What Was I Thinking?

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Our theme this year has been to consider where aerospace medicine and human performance will be in 10 years. Prognostication is not something that we humans are particularly good at. For any potential issue, chances are somebody will claim post hoc credit for correctly divining the future. Lucky guesses do not demonstrate special clairvoyance. Even experts seem to get caught unawares. Witness the recent events in Ukraine. Shouldn't the nations of the world have seen that coming further in advance?

I want to get back to the main theme of awareness of what the future may have in store for aerospace medicine and human performance. I must give a shoutout to Dr. Roger Hesselbrock for sending me a recent article from the journal *Neurology* (Johnson N, Greene E. Neurologic Therapeutics in 2035: The Neurology Future Forecasting Series. Neurology 2021;97;1121–1127). I found it interesting reading, especially because aerospace medicine does not typically acknowledge the importance of regulations and costs. My experience is that a vast majority of medical practice focuses on available, accepted therapies. A reasonable expectation since clinicians deal with commonly occurring conditions and treatments that are reimbursable under payer rules and supported by generally accepted practice guidelines. While neurologists would generally, in my observation, also fall into that category, a significant proportion of neurology is affected by new research identifying novel cellular, biochemical, and genetic abnormalities that may only benefit from very narrowly targeted treatments. Oncology has similar issues. Ironically, public health and infectious diseases arguably have the same concerns, e.g., COVID-19. Despite the remarkable progress in rapid vaccine development, there are many remaining questions around vaccine efficacy (individual variability of immune response, durability, and side-effects), post-infection immune response, and of course the impact of long-haul symptomatology. The common factor in all this is the individual, and why we each may respond differently to disease and treatment. Back to the article, authors Johnson and Greene parse the issues in neurology into the current and likely futures of development and discovery and both regulatory and payer landscapes. With apologies to the authors:

- Development and discovery: Currently, traditional medical therapeutics focus on a general "one size fits all" approach based on "evidence- or consensus-based studies of populations with a shared phenotype who respond to the same drug." Medical knowledge and biotechnology are challenging traditional approaches by identifying and targeting specific cellular epitopes, signaling pathways and ligands involved with disease. Resultant advances have given us antibody technology to target proinflammatory pathways involved with connective tissue disease and immune modulating therapies for multiple sclerosis, myasthenia gravis, and other conditions. Other advances: monoclonal antibody therapy for treatment of migraines and neurodegenerative diseases; gene therapy that targets RNA; and gene replacement, insertion, and editing. However, these approaches are limited by the number of conditions that can be treated, who can be treated, and technical issues such as size of gene insertions. Safety concerns include off-target effects of gene therapy. The future will need to address limitations of viral delivery systems which also have limitations (e.g., patient weight, age) and immune mediated therapies will need to increase tissue penetration and improve targeting. Cell-based therapies will include advances in stem and progenitor cells. The use of exosomes to deliver proteins and nucleic acids will address personalization of targeted drug delivery and regulation of cell function and intercellular communications.
- Regulatory and Payer Landscapes. Beginning with the Orphan Drug Act in 1983, regulatory burdens and hurdles have been reduced to allow more therapies to be brought to market. However, there are increased pressures to provide access to investigational therapies outside of clinical trials under so-called "right-to-try" laws. Potential unintended consequences include reduced trial participations, increased malpractice risks to providers, and need to increase post-marketing surveillance. From the payer standpoint, drug costs are significantly outpacing provider costs and are increasing out-of-pocket costs. The result has been increases in overall healthcare costs with cost increases. Future changes in these areas will need to address these issues to get therapies to market faster and at less cost.

Aerospace medicine and human performance will not be insulated from these issues but will be complicated by them. How we will conduct evidence-based risk assessments and consider the effects of mitigations in a standardized manner for each individual pilot or crewmember must be timely, but also considerate of the proliferation of novel treatments and changes to established approval processes. How do we deal with a dichotomy between pilots who can afford personalized novel treatments and those who may be relegated to "standard care?" How will changes in

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automation, aviation regulations, expansion of commercial space concerns, and progress in long-range space explorations alter our concerns and thinking? As a community, aerospace medicine will need to be proactive, flexible, and adaptive to maintain relevancy.

Keep these types of questions in mind as we prepare to meet in Reno in May. I hope that we not only continue to see abatement of COVID, but also a return to peace in eastern Europe and elsewhere. This is what I was thinking.