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The Emerging Threat of SARS-CoV-2 Variants

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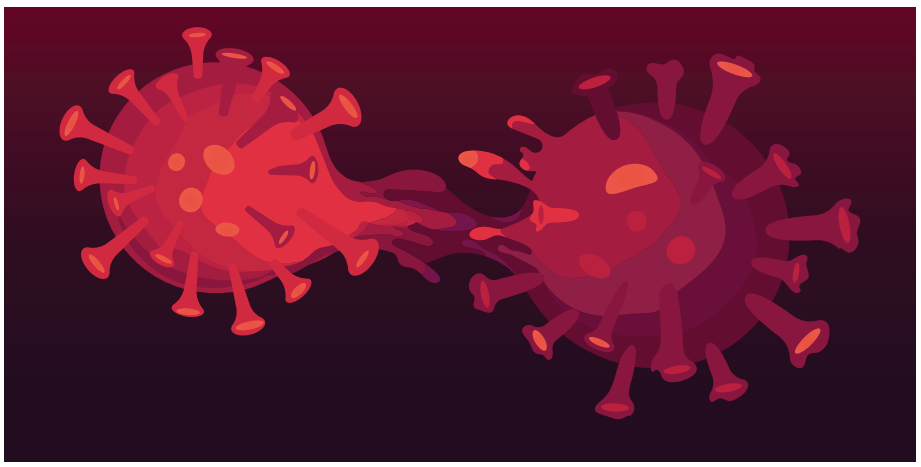

The progress of SARS-CoV-2 has been marked by the emergence of several different genetic variants. In a recent Viewpoint article in JAMA, Lauring and Hodcroft discuss the history and background of SARS-CoV-2 variants (JAMA January 2021).

Many variants substitute one amino acid for another in the "spike protein" – the spike on the outside of the virus that makes it look like a WWII underwater mine. These variants are typically named by the substitution, using single letter names for the amino acids. For example, the SARS-CoV-2 variant D614G substitutes glycine (G) for aspartate (D) in position 614. The D614G variant emerged last spring, simultaneously appearing across several geographic regions. Rapid spread is strong evidence of a survival advantage, such as greater infectiousness, ability to evade antibodies, or reduced lethality. In the case of D614G, the primary benefit was a substantial increase in infectiousness (*Science* 2020;370:1464-8).

In early November 2020, outbreaks of COVID-19 associated with mink farms were observed in the Netherlands and Denmark. Among the mutations noted there were many instances of isolated sequences having a Y453F mutation (tyrosine replaced by phenylalanine at position 453) in the receptor-binding domain (RBD) of the spike protein. This variant helps the virus escape neutralizing antibodies (*bioRxiv* November 2020). It has since spread to patients in

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Exploring the Purdue Pharma Settlement and the Opioid Epidemic

Gordon Glantz

With lawsuits piling up against drug companies believed complicit in the opioid crisis, a major precedent was set in November 2020 when Purdue Pharma was ordered to pay an $8.3 billion settlement.

The order from Judge Robert Drain, who described the ruling as a "critical building block" to resolve mounting lawsuits against the company, capped off a federal investigation of programs that offered incentives to physicians and an electronic health records company for driving opioid prescriptions.

Purdue Pharma – owned by the Sackler family since 1952 (when it was known as Purdue-Frederick) – agreed to plead guilty to three felony criminal counts of wrongdoing.

According to The Washington Post, Purdue – with headquarters in Stamford,

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Reducing Postoperative Delirium with Intraoperative Processed EEG

Jacqueline M. Leung, MD, MPH **Daniel J. Cole, MD, FASA**

Postoperative delirium is a geriatric syndrome associated with prolonged hospital length of stay and worsened functional and cognitive status after hospital discharge. Despite its prevalence, its pathophysiology is incompletely understood. Delirium is a complex interplay between patient vulnerability and precipitating factors. Although surgery is not a prerequisite for the occurrence of delirium, the prevalence of postoperative delirium after major surgery in the older patients is high, ranging from 10%-60% (*Psychiatr Clin North Am* 1996;19:429-48). Understanding the pathophysiology of postoperative delirium may also lend insight into revealing the mechanism underlying neurodegeneration such as Alzheimer's Disease, as postoperative delirium typically occurs in patients with prior cognitive impairment.

Given the powerful effects of general anesthetics on the brain and the numerous medications surgical patients are exposed to during and after surgery, some have hypothesized that anesthetics may be toxic to the brain, manifested as adverse postoperative cognitive changes, including delirium. Specifically, are we often "overdosing" our patients and unnecessarily exposing them to the potential adverse effects of general anesthetics?

Recent advances in anesthesia research have focused on neurotoxicity and neu-

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In the Know: SARS-CoV-2 Variants

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Denmark, accompanied by three additional mutations (del69_70, I692V, and M1229I). Taken together, these variants are referred to as "Cluster 5" (asamonitor.pub/35XW6jW). Authorities in Denmark quickly locked down the area, instituted aggressive testing, and culled every mink farm in Denmark. Cluster 5 is now considered extinct.

In December 2020, the U.S. Centers for Disease Control and Prevention (CDC) issued a statement regarding the emergence of the B.1.1.7 variant in the UK and the B.1.351 variant in South Africa (asamonitor.pub/3bVBFbb).* These variants appear to be responsible for several recent surges, and may complicate efforts to immunize the world's population against SARS-CoV-2.

Table 1: List of Genes and Mutations in B.1.1.7 SARS-CoV-2- Variant

Gene	Nucleotide Mutation	Amino Acid Mutation
ORF1ab	C3267T C5388A T6954C 11288-11296 deletion	T1001I A1708D I2230T 3675-3677 deletion (SGF)
Spike (S protein)	21765-21770 deletion 21991-21993 deletion A23063T C23271A C23604A C23709T T24506G G24914C	69-70 deletion (HV) Y144 deletion N501Y A570D P681H T716I S982A D1118H
Orf8	C27972T G28048T A28111G	Q27stop R52I Y73C
N	28280 GAT->CTA C28977T	D3L S235F

VB.1.1.7 (U.K.)

The first two samples of SARS-CoV-2 that would later be termed the B.1.1.7 lineage were obtained in September 2020 from Kent and greater London (asamonitor.pub/2KCxCWc). The B.1.1.7 variant has an astonishing 17 lineage-defining mutations (Table 1) (JAMA January 2021). The likely mechanism by which a single strain emerged with so many mutations is that it evolved within a single immunocompromised host (*Science* December 2020). SARS-CoV-2 evolution within immunocompromised individuals has been well documented (*medRxiv* December 2020; *N Engl J Med* 2020;3838:2291-3; *Cell* 2020;183:1901-12).

The most significant of these is the N501Y mutation, which has been associated with increased infectivity (*medRxiv* January 2021). The B.1.1.7 variant is increasingly dominant in England and has spread to more than 50 other countries. It is projected to soon be the dominant strain in the United States (*Science News* January 2021). It appears that present vaccines will be fairly effective against it (*Science* December 2020; *bioRxiv* January 2021).

B.1.351 (South Africa)

As the B.1.1.7 variant was emerging in England, another complex variant appeared in South Africa (*medRxiv* December 2020). The B.1.351 lineage is also characterized by numerous mutations in the spike protein. Initial samples in October 2020 displayed the previously noted D614G as well as five additional mutations. By the end of November, investigators identified multiple additional mutations including the N501Y mutation that increases infectiousness. Identification of multiple lineages implies that the B.1.351 variant evolved as it was transmitted through multiple hosts and arose independent of the B.1.1.7 variant.

The B.1.351 variant also has the E484K mutation. This is an "escape mutation" that may permit the virus to avoid detection by antibodies (*bioRxiv* January 2021). As the authors note: "Some mutations that reduce serum antibody binding also reduce viral neutralization by >10 fold. The site where mutations tend to have the largest effect on binding and neutralization is E484, which unfortunately is a site where mutations are present in several emerging SARS-CoV-2 lineages."

"Get vaccinated as soon as you can. Reducing the number of infected persons will reduce the emergence of variants, and this may prove a necessary step in bringing the pandemic to an end."

B.1.1.28 (Brazil)

Numerous mutations have arisen in Brazil. The B.1.1.28 variant has the same N501Y mutation as the B.1.1.7 (UK) and B.1.351 (South Africa) variants. The B.1.1.28 variant also has the same E484K escape mutation found in the B.1.351 (South Africa) lineage (asamonitor.pub/3o5RWwx). The presence of the E484K mutation in the first documented case of reinfection in Brazil is consistent with the possibility of the mutation evading existing humoral immunity (asamonitor.pub/3sL74mW). The B.1.1.28 variant also has a K417N mutation that does not appear in the other two, and may also represent another escape mutation (*bioRxiv* December 2020). The evolution of the B.1.1.28 variant has been tracked over many months, showing that it, like the B1.351 mutation in South Africa, evolved while passing through multiple hosts.

L452R Variant (California)

A new variant, L452R, in California has been tied to several large outbreaks, including an outbreak at the Kaiser Permanente San Jose Medical Center where a staff member in an air-powered Christmas tree costume infected 90 individuals (asamonitor.pub/3bTyq48; asamonitor.pub/35X-AfJk). It is not known whether this variant increases infectiousness or confers resistance to antibodies. A paper in *Cell* last October found that the L452R variant conferred resistance to several monoclonal antibodies, which raises the possibility that it is another escape mutation (*Cell* 2020;182:1284-94).

Where does this leave us?

Relative to viruses such as influenza and HIV, SARS-CoV-2 mutates relatively slowly (*Pathogens* 2020;9:829). However, in a worldwide pandemic with more than 100 million cases there is plenty of opportunity for the virus to randomly test mutations to improve survival. It is not coincidence that D614G, N501Y, and E484K arose simultaneously in multiple locations, or that they were identified in part because of new outbreaks associated with these mutations. That is how evolution works.

As David Cyranoski noted in Nature: "2021 is shaping up to be the year of COVID-19 variants" (asamonitor.pub/3o1Fv4X). Intense genomic surveillance is required to identify new mutations that are spreading in the population. The city of Manaus, Brazil, offers a cautionary tale. In October it appeared that Manaus had reached herd immunity, with 75% of the population testing positive for SARS-CoV-2 antibodies (*Science* 2021;371:288-92). This came with enormous loss of life, but hopefully the worst was over. Sadly, no. Manaus experienced another surge in December, linked to a new variant descended from B.1.1.28 (asamonitor.pub/2LN9NLG). The variant might simply be more infectious, reaching susceptible individual previously out of reach, or it might have escape mutations that permit reinfection. Either way, the horrific toll of SARS-CoV-2 returned to Manaus in the form of a variant.

With genomic surveillance we can identify variants and make key therapeutic decisions. Once a variant is identified, we can test whether existing monoclonal antibodies neutralize the virus. If they fail, they will likely be clinically ineffective. Clinical guidelines will need to incorporate geographic prevalence of specific variants to guide physicians to effective antibody regimens.

A recent study suggests that the Pfizer and Moderna mRNA vaccines' "activity against SARS-CoV-2 variants encoding E484K or N501Y … was reduced by a small but significant margin (*bioRxiv* January 2021). Fortunately, the protein encoded in the mRNA vaccines can be changed in a few weeks by synthesizing a different mRNA incorporating the variant. With adequate genomic surveillance, we may be able to update our mRNA vaccines almost as quickly as SARS-CoV-2 is able to mutate, staying ahead of novel variants.

The key to reducing mutation is to reduce viral spread. We know how to do this! Keep wearing your mask, maintaining social distancing, avoiding crowds (particularly indoors), and using proper hygiene. Get vaccinated as soon as you can. Reducing the number of infected persons will reduce the emergence of variants, and this may prove a necessary step in bringing the pandemic to an end. ■

Richard Simoneaux is a freelance writer with an MS in organic chemistry from Indiana University and more than 15 years of experience covering the pharmaceutical industry and an additional seven years as a laboratory-based medicinal chemist.

**Variant names are confusing and uninterpretable. The author (SLS) has suggested following the convention for naming hurricanes and having SARS-CoV-2 variant names assigned by the World Meteorological Organization.*