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Help Wanted: Must Have the Brain of an Internist, Hands of a Surgeon, and Heart of a Psychiatrist

Talmage D. Egan, MD, FASA

In my role as chair of an anesthesiology department at an academic medical center, every few weeks I have lunch with the medical students rotating on our service. These lunches are in part an effort to recruit our medical school's best students into our specialty. I share my thoughts and insights about a career in anesthesiology with these enthusiastic, aspiring physicians. My message is simple: anesthesiology is a wonderfully rewarding career. Imagine for a moment that you are one of these highly motivated medical students considering a career in anesthesiology. This is what you would hear from me over lunch:

A bit of history

Let us begin with a brief mention of the seminal moment in the history of anesthesia as reflected in this famous anesthesia-related painting, Robert C. Hinckley's 1893 work, "The First Operation Under Ether" (Figure 1) (*Anesthesiology* 1980;52:62-70). On October 16, 1846, on what has since come to be known as Ether Day, William Thomas Morton, a part-time medical student and practicing dentist, demonstrated the anesthetic properties of ether in a surgical amphitheater of the Massachusetts General Hospital (*Surgery* 2006;140:472-3; *Boston Med Surg J* 1846;35:309-17). After Morton had administered the ether from a handheld, blown-glass vaporizer for some minutes, the patient, a Mr. Gilbert Abbott, was rendered unconscious. Turning to Dr. John Collins Warren, a venerated surgeon at the facility, Morton boldly stated: "Your patient is ready, sir." With a gallery of curious spectators mesmerized by the proceedings, Dr. Warren commenced the

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Talmage D. Egan, MD, FASA
Professor and Chair, Department of Anesthesiology, University of Utah School of Medicine, Salt Lake City, Utah.

COVID Gets Complicated

Richard Simoneaux

Steven L. Shafer, MD, FASA, *Editor-in-Chief*

During the first two years of the pandemic, SARS-CoV-2 steadily evolved. The ancestral Wuhan strain gave way to the Alpha variant, followed by Beta, Gamma, and Delta variants, each more infectious than the last (*ASA Monitor* 2021;85:1-7). A year ago, the ultra-infectious Omicron spread out of South Africa and rapidly replaced all other strains (*ASA Monitor* 2022;86:1-7). Evolution didn't stop with Omicron. The first wave of Omicron, now called BA.1, rapidly gave way to the even more infectious Omicron BA.2 strain. Just when it seemed SARS-CoV-2 couldn't get any more infectious, Omicron variants BA.4

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You Need Me on That Wall! The World of Military Medicine

Zachary Deutch, MD, FASA

Bryan D. Laliberte, MD, FASA

Happy 2023 to all, and thank you for joining us for a very special column. As physician anesthesiologists, we work on the "front lines" of perioperative medicine – we take in-house calls, cover obstetrical and trauma units, and provide transplant and other urgent/emergent care at all hours. As practicing clinicians, military physicians do all of the above, but as members of the armed forces, they can find themselves on the "front lines" literally and figuratively. Military doctors have the responsibility of keeping our country, our fellow citizens, and our armed forces personnel healthy, protected, and safe from harm. These doctors may provide care in an existing military hospital, a temporary hospital in a forward area, an aircraft, or on a sea-going vessel and can be deployed at a moment's notice to the far corners of the world.

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NEWS THAT MATTERS

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PERIODICALS

In the Know: COVID Gets Complicated

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and BA.5 appeared. By summer, BA.2 had mostly been replaced by BA.4 and BA.5.

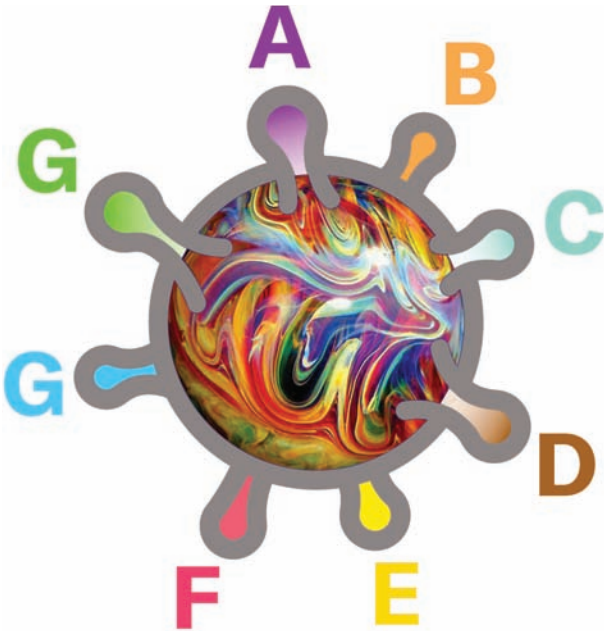
Variants have become far more complex. Figure 1 shows the most recent variant report from the Centers for Disease Control and Prevention. BA.5 peaked at 85% of U.S. cases in late August. As shown in Figure 1, from September through November 2022, BA.5 inexorably gave way to a bewildering slew of new variants: BQ.1, BQ1.1, BF.7, BA.4.6, BN.1, BA.5.2.6 (*Nature* 2022;611:213-4). These evolved from the original Omicron strain that swept over the globe a year ago. It is not known whether these "Scrabble" or "Alphabet" variants are truly more infectious or are simply able to reinfect those with prior immunity from vaccination or prior infection.

"Does this alphabet soup of mix-and-match variants mean that we need to brace ourselves for more waves of COVID-19 deaths? Probably not. Between vaccination and infection (often both), almost the entire planet has fairly good immunity to SARS-CoV-2. Yes, immunity to coronavirus infection wanes over time. Fortunately, immunity against severe illness and death is far more durable."

The rapid rise of multiple competing variants is not limited to the United States. As seen in Figure 2, multiple Omicron variants arose around the world. The pre-Omicron strains have all but vanished.

Does this alphabet soup of mix-and-match variants mean that we need to brace ourselves for more waves of COVID-19 deaths? Probably not. Between vaccination and infection (often both), almost the entire planet has fairly good immunity to SARS-CoV-2. Yes, immunity to coronavirus infection wanes over time. We've known this since the earliest days of the pandemic (*Nat Med* 2020;26:1691-93). Fortunately, immunity against severe illness and death is far more durable (asamonitor.pub/3E99YbA).

As a result of nearly 100% global population immunity, even the panoply of variants will run up against a population mostly immune to their worst sequelae. As shown in Figure 3, the Institute for Health Metrics and Evaluation at the University of Washington predicts that deaths will remain around 300-400 per day. This corresponds to 110,000 to 146,000 deaths per year – far in excess of influenza. So, SARS-CoV-2 remains a deadly threat, particularly for the frail. However, there is no evidence these competing variants will wreak disproportional havoc compared to the first two years of the pandemic.



Variant soup

A recent column in *Nature* discussed the expanding zoo of Omicron offspring (*Nature* 2022;611:213-4). "Instead of one or two fast-rising lineages, they {researchers} have identified more than a dozen to watch." In places such as the Americas, Africa, and Europe, currently (November 2022) the prevalence of BQ.1-related variants is increasing, while in places such as Singapore or India, a new lineage, XBB (a recombination of the of BA.2.10.1 and BA.2.75 Omicron variants), is responsible for rising case numbers.

We are observing SARS-CoV-2 testing out novel mutations in the spike protein in an effort to bypass global immunity. The spike protein has two specific regions of interest. The receptor binding domain, or RBD, is the part of the spike protein that latches on to the ACE2 receptor. Changes in the RBD that increase affinity for the ACE2 receptor increase infectivity (*Cell Res* 2022;32:609-20). The N terminal domain, or NTD, plays a significant role in bringing the viral and cell membranes together, permitting fusion, another potential means of cell entry (*Cell Rep* 2022;40:111220).

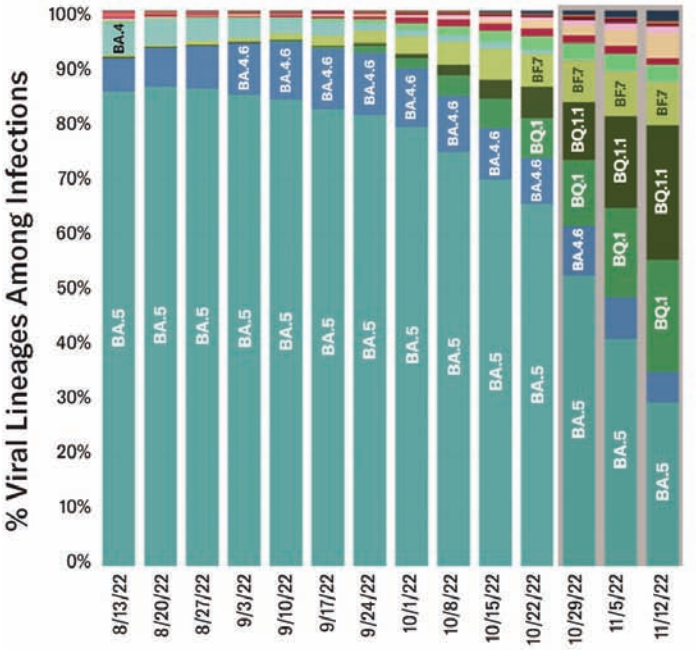
A recent preprint notes the importance of mutations in the NTD conferring evolutionary advantage through immune escape (bioRxiv 2022.09.15.507787). "XBB's advantage over the BQ.1 family might be due in part to changes outside the spike receptor binding domain." The implication is that, when compared to prior strains, XBB is probably not more infectious, *per se*, but is more immune-evading because of the mutations in the NTD.

In their preprint, Cao and colleagues discussed the immune responses to the ever-growing family of Omicron-related variants (*Cell Rep* 2022;40:111220). The early Omicrons, BA.1, BA.2, and BA.5, "demonstrated strong neutralization evasion capability, posing severe challenges to the efficacy of existing humoral immunity established through vaccination and infection." New variants, such as the emerging XBB, BQ.1.1, and BA.2.3.20 display growth advantages relative to BA.5. Cao also points out that XBB is particularly adept at immune evasion.

In vaccinated individuals, breakthrough infection from BA.2 and BA.5 following vaccination elicited a response that recognized the RBD of the original Wuhan strain encoded by the vaccine(s). In unvaccinated individuals, Omicron infections produced Omicron-specific antibodies. However, even Omicron-specific antibodies have demonstrated limited abilities to neutralize subsequent variants such as XBB, CH.1.1, and BQ.1.1.10, which suggests the novel mutations observed in the NTD of the spike protein confer significant immune evasion for those variants.

A study in triply vaccinated health care workers in the U.K. found that immune responses to Omicron (B.1.1.529) infection depended on infection history (*Science* 2022;377:eabq1841). Previously uninfected (but triply vaccinated) health care workers received boosting by Omicron infection. Health care workers who had previously been infected with the ancestral Wuhan strain were not boosted by Omicron infection. The researchers note that the "immune imprinting" suggested by this study might explain why Omicron is characterized by numerous breakthrough infections with

Figure 1: Omicron variants tracked by the CDC, as of November 13, 2020 (asamonitor.pub/3BfRTq7).



WHO label	Lineage #	US Class	%Total	95%PI
Omicron	BA.5	VOC	29.7%	27.2-32.3%
	BQ.1.1	VOC	24.1%	21.3-27.3%
	BQ.1	VOC	20.1%	17.2-23.4%
	BF.7	VOC	7.8%	6.8-9.0%
	BA.4.6	VOC	5.5%	5.0-6.2%
	BN.1	VOC	4.3%	3.0-6.2%
	BA.5.2.6	VOC	2.9%	2.5-3.4%
	BA.2	VOC	1.3%	0.8-1.9%
	BA.2.75	VOC	1.2%	1.0-1.5%
	BA.2.75.2	VOC	0.9%	0.6-1.2%
	BA.4	VOC	0.1%	0.1-0.1%
	BA.1.1	VOC	0.0%	0.0-0.0%
	B.1.1.529	VOC	0.0%	0.0-0.0%
	BA.2.12.1	VOC	0.0%	0.0-0.0%
Delta	B.1.617.2	VBM	0.0%	0.0-0.0%
Other	Other*		2.0%	1.1-3.3%

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

"relatively preserved protection against severe disease" in vaccinated individuals.

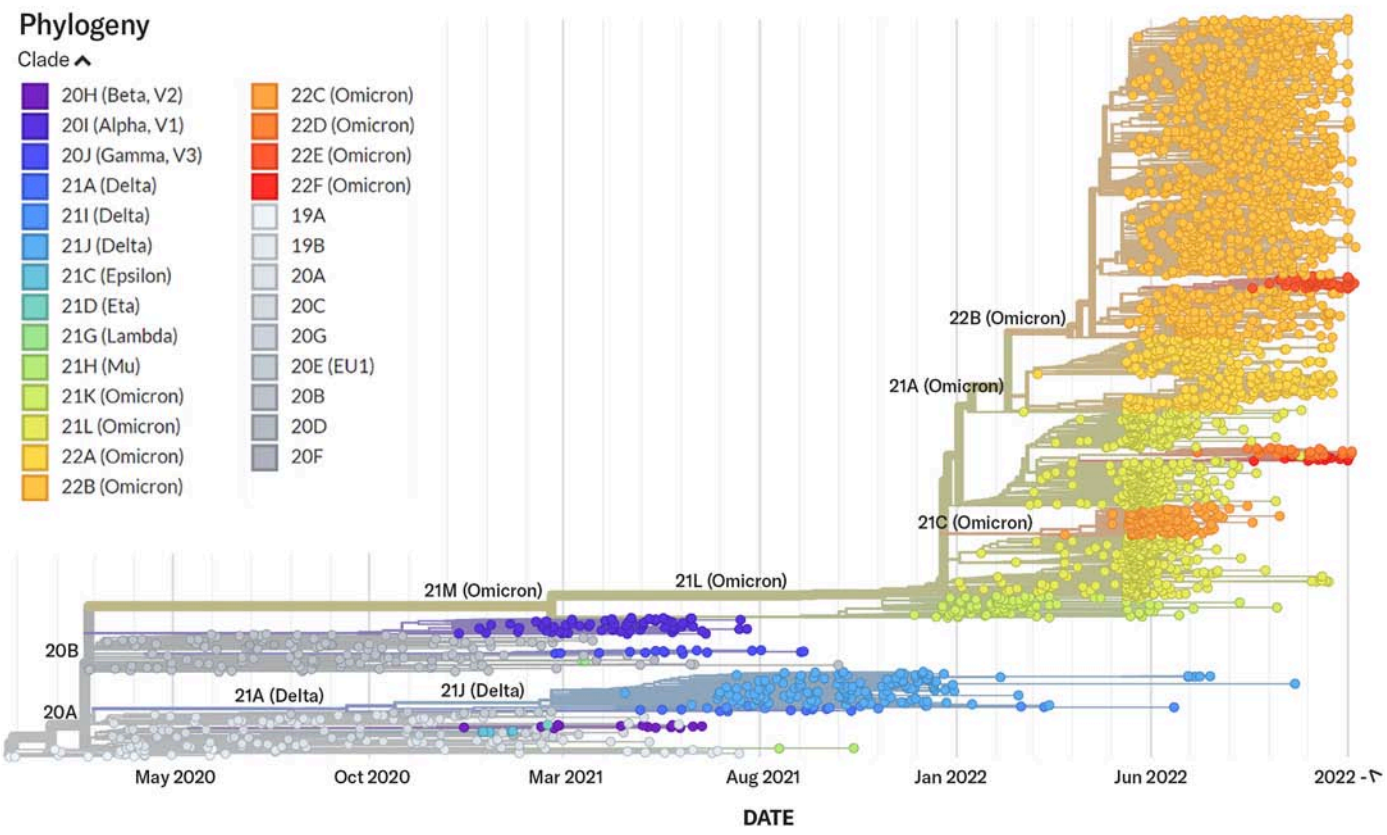
Quasispecies

Viral infection does not result in a single viral lineage replicating within our cells, but is instead a broad panoply of closely related viral genomes competing for our precious bodily fluids (*ASA Monitor* 2021;85:1-7). This panoply of competing genomes is termed "quasispecies."

The prolonged evolution of SARS-CoV-2 in immunocompromised individuals is well-documented. A recent article highlighted an immunocompromised individual from whom investigators identified different quasispecies isolated 222 days apart (*Virus Evol* 2022;8:veac042). These two quasispecies exhibited vast differences in their cellular entry. The Day 0 quasispecies displayed traditional endocytosis cellular entry. The Day 222 quasispecies primarily utilized plasma membrane fusion, a completely different mechanism. Given that these were both derived from the original SARS-CoV-2 infection in this individual, it shows the remarkable capacity of the virus to mutate even fundamental processes like cellular entry.

In vitro competition studies demonstrated that the Day 222 quasispecies rapidly predominated over the Day 0 quasispecies. Further analysis found that the quasispecies from Day 222 produced proteins that hindered cellular entry of SARS-CoV-2 via endocytosis. In effect, the Day 222 lineage knocked out the ability of the competing Day 0 lineage to enter cells, while maintaining its own mode of entry via membrane fusion. The authors note, "This finding may explain, at least in part, the extraordinary rapid worldwide turnover of variants of concern that use the plasma membrane fusion pathway to enter into target cells over the original pandemic strain."

Figure 2: The many variants can be seen in the genomic analysis from Nextstrain, which visualizes the global genomic sequencing documented in GISAID (asamonitor.pub/3hKDb55). As seen below, all currently circulating SARS-CoV-2 variants are derived from Omicron. The next strain nomenclature differs from the CDC nomenclature, with the first two numbers denoting the year in which the strain appeared. Five major strains, 22A through 22F, have appeared this year.



S-protein/mRNA nuclear translocation

A recent preprint from researchers at the National Institute of Allergy and Infectious Diseases described a feature of SARS-CoV-2 unique among betacoronaviruses: the spike protein of SARS-CoV-2, along with its corresponding mRNA, can translocate to the cellular nucleus in infected airway epithelial cells (bioRxiv 2022:2022.09.27.509633). In SARS-CoV-2, the peptide sequence "P-R-R-A-R-S-V" constitutes a nuclear localization signal, a sequence that includes the so-called "furin cleavage site." This polybasic cleavage site was initially thought to be unique to SARS-CoV-2, and possibly evidence of human genomic engineering. It has since been identified in other coronaviruses (*ASA Monitor* 2021:85:1-6). It is possible that the translocation of the spike protein contributes to the uniquely rapid evolution and development of immune evasion by SARS-CoV-2.

Amyloidogenesis of spike protein

Research published in the *Journal of the American Chemical Society* highlighted the potentially amyloidogenic nature of the SARS-CoV-2 spike protein (*J Am Chem Soc* 2022;144:8945-50). Using computational methods, the authors identified peptide segments of the spike protein with the potential for amyloid formation. *In vitro* testing confirmed the amyloidogenic activity of these sequences.

Additionally, the authors showed that "amyloid-like fibril" formation occurred with proteolysis of the full-length spike protein by neutrophil elastase *in vitro*. This protease was chosen because of the propensity for neutrophil recruitment with respiratory viral infections. The

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Help Wanted

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one makes fun of them, and that the patient's modesty is preserved, among other similar actions of respect and reverence. Defense of patient dignity is, of course, an important duty of the entire operating room team, but because the anesthesiologist has rendered the patient unconscious and defenseless, we have a special obligation to perform this function. This is a weighty part of the job description that we need to emphasize more fervently.

A uniquely heavy and rewarding burden

The anesthetized state is unlike any other circumstance in the course of human experience. There is no other time in human-to-human interaction where one person voluntarily surrenders their well-being more fully and absolutely to another person. The anesthetized patient is utterly and completely helpless. They can do nothing for themselves. In this very vulnerable and powerless state, the anesthetized patient is depending on the anesthesiologist to keep them safe by conducting the anesthetic, supporting their vital functions, and defending their human dignity. Physicians of all sorts take on heavy responsibilities in caring for patients; there is plenty of risk to go around. But the unique nature of the anesthetized state means that the anesthesiologist carries a particularly heavy burden. It is the anesthesiologist who has rendered the patient wholly defenseless; it is therefore incumbent upon the anesthesiologist to take the lead in defending the patient's well-being, including their dignity as a person.

The day a person has their anatomy and physiology irrevocably altered by a surgeon's knife is a landmark day in their lives. The anesthesiologist is their guide on this sometimes perilous journey, standing by their side from induction to emergence and beyond, defending them against all the dangers they may encounter along the perioperative path. Executing this duty with skill, equanimity, and poise is an incredibly rewarding endeavor.

A simple conclusion

A job posting for an anesthesiologist could read something like this: "Help wanted! Must have the brain of an internist, the hands of a surgeon, and the heart of a psychiatrist." Our specialty seeks to attract the most talented medical students into the discipline. We need energetic, intelligent, compassionate people drawn from a diverse talent pool, and we will enthusiastically welcome them to the team and help them mature into terrific anesthesiologists who will, I am confident, enjoy a wonderfully rewarding professional adventure. ■

Disclosure: *Dr. Egan is a scientific advisory board member for Acacia Pharma, a founder and equity partner of Applied Medical Visualizations, and a grant recipient of Medtronic.*

In the Know: COVID Gets Complicated

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amyloid-like fibrils may explain some of the persistent neurologic injuries observed after SARS-CoV-2 infection.

The researchers also studied the role of the spike protein in thrombogenesis. Microclots have been associated with COVID-19 infection and are a known mechanism of end-organ injury. The authors added spike protein-derived fibrils to standard clotting assays and found that a mixture comprising just 2% of spike protein fibrils produced "increased persistent plasmin indigestible fibrin." Since the clots cannot be digested by plasmin, the enzyme responsible for clot resorption, this may explain some of the microthrombotic injury from SARS-CoV-2 infection.

We are now watching a battle for dominance among multiple SARS-CoV-2 variants. Cao and colleagues made the disquieting observation that "as few as five additional mutations on BA.5 or BA.2.75 could completely evade most plasma samples, including those from BA.5 breakthrough infection, while maintaining high human ACE2-binding capability" (bioRxiv 2022.09.15.507787).

The Scrabble variants highlight the importance of developing broadly neutralizing SARS-CoV-2 vaccines and antibodies (*Nat Rev Immunol* 2022:1-11). Currently, more than 200 papers appear in PubMed identifying broadly neutralizing antibodies or vaccines. Unfortunately, the science is likely years ahead of commercial development. Few (if any) of these broadly neutralizing vaccines and antibodies have progressed from basic science laboratories to human trials.

The Scrabble variants suggest that SARS-CoV-2 is struggling to make inroads against a better defended global population. As COVID gets more complicated, our best defenses remain vaccination and nonpharmaceutical interventions (masking, social distancing, avoiding indoor crowds). That part is simple. ■

Figure 3: Daily deaths from COVID-19, based on the projection of the Institute for Health Metrics and Evaluation at the University of Washington (asamonitor.pub/3Gf7f2U). Note that these are deaths attributed to COVID-19 and not deaths of patients dying from a different cause who happened to test positive for COVID-19 at the time of death.