IMMUNE DYSFUNCTION and CHRONIC INFECTIONS

The immune system begins to shut down as we age due to the loss of vital **naïve immune cells** and an accumulation of excess levels of older **memory cells**, which makes us vulnerable to disease. Research shows that about **60** to **90%** of adults harbor viruses such as Epstein-Barr **cytomegalovirus** (CMV), and other **herpes viruses** which depletes naïve immune cells. CMV may increase mortality in healthy older adults.

REFERENCE: A Common Virus. LIFE EXTENSION MAGAZINE, SCIENCE AND RESEARCH. JANUARY 2015

A Common Virus

Approximately 60 to 90% of adults are infected with cytomegalo-virus. The result of chronic infection with this virus is depletion of the vital naïve immune cells that are necessary to fight new malignancies and infectious agents. Fortunately, there are steps you can take to offset the age-accelerating effects of cytomegalovirus.

A major reason why our immune system fails with aging is that we lose vital **naïve** (virgin) immune cells while we accumulate excess levels of senile **memory cells**.[1,2]

Naïve immune cells are needed to respond to new malignancies and infectious agents,[3] whereas memory immune cells only respond to the original antigen, i.e. bacteria, virus, or cancer cell.[4]

Once our reserve of **naïve immune cells** is depleted, we become vulnerable to diseases that were fought off in our youth.

Some people suffer accelerated **immune senescence** that wreaks havoc throughout their body. These individuals are unable to fend off new invaders because of **naïve cell** depletion. They may also suffer systemic damage caused by ***inflammatory*** signals emitted from senescent **memory cells**.[1]

A growing body of evidence has identified a **virus** (cytomegalovirus) that causes us to more rapidly deplete vital **naïve immune cells** with the consequential buildup of excessive **memory cells**.[1]

A disconcerting **60** to **90%** of us are estimated to harbor this insidious virus.[5] Fortunately, there are steps one can take to help offset the ***age-***

accelerating effects inflicted by the **cytomegalovirus (CMV)** and thus retain more youthful **immune function**.

There is a limit as to how many **naïve immune cells** our bodies normally produce and this number declines with age.[6-9] Once a **naïve** cell is exposed to an antigen, it converts to a **memory** type immune cell that only responds to the same virus, bacteria, or other foreign agent.[4,10]

When we develop certain chronic viral infections, our immune system goes into constant overdrive, producing high levels of **naïve cells** that convert into **memory cells** upon exposure to new copies and strains of the virus replicating in our cells. Unfortunately, there are only limited numbers of these vital **naïve immune cells** our bodies can naturally make.

Those inflicted with **HIV** suffer an *accelerated* form of aging as their immune system works to fight the virus, despite the advent of anti-HIV drugs.[11,12] **Hepatitis C** infection creates this same problem.[13] The breakthrough news about hepatitis C is that new drugs are curing up to **90%** of those infected.[14]

Most of us, however, are not infected with hepatitis C or HIV. What the vast majority of us do harbor in our bodies is the **cytomegalovirus**. Lab tests revealed that it is present in approximately **60%** of the general population, and in **90%** of those over the age of **80**.[5]

The insidious property of **cytomegalovirus** (**CMV**) is that it leads to the continuous production of viral proteins that have the ability to establish secondary infections with *differing* **CMV** strains.[15-17] The deadly consequence that has been observed is continuous stimulation (and subsequent depletion) of **naïve cells** and excess accumulation of dysfunctional **memory cells** leading to the development of accelerated **immune senescence**.[18-20]

Unless one is immune compromised, most of us infected with CMV are **asymptomatic**—or so we think.[21] The harsh reality is that chronic CMV infection is associated with **frailty**, **cognitive decline**, and **arterial occlusion**—hallmark pathologies of "normal" aging processes.[22,23]

CMV Shown To Shorten Life Span

CMV infection can increase mortality (death) rate in otherwise healthy, older individuals. This is most clearly seen by an increase in vascular deaths and immune senescence.[22,24]

One study found that high CMV antibody levels (associated with CMV exposure) were independently associated with a **179%** greater mortality rate over a five-year period.[22] Another study showed a **35%** increase in cardiovascular disease mortality in those with elevated CMV indicators.[25] In still another study, CMV reduced life expectancy by **3.7 years** after adjusting for other factors.[24]

What scientists are finding is that chronic CMV infection "exhausts" the immune system. It does this by depleting **naïve cells** needed to ward off new CMV strains and leaving behind a large population of pro-inflammatory senile **memory cells**.[18,26]

Of interest, however, was a study on long-lived family members whose offspring enjoy a **30%** reduced mortality rate.[27] These rare individuals, genetically enriched for longevity, were less susceptible to the characteristic CMV-driven impairments of immune function. This study showed that CMV infection was strongly associated with an age-related reduction in vital **naïve T-cells** and accumulation of **memory T-cells** in the general population, but not in members of long-lived families.[27] These long-lived individuals also showed lower **pro-inflammatory** status as measured by **C-reactive protein**. This study implies that by initiating strategies to boost **naïve T-cell** populations and suppress excess **memory cells**, one might derive some of the enhanced longevity benefits enjoyed by genetically programmed long-lived individuals.

CMV Adversely Affects Cognitive Thinking

T-helper cells are needed to help initiate an immune attack against foreign invaders. **Regulatory T-cells** (also known as suppressor T-cells) turn down immune responses, preferably after the pathogen has been brought under control.[28]

For optimal immune health, one should have approximately **one** to **four** T-helper cells for every **one regulatory** T-cell.[29,30] As a result of normal aging, **regulatory T-cell** counts elevate,[31,32] while **T-helper** counts decline.[33] Certain cancers appear able to boost regulatory T-cell counts in order to protect themselves against an immune attack.[34-36]

A study published in **2014** evaluated 360 adults (aged 60-103) and found that those with higher CMV activity had an **8-fold** increased risk of an inverted T-helper/regulatory T-cell ratio, meaning they had more **regulatory T-cells** than **T-helpers**.[37]

These human study subjects with inverted T-helper/regulatory T-cell ratios had **impairments** in some **cognitive dimensions** and more functional disability and dependency compared to subjects with higher T-helper counts and lower regulatory T-cell counts.

Humans with lower T-helper counts and higher regulatory T-cell counts die sooner.[38] It is thus important for aging individuals and certain cancer patients to take aggressive steps to maintain higher youthful levels of T-helper cells and keep regulatory T-cell counts from increasing too much.

CMV MAY SPEED UP IMMUNE SENESCENCE

- An aging immune system fails because, as we age, the body loses vital naïve immune cells and accumulates excess levels of senescent memory cells.
- This makes us vulnerable to diseases that were easily overcome in youth.
- Growing evidence shows that a virus called cytomegalovirus (CMV) depletes naïve immune cells and infects approximately **60** to **90%** of people.
- CMV infection can shorten the life span of otherwise healthy older adults. Bolstering natural killer cell (NK) activity may suppress CMV.

How CMV Inflicts So Much Damage

CMV attacks the **endothelial** lining of our arteries, which explains the high prevalence of **vascular death** seen in those with active CMV infection.[39-45]

Immune cells are highly dependent on ***telomerase activity*** in order to maintain youthful function.[46] CMV causes immune cells to lose telomerase activity.[47-49]

CMV also forces vital **naïve immune cells** to be used to suppress active infection. The result is accelerated **immune senescence**.[50-52] As **naïve immune cells** decline, aging humans lose their natural protection against bacteria, viruses, and cancer.

Naïve cells are lost to normal aging, making CMV infection particularly deadly in the elderly.[24,53]

Active CMV infection is present in virtually all **glioblastoma** (fatal brain tumor) patients.[54]

Another way to suppress CMV may be to bolster **natural killer cell** activity. An important function of natural killer (NK) immune cells is to destroy **virus-infected** cells throughout our body.[58]

"An effective defense against CMV in immune competent subjects requires the participation of NK cells and T-lymphocytes… It has been shown that CMV chronic infection in old individuals is associated with accumulations of late-differentiated CD8 T-cells, characteristic of CD8 T-cell immunosenescence, and with the development of an 'Immune Risk Phenotype' (IRP), predictive of early mortality in the elderly indicating that this virus is a major driving force of T-cell immunosenescence."[82]

Reference: *Current Opinion In Immunology*—January 2014, "Shaping Of NK Cell Subsets By Aging."

CMV-INDUCED IMMUNE CELL EXHAUSTION

Immune cells used to suppress chronic infections like **cytomegalovirus** (CMV) become senile or "exhausted" over time.[18,50,59,60]

As people accumulate **exhausted T-cells**, an adverse consequence is that the senile cells emit ***pro-inflammatory cytokines*** that exacerbate the **chronic inflammation** observed in elderly persons.[61,62] These individuals suffer higher mortality.[63,64]

The deficit of **naïve immune cells** combined with over accumulation of **exhausted T-cells** decreases the efficacy (antibody response) of **vaccinations**.[65-67]

Persistent **CMV infection** and the consequent accumulation of pro-inflammatory **exhausted T-cells** are associated with increased risk of **coronary heart disease**, **impaired vascular function**, **vascular inflammation**, and **endothelial dysfunction**.[39,41,68-72] This all leads to increased **blood pressure** and contributes to **atherosclerosis**.[73]

An accumulation of **exhausted T-cells** has been seen in persons suffering from **rheumatoid arthritis** and other chronic inflammatory conditions.[74,75]

A strong body of evidence, mostly published over the past few years, indicates that **persistent CMV infection** and the accumulation of **senile** (exhausted) **T-cells** initiates and accelerates a broad array of age-associated and inflammatory diseases.[76-81]

An Immune Cell That Destroys CMV

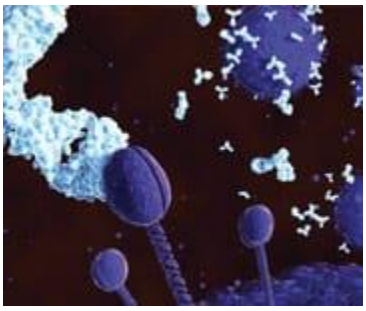
Cytomegalovirus (CMV) invades cells throughout the body and spews out copies that infect other cells.[83]

The first line of defense against virus-infected and malignant cells is our **natural killer (NK) cells**.[84-87] Young individuals have high levels of functional **natural killer** immune cells, but this declines with aging.[88-90]

In elderly subjects, decreased **NK cell activity** is associated with an increased incidence and severity of **viral infections**, which explains why **90%** of older people show **CMV** infection compared to about **60%** of the general population.[5]

Healthy **NK** function is critical in eliminating transformed cells before a viral infection or **malignancy** develops.[59,91,92] **NK cells** are involved in immune regulation, antimicrobial immune responses, and elimination of senescent cells that otherwise cause **chronic inflammation**.[59]

The age-related decrease in healthy **NK cell function** is likely to have wider implications for the health of older adults than currently understood by the mainstream. If an aging person is to control debilitating and deadly **CMV** replication, maintaining more youthful **NK function** would appear to play a critical role, as would restoration of the **naïve immune cell** population.



"…several features of the aging process, such as the reduced efficacy of vaccination, the appearance of senescent cells, and the higher rates of fungal infection may be attributable in part to the decline in NK cell function that accompanies human aging. If true, then developing strategies to prevent, delay, or reverse NK cell immunesenescence may be one way by which to improve the health of older adults."[59]

Reference: *Ageing Research Reviews*—September 2013

"The Impact Of Aging On Natural Killer Cell Function And Potential Consequences For Health In Older Adults."

Suppressing CMV Infection

Immune compromised people, such as HIV patients, organ transplant recipients given immune-suppressing drugs, and certain cancer chemotherapy patients are particularly vulnerable to **acute CMV infection**.[93-96] These individuals facing blindness,[97] pneumonia,[98] and possible death from an uncontrolled CMV infection are prescribed a drug like **valganciclovir** that is highly effective in controlling viral replication.[99-101]

One of the side effects of this drug is **bone marrow** suppression, which can hasten **immune senescence**.[102] That's because immune cells are formed in our bone marrow where they are released into the bloodstream for further differentiation into specific disease-fighting cells like macrophages and NK cells. Valganciclovir is therefore not recommended for most CMV-infected individuals who are asymptomatic.

Since we know that **NK cells** hunt down virus-infected cells and eliminate them, it makes sense to take steps to boost the *functionality* of our aging **NK cells** to suppress CMV activity.

Enhanced NK cell function alone will not likely eradicate CMV, but it can downregulate active CMV infection to reduce the damage inflicted on the body and theoretically reduce the number of **naïve immune cells** that will be used up fighting it.[103]

As people age, and/or contract an illness such as cancer, they often produce too many **regulatory T-cells**[111,112] that prematurely shut down needed immune activity.[113-118] Aging also results in a decline of **T-helper cells** that initiate immune responses to virus-infected and cancer cells.[119]

T-helper cells are required for the immune system to react to new infections and malignancies.[120,121] They help activate the secretion of antibodies and macrophages to destroy ingested microbes and help activate cytotoxic T-cells to kill virus-infected target cells. To fully appreciate the importance of T-helper cells, you may know that HIV invades and destroys T-helper cells.[122] As T-helper cell counts decline, AIDS patients become vulnerable to a host of opportunistic infections.[123,124]

There Is Not Yet Universal Consensus On CMV And Immune Senescence

Not all published scientific papers agree that CMV infection accelerates **immune senescence**. The topic is currently being debated by immunologists around the world.[126] The studies supporting the pathologic impact of CMV on immune status are compelling, as is the data associating active CMV infection with shortened human life spans. But as critics accurately point out, "association" is not always the same as "causation."

For an aging human concerned about their health and longevity, it does not necessarily matter if **CMV** is accelerating **immune senescence**. That's because maturing individuals are already suffering a decline of naïve T-cells, reduced T-helper cells, loss of NK cell activity, accumulation of worn out memory cells (that emit chronic inflammatory signals), and an increase in regulatory T-cells.

Summary

The immune system begins to shut down as we age due to the loss of vital **naïve immune cells** and an accumulation of excess levels of older **memory cells**, which makes us vulnerable to disease. Research shows that about **60** to **90%** of adults harbor a virus called **cytomegalovirus** (CMV), which depletes naïve immune cells. CMV may increase mortality in healthy older adults.

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