DEDICATION

The THEORY is fondly and lovingly dedicated to those who inspired it:

To Dave H. of the Wednesday Night Group... who never stopped talking to me about it
&
To Dr. G of Tarzana... who never stopped listening to me about it

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Dickie’s Personal HIV Theory

Part One: A BRIEF HISTORY OF THE THEORY

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

My theory has its earliest roots in the days when I was coming down with a mysterious series of symptoms and illnesses that could not be explained by my doctors. (The starting time frame would have been late 1980 through late 1982.) All attempts at diagnoses proved to be dead-ends. Through a process of elimination, it appeared that my condition shared many of the characteristics of autoimmune diseases like Lupus, although all autoimmune diseases known at the time had been ruled out diagnostically. Still, I felt my symptoms were immune-based, and probably involved some sort of autoimmune process.

Several years later, I would come to be the co-facilitator of an AIDS support group that was very large, and was attended by many people who were very savvy both medically and pharmaceutically. Facilitating that group also brought me into contact with many providers of services to people with HIV / AIDS, and eventually earned me the label of being an "AIDS Activist", although that was never my intention. I was just trying to survive and to help others. (The term "activist" always held a much more political connotation for me.)

Beyond all of the above, you should know that I was raised a small-town-boy in a forested environment. My observation of nature had taught me that any organism that rapidly and aggressively destroys the environment it requires for life, soon becomes extinct. Also, it seemed to me to be generally true that organisms that produce many multiples of offspring rapidly, do so because the individual offspring have a poor chance of survival. This led to the simple idea that HIV was NOT very effectively infecting its environment; and that some other mechanism must be at work to enable HIV to eventually cause the death of the patient.

The THEORY has some foundation in my own philosophical approach to people: namely that, if a person is ill, it is NOT because there is something "wrong" with them. Stated this way, it seems fairly easy to see, but the following dialog illustrates the principle:

PATIENT: "Doctor, what's wrong with me?"
DOCTOR: "You have AIDS."
PATIENT: "I'd like a second opinion."
DOCTOR: "Okay: You're ugly, too!"

It's an old joke, I know; but it illustrates a certain point. When someone (including ourselves) is sick, we tend to ask: "What is wrong with them?" It's somewhat ingrained

in us to look for what is wrong with people. I'm as guilty of it as anyone else. When examining a new disease like AIDS, it is very easy to ask: "What is wrong with these patients?" But if that is your starting point, then you might easily find yourself looking for flaws in the patient that are not there.

The assumption was quickly made that HIV "destroys" the immune system; and that "what is wrong" with AIDS patients is that their immune systems have been crippled. Many - if not most - people assumed that the disease was gradually "wearing out" the immune system; and that people who had been infected for a long time had hopelessly lost their immunities.

But, I asked it the other way around: What if there is NOTHING wrong with the patient? What if the patient's immune system is properly responding to an improper signal (or NOT responding to a LACK of a proper signal) from HIV-infected cells? It threw a different light on the issue, and suggested different avenues to investigate. Moreover, it suggested that chronically infected individuals COULD respond to treatment, and should not be given up for lost. All-in-all, it seemed a more positive approach, and it appealed to me.

After some time observing the pattern of HIV in others, I decided I wanted to try to find ONE known disease or condition that could explain all of what we were seeing. This necessitated the reading (and deciphering) of medical texts and reference books which, in turn, required accumulating SOME knowledge of microbiology.

I want to make it clear that I am NOT a doctor, med student or scientist. I DO want to stress that my knowledge in these areas is incomplete.

I eventually came to the conclusion that the only known condition that was likely to explain most of what we see in the development of AIDS was something called "Polyglandular Deficiency Syndrome"; which, it turned out, is an autoimmune disease.

Polyglandular Deficiency Syndrome is actually not one single condition, but a whole constellation of potential manifestations of disorders that can occur when the body's endocrine (or glandular) system is mistakenly attacked by the immune system. Further investigation convinced me that such a condition - if it played a role in AIDS - had to be occurring at the level of the adrenal glands or higher.

The adrenal glands produce a substance called "cortisol" that has a role in regulating inflammatory processes. I concluded that, if the adrenals were malfunctioning as a result of an autoimmune attack, then the cortisol levels in the body might be too low. **(WARNING! This has NOT proved to be the case!)**

To understand the next part of this tale, you have to understand the general atmosphere surrounding AIDS back in those days, and what we, as AIDS patients were facing. There was no effective treatment for HIV back then. An AIDS diagnosis was almost certainly a one-way ticket to an ugly death. There were ideas and theories floating

around, some of which were well-grounded in fact, and some of which were truly idiotic. Some of the more well-grounded theories were not being investigated, mostly because they were not "fundable". (That is to say, nobody was going to make money off any discoveries that came from investigating them.)

And, some people that I loved very much were dying.

So, knowing that I had a little bit of knowledge that would help me sort out the science from the fiction, I decided to use myself as the guinea pig in a series of experiments designed to test out some of these theories. (What can I say? Love makes you do strange things.)

I won't go into all the experimentation, but I decided to try out the "adrenally-induced low cortisol" theory by supplementing my own cortisol levels. However, just before starting the experiment, evidence emerged that persons infected with HIV actually develop cortisol levels that are too HIGH, so I aborted the experiment. (Many thanks to Dr. Don Kotler.)

I decided to attack the endocrine theory from another direction: If the adrenals are being caused to malfunction in some way, is it because of a direct attack on the adrenals by the HIV virus; or is there an autoimmune process that is causing this malfunction? I looked into the possibility that the body was being "misled" into attacking itself due to false signals being sent by HIV infected cells.

This led me back into microbiology, and the emerging importance of cytokines in cellular communication. Cytokines are bits of proteins that are used as signaling devices between cells. It seemed likely to me that, if the cells of the immune system were attacking the wrong tissues, then cytokines must somehow be involved. If this was a condition that developed as a result of cellular infection by HIV, then, more than simply infecting a cell and highjacking its reproductive system, HIV must be highjacking the cellular communication system as well. This idea, coupled with the observation that HIV infection commonly takes several years to produce clinical disease, led to the theory that T-cell decline and the failure of the body to ultimately control infection was being caused by modifications the virus was making in the cellular communication network.

These ideas taken together led to the creation of The THEORY. (Throughout this dissertation, I am putting the term "theory" in capital letters when referring to my own theory, so as to distinguish it from the theories of others. I suppose I could have just given The THEORY a name - something like "The Dickie Theory" or the "More-Positive-Way-Of-Looking-At-It Theory" or some such nonsense; but capitalizing it seemed simpler, and only slightly less pompous than naming it after myself. It's not meant to be pompous, however. It is merely meant to differentiate it.)

Almost none of the individual ideas in The THEORY are entirely my own creation. I have borrowed heavily from many other sources. The THEORY is, rather, a quilt-work of ideas that form a thematic whole.

My purpose in presenting The THEORY here is to follow the pathway down which a slightly different point of view might lead us.

The THEORY is not intended to be the one-and-only Truth, and should not be regarded as such. It is simply an exercise in listening to a different drumbeat, so to speak.

In an attempt to make The THEORY more readable and more easily understood, I intend to present it in three progressively more detailed and complex formats, which should be read in sequence.

First, we will take “**THE NICKEL TOUR**“ of The THEORY.

In order to respond to some of the more obvious questions that may arise out of The NICKEL TOUR, a more detailed explanation will follow it - referred to as "**THE DIME TOUR**."

Following that will be a very complex discussion of the possible microbiological mechanisms involved. That discussion will be referred to as "**THE FULL MONTY**".

Bear in mind that each discussion becomes progressively more technical, and each question, as is the want of questions, raises yet more questions.

Also bear in mind that I do not insist that each and every individual element of The THEORY is absolutely correct. In fact, I will pretty much guarantee that parts of it will be proven wrong. But, as a working model to try and predict the behavior of HIV disease, it has worked fairly well in the past; and can hopefully be useful as a starting point for more accurate and comprehensive theories.

On to **THE NICKEL TOUR**.

Part Two: THE NICKEL TOUR

The THEORY proposes that, when particles of HIV first enter a person's body, that person's body, having never been exposed to this disease before, has no effective defense against it. The body must manufacture a new antibody to neutralize the invading HIV. This process apparently can take up to six months, during which time the virus moves about freely and operates relatively unfettered.

I propose that it is during this early period that the greatest number of cells are successfully infected by HIV. Once the antibody to HIV has been formed, any virus in the bloodstream is quickly attacked and destroyed, and the virus can no longer move freely through the bloodstream to infect other cells. But the virus survives, hidden inside the cells it successfully infected before the antibody appeared.

These chronically infected cells persist for years, forming a "reservoir" of live virus. This would result in an apparent "latent" or "dormant" phase of the disease.

It would also result in a "set-point" phenomenon in which the reservoirs of infected cells continue to produce virus at a certain level. Variations in this viral level may be brought on temporarily by environmental factors, such as the introduction of other diseases, or the initiation of drug therapy, which would disrupt viral reproduction in some way. But removal of the cause of the disruption would always result in HIV levels returning to their "set-point", because the reservoir of infected cells hasn't been killed, and newly created virus has been unable to infect new cells.

The THEORY is also predicated on the idea that the body's immune system is not "worn out" as many had believed (and some still do). Rather, the immune system is “confused" - intentionally misled by the virus' ability to hijack the communication system between cells. Many now subscribe in one way or another to this part of The THEORY. A "die-off" of infected cells should theoretically allow the immune system to restore itself. This prediction has proven to be true by the reconstitution of the immune system during effective treatment with protease inhibitors and other antiretrovirals.

The THEORY proposes that, once infected, a cell's ability to communicate with other cells becomes disrupted and sends "false signals" -- or NO signals -- to the immune system, causing it to shut down some parts of the immune response, while hyperactivating it in others.

The THEORY also predicts that, under some circumstances, treatment with certain immunosuppressive agents (such as prednisone or even aspirin) could result in an unexpected rise in T-cells. This has also been observed.

From a treatment standpoint, what this means is essentially very simple:

Since what matters most is not how much virus is detectable in your bloodstream, but how many CELLS are virally infected, a simple, effective treatment would be one that destroys virally infected cells, rather than relying on retarding viral replication. Cell death is the major key component to The THEORY.

Unfortunately, as far as we know, no one has yet figured out how to target only infected cells with a cytotoxin (a substance poisonous to cells). Currently approved therapies rely on interrupting the viral reproductive process, and waiting for cells to die off on their own. The THEORY predicts that this is likely to leave a reservoir of live infected cells that may at some point produce a mutation resistant to treatment. (This is, in fact, what we see in actual practice now.)

So, if killing off infected cells should be the goal, but we have not yet reached that goal, is there an alternative?

I think there is, but the very idea of it has terrified virtually every doctor to whom I've ever explained The THEORY. The alternative would be to kill off immune cells regardless of whether or not they are infected, and let the immune system restore itself naturally. This, of course, would require a strictly supervised procedure in a patient absent of any potentially damaging infection.

It is likely that killing off ALL the immune cells would prove unnecessary. Killing off a substantial number of cells might be sufficient. This part of the theory predicts that useful treatments might include already available and relatively inexpensive treatments for leukemia. This has proven to be true in the case of hydroxyurea, which was finally researched and is now used in "salvage therapy" treatments when other medications have failed. It might be best to use hydroxyurea as a "first line" treatment, however, in order to avoid potential complications from blood cell disorders that commonly occur in late-stage patients. There are likely to be other drugs that work as well or better than hydroxyurea already on the market.

In addition, The THEORY also predicts that, against the expectations of most - if not all - other theories, an HIV-positive patient being readied for a bone marrow graft (either from a human donor or a baboon or whatever) would eventually recover a significant part of his immune function, despite failure of the marrow graft. This phenomenon has been observed as well.

I think it is too much to hope that we could ever destroy the total reservoir of infected cells by this - or any other - method. Eventually, you would expect to see viral rebound, and the process would have to be repeated - perhaps every 12 to 18 months or so.

Obviously, with the advent of HAART (Highly Active Anti Retroviral Treatment), the ideal thing would be to combine BOTH therapies; and treat the patient with currently available anti-HIV regimens while the immune cells are being restored by the body.

That's essentially it - in extremely simplified and condensed form. (But at least it's understandable when it's condensed to this point.)

For those of you who want more detail, I offer the "**THE DIME TOUR**" explanation immediately following this summary.

If you want still more information - and enjoy being confused as heck - a detailed examination of the possible mechanisms involved follows the DIME TOUR, under the heading of "**THE FULL MONTY**". (WARNING! "THE FULL MONTY" explanation is highly technical, and has been known to give even students of microbiology very severe headaches.)

On to THE DIME TOUR

Part Three: THE DIME TOUR

So, okay: you've read the Nickel Tour and you're still not bored, but you may have a few questions.

First of all: if HIV is not really successfully infecting a lot of new cells all the time, what accounts for the decline in the number of T-cells?

T-CELL DEPLETION - PART ONE: APOPTOSIS
(Uh-oh...Big Words Already)

You can SEE T-cells die off. This MUST disprove the principle of The THEORY, right? Well, not necessarily. Remember that the basic principle of The THEORY is that none of the participants (you, your cells or HIV) are doing anything WRONG. All organisms involved are just trying to do the best they can. HIV doesn't know YOU exist. It is simply utilizing the available resources (your cells) the best way it can.

From a Darwinian point of view, this would almost HAVE to happen sooner or later...the virus that does the best job of utilizing resources would have a survival advantage over varieties that do not accomplish that.

HIV reproduces rapidly and in vast numbers. And it makes a lot of mistakes when it replicates. Hence, it mutates very rapidly. This allows it to quickly select for variations that are better adapted to the environment in which it finds itself. A "hungry" virus that eats up every cell around would rapidly run out of its "food" supply. But one that invaded a cell and kept it alive as long as possible would live to produce more offspring like itself, and hence would have a survival advantage.

***THEORY: HIV is really trying to keep the infected cells ALIVE, not kill them.**

Okay, so all that makes sense. But you can still SEE T-cells die off. How would The THEORY explain that? Well, remember that your body's CELLS are also doing their best to survive. What makes them different from the HIV virus is that the cells in your body have evolved over millions of years into a life form that lives in colonies. Your body's cells each have a highly specialized function, and require the support of other cells in the colony (a.k.a.: your body) to perform other functions.

In other words: each cell of your body does its own special part to work TOGETHER with others to assure the survival of the whole colony. (Unlike many people, it seems.) When a cell becomes infected, it communicates to the rest of the body that it is "sick". If the other cells of your body can't save the infected cell fast enough, it may "commit suicide" in order to protect the surrounding cells from infection. (Very romantic, eh?) Cellular suicide ("programmed" cell death) is referred to as "apoptosis".

Now the picture begins to come together a bit:

***THEORY: T-cell death in newly infected cells occurs through apoptosis.**

Once the HIV virus enters a cell, it would have to move rapidly in order to save the very life of the cell it has infected before the cell "calls for help" and commits suicide. The result is a biological race against time. I assert that this is a race that HIV often loses. In an ironic sense, this would imply that a certain amount of T-cell death might actually be a "good" thing.

Now, from an evolutionary standpoint, this makes perfect sense. HIV would likely have evolved rapidly into a form that keeps the cell alive as long as possible. And your body's cells have evolved to cooperate with other cells in order to preserve the whole organism (namely: YOU) - even to the point of suicide.

The result is an ironic evolutionary twist: to the outside observer, it would be natural to assume that the virus is trying to kill the cell, and that the cell is trying to survive; when, in fact, the virus is trying to SAVE the cell, and the cell is trying to destroy itself. This seems to me to be so likely as to be probable, rather than possible.

But what's the big deal? One way or the other, HIV is causing cell death. We've really just described a mechanism for T-cell depletion that would seem to support currently accepted theories rather than THE THEORY, haven't we?

Well, I'm not done yet. Don't be so impatient.

Cells in your body die all the time, and have to be replaced. But if your body just replaced cells on a simple "time clock" basis, producing new cells at a regular pace, you'd end up with either too many or too few cells almost all the time, due to errors and delays in synchronizing the timing.

***THEORY: Cells must somehow signal the body when they die, so that they can be replaced.**

If this is true (and there is a large body of scientific evidence that cells do send out chemical signals), then dying infected cells would be replaced by healthy new ones at about the same rate as they die off.

The expected consequence of this would be that T-cell counts would remain at a certain relatively constant level for a very long time, despite the presence of HIV infection. This is a known fact. The average time from infection to death (in the absence of treatment) is about eleven YEARS. Critical decline in numbers of T-cells doesn't really occur until about the last three years of the illness.

But T-cell depletion DOES occur slowly, and then suddenly accelerates. How does The THEORY explain that?

T-CELL DEPLETION - PART TWO: SYNCYTIA

"Syncytia" is a fancy word used to describe cells infected by viruses (including measles, cytomegalovirus, and HIV) that can cause the infected cells to be able to absorb other cells.

Now, you will often see syncytia described as "cell clumps" or "cell clusters". This conjures up images of cells gathered together like bunches of grapes. But, if you ever see pictures of syncytia, what you see appears to be much more like one big cell with a whole bunch of nuclei.

So, why is this important?

Remember that The THEORY requires that HIV must have a mechanism for keeping a cell alive.

***THEORY: By ABSORBING rather than killing other cells, the virus incorporates the nutrients and mechanics of the absorbed cell into the infected cell, thereby increasing the pool of resources available to the virus.**

Think of it like going out and buying a second car, and using the parts from it to repair your first car. The more cars you buy, the more parts you have to keep the original car running.

What would be the consequences of such a mechanism to the human body as a whole?

Well, remember that we have theorized that dead T-cells would signal the body to replace them.

BUT: if the cells are absorbed rather than killed, then there are no dead cells to send the replacement signal. Absorbed cells would not be replaced. Over time, the population of individual cells would decline in number.

However, we don't really see a large number of syncytia until the late stages of the disease. The percentage of syncytial HIV-infected cells in the bloodstream appears to be fairly low until the later stages of infection. So, if we don't see them in the bloodstream, where are they?

T-CELL DEPLETION - PART THREE: HIV MEETS TV-LAND: "MY LITTLE MARGINATION"

Giant syncytial cells don't work as well as normally sized cells.

It is one of the functions of white blood cells (of which T-cells are a part) to be able to squeeze through the walls of capillaries and such in order to be able to reach sites of infection and inflammation. A giant cell just wouldn't be able to squeeze through the

membranes very well. In fact, as it grew in size, a syncytial cell (more properly called a "syncytium") would approach the point at which it couldn't squeeze through at all. But, before that, it would likely reach a point where it would be able to squeeze partway through, and then get stuck.

The process by which blood cells get stuck in surrounding tissues and therefore no longer circulate through the bloodstream is called "margination".

I will use the term "margination" in a somewhat broad sense in this section. When I use the term here, I mean it to refer to any process by which blood cells cease to circulate and become stuck to or imbedded in surrounding tissues. Some white cells and T-cells might do this by a process different from the one described above.

***THEORY: HIV infected cells that have become syncytia marginate into surrounding tissues and get "caught".**

Margination can cause inflammation of the tissue in which the cells are caught. The function of white cells is to migrate to sites of infection and inflammation in order to control disease processes. Inflammation attracts white cells. An HIV-infected syncytium absorbs other white cells, becoming larger. Larger cells would tend to marginate.

Hmm... notice a pattern here? Now we can see a kind of process at work:

HIV would cause a successfully infected cell to absorb other cells. At first, this would hinder movement of the HIV syncytium only slightly, and the cell would be less functional, so its chances of coming into direct contact with another T-cell is only just so-so, and disease progression is slow.

But, over time, the infected cell would gradually grow in size until it marginated, causing inflammation and attracting other T-cells to it. After a certain critical point is reached, disease progression would become rapid. Kind of like a dying star in space growing in mass continually: eventually it forms a "black hole", and everything nearby gets sucked into it. The cells getting absorbed into an HIV syncytial "black hole" would never be replaced, and the immune system would collapse.

SUMMARY

Congratulations! You made it to the point where we can now summarize the basic concepts, and put the whole THEORY together for the first time! (That really wasn't so bad, was it?)

If you will notice, throughout The DIME TOUR, we have encountered certain "bullet points" marked by the word "*THEORY" in capital letters. If we pull all these concepts together, along with a basic concept or two presented in the NICKEL TOUR, we should get a summary of The THEORY in simplified form:

THE THEORY

HIV is trying to keep cells ALIVE - not kill them.

HIV does not really move very well from one cell to another through the bloodstream, and must produce a vast number of offspring in an attempt to accomplish that task.

Once the human body mounts a defense against HIV, the virus's ability to move from cell to cell is even more severely curtailed.

Many of the newly infected cells will kill themselves through apoptosis.

The T-cells that die signal the body to produce more T-cells to replace them.

Cells that have been successfully infected by HIV become syncytia and absorb other cells, rather than killing them.

The absorbed cells send no signal to the body, and so are not replaced.

HIV syncytia marginate into the surrounding tissues, causing inflammation.

Inflammation draws other T-cells to the marginated syncytia, where they are absorbed by them.

This process repeats itself until enough cells have been absorbed to cause the immune system to collapse.

WHAT'S THE BIG DEAL?

The big deal is that The THEORY suggests certain diagnostic and therapeutic options that are contradictory to most of our current approaches to investigating and treating HIV.

It also predicts that the newly developed treatments will likely never eradicate the virus, since virtually none of them kill off infected cells. This would require HIV patients to continue treatment with high levels of expensive and toxic medications forever, placing a strain on both the body of the patient, and the price of healthcare. Like it or not, this IS the scenario that is currently playing itself out.

WE NEED TO FIND BETTER AND CHEAPER TREATMENT OPTIONS.

To that end, we need to keep an open mind and investigate all leads. Otherwise, we risk trapping ourselves in a scientific cul-de-sac that results in the development of expensive therapies that are only partially successful.

For those of you who have stuck around this far: the basic THEORY has been described in this section and The NICKEL TOUR. Virtually all of what you really need to know has already been presented. It is my intention to present one more segment, called The FULL MONTY. It will deal primarily with the implications, consequences and additional questions that THE THEORY raises in light of more detailed scientific investigation. (Things might get ugly.) It will touch upon such complex and hard-to-understand things as cytokines, inflammatory responses and Howard, The Aspirin Guy. (Sorry, Howard: I couldn't resist.)

So, if any of you feel you'd like to leave now.... well, you've been warned.

On to THE FULL MONTY.