Motivation

The operation was a success, but the patient died.
Prevailing Dogma in the 1960’s

Feeding entirely by vein is impossible; even if it were possible, it would be impractical; and even if it were practical, it would be unaffordable.

Total Parenteral Nutrition was considered a “Holy Grail” or a “Gordian Knot” pursuit by most physicians and surgeons at the time.
Definitions

**Challenge** - A test of one’s abilities or resources in a demanding, but stimulating, undertaking. (Existing limitations, or practices/prejudices resisting change)

**Minefield** - An area containing explosive mines. (Unanticipated, undesirable, or difficult situation)

**Out-take** - A section or scene, as of a movie that is filmed, or of a recording, that is cut from the final version. (What really occurred, but was “sanitized” for presentation or publication, per convention)
Challenges to the Development of Total Parenteral Nutrition (1960-1970) - I

Formulate complete parenteral nutrient solutions *(did not exist, not possible)*

Concentrate substrate components to 5-6 times isotonicity without precipitation *(not easily done)*

Demonstrate utility and safety of long-term central venous catheterization *(not looked on with favor by hierarchy)*
Challenges to the Development of Total Parenteral Nutrition (1960-1970) - II

Demonstrate efficacy and safety of long-term continuous central venous infusion of hypertonic nutrient solutions *(contrary to all clinical practices at the time)*

Maintain asepsis and antisepsis throughout the entire process of solution preparation and delivery *(required culture change)*

Anticipate, avoid, and correct metabolic imbalances or derangements *(a monumental challenge & undertaking)*
Minefields – I A

Hypertonic Dextrose - Long Term Infusion

Effects on venous intima, heart, lung vasculature, RBC’s, WBC’s, platelets

Effects on body cell mass by bypassing liver and pancreas on first pass of circulation

Effects on patients with diabetes mellitus

Effects on pancreatic insulin - stimulatory
Minefields – I B

Hypertonic Dextrose - Long Term Infusion

Effects of exogenous insulin - shock, stroke

Effects of overzealous administration:
- Hyperglycemia, hyperosmolarity,
- diuresis, glucosuria, dehydration,
- hypervolemia, non-ketotic coma, CNS irritability, convulsions

Caramelization; Maillard with amino acids
Protein Hydrolysates

The only nitrogen sources available for IV use:
- Fibrin - Acid hydrolysis - Hydrochloric acid
- Casein - Enzymatic hydrolysis - Pancreatic

Non-standard composition - *Every* lot varied

Peptides comprised 15% - 20% of total nitrogen
- Di-, Tri-, Deca-peptides - allergic reactions

Free amino acids comprised 80% - 85% of total nitrogen. Supplementation with amino acids required to produce balanced formula
Minefields – II B

Protein Hydrolysates

Acid pH - High chloride and hydrochloride content

Contaminants introduced during processing
Various minerals, especially zinc, were in high concentration in early formulas

Unstable, especially in light, heat or with time

Short shelf life - Maillard (browning) reaction
Crystalline Amino Acids

Preferred for purity, consistency and scientific desirability for precision formulation

Derived from microbial biosynthesis rather than the more expensive chemical synthesis

Standardization advantage over hydrolysates

Ratios and doses of amino acids modifiable with individual amino acid additives
Crystalline Amino Acids

Special condition-related formulas possible, e.g., pediatric, neonatal, kidney, liver

Mostly HCL or CL salts - originally high acid load (pH 4.5 – 5.0)

Danger of acidosis in premature infants

Corrected by acetate salts of amino acids
Minefields – IV A

Minerals and Trace Elements

Exact requirements unknown for IV feeding

Extrapolation from PO to IV - a “guesstimate”

Compatibility unknown with base formulas, other minerals and other additives

Interactions of elements - precipitation
Minerals and Trace Elements

Which salts or forms of the elements to use?

How to measure their effectiveness?

How to determine toxicity?
  Usually less of, or not a problem, with GI intake & regulation

How to modify dosages and ratios specifically for various pathophysiologic conditions?
Vitamins

No complete IV formulation existed

Requirements with IV feeding not known

Requirements different for animals and man

PABA a dog vitamin; ascorbic acid (C) not

Requirements different for adults, children

Unique for premature and newborn infants
Vitamins

Requirements vary under different conditions

No complete IV fat soluble vitamins available
IV vitamin K under development;
no A, D, E

Emulsifying agents for A, D, E, K required for water solubility - allergy, asthma, rash, anaphylaxis
Fat Emulsion

Cottonseed oil emulsion

Non-standardized - particles 1 to 10 microns
   Fat globules not equal to chylomicrons

Unstable, heat sensitive, refrigeration required

Impure or inadequate emulsifying agents

Contaminants during manufacturing process;
   Industrial oil, other oils, particulate matter,
   cotton fibers, housefly’s leg and eye
   seen on scanning electron microscopy
Minefields – VI B

Fat Emulsion

Capillary microperfusion problems - large fat globules occluded capillaries in peripheral and/or pulmonary circulation

Seroid pigment deposits in liver
Significance unknown

Incompatible with crystalloid solutions

Withdrawn abruptly by the FDA during the puppy studies
Microbial Contamination and Infection

Nutrient mixture contaminated in formulation

Contaminated by additives in pharmacy

Contaminated by additives at bedside

Contamination of infusion delivery apparatus

Contamination by various manipulations of the infusion system
Minefields – VII B

Microbial Contamination and Infection

Using central catheter for blood drawing

Using central catheter for non-nutrient fluids

Unfiltered air bubbling through solution bottle

Catheter contamination during insertion

Catheter exit site inadequately protected

Catheter infected from remote source in body
Indwelling Central Venous Catheters

Essential for long-term central venous feeding

Polyethylene, polyvinyl chloride, Teflon, vinyl; Silicone rubber tubing not yet available

All available medical grade catheters caused venous intimal inflammation, cellulitis, thrombophlebitis

Concern for reactivity with platelets, RBC’s and WBC’s - Heparin, steroids, procaine not safe or efficacious prophylactically
Microbial Contamination and Infection

Catheter-associated thrombosis, fibrin sheaths

Polymerization of catheters by body fluids

Catheter misplacement, migration, embolization

Too soft, too rigid, too thin, lumen too small

Non-radiopaque, not durable, brittle

Risk of infection 100% eventually with time
Hypertonic Nutrient Solution

Inevitable - to provide requirements by vein within the tolerances of fluid administration

Inability to sterilize by heat or autoclaving

Requires central venous catheterization

Requires long-term central venous infusion

Requires infusion precisely at rate of metabolic utilization or assimilation - pump
Hypertonic Nutrient Solution

Effects of acute and long-term hypertonic nutrient infusion unknown

Risks of contaminating the solution, tubing, catheter, patient with micro-organisms

A growth medium for some micro-organisms
**DRY METHOD**

165 gm anhydrous glucose

860 cc 5% glucose with 5% fibrin hydrolysate

350 cc 50% glucose

750 cc 5% glucose with 5% fibrin hydrolysate

membrane sterilization

Nutritional 1 V
1000 cc
1 calorie/cc
6 gm nitrogen/L

**WET METHOD**

1100 cc
1000 calories
5.25 gm nitrogen/L
Composition of the Oral Control Diet and the three Intravenous Study Diets compared with the oral diet recommended by the Food and Nutrition Board, National Research Council, for growing puppies

<table>
<thead>
<tr>
<th></th>
<th>Oral recommended</th>
<th>Intravenous Balanced</th>
<th>Intravenous Essential</th>
<th>Intravenous Fat-free</th>
<th>Oral control</th>
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<tbody>
<tr>
<td><strong>Protein</strong></td>
<td>8.8</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>10.5</td>
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<td>(gm/kg/d)</td>
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<tr>
<td><strong>Carbohydrate</strong></td>
<td>15.9</td>
<td>25.0</td>
<td>30.0</td>
<td>31.0</td>
<td>18.0</td>
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<tr>
<td>(gm/kg/d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fat</strong></td>
<td>2.6</td>
<td>2.6</td>
<td>0.6</td>
<td>0.0</td>
<td>3.3</td>
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<td>(gm/kg/d)</td>
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<tr>
<td><strong>Calories</strong></td>
<td>140-200</td>
<td>140</td>
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<tr>
<td>(kcal/kg/d)</td>
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<td></td>
<td></td>
<td></td>
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<td><strong>Water</strong></td>
<td>--</td>
<td>130-190</td>
<td>130-160</td>
<td>130-160</td>
<td>100-140</td>
</tr>
<tr>
<td>(ml/kg/d)</td>
<td></td>
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</table>

To date 12-week old male Beagle pups have received their total nutritive requirements by a near-continuous intravenous infusion for 175, 72, 30 and 30 days. The daily per kilo intake of water, calories, glucose, amino acids (Aminosol), Ca and P has been 150-180 ml., 120-140, 25 gm., 4 gm., 3 meq. and 3 meq., respectively. Fat (Lipomul) equal to 2.6 gm/Kg was infused separately. All vitamins and other minerals known to be required for the dog were supplied also by vein. Only tap-water was available for oral consumption. After 12 weeks of intravenous feeding a diuretic (Diurol) was given to facilitate the excretion of the surplus water injected. Long bone X-rays and metabolic studies were made regularly. Body size and metabolic responses were comparable to those observed in their litter-mate controls which received orally a standard ration at the same caloric level. The animal which was infused the longest period increased in weight from 3.4 to 11.2 Kg. (Supported by a grant from NIH - 5 POI AM-04825-05.)

Zinc Deficiency

With initial TPN in patients, no trace elements were available, but zinc deficiency was only rarely observed or documented in this country.

Plasma infused to provide zinc to patients who were clinically and/or chemically zinc-deficient.

At that time protein hydrolysates were the source of nitrogen, and it was later learned that zinc was present as a contaminant of the manufacturing process of hydrolysates in USA.
Zinc Deficiency

When the Japanese developed affordable pure crystalline amino acid solutions, they were absolutely zinc-free.

When they were used initially throughout Asia, Australasia & Germany, zinc deficiency occurred quite frequently.

When this inadvertent problem was identified, it was solved by adding zinc to the solutions.
In first adult TPN patient, apathy, lethargy, muscle weakness, decreased activity and altered breathing pattern occurred surreptitiously with the high glucose and amino acid infusion. Phosphate level was zero, which was never recorded before in our clinical laboratory. Increasing the phosphate dose in the TPN led to dramatic and prompt reversal of symptoms and full recovery.
In the first infant fed with TPN, growth and development, which had been normal for months, reached a plateau. The serum phosphate level was very low, and when IV phosphate dosage was increased, and the hypophosphatemia was corrected, growth and development were restored to normal.
Minefields – XII A

Glucose Metabolism

In patients with diabetes mellitus, TPN required insulin supplementation as with oral feeding. With subcutaneously administered insulin, it was difficult to regulate blood sugar levels finitely because of the irregular peaks and valleys of insulin absorption into the bloodstream from the bolus subcutaneous injection sites.
Glucose Metabolism

When we added insulin to the nutrient solution, it was much easier to control blood sugar levels, and it was safer for the patients.

However, many of our medical colleagues insisted that IV insulin was dangerous; that insulin would somehow be altered by adding it to TPN; that the insulin would adhere to the glass bottles and plastic tubing; et cetera.

Today, IV insulin administered by pumps in the ICU is standard for maintaining normoglycemia.
Biotin deficiency developed in first set of TPN-fed puppies

Biotin was not present in any human water-soluble Vitamin B complex formulation available at that time

Biotin was added separately to the TPN formula and reversed the deficiency
Biotin deficiency in puppies was manifested by premature graying of coat; same for adult human hair, plus advancing subungual white discoloration from nail bed as nails grew.

Biotin subsequently was added to human vitamin formulations for adults and infants after biotin deficiency was confirmed in one early adult patient after nine months of TPN.
Out-takes – II A

Complete IV Vitamin Mixture - Not existent

Only Vitamin B Complex, Vitamin C, Vitamin K

No IV Biotin nor Fat Soluble Vitamins A, D, E

Oral liquid complete pediatric vitamin mixture was micropore-filtered and given to puppies intravenously without untoward effects and subsequently given to the first TPN infant
Complete IV Vitamin Mixture - Not existent

Vitamin manufacturers reluctant to provide complete IV mixtures – “no market”

US Vitamin, owned by Revlon®, responded to my appeal to Lance Revson and developed the prototype Multiple Vitamin Infusion which contained all of the fat and water soluble vitamins in intravenous form
Antimicrobial Ointment - Catheter Exit Site

Triple antibiotic ointment initially was applied at the catheter exit site of puppies daily to reduce the risk of infection via the tract.

Fungal infections, deemed opportunistic, complicated the early puppy studies.
Antifungal ointment was mixed with antibiotic ointment and ameliorated the problem, but was cumbersome for patient care.

Iodine was known to be uniformly cidal for all unicellular organisms, but irritated the skin.

Organically bound iodine ointment developed as povidone-iodine solved the problems.
Out-takes – IV A

Mineral and Trace Element Lessons - Copper

During development of long-term TPN in rats, all animals died within seven days with both hematuria and hemoglobinuria.

Serendipitous observation led to discovery of copper toxicity caused by leaching of copper by amino acids from the inner surfaces of the brass IV swivel apparatus and the brass chrome-plated needles.
Mineral and Trace Element Lessons - Copper

Copper, which is essential for hematopoiesis and leukopoiesis, causes hemolysis at excessive blood levels.

The blood copper levels in the rats were astronomically high.

Swivel-infusion apparatus was redesigned with plastic components, and solved problem.
Central Venous Catheter Lessons

Every commercially available medical grade catheter caused phlebitis, thrombosis and cellulitis when inserted into the puppies.

Every conceivable tubular material was tested for inertness and its potential to be used safely and effectively for central venous infusion.
Central Venous Catheter Lessons

Polyvinyl electrical insulation tubing obtained at the Pep Boys Store “Manny, Moe and Jack” had the characteristics sought for success.

It was inert, pliable, durable, did not cause inflammation and could be autoclaved.
Millipore® 0.22 micron membrane filters were used successfully to sterilize the TPN base solutions and some of the additives.

To minimize infection, we hypothesized that an in-line filter in the infusion tubing might be helpful. We designed our own for the puppy swivel-infusion apparatus, and it was helpful.
Out-takes – VI B

Micropore Membrane Cold Sterilization

The Millipore Company was asked to produce an IV “final filter” for human nutrient infusion.

When their “officials” turned us down, I asked Dr. Rhoads to intervene with his fellow Haverford Alumnus, Mr. John H. Bush, who was Millipore Founding Chairman & CEO and a Trustee of the Board of Haverford College.

Five days later, the “officials” met with me again and three weeks later, our “final filters” arrived.
# Adult Total Parenteral Nutrition Solution

## Base Solution
- **40-50% dextrose in water**
- **8.5 - 15% crystalline amino acids**

## Additives to Each Liter
- Sodium chloride, acetate or lactate
- Potassium chloride
- Potassium acid phosphate (10-20 mM phosphorus)
- Magnesium sulfate

## Additives to One Unit Daily
- Calcium gluconate 10%
- Zinc sulfate
- Copper sulfate
- Iron-dextran
- Chromium chloride
- Manganese Chloride
- Selenium (sodium selenate)
- Multivitamin Infusion
- Calcium gluconate 10%
- Zinc sulfate
- Copper sulfate
- Iron-dextran
- Chromium chloride
- Manganese Chloride
- Selenium (sodium selenate)
- Multivitamin Infusion

## Additive to One Unit Twice Weekly
- Vitamin K

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
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</thead>
<tbody>
<tr>
<td>Carbohydrate calories</td>
<td>850 kcal/liter</td>
</tr>
<tr>
<td>Protein calories</td>
<td>150 kcal/liter</td>
</tr>
<tr>
<td>Fat calories</td>
<td>1000-2000 kcal/liter</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>6.5 - 12 gm/liter</td>
</tr>
<tr>
<td>Amino acids</td>
<td>40 - 75 gm/liter</td>
</tr>
</tbody>
</table>

- Intravenous Fat Emulsion 10% or 20%
  - 500 ml 2-7 times weekly
  - 50-100 gm
NUTRITIONAL IV
1 CALORIE PER CC OF SOLUTION
6 GM. OF NITROGEN PER LITER

HOSPITAL of the UNIVERSITY of PENNSYLVANIA
PHARMACY-SUPPLY SERVICE
300 SPRUCE STREET, PHILADELPHIA, PENNSYLVANIA
Body weight
C.O. 77 y.o. pyloric stenosis

Nitrogen Balance

Daily mean
Nitrogen given 16.9 grams
Calories given 2,258
Nitrogen balance +2.25 grams

Intravenous Calories

Days of Treatment
operation

Oral intake
No IV pumps were available for clinical hospital use. All IV solutions were administered by gravity drip with variations in infusion rates.

Nurses often increased speed of infusion near the end of the shift if intake was behind the ordered volume. Not a safe practice with TPN because of the high dextrose concentration. IV pumps introduced clinically to enhance patient safety and nursing efficiency.
Out-takes – VII B

Miscellaneous Adventures
Early Adult TPN Patients

Pumps now standard. Infiltration or occlusion alarms, end-of-infusion alarm, air-in-line alarm, DC battery back-up for AC power, large volume for adult and small volume for infants, power surge and voltage drop protection were all developed in our laboratories for safety and efficacy – later produced and exploited by commercial manufacturers.
### Pediatric Total Parenteral Nutrition Solution

**Base Solution**
- 40% dextrose in water: 500 ml
- 8.5 crystalline amino acids: 500 ml

**Additives**
- Sodium chloride: 25-30 mEq
- Potassium acid phosphate: 30-40 mEq
- Magnesium sulfate: 12-15 mEq
- Calcium gluconate: 25-35 mEq
- Zinc sulfate: 2 mg
- Copper sulfate: 0.5 mg
- Iron-dextran: 0.05 ml
- Chromium chloride: 10 mcg
- Manganese chloride: 0.25 mg
- Selenium (sodium selenate): 30 mcg
- Multivitamin infusion: 10 ml
- A: 0.7 mg
- D: 10 mcg
- E: 7 mg
- K: 200 mcg

**Infusion rate** = 115 ml/kg/day
- 115 kcal/kg/day
- 3 gm protein/kg/day

**Intravenous Fat Emulsion 10%**
- 50-75 ml/kg 3-7 times weekly

<table>
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<tr>
<th>Additive</th>
<th>Amount</th>
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</thead>
<tbody>
<tr>
<td>Ascorbic acid</td>
<td>80 mg</td>
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<tr>
<td>Folic acid</td>
<td>140 mcg</td>
</tr>
<tr>
<td>Niacinamide</td>
<td>17 mg</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>1.4 mg</td>
</tr>
<tr>
<td>Thiamine</td>
<td>1.2 mg</td>
</tr>
<tr>
<td>B6 (pyridoxine)</td>
<td>1.0 mg</td>
</tr>
<tr>
<td>B12 (cyanocobalamin)</td>
<td>1 mcg</td>
</tr>
<tr>
<td>Dexpanthenol</td>
<td>7 mg</td>
</tr>
<tr>
<td>Biotin</td>
<td>20 mcg</td>
</tr>
</tbody>
</table>
Out-takes – VIII A

Miscellaneous Adventures with the 1st TPN Infant

Essential fatty acid deficiency with no available IV fat emulsion - rubbing linoleic acid on the skin initially, and later preparing a “physiologic fat emulsion” with the help of the patient’s parents and the blood bank prevented the deficiency.

Infusion volume failure every night despite pump. Voltage drop detected serendipitously; resistor incorporated into pump to maintain pump rate despite voltage drop up to 15% - now standard.
Out-takes – VIII B

Miscellaneous Adventures with the 1st TPN Infant

Vitamin D thought not to be essential by vein if calcium is provided intravenously. Vitamin D allegedly only required for absorption of calcium across bowel mucosa. After a few months of TPN with suboptimal vitamin D, patient developed florid rickets. Responded to IV vitamin D increase in TPN. Vitamin D physiology and function better understood as a result of this experience.
Essential Fatty Acids

NORMAL:
Linoleic to Arachidonic acid
Triene:Tetraene ratio <0.4

BORDERLINE:
Triene:Tetraene ratio >0.4 <0.7

DEFICIENCY:
Oleic to 5,8,11- Eicosatrienoic acid
Triene:Tetraene ratio >0.7
May 19, 2004

Dear Dr. Dudrick:

How have you been? I hope both you and Mrs. Dudrick are doing fine.

Attached is a photo of our new TPN product that is close to the idea you proposed in JAMA in 1971.

We have not launched the product yet, but the launch is just around the corner.

It has taken more than 30 years for the idea comes true since your proposal.

I hope you like it. Talk to you soon.

Best regards,

Akira

Akira Momii, Ph.D.
Otsuka Pharmaceutical Factory, Inc.
Naruto, Tokushima 772-8601
Japan
Telephone +81-88-684-2203
FAX +81-88-686-8123
E-mail: momiiak@otsukakj.co.jp
Upper compartment for amino acids, electrolytes and vitamins (nicotinamide and folic acid)

Third compartment for fat-soluble vitamins and riboflavin

Lower chamber for dextrose, electrolytes and vitamins (thiamin, pyridoxine, cyanocobalamin and panthenol)

Rubber Stopper for IV Set
Definition of Malnutrition

1. Body weight loss >10%

2. Serum albumin <3.5 gm/dL and/or total serum protein <5.5 gm/dL

3. Peripheral lymphocytes <20% or total lymphocytes <1200/mm³

4. Delayed cutaneous hypersensitivity

Other evidence of compromised immunity
Basic Indications for Total Parenteral Nutrition

Patients who **Cannot Eat**
Patients who **Will Not Eat**
Patients who **Should Not Eat**
Patients who **Cannot Eat Enough**

Patients with Complex Metabolic Problems
Treating malnutrition is...

10% Science
10% Experience
10% Skill
20% Patience
50% Attitude
The three stages of a new idea:

First    It will never work.
Second   It will be too expensive.
Third    I knew it was a great idea all along.

Author Unknown
All truth passes through three stages:

First, it is ridiculed.

Second, it is violently opposed.

Third, it is accepted as self-evident.

Arthur Schopenhauer
“Any other bright-minded fellow can accomplish as much if he will stick like hell and remember (sic) nothing that’s any good works by itself. You got (sic) to make the damn thing work.”

*Thomas Alva Edison*
“All deaths are hateful to mortals, but the most pitiable is to starve to death.”

Homer
The Ultimate Nutritional Goal

To provide optimal nutrition to all patients, under all conditions, at all times

Stanley J. Dudrick, MD - 1977
Presidential Address, ASPEN