3 Types of malnutrition
1. **Marasmus**: lack somatic proteins
2. **Kwashiorkor**: lack visceral proteins
3. **Mixed Marasmus/Kwashiorkor**: a bit of both

3 Protein compartments
1. **Somatic**: muscle proteins
2. **Visceral**: produced by organs, e.g. albumin, transferrin
3. **Immunity**: a subset of visceral, e.g. antibodies, clotting factors

5 Steps to assess nutritional status
1. **Visual assessment**
   - Marasmus vs. Kwashiorkor
2. **Patient’s history**: present and past weight
3. **Physical exam**
4. **Protein compartments**
   - Weight/Height measurements
     - Edema/obesity/pathologies distort results
   - Anthropometric measurements: muscle vs. fat amounts
     - Triceps skin fold
     - Mid-arm circumference
     - Creatinine/height index (CHI)
       - Urinary creatinine is decreased in malnutrition and renal disease
       - Better in terms of height than weight
       - CHI = actual/normal mg excreted (where 90%-100% is normal)
   - Albumin: 50-60% of total serum proteins
     - Normal conc. = 3.4-5g/100ml of blood
     - Catabolic stress = ↓albumin = ↑insulin = further ↓aa
     - Interplay between 2 types of malnutrition: somatic aa used as building blocks for visceral aa
     - Easier to detect drop in serum conc. of transferrin than albumin
5. **Immune competence** *(anergy = inability of a patient to respond to an infection)*
   - Lymphocyte counts
   - Antigen-skin tests: Multitest CMI system (think Cooties game)
     - Ability of lymphocytes and immunoglobulins to respond to antigens
     - >1 grade of swelling/redness indicates some immune response
     - 0 grade = lack of response = indicative of anergy and malnutrition

4 Roles of pharmacists in nutrition
1. Help diagnose type/degree of malnutrition
2. Recommend treatment/method
3. Evaluate treatment, suggest changes
4. Management

If the GI tract works, use it!
- Into mouth (**nasogastric tube**)
- Into stomach (**gastrostomy**)
- Into small intestine (**jejunostomy**)

If not, use parental/IV administration
- Protein sparing
  - Mild patients
Peripheral arm vein
- Isotonic: 2.75-3.5% solution (+vitamins, minerals, electrolytes)
- Not a TPN modality: no fat or dextrose given

- Peripheral TPN
  - Mild to moderate patients for limited time (<10 days)
  - Patients with septicemia
  - No fluid restrictions

- Central TPN
  - Moderate to severe patients
  - Burn patients (no peripheral veins available)
  - Longer duration (2-3 weeks)
  - Subclavian or internal jugular vein

### Numbers to know

**Nitrogen balance**

\[
\text{Nitrogen balance} = \left( \text{Protein intake} \times 16\% \right) - \left( N_{\text{excreted}} + C \right) \rightarrow \text{should have positive N balance of 4-6g}
\]

**Caloric conversions**

- Dextrose: 3.4kcal/g
- Lipid emulsion: 9kcal/g

**Nutritional requirements**

- **Protein** (supplied in 3.5-15% conc.)
  - Maintenance 0.8-1.6g aa/kg/day
  - Mild trauma 1.6g-2.0g aa/kg/day
  - Severe trauma 2.0-3.0g aa/kg/day

- **Nitrogen**
  - 16% of protein -or- protein/6.25 (in grams)

- **Calories**
  - Mildly stressed 125-150kcal/gN2
  - Highly stressed 80-100kcal/gN2 (note: less calories needed for severe pts because less mobilized)
  - Provided as dextrose and fat (50/50, 40/60)
    - **Dextrose** supplied as 5-70% concentration (e.g. D5W=50g/L, D50W=500g/L)
    - **Lipid emulsion** supplied as 10-20% concentration
      - 200 extra kcal from glycerin and emulsifiers
      - Now favored over dextrose because
        - ↓Hyperglycemia risk
        - Dextrose → fat (accumulates in liver)
        - ↓Osmolarity of aa/dextrose solutions to facilitate peripheral admin
        - ↓Severity and frequency of phlebitis
        - ↓Chance of essential FA deficiency

- **Molecular weights**
  - Dextrose: 180g/mol
  - NS: 58.5g/mol

### CALCULATIONS

**Solve for nutrition**

1. Solve for volume (ml) of **amino acids** needed [use: degree of trauma, weight of pt, concentration]
2. Solve for amount (g) of **nitrogen** needed [use: grams of amino acid from part 1]
3. Solve for kcal needed [use: degree of trauma, grams of nitrogen from part 2]
   a. Determine ratio of dextrose/lipid
4. Solve for volume (ml) of **dextrose** needed [use: ratio, concentration, caloric conversion]
5. Solve for volume (ml) of **lipid emulsion** needed [use: ratio, concentration, caloric conversion]

### Solve for tonicity
- **Amino acids:** will be given mOsm/L, use known volume to solve
- **Dextrose:** solve knowing D5W=280mOsm/L, multiply by known volume
- **Lipid emulsion:** 2.25g glycerin/100ml...

### Incompatibility charts

<table>
<thead>
<tr>
<th>ANIONS</th>
<th>Monovalent Cl</th>
<th>Divalent CO$_3$$^{2-}$</th>
<th>Trivalent PO$_4$$^{3-}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CATIONS</td>
<td>Monovalent Na$^+$, K$^+$</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td></td>
<td>Divalent Ca$^{2+}$, Mg$^{2+}$</td>
<td>Soluble</td>
<td>Insoluble</td>
</tr>
<tr>
<td></td>
<td>Trivalent</td>
<td>Soluble</td>
<td>Insoluble</td>
</tr>
</tbody>
</table>

Mg$^{2+}$ behaves differently → important when considering lactate ringers and ringer solutions

### Ion pair incompatibilities

Mixing of a weak acid drug with a weak basic drug
- Barbiturates: weak acids
- Heparin: weak bases

Na+Phenobarb- + Morphine+SO4- → big insoluble salt
Na+Phenobarb- + Tetracycline+Cl- → big insoluble salt

90% of reactions are some form of ion pair incompatibility

### LVP

<table>
<thead>
<tr>
<th>SVP</th>
<th>LVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine HCl (basic)</td>
<td>D5W + 5%NaHCO$_3$ (basic)</td>
</tr>
<tr>
<td>NaPhenytoin (acidic)</td>
<td>I (free base)</td>
</tr>
<tr>
<td>KPenG (acidic)</td>
<td>I (base hydrolysis)</td>
</tr>
</tbody>
</table>

SVP: have added sodium hydroxide (basic) but drug itself may be acidic

Penicillins: beta lactams or lactones, cyclic esters or amides

Beta lactam rings are sensitive to both acids and bases which cause hydrolysis

A lot of lactates are soluble: low enough molecular weight

NaPhenytoin is only soluble in NS and needs to be given w/in a ½ hr of making it up

NaPhenytoin is a weak acid but likes base, it is a very insoluble drug (in order to keep it ionized, need a lot of cosolvents and need to raise the pH really high)
Benzyal alcohol: preservative
Sodium biphosphbate anhydrous: buffer (phosphates are trivalent)
Ascorbic acid: antioxidant
Ampicillin can’t be given in dextrose: it will hydrolyze the ampicillin
Hydrocortisone is an ester: ester hydrolysis
Tetracycline: don’t take with milk or cheese because of it reacts with calcium
Barbituates: weak acid
Morphine sulfate: weak base

<table>
<thead>
<tr>
<th>LVP</th>
<th>RL +20000 NaHep (basic)</th>
<th>D20W + 4.25% aas (acid)</th>
<th>NS+50mg Hydrocortisone NaSucc ((acid))</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVP</td>
<td>Lidocaine HCl (base)</td>
<td>I (ion pair, free base)</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>NaKochalate (acid)</td>
<td>C</td>
<td>I (ion pair)</td>
</tr>
<tr>
<td></td>
<td>Haloperidol lactate ester</td>
<td>I (base hydrolysis of ester)</td>
<td>I (acid hydrolysis of ester)</td>
</tr>
</tbody>
</table>

When have big amounts of heparin → probably basic
If small amounts → not going to make it basic
In general, not good to put drugs in TPN

**IMMUNE STIMULANTS**

**Vaccines**
- Attenuated(live) or inactivated (killed)
- Whole or fractions
- Take virus → sonicate to death → differential centrifugation to isolate portion important for immune response

**Toxoid**
- Modified exotoxin rendered non-toxic
- Easy for companies to make
- Require refrigeration and/or reconstitution (freeze dried powder)

**Passive immunity**
- **Human immune sera**
  - Immunoglobulin: e.g. measles, hepatitis A
  - Hyper immune serum: e.g. hepatitis B, rabies
- **Animal immune sera**
  - Antitoxin: e.g. botulism, diphtheria, tetanus
  - Antiviral serum: e.g. rabies
  - Antivenin: e.g. rattlesnake, black widow spider, scorpion
- **Viral vaccines** e.g. measles, mumps, influenza
  - Isolated by: disintegration, column filtration, differential centrifugation
- **Viral vaccines in human tissue culture**
Allergen extracts
- **Types:** food, animals, grasses, insects, molds, trees, weeds, inhalants
- **Extraction process:** percolation/decoction
- **Diagnosis:** scratch/prick test using very dilute solutions of allergen extracts

Immunotherapy
- Treatment of disease by inducing, enhancing, or suppressing an immune response
- **Goal:** to increase IgG
- Small subcut doses → weak dose qwk → increasing strength or # of doses over a few months
- IgG competes with IgE: IgG>>IgE with increased dosing with allergen
- **Problems:** difficult to standardize and establish potency
- **Dosage forms:** solutions, suspensions, lyophilized powders requiring reconstitution
- **Additives**
  - Human serum albumin: protein preservative
  - Normal saline: tonicity
  - Phenol: antimicrobial
  - Glycerin: protein preservative
  - Aluminum precipitated allergen: slows absorption/action of allergen
- **Use & Handling**
  - Aseptic and sterile procedures
  - Proper documentation
  - Generally require refrigeration (never frozen)
  - Sterility testing required (particulate/pyrogen testing not)

Hymenoptera venoms
- Honeybee, wasp, hornets
- Purified, lyophilized
- Usually only venom collected, not whole insect (exception: fire ants)

PROTEIN PHARMACEUTICALS

Biotechnological products techniques
- Recombinant DNA
- Monoclonal antibodies
- PCR
- Gene therapy
- Nucleotide blockade/antisense (mRNA)

Chemical instability
**Change in structure due to breaking of bonds**
- Proteolytic cleavage
  - Proteases
  - Hydrolysis: solution is to lyophilize the product
- Deamidation: cleave NH3 group
- Oxidation: Met, Cys (also His, Trp, Tyr)

Physical instability
**Change in structure not due to bond breaking/forming**
- Aggregation: precipitation, normal Brownian motion
- Conformational stability: denaturing/unfolding of protein
Additives in biotech formulations

- **Serum albumin**
  - Flood the system so active proteins won’t be bound, i.e. inhibit adsorption
  - Adsorption binding sites may be hydrophilic or lipophilic, proteins have both, which makes it a problem
  - Tubing: use polyester or nylon, not PVC, which has more binding sites
  - Resembles nascent complexing proteins: w/o nascent proteins, active proteins are more active
  - Cryoprotectant: protects while freeze drying, almost as good as mannitol
  - Examples when albumin is used: interferon, IL-2, TPA

- **Amino acids (Gly)**
  - Chelate trace elements to prevent aggregation: trace elements allow aggregation, e.g. Zn in insulin
  - Take up adsorption sites to reduce surface adsorption
  - Inhibit aggregate formation
  - Inhibit thermal induced inactivation: neutral amino acids like glycine protect the formulation if heated

- **Fatty acids & phospholipids**
  - 7-8 carbon length is optimal
  - Liposomal systems help stabilize proteins and peptides through nonpolar interactions
  - Protection of non-polar portion of protein interacting with non-polar lipid (emulsifiers for lipids are phospholipids)

- **Surfactants**
  - Charged surfactants (cationic/anionic) cause denaturation
  - Non-ionic surfactants stabilize by reducing interfacial tension
  - Reduce tendency for protein to unfold, help retain structure
  - Examples: Tween 80, Brij, poloxamer)

- **Metals**
  - Ca\(^{2+}\) and Cu\(^{3+}\) stabilize proteins
  - Bridge between disulfide bonds: helps stabilize bonds and tertiary structure

- **Polyols**
  - Polyhydroxyl groups: carbohydrates, sorbitol, mannitol, glycerol
  - Used in lyophilized dosage forms to prevent aggregation by adding bulk
  - Aids reconstitution: polyols are very water soluble, help the water get to the amino acid very quickly
  - Protects against oxidation
  - Strengthens intra hydrophobic bonds by reducing the interaction between water and protein
  - Humectant: helps hydrate the protein for protection and stabilization

- **Reducing agents**
  - Reduce disulfide bond formation, which tends to lower protein activity
  - Agents: glutathione, thioethanolamine, thiodiglycol, thioacetic acid, N-acetylcysteine

- **Chelating agents**
  - Problem: Cu, Fe, Ca, Mn act as catalysts in oxidation reactions by using up the oxygen
  - Chelating these metals help stabilize the formulation by using up the active sites on the metals
  - Agents: EDTA, diNa, CadiNa, tetraNa

- **Miscellaneous**
  - Hydrolyzed gelatin: available amino acids
  - Ammonium sulfate: adjusts pH