

# IMMUNONUTRITION FOR HEALTH & DISEASE

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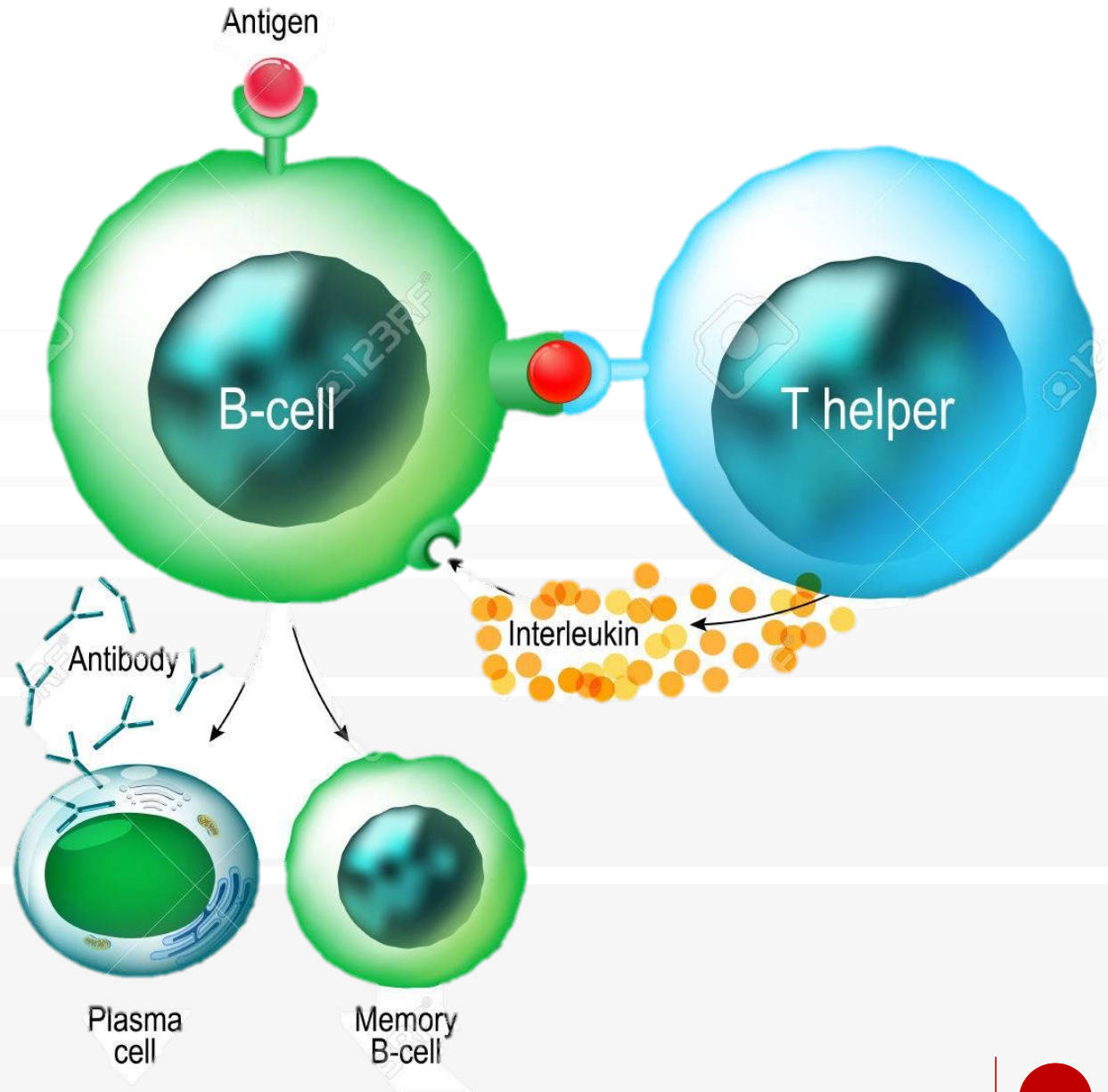
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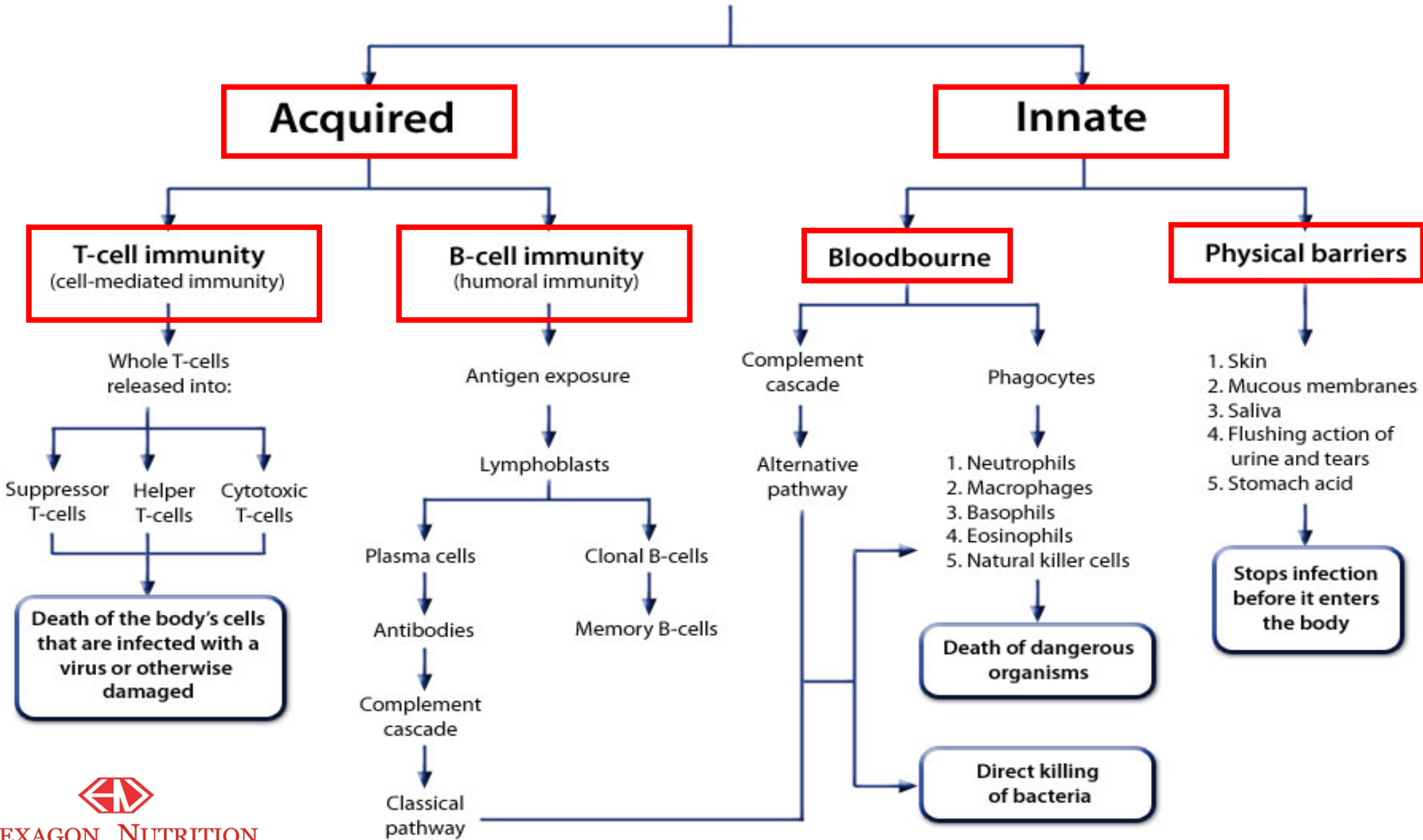
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# Overview of Immune System





# Immune system



## Cell Signalling Molecules

- Interleukin
- Tumour Necrosis Factor
- Interferons



**Immunonutrients are nutrients, which have an effect on the immune system.**



# Is Immunonutrition Overrated?

- ↓ incidence abdominal sepsis (OR 0.26)
- ↓ incidence nosocomial pneumonia (OR 0.54) and bacteremia (OR 0.45)
- ↓ time on mechanical ventilation, ICU stay, hospital stay

No reduction in mortality rates as a whole  
BUT the severity of illness influenced by efficacy of immunonutrition.

Severely or mildly ill patients least likely to benefit.



# Role of Immunonutrients

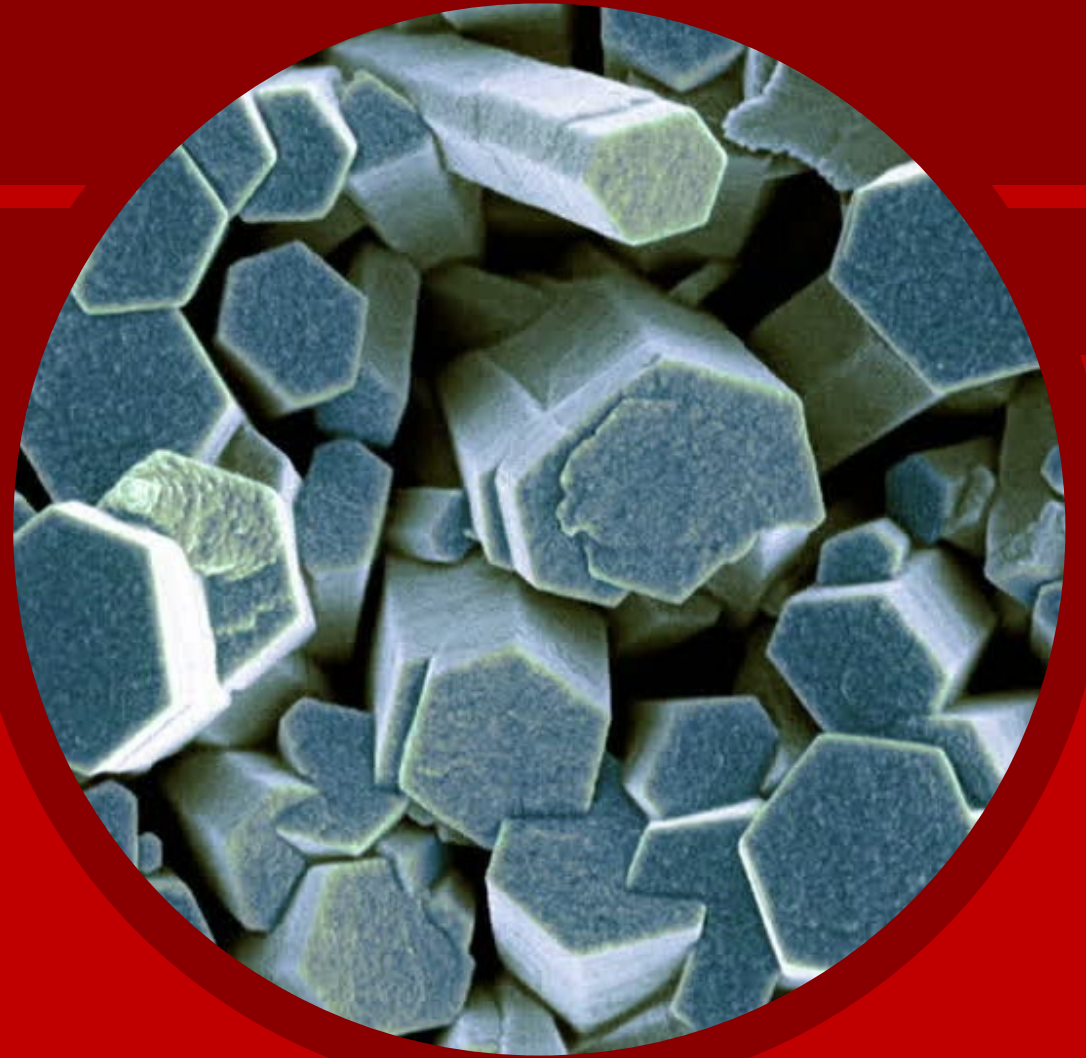
- Immunonutrients are nutrients, which have an effect on the immune system.
- Specific nutrients and dietary components, including
  - arginine,
  - glutamine,
  - selenium,
  - omega-3 (n-3) fatty acids, (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]),
  - the omega-6 gamma-linolenic acid [GLA], nucleotides and/or
  - antioxidants

have been implicated for their potential to modulate the metabolic response to surgery or stress by enhancing immune function





- **Zinc** affects multiple aspects of the **immune** system.  
**Zinc** is crucial for normal development and function of cells mediating innate **immunity**, neutrophils, and NK cells. Macrophages also are affected by **zinc** deficiency.  
▶ Phagocytosis, intracellular killing, and cytokine production all are affected by **zinc** deficiency.



**Selenium (Se)** is a potent nutritional antioxidant that carries out biological effects through its incorporation into selenoproteins



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▶ Glutamine is a major metabolic fuel for the small intestine & helps maintain its digestive function and protects its mucosal integrity.



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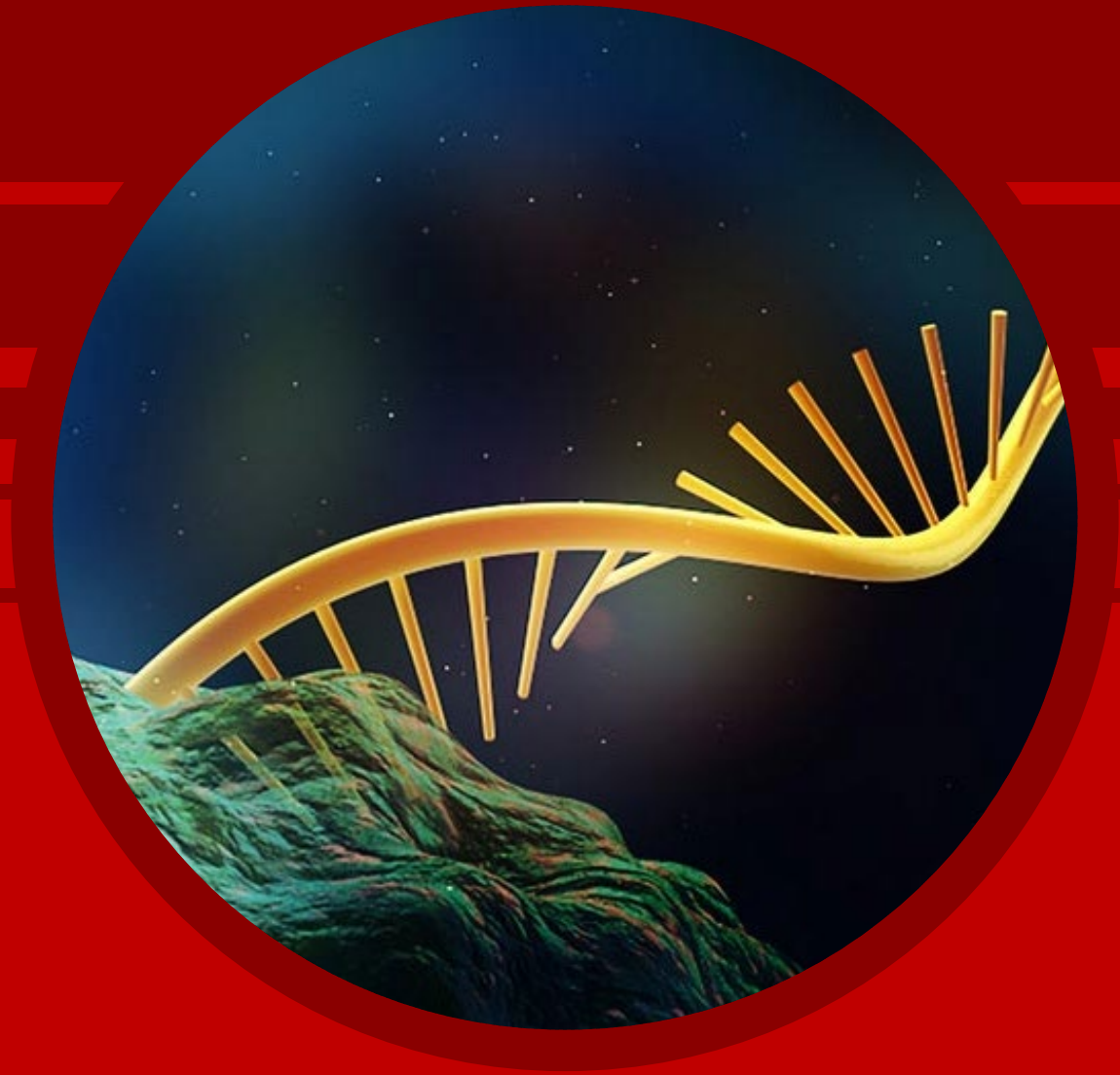
Ref: Guoyao Wu, 2012

# Glutamine & Oxidative Stress in Chronic Conditions

- Concentrations of glutathione are suboptimal in clinical conditions including HIV infection, hepatitis C infection, cirrhosis, type II diabetes, ulcerative colitis, and myocardial infarction.
- **Glutamine is easily converted to glutamic acid and produces an antioxidant glutathione.**
- Supplementation of glutamine may have beneficial effects for reducing symptoms of inflammatory disorders and may protect against the damaging effect of oxidative stress



**Dietary nucleotide  
supplementation has been shown  
to have important effects on the  
growth and development of cells**  
▶ **which have a rapid turnover such as  
those in the immune system and  
the gastrointestinal tract.**



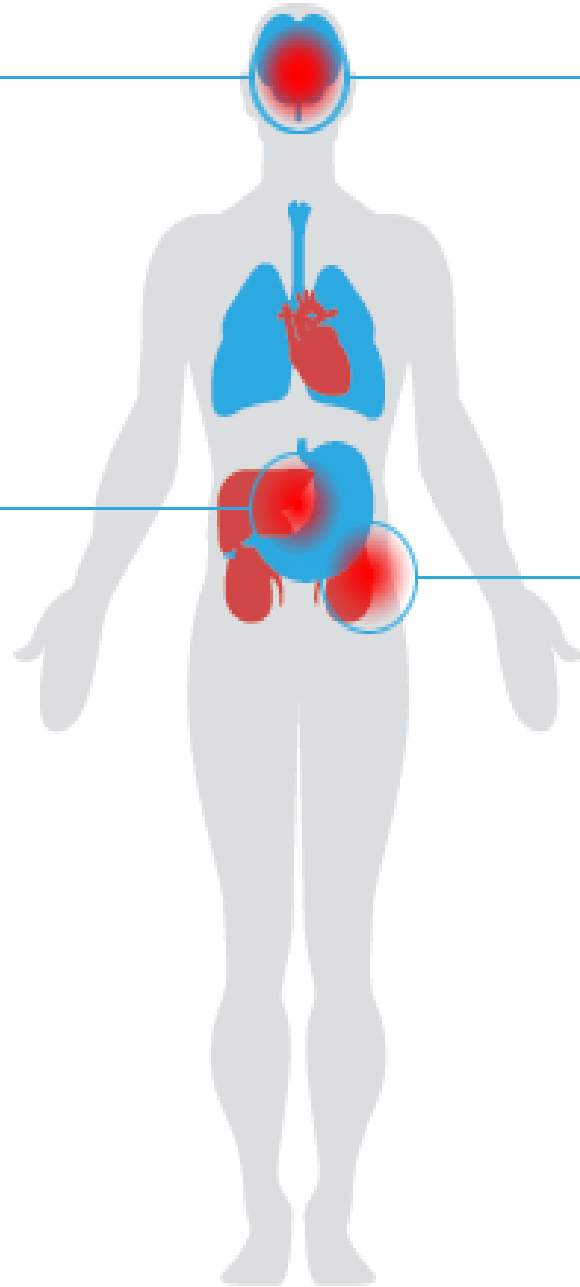


## Memory support

RNA may help maintain memory recall and improve absent-mindedness. A combination of RNA and DNA is typically used for this purpose.

## Digestive health support

RNA may support the health of the intestines, where rapid cell proliferation is important. This property is especially helpful for digestive conditions.



## Aging support

RNA supplements may also help defy the visible signs of aging, which most often affects the skin.

## Injury management

RNA may be able to support the body's natural ability to heal itself after an injury or surgery. This use of RNA is often combined with eicosapentaenoic acid and l-arginine.

Image Courtesy: Xtend Life, 2018



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Ref: Natural Medicines Comprehensive Database, Prescriber's Letter, and Pharmacist's Letter, 2018



## Dietary Ribonucleic acid is semi-essential

- In sub-well, diseased, or under conditions of stress or poor diet dietary nucleotides may be "**semi-essential**", optimising the function of the gastrointestinal and immune systems.
- Enhance the intestinal **absorption of iron**
- Exogenous supplies of nucleotides may optimise tissue function particularly during **recovery from mucosal injuries** when the endogenous supply may limit the synthesis of nucleic acids.

Ref: Dancey et al., *Nutrition Journal* 5 (2006): 16. *PMC*.

## MECHANISM OF ACTION -DIETARY Ribonucleic Acids

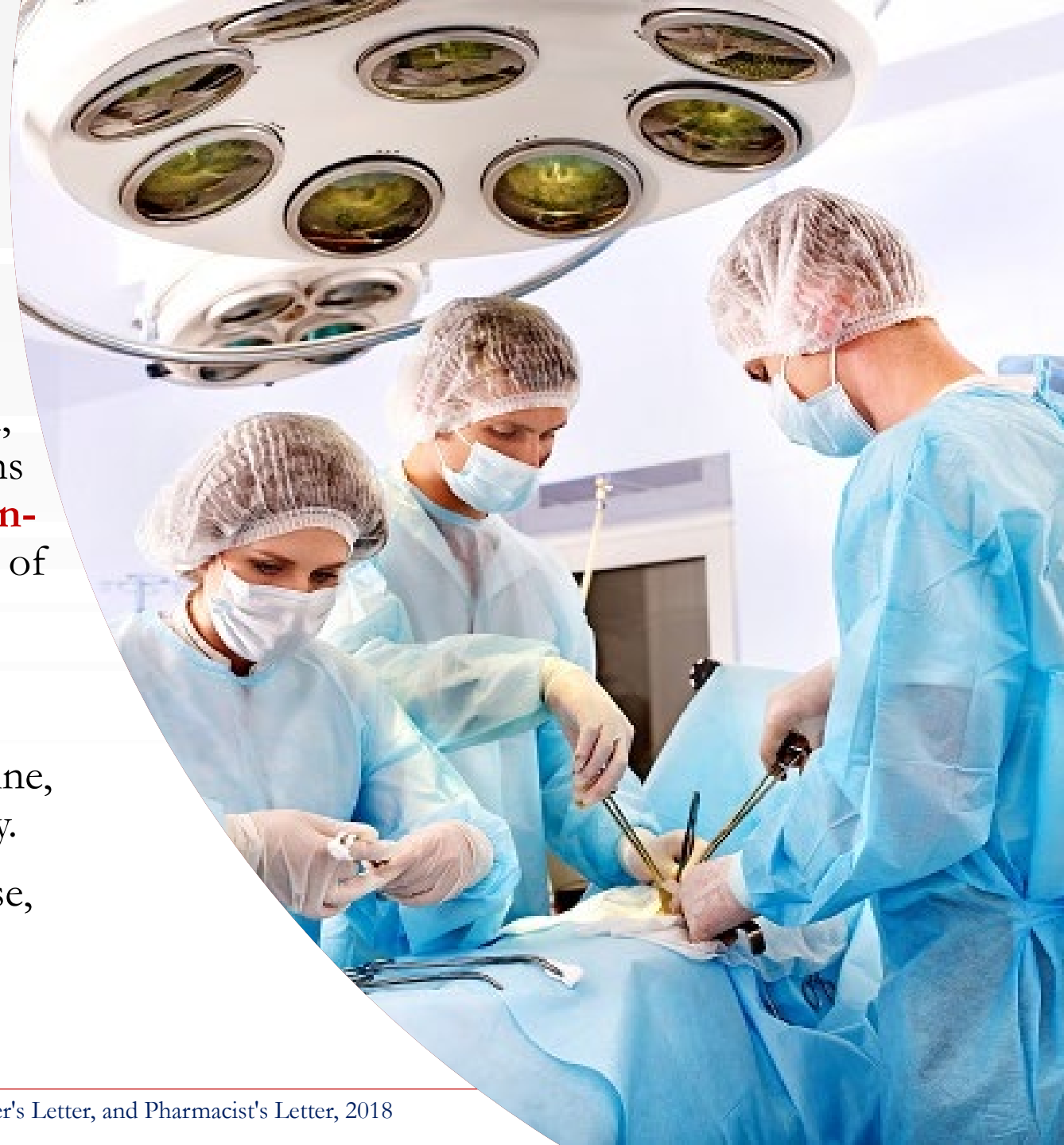
- Preformed RNA- **degraded to free bases** in the intestine before absorption
- Incorporated in the **hepatic pyrimidine nucleotide pool**- thereby affecting the hepatic RNA content
- Hepatic RNA content- **affects the recovery time** from liver injury
- In protein deprived animals, dietary RNA appears to **benefit the intestinal tract.**
- **Restore immune function** by restoring the **nitrogen balance**
- In the absence of nucleotides, **normal T-lymphocyte maturation** is blocked



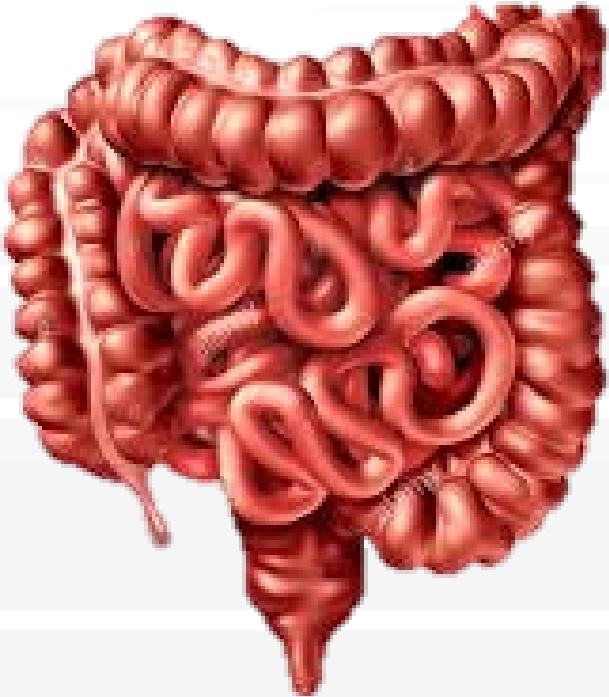


# Evidence in various disease conditions

- Supplementing an enteral diet with arginine, RNA, and omega-3 fatty acids can **reduce** concentrations of **tumor necrosis factor alpha, and interleukin-6** and accelerate the recovery in the concentration of **interleukin-1 beta and interleukin-2 alpha receptor**
- Supplementing the diet of patients undergoing **major surgery** with enteral or oral RNA, L-arginine, and eicosapentaenoic acid might improve recovery.
- In **perioperative period** -boosts immune response, reduce perioperative infections, improve wound healing, and shorten recovery time



## Evidence in various disease conditions



- In **infants**, the **incidence and duration of diarrhoea** is lower when nucleotide supplementation is given
- A **Crohn's disease** model in rats shows RNA has a highly significant effect upon the healing intestinal ulcerations
- Animal studies show that **villi height and crypt depth** in the intestine is increased as a result of dietary nucleotides.
- Nucleotide supplementation is associated **with increased jejunal adaptive growth** after massive small bowel resection in rats.





## Evidence in various conditions

- Dietary nucleotides have been found to help **athletes** by reducing the release of stress related hormones and chemicals in the body, and by maintaining a higher level of antibodies, which enables the immune system to work more effectively.
- In people with a **chronic illness such as IBS** whose primary symptoms relate to the gastrointestinal tract, nucleotide supplementation may improve symptoms via improved gut function or by an enhancement of the immune system.







## “Recommended Dosage

A typical enteral dose of RNA is 30 mg/kg/day along with arginine and omega-3 fatty acids



Arginine is a “conditionally essential amino acid,” which should be supplemented at times of physical stress such as after surgery or trauma.



# Arginine and Immune Cells

- Arginine is the sole amino acid substrate for the **production of NO** by all isoforms of NOS.
- **T lymphocytes** depend on arginine for multiple key biological processes, including **proliferation, the expression of the TCR complex and the  $\zeta$ -chain peptide**, and the development of memory
- arginine could have some beneficial effects in **restoring T lymphocyte counts** under conditions of stress



# Arginine is essential in CERTAIN TYPES of critical illness.

- Arginine produces growth hormone, insulin like growth hormone and insulin which play a role in protein synthesis and wound healing
- Beneficial effects:
  - Secretagogue for **release of anabolic hormones (GH, IGF)**
  - Supporting **immune (especially T-cell) function**
  - Detoxification of ammonia
  - Improving **wound healing** via metabolism of polyamines to proline
- **BUT** excessive production linked to mortality in septic shock (3 studies)





Combination of Arginine, n-3 fatty acids and nucleotides are known to reduce infections in patients undergoing high-risk surgery such as colon or pancreatic resection.

Trauma patients also appear to benefit from these diets, but they must be started soon (ideally within 24 h) after injury.





“Recommended Dosage

Normal intake 3-5 g/day

Additional required in diseased  
states



$\omega$ -3 fatty acids is a potent antioxidant....



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# $\omega$ -3 fatty acids are anti-inflammatory

- Displaces AA from phospholipid core of the inflammatory cell (macrophage, neutrophil) membrane, **reducing synthesis of pro-inflammatory eicosanoids**
- Reduction in synthesis of pro-inflammatory eicosanoids by competing with AA for metabolism by the enzymes COX and lipoxygenase
- Reducing **leukocyte and platelet adhesive interaction with endothelium**
- Inhibition **inflammatory gene expression**
- **Reduction of oxidative injury** by stimulating glutathione production
- **Lung-protective effect** mediated by reducing release of gut-derived inflammatory mediators into mesenteric lymphatics and thoracic duct.



# $\omega$ -3 fatty acids

- **ARDS effects demonstrated in 3 major RCT**
  - ↓ duration ventilation
  - ↓ ICU and hospital stay
  - ↓ new organ failure
  - 2 studies also showed mortality reduction
- Meta-analysis of 3 trials (n=441)  
**Nutrition Therapy to save an additional life at 28 days**



# $\omega$ -3 fatty acids

- **In animal models, fish oil has shown beneficial effects**
- May increase bacterial killing
- **Improves survival**
- Maintains blood flow to intestine



# $\omega$ -3 fatty acids

- Enteral omega 3
  - **Prevention infections**
  - Reduced length of hospital stay
  - **Pre-op use in cardiac surgery patients -enhanced post-op recovery, reduction length of hospital stay**
  - **Good safety profile**



# ASPEN, ESPEN, CCPG

Immune nutrients for specific patient populations: summary of clinical practice recommendations

Nutrients	Elective surgery	General	Septic	Trauma	Burns	ALI/ARDS
<b>Arginine*</b>						
CCPG	No rec	No benefit	Harm	No benefit	No benefit	No benefit
ESPEN	Benefit (B)	No rec	Benefit (mild) (B) Harm (severe) (B)	Benefit (B)	No rec	No rec
SCCM/ASPEN	Benefit (A)	Poss benefit (A)	Poss benefit (mild/mod) (B) Poss harm (severe) (B)	Benefit (A)	Benefit (A)	No rec
<b>Glutamine†</b>						
CCPG	No rec	No rec	No rec	Poss benefit	Poss benefit	No rec
ESPEN	No rec	No rec	No rec	Benefit (A)	Benefit (A)	No rec
SCCM/ASPEN	No rec	Poss benefit (B)	No rec	Poss benefit (B)	Poss benefit (B)	No rec
<b>Ω-3 fatty acids‡</b>						
CCPG	No rec	No rec	No rec	No rec	No rec	Benefit
ESPEN	No rec	No rec	No rec	No rec	No rec	Benefit (B)
SCCM/ASPEN	No rec	No rec	No rec	No rec	No rec	Benefit (A)
<b>Antioxidants§</b>						
CCPG	No rec	Poss benefit	No rec	No rec	No rec	No rec
ESPEN	No rec	No rec	No rec	No rec	Benefit (A)	No rec
SCCM/ASPEN	No rec	Benefit (B)	Benefit (B)	Benefit (B)	Benefit (B)	Benefit (B)

\* Arginine administered in context of immune-enhancing diet that also contains fish oil, antioxidants, ± nucleotides.

† Enteral glutamine added to enteral nutrition regimen.

‡ Fish-oil-derived Ω-3 fatty acids (EPA and DHA) administered in context of immune-enhancing diet that also contains borage oil and antioxidants.

§ Antioxidant vitamins (including selenium) and trace elements.







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*Thank you for patient hearing!*

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