Dickie's Personal HIV Theory

The FULL MONTY
CHAPTER ONE: DECONSTRUCTING THE THEORY

by Dick Remley, every doctor's nightmare:
A Patient with an Informed Opinion

Throughout The THEORY, certain mechanisms -- such as Apoptosis, Syncytia formation and Margination -- have been introduced as models of known biological processes that might fill in some of the details as to how The THEORY accomplishes its goal. None of these processes are critical to the heart and soul of The THEORY. They are a means to an end. Although ALL of these processes are known to occur in HIV infection, in truth, they might not be the most significant factors involved. Cell death might occur through other processes in addition to apoptosis. Long-lived HIV infected cells might exist for reasons that are not syncytial. Infected cells might migrate out of circulation and become sequestered in tissues through means other than margination.

These three processes, however, provided the simplest and most direct means of explaining The THEORY through known biological models. They may or may not be critical to the process The THEORY attempts to describe. The THEORY is married to none of them.

What IS critical to The THEORY is its basic framework. The critical postulates of The THEORY are these:

1. T-cell depletion is caused by the failure to replace some infected cells, not by the wholesale death of cells.

2. This failure to replace cells is the result of a failure to receive a "replacement signal" from dying cells.

To my knowledge, neither of these postulates has been proven or disproven (that's why its called "The THEORY" and not "The CERTAINTY").

These two postulates are important, because they help explain most of the anomalies that we see in HIV disease that currently accepted theories do not explain - at least not without great difficulty.

The Currently Accepted Theory (which, hereinafter, we will refer to as "the CAT") is that there is this "raging war" going on between HIV and the human body's ability to replace T-cells. In the CAT, HIV releases millions - perhaps billions - of viral particles into the bloodstream constantly; and a percentage of these particles infect and kill T-cells in a wholesale slaughter of the body's immune system. The body responds by pumping out

new T-cells as fast as it can. But the body is apparently supposed to be always just one step behind the virus, and slowly loses the war.

I don't buy it.

This currently accepted explanation seems to me to fall short in accounting for some major anomalies seen in HIV disease. We will now pit elements of The THEORY against the Currently Accepted Theory (CAT) by exploring some of these anomalies. In the process, we will likely see The THEORY reconstruct itself.

SKINNING THE "CAT" -- EXPLORING ANOMALIES

ANOMALY #1: HIV viral load (the amount of free-floating virus in the bloodstream) can increase to VERY high levels during outbreaks of other viral illnesses such as herpes or the flu. Even vaccination can cause an increase in viral load. But increases under these circumstances are almost always temporary. Once the illness has passed, HIV viral load tends to decline back to the level it was at prior to the occurrence of the illness. Why?

If the HIV virus is overwhelming the immune system gradually by some very fine margin of cell-death vs. cell replacement, then these increases in viral load should nearly always be disastrous for the patient. More virus would mean a greater number of T-cells would be infected, which would mean more infected cells producing more virus and then dying off. If the immune system is just barely able to keep up with HIV infection in the first place, then this set of circumstances would logically be expected to result in the HIV gaining a decisive edge in this contest. Viral load would spiral upward, and T-cell counts would crash. In fact, this usually doesn't happen. Viral load jumps - and then falls back down. Patients usually survive this temporary increase in viral burden relatively unscathed. How can this be?

I can think of four possible explanations for why this would happen:

1. The immune system somehow responds more strongly to the increase in viral load, and wipes out the extra burden.

2. The additional viral particles (virions) formed by this process are non-infectious mutations.

3. The increase in viral load in the bloodstream does not represent the stimulation of viral replication at all, but is caused by the return to circulation of virally infected cells that are usually sequestered outside the bloodstream.

4. The increase in viral load represents an increase in free-floating virus that was never all that critical to reducing T-cell counts in the first place (The THEORY).

Now, of the above explanations, # 1 seems to me to be the least likely. If the immune system can control additional viral load and effectively eradicate it, then why wouldn't it go on to wipe out the rest of the viral particles as well?

Explanation # 1 implies that the immune system commonly gains an edge in the war against HIV. But, if that were the case, then the immune system ought to be able to wipe out the virus completely, and progression to fatal illness would not occur. This is obviously not the case, and I am dismissing explanation # 1 on those grounds.

Explanation # 2 (that additional virions produced by environmental factors are almost always noninfectious mutants) seems possible, but has a slight problem: why would the newly stimulated viral growth be any more prone to non-infectious mutation than the virus as it is normally found? Wouldn't virions produced under most conditions have the same percentage chance of survival as virions formed under normal circumstances?

Explanation # 3 (that the increased viral load represents a return to circulation of infected cells that HAD been sequestered somewhere outside the bloodstream) also seems possible, but you'd still have to explain why the increased viral load isn't doing more damage. Wouldn't the increased level of virions also give rise to an increase in cell infection and death? I suppose one could endeavor to explain this by saying that the sequestered cells were always causing the same amount of damage - they just weren't SEEN doing this because they were in sequestration. The net effect of returning them to circulation would therefore be zero. But it could also be true that the new virions are largely noninfectious - just as required in explanation #2 above. For Explanation # 3 to work, it would have to concede at least one (and perhaps both) of two major issues in The THEORY: That infected cells are often found OUTSIDE the bloodstream, and that they produce virions that are unlikely to infect other cells in the bloodstream.

This leaves explanation # 4: that HIV virions are USUALLY not responsible for the decline in T-cell counts. This explanation is not exclusive of any of the other explanations, and declares the increase in viral load largely irrelevant to the outcome of the disease process.

To summarize: of the four explanations, #1 seems impossible, #2 seems improbable, #3 must claim the whole effect is something of an illusion, while conceding at least one key issue to The THEORY, and #4 claims the issue is mostly irrelevant.

The CAT relies on at least one of the first three explanations being true, while the fourth one MUST be untrue.

The THEORY suggests that explanation # 4 is true regardless of whether any of the others are true or not.

ANOMALY #2: In a certain, small percentage of cases, patients undergoing successful antiretroviral therapy experience BOTH an increase in viral load, AND an increase in T-

cell counts. The increased T-cell counts tend to be sustained and correlate well with an increase in immune response leading to a favorable clinical outcome. Why is that?

Again we are faced with the issue of increasing viral load, and we return to the four explanations offered above.

The CAT tells us that the new virions are non-infectious because the antiretroviral therapy has resulted in poorly formed viral particles. I can believe that. So, it now looks like the CAT favors explanation #2. This is the only consistent hypothesis the CAT offers us to explain viral load anomalies. This suggests that only virions produced under natural circumstances are capable of initiating successful infection leading to viral reproduction and cell death. To me, that seems possible, but a little hard to swallow.

The THEORY suggests that explanation #4 (that the death of cells is NOT what gives rise to T-cell depletion) would hold true in virtually all circumstances.

I have no problem accepting the idea that any of the first three explanations might turn out to be true - although, clearly we've seen some problems with making them "fit". The reason explanation #4 was chosen to be incorporated into The THEORY is its pure simplicity. The other three explanations all require acceptance of the idea that there are times when circulating viral load does not cause a decline in T-cell counts. Explanation #4 simply says, "Yes: and that is MOST of the time."

As we examine this issue further, you may begin to see why I think explanation #4, as offered by The THEORY, simply collapses the complex arguments implied in explanations #1, 2 and 3 down to a more basic point: virions in the bloodstream are clearly not always deadly, and CAN be controlled by the body's immune system.

There are other, similar circumstances in which increases in HIV viral load do not correlate well with expected disease progression. However, the situations we examined above are the clearest and simplest examples. The arguments and explanations in all cases would be the same. Taken together, the incidence of HIV viral load NOT correlating well with consequent impact on the immune system - while it is the exception rather than the rule - seems to me to be sufficiently high so as to make HIV viral load appear to be useful as a surrogate marker, but not as an explanation for T-cell loss. Viral load might give you an indication of how many cells are already infected, or the rate at which already infected cells are producing virus, but not of how many cells are likely to BECOME successfully infected through the bloodstream. If infectivity through the bloodstream were the cause of the decline in T-cell counts, then I would expect there to be a more consistent cause-and-effect relationship between viral load and T-cell counts.

ANOMALY #3: This is actually more of a puzzle than an anomaly, because it occurs universally: when HIV viral load is brought under control, T-cell counts do not return to normal automatically. In fact, recovery of the immune system literally takes years, even in the presence of viral load brought so low as to be undetectable. If there really were a

raging battle going in which the body was constantly replacing rapidly disappearing T-cell populations, then removal of the causative factor ought to result in an immediate huge jump in T-cell counts to nearly normal levels. This just simply NEVER EVER happens. I've never seen it occur even once. I've never heard of a REPORT of it happening. Immediate and significant T-cell increases do occur, but not in huge numbers. T-cell counts increase gradually over a period of years - and usually in spurts. Why?

I've never seen a really satisfactory explanation of this that adheres to currently accepted theories. The closest anyone has ever come to an explanation involves thymic function: T-cells are said to "mature" in the thymus gland. The condition of the thymus declines with age, and could decline even more rapidly in the presence of disease. Therefore, CD-4 replacement would be retarded.

The problem with this explanation is that it is not really consistent with the description of slowly declining T-cell numbers being caused by a war between HIV and the body's ability to replace T-cells. Supposedly, the reason for the decline in numbers of T-cells occurring slowly over a number of years is because HIV has a slight edge over the body's replacement capabilities. The CAT describes the body as being unable to replace CD-4 cells quite as quickly as HIV destroys them, and so the body gradually loses the war. But, if this is true, then where did all those replacement CD-4 cells that DID appear during this "war" come from? Didn't THEY require a healthy thymus in which to mature? What happened? Did the thymus suddenly "poop out" just at the moment when effective treatment was applied against the virus? In EVERY patient? ALL THE TIME?!?

Baloney.

It seems far more likely to me that the cells are being replaced as they die off. Remember that current treatments do not kill off infected cells - they only curtail viral reproduction. (Think of it as being more like a chastity belt than a gunshot to the head.) If certain cells are exceptionally long-lived, then they will be replaced only after a long time passes. And a cluster of cells dying out all at once would create a "spurt" of replacement. Syncytia are sometimes described as "cell clusters". Hmmmm...

But wouldn't the replacement of dying cells require some sort of signal from the cell to the body that death was occurring? Hmmm...

(But let's not get ahead of ourselves.)

There are other, more scientific, reasons for doubting the thymus hypothesis. Some studies have been published comparing the rate of T-cell replacement in persons with a relatively normal thymus gland to that of persons whose thymus has been completely removed. I am aware of at least one study that concluded there was no difference.

I have heard it rather peripherally argued that the NUMBER of T-cells that re-appear in the bloodstream is not what is significant: what counts is whether they are mature and functional. It is argued that patients need a healthy thymus in which these cells can mature to a more functional state. I have two replies to that: First, the NUMBER of T-cells is precisely what we are talking about, since that is the most commonly used way to monitor recovery in AIDS patients. Secondly, in my involvement with lending support to AIDS patients, I spent a lot of time in hospitals and hospices. When effective drug treatment finally became widely available about three years ago, the "AIDS wards" of hospitals and hospices emptied out literally in a matter of weeks. Patient recovery was so startlingly rapid that it placed a financial strain on some hospitals and doctors whose practices consisted largely of HIV-positive patients. If those new T-cells weren't working, I'd like to hear a really good alternative explanation for why that happened.

Don't get me wrong: I think it is better to have a healthy thymus than NOT to have one. I just don't think it figures critically into this issue.

To recap a bit: among the things that the CAT has asked us to accept so far, are the following two premises:

1. Free-floating virus in the bloodstream does not ALWAYS result in cell death and the decline in T-cell counts.

2. Many of the T-cells that DO die get replaced - and rather rapidly, at that.

There may be more than one way to skin a cat; but the more you scratch the surface of THIS CAT, the more it begins to resemble The THEORY.

ANOMALY #4: HIV-infected patients who are placed on immunosuppressive therapy, and then have that therapy withdrawn, have been known to exhibit a rebound in T-cell counts to ABOVE the level they were at before the suppressive therapy was administered. Why?

If currently accepted theories are correct, and the immune system is only just barely losing the war against HIV, then suppressing immune function ought to have an additive effect on the course of the disease. (That is: clinical decline in the patient ought to be accelerated.) I am aware of no explanation that The CAT offers to reveal how lost T-cells would be replaced under such conditions, let alone result in a net gain in numbers of cells.

But, if inhibiting the immunological inflammatory responses resulted in the attraction and absorption of fewer cells into syncytia, then CD-4 counts might actually rise following the withdrawal of the immunosuppressive therapy. (The therapy itself might likely lower T-cell counts while it is underway.) This idea implies that cell ABSORPTION accounts for the critical decline in T-cell counts.

Hmmm... there's that "syncytia" thing, again.

The point I'd like to make here is that, if syncytia figure prominently in the clinical decline of the patient, then the explanation that declining T-cell counts are due to the FAILURE of cells to die becomes much more plausible. This would lead to the "companion" conclusion that dying cells are being replaced, probably by sending some sort of replacement signal to the body.

It should be noted that the above postulates are based on my observation of patients, not on laboratory experiments using test tubes, microscopes, flow cytometry or the like. It would be nice to have some sort of experimental evidence to help prove or disprove the premise of The THEORY. But how could we devise such a test?

On to THE FULL MONTY - CHAPTER TWO: THE EXPERIMENT

THE FULL MONTY
CHAPTER TWO: THE EXPERIMENT

Remember how I've been promising you that this stuff is going to get real technical eventually? Well, this is the last chapter in which I am NOT going to get all that fancy. In the chapter following this one, I'm going to get as technical as I both need to be and know how to be. So, listen up:

First, let's recap where we are at:

According to the CAT (Currently Accepted Theories), HIV disease is caused by the HIV virus producing gazillions of viral offspring that gradually overwhelm the immune system by killing off T-cells. The slow decline to AIDS is explained by the body's apparent inability to replace the T-cells as quickly as they are destroyed.

The problem I have with that idea is that it appears to be describing a delicate state of equilibrium that is reached between the virus and the human body. Yet, as we have observed, that state of equilibrium seems extremely difficult to perturb. Very significant increases in viral load during illnesses don't seem to tip the scale in favor of the virus. Similarly, decreases in viral load don't seem to give the body much of an edge, either, unless the viral load is reduced to almost negligible amounts.

Most attempts to explain these phenomena do so in a vacuum. That is to say, they advance an explanation in one part of the CAT that contradicts another part of it. If declines in T-cell counts are caused by the rapid kill-off of T-cells by the virus, then disease progression ought to be rapid in most cases - and it is not. If the slow decline in T-cell counts is accounted for by rapid T-cell replacement, then giving the body even a slight edge ought to allow the body to overcome the disease - and it does not. How can it be that, in the vast majority of cases, T-cell replacement and the decline in T-cell counts reach some state of equilibrium? Given the wide range of viral load counts that patients exhibit, shouldn't that be the exception, rather than the rule?

There appears to be something wrong with the CAT. (Furballs, perhaps?)

All sorts of elaborate schemes have been advanced to explain these apparent difficulties. Elaborate schemes in science make me nervous. Fairly predictive models to describe the motions of the planets with the Earth as the center of the universe were advanced many centuries ago. The tip-off that these models were incorrect is that they all relied on very elaborate mechanisms. The answer, of course, turned out to be relatively simple: the Earth is not the center of the solar system - the sun is.

Not that elaborate explanations can NEVER be right - they just tend to make me nervous.

The THEORY, however, advances a relatively simple explanation: Dead T-cells are replaced. Absorbed T-cells are not.

Now, it is possible that the replacement of dead T-cells requires a complex bodily mechanism akin to taking a physical inventory. (I can sense many of you in the retail trade shuddering already.) However, it is well known that the cells of the human immune system use a biochemical process to communicate with one another, and with the body as a whole. Certain chemicals are released by cells at the sites of infection. These chemicals are various in number, and can turn the inflammatory response on, stimulate production of other cells, etc. They are generally known as "cytokines" (which means "that which moves between cells"). Some examples of cytokines are: Tumor Necrosis Factor (TNF), the Interleukins (IL-1, IL-2, IL-12, etc.) and the Interferons. Since cytokines present a known biological model for cellular production and communication, why bother to introduce complex mechanisms until we've checked out the obvious one?

As far as I know, no cytokine that performs the signaling function that The THEORY requires has yet been identified. But does it even exist? Could we attempt to prove its existence experimentally? What form might such an experiment take?

Well, I have some ideas about that. (What, you thought I wouldn't?)

If dead T-cells are required to stimulate production of new T-cells, then why not introduce a lot of dead T-cells into an HIV-infected individual's bloodstream and see what happens? Now you could try to do this by killing off a person's T-cells while they are still inside his body, but there is a real danger of complications arising out of this method. Besides, just try and suggest the attempting of such a procedure to a doctor. I have. They tend to either run from the room screaming, or subtly ask you if anyone has ever suggested that you might like to try some anti-psychotic medication. I'm exaggerating, of course; but they REALLY don't want to do that. And not without legitimate concerns.

However, there is another way:

Over a period of time, draw a supply of blood from an HIV-infected patient who has relatively low CD-4 counts. Draw a sufficient quantity of blood to roughly equal the volume of blood in his body. (This is the reason for drawing the blood over a period of time.) Store the blood until you have about the right amount. Separate out the CD-4 cells. (There are existing techniques for doing this.) Or, separate out the CD-4 cells BEFORE storage. It shouldn't really matter because of the next step: Kill the CD-4 cells. Infuse them back into the patient.

If the number of LIVE CD-4 cells in the patient rises to about double what he started with - congratulations!: you've demonstrated a connection!

It doesn't sound that difficult to me. Nor particularly expensive by scientific research standards. And, it has the added benefit of not requiring that the mechanism for any T-cell increase be known, whether it is complex or not. It simply proves that such a mechanism exists.

Now, I don't do this sort of thing for a living, so I don't really know all the practical details, but I'm going to suggest the one problem I can imagine, and leave the rest open for discussion by someone who knows about these things.

The problem could involve a possible inflammatory response. What if the cytokines in the cells induce a massive inflammatory cascade? (As if your body thought all your blood was being destroyed and had a violent response to it.) It could get ugly. Or worse.

However, this fear might be unfounded. As I said, I just don't know. I suppose this question could be answered by experimenting first on animal models (such as SCID mice) and adjusting the rate of infusion, if necessary; although that would significantly increase the cost of the experiment. I'd personally be willing to volunteer in place of the animals, though.

Now some issues involving the details:

The reason for using the patient's own blood instead of blood from donors is that we don't really know what the mechanism is, if it exists. The process could turn out to be host specific (meaning that the exact chemicals involved are unique from person to person, and might not be transferable to another patient). Using the patient's own blood avoids the problem of having to confront this issue later, if the results are negative.

The reason for using such a large quantity of blood from a patient with a relatively low CD-4 count, is that you want the result to be definitive. You don't want to get a modest increase in a relatively normal patient. That could give rise to the argument that an affirmative result was just a matter of chance. If we're going to do this thing, let's at least try to do it right.

In killing off the CD-4's in the blood drawn, the method chosen to kill them must be one that doesn't also destroy a potential chemical messenger. (This chemical would almost certainly be peptide-based.) It is a little beyond the scope of my knowledge to be able to say which would be the best method of accomplishing this. It would be very simple and inexpensive, at any rate. You just don't want to reduce the cells to an incomprehensible slag of simple atoms.

The rest of the details are pretty easy to figure out: you'd want to check the patient's baseline CD-4 count as close to the time of the infusion as possible; you'd probably want to do multiple, frequent CD-4 counts on the patient prior to the experiment to check for natural variability of results; etc. That sort of thing ought to be fairly standard experimental procedure.

I'm going to spend the rest of this dissertation explaining the details of HOW I think the process described in The THEORY might be taking place, rather than WHY I think it might be happening. So, in the next chapter, I'm going to embarrass myself by attempting to explain these processes in a very technical way.

But, you might want to stay tuned... because I am also going to go way out on a limb and tell you exactly WHERE in the cell I think we should look for this mysterious chemical "messenger".

NEXT: AT LAST!
THE THIRD AND CONCLUDING CHAPTER OF THE FULL MONTY
Chapter 3: THE "TECH" STUFF

THE FULL MONTY
CHAPTER THREE: THE "TECH" STUFF

HIV Disease and The THEORY- In A Nutshell
(A Really BIG Nutshell!)

Okay, now we're going to get into the mechanics of this. This chapter will deal with the technical details of The THEORY and its description of the process by which HIV causes clinical disease.

This is not intended to be a textbook on microbiology. I will still attempt to simplify things by leaving out extraneous issues that may be true in detail, but don't really impact this discussion. (Such as how viruses other than HIV might replicate or cause disease.)

This is also my weak suit. Not being trained in microbiology or immunology, I am dealing with an area in which I admit my knowledge is incomplete. By way of fairness, however: EVERYBODY'S knowledge of microbiology and immunology is incomplete. New discoveries are made daily, and the field can change literally overnight. I present The THEORY as a means of grasping the complex issues of HIV infection. It is meant to be a reasonably predictive model. Much like the idea of the structure of an atom being like a tiny solar system: untrue in detail, but workable on many practical levels.

With that in mind, let us proceed onward.

First, we need some background information:

IMITATION OF LIFE ?

Viruses have traditionally been thought of as very simple things. So simple, in fact, that there has been past debate as to whether viruses qualify as life-forms at all. Often, they are thought of as just a bag of chemicals randomly floating around until they bump into a host cell and break open.

It's not quite that easy.

What seems to fuel the debate about whether viruses are living things, or whether they merely MIMIC living things, is the issue of reproduction. Viruses cannot reproduce on their own: they lack the necessary equipment. They "borrow" that equipment from the cells of the host they infect. Viruses merge with those cells in one way or another in order to produce offspring. In some ways, that makes viruses a lot like men: not really self-sufficient, they just roam around looking for a chance to procreate.

Ask any woman.

Actually, there ARE similarities between viral reproduction and sexual reproduction. In some ways, the virus is like a sperm cell, and the host cell is like an egg. But we're not going to debate these similarities. They are somewhat superficial.

Like men.

Ask any woman.

Okay, okay...I know: what's with all these "men are like a virus" jokes? Well, in an effort not to get too sidetracked by the issue of whether or not viruses are living things, I'm going to take the position that viruses are no less alive than men, and put that whole debate aside. I'm going to refer to viruses as if that issue has been settled, and we've decided viruses are living things. It's mostly definitional, and irrelevant to the other issues we're going to discuss here. I just wanted to get it out of the way.

Later on, I'm going to give men a break by claiming that they really DO do more than just reproduce. I'm going to claim the same thing about the HIV virus.

PROTEIN SYNTHESIS: TEENAGERS IN LOVE

I think most of you will probably recall from high school biology that, inside the nucleus of each cell there is a double-stranded molecule that determines our genetic make-up. It is called DNA, and it is twisted into a double-helix formation. I'm not going to go into the details of how genes are composed of DNA, and how DNA is composed of nitrogen-based nucleosides attached to sugar molecules and phosphate groups. I tried doing that in a rough draft of this work, and, trust me, it was boring as all heck. If you want to know the details of all that stuff, E-mail me and I'll tell you about it. All I want you to remember right now is that, when a cell divides, the two strands of DNA separate, and the molecule "unzips" lengthwise down the middle. This exposes the nucleoside components of the molecule, which then act as templates for the formation of new copies of the DNA.

But this is not the only thing DNA does. Many times, the DNA will not completely separate from end to end; but will only partly unzip starting and ending somewhere in the middle of the molecule. When it does this, protein synthesis begins.

In protein synthesis, the exposed nucleosides in the middle of the DNA molecule serve as templates for the formation of RNA rather than DNA. The nucleosides of RNA then serve in groups of three (called codons) as receptor sites for amino acids which are carried to those sites by another, slightly different form of RNA. Amino acids can behave kind of like teenagers in love: when they get close to one another, they want to "hold hands". But there are atoms on each side of the amino acid molecules that prevent that. So, along comes a special enzyme that removes those atoms. The atoms that are removed are hydrogen and oxygen, in a ratio of two-to-one. Once the hydrogen and oxygen are out of the way, the amino acids link up by forming a special attachment to one another. This attachment is called a "peptide bond". After the amino

acids along the RNA molecule are all strung together like pearls on a necklace, they are released in this string-like formation.

But wait! What about the hydrogen and oxygen atoms the enzymes freed from the amino acids? Well, they come together and form water molecules (H2O).

Here's where things get interesting. (You mean they're FINALLY going to get interesting?): Water molecules are polar. No, that doesn't mean it's ice water - "polar" in another sense. Water molecules are not symmetrical. The hydrogen atoms tend to be grouped off to one side of the molecule, leaving the other side to be mostly oxygen. Hydrogen and oxygen have different electromagnetic charges, and this makes the water molecule polar like a magnet: one end is positively charged, and the other end is negatively charged.

Amino acids also have an electromagnetic structure, but the amino acids are not all alike. There are 20 amino acids, and when they line up in this peptide chain we've described, some of the amino acid structures are attracted to the water that is formed, and some are repelled by it. There is a kind of push-pull, attract-and-repel activity that occurs at this point. The amino acid chain is forced to kink, coil and fold until it finds a stable shape. This "dance" between the amino acids and the surrounding water limits the number of choices of shapes the molecule has. In fact, it limits it to about one choice, dependent on its amino acid composition. Even though these molecules, when seen with electron microscopes and x-ray crystallography appear to have about as much shape as a ball of lint, that shape is consistent with each molecule's amino acid sequence. These "folded-up" strands of amino acids are called "proteins". Their individual shapes largely determine the uniqueness of their functions. Besides water, most of the parts of living things - including you and HIV - are made of proteins.

Proteins are often called something else, depending on their form and function. For example, some proteins are called "enzymes". Enzymes are proteins that facilitate or speed up chemical reactions in the body. Think of them like the flame on your stovetop burner. You could dump a whole bag of unpopped popcorn into a pot with some oil, put it on the burner, and wait for the temperature of the air in the room to get high enough to pop the corn; but you're gonna wait a really long time before that corn pops. And then, if it ever DOES pop, you'd better run like heck, because it probably means the kitchen is on fire! However, if you turn the burner's flame on, the corn pops quickly as soon as it reaches the right temperature range; and you remain relatively unscathed. Not a perfect analogy... but you get the point. Many chemical reactions in your body would require too much heat to occur safely within your cells. Your body would burn up if enzymes didn't initiate and contain these processes, making them faster and easier.

You should also know that the amino acids in a protein can be linked to other types of molecules - like fats, sugars, metals, etc. Scientists sometimes categorize proteins into groups named for these other molecules. For example, a protein in which the amino acids are linked to sugar molecules can be referred to as a "glycoprotein".

So, why am I telling you all this?

Well, I thought it might be helpful to your ability to understand the rest of The TECH Stuff...

VIRAL REPRODUCTION

There are different kinds of viruses and they reproduce somewhat differently, depending on their type. We are only going to discuss HIV here.

When HIV successfully infects a cell, it does so by using protein structures on its surface to attach to protein structures on the host cell's surface. Once attached, the virus "fuses" with the host cell and injects an inner capsule-like structure (called the "capsid") into the interior of that cell. The outer protein coat of the HIV is discarded by the virus and left behind. That outer coat may then break up and float off into the bloodstream. Now, if those proteins are floating around in the bloodstream, how is the body to differentiate between them and a fully formed copy of the virus? (Fully formed viral structures are referred to as "virions" so as to distinguish them from the various individual parts into which the virus breaks down.) HIV MUST break down in order to incorporate itself into the cell. This sometimes makes clarity of discussion difficult in regard to HIV, because at some point the virus has scattered bits and pieces of itself around and deposited them in various places. It can eventually become difficult to define just where the virus is, and just exactly what it consists of.

Might this not confuse the body's immune system? What should the body do? Where should it attack? Should it attack while the virus is still inside its protein coat - or wait until the virus has fully disassembled itself? Why not leave the part of the virus inside the cell for the cell itself to deal with (by apoptosis, for example), and hone in on the outer protein coat?

The immune system attacks in as many ways as it can.

But, if much of the viral protein in the bloodstream is actually made up of discarded shell left behind by the virus, wouldn't the body's immune system be over-responding? Could this not hyperactivate the immune system needlessly? This is part of what I meant earlier when I said the body might be responding to a "false signal" sent by the virus. Host-produced antibodies might be expending a lot of wasted energy cleaning up what is really just so much discarded junk. If that "junk" were to lodge in tissues, it might be possible that the body would begin to attack those tissues needlessly. Unable to distinguish between the fully assembled virions and the useless junk, the body would respond by kicking into "hyperdrive" in order to cover all bases. This might be one way in which HIV causes autoimmune disease and allergy-like symptoms. Meanwhile, as the body is busy rounding up all this "junk", the really effective part of the virus sinks quietly into the cell.

Once inside the cell, the capsid containing the parts of the virus essential to replication migrates toward the cell's nucleus where the virus undertakes the process of incorporating itself into the DNA - the host's genetic material. In so doing, the virus once again removes its outer surface - this time the capsid shell. The capsid's contents (two strands of RNA and a few enzymes) emerge to integrate themselves into the host's DNA structure. HIV accomplishes this task with the help of a couple of the enzymes it carries along with it - one called "Reverse Transcriptase" and one called "Integrase". (Whenever you see the suffix "ase" at the end of a word, it generally means that word is describing an enzyme.) The reverse transcriptase "reads" the RNA strands as a template to create a DNA image of itself, which is then integrated into the host's own DNA structure.

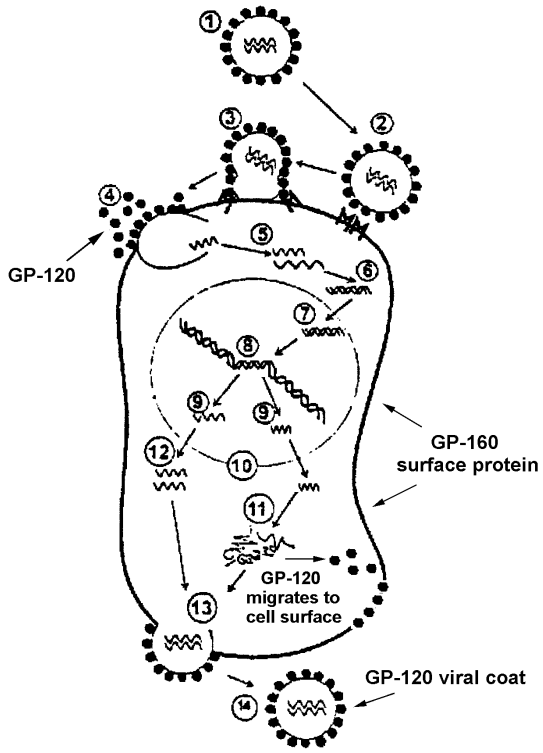
Successfully integrated, the original distinguishable virus has now all but disappeared. At this point, HIV has become a "pro-virus" - a sort of "machine" that may lie dormant, or may use the host cell's ability to replicate in order to crank out copies of the proteins the virus uses to assemble itself. Once again referring back to previous parts of this work: this development of provirus is what I meant when I referred to the "successful" infection of a cell or to "successfully infected" cells.

Another enzyme the virus uses is called "Protease". Protease facilitates a process by which a cellular protein called GP-160 is cut up into GP-120 and GP-41. "GP" just stands for "glycoprotein", and the number following it tells you by weight, how many amino acid – sugar structures are in its composition. You may notice that the numbers don't add up: GP-160 minus GP-120 would equal GP-40, not GP-41. This is because some dummy didn't round things off correctly and GP-160 is REALLY GP-161. [Okay, now before I start getting hate mail from that dummy and all of his or her supporters, let me acknowledge that this was really due to a problem with the sensitivity level of the equipment used to measure the components, rather than to a mistake by the observer. So don't go judging them as harshly as I just did. Sometimes I have problems with the sensitivity of MY equipment, too, you know.] As far as I can tell, scientists let the GP-160 misnomer stand because... well, because... well, because they seem to get a kick out of knowing something you don't know, and leaving things misnamed allows them to maintain this feeling of superiority. [Whoops! There goes the sensitivity level of my equipment again!]

Anyhow, GP-160 is a part of the surface of the cell, and migrates to the exterior of the cell where it belongs. When GP-160 is cut down to GP-120, the GP-120 also migrates to the cell surface. The difference is that, while GP-160 belongs there, GP-120 does not. In fact, GP-120 really has no business being on the cell's surface at all... but for one little detail: GP-120 is the protein that makes up the outer coat of the HIV virion.

At the end of its replication cycle, HIV collects together its necessary components and, along with a newly formed capsid, migrates to any portion of the cell surface that is composed of GP-120. The virus then uses the GP-120 as an exiting point from the cell. It breaks out of the cell by wrapping itself in the GP-120. This process is often described as "budding". The newly born virion then floats off into the bloodstream, shrouded in its new GP-120 coat.

The following graphic illustrates the process in a simplified form:



1. Free Virus
2. Attachment
3. Fusion
4. Uncoating
5. Reverse Transcription
6. Viral DNA Synthesis
7. Migration to the Nucleus
8. Integration into Cell DNA
9. RNA Transcription from DNA
10. Migration from the Nucleus
11. Protein Production
12. Viral RNA Production
13. Packaging and Budding
14. Maturing Virus

Now, I contend that, in the early stages of infection before the formation of antibodies to HIV, this process might well be fairly straightforward... but that, once the body has kicked into immunological hyperdrive and formed antibodies to GP-120 and HIV, most of these new virions are destroyed right away.

How, then, could HIV infect new cells?

Well, remember how we discussed that HIV must use its outer protein structure to attach to a cell's surface? And remember how we discussed that the outer surface of HIV is formed out of GP-120? And remember, too, that HIV infected CELLS display GP-120 on their surfaces? Well, what if the GP-120 on the cell surface allowed successfully infected CELLS to attach to other cells and infect them directly without HIV ever having to emerge into the bloodstream? In this way, cells could clump together and HIV could move from cell nucleus to cell nucleus rather than from cell surface to cell surface, avoiding the bloodstream altogether.

The next issue, of course, is obvious: What's to prevent the body from identifying the GP-120 on an infected cell's surface, and attacking the cell directly? There are some complex explanations for this - one of which involves a gene called Vpr - but, you know

me and my distaste for complex explanations. Instead, I'm going to offer a very simple one: What if the cell simply leaves the bloodstream and migrates - or marginates - into tissues where it cannot be reached very well by the circulating antibodies? Getting "out of the line of fire", so to speak.

The result of all this would be that the body expends a lot of immunological energy cleaning up "junk" GP-120 left behind by virions attempting to infect cells directly from the bloodstream, while the successfully infected cells slip away into the surrounding tissues. In oversimplified terms: the virus throws up a smoke screen while infected cells slip out the back door.

How efficient would this process be? Not very. In order to pass on the virus, the infected cells imbedded in the tissues would have to rely on drawing other cells to them. Meanwhile, the GP-120 on the infected cell's surface might make it vulnerable to other immunological defenses. Only a certain small percentage of infected cells would find a safe hiding place. It would likely take a long time before the virally infected cells caused immunological collapse. Like, oh, say...about eleven years or so. Meanwhile, the host would often not feel well, and might begin developing autoimmune and allergy-like symptoms.

Sounds like HIV disease to me.

Of course, the next problem is to account for the body's failure to replace the infected T-cells. You COULD say that this effect is simply the result of a slow process. But it also seems possible to me that the cells might need to send out a signal for replacement, and that HIV prevents this.

Of course, THEN you'd have to explain HOW HIV prevents that.

Well, I'm going to take a shot at that explanation. (You didn't think I could resist THAT did you?)

OUT ON A LIMB

Remember how I promised to vindicate men a bit by taking them out from under the "all they do is wander around looking for a chance to reproduce" label I've stuck on them? Well, this is it:

I seem to remember from back in my high school biology days that the criteria for determining whether or not something is a living thing consists of several factors, not just whether the thing can reproduce. In fact, from an evolutionary point of view, living things have to do two critical things in order to survive as a species: 1.) They must produce offspring; and 2.) They must be able to defend themselves so they can live long enough to reproduce. They can defend themselves either by fighting or running away.

Men do that. Men have the urge to merge and the urge to fight. Then they often run away. They are constantly causing trouble and then trying to making things all right again by having sex. Fighting and making up...that's how guys organize their relationships. See? Guys ARE good for something other than sex: they're good for fighting with, too.

Ask any woman.

Sorry, guys: I guess that wasn't quite as complimentary as we all had hoped.

The HIV virus behaves similarly: it attacks the cell, then merges with it. HIV is incompletely equipped for either reproduction or self-defense, so it must borrow both functions from the cell's already existing apparatus. But just what PART of the cell's defense apparatus could it use?

This is where we're going to get into cytokines a bit. I've mentioned them before, and we're now going to take a brief but closer look at them:

Cytokines are tiny bits of protein that connect to receptor sites on cells and that can stimulate some portion of the immune response. Cytokines like Tumor Necrosis Factor (TNF) start the inflammatory cascade. Blood vessels dilate, and the walls of those blood vessels become more permeable, allowing white cells to travel across this barrier more freely. Cytokines such as IL-2 cause the proliferation of certain white cells (including CD-4's) so there are more of them available to attack infection. However, I don't think IL-2 causes the creation of new T-cells so much as it causes existing T-cells to divide. The reason for me thinking that is the phenomenon of viral load increase: When IL-2 is used to cause T-cell proliferation, it also causes HIV viral load to go up. This is what you would expect to see if cells carrying the HIV provirus were stimulated to divide. IL-2 is a useful tool, but only if you can suppress viral replication at the same time you administer IL-2... otherwise, it's kind of a wash. Other cytokines assist in the inflammatory process as well. Cytokines offer us a model of a mechanism for activation of the immune system, and for cellular replication. To create brand new cells, a cytokine would have to stimulate cellular production in the bone marrow, which is ultimately where all blood cells originate. It is possible to think of cytokines as being part of the cell's defense system: the part that sends for help.

Now, if the cytokines are inducing and regulating inflammatory responses, they can't just be present in your bloodstream in significant numbers all the time. If that were the case, you'd walk around inflamed all the time. The cytokines must be coming from somewhere. Obviously, they are coming from somewhere in the cells. This, then, means that the cells must produce cytokines. But are the cytokines being produced and stored inside the cell, or are they not produced until infection occurs?

The following is sheer guesswork on my part:

Logically, it makes more sense for cells to produce and STORE cytokines so they can be released as rapidly as possible when a cell is attacked by an outside invader. Where would the cell store these cytokines? Again, the logical answer would be: "in the location where they would be most readily available". In other words, they must be at or near the cell surface, so that any initial breach in that surface would immediately induce inflammation.

Well, what if they are ON the cell's surface? What if they are strung together so they function as ONE kind of protein while the cell is intact, and like a DIFFERENT kind of protein when the cell's surface is disrupted? Breaching the cell surface would break the amino acid chain of the protein string, disrupt the electromagnetic balance of the structure, and cause the protein and any fragments of it to re-fold, giving them a new shape. Since the shape of a protein largely determines its function, these fragmented proteins could take on a new role. Perhaps a cytokine-like role.

And what if this theoretical string of cytokines forms a surface protein commonly known as GP-160? This would make the amino acid sequences in GP-160 an essential part of the cell's ability to induce inflammation and stimulate cell growth.

But if GP-160 were cut down into a smaller chain of amino acids - say, GP-120 - wouldn't some of that amino acid sequence now be missing? And what if the missing sequence was part of a cytokine that stimulates new T-cell production? Then the cell would become deficient in it's ability to signal T-cell production.

It's just a theory.

And certainly not essential to The THEORY as a whole. But what if it's right?

The implication would be that there might be a whole other approach to HIV treatment: using anti-inflammatory agents to cut down on autoimmune symptoms and slow the syncytial process, one could then administer doses of the proper T-cell producing cytokine and restore near-normal immunity without ever having to directly attack the HIV virus at all. In other words, you'd assist in the creation of a symbiotic relationship, and allow the virus and the host to co-exist.

Live and let live.

What a concept!

Of course, you couldn't constantly immunosuppress the host unless you had an effective suppressant that worked only on the overproduced inflammation, as opposed to ALL the body's inflammatory processes. Using current commonly available immunosuppressants, you'd have to go on and off them every few weeks to allow the body to fight infections other than HIV.

It would be interesting to compare the amino acid sequence of GP-160 to known cytokines to determine if the process I described above might be possible. And it would be at least equally as interesting to compare the amino acid sequence of GP-160 to GP-120 to see what part is missing or chopped up.

Just a thought.

Okay, we are now at the point where we can once again summarize The THEORY, but in detailed terms, and with the addition of some predictable consequences.

The THEORY

When HIV enters the bloodstream, it may do so as free-floating virions, or it may gain entry as a provirus inside an infected cell. This implies that co-infection with a disease that draws white cells to the site of transmission (usually the genital area) would increase the risk of transmission significantly. In other words: you'd be more likely to spread HIV if you also have a venereal disease. Other non-venereal inflammations in the pelvic area would also increase the risk for both parties involved.

It takes a little while for the body to produce an antibody to the HIV virions. During this stage, HIV would more easily move from cell-surface to cell-surface through the bloodstream. Also, provirally infected host cells that have expressed HIV-created proteins such as GP-120 on their surfaces would have a better opportunity to become syncytial and migrate out of the bloodstream. One of the major factors in the body's defense against the virus at this point would be apoptosis. Because of this, T-cell counts would fall dramatically in the time just following initial infection.

Once the antibody to HIV appears, HIV's chances of survival in the bloodstream would drop significantly. It might occasionally infect a cell through the circulatory system and then go on to create a provirus, but the odds would be against it. As the immune system gears up, the infection of new cells would be severely curtailed. T-cell decline would slow down at this point. In fact, the number of T-cells would perhaps even RISE for a while after the body begins antibody production; but T-cell counts would never rise completely back to normal. Some provirally infected cells would already have become syncytial and migrated or marginated out of the bloodstream into the tissues of the lymphatic system, the liver, the spleen and into the brain-blood barrier, as well as to other sites. These cells would have a slight edge in survival, but it would take years for such a small survival advantage to greatly impact the host.

Among other things, the process described above implies that it would be unlikely for a person already infected with HIV to become re-infected by someone else.

Free-floating fragments of GP-120 would continue to hyperactivate the immune system. This, coupled with inflammation induced by the marginated or sequestered proviral cells, would frequently induce symptoms of allergy or autoimmune disease. In addition to other things, this might cause Polyglandular Deficiency Syndrome by altering adrenal

function. Because of this, an HIV infected individual might feel very ill for years, despite continually demonstrating lowered, but adequate T-cell counts.

Eventually, the syncytial nature of the marginated and sequestered proviral cells would allow them to absorb other white cells drawn to them by inflammation. This absorption of cells would prevent them from alerting the body that those cells need to be replaced, and cell counts would begin to decline more rapidly. An HIV-induced deficiency in proteins necessary to send this "alert signal" might slow the process of T-cell replacement even more.

With the decline in T-cell counts accelerating, the host would lose his ability to fight off other illnesses, and would eventually die.

Relying on an inefficient system of infection, and with the body attacking it from all directions, the chances of viral survival would ordinarily be very slim. Only provirally infected cells that have found a "safe haven" somewhere in the body would have significant longevity. The percentage of viral offspring lucky enough to have survived would be very small. The means Nature commonly uses to overcome such enormous odds against survival is to produce equally enormous numbers of offspring to compensate. This production of huge numbers of progeny results in a huge number of mutations as well, allowing the virus to adapt to its environment quickly and overcome drug treatment.

Treatment with medications that block production of GP-120, or that prevent syncytial fusion would prove effective; but only to the extent that they prevent the virus from moving into another cell and producing more provirus. Complete blockage of the syncytial process would halt disease progression. Eventually, provirally infected cells would die, and any GP-160 on their surfaces would degrade to signal the production of new T-cells. If provirally infected cells were long-lived and did NOT readily die off for some reason, the blocking of syncytial fusion would still slow or halt disease progression in spite of elevated viral load counts. However, without the death of these cells, the necessary "replacement signal" would not be sent, and T-cell counts would not rise beyond a certain point. In rare cases, a strain of HIV might exhibit resistance to drug treatment because of the production of a variant of GP-120 that is less efficient. The result would be the otherwise bizarre situation that viral load and T-cell counts might BOTH rise. All of this implies that the level of HIV viral load is a "surrogate" marker, indirectly measuring the number of, and the level of activity of, provirally infected cells.

Now, I don't know about you, but that sure SOUNDS like what I've observed first-hand over the years. The THEORY might not be correct in every detail, but it sure has been useful to me as a model for how to think about this disease. At least from a patient's point of view.

Three things have caused me to think long and hard before publishing The THEORY:

1. Some people believe everything they read. By publishing this, I take the risk that people will absolutely and totally believe that everything I've written about is a known fact. I want to make it clear that, as of the time I am writing this, that is not the case. The THEORY is a theoretical model of HIV disease that has not been proven, and might never be proven. It could be wrong.

2. Some of this has already been discussed with the few doctors and scientists I've been able to find who were willing to listen to me. Occasionally, I've been asked to keep silent about some aspects of The THEORY while those aspects were being investigated.

3. Howard, the Aspirin Guy.
   Okay, # 3 is going to require a little explanation: Howard is this guy who, for years now, has been showing up at medical conferences, vocally advocating the investigation of the use of aspirin in treating HIV infection. Howard claims that significant slowing of the progression of HIV disease can be accomplished by the proper administration of aspirin. He observed this phenomenon himself many years ago. Nobody every seemed to want to listen to Howard. There aren't big bucks to be made off aspirin, so no one wanted to invest money in investigating it. Through a sense of duty to the community, Howard became very vocal about this. He researched the topic, debated doctors and scientists, and stood up at medical conferences to ask for money to do proper clinical trials. Howard has done so much research on aspirin that he is now probably one of the world's leading experts on the topic. His theory about aspirin is so technical I don't even understand it. Thanks to Howard, some limited scientific research on the use of aspirin to treat HIV has been done.

   I don't mean to imply that aspirin always works for everybody, and is the answer to the epidemic. Even Howard doesn't claim that.

The point of the story is this:

My initial response upon first hearing Howard bring up the issue at a medical conference was: "Hmmm... another anti-inflammatory." I had been observing for years that anti-inflammatories and immune suppressants such as prednisone and cyclosporin had a positive effect on HIV disease, though no doctor would help investigate them. The response to Howard from the majority of the other participants at that conference was: "Uh-oh...a nut!"

Despite years of very good research by Howard, and despite his insistence that aspirin can be used to TREAT HIV disease, not CURE it, Howard is still saddled with the label: "That nut who thinks aspirin cures AIDS." To his credit, Howard continues the fight for aspirin research to this day.

The reason Howard is item # 3 above is this: I just didn't want to be labeled as "That nut at Steve's website with that incomprehensible AIDS theory."

I have decided, however, that The THEORY presents a pretty comprehensive model of AIDS, and is worth advancing... as a mental exercise, if for no other reason.

I guess that makes ME the nutshell that contains The THEORY.

So, there you have it.

I'm finished.

That's my mental exercise for a while.

I'm gonna go back to bed and rest up, now.

Perhaps, if I get enough rest, I will next attempt to explain why Barney, the Purple Dinosaur is so popular.

Naw! I don't think even I could tackle that one!

;-)
.....Dickie

Completed: December, 1998

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