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STICKY WICKET

Corona XLVII – flash

Mole

Original artwork by Pete Jeffs - www.peterjeffsart.com

Well, that was fast. First, the Omicron variant appeared in South Africa, amidst a chorus of "I told you so's." Perfectly appropriate, that. We had been repeatedly warned that if developed nations did not work to distribute vaccines in the less developed world, the latter would be fertile soil for the emergence of new variants. We had seen this before (remember Delta? And before that, B.1.1.7?), but there was never much urgency to dispense with international vaccine patents and roll out the goods. Short-term profits over long-term, um, well, profits. Because controlling the virus worldwide would certainly have profited all of us. So, have we learned anything? Probably not.

Within literally days, Omicron has become the major variant throughout my country, and probably yours (if not, wait for it. It will). The good news is that it has turned out to cause less severe disease, especially among the vaccinated. The bad news is that, even with milder disease cases, we are facing a tsunami of hospitalizations, simply because it spreads so quickly.

When I was a molet, I loved comic books. I rarely actually *bought* any – they were too expensive for my family's modest budget, but I would read them tirelessly when visiting friends. One of my favorites was The Flash, Jay Garrick, who as a college student had a laboratory accident that gave him his superpower. (I think the fact that he worked in a lab was what did it for me – I was always a science geek). My memory of this accident had him tumbling into a bathtub of chemicals, but a bit of research informs me that I remember wrong. It appears that what happened was that he took a break to smoke a cigarette (this was 1940, a time when I guess people smoked in labs; no, I'm not that old, but my friend had a lot of old comic books). During his break, he accidently inhaled fumes from 'hard water,' whatever that was supposed to be. I think later this was re-envisioned as 'heavy water,' probably because anything associated with radioactivity was considered pretty cool. Nevertheless, the fumes imbued him with the power to move really, really quickly. So fast that everything around him came to a relative stop. And so, he did what any college student of the time would do, he became a football star (American football, not the sort most of you play). Then he decided to fight crime.

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This idea, of moving really fast (like a Flash, see?) captivated not only my young self, but also lots of television and movie writers. I doubt that it originated with The Flash, though. Mercury moved very quickly, although he used this to deliver messages, not fight crime. I vaguely remember an old episode of 'The Wild Wild West' (also a favorite of my young self), in which criminals gained this ability in order to *commit* crimes, apparently via an elixir they distilled from diamonds (which made perfect sense to 8-year-old me). But I digress. ("Really, Mole?" "Yes, but we'll get back on track in a jiffy").

So, Omicron is The Flash. (You knew I was going there, because you are very smart). It is spreading so fast that it is leaving other variants, such as Delta, standing still. But why? Omicron has 37 mutations compared to the original Wuhan strain, with 15 of these in the receptor-binding domain of the spike protein. The latter increase its receptor-binding affinity (compared to Wuhan) but that is not very different to that of Delta. We know that it appears to replicate very quickly, resulting in high viral titers early in the infection, but to date I have not found any insights into which mutations might be responsible for this. But such rapid, high titers, especially in the nasal passage, may account for its rapid transmission. It may also account for why the immune response, even among those of us who are vaccinated (and boosted, thank you) struggles to keep up, although, fortunately, it appears that it *does* catch up, rendering the symptoms mild. There are a lot of mysteries here. If it is replicating so quickly, why doesn't it appear to produce the loss of smell and taste we have seen among those infected by other strains? (This loss of taste and smell is also not well understood, so this may be a double mystery). And why is it apparently not as lethal? (We talked about this last time – viruses don't 'care' if they cause disease unless the disease assists in transmission).

This 'less lethal' thing may be an illusion due to the ability of Omicron to spread among vaccinated individuals – Omicron infections in the unvaccinated may well be as bad as Delta infections. On the other hand, emerging data show that Omicron does not replicate as well in the lung as do other strains, which may account for reduced morbidity. Oh, and for you hamsters out there (I'm talking to you, Prof. Hamster), unlike all the other strains to date, Omicron does not appear to transmit well in your species. This may account for the many recent hamster parties I've been invited to (Regrets, Prof. Hamster, I'm not doing parties yet).

Most of what I read in pre-prints and in the news media and hear from infectious disease specialists admonish me that I am being naïve – clearly the mutations in Omicron are evading immunity that was induced either by infection with another strain or by vaccination. So, of course it will spread more quickly. Catch up, Mole, you're being slow. (As slow as Jay Garrick, when The Rival not only took away his superpower but rendered him super slow).

It is true that two out of the three monoclonal antibodies that are in therapeutic use to treat COVID infections are ineffective against Omicron. This is not particularly surprising. Monoclonal antibodies (being produced by a clone of a single antibody-forming cell – although now we have other ways to make them) bind to one specific *epitope* in the spike protein. ("Slow down, Mole, now you're going to fast." Right, sorry). An epitope is the 'thing' that one antibody binds to. It can be a linear sequence of amino acids, or a selection of amino acids brought together by the target protein's conformation, as long as it is exposed on the protein. (Epitopes do not have to be amino acids, almost any chemical structure can be an epitope, but the antibodies we are talking about recognize amino acids in the receptor-binding domain of the spike protein). Change a few of the key amino acids, and the antibody doesn't bind.

But our immune response is not monoclonal. (We've talked about this before, but that was before Omicron, so stick with me). When we respond to vaccination with the spike protein (folded into the conformation found in the actual spike protein – although not all vaccines use this trick and they work pretty well anyway), we make antibody responses to many different, exposed epitopes. Some mutations will render some of our antibodies ineffective, but we have other antibodies that still do the job. This is partly why we seem to have good protection against Omicron (those of us who are vaccinated, of course).

Immunity to virus is not only via antibodies or the cells that make them (B cells). Viral infection, as well as the COVID vaccines in use, induce two other cell types. One of these is the 'helper' T cell that instructs B cells to make more antibody (technically these are follicular helper cells). The second is another type of T cell, the 'killer' T cell. These act to kill virally infected cells. Both types of T cells recognize 'bits' of protein (peptides) that are 'presented' on the surface of cells, bound to our own MHC molecules. MHC stands for major histocompatibility complex, because it turns out that differences in these same molecules are the major reason we might reject an organ graft (there is some very cool immunological history that we won't go into here, but it is worth looking up).

When a helper T cell recognizes its specific 'bit' on a B cell, it itself proliferates, while producing signals to cause the B cell to multiply and produce its antibody (each B cell makes only one antibody specificity, and each T cell recognizes only one peptide on an MHC molecule). When a killer T cell recognizes its specific bit of viral protein, it kills the cell displaying it, and can go on to kill the next infected cell. Each time we receive vaccine, or become infected, our T cells and B cells proliferate, expanding the clones of cells capable of recognizing and responding to the infection.

Next time we'll talk about how mutations in viruses that influence the ability of the immune response to be fully effective in combating infection can be evolutionarily selected, and why this does not apply to the pandemic we are experiencing. Recently, I was shown a video from a very well known 'wellness guru,' who admonished us that there was no point in being vaccinated, explaining that every year we will have virus that evades the vaccine, necessitating the production of new vaccines that, by the time they are developed, do not work against the new variant. Anyone who thought otherwise was, well, a fool.

It's not the first time I've been called a fool. But this time, I'm not the one being foolish. I'm told that this guru has a fantastic hiccup cure, and that might be true. But he doesn't 'get' viruses and immunity. He should stick to hiccups because the anti-vax nonsense he is peddling is hurting people. We'll see why this is nonsense next time. Meanwhile, if you haven't gotten your third shot (I *hope* you have gotten at least two), go get it. And I'll be back.

In a flash.