To my valued patients and colleagues

Introduction

In the last newsletter we wandered into epidemiology and economics. Today, we are going deep into science. So, for those who enjoyed economics and opinion, sorry, this time we are wading into the thickets. For those readers who enjoy the sciences more, you are in luck.

Really hopeful news

I read a most interesting, heavily scientific article. The news at the end is potentially incredibly good and I have tried to convey the results of the study more in lay terms than in scientific terms.

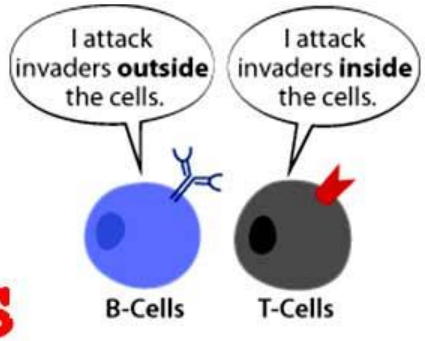
A group of scientists from La Jolla Institute for Immunology, University of North Carolina, University of California San Diego, and Mt. Sinai NY have studied T cells. T cells are a type of white blood cells (WBC) your body makes. Whereas red cells carry oxygen, white blood cells are there to help you fight various infections. A common type of WBC is the poor little lymphocyte (lymph). When doctors order your blood counts, a report comes back, as shown below. WBC and lymphs are circled below in red.

Ordered Items
CBC With Differential/Platelet; Blood Drawing

TESTS	RESULT	FLAG	UNITS
CBC With Differential/Platelet			
WBC	6.6		x10E3/uL
RBC	**4.07**	**Low**	x10E6/uL
Hemoglobin	15.6		g/dL
Hematocrit	45.5		%
MCV	**112**	**High**	fL
MCH	**38.3**	**High**	pg
MCHC	34.3		g/dL
RDW	14.2		%
Platelets	256		x10E3/uL
Neutrophils	57		%
Lymphs	32		%
Monocytes	8		%
Eos	2		%
Basos	1		%
Neutrophils (Absolute)	3.7		x10E3/uL
Lymphs (Absolute)	2.1		x10E3/uL
Monocytes(Absolute)	0.5		x10E3/uL
Eos (Absolute)	0.1		x10E3/uL
Baso (Absolute)	0.0		x10E3/uL
Immature Granulocytes	0		%
Immature Grans (Abs)	0.0		x10E3/uL

Lymphocytes can be subdivided into three subtypes: T cells, B cells and NK (natural killer) cells (Don't you love the name of the last type of lymphocyte?). The B cells work by mostly producing antibodies. Antibodies are proteins that fight infection by latching onto the outside of the virus and signaling the other cells that the virus needs destruction. For those of you who have come to the office for "antibody" testing, the antibody test measures whether you have previously been exposed to the infection.

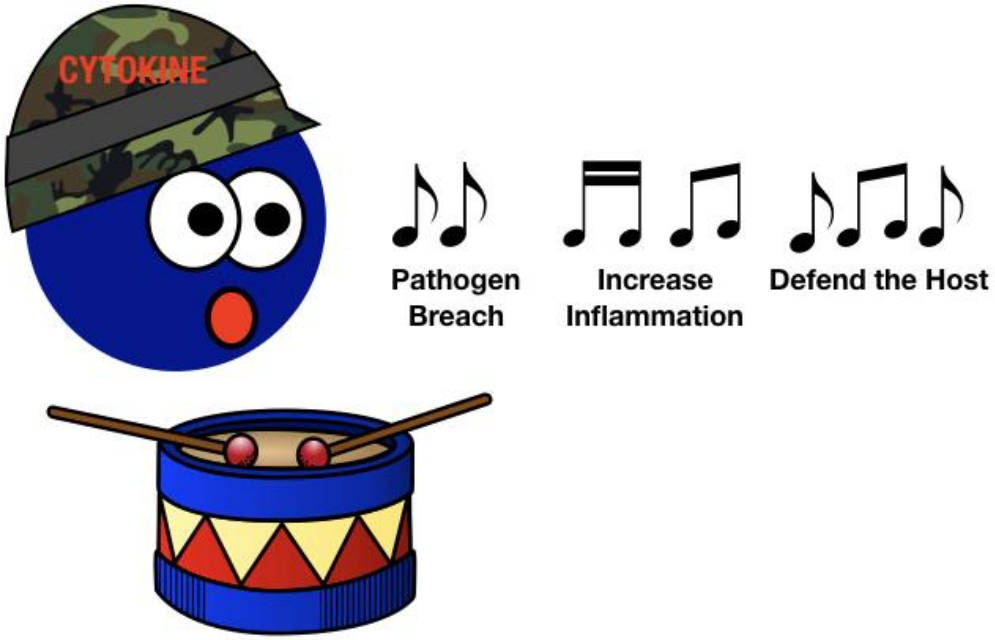
Differences Between B-Cells and T-Cells



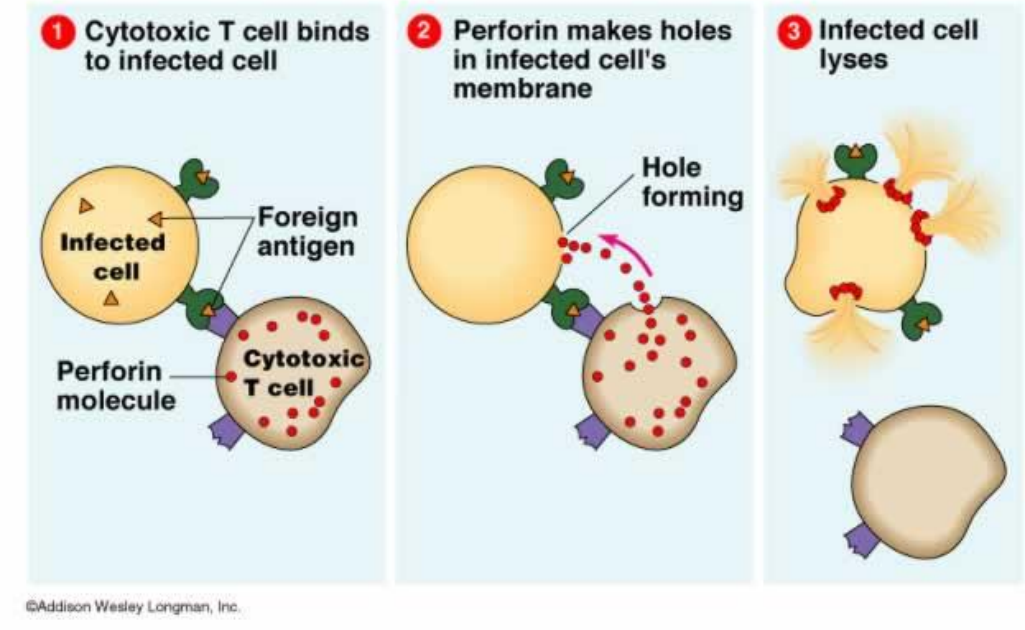
This research paper, though, is mostly about the T cell variety of lymphocytes. T cells act totally differently than B cells. The T cells have a particular surface protein called the T cell receptor (red in the picture above). There are a huge number of T cell receptors of different types waiting to recognize an invader (antigen).

Got it so far? The most direct of these T cells are the cytotoxic T cells, also known as CD8+ T cells. I firmly believe the names of T cells is a way to make researchers in immunology think they are better than the rest of us by using terms that make immunology hard to understand. Anyway, these CD8+ T cells do not go after virus particles. They go after cells infected by the virus and kill them off before the cells can cast off thousands of new viruses.

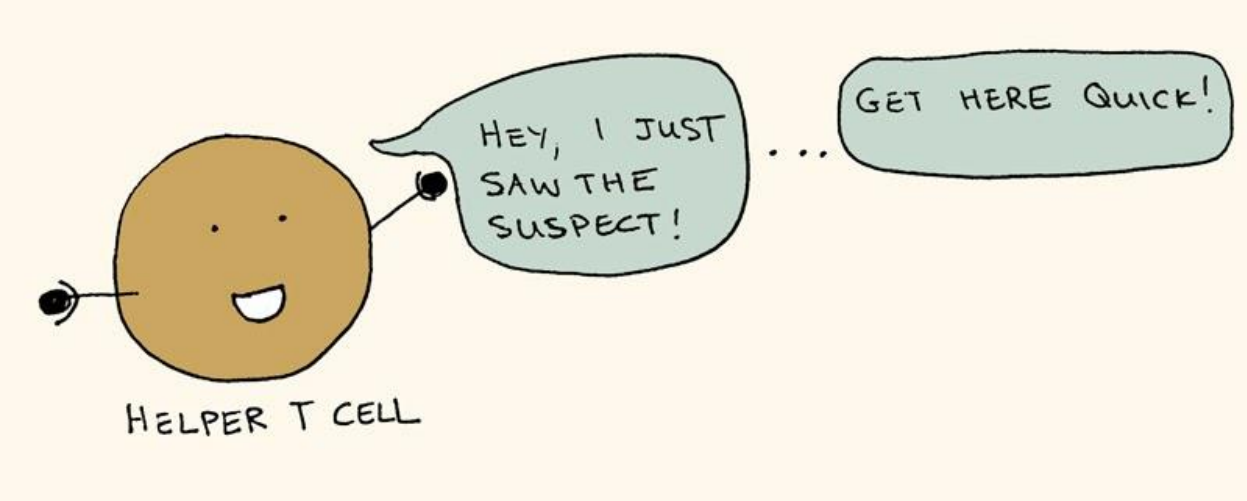
How do CD8+ T cells kill off virus-infected cells? One way is that they secrete cytokines. What are cytokines? Cytokines are particularly important small proteins that signal other cells and molecules where and how to fight an infection. Basically, they are communicators. They aid cell-to-cell communication and can stimulate selected cells to travel to the sites of inflammation and infection. Some of these cytokines have complex names such as TNF-alpha and interferon-gamma.



But there is another critical way that the CD8+ T cells act to fight infection. They move in close to the infected cells. The CD8+ T cells then deliver mass destruction to the infected cells by opening pores in the target cell and doing the "barbarian thing" of murder and pillage, thus destroying the infected cells.



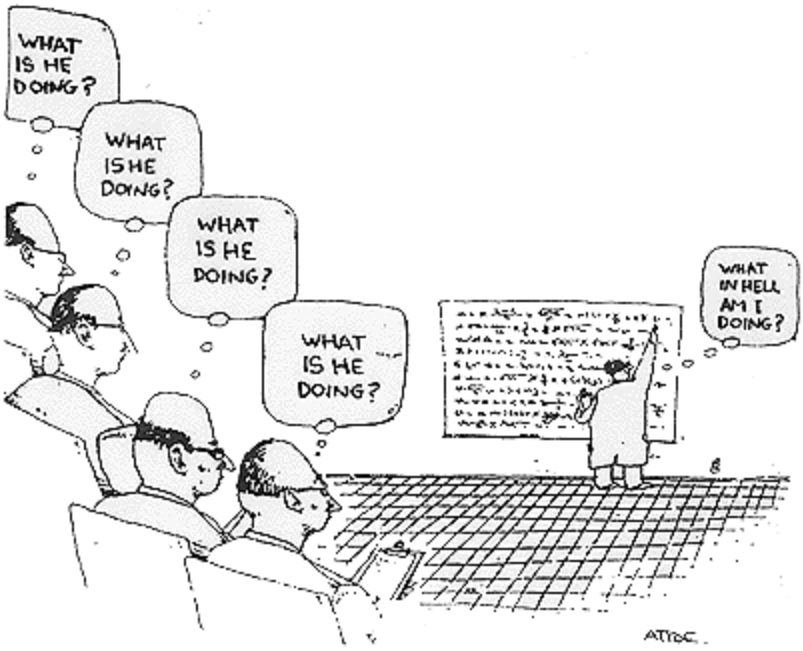
There is another T cell called CD4+ which is known as a T helper cell. CD4+ T cells work with other cells called antigen-presenting cells to activate the CD8+ T cells and B cells to start the whole immunological process. This is comically depicted below. It is not really that simple. But it is the way I get my head around it.



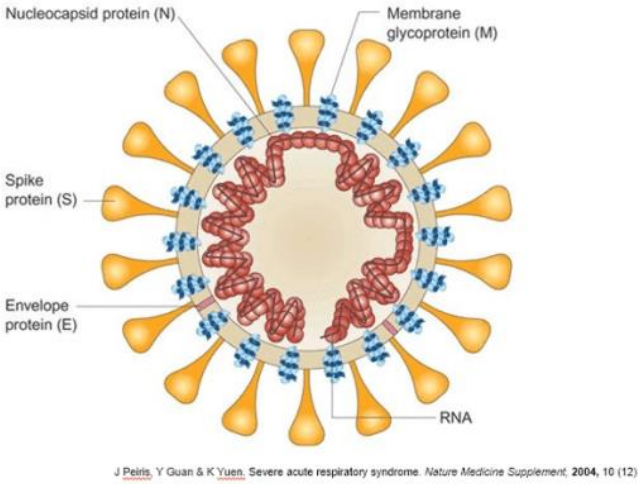
I hope you stayed with me, because I am about to explain the new findings from the study using this terminology. We are going to look at the CD8+ T cells and CD4+ T cells that have been made in response to infection in patients who have had coronavirus.

CD8+ T cells and CD4+ T cells are especially important in modulating the body's immune response. If CD8+ T cells and CD4+ T cells do not have enough of a response to an infection, the body could be vulnerable to a new infection. If the body overreacts with CD8+ and CD4+ T cells revving up too much to an infection, the body can be overwhelmed as cytokines pore out and destroy good and bad tissue alike. Think of this over-reaction as using a cannon to kill a housefly in your house. You may hit the fly, but you just tore out the bedroom, living room and kitchen.

Side note: While we are talking about immunity, did you ever wonder why old people like me are more at risk? One reason, among many, is that the antigen-presenting cells decline with age so one of the key early steps in getting rid of infection goes down in effectiveness. This can lead to a late heavy-handed response from the T cells which causes a cytokine storm.



Now let us look at the actual research findings in the article by Grifoni et al. By studying coronavirus patients and normal patients, these researchers discovered that a particular protein on the coronavirus called the spike protein antigen could elicit a good immune response form the CD4+ T cells if the spike protein antigen is introduced into a body for vaccination. But the CD8+ T cells responded differently. There was no single dominant protein antigen of the virus that really worked to cause a good CD8+ T cell response. The spike protein and the M protein were both strong but other proteins were needed for a full response. Therefore, it appears the first vaccines will be against the spike protein and later ones may target the other proteins if necessary.



J Peiris, Y Guan & K Yuen. Severe acute respiratory syndrome. *Nature Medicine Supplement*, **2004**, 10 (12)

Figure 1. Schematic diagram of coronavirus structure.

Now here it gets interesting. Surprisingly when these researchers studied the CD4+ T cells in people who never were exposed to SARS-CoV-2 (our present day coronavirus), 40-60% of these never-exposed patients had CD4+ T cells that responded to the this present day coronavirus. What? How did that happen? How could people who never saw this coronavirus have CD4+ T cells that act like they already saw this infection? Perhaps people exposed to another coronavirus, such as the one causing the common cold or perhaps another virus, had activated their CD4+ T cells to at least partially respond to this virus. We do not know yet since this was just seen for the first time**. But this would be wonderful news if half the population already had some immunity to this disease.** This is rather exciting.

Here is a nice video on our immune system.

https://www.youtube.com/watch?v=PzunOgYHeyg

More science

It appears that an individual's genetic makeup makes more difference than the genetic make-up of the coronavirus in determining the level of sickness experienced over the course of the infection. A person's age, white blood cells and T cells can play a factor. Older people and those with low T cells and high levels of immune chemical IL-6 tended to be sicker. But the version of the coronavirus they got made no difference.

Types of SARS-CoV-2

A recent study divided coronaviruses into clade I (strain I) and clade II (strain II) by examining the genetic markers of the virus from 94 coronavirus patients. Two mutations distinguish clade I from clade II. Researchers speculated that the two different strains may have different virulence. But their data showed no difference.

Clade I was associated with six cases from the Huanan Seafood Wholesale Market in Wuhan. Clade II was found in early cases in Wuhan that were not associated with the market. Using their data, researchers conclude that the virus probably made the leap from animal to humans in late November 2019. The seafood market was not the place where the virus originated, but it was where people became infected with clade I.

Do you remember?

Do you remember when there was concern that some blood pressure medications may be harmful if taken by people infected with coronavirus? A new nationwide US observational study suggests that ACE inhibitors may protect against severe illness in older people with COVID-19. This is exactly opposite of the initial concern regarding ACE inhibitors. The investigators analyzed 10,000 patients who tested positive for coronavirus and had received prescriptions for high blood pressure. Study patients were enrolled either in a Medicare Advantage or commercial health plan.

Results showed that the use of ACE inhibitors was associated with an almost 40% lower risk for COVID-19 hospitalization for older people in the Medicare program. No benefit was seen in the commercially insured younger people or for patients in either group being treated with ARBs. Darn…. I take an ARB for my blood pressure. There are varying opinions as to the validity of the observational study, but it does appear at least, that drugs that act through the renin angiotensin system such as ACE inhibitors and ARBS, do not pose a risk in COVID-19.

A randomized trial of ACE inhibitors and ARBs is currently underway. While we await the results of the randomized trial, it is not recommended that anyone change their medications. There are currently 4 ongoing studies of these blood pressure medications.

Just asking for 3 minutes and 14 seconds of your time - music

Check out this video. Jonas Kaufman is exceptionally talented, and this is a recording session of an extremely popular opera Turandot, Atto III: Nessun Dorma by Puccini. Recording sessions are not usually made public, but here we have a unique opportunity to view one.

I want you to have fun with this. Please watch carefully at the end to see Mr. Kaufman's response. He knows he hit it out of the park.

https://www.youtube.com/watch?v=xN-JCdM4or0

Once you have watched once, check this out.

- The horn player off to the left at 0:59 starts getting into it, dramatically mouthing the words.
- The guy in the blue shirt seems to have nodded off.
- At the beginning of the recording, the singers in the back have their legs crossed. When asked to sing, they uncross their legs in unison at 1:06.
- This is probably a perfect melding of two different takes because there is no choir at the end and there is one at the beginning. Splice is somewhere around 2:08.