate that at least 5 to 10 mEq per day are needed and 10 to 25 mEq per day are given (43, 71) This seems reasonable as body magnesium stores may be depleted, but the amount given will have to be reduced if renal failure supervenes.

TRACE ELEMENTS

These elements have been demonstrated to be needed by man but deficient diets produce clinical abnormalities slowly and inconsistently.

Iron

Iron deficiency is not uncommon in parenteral alimentation, and supplemental iron therapy has been widely advocated. Treatment is usually by Imferon (intramuscular iron) or rarely by intravenous iron. The latter may be associated at times with severe allergic reactions (72). Once pre-existing iron deficiency is corrected, monthly therapy will usually suffice.

Iodine

Iodine is recommended at a dose of 1 ug/kg in adults. Findings of iodine lack have not been reported and 1 ug/kg is felt to be well below toxic levels (78).

Copper

Copper recommendations have ranged from none to 1.0 mgm per day. Supplementation with .4 mg cupric ion daily for a prolonged period to one adult patient was associated with a normal plasma copper and ceruloplasmin (73). Children should receive copper but since adults have significant copper stores it is not clear whether they should receive IV supplementation.

Zinc

Zinc appears to be needed by man even though a pure deficiency state has not been described. Lack of zinc may be characterized by growth retardation, skin lesions, impaired reproductive development and function and poor wound healing (73). Tentative IV recommendations are 2 to 4 mg per day for adults.

Fluoride

If children are alimented intravenously for extended periods of time, fluoride should probably be provided. If adults need fluoride, adequate amounts are probably present as contaminants of solutions and medication.

Manganese

As with copper it is not clear that adults need supplemental manganese.

Small amounts have been given without elevating serum levels or producing obvious clinical changes, but an honest appraisal would be that we do not know if manganese, copper or fluoride are needed.

It is apparent that recommendations for trace elements are vague and they will continue to be so until the following problems are solved:

(1) Trace element contamination of solutions, water, medications and infusion apparatus must be carefully quantitated.

(2) Actual needs for normal and stressed individuals must be determined.

(3) Safety of intravenous versus oral routes must be determined.

Needs and toxicity in different diseases are likely to be different.

Current practice has been to replete obvious iron deficiency and then give IM iron monthly to maintain stores. The need for the other trace elements has been handled in one of three ways: (1) Ignored, (2) Given as plasma 10 ml/kg once or twice weekly, or (3) directly added to solution. (73).

TABLE 4

TRACE ELEMENT REQUIREMENTS FOR ADULTS

Iron	Men and non-menstruating women	1 mg/day
	Menstruating women	2 mg/day
Iodine		2 ug/kg
Copper		1 mg/day
Fluoride		?
Zinc		2-4 mg/day
Manganese		1-2 mg/day
Chromium		15 ug/day

Adapted from Shils

VITAMINS

It is difficult to formulate vitamin needs for intravenous feeding for the following reasons:

(1) The precise amount of each vitamin needed by mouth is still not clear in many instances.

(2) Most patients requiring parenteral alimentation are seriously ill. These patients probably need extra vitamins for:

(a) Prior depletion

(b) Increased metabolic requirements associated with fever, infection and stress.

(c) Needs of anabolic processes

(d) Accelerated catabolism of vitamins. (74)

(3) Urinary excretion of water-soluble vitamins is higher following IV than p.o. administration. Folic acid, pyridoxine and riboflavin all have high urinary losses with greater than 60% of folic acid, 70% of

pyridoxine and appreciable amounts of riboflavin dosages being found in the urine. The explanation is assumed to lie in the process of intestinal absorption and subsequent removal of the vitamins from the portal circulation by the liver.

Water Soluble Vitamins

The various water soluble vitamins are given in dosages (Table 5) many times greater than the recommended daily allowance (RDA) for oral needs. In time some of the recommendations may be scaled down but since excesses of water soluble vitamins are felt to be readily excreted or catabolized any excess that exist are not felt to be dangerous.

Fat Soluble Vitamins

Obviously the fat soluble vitamins (A, E & D) can't be given with impunity. Vitamin D intoxication is manifested by symptoms of hypercalcemia such as anorexia, nausea, vomiting, constipation, epigastric pain, polyuria, stupor and eventually coma progressing to death. The serum calcium and alkaline phosphatase will be elevated and renal insufficiency often will supervene.

In adults hypervitaminosis A will result in headache, blurred vision, nausea, vomiting and bone pain. Peeling of the skin, neuritis, chelosis, coarsening of the skin and alopecia are seen on physical examination and radiology reveals periosteal new bone formation and calcifications of ligaments and tendons.

None of the various vitamin preparations is suitably complete and several preparations must be used concurrently. The second column of Table 5 is calculated by giving three ampules of Multi-Vitamin Infusion (USV Pharmaceutical Corp) and two ampules of Berroca C (Roche Pharmaceutical Co.) per week. Folate, B_{12} and Vitamin K are given IM.

TABLE 5

VITAMIN REQUIREMENTS FOR ADULTS DURING PARENTERAL NUTRITION

	RDA	One ampule MVI 3X wk & Berroca 2X wk
Ascorbic Acid	200 mg	240 mg
Thiamine	10-20 mg	23 mg
Riboflavin	5 mg	7 mg
Niacin	30-50 mg	60 mg
Pyridoxine (B_6)	6 mg	14 mg
Pantothenate	10-15 mg	16 mg
Folate	1.0 mg	10 mg IM/wk
B_{12}	5-10 mcg	250 mcg IM/mo
Biotin	300 mcg	57 mcg
Vitamin A	3000-8000 units	4300 u
Vitamin D	400 units	500 u
Vitamin E	60 units	2 u
Vitamin K	1-2 mg	10 mg IM/wk

INDICATIONS FOR PARENTERAL ALIMENTATION

Before listing specific diseases and problems, it is helpful to discuss generally what a program of total parenteral alimentation can achieve.

(1) It can provide enough nutrients for repair and growth to occur in animals and man (75,76).

(2) It is associated with decreased mechanical and secretory activity of the alimentary tract, i.e., bowel rest (77).

(3) By infusing essential amino acids and very little non-essential nitrogen the urea pool can be reduced while nutrition is maintained.

(4) It can reduce the urgency of surgery or other types of treatment and allow greater flexibility of care.

Until controlled studies indicate the need for more aggressive therapy, a conservative course should be adopted. The following general rules are promulgated in an attempt to control over-enthusiastic treatment:

(1) When the patient has lost 10% of his edema-free body weight and the processes responsible for the catabolism are still operative, total parenteral nutrition should be considered.

(2) If an individual has been on intravenous glucose therapy for four weeks and the prospects are for continuation of this type of intravenous therapy, then total parenteral nutrition should be started even if the patient has not lost 10% of his edema-free body weight.

(3) In certain specified diseases (see below) these rules are waived and they are also modified by the nutritional status present before the onset of the current episode.

(4) Parenteral nutrition should never be undertaken if the GI tract can be safely utilized.

SPECIFIC INDICATIONS FOR TOTAL PARENTERAL NUTRITION IN ADULTS

Review articles of TPN almost always contain a long list of situations in which

TPN is indicated. How efficacious parenteral alimentation is in each situation is not considered. In addition the problem treated by TPN may have been one case described in a letter-to-the-editor or 200 cases carefully presented in ten articles, but you can't tell without searching the reference.

In an attempt to avoid these problems the situations where TPN has been advocated will be divided into three categories based on apparent efficacy at this time. Category A will be those diseases where data indicates an improvement of morbidity and mortality over previous forms of therapy (Table 6). Category B includes problems that are frequently treated by TPN, and that probably benefit from TPN, when cases are carefully selected. Category C contains a large assortment of illnesses that have been treated by TPN. Possibly some cases are benefitted, but at times the rationale for treatment is tenuous and the reported cases are either few in number or contain mixed results.

TABLE 6

INDICATIONS FOR TOTAL PARENTERAL NUTRITION

Category A - TPN Indicated:	Gastrointestinal tract fistulae Short bowel syndrome Acute renal failure (severe)
Category B - TPN Probably Effective:	Gastrointestinal tract obstruction Burns Multiple trauma Functional colostomy needed
Category C - TPN Possibly Effective:	Inflammatory bowel disease Severe malabsorption Oropharyngeal dysphagia Hyperemesis gravidarum Adjunct to chemotherapy Anorexia nervosa Congestive heart failure Chronic severe respiratory insufficiency Tetanus Pancreatic ascites Chronic pancreatitis Pancreatic necrosis Liver disease

Category A - TPN Indicated

(1) Gastrointestinal Tract Fistulae: The formation of a GI tract fistula whether internal or external introduces the patient and physician to an illness of long duration, high mortality, poor results and great expense (78). As outlined in Table 7, TPN has resulted in less surgery, more closures, lower mortality and shorter hospitalization (79-81). The overall closure rate with TPN was 94%, by far the best results obtained. This is in spite of the fact that many of the fistulae were secondary to regional enteritis, fistulae that are quite refractory to treatment. Only 60% of the internal fistulae closed spontaneously although most of the remainder (5/6) were then closed surgically. Only 40% of the ileal fistulae closed spontaneously, probably a reflection of the underlying disease (regional enteritis).

The good results are produced by the combination of decreased motility and secretion and improved nutrition.

TABLE 7

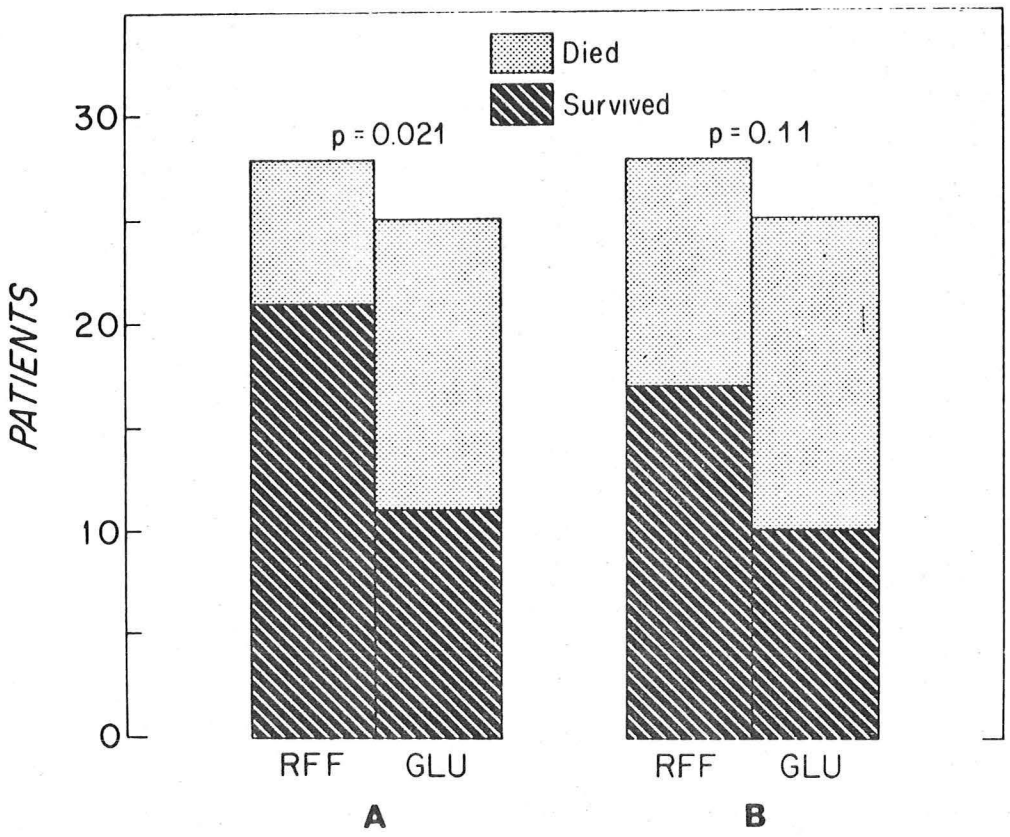
TREATMENT REGIMENTS FOR GASTROINTESTINAL FISTULAE

	Spontaneous Closure	Surgical Closure	Mortality	Duration Therapy until Closure	Comments
Standard Therapy Low calorie (78)	39%	60%	40-65%	Months	All external
Calories & Protein by tube & vein (79)	58%	52%	16%	60 days	Not all patients could have tube placed - no inflammatory bowel disease
Total Parenteral Nutrition (80,81)	71%	74%	7%	35 days	High percentage inflammatory bowel disease - internal and external fistulæ

(2) Short Bowel Syndrome: (See case history). It is not uncommon to see patients who have lost the major portion of their small intestine from vascular insults, trauma, or inflammatory bowel disease. Those individuals who have lost 75% or more of their bowel have a poor prognosis especially if the ileocecal valve or duodenum are lost (82,83). Postoperatively patients with massive resections rapidly develop problems when feeding is resumed. If suture lines don't break down (causing abscesses, fistulae and peritonitis) the patients soon develop severe diarrhea with skin maceration and massive steatorrhea with all its attendant problems. In the past their recovery has been difficult and associated with extreme morbidity. TPN avoids many of these problems and allows the physician to aid the patient while he adapts to his handicap. If the patient can be maintained for several weeks, the small bowel will increase its absorptive capacity (82,74-86). Cellular hyperplasia is largely responsible for this adaptation (82,84-86). Then oral feedings can be reintroduced gradually with parenteral nutrition making up any deficits. Whether food must be present within the lumen for hyperplasia to occur is not settled, but certainly bulk foods are not necessary and a hormonal mechanism has been proposed (82,85,86). If the entire small bowel is removed below the Ligament of Treitz salvage is not possible, and TPN should not be started (83).

(3) Acute Renal Failure: In chronic uremia the administration of essential amino acids by mouth or vein results in re-utilization of urea nitrogen, reduction of the BUN and symptomatic improvement (87,88). Dudrick administered amino acid solutions to individuals with acute and chronic uremia plus gastrointestinal dysfunction, and demonstrated weight gain, wound healing, positive nitrogen balance, stable or falling BUN and clinical improvement (89).

Fig 14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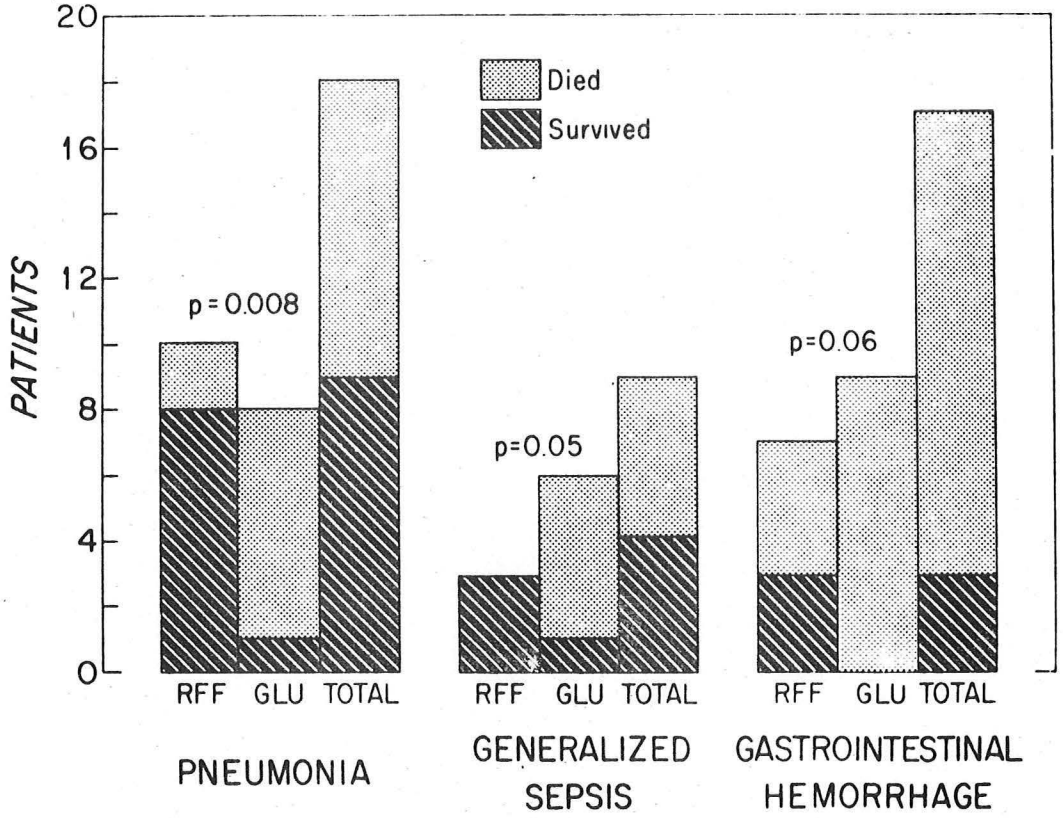
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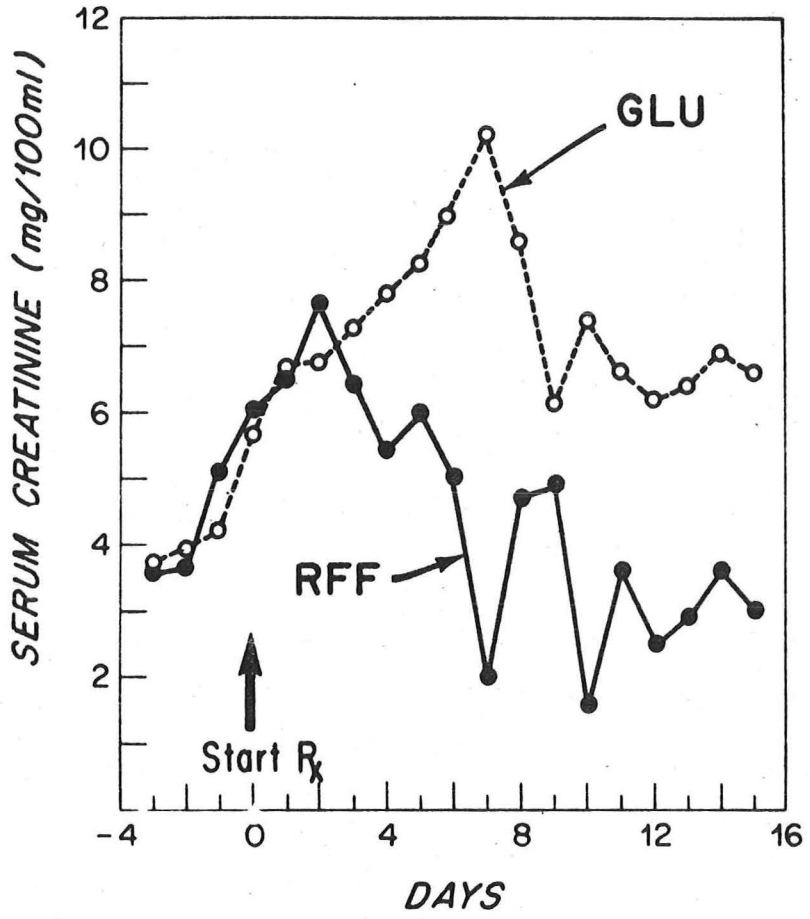
PNEUMONIA
GENERALIZED SEPSIS
GASTROINTESTINAL HEMORRHAGE

Fig 15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10
8
6
4
2
GLU
RFF
Start Rx
-4
0
4
8
12
16
DAYS

Fig 16

In the only prospective, double-blind study yet conducted in the field of hyperalimentation, Abel et al evaluated the impact of TPN on the course of acute renal failure precipitated by renal ischemia usually in a surgical setting (90). Fifty-three patients were treated with parenteral nutrition; 25 received glucose, minerals and vitamins, while 28 received essential amino acids plus glucose, minerals and vitamins. The solutions were iso-caloric and infused by catheter into the superior venae cavae. As seen in Figure 14A 75% of those receiving the amino acids survived compared to only 44% of those receiving glucose. In patients with oliguric acute renal failure, treatment with amino acid containing fluid seemed to be particularly efficacious, since 14 of 18 such patients recovered as compared to only 7 of 16 receiving the glucose solution ($p=0.05$). Those patients who received glucose alone while undergoing dialysis did poorly (2 of 11 survived), while those who received protein did much better (11 of 17 survived).

Complications, such as pneumonia, sepsis and stress bleeding were much less serious in individuals receiving amino acids (Figure 15). In addition renal function as reflected by serum creatinine improved more rapidly in these patients (Figure 16). It thus becomes reasonable to treat patients with severe acute renal failure plus gastrointestinal tract dysfunction with TPN, the protein being supplied by essential amino acids.

Category B - TPN Probably Effective

(1) Gastrointestinal tract obstruction: Most of the patients presenting with some form of chronic obstruction have sustained significant weight loss when they present to the physician (Table 8). These cases must be handled individually, and it is particularly important that a specific goal is established and other routes of feeding are utilized if possible.

TABLE 8

GASTROINTESTINAL TRACT OBSTRUCTIONS AMENABLE TO TOTAL PARENTERAL ALIMENTATION

1. Esophageal
   - Carcinoma
   - Advanced Achalasia

2. Gastric Outlet Obstruction
   - Peptic Ulcer Disease
   - Tumor

3. Small Bowel Obstruction
   - Postoperative
     - Paralytic ileus
     - Anastomotic leaks
     - Peritonitis
   - Scleroderma
   - Pseudo-obstruction

Patients with peptic ulcer disease and gastric outlet obstruction, for example, who present with a large atonic stomach, marked weight loss and complicating medical problems are good candidates for TPN. The medical care of these patients is made easier and the operative mortality appears to be reduced (91-93). The stomach can be completely decompressed, nitrogen balance restored, and complicating illnesses treated prior to surgery. In addition, postoperative ileus is common when outlet obstruction has preceded surgery and TPN can be continued postoperatively if needed (91).

(2) Burns: Extensive burns are associated with huge caloric expenditures and markedly negative nitrogen balance. TPN often supplemented by oral or tube feedings can provide the needed calories and nitrogen and thereby stabilize weight and promote wound healing (94).

(3) Multiple Trauma: Trauma victims and combat casualties often have gastrointestinal tract trauma or dysfunction, impaired sensorium, sepsis and recent surgery. Clearly some of these patients are candidates for TPN but the benefits and relative risks have not been determined (95).

(4) Functional Colostomy: Paraplegics often have indolent decubitus ulcers in the pelvic area. TPN will markedly reduce fecal contamination and allow spontaneous healing or successful grafting procedures.

Category C - Possibly Effective

(1) Inflammatory bowel disease: Bowel rest has long been advocated as treatment for inflammatory bowel disease since bowel rest and good nutrition could be simultaneously provided. No controlled data is available, but uncontrolled data suggests:

A. Approximately 50% of patients with ulcerative colitis will have a temporary remission but the remission is only partial and it seems unlikely, except in instances of advanced protein malnutrition, that TPN will become an important therapy for ulcerative colitis (96,97).

B. Regional Enteritis.

(1) Individuals with regional enteritis of the small bowel treated with TPN have good symptomatic relief with improvement of constitutional symptoms, pain and diarrhea (98).

(2) Fistulae may close if distal obstruction or abscesses are not present.

(3) X-rays may show improvement but this probably represents resolution of edema and biased reading of the films.

(4) High-grade obstruction will seldom respond but if an individual was severely debilitated, TPN might be indicated preoperatively.

(5) Those patients in whom the disease is so extensive that resection would produce a short bowel syndrome should probably receive TPN in conjunction with other forms of medical therapy.

C. Granulomatous colitis may respond better than granulomatous disease of the small bowel.

A detailed discussion of the remaining problems listed below (Category C - Possibly Effective) will not be given, except for liver disease, because experience regarding these other problems is too anecdotal and incomplete, although a reasonable rationale and/or case report is sufficient reason to include them in this list. Eventually TPN may prove helpful in these problems but, pending reliable information, TPN should be done only when it is clear that a potentially salvagable patient is starving and the tenuous nature of the therapy is understood.

(2) Severe malabsorption (13, 99)

(3) Oropharyngeal dysphagia (99)

(4) Hyperemesis gravidarum (99)

(5) Adjunct to chemotherapy (100)

(6) Anorexia nervosa (101)

(7) Congestive heart failure (99)

(8) Chronic severe respiratory insufficiency (99)

(9) Tetanus (102)

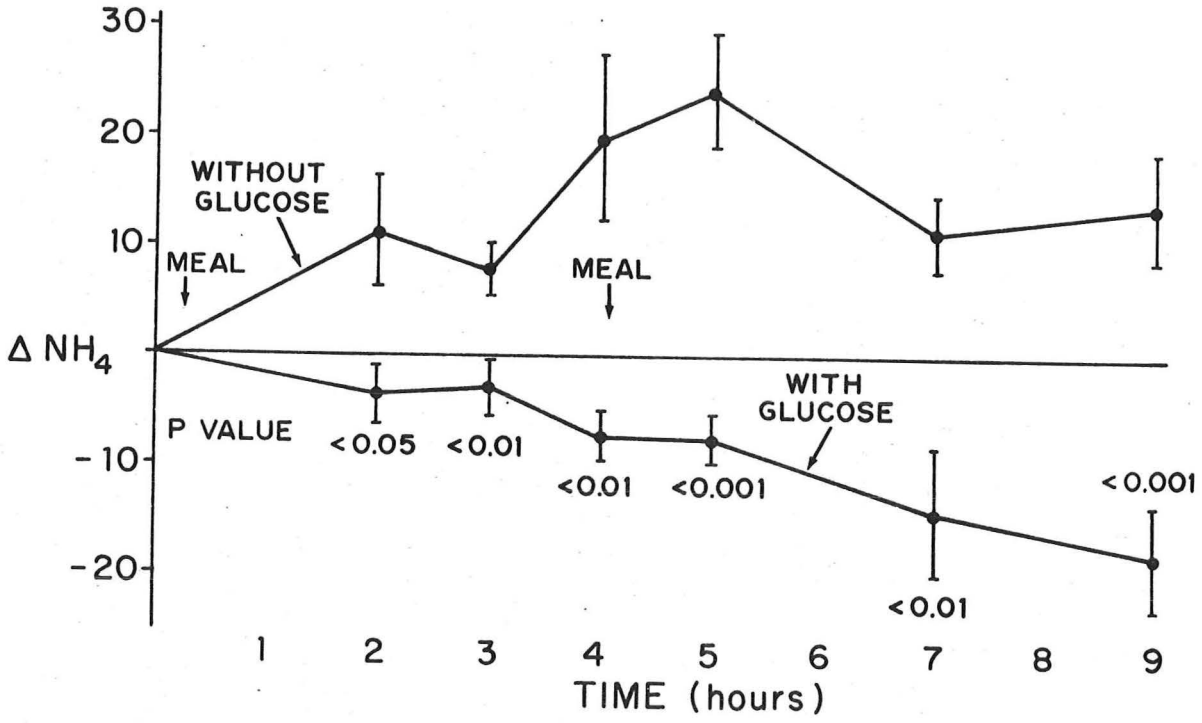
(10) Pancreatic ascites (103)

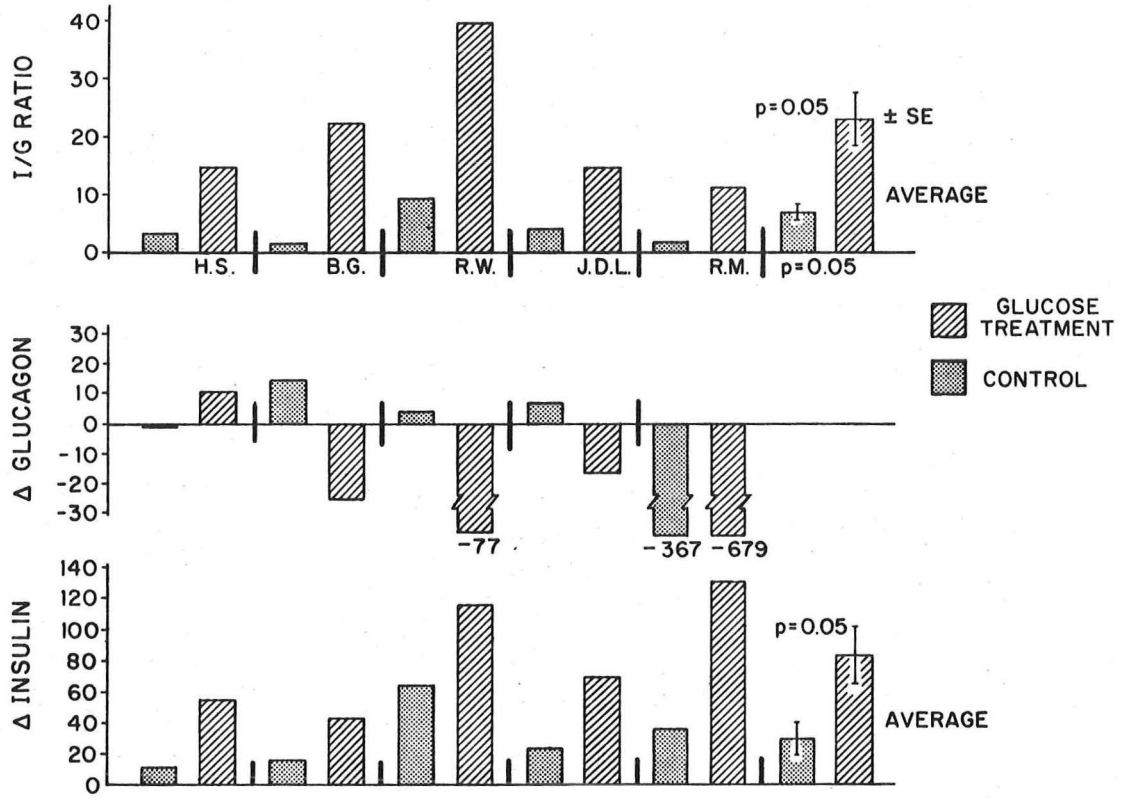
(11) Chronic panreatitis (103)

(12) Pancreatic necrosis (103,104).

(13) Liver disease: The treatment of liver failure of diverse etiologies often presents the physician with a dilemma. It has been repeatedly demonstrated that protein is necessary for repair of the liver, yet the administration of protein may precipitate or worsen hepatic encephalopathy (105). The ingested protein is inefficiently utilized and the urea pool is expanded (106). The urea diffuses into the gut where it is hydrolyzed to ammonia which can then induce encephalopathy (107). Hyperglucagonemia is present

Fig 17





AVERAGE CHANGE FROM BASAL - AVERAGE OF SIX VALUES OVER 9 HOURS

Fig 18

in cirrhotics who have portal systemic shunting and/or advanced disease (108). Many previous studies have demonstrated glucose intolerance and insulin resistance in patients with liver disease (109). Thus we have a hormonal situation similar to that found in stress, i.e., insulin resistance, high glucagon and a catabolic state.

We have recently completed studies in cirrhotic patients pertinent to this problem (110). Stable cirrhotics whose blood ammonia elevated after modest protein intake were evaluated. While nitrogen balance was maintained, blood ammonia, insulin and glucagon were measured throughout the day from breakfast to just before the evening meal. Several control days were done between treatment days. Treatment consisted of 20 grams of glucose per hour throughout the day (total 200 gms or 800 Kcal). Nitrogen intake was identical yet ammonia did not rise when the supplemental glucose was given (Figure 17).

Concomitant with the fall in ammonia generation, blood insulin rose, glucagon fell and the molar insulin:glucagon ratio was significantly higher (Figure 18). Such a hormonal set would inhibit gluconeogenesis and urea formation.

In addition to improving the insulin:glucagon ratio, an oral or intravenous nitrogen load composed of essential amino acids should further depress the urea pool. If given peripherally, such AA should be preferentially utilized by the carcass, thereby increasing muscle strength.

When treating cirrhotics by TPN the solution should be compounded by the following rules:

(1) Modest total nitrogen load, e.g., 9 gms/day or less.

(2) High calorie to nitrogen ratio, e.g., 300 or 400 Kcal/gm nitrogen.

(3) Nitrogen should be composed of essential amino acids plus histidine, arginine and alanine.

Use of TPN for coexisting problems in stable cirrhotics has been safely accomplished, with the major problems being occasional enzyme rises and modest acidosis from the essential amino acid solution (111). Blood ammonia rose modestly and portal pressure remained unchanged.

Studies utilizing TPN for treatment of liver failure were uncontrolled and evaluated only a few patients (1/2). Further research as to the applicability of TPN in liver failure is warranted (112).

TECHNIQUES OF TOTAL PARENTERAL ALIMENTATION

A. Solution Preparation

1. The concensus is that the solutions should be mixed under a laminar flow hood, by a pharmacist (113). The pharmacist should scrub and all bottles should be wiped with iodine solution.

2. New techniques allow the pharmacist to rapidly and safely mix these solutions including the addition of all minerals and vitamins.

3. The solutions must be refrigerated pending their use and fluids should not be in use for more than 12 hours.

B. Solution Incompatibilities (114)

1. Calcium - not compatible with sodium bicarbonate. CaCl precipitates with $MgSO_4$ but Ca gluconate reacts very slowly with $MgSO_4$.

2. Insulin - not stable in presence of sodium bicarbonate.

C. Delivery System

1. Viaflex (PL-146 polyvinyl) made by Travenol is probably the best system (114,115). Infusion pumps are optional but their use ensures more even flow and possibly reduces infection and thrombosis.

2. Filters should be used in mixing the solutions but they are not regularly used during infusion into the patient.

3. Tubing - changed daily. Some clinicians wash off all tubing connections with Betadine and apply Iodophor ointment.

4. Catheter site - in adults the subclavian or internal jugular vein should be used. If infusion is contemplated for greater than six to eight weeks an internal A-V shunt should be constructed. Such a shunt must mature for six weeks before being catheterized (116). The actual catheter insertion should be accomplished in the operating room or clean procedure room under rigid aseptic technique and checked for proper placement fluoroscopically. Physicians placing catheter should scrub and wear masks.

The catheter must be anchored securely to prevent irritating to-and-fro motion and to avoid potential transport of cutaneous bacteria into the puncture wound.

5. Catheter Care - The site should be reprepped at least three times a week. Acetone is used to defat the skin, followed by 1% iodine in 70% alcohol which is allowed to dry for 30 seconds and then washed off with 70% isopropyl alcohol. Alternatively one may prep with Betadine which need not be washed off. Betadine ointment is then applied. The site should be kept dry, but if this is difficult, a sterile dressing is not used and the site is reprepped several times per day. The individuals reprepping the site should utilize gown, mask, gloves and sterile field. The catheter must be discontinued if purulence, thrombosis or extravasation of fluid are noted. The catheter site should be changed at least every 30 days. The TPN system should not be used to measure central venous pressure, administer blood products or "piggy-back" medications, or obtain blood samples.

D. Patient Evaluation

Vital signs - q 4-6 hours - daily weights
Complete I&O
Blood Measurements

	First Week	Later
Serum electrolytes	Daily	3X weekly
BUN - Glucose	Daily	3X weekly
Creatinine	3X weekly	2X weekly
Serum Ca & PO_4	3X weekly	2X weekly
Serum enzymes	3X weekly	2X weekly
Protein - total & fraction	weekly	weekly
CBC	weekly	weekly
Magnesium	weekly	weekly

Urine

Glucose	4-6X daily	daily
Sp. Gr. or osmolarity	2X daily	2X weekly
Na or K	daily	2X weekly

$$\text{Plasma osmolarity} = 2X\,(Na) + \frac{(\text{glucose})}{18}$$

(mOsm/kg H_2O) mEq/L mg/100 ml

E. Quality Control

1. Protocol - each hospital should establish a protocol which clearly establishes procedures for mixing, storing, sampling for contamination, and administering the alimentation solutions. It should clearly designate nursing procedures and responsibility, should also specify an area within the hospital where the alimentation must be done. Procedures for catheter instillation and care should be set up and guidelines as to what should be infused can be suggested. Lastly, the protocol should clearly limit the use of this therapeutic modality to physicians who are themselves qualified by virtue of a solid knowledge of alimentation or have access to such an individual via consultation.

2. Total Parenteral Nutrition Team - a physician or group of physicians with a particular interest and in-depth knowledge of the metabolic and infectious liabilities of TPN should be responsible for administering the hyperalimentation program (114,117-119). Hyperalimentation nurses are the backbone of a successful program much as they are in dialysis or coronary care units. Where alimentation is done on several wards, they serve as roving educators, data collectors and infection control nurses. Where IV alimentation is localized to a metabolic unit or portion of a single ward, nurses or other paramedical personnel can be utilized even more effectively in the management of the patients.

The pharmacy is the logical place to mix these solutions and ideally one pharmacist should direct this aspect of the program (114). This pharmacist then becomes an important member of the alimentation team.

Finally, it is useful to have a close liaison with an infectious disease consultant who periodically reviews techniques and procedures and helps in the investigation of those infections that occur.

This TPN team is responsible for writing protocols, educating personnel, and either caring for or consulting on the TPN cases.

3. Responsibility of TPN Team. The function of the above group of individuals will vary depending on the type of hospital and the number of physicians qualified to perform TPN. Presently, in most institutions, if intravenous alimentation is to be done with an acceptable risk, this team should have direct responsibility for all cases. The primary physician cannot consistently concern himself with the myriad of details that are needed for smooth implementation, including the compulsive catheter care necessary to reduce infection.

4. Site of TPN. The majority of authors would list their preferences in the following manner (120,121).

a. Metabolic Unit for TPN
b. Intensive care unit - obviously needed at times in many patients. The TPN unit should be contiguous so that supervision can be offered.
c. Localized to one ward.
d. Localized to several wards, e.g., one on Medicine and one on Surgery.
e. On most wards.
f. No restriction.

The further down the list, the more important it becomes that trained nurses be available for education of the personnel involved. In addition the further the patient is from a special unit, the more difficult it is to utilize pumps for infusion, insulin for optimal glucose utilization, or obtain accurate intakes and outputs.

COMPLICATIONS OF TOTAL PARENTERAL NUTRITION

As stated earlier, TPN is the parenteral provision of all energy (calories) - nitrogen, minerals and vitamins needed for body maintenance and repair. Problems can and do occur in every component of the system (Table 9).

TABLE 9

COMPLICATIONS OF TOTAL PARENTERAL NUTRITION

I. Calories - glucose
   A. Hyperglycemia -- glycosuria -- osmotic diuresis -- hyperosmolar non-Ketotic dehydration and coma
   B. Diabetic Ketoacidosis
   C. Post-infusion hypoglycemia

II. Nitrogen
   A. Hyperchloremic metabolic acidosis
   B. Serum amino acid imbalance
   C. Hyperammonemia
   D. Pre-renal azotemia

III. Minerals
   A. Calcium
      1. Hypercalcemia
      2. Hypocalcemia
   B. Phosphorus - hypophosphatemia
   C. Potassium
      1. Hyperkalemia
      2. Hypokalemia
   D. Magnesium - hypomagnesemia
   E. Iron - deficiency

IV. Vitamins
   A. Vitamin D
      1. Hypervitaminosis D
      2. Deficiency
   B. Vitamin A - Hypervitaminosis A
   C. Vitamin K - Deficiency
   D. Folic Acid - Deficiency
   E. B_{12} - Deficiency

V. Catheter
   A. Pneumothorax - hemothorax - hydrothorax - tension pneumothorax
   B. Arterial puncture - AV fistula
   C. Lymphatic duct puncture
   D. Embolus - air - catheter
   E. Venous thrombosis
   F. Phlebitis
   G. Nerve injury
   H. Hydromediastinum
   I. Cardiac perforation

VI. Infection

VII. Miscellaneous
   A. Liver function abnormalities
   B. Allergic reaction to alimentation fluid
   C. Essential fatty acid deficiency
   D. Acute papulopustular acne

I. When glucose is infused more rapidly than can be utilized, the outcome may be more than simple hyperglycemia and glycosuria. Severe dehydration and hyperosmolar non-ketotic coma can occur. The syndrome is initiated by glucose infusion rates which are too rapid for the prevailing hormonal conditions, i.e., too little insulin or too much glucagon, catacholamines, glucocorticoids or growth hormone. It is prevented by utilizing low-glucose infusion rates during initial therapy (0.2-0.3 gm/kg/hr), judiciously adding insulin, and carefully monitoring the urine and blood for glucose. Any stress occurring during the course of alimentation can impair glucose tolerance. If a patient who has been tolerating the infusion suddenly develops hyperglycemia, some new source of stress can usually be identified. Examples would include infection, surgery, hepatic dysfunction, pancreatitis or an error in the infusate mixture or infusion rate (122,123).

In the patient with pre-existing diabetes, keto-acidosis can be precipitated, but if glucose is added slowly some diabetics can be successfully alimented.

Hypoglycemia can occur if the infusion is suddenly discontinued and another source of glucose is not begun.

II. Nitrogen. Metabolic acidosis is occasionally seen in infants being alimented with synthetic L-amino acid mixture (124). The acidosis occurs because the mixture contains an excess of cationic amino acids that release hydrogen ion when metabolized. This can be avoided by adding extra acetate, lactate or anionic amino acids to the solution.

In adults who have liver disease or some underlying cause for metabolic acidosis some of the alimentation solutions can precipitate acidosis. The protein hydrolysates and synthetic AA solutions have a modest titratable acidity. The necessary sodium content can be added as $NaHCO_3$ to neutralize the acid.

III. Minerals. The complications of mineral deficiencies and excesses were discussed earlier.

IV. Vitamins. Vitamin excesses which occur have usually been due to medication error. Deficiencies have occurred because the vitamin in question was not given.

V. Catheter. Since complications of catheter insertion are not uncommon, it is important to obviate as many as possible by utilizing proper technique and by having the proper equipment (125,126). Excluding sepsis which will be discussed subsequently, the most frequent complications are pneumothorax, inadvertent areterial puncture and unsatisfactory catheter direction. The arterial stick will occasionally leave a hematoma. A pneumothorax will frequently have to be treated by needle aspiration or chest tube. Incorrect positioning of the catheter can be avoided by using fluoroscopy.

VI. Infection. In a current CDC review septicemia occurred in 6 to 27 per cent of patients receiving TPN (127). However, three recent papers report septicemia rates between one and four per cent when stringent techniques were adopted (128-130). Freeman et all saw their septicemia rate fall from 21% of 20 patients to 2% in 43 patients to 0% in 35 patients as they progressively improved their technique.

Up to 50% of the infections have been caused by Candida and, although simply removing the catheter will frequently lead to resolution of the candidemia, fatalities from disseminated candidiasis are not uncommon. Other organisms which grow well in these hypertonic solutions and have been incriminated in alimentation sepsis are Staph aureus and albus, Klebsiella and E coli.

When sepsis appears, the TPN solution and administration set are discontinued and cultured. Twenty ml of fluid is withdrawn through the tubin, 1 ml used to prepare a pour plate and the rest placed in a blood culture bottle (127). Ten per cent glucose is substituted; blood cultures are taken from a peripheral vein and from the catheter; and if no diagnosis is made within 24 hours the catheter is removed and cultured.

Septicemia occurring in a patient being hyperalimented should not be automatically attributed to catheter sepsis. Less than one/half of these septic episodes can be traced to the catheter (129). To prove that the catheter is the nidus of infection, the following procedure should be followed:

a. Draw a blood culture from an extremity not involved with the infection.

b. Draw a blood culture through the TPN catheter.

c. Using a mask and sterile gloves, the operator should meticulously cleanse the insertion site, withdraw the catheter, and promptly culture the tip.

d. Other known or potentially infected sites should be cultured and a search made for cryptic locations.

When the catheter is responsible, blood and catheter-tip cultures will usually be positive for the same organism.

Prevention of infection is accomplished by religious attention to the techniques and quality control of TPN listed earlier (126-130). If the hospitals and physicians involved are willing to devote the time and allocate the resources to perform total parenteral alimentation correctly, it is a useful and promising technique; if not, the infection rate is usually too high to justify utilization of this new treatment technique.

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