Nutritional and Lifestyle Medicine in Immunity:

Optimize Your Immune System and Protect Your Health

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2019 Quote – Frontiers of Immunology Journal

"It is well-established that nutritional deficiency or inadequacy can impair immune functions. Growing evidence suggests **that for certain nutrients increased intake above currently recommended levels may help optimize immune functions** including **improving defense function** and thus **resistance to infection, while maintaining tolerance."**

Reference: Wu, D, Lewis ED, Pae, M, Meydani SN. Nutritional modulation of immune function: Analysis of evidence, mechanisms, and clinical relevance. Frontiers of Immunology. **January 2019**, 9/article 3160 https://www.frontiersin.org/articles/10.3389/fimmu.2018.03160/full

Especially True it Seems for:
Vitamin C

Vitamin E

Selenium

Vitamin D

NIH Feb 3, 2021: Review of Supplements and Nutraceuticals in Covid-19 Prevention and Treatment https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7872359/

- "Optimal nutritional status can prime an individual's immune system to protect against the effects of acute respiratory viral infections by supporting normal maintenance of the immune system [1,5].

- **Nutritional strategies** can also play a role in the **treatment of hospitalized patients, as malnutrition is a risk to COVID-19 patients** [245].

- Overall, **supplementation of vitamin C, vitamin D, and zinc may be an effective method of ensuring their adequate intake to maintain optimal immune function**, which may also **convey beneficial effects against viral infections** due to **their immunomodulatory effects**. "

- “Some of the **main risk factors for severe COVID-19**, which also happen to be **linked to poor nutritional status, include obesity, hypertension, cardiovascular diseases, type II diabetes mellitus, and indeed age-related malnutrition** [1,3,242]. ”

- “Individuals should pay attention to their nutritional status, particularly their intake of vitamin D, **considering that vitamin D deficiency is widespread.** The prevailing evidence seems to indicate an **association between vitamin D deficiency with COVID-19 incidence and, potentially, severity** [133]. “

- “As a result, some international authorities have advised the general public, particularly those at high risk of infection, to consider vitamin D supplementation.

- However, further well-controlled clinical trials are required to confirm these observations.”

Reference: Lordan R et al. Dietary Supplements and Nutraceuticals Under Investigation for Covid-19 Prevention and Treatment. National Institutes of Health Preprint Pilot. Feb 3, 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7872359/

Function & Modulators of Immune System

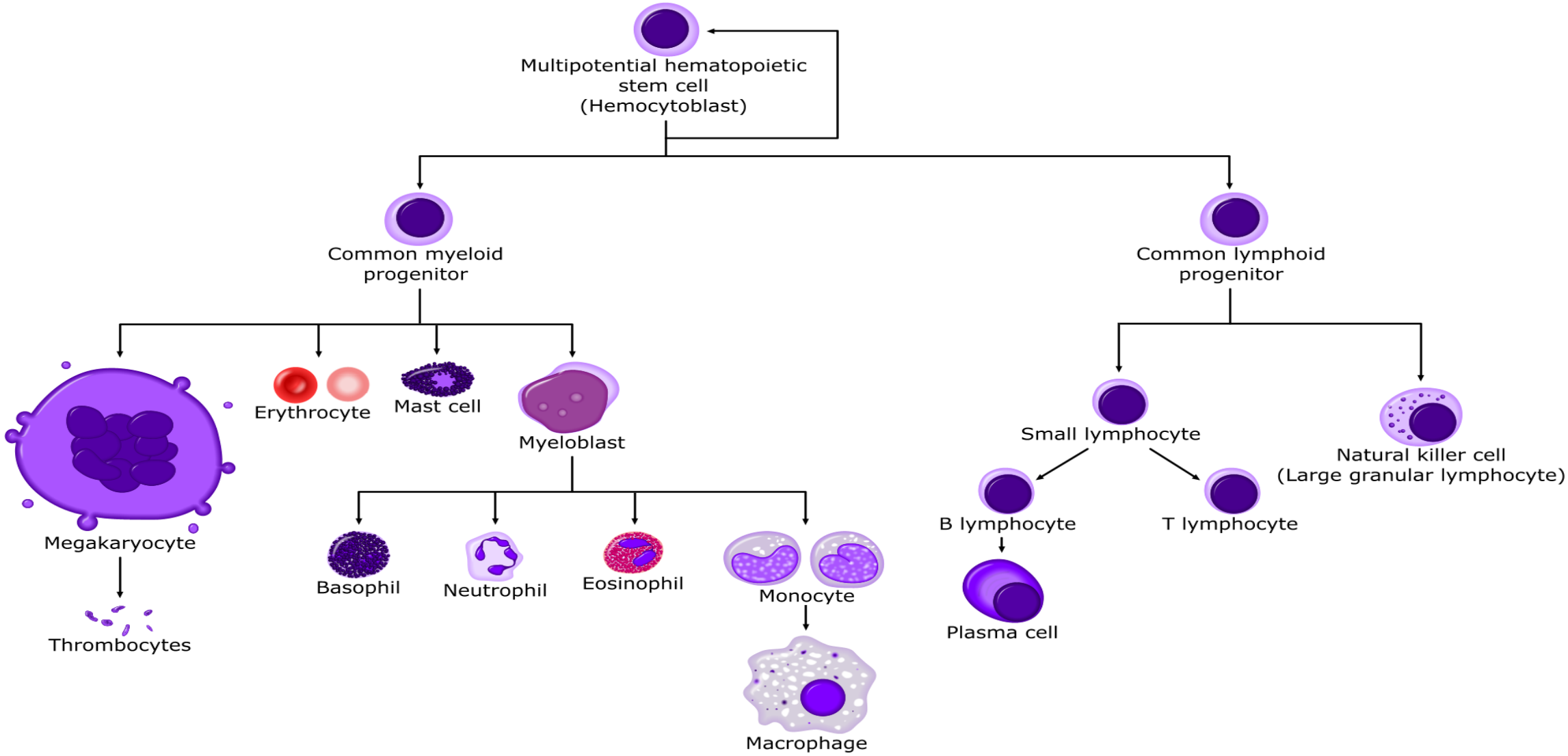
"The main functions of body's immune system are to **protect the host against infection** from pathological microorganisms, **to clear damaged tissues,** and to provide **constant surveillance of malignant cells** that grow within the body.

Additionally, the immune system develops **appropriate tolerance** to avoid unwanted response to healthy tissues of self or harmless foreign substances.

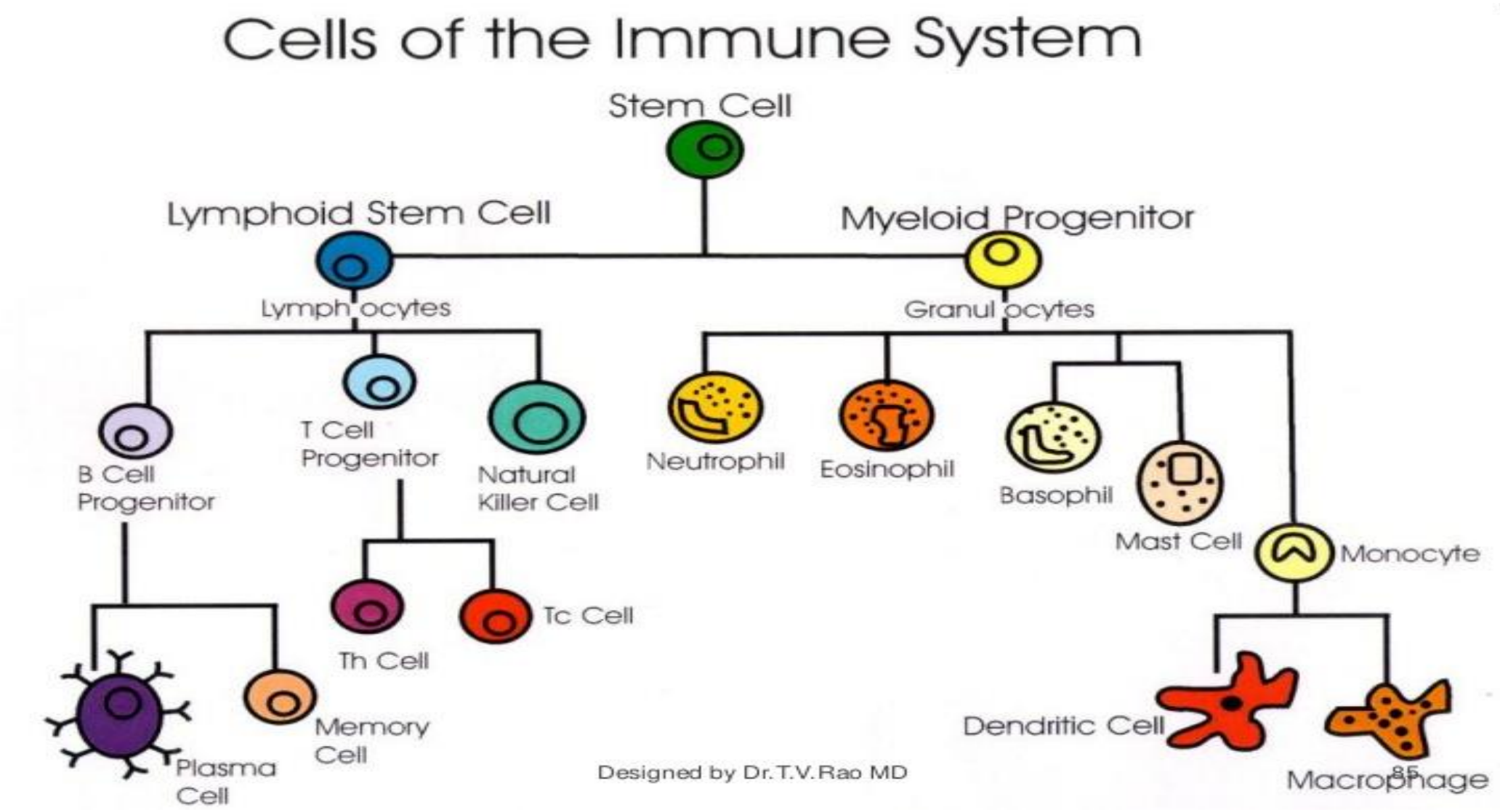
There is considerable heterogeneity among individuals in the vigor of their immunological function, largely owing to factors such as **genetics, environment, lifestyle, nutrition,** and the interaction of these factors."

Reference: : Wu, D, Lewis ED, Pae, M, Meydani SN. Nutritional modulation of immune function: Analysis of evidence, mechanisms, and clinical relevance. Frontiers of Immunology. 2019, 9/article 3160 https://www.frontiersin.org/articles/10.3389/fimmu.2018.03160/full

Red Blood Cells, White Blood Cells and Platelets



Note that Monocytes Give Rise to:
Macrophages, “Dendritic Cells”, Osteoclasts, Kupffer Cells and Microglia



Normal White Blood Cell Panel
Adults and Individuals Over 2 yr. of Age

Total White Blood Cells Count: 5,000 – 10,000 WBC/mcL blood

Neutrophils – 55-73%

Lymphocytes – 20-40%

Eosinophils – 1-4%

Monocytes – 2-8%

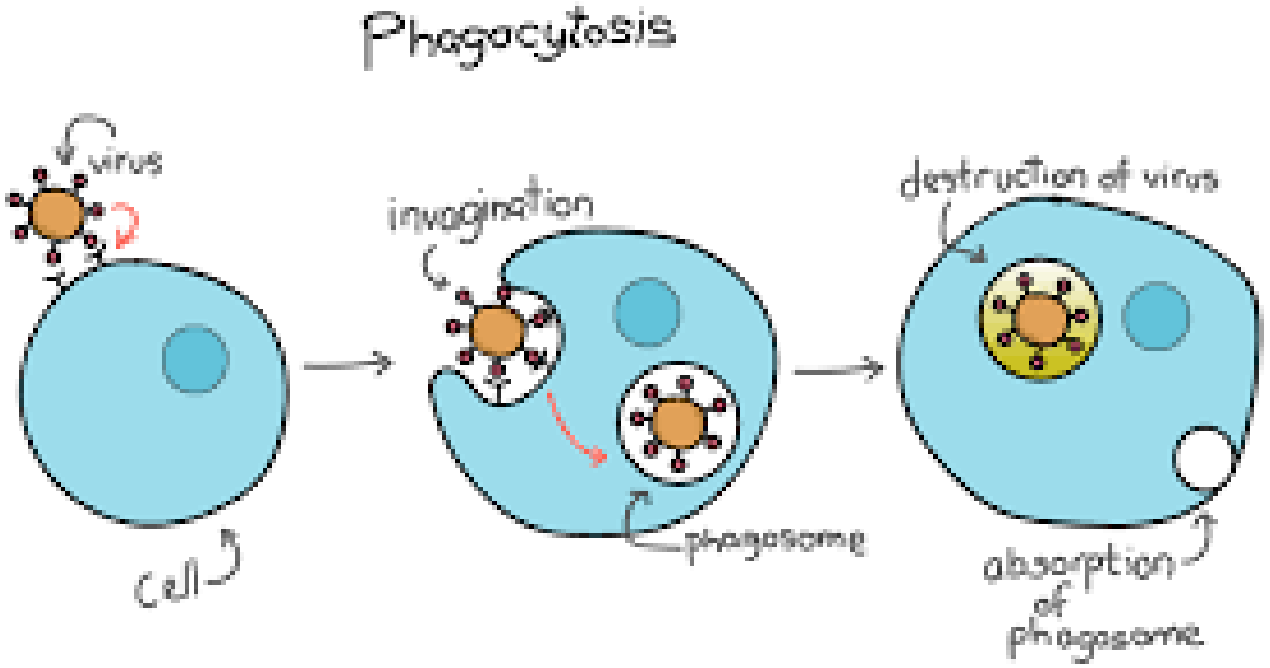
Basophils – 0.5-1%

During an infection these numbers rise significantly

What are these WBC's Doing?

Innate Immune System: Macrophages (monocytes), Natural Killer Cells, Neutrophils,

Other: Phagocytosis on Contact.



Adaptive Immune System – **generates specific antibodies** against pathogens or cancer cells displaying none-self MHC I and sometimes MHC II as well (spiky proteins)

Major Histocompatability Complex = Antigen (protein) MHC I – on all cells; MHC II - only on some specialized cells. On WBC's MHC called HLA (e.g. HLA B27)

Any infectious agent (i.e. virus, bacteria, fungus etc.) that enters your body will eventually be taken up in your lymphatic system. Foreign agents (i.e. virus) have proteins on cell surface (MHC) that act as antigens

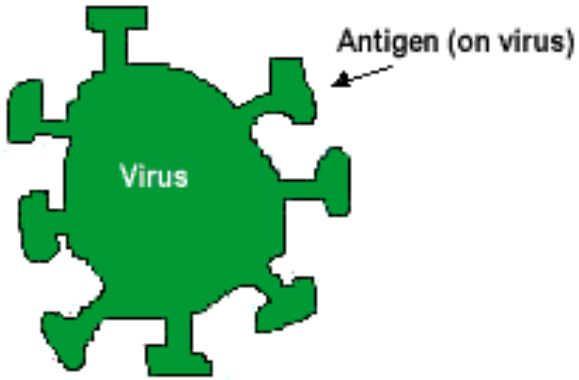
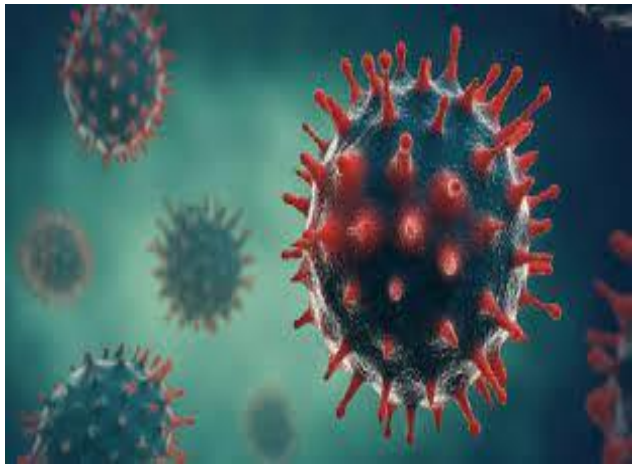


Figure 1



This may happen very soon after infection, or it may not happen until the invader has found a niche and begun to replicate. In one of your lymph nodes, the infectious agent will bump into a macrophage. The macrophage will ingest the invader. **Neutrophils and dendritic cells also ingest invaders upon contact as part of innate immunity.**

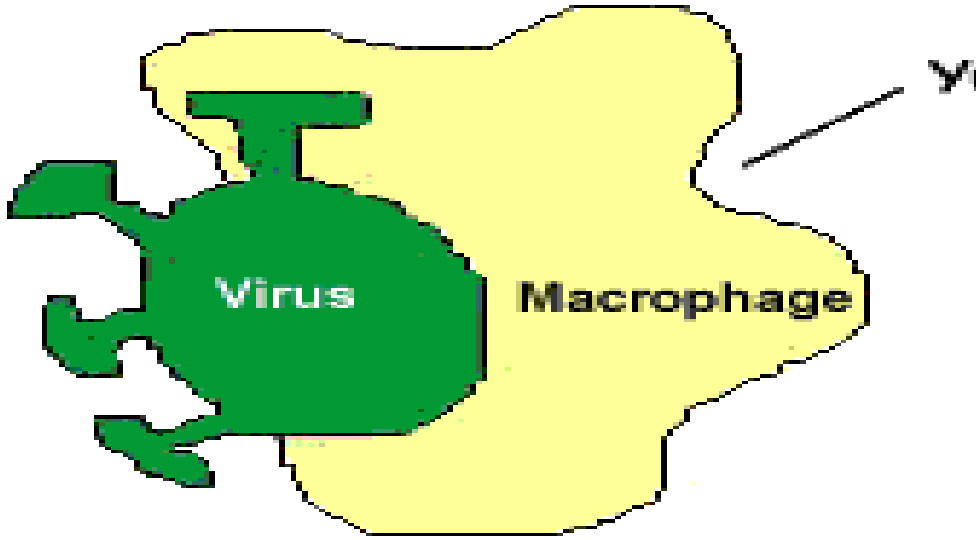


Figure 2
Macrophage surrounds/"eats" the virus

Then the **macrophage and dendritic cells take the invader apart and displays the viral antigens on its surface** for other immune cells to read **(APC cells)**

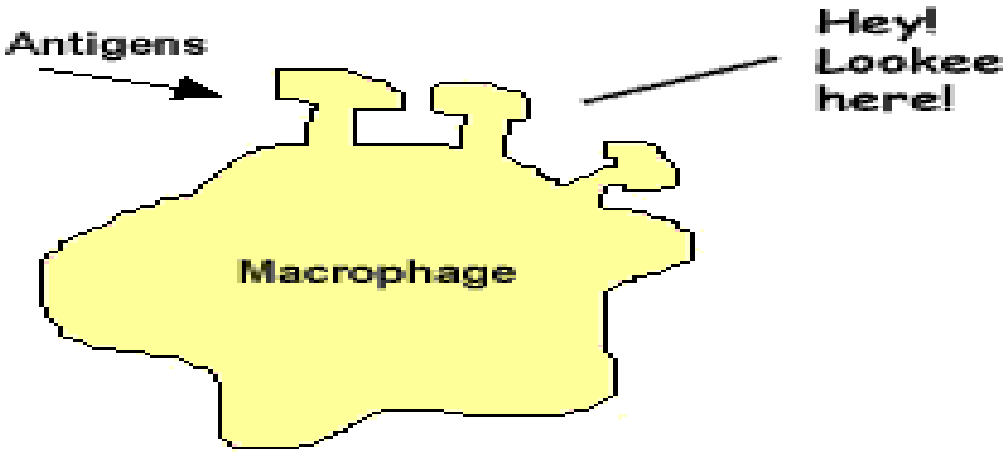


Figure 3
Macrophage displays the antigens of the virus on its surface to alert and activate the other cells.

The **antigens act as an identity card** that allows our immune system to recognize invaders

After displaying the agent's antigens, the macrophage and dendritic cells will send out a message (cytokines) to a **T-helper cell (CD4 cells**) to read and recognize the antigens.

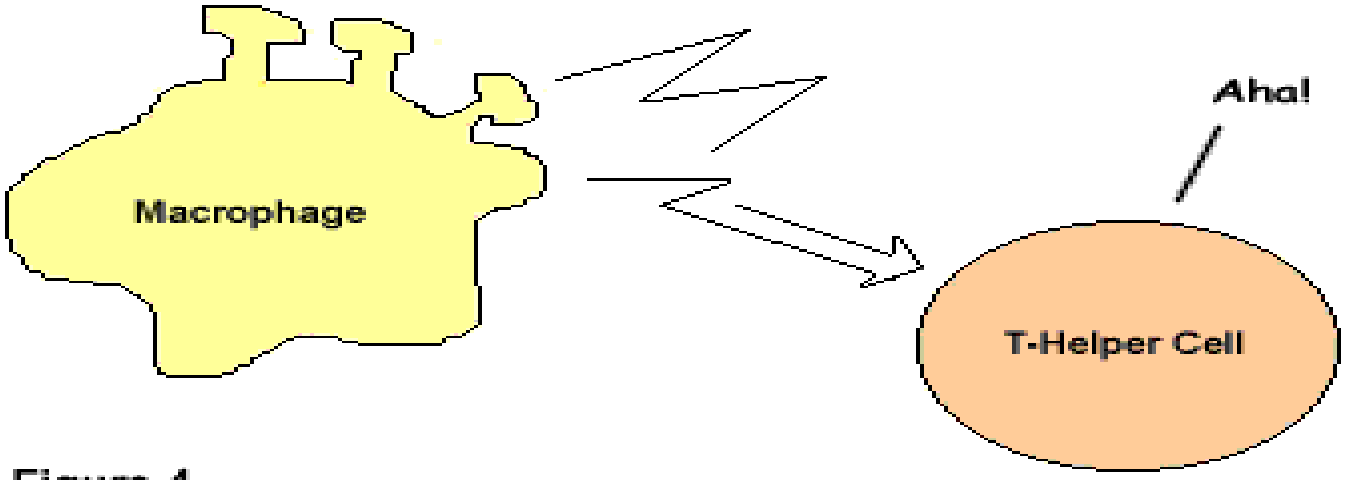


Figure 4
T-helper cell reads and recognizes the antigens

This message activates T-helper cells and triggers the immune response. Once the T-helper cells reads antigens, it sends out messages to activate **B cells (lymphocytes**), which read antigens from the macrophage's surface

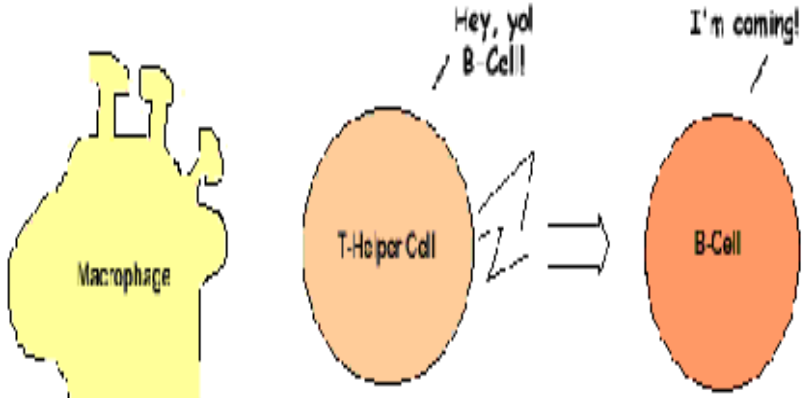


Figure 5
T-helper cell is activated and triggers the immune response, sending out messages to activate the B-cells.

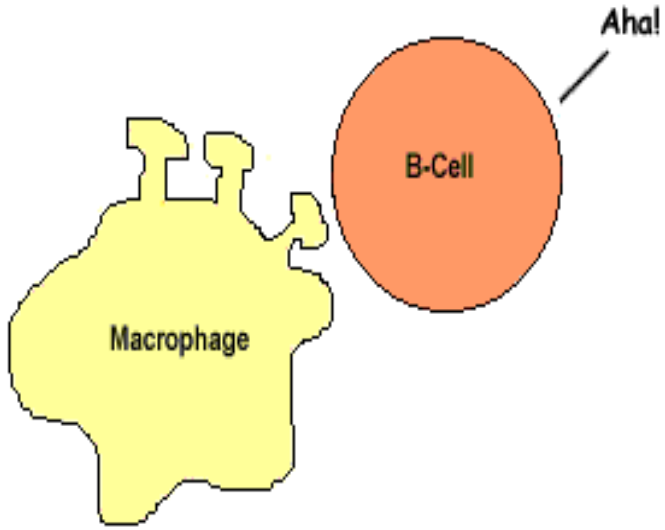


Figure 6
B-cells, in turn, come and read the antigens on the macrophage

The activated B lymphocytes morph into Plasma B cells and produce millions of antibodies. The antibody is a protein that will bind to a specific antigen, for example, a measles antibody will only bind to a measles virus. We produce antibodies because, given the high concentration of infectious agent that is needed to cause disease, our macrophages could not go after the invaders alone. However, antibodies can outnumber the invaders and help us get rid of them. Some activated B cells morph into **memory B cells**, which store the antigen data in case the invader presents itself in the future (acquired immunity and vaccination premise).

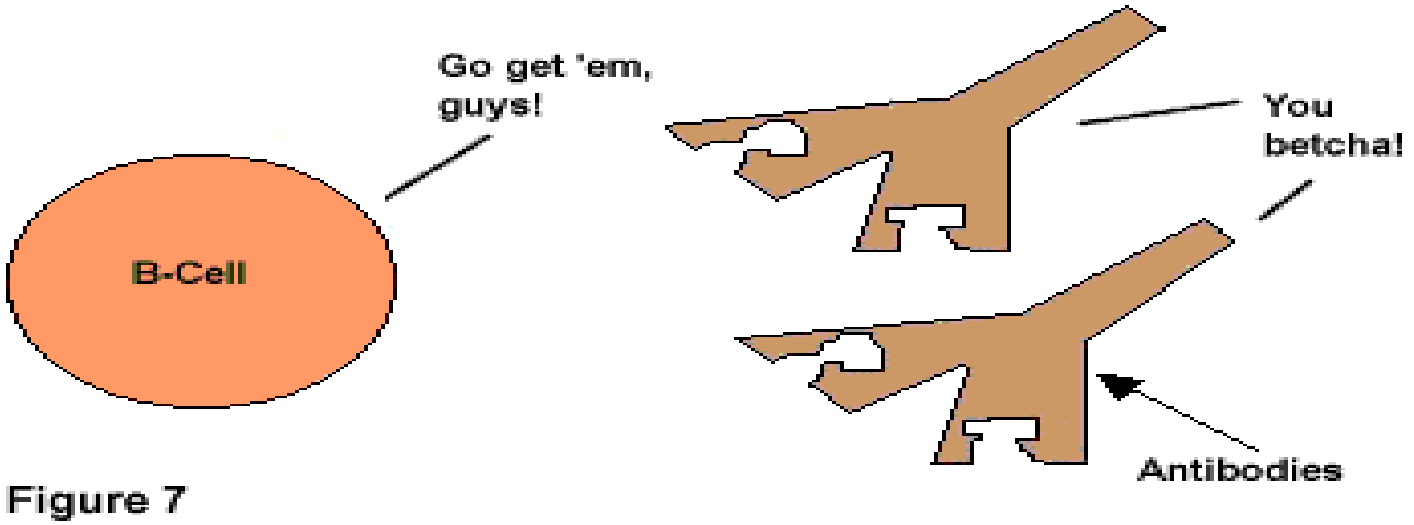


Figure 7

Once an antibody has "coated" an invader, it broadcasts a signal that says, "eat me and whatever I have captured". A macrophage will in turn get the message and will devour the antibody-antigen complex and rid the body of the infectious agent

See Next Slide For Illustration

Macrophage Ingests antigen-antibody complex

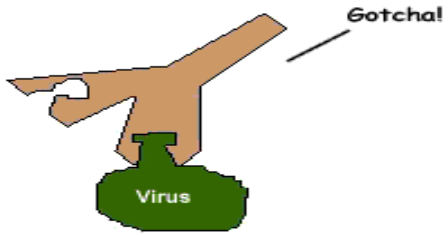


Figure 8

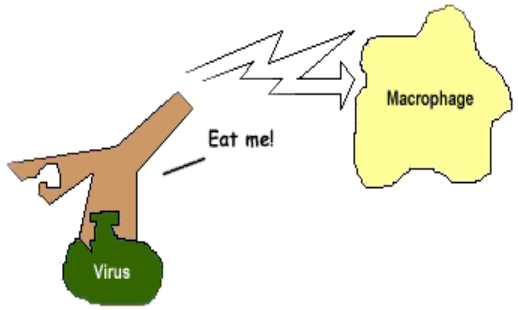


Figure 9

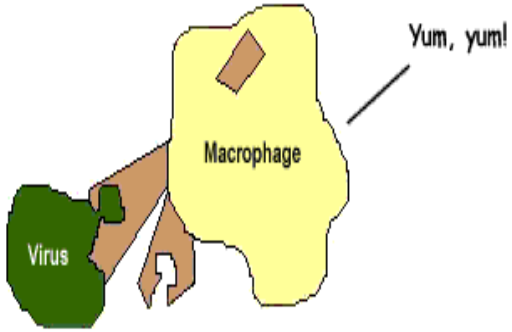


Figure 10

Ending The Battle

Eventually, as this process continues, the number of infectious agents will decrease, and the body will need to stop the battle. However, all the cells are still activated, and the immune system needs to put them to rest. **Another kind of T cell, the T-suppressor cell or T-reg cell (T8 or CD8 cell), will send out cytokines to other cells and "de-activate" them**. Without the T-suppressor cells, the body would continue trying to fight off a disease that no longer exists (and eventually would end up fighting its own cells – as in **autoimmune diseases**). For An-Depth Review of How Immune System Works I Recommend the following 2019 review article: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6723551/

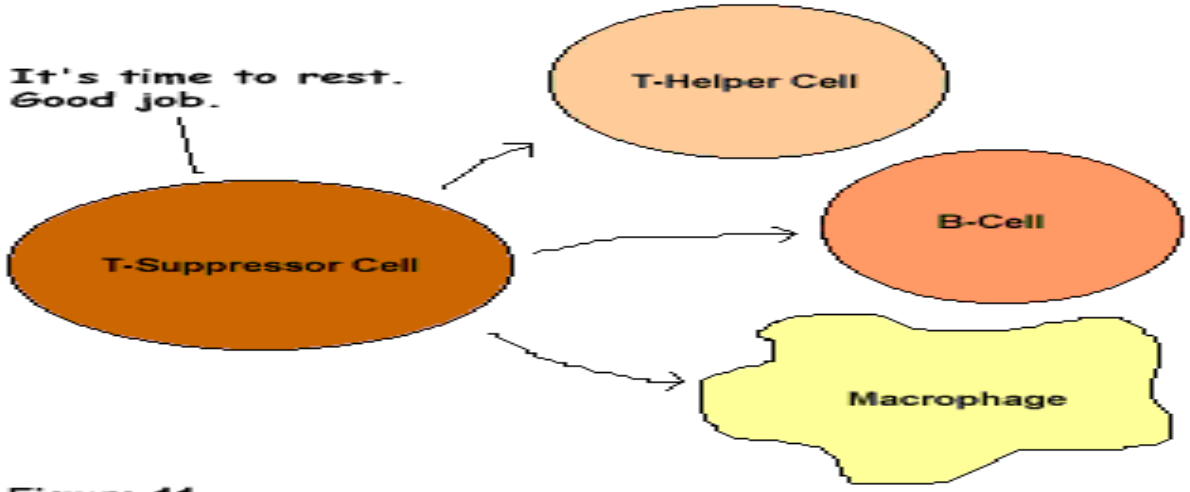


Figure 11

Many Factors Can Impact Immune System Competency:

- Aging
- Diet and Alcohol
- Supplements
- Physical Activity
- Sleep
- Stress/Depression
- Health Conditions (Diabetes, HIV infection)
- Drugs (many drugs suppress immune function)

Aging:

By age 55-60 – Immune function declines due to:

1. Thymus Gland Involution (T-cells less intelligent) –zinc shown to reverse this problem to some degree (we will see later)

2. Cumulative Free Radical Damage to Immune Cells – Immuno-senescence

3. Decreased Respiratory Bursts by Neutrophils - vitamin C transporter less efficient, thus decreased peroxide generation to destroy viruses and other microbes and emerging cancer cells. But higher vitamin C intake and/or IV vitamin C can counter this age-related change, as seen in elderly patients with respiratory tract infections (- http://www.aginganddisease.org/EN/10.14336/AD.2020.0918).

Diet and Alcohol:

Refine Sugar Weakens Immune Function – decreased anti-microbial peptides

- Kiselar J, Wang X, Dubyak GR et al. Modification of beta-defensins-2 by dicarbonyls methylgyoxal and glyoxal inhibits antibacterial and chemotactic function in-vitro. PLOS One. August 2015. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0130533
- https://www.sciencedaily.com/releases/2015/08/150806151354.htm
- Myles IA. Fast food fever: reviewing the impacts of the Western diet on immunity. Nutrition Journal. June 2014. https://nutritionj.biomedcentral.com/articles/10.1186/1475-2891-13-61

Alcohol Weakens Immune Function – dose-dependent relationship, but all-or-none effect has been shown

Sarkar D, Jung M, Wang HJ. Alcohol and the immune system. Alcohol Research. 2015;37(2):153-155 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4590612/

Addiction Campus: The effect of alcohol abuse on the immune system. (2019). https://www.addictioncampuses.com/alcohol/effect-on-immune-system/

Kovacs E, Messingham K. Influence of alcohol and gender on immune response. Alcohol Research Current Review. 2002;26(4):257-263 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6676685/#!po=84.7222

Sarkar D, Jung M, Wang HJ. Alcohol and the immune system. Alcohol Research. 2015;37(2):153-155 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4590612/

CBD and THC Weaken Immune Function - "Overall, the data overwhelmingly support the notion that **CBD** is immune suppressive and that the mechanisms involve direct suppression of activation of various immune cell types, induction of apoptosis, and promotion of regulatory cells, which, in turn, control other immune cell targets." (2020 Review: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7173676/) **THC** also appears to be immunosuppressive. https://link.springer.com/article/10.1007/s11481-015-9603-3

Physical Activity: Light to Moderate Exercise Strengthen Immunity, but Over Training Weakens Immunity – increasing URTI incidence

https://www.sciencedaily.com/releases/2020/03/200331162314.htm

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5911985/

April 2020 Review: https://www.health.com/fitness/does-exercise-boost-immunity

British Medical Bulletin: https://academic.oup.com/bmb/article/90/1/111/324145

https://pubmed.ncbi.nlm.nih.gov/23540172/

Smoking Weakens Immune Function: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5352117/

Insufficient Sleep Weakens Immunity

Reference: Besedovsky L, Lange T, Born J. Sleep and immune function. European Journal of Physiology (2012) 463:121-137 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256323/

Depression Weakens Immunity - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3002174/

Stress Weakens Immunity https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1361287/

Certain Nutrients May Depress Immune Function (omega-3 fats, green tea catechins, vitamin D blood level above 140nmol/L or 56ng/mL. (Wu, D, Lewis ED, Pae, M, Meydani SN. Nutritional modulation of immune function: Analysis of evidence, mechanisms, and clinical relevance. Frontiers of Immunology. 2019, 9/article 3160 https://www.frontiersin.org/articles/10.3389/fimmu.2018.03160/full

2. **Some Drugs:** Corticosteroids (Prednisone), TNF-inhibitors for autoimmune disease (i.e. Humira, Remicade), Anti-rejection drugs used by transplant patients (i.e. Cyclosporin) https://www.healthline.com/health/immunosuppressant-drugs#treatment

3. **Comorbidity Health Conditions Increasing Risk for Severe Covid-19 Infection –** Hypertension, Diabetes, Over 65 yr, Cancer Patients, Chronic Kidney Disease, HIV-infection – CKD and HIV positive pts have highest mortality risk
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7314621/

https://pubmed.ncbi.nlm.nih.gov/33563817/

https://www.medrxiv.org/content/10.1101/2020.07.02.20145185v2

Proactive Strategies to Maintain a Strong Immune System:

1. Get enough **Sleep**- your immune system recharges during sleep.

2**. Don't Overtrain** – light to moderate exercise strengthens immunity, but over exertion and over-training weakens immunity, even in high performance athletes – (more URTI)

3. **Stress Management-** keep cortisol levels in check (meditation, mind-body, don't over train)

4. Minimize or Eliminate agents that Suppress Immunity (Smoking, Alcohol, Certain Recreational Drugs etc.)

4. Optimize Intake of Nutrients that Support Immune Function

Nutritional Factors We Will Review

1. Vitamin C
2. Vitamin E
3. Zinc
4. Selenium
5. Vitamin D
6. Probiotics
7. Medicinal Mushrooms
8. Astragalus
9. Milk Thistle
10. Indole-3-Cabinol
11. Melatonin
12. L-Glutamine
13. Quercetin

Vitamin C and Immunity

- Neutrophils require Vitamin C to generate virus-killing respiratory bursts (free radical-peroxides)
- Neutrophils pump Vitamin C into their cells against a concentration gradient, thus have higher Vitamin C concentrations than blood
- With aging, Vitamin C pump (transporter) is more sluggish, reducing neutrophil Vitamin C levels, which makes the neutrophil less capable of killing viruses (especially after age 60)
- Studies show that higher intakes of vitamin C in older subjects can improve neutrophil function, by enabling neutrophils to access more vitamin C.
- Vitamin C also protects neutrophils against the free radicals they use to kill viruses.

- Vitamin C increases movement of neutrophils and other immune cells towards virus location in the body (chemotaxis)

- Vitamin C strengthens the physical barrier to infection in lungs, intestinal tract and elsewhere.

- Vitamin C is also required by adaptive immune system, enhancing maturation and replication of B-cells and T-cells (lymphocytes)

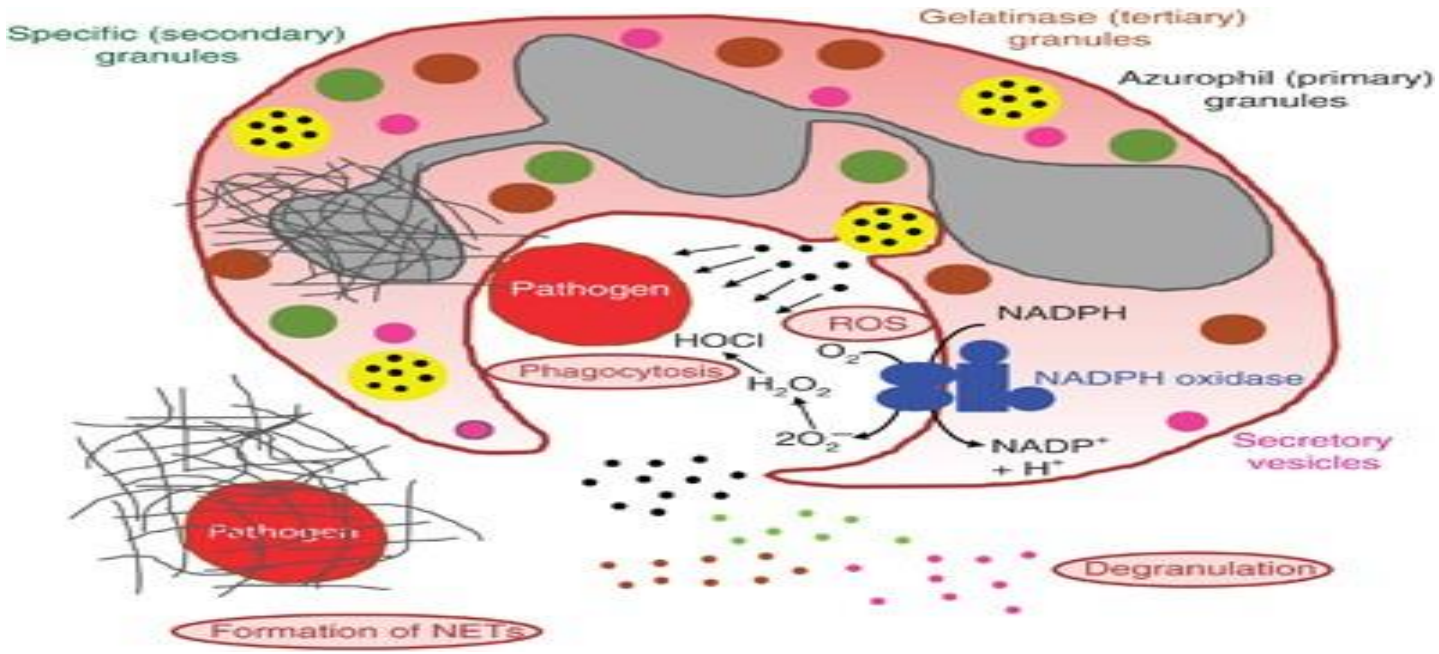
- Vitamin C turn over rate is much faster during an infection, thus further increasing vitamin C requirement.

- Sub-optimal Vitamin C increases risk of NETosis – NETs, which trigger life-threatening cytokine storm. (see next slides)

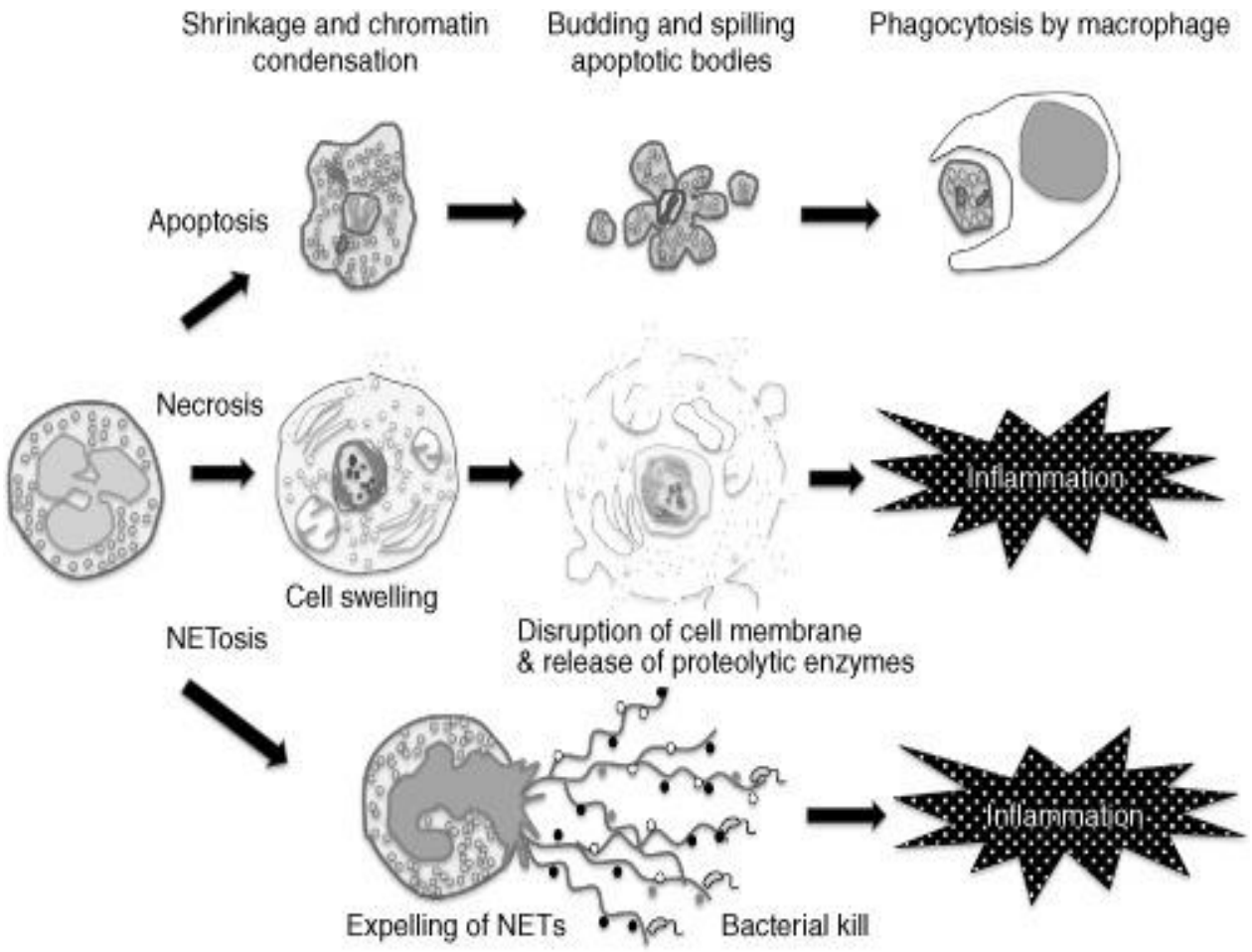
Reference: 2017 Review: Vitamin C and Immune Function
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5707683/

Neutrophils:

1. Generate Respiratory Bursts at Pathogen
2. Generate Neutrophil Extravascular Traps (NET's) – Too many NET's can trigger cytokine storm
3. Vitamin C is required for all these functions
4. Neutrophils pump vitamin C into their cells from bloodstream against a concentration gradient – thus have higher conc. of vitamin C than plasma



Insufficient Vitamin C prompts Necrosis and NETosis leading to cytokine storm/inflammation (https://jlb.onlinelibrary.wiley.com/doi/pdfdirect/10.1189/jlb.0806541

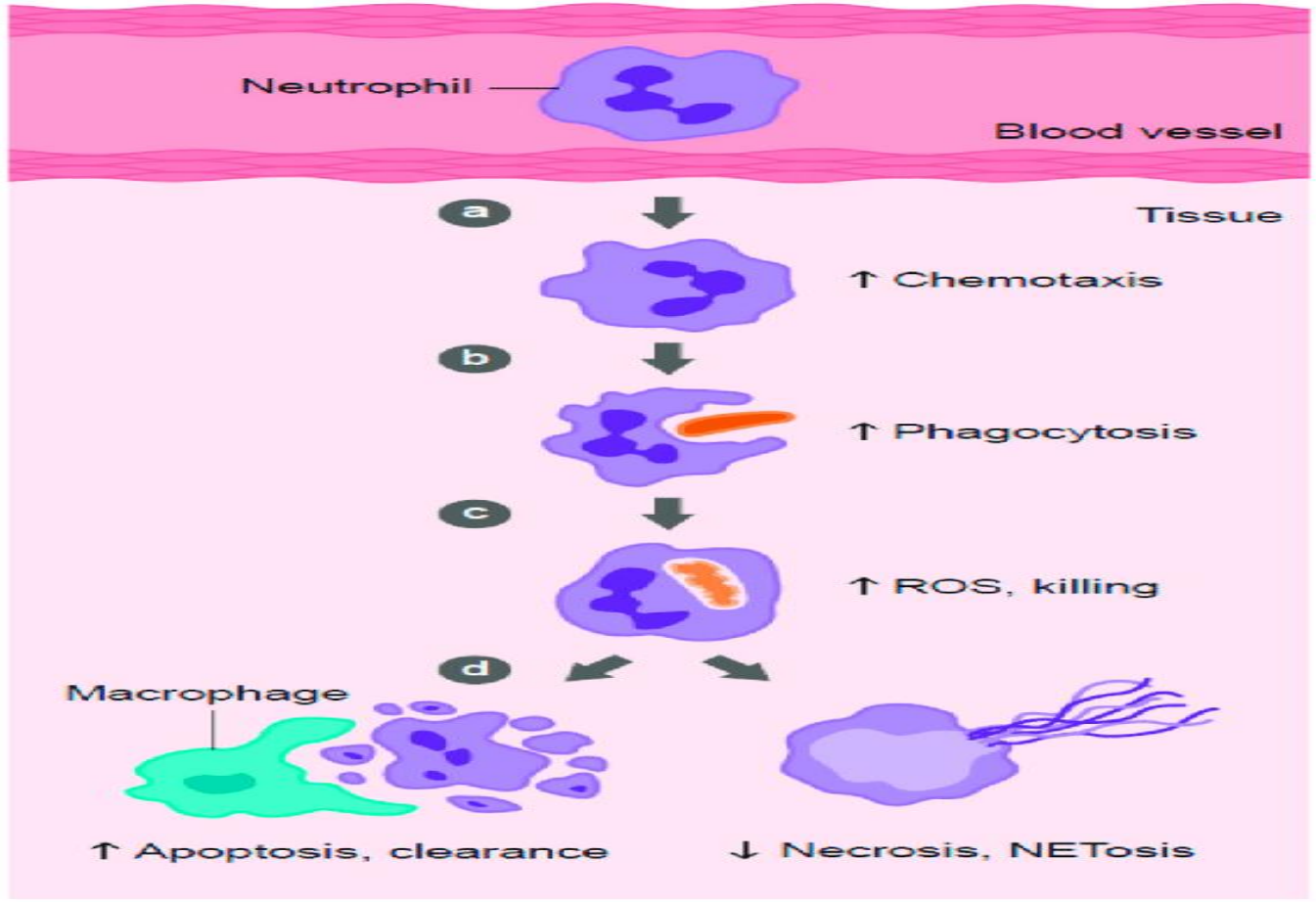


To optimize immune system function in healthy young people, requires 100-250 mg of Vitamin C daily – which achieves a blood level of at least 50 umol/L)

For older individuals, the Vitamin C requirement is 1,000 mg per day, along with at least 200 IU of Vitamin E to optimize immune function, especially after age 60

Reference: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5707683/

Vitamin C required for all these functions: Neutrophils



Vitamin C and Immunity Summary Table https://www.researchgate.net/figure/Role-of-vitamin-C-in-immune-defense_tbl1_320843979

Immune System	Function of Vitamin C	Refs.
Epithelial barriers	Enhances collagen synthesis and stabilization	[30–35]
	Protects against ROS-induced damage [1]	[36–40]
	Enhances keratinocyte differentiation and lipid synthesis	[41–45]
	Enhances fibroblast proliferation and migration	[46,47]
	Shortens time to wound healing in patients	[48,49]
Phagocytes (neutrophils, macrophages)	Acts as an antioxidant/electron donor	[50–53]
	Enhances motility/chemotaxis	[54–63]
	Enhances phagocytosis and ROS generation	[64–71]
	Enhances microbial killing	[54,55,57,58,70,72]
	Facilitates apoptosis and clearance	[71,73,74]
	Decreases necrosis/NETosis	[73,75]
B- and T-lymphocytes	Enhances differentiation and proliferation	[62,63,76–82]
	Enhances antibody levels	[78,83–85]
Inflammatory mediators	Modulates cytokine production	[75,77,86–94]
	Decreases histamine levels	[56,61,95–101]

Do Most People Have Optimal Vitamin C Status for Immunity? No

In North America **low Vitamin C blood levels** are very common (**below 23 umol/L**) and Vitamin C deficiency **is 4th leading nutrient deficiency in U.S. (below 11 umol/L)**

40% of U.S. population have low levels of vitamin C and 88% don't meet the RDA requirement for Vitamin E (15 IU per day)

Reference:

https://www.medpagetoday.com/casestudies/infectiousdisease/87976

Very importantly, higher levels of intake (1,000 mg vitamin C per day) have been shown to prevent the decline in vitamin C depletion within white blood cells during an infection.

Reference: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5707683/

Has Vitamin C Supplementation Been Shown to Help Fight Viral Infections? Yes

Elderly pneumonia patients with severe disease who were given Vitamin C supplementation in hospital showed faster recovery, as well as normalization of chest-X-ray, temperature and ESR – given up to 1600 mg per day Vitamin C

Reference: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5707683/

Shanghai Clinical Treatment Expert for Covid-19 – included intravenous Vitamin C Therapy, as part of treatment protocol for moderate to severe Covid-19 infections

- The recommendation for the use of intravenous vitamin C is largely based on a study they conducted of **358 total Covid-19** patients, of which **fifty of these patients had moderate to severe Covid-19 infections**.

- **The results showed that all the patients who received intravenous vitamin C therapy, as part of Covid-19 treatment, improved, none of them died, and it shortened their hospital stay by 3-5 days compared to the non-vitamin C treatment group. "**

References:

Comprehensive treatment and management of corona virus disease 2019: expert consensus statement from Shanghai. Chinese J Infect Dis, 2020 http://rs.yiigle.com/yufabiao/1189815.htm

NIH Feb 3, 2021 Vitamin C and Covid-19

- ”It has been shown that as little as 0.1 g/d of vitamin C can maintain normal plasma levels of vitamin C in healthy individuals, but **higher doses of at least 1–3 g/d are required for critically ill patients in ICUs** [108]. “

- **“Indeed, vitamin C deficiency appears to be common among COVID-19 patients** [109,110]. COVID-19 is also associated with the formation of **microthrombi and coagulopathy** [111] that contribute to its characteristic lung pathology [112], **but these symptoms can be ameliorated by early infusions of vitamin C to inhibit endothelial surface P-selectin expression and platelet-endothelial adhesion [113].”**

- “Intravenous vitamin C also **reduced D-dimer levels**, which are notably elevated in COVID-19 patients [114,115], in a case study of 17 COVID-19 patients [116]. There is therefore preliminary evidence suggesting that vitamin C status and vitamin C administration may be relevant to COVID-19 outcomes.”

- “The first trial to report initial results took place in Wuhan, China [120]. These initial results indicated that the administration of 12 g/12 hr of intravenous vitamin C for 7 days in 56 critically ill COVID-19 patients resulted in a promising reduction of 28-day mortality (p = 0.06) in univariate survival analysis [121]. Indeed, the same study reported a significant decrease in IL-6 levels by day 7 of vitamin C infusion (p = 0.04) [122].”

- “To maintain vitamin C status, it would be prudent for individuals to ensure that they consume the recommended dietary allowance of vitamin C to maintain a healthy immune system [1]. The recommended dietary allowance according to the FDA is 75–90 mg/d, whereas EFSA (European Food Safety Association) recommends 110 mg/d [123].”

Reference: Lordan R et al. Dietary Supplements and Nutraceuticals Under Investigation for Covid-19 Prevention and Treatment. National Institutes of Health Preprint Pilot. Feb 3, 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7872359/

Factors that Deplete Vitamin C from the Body

- Air Pollution
- Smoking
- Being Overweight
- Hypertension, Congestive Heart Failure, Coronary Artery Disease
- Diabetes
- Autoimmune Diseases and other Inflammatory States
- Infections
- Malignancy (1)
- Caffeinated Foods and Beverages (coffee and tea) (2)
- Alcohol (3)
- Stress (4)
- Aerobic – Endurance Exercise (5)

Reference:

1.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7400679/#:~:text=High%20dietary%20fat%20and%20sugar,vitamin%20C%20intake%20and%20status.&text=Staple%20foods%20such%20as%20grains,lower%20overall%20vitamin%20C%20intake

2. https://medium.com/beingwell/coffee-depletes-vital-micronutrients-659cefc408da

3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7678474/

4. https://www.sciencedirect.com/science/article/pii/S0955286320304915

5. https://www.researchgate.net/publication/10591057_Vitamin_C_Effects_of_Exercise_and_Requirements_with_Training

Vitamin C Intake Considerations During Pandemic:

1. Adeeva All-in-One Multiple Vitamin – 1,000 mg per day – adds up to a total of 1,000 mg vitamin C/day (500 mg per dose, taken twice per day)

2. Additional 500 mg of Vitamin C, twice daily, separated by 2-3 hours

3. Taking more than 500 mg vitamin C in one dose is not as effective, as beyond 500 mg per dose see dramatic decline in absorption.

4. At the first sign of URTI infection I would consider taking 4,000-5,000 mg/d, in 500 mg doses spread out throughout the day (my opinion)

Dr. Frederick R. Klenner M.D. (https://www.seanet.com/~alexs/ascorbate/198x/smith-lh-clinical_guide_1988.htm)

In 1948, he published his first paper on the use of large doses of Vitamin C in the treatment of virus diseases.

His published papers showed success in human cases of:

- Polio virus infection - During the epidemic of poliomyelitis, he had cured all 60 patients suffering from this disease by using massive doses of vitamin C, sometimes 300,000 mg daily. None had been left with any paralysis.(https://www.pharmacistsmb.ca/files/2014/winnipeg_freepress/winnipeg_free_press_-_vitamin_c_a_legitimate_weapo.pdf)
- Influenza
- Viral Pneumonia
- Viral Hepatitis
- Mumps
- Mononucleosis
- Others

During his career Dr. Klenner published 28 scientific papers on these observations. (https://isom.ca/profile/frederick-klenner/)

Dosage: 65 mg/kg – 250 mg/kg/d (IV) depending on infection severity and person's immune competence

Vitamin E and Immunity

- Vitamin E Protects Immune Cells from Free Radicals, preserving their function
- Decreases PG-2 synthesis, which otherwise impairs immune cell function
- Enhances T-cell immune function
- **Human Studies** – show 100-400 IU per day decreases URTI infections and improves objective parameters of immunity in older subjects

Vitamin E References:

- Lee GA, Han SN. The role of vitamin E in immunity. Nutrients. 2018, 10;11:1614 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6266234/
- Annals of Clinical & Laboratory Science, vol. 30, no. 2, 2000 145 Review: Free Radicals, Antioxidants, and the Immune System Joseph A. Knight Department of Pathology, University of Utah School of Medicine, Salt Lake City, Utah
- Marcos A, Nova E, Montero A. Changes in the immune system are conditioned by nutrition. European journal of Clinical Nutrition. 2003. 57 (Suppl 1): 566-569 https://www.nature.com/articles/1601819.pdf?origin=ppub

Zinc and Immunity

Zinc affects multiple aspects of immune system

Macrophages, T-cells, B-cells highly dependent upon adequate zinc to kill viruses

Zinc deficiency, which is common, decreases Thymus Gland secretion of thymulin hormone – modulates immune cells (Thymulin is a zinc-containing hormone)

Zinc deficiency also impairs other critical aspects of immune function

Zinc supplementation shown to **increase thymulin secretion**, immune cell function and has **decreased incidence and severity of upper respiratory tract infections in older subjects**

References:

1. Prasad AS. Zinc in human health: Effect of zinc on immune cells.Molecular Medicine 2008, 14(5-6):353-357 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2277319/

2. Wu, D, Lewis ED, Pae, M, Meydani SN. Nutritional modulation of immune function: Analysis of evidence, mechanisms, and clinical relevance. Frontiers of Immunology. 2019, 9/article 3160 https://www.frontiersin.org/articles/10.3389/fimmu.2018.03160/full

- Given the fact that **both zinc Deficiency and zinc Overload Impair Immune Functions, zinc supplementation should not exceed a certain dose.**

Reference: Johnson AR et al. High dose zinc increases hospitalization admissions due to genitourinary complications. Urol. 2007,177;2:639-43 https://pubmed.ncbi.nlm.nih.gov/17222649/

- My feeling is that 15 mg of zinc is adequate from supplementation

- Human studies show that supplementation with 10-20 mg of zinc improves immune system's ability to ward off infections. In some studies, higher doses of zinc have been used to help fight existing infections, but for short periods (e.g., 60-90 mg per day for 7-10 days)

Reference: The Potential Impact of Zinc Supplementation on COVID-19 Pathogenesis. Frontiers of Immunology 2020: https://www.frontiersin.org/files/Articles/563256/fimmu-11-01712-HTML/image_m/fimmu-11-01712-t001.jpg

- North American population studies show that at least **55% of adults do not ingest the amount of zinc per day that is recommended by government agencies**.

- **Zinc Recommendations**: Adult males and non-pregnant Females should consume **15 mg** of zinc per day.

- Studies show that **adult males and females** in North America average about **11** mg of zinc intake per day from food.

- **Elderly** individuals (over 71 yr of age) average about **8 mg.**

- Thus, **A High-Potency Multiple Vitamin containing 15 mg of zinc** is a strong consideration to guard against marginal zinc deficiency and help correct marginal zinc deficiency in my view.

- **In North America and in many developed countries 30% of elderly individuals shown to have mild to moderate zinc deficiency.**

- Other groups where marginal zinc deficiency is more common includes Black Americans and Mexican Americans, premenopausal women of childbearing age, including females 12-19 years of age, who are very prone to zinc deficiency.

Zinc References:

- Gammoh NZ et al. Zinc in infection and inflammation. Nutrients 2017 (June). 9(6):624 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5490603/
- Prasad A. Zinc is an antioxidant and anti-inflammatory agent: it's role in human health. Frontiers of Nutrition (Review Article) 2014. https://www.frontiersin.org/articles/10.3389/fnut.2014.00014/full
- Briefel RR et al. Zinc intake of the U.S. population: Findings from the Third National Health and Nutrition Examination Survey, 1988-1994. The Journal of Nutrition 2000. 130(5):1367s-1373s https://academic.oup.com/jn/article/130/5/1367S/4686375
- . Wu, D, Lewis ED, Pae, M, Meydani SN. Nutritional modulation of immune function: Analysis of evidence, mechanisms, and clinical relevance. Frontiers of Immunology. 2019, 9/article 3160 https://www.frontiersin.org/articles/10.3389/fimmu.2018.03160/full

The typical chronic sub-optimal intake of zinc across our population often leads to signs and symptoms of mild to moderate zinc deficiency, which includes any combination of:

- **Decreased immune function** or compromised immune function (decreased natural killer cell lytic activity), decreased interleukin-2 activity of T-helper cells, decreased serum Thymulin activity - required for maturation of T-lymphocytes)
- **Decreased taste acuity (**https://pubmed.ncbi.nlm.nih.gov/17651517)
- **Decreased dark adaptation**
- **Decreased lean mass**
- **Decreased wound healing** - treating skin wounds that heal slowly, or not at all, with a topical zinc ointment has been shown to solve the problem in many cases. **But the real problem is often an internal zinc deficiency in the first place.**

References Zinc, Lean Mass and IGF-1)

Devine, A. et al. Effects of zinc and other nutritional factors on insulin-like growth factor-1 and insulin-like growth factor binding proteins in postmenopausal women. Am J Clin Nutr 1998, 68; 1: 200-206

Roth, H.P., et al. Influence of alimentary zinc deficiency on the concentration of growth hormone, insulin-like growth factor-1 and insulin in the serum of force-fed rats. Horm Metab Res. 1994; 26: 404-408

Additional Zinc References

- *Devine, A. et al. Effects of zinc and other nutritional factors on insulin-like growth factor-1 and insulin-like growth factor binding proteins in postmenopausal women. Am J Clin Nutr 1998, 68; 1: 200-206*

- *Dorup, I. Et al. Role of insulin-like growth factor-1 and growth hormone in growth inhibition induced by magnesium and zinc deficiencies. Br J Nutr. 1991; 66: 505-521*

- **The Potential Impact of Zinc Supplementation on COVID-19 Pathogenesis.** Frontiers of Immunology 2020: https://www.frontiersin.org/files/Articles/563256/fimmu-11-01712-HTML/image_m/fimmu-11-01712-t001.jpg

NIH Feb 3, 2021 Zinc and Covid-19

- "An observational study showed that **COVID-19 patients had significantly lower zinc levels in comparison to healthy controls and that zinc-deficient COVID-19 patients (those with levels less than 80 µg/dl) tended to have more complications** (70.4% vs 30.0%, *p* = 0.009) and **potentially prolonged hospital stays** (7.9 vs 5.7 days, *p* = 0.048) relative to patients who were not zinc deficient [84]."

- "In coronaviruses specifically, *in vitro* evidence has demonstrated that the combination of zinc (Zn^{2+}) and zinc ionophores (pyrithione) **can interrupt the replication mechanisms of SARS-CoV-GFP (a fluorescently tagged SARS-CoV-1) and a variety of other RNA viruses** [85,86]. Currently, there are over twenty clinical trials registered with the intention to use zinc in a preventative or therapeutic manner for COVID-19."

Reference: Lordan R et al. Dietary Supplements and Nutraceuticals Under Investigation for Covid-19 Prevention and Treatment. National Institutes of Health Preprint Pilot. Feb 3, 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7872359/

Selenium and Immunity

- Like Zinc, Selenium helps support immune function in various way
- In animals, low selenium status increases risk of viral and other infections, and selenium repletion reverses the risk.
- Like vitamin D, Selenium supplementation shown to slow progression of HIV disease in humans
- More optimal Selenium status shown to decrease virus MUTATION and Replication in the body
- Selenium shown to inhibit life-threatening cytokine storm experimentally
- Selenium may help prevent abnormal clots seen is Covid-19 patients

Frontiers of Nutrition Journal Sept 2020: https://www.frontiersin.org/articles/10.3389/fnut.2020.00164/full

Selenium supplementation shown to enhance efficacy of polio virus in human studies

Mol Nutr Food Research 2013 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3723386/

Selenium shows an impressive array anti-cancer properties in human epidemiological studies and anima experiments

Int J Mol Sci. Tan HW et al. Selenium species: Current status and potentials in cancer prevention and therapy. 2019; 20(1):75
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6337524/

Mol Nutr Food Research 2013
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3723386/

Selenium Status and Covid-19

- Studies in **China, Germany and Sweden** have shown that the lower a person's selenium status, the greater is the risk of mortality in Covid-19 patients

- In China, the rate of recovery from Covid-19 shown to be 3x higher in areas where selenium nutritional status is superior

- In Germany, Very low serum Se status was present in 44.4% of their patients. 65% percent of the deceased had low Se vs 39% in those who survived. **The lowest serum Se were strongly associated with mortality.**

- **In Sweden, 71% of elderly are Se deficient when admitted to Intensive Care Unit.**

- **Studies have shown that Se supplementation has significantly reduced infections in institutionalized elderly people.**

- The **RDA for Selenium appears to be too low to optimize immune function** (55 mcg/d)

- The recommendation in **Sweden is for citizens to supplement with 200 mcg** per day of selenium to help optimize immune function and decrease viral replication and mutation.

- In addition, **200 micrograms of Se daily have been given in the elderly for years with significant positive results lowering viral infection rates** and cardiovascular mortality.

- **Similarly, 4-year Se supplementation** in Swedish elderly people reduced cardiovascular mortality risk by more than 40%, even **12 years after intervention. (also included CoQ10)**

Reference: Hiffler L et al. Selenium and RNA virus interactions: Potential implications for SARS-CoV-2 infection (COVID-19). Frontiers in Nutrition. September 2020: https://www.frontiersin.org/articles/10.3389/fnut.2020.00164/full

Vitamin D and Immunity

Overview:

1. Achieving a vitamin D status above **75-80nmol/L (30-32ng/mL)** is critical for optimal function of the **Innate Immune System**, which kills pathogens on contact. This level of vitamin D status also supports function of adaptive immune system. Most North Americans have vit D blood levels below 75nmol/L, and **government considers 50nmol/L to be adequate**.

2. However, if vitamin D status exceeds **140nmol/L (56ng/mL),** it inhibits key aspects of **Adaptive Immune System**, making it difficult to synthesize antibodies and secrete cytokines required to fight infections effectively. This may be desirable for autoimmune disease management, tamping down an overzealous immune system, but this is undesirable as way to fight infections.

3. So, target blood Vitamin D level for Non-Autoimmune Patients =

(80-140nmol/L or 32 – 56ng/ml). In Canada **50 nmol/L** is considered adequate, but this is true for bone health, not for optimal immune function**.**

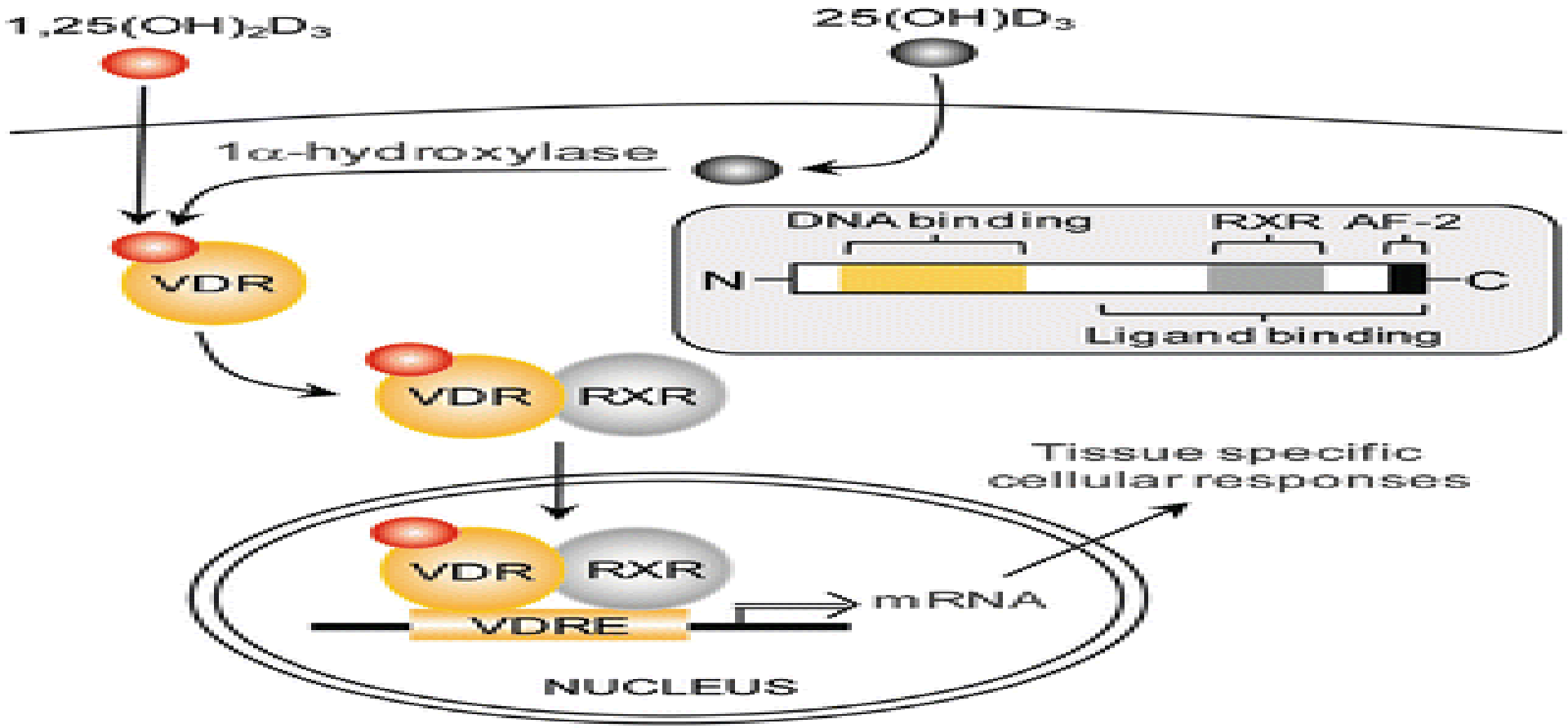
- Need sufficient Vitamin D fo**r innate immune cells to synthesize anti-microbial peptides** (e.g. cathelicidin) that puncture holes in virus and other pathogens, destroying them on contact.

- High Blood Levels of Vitamin D and High Single Doses of Vitamin D inhibit Adaptive Immunity (T and B-cells), **decreasing antibody production and synthesis of key cytokines needed to fight infections**.

- However, High Dose Vitamin D can be used to improve some Autoimmune Diseases (e.g., MS, Crohn's etc.), by inhibiting over zealous Adaptive Immune System Function.

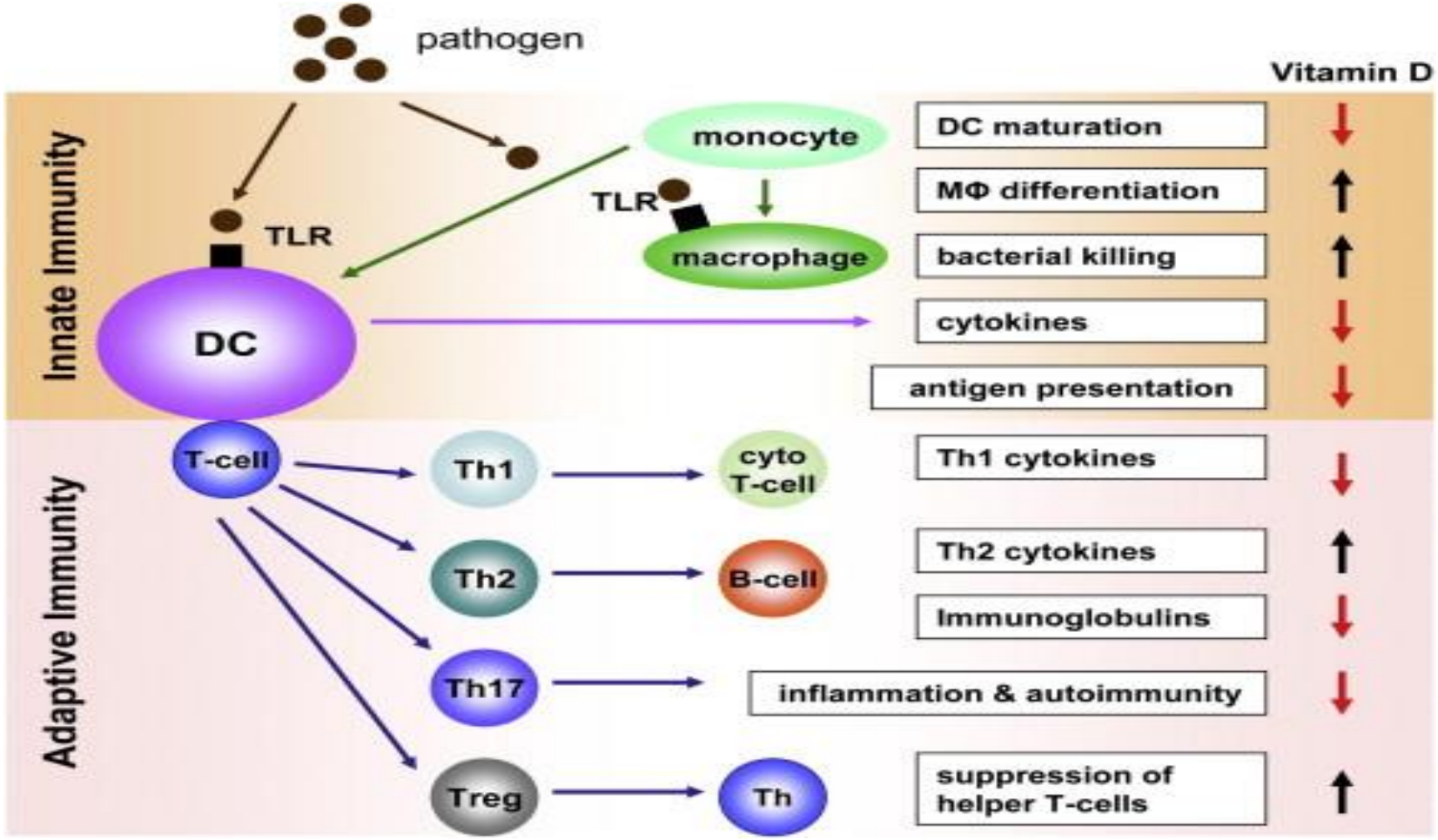
- It's helpful to know your blood Vitamin D level, but most people attain optimal blood Vitamin D blood level with 1,000 – 2,000 IU per day in this part of the world, where there is lack of Vitamin D synthesis in skin between October and May. Vitamin D Toxicity begins at 250 nmol/L.

Once inside Immune Cells, Vitamin D transferred to Nucleus, Affecting Genes that Increase Immunity



Rheumatic Disease Clinics: Vitamin D and the immune system: New Perspectives on an old theme. April 2012.

https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.rheumatic.theclinics.com%2Farticle%2FS0889-857X(12)00013-0%2Fabstract&psig=AOvVaw0sAD4JJHv37C2bOIL5qsXQ&ust=1605034828123000&source=images&cd=vfe&ved=0CAIQjRxqFwoTCLjk9-mS9uwCFQAAAAAdAAAAABBI



Vitamin D References Thus Far:

1. Laaksi I et al. Vitamin D supplementation for the prevention of acute respiratory tract infection: A randomized, double-blind trial among young Finnish Men. Journal of Infectious Diseases, Vol 202, Issue 5. September 2010. https://academic.oup.com/jid/article/202/5/809/1746565

2. Holick MF. Vitamin D: Importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutr. Vol 79, Issue 3. March 2004

3. Wu, D, Lewis ED, Pae, M, Meydani SN. Nutritional modulation of immune function: Analysis of evidence, mechanisms, and clinical relevance. Frontiers of Immunology. 2019, 9/article 3160 https://www.frontiersin.org/articles/10.3389/fimmu.2018.03160/full

4. Bergman P, Lindh A, Bjorkhem-Bergman, Lindh J. Vitamin D and respiratory tract infections: A systemic review and meta-analysis of randomized controlled studies. PLOS (peer-reviewed, open access journal). 2013; 8(6):e65835 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3686844

Vitamin D and Covid-19 Studies

The first indication that the low vitamin D blood levels may impact Covid-19 patients emerged in an **April 2020 publication.**

Led by Northwestern University, the research team conducted a statistical analysis of data from hospitals and clinics across China, France, Germany, Italy, Iran, South Korea, Spain, Switzerland, the United Kingdom (UK) and the United States.

The researchers noted that patients from countries with high COVID-19 mortality rates, such as Italy, Spain, and the UK, had lower levels of vitamin D compared to patients in countries that were not as severely affected.

Lead researcher Vadim Backman and his team chose to examine vitamin D levels after noticing unexplained differences in COVID-19 mortality rates from country to country.

Some hypothesized that differences in healthcare quality, age distributions in population, testing rates or different strains of the coronavirus might be responsible.

But Backman remained skeptical, stating, "**None of these factors appears to play a significant role." "The healthcare system in northern Italy is one of the best in the world. Differences in mortality exist even if one looks across the same age group**.

And, while the restrictions on testing do indeed vary, the disparities in mortality still exist even when we looked at countries or populations for which similar testing rates apply. "**Instead, we saw a significant correlation with vitamin D deficiency,"** he said.

- **Of note is the fact that low vitamin D levels were also associated with poorer outcomes during the SARS epidemic (2003), which was also a coronavirus.**

Who Is At Risk?

1. **Older subjects**, especially those **over 80 years old**, are in a high-risk category for vitamin D deficiency in many developed countries. They **make less vitamin D in their skin** upon sunlight and their **kidneys convert less 25OH vitamin D into 1,25 diydroxy vitamin D**. You **can't make vitamin D through a windowpane,** although it can cause photo-aging and skin damage linked to skin cancer.

2. **Darker-skinned individuals –** especially those who live in regions within developed countries that are above or below the 40th degree latitude tend have lower vitamin D blood levels**. From October and May** the wave lengths from the sun required to make vitamin D in our skin does not reach the earth during the winter months if live in these zones. The situation appears worse for darker-skinned individuals who often have lower vitamin D blood levels year-round due to higher amounts of melanin pigment in the skin, which blocks UV-light from generating vitamin D synthesis in the skin.

3. Overweight individuals - especially many type 2 diabetics. This is because **vitamin D is a fat-soluble vitamin, and thus it gets stored in fat tissue**. The more fat you have on your body, the more vitamin D you store in your fat cells and thus, lower amounts circulate through the bloodstream.

Overweight subjects also tend to **secrete more inflammatory cytokines from their fat cells, known as adipokines, which also lower circulating vitamin D blood levels.**

These sub-groups of people (as well as those other with other chronic inflammatory conditions, such as **autoimmune disease patients**) **tend to have lower vitamin D levels** and have been shown to be susceptible to more severe and more life-threatening coronavirus infections outcomes.

The authors of a study (Irish Medical Journal – April 2020) state the following," **the authors propose that, whereas optimizing vitamin D levels will certainly benefit bone and muscle health, the data suggests that it is also likely to reduce serious COVID-19 complications.**

This may be because vitamin D is important in regulation and suppression of the inflammatory cytokine response, which causes the severe consequences of COVID-19 and 'acute respiratory distress syndrome' associated with ventilation and death".

Reference:

Ali Daneshkhah, Vasundhara Agrawal, Adam Eshein, Hariharan Subramanian, Hemant Kumar Roy, Vadim Backman. The Possible Role of Vitamin D in Suppressing Cytokine Storm and Associated Mortality in COVID-19 Patients. *medRxiv*, Posted April 30, 2020
https://www.medrxiv.org/content/10.1101/2020.04.08.20058578v3

The Seneca Study, Vitamin D and Covid-19

The Seneca study showed that the average vitamin D blood level in older individuals in Spain is 26 nmol/L (10.4 ng/mL) and in Italy it's 28 nmol/ (11.2 ng/mL), whereas higher levels of 45 nmol/L (18 ng/mL) are found in Nordic countries.

In Switzerland, the average vitamin D level is 23 nmol/L (9.2 ng/mL). In nursing homes and in **Italy 76% of women over 70 years of age have vitamin D levels below 30 nmol/L (12 ng/mL).** These are the countries with high number of cases of COVID-19 and the aging population is the group with the highest risk for morbidity and mortality from the Covid-19 virus.

The researchers state that vitamin **D deficiency is a major public health problem worldwide in all age groups**, but vitamin D status deteriorates with age, **above 70 years** of life, due to decreased sun exposure and decreased ability of the skin to synthesize vitamin D from sunlight exposure.

Vitamin D status is especially poor in institutionalized people (people in nursing homes) 75% of them being severely vitamin D deficient, with blood vitamin D levels below 25 nmol/L (10 ng/mL).

- They also state that **Southern European countries** have lower blood levels of vitamin D, compared to Northern European countries because of decreased sun exposure (**prefer the shade in strong sun) and they tend to have darker skin**, compared to Northern Europeans), which reduces the amount of vitamin D made in the skin upon exposure to sunlight.

- **Northern Europe's average vitamin D blood levels are higher** because they know that they don't get adequate sunlight enough of the year to synthesize required amounts of vitamin D to prevent osteoporosis, so **they consume cod liver oil, and they take vitamin D supplements (which are very inexpensive) and they fortify their milk and milk products with vitamin D (Finland).**

Reference: Petre Cristian Ilie, Simina Stefanescu, Lee Smith. **The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality**. *Aging Clinical and Experimental Research*, 2020. https://link.springer.com/article/10.1007/s40520-020-01570-8

Studies like these prompted a **Spanish Hospital Study to be undertaken whereby 76 consecutive patients with laboratory confirmed Covid-10 cases, who were admitted to the hospital, were provided with standard medical treatment for Covid-19, but 50 of them were given vitamin D supplementation and 26 were not given vitamin D.**

The study was done using a computer-generated randomized approach, as to who received vitamin D and who did not, to eliminate risk of doctor bias.

The results showed that of the 26 patients who did not receive vitamin D supplementation, fifty percent of them (13) had their infection progress to the point where they required admission to the intensive care unit and two of them ultimately died. Of the 50 patients treated with vitamin D, only one required admission to the intensive care unit and none of them died.

- **The positive results of the study have prompted a larger, multi-center trial, involving 15 hospitals across Spain, to be undertaken immediately.**

- The new study will treat Covid-19 patients with either vitamin D or no vitamin D, concurrently with other standard treatments for Covid-19 that are approved in that country - which by the way include the use of hydroxychloroquine and azithromycin, and in patients with pneumonia, the addition of a broad-spectrum antibiotic.

- For patients on ventilators the steroid drug dexamethasone is also used, as it has been shown to reduce mortality in hospitalized patients with Covid-19, who are on respiratory assistance

Reference: Castillo ME et al. Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot study. J Biochem Mol Biol. 2020; 203:105751
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7456194/

NIH Feb 3, 2021 Vitamin D and Covid-19

- “Indeed, it has been estimated that **each degree of latitude north of 28 degrees corresponded to a 4.4% increase of COVID-19 mortality**, indirectly linking a person’s vitamin D levels via exposure to UVB light to COVID-19 mortality [133].”

- “**Indeed, serum concentrations of 25-hydroxyvitamin D above 30 ng/ml (75 nmol/L), which indicate vitamin D sufficiency, seems to be associated with a reduction in serum C-reactive protein, an inflammatory marker, along with increased lymphocyte levels, which suggests that vitamin D levels may modulate the immune response by reducing risk for cytokine storm in response to SARS-CoV-2 infection** [142].”

- “**A study in India determined that COVID-19 fatality was higher in patients with severe COVID-19 and low serum 25-hydroxyvitamin D (mean level 6.2 ng/ml – 15.5 nmolL) levels versus asymptomatic non-severe patients with higher levels of vitamin D (mean level 27.9 ng/ml- 70 nmol)** [143].

- In the same study, vitamin D deficiency was associated with higher levels of inflammatory markers including IL-6, ferritin, and tumor necrosis factor α. Collectively, these studies add to a multitude of observational studies reporting potential associations between low levels of 25-hydroxyvitamin D and COVID-19 incidence and severity [136,141,142,144,145,146,147,148,149,150].”

- **“Both Public Health England and Public Health Scotland have advised members of the Black, Asian, and minority ethnic communities to supplement for vitamin D in light of evidence that they may be at higher risk for vitamin D deficiency along with other COVID-19 risk factors, a trend that has also been observed in the United States** [172,173].”

Reference: Lordan R et al. Dietary Supplements and Nutraceuticals Under Investigation for Covid-19 Prevention and Treatment. National Institutes of Health Preprint Pilot. Feb 3, 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7872359/

U.K Government Sending Vitamin D Supplements to High-Risk Elderly

- In November 2020, the UK Government announced they are offering 2.5 million people living in Care homes in England, free shipments of 4-month supply of Vitamin D Supplements (400 IU/d)

- They claim that it is to help prevent bone loss and osteoporosis, but they have seen the evidence on low Vitamin D and Covid-19 mortality.

- The Guardian States, “Research is ongoing to investigate the link between vitamin D and Covid-19 protection, including a project at Queen Mary University of London investigating if correcting people’s vitamin D deficiencies over winter can reduce the risk and/or severity of Covid-19 and other acute respiratory infections. “

References:

https://www.theguardian.com/society/2020/nov/28/more-than-25m-people-in-england-to-get-free-vitamin-d-supply

https://www.gov.uk/government/publications/vitamin-d-for-vulnerable-groups/vitamin-d-and-care-homes-guidance

3 Meta-Analysis Show Vitamin D Supplementation Would Reduce 30,000 Cancer Deaths Per Yr in Germany (Feb. 2021 Study Molecular Oncology)

- In recent years, three meta-analyses of clinical studies have come to the conclusion that vitamin D supplementation was associated with a reduction in the mortality rate from cancer of about **13 percent**

- Scientists at the German Cancer Research Center (DKFZ) have now transferred these results to the situation in Germany and calculated: **If all Germans over the age of 50 were to take vitamin D supplements, up to 30,000 cancer deaths per year could possibly be avoided and more than 300,000 years of life could be gained -- in addition, health care costs could be saved**.

- The scientists based this calculation on **a daily administration of 1,000 international units of vitamin D** at a cost of 25 euros per person per year. In 2016, approximately 36 million people over the age of 50 lived in Germany, resulting in annual supplementation costs of 900 million euros.

- Factoring in a reduction in cancer care costs of **13% fewer cancers per year, this model calculates an annual saving of €254 million if citizens over 50 were provided with 1,000 IU Vitamin D per day**.

Reference:

- Tobias Niedermaier, Thomas Gredner, Sabine Kuznia, Ben Schöttker, Ute Mons, Hermann Brenner. Vitamin D supplementation to the older adult population in Germany has the cost-saving potential of preventing almost 30,000 cancer deaths per year. *Molecular Oncology*, 2021 https://febs.onlinelibrary.wiley.com/doi/10.1002/1878-0261.12924

March 21, 2021: Annual U.S Endocrine Society Meeting

- Annual Endocrine Society Annual meeting on March 21, 2021, reported that patients with low vitamin D levels, who were hospitalized for COVID-19, had a lower risk of dying or requiring mechanical ventilation if they received vitamin D supplementation of at least 1,000 units weekly.

- They studied involved 124 adult patients with low vitamin D blood levels, which was measured up to 90 days prior to their admission to the hospital for COVID-19. Researchers compared the patients who were supplemented with at least 1,000 units of vitamin D weekly to those who had not received vitamin D supplements in terms of whether they were mechanically ventilated or died after admission to hospital.

They found that patients who were supplemented with at least 1,000 IU of vitamin D weekly were less likely to be mechanically ventilated or to die following hospital admission for Covid-19.

They also found that more than half of the patients with low vitamin D levels, who should have been recommended to take vitamin D supplements by their doctor, were not told to do so

Reference: https://www.sciencedaily.com/releases/2021/03/210321215452.htm

April 14, 2021, Spanish Society of Geriatrics and Gerontologists
Position Statement: Vitamin D

- They state that vitamin D receptors are expressed by most immune cells, including B-lymphocytes, T-lymphocytes, monocytes, macrophages and dendritic cells and that vitamin D stimulation of these immune cells produces anti-inflammatory effects, which help suppress the cytokine storm that typically causes death to occur in advanced Covid-19 cases.

- They also reinforce the fact that vitamin D also is required for certain immune cells (dendritic and T-T-reg cells) to fully mature and respond in appropriate ways to help ward off and fight viral and other infections. They state that, in this context, some studies have reported that vitamin D treatment could be useful for the prevention and treatment of COVID-19:

- They go on to state that some preliminary studies have already shown promising results with vitamin D supplementation in hospitalized COVID-19 patients.

- They cite a meta-analysis study showing a lower mortality rate in patients given vitamin D supplementation (10.6%) compared to controls (23.9%). Two retrospective studies included in this meta-analysis showed a decrease in the Clinical Symptom Score (WHO Ordinal Scale for Clinical Improvement) in the patients treated with vitamin D, and a third study demonstrated a lower rate of admission in intensive care units for Covid-19 patients given vitamin D supplements.

- A fourth study cited showed a significant decrease in serum fibrinogen levels in Covid-19 patients given vitamin D supplements. As a rule, lower fibrinogen blood levels translate into a lower risk for developing abnormal blood clots and blood vessel inflammation.

- Another study showed that patients with low blood levels of vitamin D, who were administered vitamin D supplements within a month before contracting Covid-19, had less severe symptoms, better recovery and a lower risk of mortality than patients identified with low vitamin D blood levels who were not recommended to take vitamin D by their doctors, and who subsequently contracted Covid-19 within the next month.

- Based on the available evidence the **Spanish Society of Geriatrics and Gerontologists have established recommendations for vitamin D supplementation for patients testing positive for Covid-19**. The vitamin D recommendations are based on the patient's vitamin D blood level; the lower the patient's blood level of vitamin D, the more aggressive is the vitamin D supplementation protocol. (see protocol next slide)

Blood Level - 25 Hydroxycholecalciferol in Covid-10 Patients and Recommended Oral Doses of Cholecalciferol (Regular Vitamin D Supplements):

- Blood Level Less than 10 ng/mL = 25 nmol/L - 8 weeks – 7,000 IU/d; then 3,500 IU/d for 8 weeks

- Blood Levels between 11-20 ng/ml (27.5 – 50 nmol/L) – 2 weeks – 7,000 IU/d; then 3,500 IU/d for 14 weeks

- Blood Levels between 21-29 ng/ml (52.5 – 72.5 nmol/L) – 4 weeks – 7,000 IU/d, then 3500 IU/d for 12 weeks

- Blood Levels between 30 – 40 ng/ml (75 – 100 nmol/L) – Single Dose – 50,000 IU; Later 3,500 IU/d for 12 weeks

- Blood Level between 41-60 ng/ml (102.5 – 150 nmol/L) – 25,000 IU biweekly for 12 weeks

Reference: Vitamin D supplementation for the prevention and treatment of COVID-19: a position statement from the Spanish Society of Geriatrics and Gerontology https://www.sciencedirect.com/science/article/pii/S0211139X21000044?via%3Dihub

Probiotics and Immunity

- Probiotics are live microorganisms (specific strains of friendly gut bacteria and yeast) that may improve health by bolstering local and systemic immunity.

- Their mechanism of action is thought to occur through **enhanced phagocytic capacity and activity, stimulation of higher levels of specific immunoglobulins, and enhancement of gut barrier functions.**

- Probiotics **have increased the levels of immunoglobulin A**, which is a key antibody that protects the respiratory passages and the intestinal tract against infectious agents, including viruses.

Reference: Long JD and Morris. Probiotics in preventing acute upper respiratory tract infections. A. American Journal of Nursing. Dec 2017
https://journals.lww.com/ajnonline/Fulltext/2017/12000/Probiotics_in_Preventing_Acute_Upper_Respiratory.37.aspx

- As outlined in a review paper in the journal Current Opinion in Gastroenterology, "**probiotics showed therapeutic potential for diseases, including** several immune response-related diseases, such as allergy, eczema, **viral infection, and potentiating vaccination responses.**"

- Researchers cite studies showing that **probiotics regulate our innate and adaptive immune responses by modulating the functions of dendritic cells, macrophages, and T and B lymphocytes**.

- Reference: Yan F and Polk DB. Probiotics and immune health. Curr Opin Gastroenterol. October 2011. https://www.ncbi.nlm.nih.gov/pubmed/21897224

- **With respect to probiotics and upper respiratory tract infections**, the **Cochrane Review of 12 trials** were included in a recent meta-analysis, and data from **3,720 participants** in randomized controlled studies conducted between 2002 and 2013, involving **eight different countries, were analyzed**.

- The researchers concluded the following, "**probiotics were found to be more effective than placebo—reducing the number of participants who experienced episodes of acute URTI by about 47% and the duration of an episode by about 1.89 days.**

- Probiotics also slightly reduced antibiotic use and cold-related school absences.

- In older adults, although probiotics did not reduce the rate of URTIs, the **duration of the infection was decreased.**

- Subgroup analysis of all age groups suggest that probiotics **reduced the number of children experiencing acute URTIs.**

- Overall, probiotics were found to be safe with few adverse effects (mostly gastrointestinal symptoms).”

- These studies included a variety of different probiotic combinations, and thus, it is **difficult to know what combination** of live bacteria and yeast are the most ideal. In fact, no one knows, at this point in time, what the most ideal probiotic combination should be.

Reference: Long JD and Morris. Probiotics in preventing acute upper respiratory tract infections. A. American Journal of Nursing. Dec 2017
https://journals.lww.com/ajnonline/Fulltext/2017/12000/Probiotics_in_Preventing_Acute_Upper_Respiratory.37.aspx

Below is a list of various lactobacillus, bifidus, and streptococcal bacterial strains that show impressive probiotic results in clinical studies, along with the yeast species – Saccharomyces cerevisiae:

List of Promising Probiotics:

- Lactobacillus such as L. acidophilus, L rhamosus, rheuteri. L. plantarum. L casei. L. salivarius
- Bifidobacterium, such as B. bifidum, B. animalis, B. breve, B. longum
- Streptococcus thermophilus
- The yeast species – Saccharomyces cerevisiae

You may want to consider a **probiotic supplement containing a mixture** of these impressive probiotic species, in a form that provides 2 – 10 billion living microorganisms per day.

References: Yan F and Polk DB. Probiotics and immune health. Curr Opin Gastroenterol. October 2011. https://www.ncbi.nlm.nih.gov/pubmed/21897224

4 Other Immunity Superstars

Synergistic Effects of Medicinal Mushrooms, Astragalus, Milk Thistle and Indole-3-Carbinol On Immune System Function

Medicinal Mushrooms and Immunity

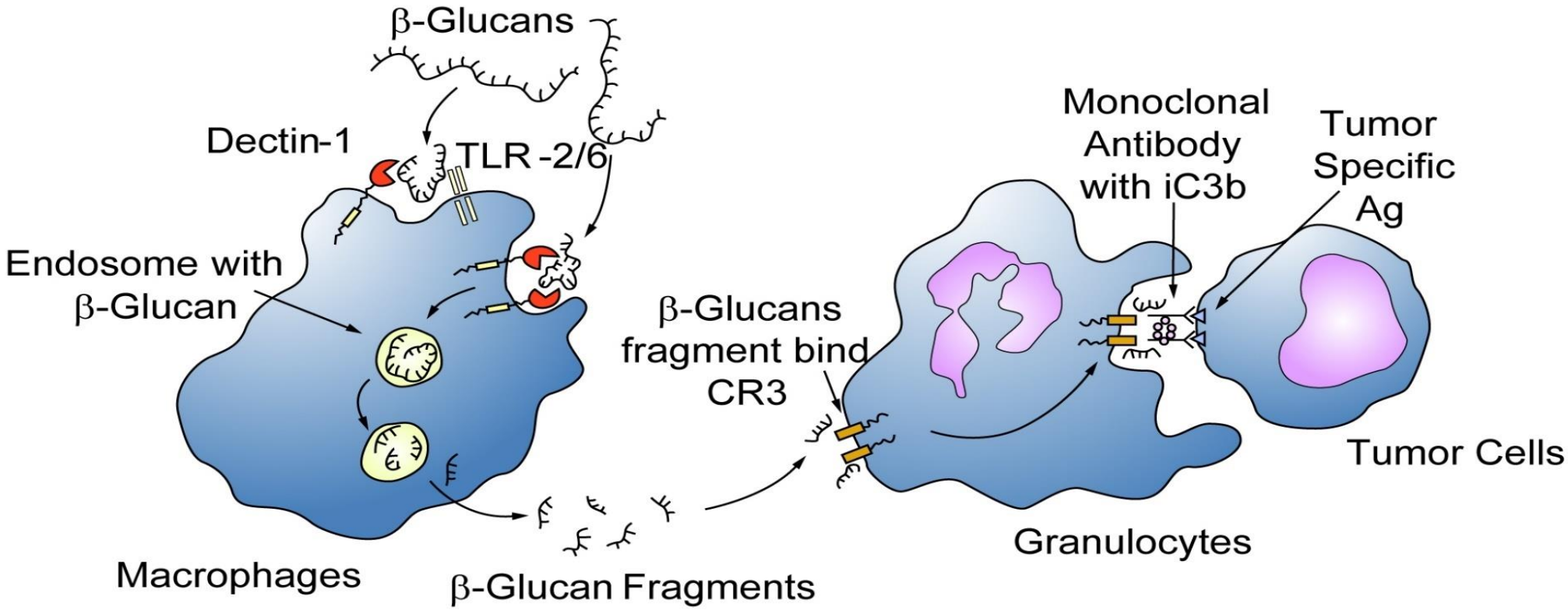
Reishi Mushroom Extract and other Medicinal Mushrooms **(Shiitake, Maitake, Cordyceps, Trametes Versicolor, Turkey Tail and others)**

- **Medicinal mushrooms contain unique ingredients (beta-D-glucans, triterpenoids and ergosterol).** Analytical method show that especially beta-glucans can not only stimulate immune cells to work more efficiently, but **they fit perfectly into immune cell receptors** (i.e macrophages in the gut) – SEE NEXT SLIDE

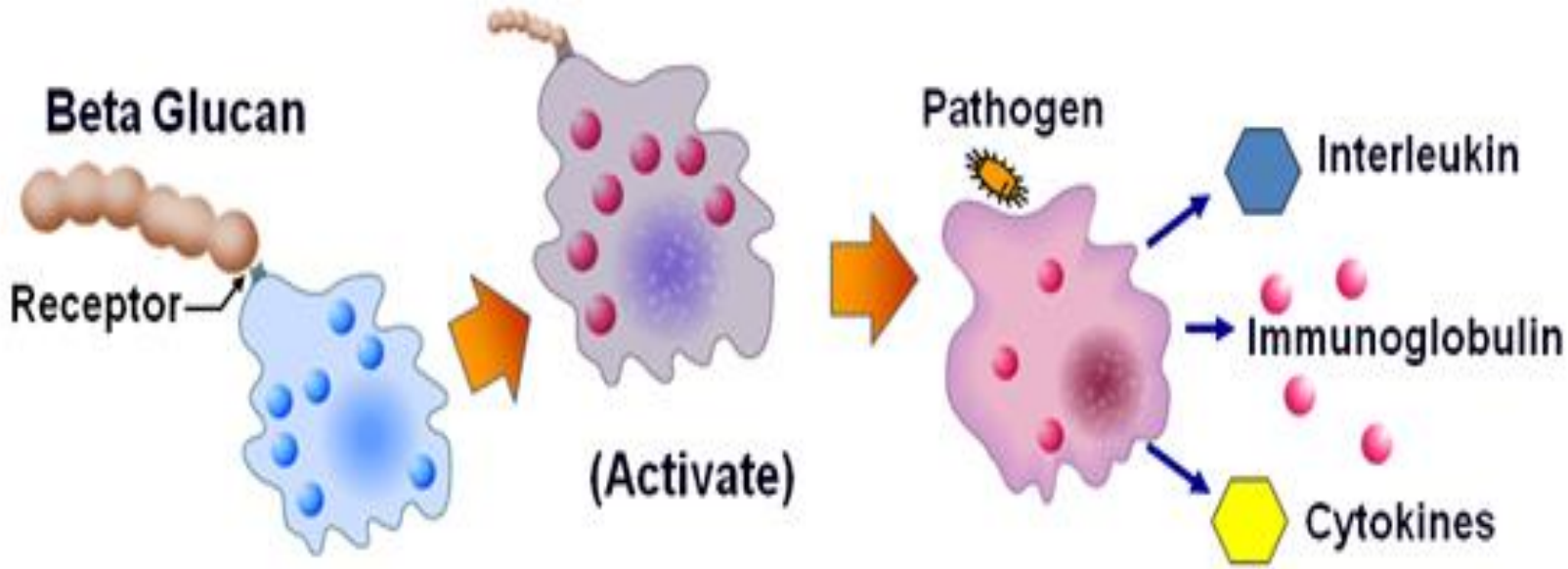
- The binding of these constituents to the immune cell receptors **generates a response from the immune cell that heightens and greatly optimizes its ability to combat foreign viruses, bacterial and cancer cells.**

- As one of the researchers stated, **"(Medicinal) Mushrooms have been shown to have the ability to stimulate the immune system, modulate humoral and cellular immunity, and potentiate antimutagenic and antitumorigenic activity, as well as rejuvenating the immune system weakened by radiotherapy and chemotherapy in cancer treatment".**

Medicinal Mushrooms – beta-glucans and macrophage receptors



How Does Beta Glucan Work?



Macrophage activation via cell surface receptor

The research review papers listed below are a worthwhile read to gain a more in-depth understanding of medicinal mushrooms and immunity:

1. Alena G. Guggenheim, ND; Kirsten M. Wright, BS; Heather L. Zwickey, PhD Immune Modulation From Five Major Mushrooms: Application to Integrative Oncology. Integrative Medicine Vol 13 No 1. February 2014
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4684115/

2. Cristina Lull,1 Harry J. Wichers,1 and Huub F. J. Savelkoul. Antiinflammatory and Immunomodulating Properties of Fungal Metabolites. Mediators of Inflammation 2005: 63-80

3. Peter Amwoga Ayeka. Potential of Mushroom Compounds as Immunomodulators in Cancer Immunotherapy: A Review. Evidence-Based Complementary and Alternative Medicine Volume 2018 (9 pages)

Astragalus and Immunity

- The Memorial Sloan Kettering Cancer Centre website does a great job of summarizing the research on Astragalus. They cite studies showing that medicinal constituents in astragalus can **boost immune system competency** and **exert direct anti-viral effects.**

Reference: Memorial Sloan Kettering https://www.mskcc.org/cancer-care/integrative-medicine/herbs/astragalus

- A 2012 review of all astragalus studies showed the many ways that astragalus enhances immune system function, including **boosting the release of interferon and interleukin-2 from key immune cells, which are well established strong boosters of immune function.**

Reference: Zhuge Z-Y, Zhu Y-H, Liu P-Q, Yan X-D, Yue Y, Weng X-G, et al. (2012) Effects of Astragalus Polysaccharide on Immune Responses of Porcine PBMC Stimulated with PRRSV or CSFV. PLoS ONE 7(1): e29320. **https://doi.org/10.1371/journal.pone.0029320**

Milk Thistle and Immunity

- The herb Milk thistle has also shown **impressive immune-modulating properties** in recent years. Milk thistle has primarily been used to **support liver detoxification** function and to help repair damaged liver cells, if the damage is not beyond repair.

- But the silymarin flavonoid in Milk thistle also shows immune modulation properties. It **increases lymphocyte proliferation and boosts secretions of immune modulating cytokines, particularly interferon gamma, interleukin-4 and interleukin-10, which are required responses when body is facing a virus that is trying to take hold and start an infection.**

The researchers state, “Our study has uncovered a novel effect of milk thistle on the immune system. **This immunostimulatory effect may be of benefit in increasing the immunity to infectious diseases**”. (1)

1. Medicine and Science Monitor (2002) https://www.ncbi.nlm.nih.gov/pubmed/12444368
2. American Surgery Journal (2002) https://www.ncbi.nlm.nih.gov/pubmed/12412711

Indole-3-Carbinol and Immunity

Indole-3-carbinol

Indole-3-carbinol is a constituent unique to **cruciferous vegetables**, such as broccoli, brussels sprouts, cabbage, cauliflower, Bok choy, and turnips.

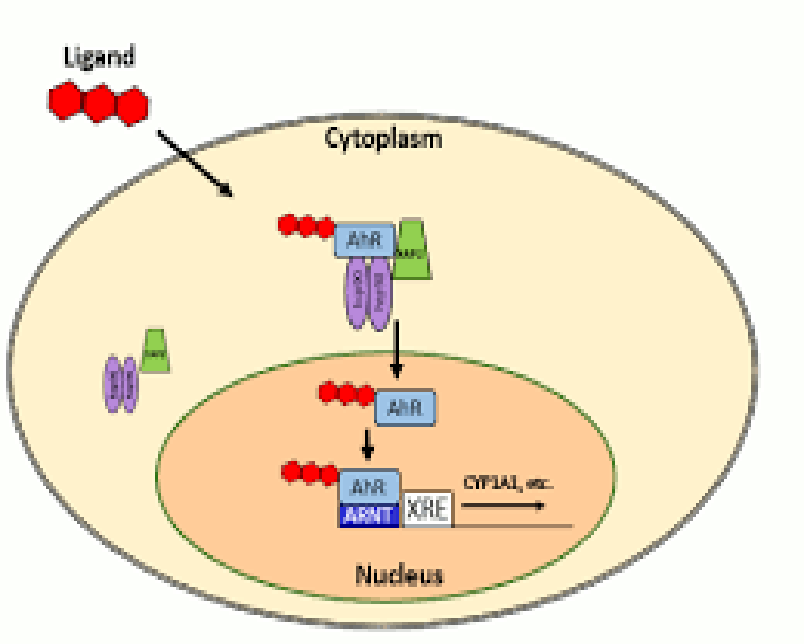
- Supplementation with indole-3-carbinol has been shown to activate **the aryl hydrocarbon receptors on the adaptive immune system, which stimulates immune cells to better respond to and fight any virus or foreign cell that enters the body**.

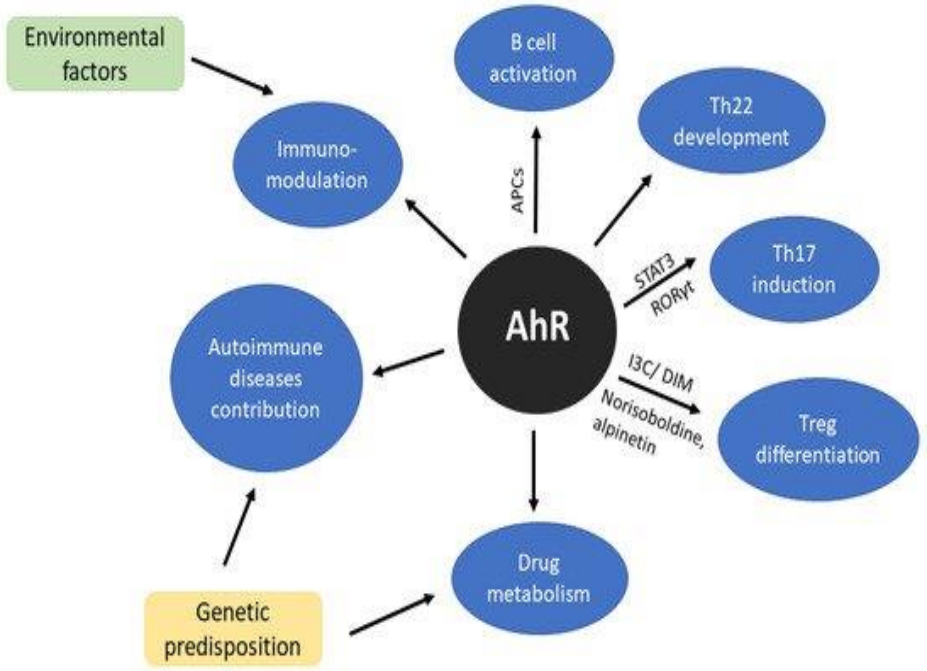
- More specifically, it **helps the T-lymphocytes proliferate faster and improves the ability of other immune cells to ingest and devour any threatening viruses or bacteria that is deemed threatening to the body.**

PHARMACOLOGICAL REVIEWS Pharmacol Rev 65:1148–1161, October 2013 Aryl Hydrocarbon Receptor Control of Adaptive Immunity
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3799235/pdf/pr.113.007823.pdf

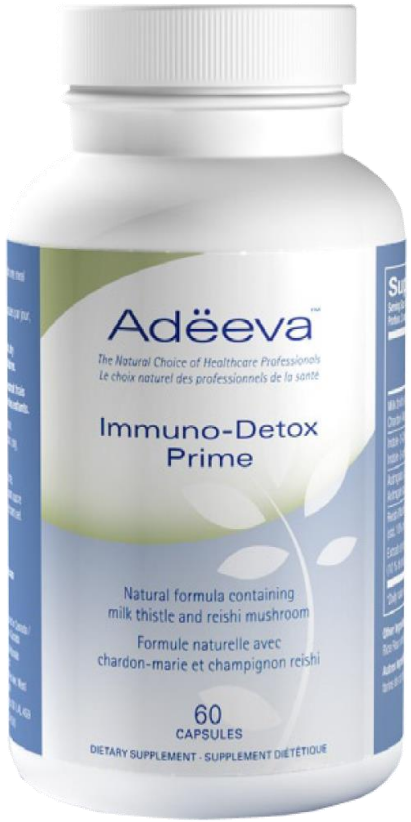
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5743052/pdf/nihms823331.pdf

Indole-3-Carbinol Binds to Aryl Hydrocarbon in Immune Cells, Prompting this Transcription Factor to Translocate to the Nucleus and Affect Key Genes in Adaptive Immunity





Adeeva Immune and Detox Support Supplement



1. Reishi Mushroom Extract – 60 mg (std to 10% polysaccharide and 4% terpene content)
2. Astragalus – 200 mg (2:1 extract)
3. Milk Thistle – 300 mg (std to 80% silymarin)
4. Indole-3-Carbinol – 50 mg

Normally: Recommend that people over 50 yr. take 2 capsules per day, but during Pandemic it may help those younger than 50 yr as well.

At first signs of symptoms, I would take 4 capsules, twice or three times daily.

Melatonin and Immunity

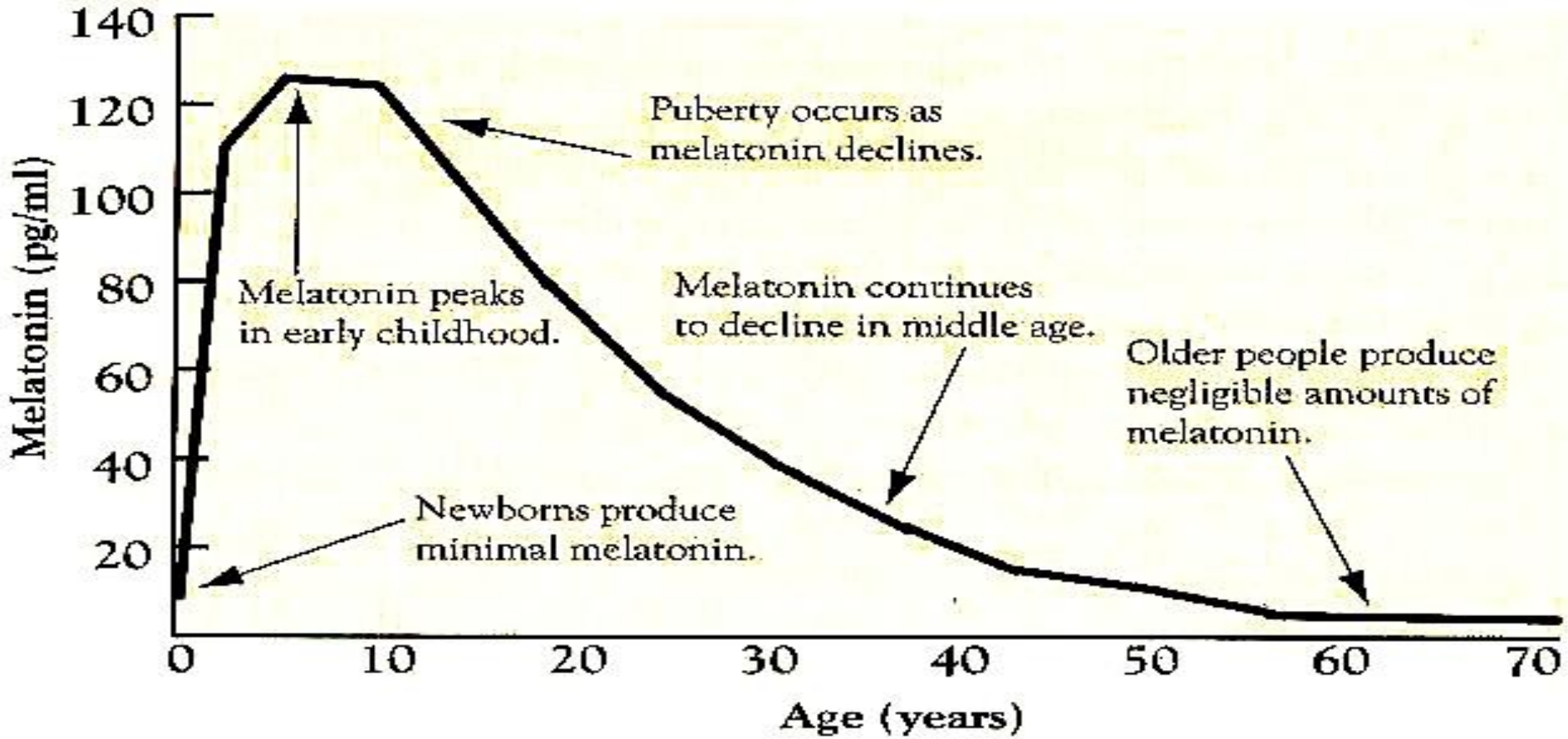
The **age-related decline in** melatonin secretion appears to be part of the reason that our **immune function also declines** in the aging process, a condition known as immuno-senescence.

Studies show that **T-lymphocytes known as CD4 cells (T-helper cell), have melatonin receptors.**

With decline in melatonin levels in aging, there is less CD4 cell modulation by melatonin and the immune system becomes weaker and less efficient.

Experimental studies show that many immune parameters improve to more youthful function when melatonin is administered to aging animals. The same is likely true in humans

Age-Related Decline In Melatonin



Melatonin Receptors on T-Helper Cells (CD4 Cells)

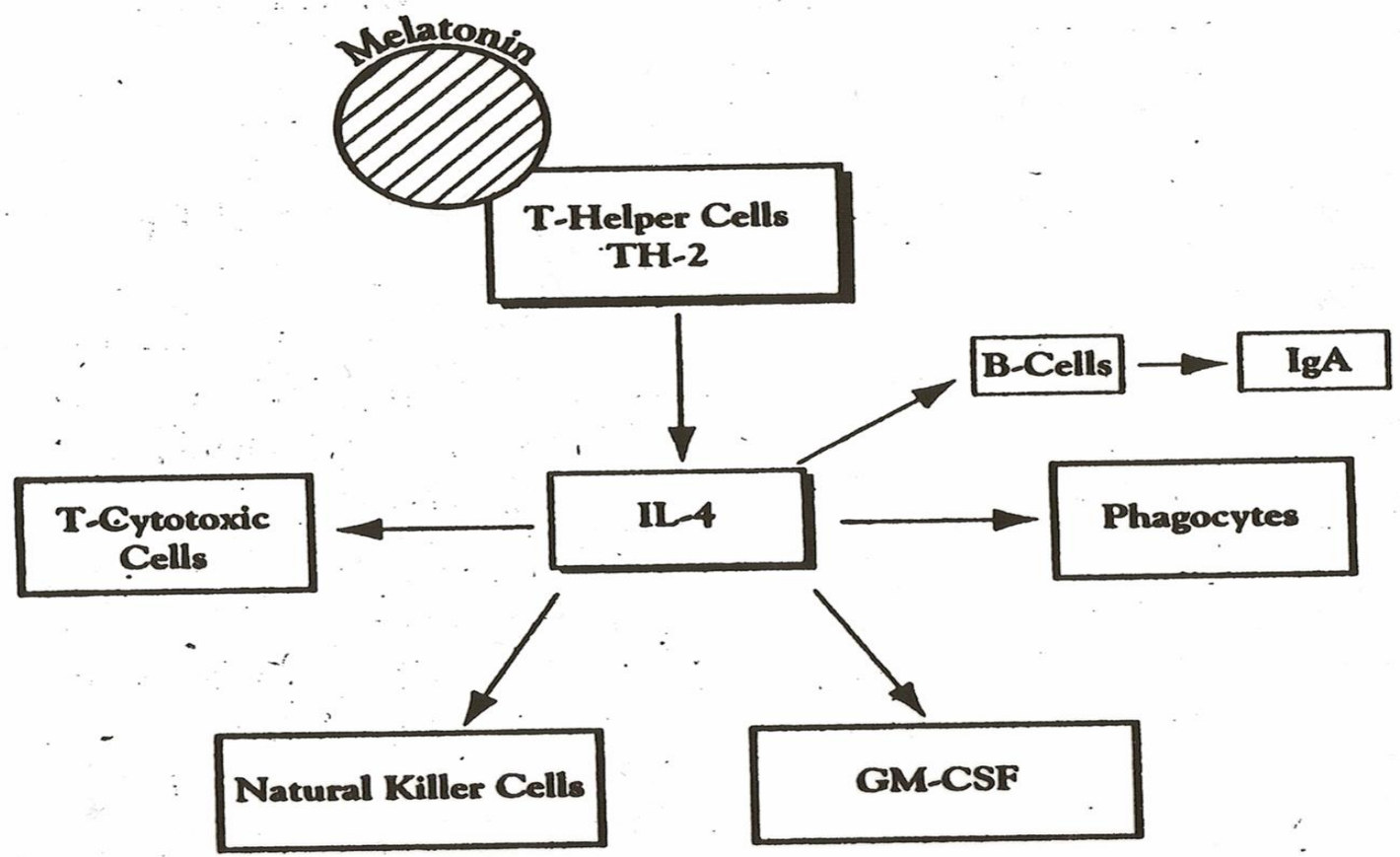


Figure 7. **Melatonin Stimulates T-Helper Cells**

Melatonin Receptors on T-Helper Cells (CD4 Cells)

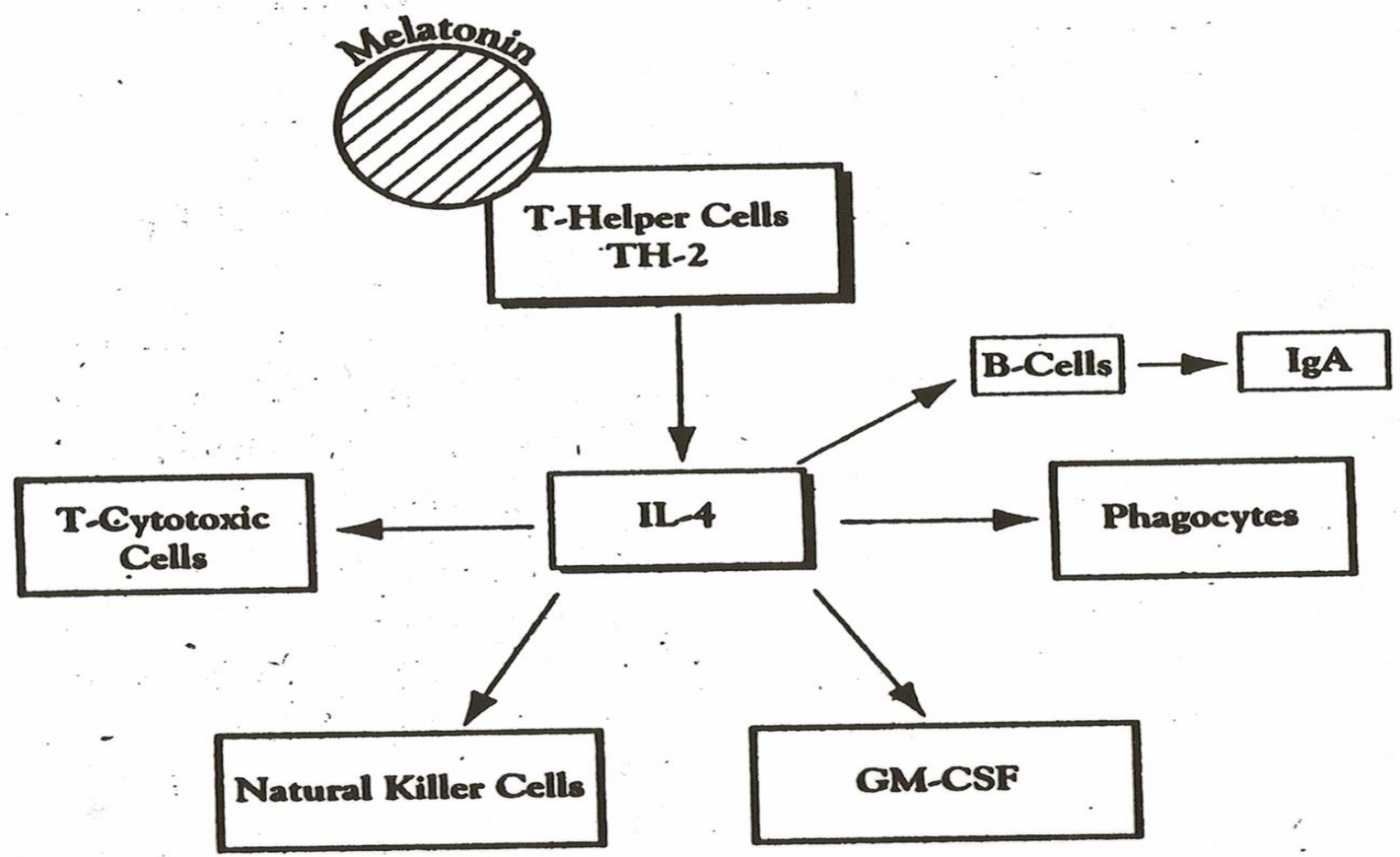


Figure 7. **Melatonin Stimulates T-Helper Cells**

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4946322/

J Biomed Res. 2016 Jul; 30(4): 314–321.
Published online 2016 May 20. doi: 10.7555/JBR.30.2016K0010
PMCID: PMC494632
PMID: 27533940

Pharmacological advantages of melatonin in immunosenescence by improving activity of T lymphocytes

Yeong-Min Yoo,[1,Δ] Su Kil Jang,[2,Δ] Gwang-Hoon Kim,[2] Jung-Youl Park,[3] and Seong-Soo Joo[2,✉]

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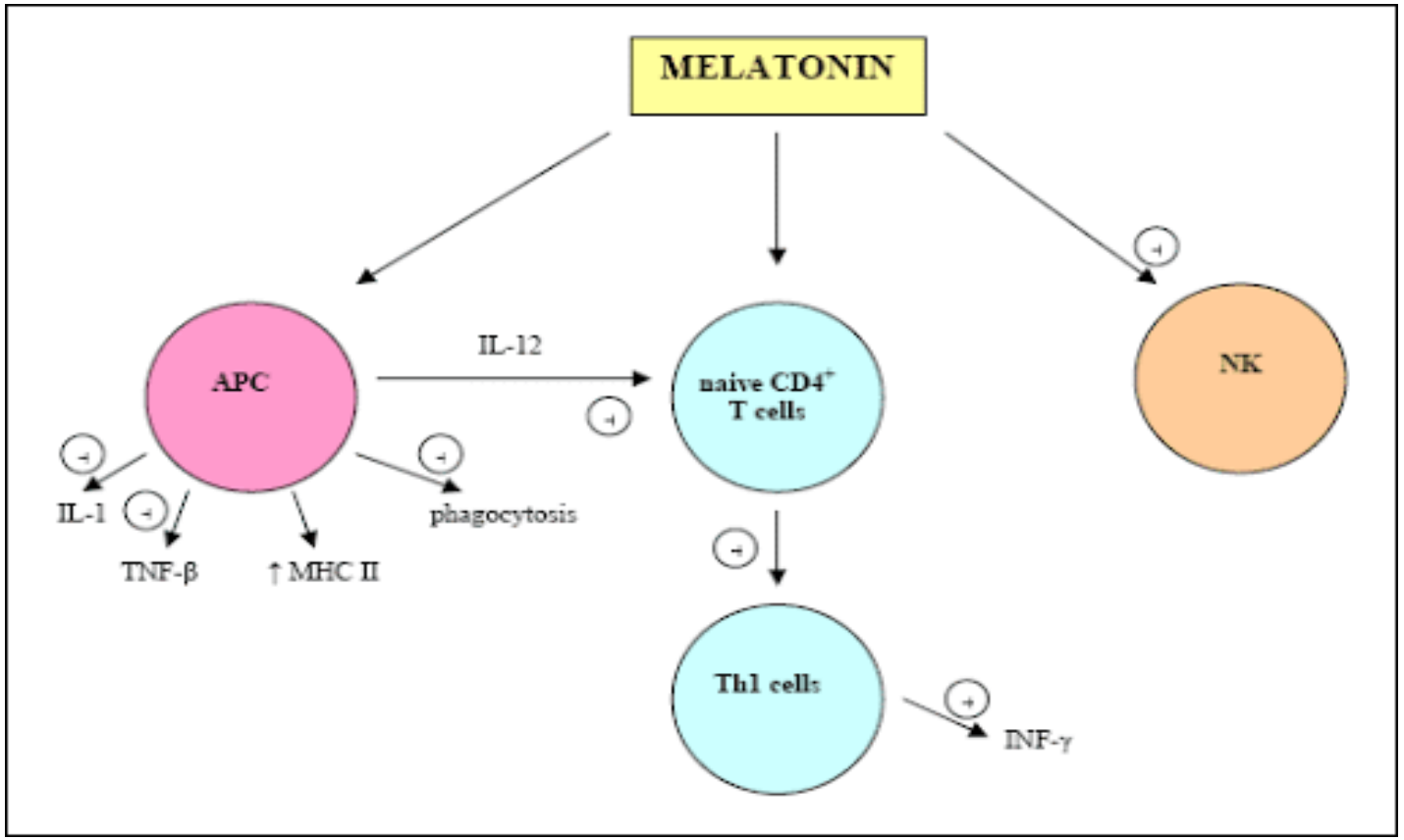
Abstract

Go to:

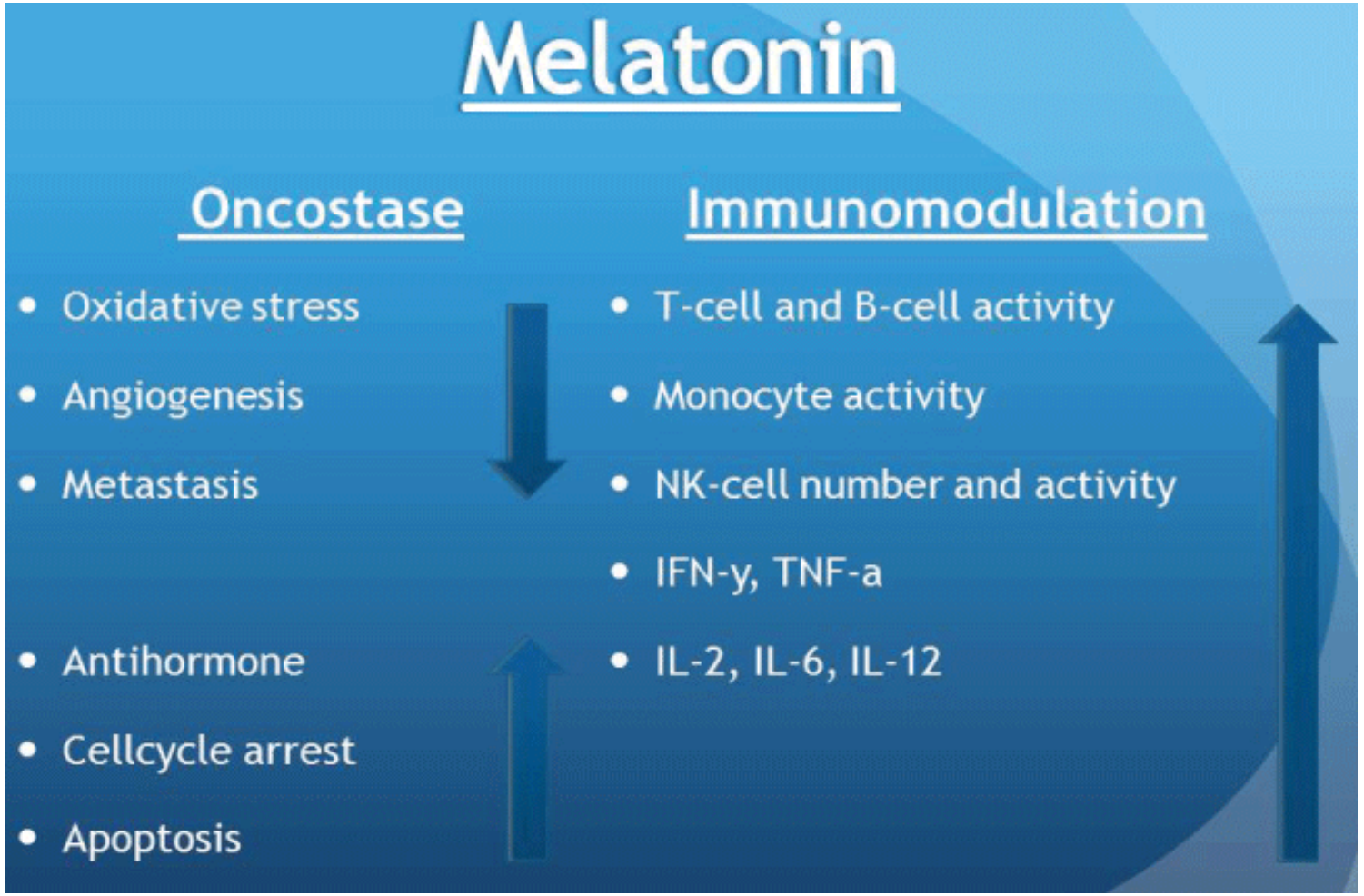
Melatonin plays a critical role in regulating photoperiodic signals and has recently been shown to decrease immunosenescence with age. In this study, we examined whether melatonin activates T lymphocytes as major adaptive immune cells in *in vitro* and *in vivo* models. Splenocytes, $CD4^+$, and naïve CD4 T lymphocytes were isolated from the spleen of BALB/c mice and the cell population patterns and mRNA profiles associated with T cell activation (CD28 and p21) and the melatonin receptor (MT1A and MT1B) were assessed. The T cell activation-related proteins Ki67 and Bcl2 were also evaluated to confirm the relationship between gene and protein levels. Our data clearly revealed that CD28, p21, MT1A, and MT1B mRNA were highly expressed in the presence of melatonin. Co-culture of $CD4^+$ T lymphocyte and peritoneal macrophage 7 days after melatonin administration to young and aged mice significantly increased APRIL mRNA, suggesting induction or maintenance of T lymphocyte responses. We also found that the intracellular amount of Ki67 and Bcl2 proteins were significantly upregulated in aged $CD4^+$ T lymphocytes, suggesting enhancing T cell proliferation and ling-term maintenance of memory T cells. Taken together, we conclude that melatonin supplementation may enhance immunity in aged individuals by upregulating immunosenescence indices in association with T lymphocytes and may be an attractive pharmacological candidate for aged and immunocompromised individuals.

Keywords: melatonin, aging, $CD4^+$, naïve CD4, melatonin receptor

Melatonin and its influence on immune System Review article http://jpp.krakow.pl/journal/archive/12_07_s6/articles/09_article.html



The influence of melatonin on immune system function and cancer: Int j cancer clin res.2015 https://clinmedjournals.org/articles/ijccr/international-journal-of-cancer-and-clinical-research-ijccr-2-024.php?jid=ijccr



NIH Feb, 3 2021 Melatonin and Covid-19

- “Melatonin is another supplement that has been identified as a potential antiviral agent against SARS-CoV-2 using computational methods [235], and it has also been highlighted as a potential therapeutic agent for COVID-19 due to its documented antioxidant, anti-apoptotic, immunomodulatory, and anti-inflammatory effects [68,236,237].

- **Notably, melatonin, vitamin D and zinc** have attracted public attention because they were included in the treatment plan of the **former President of the United States** upon his hospitalization due to COVID-19 [238].”

Reference: Lordan R et al. Dietary Supplements and Nutraceuticals Under Investigation for Covid-19 Prevention and Treatment. National Institutes of Health Preprint Pilot. Feb 3, 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7872359/

L-Glutamine and Immunity

- During exercise L-Glutamine (most prevalent amino acid in blood stream) is shunted to liver and converted into glucose (sugar) and sent to exercising muscles for energy production.

- L-Glutamine is a primary fuel for many immune cells. Thus, during exercise and in post-recovery period the decline in available L-Glutamine shown to weaken immune function, increasing risk of URTI, especially in those training hard.

- As well, high exertional workouts increase Cortisol release, which also weakens immune function and suppresses antibody production for up to 48 hours after workout.

- Studies show that athletes taking L-Glutamine Powder Supplementation (2-5gm) per day, have fewer UTRI than non-supplemented athletes.

Glutamine Clinical Studies References

- Castell, L. M. & Newsholme, E.A. (1998). Glutamine and the effects of exhaustive exercise on the immune response. Canadian Journal of Physiology and Pharmacology, 74: 524-532.

- Castell, L.M., Poortmans, J.R. & Newsholme, E.A, (1996). Does glutamine have a role in reducing infections in athletes? European Journal of Applied Physiology, 73 (5): 488-90.

- Maughan, R. J., Burke, L., Dvorak, J. et al (2018). IOC consensus statement: Dietary supplements and the high-performance athlete. International Journal of Sport Nutrition and Exercise Metabolism, 28: 104-125.

Recent Integrative Medicine Approach by FLCC

Medscape Today – January 6, 2021

- **FLCC = Front Line Covid-19 Critical Care Alliance.** The group -- led by three physicians, are advocates for using the anti-parasitic drug **Ivermectin** to treat Cov-19, and possibly to prevent the infection, in conjunction with supplementation.

- HAT - This group developed the HAT Protocol for Sepsis

- Dr. Marik said the group adapted the HAT protocol for COVID-19, using a more potent steroid and adding an anticoagulant, along with other elements. **The new name was MATH+, for methylprednisolone, ascorbic acid, thiamine, and heparin, plus a statin, zinc, vitamin D, famotidine, melatonin, and magnesium**

- They recently published their observational experience with MATH+ in COVID-19 from two centers. **Results - "The average hospital mortality at these 2 centers in over 300 patients treated is 5.1%, which represents more than a 75% absolute risk reduction in mortality compared to the average published hospital mortality of 22.9% among COVID-19 patients."**

- But since then, some governments and hospitals began using the drug ivermectin in an attempt to prevent or treat COVID-19.

- So arose the group's I-MASK+ protocol, which focuses on **ivermectin, but also includes vitamins C and D, quercetin, zinc, and melatonin for prophylaxis, and adding aspirin;** higher doses of some of the individual components may be used for early outpatient treatment.

Reference: Medscape Today https://www.medpagetoday.com/infectiousdisease/covid19/90552 January 6, 2021

Quercetin Quick Summary:

Thus, Quercetin represents a potential supplement (or IV therapy) **to inhibit viral replication prophylactically and therapeutically.**

But, because it spontaneously oxidizes to QQ, which forms toxic compounds when bound to thiols, and loses it anti-viral properties once oxidized**, co-administration with vitamin C should be strongly considered.**

Vitamin C recycle QQ back to Quercetin antioxidant state; the state in which it shows anti-viral properties.

Reference: https://www.frontiersin.org/articles/10.3389/fimmu.2020.01451/full

Supplementation Consideration:

For every 250 mg of Quercetin supplemented, consider 500 mg of concurrent Vitamin C supplementation, up to a daily max of 1,000 mg Quercetin Supplementation.

Summary and Practical Strategies for Immune Support

1. Mild to Moderate Regular Exercise (Don’t Over Train) – Free Step Tracking App – Play Store: Meschino Wellness

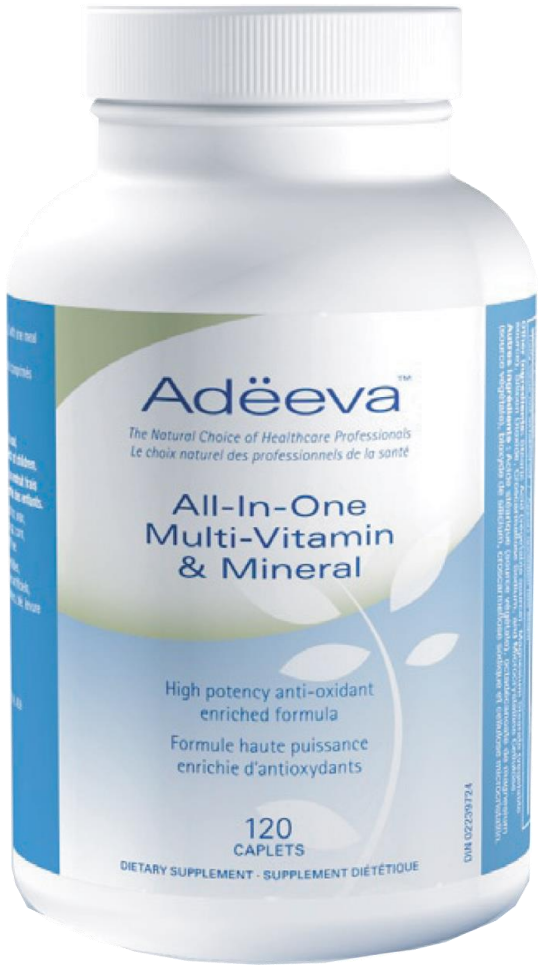
2. Don’t Smoke, Avoid or limit Alcohol and Recreational Drugs that Weaken Immune System, including THC and CBD

3. Get Sufficient Sleep

4. Manage Your Stress (Mind-Body, Hobbies, Other Distractions etc.)

5. Keep your Omega-3 Supplementation limited to 2,000mg per day

Supplement Considerations



1. Adeeva All-in-One Multiple Vitamin and Mineral:

Vitamin C – 1,000 mg

Vitamin E – 400 IU

Selenium – 200 mcg

Zinc – 15 mg

Vitamin D – 1,000 IU

Bioflavonoids – 50 mg

Plus: Vitamin A, Beta-Carotene – 15,000 IU, B-50 complex, A-Zinc formula

Dosage: 2 caplets, twice daily with food (Full Adult Dosage)

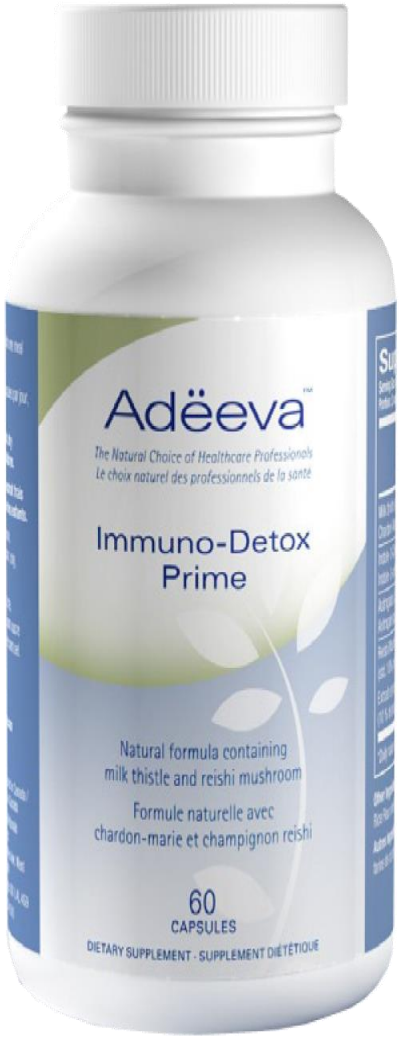
High Potency Multiple Vitamin and Mineral: 2 caplets, twice daily with food provides the following:

All-In-One Multi Vitamin and Mineral		
Vitamin A		2,500 I.U.
Beta Carotene		15,000 I.U.
Vitamin C		1,000 mg
Vitamin D		1000 I.U.
Vitamin E succinate		400 I.U. (natural)
Thiamin		50 mg
Riboflavin		50 mg
Niacin		50 mg
Vitamin B-6		50 mg
Folic Acid		400 mcg
Vitamin B-12		50 mcg
Biotin		300 mcg
Pantothenic Acid		50 mg

High Potency Multiple Vitamin and Mineral Continued

All-In-One Multi Vitamin and Mineral Continued		
Calcium		500 mg
Iron		6 mg
Magnesium		200 mg
Zinc		15 mg
Selenium		200 mcg
Copper		2 mg
Manganese		5 mg
Chromium		50 mcg
Molybdenum		50 mcg
Bioflavonoids		50 mg
Lutein		6 mg
Lycopene		6 mg

2. Adeeva Immune and Detox Support Supplement



- Reishi Mushroom Extract – 60 mg (std to 10% polysaccharide and 4% terpene content)
- Astragalus – 200 mg (2:1 extract)
- Milk Thistle – 300 mg (std to 80% silymarin)
- Indole-3-Carbinol – 50 mg

Dosage:

A. Prevention – 2 capsules per day with food

B. First Sign of Infection – 4 capsules, up to 2-3 times daily with food.

Plus: Adeeva Orega-Sept Capsules (P73 Wild Oregano) – 4 capsules, three times per day

3. Additional Vitamin C – 500 mg, twice daily (First sign of infection: increase total daily dosage to 4,000 -5,000 mg, using 500 mg doses throughout the day). **Also consider, Quercetin** with Vitamin C, with maximum daily dosage of Quercetin – 1,000 mg.

4. Additional Vitamin D – most people likely to benefit from at least additional 1,000 IU of vitamin D, but it depends on their current blood level and co-morbidity issues. **(Ideal Range = 80-140nmol/L or 32 – 56ng/ml).**

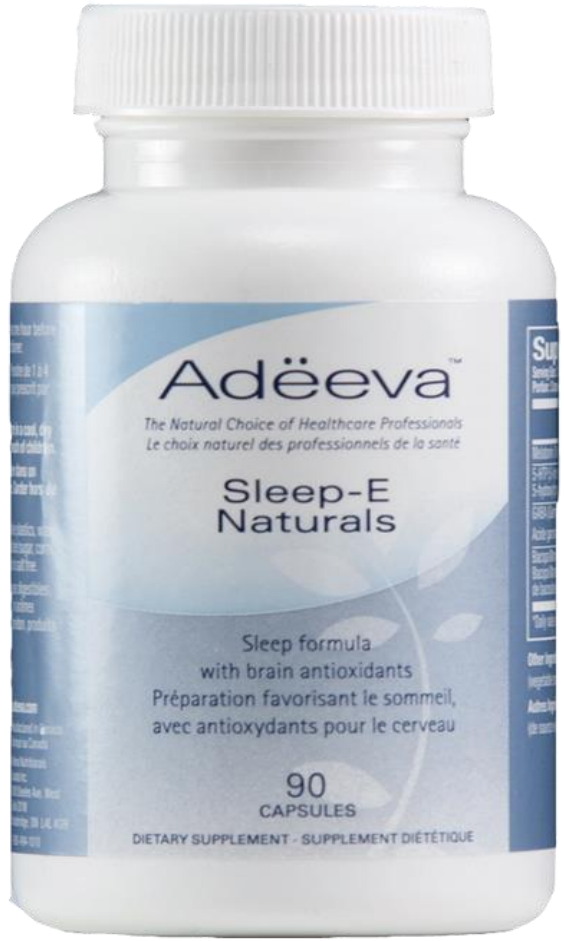
5. Medicinal Mushroom Powdered Blend – 1-2 teaspoons or scoops per day (mixed into juice as an example):

- 14 Mushroom Blend: www.mushroomharvest.com
- Om FIT Mushroom Superfood

6. Adeeva Sleep-E Naturals (Beginning at age 40)

One Capsule Contains:

- Melatonin – 0.5 mg (500 mcg)
- 5HTP – 10 mg
- GABA – 25 mg
- Bacopa monnieri (20% Bacosides) – 15 mg



Dosage Considerations:

Age: 40-50 – 1 capsule (90 mins before bedtime)

Age 51-60 (65) – 2 capsules (90 mins before bedtime)

Age 66 – 75 – 3 capsules (90 mins before bedtime)

76 Plus – 4 capsules (90 mins before bedtime)

7. **Probiotics –** broad spectrum (and consume fermented foods)

8. **L-Glutamine** – 5,000-10,000 mg per day, mixed into juice or protein shake – especially if exercising.

Supplementation Strategy Summary:

1. Adeeva All-in-One Multiple Vitamin and Mineral
2. Adeeva Immune and Detox Support Supplement
3. Adeeva Sleep-E Naturals (over 40 yr.)
4. Additional Vitamin C – 1,000 mg per day (possibly with 500 mg Quercetin)
5. Additional Vitamin D (if necessary) – to achieve blood level in ideal range
6. Probiotics
7. Medicinal Mushroom Blend
8. L-Glutamine Powder

Dr. James Meschino
drjames@adeeva.com

Thank you for attending.