CELLULAR DEPLETIONS….WHY SHOULD YOU CARE?

READERS SUMMARY:

1. How do we tie the squabble at AHS to Neolithic disease generation?
2. How does a cell react to acute stress and what results?
3. How does this stress get measured by labs and my doctor?
4. What happens when this stress lasts too long?
5. Why cholesterol is always good for us, but why the surrounding terroir dictates the disease we get?

Let's continue talking about cellular stress and depletions of things in a cell. We got on that topic because of the macronutrient squabble from AHS. But after following some twitter feeds (@Drjackkruse if you want to follow me on twitter or instagram) about supplement regimes I thought I might try to tie some cellular mineral depletions together with how it causes the cell stress and causes it to affect its cellular terroir and our resultant hormone status. I think this story will help you understand just how important following the trial of biochemistry is.

Any type of cellular stress lowers our stores of ATP and of magnesium (Mg) because they are coupled together by our ATPase enzyme as we saw in this post. This is classically seen in diabetes development as we mentioned there. Another interesting thing also occurs to the cell, that we clinicians can follow on our patients regular labs like a Chem 7. Their carbon dioxide (CO2) levels also fall, while cells become dehydrated, because mitochondria are actively transfer tons of electrons to O_2 to make more ATP to replace the deficit from the stress. This causes a simultaneous drop in CO_2. The normal cellular response to ANY cellular stress however is rather telling to review for most lay people and MD's because they

may have forgot how that biochemistry works via its connection to the environment. The simultaneous fall in ATP and Mg^{2+} stimulates the cell to make LDL cholesterol! Yes, you read that correctly folks, the supposedly bad LDL stuff, LOL! It is obviously not bad if the cell is making it for some reason. Let us look why the cell does this. You may want to reread this blog on cholesterol.

The cell responds to all stress by increasing cholesterol production. If you go into an ICU with a patient with an acute infection and draw their lipids (not often done except by a tool like me) you will find sky high LDL cholesterol. And that is both LDL and HDL, but they LDL fraction is much higher. Higher LDL cholesterol stabilizes the inner mitochondrial membrane function during heavy oxidative phosphylation (cellular energy production). And since the cell is trying to recover from a stress it needs a good inner mitochondrial membrane in which to transfer its electrons to make ATP. That is the reason why this occurs. You can review this in this post.

But here is why the cholesterol story tends to trip clinicians up. The cholesterol is needed by the cell for many uses. To be used properly, cholesterol is made to stabilize membranes and make all our hormones. To do this several co factors are also required. If the cells have a lot of toxins around or the use of the cholesterol is too slow it can oxidize and become the real bad stuff called the sdLDL that is oxidized easily (sdLDLox). This is the stuff that can hurt you. How does this happen? Well to make steroids we need an adequate amount of thyroid hormone (T3) and vitamin A around to convert the cholesterol to pregnenolone and then to DHEA. Remember the blog post that spoke of pregnenolone steal syndrome? So if someone is hypothyroid and/or has low vitamin A levels they can accumulate higher sdLDLox and this lowers the HDL level. Remember from the VAP post that a lower HDL means less filtering ability (endocytosis clearing by the liver) in the

liver's portal circulation for endotoxins. That means that the liver is no longer as good a sieve to filter any toxins from our guts to keep the antioxidant burden in our general circulation low. Continuing on, the lowered HDL causes a "leakier" gut too to proteins, toxins and unwanted bacterial toxins that can further oxidize the plasma and even the increased amount of cholesterol the body just made to combat the stress. This is precisely why patients with chronic hypothyroidism tend to have higher levels of heart disease and other neolithic diseases like autoimmune conditions.

They can't use their newly minted cholesterol fast enough to make steroids or new mitochondrial membranes because they don't have enough T3 and or Vitamin A. So the excess cholesterol oxidizes and is taken up by the arteries and deposited in macrophages that will later become foam cells and eventually an atherosclerotic plaque that could make your coronary artery blow up or clot and cause a heart attack. Any cellular stressor can do the same thing. Infection, high cortisol levels, obesity, trauma, even sleep apnea can cause this.

The other affect of hypothyroidism (low free T3) is that it causes decreased steroid synthesis due to pregnenolone steal syndrome. Remember steroids secretion are how the brain maintains control over the twenty trillion cells in our bodies. If you can't make the chemicals the brain needs (cortisol) to maintain this control all hell can break loose from a control stand point. It also stands to follow that the lowered levels of these hormones are predictive of this process to the inquiring physician by lab testing. What I look for in these actue cases like this is a raised cortisol level with a decreased hormone panel early on the disease process. As this process become chronic cortisol and the hormone panel become flat lined. The steroid cascade from cholesterol's conversion is disrupted because of a lack of either T3 and/or Vitamin A are required for steroid conversion. After

cholesterol is converted by this process it becomes pregnenolone , DHEA, and progesterone and the remained of the sex steroid hormones. Those bio-chemicals are very proximal to the cholesterol conversion defect. T3 is a measure of a lack of sunlight and Vitmin A abnormalities are a proxy for a badly lit environment of the patient by fake light or a lack of sunlight during daytime. If they are lowered then we know we really have got a problem brewing. So this is why I use those hormone assays as clues to what is going on in the cell during stress. For example, in ICU patients who are sick and cant sleep well they suffer from very low levels of DHEA. Low DHEA levels correlate with very high IL-6 levels and poor sleep. If this is allowed to go on long enough patients may get an acute ICU psychosis called delirium. In brain trauma patients we see very low levels of progesterone and this correlates with poor neurologic outcome because progesterone is a co factor in brain derived growth factor to make new neurons.

This means that all the steroids formed from cholesterol will also be lower if this chronically goes one. That means the sex steroid hormones also fall, and so does Vitamin D3 levels. This is why low estrogen, testosterone, progesterone and vitamin D levels are all associated with heart disease, many cancers, autoimmune diseases and a chronic leaky gut and lower HDL level! Its all simple cellular biochemistry that many of us have forgotten.

Now that we have covered an acute cellular stress response lets talk about a chronic one we all will become familiar with…..aging. In aging, our metabolic rates drop we tend to sleep less. This means that we will have a lower T3 level as we age as heteroplasmy rates in mitochondria rise. This is, in fact, what we see in aging. We just reviewed above what a low T3 can do in acute cellular stress. What do you think happens with aging? You’re catching on now. It does the same thing but the onset is more insidious. And as this happens slowly over

time what occurs? Our hormone levels all decline slowly as mitochondria become pseudohypoxic and have lowered voltage and a low NAD^+ level. For some this decline happens to certain hormones quicker than others. But with testing we can predict what this means means to the aging person's cellular stress.

In the acute cellular example I gave you I told you about needing more cholesterol for stabilizing the inner mitochondrial membrane to make more ATP (energy). In aging, we need to raise cholesterol for another more dire reason. As we age our cell divides multiple times over the decades. As it does this over and over again it shortens a part of chromosomes called a telomere. This is actually a biomarker for really how old our cell is. But here is the important part. As a cell divides it needs cholesterol to make a new cell and new chromosomes. Cholesterol is found in the nucleus in our chromosomes. It is even bound to our DNA and to the nuclear terroir surrounding our chromosomes. This cholesterol helps to control how a cell's chromosomes divide. This is called a mitotic spindle. Cholesterol also is needed to activate our genes and their epigenetic switches that turn them on and off. If that cholesterol is not present, chromosomes don't divide properly and genes get turned on and off at the wrong times. This results in bad signals and sometimes the wrong number of chromosomes. This is called cellular aneuploidy. When this happens we generally see can cancer form in the the cell. This is why we see cancer develop in older people. This is also much more common when the LDL cholesterol is low. This is also why people with lower levels of LDL cholesterol have higher rates of cancer in multiple studies! Even the highly touted Framingham Heart study showed this realtionship between cancer and low LDL to be true. Ironically, however we still think in medicine a lower cholesterol is somehow better? So as we age the cell's normal response is to make more cholesterol to make cell division perfectly safe and carefree. It also help the inner

mitochondrial membrane make CO_2 and ATP properly.

So the moral of this story that when you see something in the cell that is depleted or unregulated normally in response to an acute or chronic stressor you would be wise to pay attention to the cellular biochemistry to dictate what you should consider doing. Cellular signaling and depletions can lead to neolithic diseases. With depletion of magnesium due to high insulin levels we saw how diabetes becomes a problem. With cholesterol depletion acutely and chronically we see how it can lead to heart disease, acute delirium, poor sleep, complete hormonal disruption and if allowed to go on chronically you may eventually get cancer. If you are thinking that incidences of all these diseases has gone up in the last 150 years you are correct. They all go up as we age. So if you choose to do things differently than how most people handle acute and chronic cellular stressors you may exert control over your cellular fates (Levee One). If you pay attention to the cellular levees and protect against them you may never face any of these neolithic diseases. Ponder those thoughts for a while, it could save your life and likely change your DNA too.