

NEWS IN NEUROVIROLOGY

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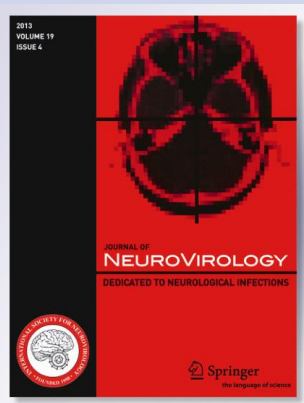
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A Message from the President

By Bruce Brew

The ISNV board and I wanted to address you at this terrible and trying time.

For those of you who have lost loved ones, our hearts go out to you. To lose someone you love and yet not be able to be with them at their last moments of life is unimaginable.

For those of you in lockdown, we understand how frustrating it is to have your work curtailed. Some of you may not be able to carry out any laboratory work while others may still be able to do so but to a much lesser extent. Perhaps take this time to re-prioritise your research. As summarized in this newsletter, there are many aspects of COVID-19 that suggest brain involvement but equally there are many unanswered questions. Clarification of these issues will have direct benefit to patients.

For those of you in the frontline, we thoroughly support you. Clinical laboratory tests and clinical care must continue so that care can be delivered not only to those with COVID-19 infection but also to those who do not, lest they are abandoned, and their illnesses magnify through unintentional neglect. Yet there are opportunities to go beyond service delivery to contribute knowledge to improve patient management. This can be done through observational cohort studies that can be independent or “piggy backed” on to existing cohorts.

This is a special edition of our newsletter for a unique time. I thought it best to bring you up to speed with the current status of COVID-19 from a neurologic perspective. This is not just a respiratory illness; there is increasing evidence for neurological involvement both as a direct and indirect phenomenon. Further, there is the unknown effect of COVID-19 on existing neurological diseases and therapies as well as their effects on COVID-19. To this end I have asked some of our colleagues to address important issues beginning with an understanding of what is known and suspected. These will be approached from scientific and clinical perspectives particularly in relation to preparedness for the neuro-ICU and neurologic focussed autopsies. There will be a discussion on funding opportunities, concluding with some thoughts on priorities for neuro research.

At a time when COVID-19 dictates that we be physically apart, let us be together intellectually and emotionally. Let us turn our sorrow and fear into a redoubled effort to have Science and Medicine serve our fellow human beings.

Neurovirology of COVID-19

By Avindra Nath

We are living in unprecedented times. Our biggest nightmare is playing in front our eyes. This is a lethal virus spread by droplets that has travelled across the globe and killed people in every country in the world in a matter of less than four months. Yes, it is coronavirus disease-19 (COVID-19) which is caused by SARS-CoV-2. It is expected that a virus that is airborne would cause a respiratory illness, however we are only now beginning to realize that it can also cause a wide variety of neurological complications. This should come as no surprise to most neurovirologists. We have always known that nearly all lung infections end up in the brain. This includes viruses, bacteria and fungi. Neurological complications with COVID-19 occur in a smaller number of infected individuals but when they do occur they can be devastating (1). In some cases the virus can cause a meningoencephalitis (2). These patients present with seizures, altered consciousness and sometimes with psychosis or delirium. However, it remains unknown if the virus directly invades the brain or if these complications are due to an immune mediated phenomenon or due to metabolic abnormalities caused by impairment of other organs (3). At least in one case, the virus was shown to infect brain endothelial cells and neural cells as seen at autopsy (4). Another study found punctate hemorrhages in the brainstem and subarachnoid spaces of one case each but were unable to detect the virus in the brain of these two cases (5). No matter what the underlying cause, involvement of the brain is the most fearful since it can change our behavior, personality, mood and cognitive abilities.

The majority of patients develop a loss of smell and taste (6), myalgias and fatigue or malaise. While many patients recover with only mild flu like symptoms, some develop an acute respiratory distress syndrome (ARDS) requiring ventilatory support. This carries a high mortality rate. Patients with ARDS due to SARS-CoV-2 have a hypercoagulable state and frequently develop strokes and deep vein thromboses. Some patients develop myocarditis (7, 8) but it is unknown if other muscles are similarly involved although a case of rhabdomyolysis has been described (9). A number of autoimmune syndromes have been reported with the infection (Table1). It needs to be determined if these syndromes are being mediated through the process of molecular mimicry. For example, the E protein of the virus is encased in a phospholipid bilayer and hence it could potentially trigger antiphospholipid antibodies. Similarly, anti-proteolipid antibodies have been considered to be pathogenic in the various forms of Guillain Barre syndrome.

Coronaviruses are enveloped viruses with a positive-sense single-stranded RNA genome. The word corona is derived from “crown” which describes the spike like proteins on its surface. They are classified as four genera: alpha, beta, gamma and delta. The α , β and δ coronaviruses infect mammals, whereas γ and δ coronaviruses infect avian species.

Table 1: Postviral/Autoimmune syndromes with COVID-19

<u>Clinical Syndrome</u>	<u>Proposed pathophysiological mechanism</u>
^{15, 16} Guillain Barre syndrome	Antibody mediated
Demyelinating	
Axonal	
Sensory	
Miller Fisher	
¹⁷ Transverse Myelitis	Immune cell mediated
¹⁸ Acute disseminated encephalomyelitis	Immune cell mediated
¹⁹ Acute hemorrhagic encephalomyelopathy	cytokine mediated
²⁰ Strokes	hypercoagulability, Antiphospholipid antibodies

However the virus has the ability to jump between species leading to the emergence of Middle East respiratory syndrome (MERS) caused by MERS-CoV, severe acute respiratory syndrome (SARS) caused by SARS virus, and COVID-19, caused by SARS-CoV-2, with deadly consequences (10). To date, seven human coronaviruses have been identified (Table 2). SARS virus and SARS-CoV-2 are thought to have originated from bats (11). They use the “spike proteins” to attach to angiotensin converting enzyme receptor type 2 (ACE-2) which is highly expressed in the respiratory tract (12).

(Continued on page 3)

Expression in the brain is minimal but could possibly be induced in the setting of inflammation. It also needs to be determined if the virus may use alternative receptors in the brain particularly since it is a RNA virus and has the ability to mutate and adapt to the host.

The virus has four main structural proteins: Spike (S)-protein is a trimeric protein that mediates attachment to the host receptor, and is made of two separate polypeptides called S1 (binding domain) and S2 (stalk) (13). The membrane protein is the most abundant structural protein in the virion. The envelope protein facilitates assembly and release of the virus. The ion channel activity in SARS virus envelope protein plays a critical role in pathogenesis. The N-protein constitutes the nucleocapsid that binds the viral RNA. The hemagglutinin-esterase protein is present in a subset of β -coronaviruses and binds sialic acids on surface glycoproteins and contains acetyl-esterase activity (10). The neuropathogenesis of coronaviruses has been best studied in a mouse model infected with the mouse hepatitis virus and is considered to be a model of multiple sclerosis. In this model trans-neuronal spread of the virus has been demonstrated (14). However, it is imperative that we develop similar models for studying the effects of SARS-CoV-2 on the nervous system.

Our current experience shows how unprepared we are for managing a pandemic of this nature. It has been a disaster from so many perspective. The public health measures were not in place, the medical community has been unable to treat the large numbers of infected patients or even protect themselves while treating patients, and we have no treatments against these viruses. This may have been the worst pandemic that we have seen in our life-times but unfortunately, it may not be the last. There have been many warning signals that we have ignored. Recent pandemics of encephalitis include Dengue, Zika, West Nile, Chikungunya, Nipah

Alpha	Receptor
HCoV-NL63	ACE2
HCoV229E	
Beta	
SARS virus	ACE2
SARS-CoV-2	ACE2; TMPRSS2
MERS	DPP4
HCoV-OC43	Unknown
HCoV-HKU1	Unknown

ACE=angiotensin converting enzyme; DPP4=Dipeptidyl peptidase 4;
TMPRSS2=Transmembrane protease serine 2

and Ebola. Venezuelan encephalitis virus is on the list of bioterrorism agents. Yet, the pathophysiology of these illnesses have been poorly studied and to date we have no antiviral treatments. It is critical that the neurovirology community play a leading role in developing relevant in vitro and animal models for these diseases and engage in developing disease specific treatments. Some of the agents such as SARS-CoV-2 require biosafety level-3 (BSL-3) laboratories which we have realized is the biggest bottleneck for studying the virus and for drug development. Resources invested into developing such facilities in most academic institutions will have long-term payoffs. Considering the fact that the cost of SARS-CoV-2 infection is in the trillions of dollars, every dollar spent on research development would reap huge benefits. This should be a wake up call to all Neurovirologists and we should lead the effort to demolish these diseases before they devastate humanity as we know it. We cannot afford to wait for the next pandemic. The time for action is now (Table 3).

Table 3: Call to action for Neurovirologists

1. Develop a central repository of reagents: Cell lines, viral stocks, antibodies, plasmids with viral genes and receptors,
2. Develop a repository of clinical samples, including autopsy tissues
3. Expand numbers of BSL-3 labs for in vitro and in vivo research
4. Develop robotic systems for conducting autopsies
5. Develop relevant animal models
6. Develop targeted therapies including small molecules and antisense oligonucleotides that enter the CNS
7. Develop clear guidelines for preclinical drug development, regulatory approval process and clinical trials
8. Enable academic institutions to play major role in all aspects of preclinical studies and manufacturing processes
9. Develop innovative multicenter clinical trials that can be initiated expeditiously during the epidemic

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One Neurology Department's Response to Prepare for COVID-19

By John C. Probasco, MD and Jose Ignacio Suarez, MD
Johns Hopkins University School of Medicine

In December 2019, the first cluster of patients with pneumonia, later confirmed as due to infection with the novel coronavirus SARS-CoV2 (COVID-19), was identified in Wuhan, China. Today, over 3.5 million people worldwide have been confirmed as infected with COVID-19, of whom over 249,000 have died (<https://coronavirus.jhu.edu/map.html>. Accessed 5/4/2020).

As the first COVID-19 cases in the US were confirmed in late January 2020, hospitals across the US moved forward with preparations for the anticipated surge of patients with COVID-19. At our institution and elsewhere, neurologists joined their emergency, internal medicine, and critical care colleagues in caring for COVID-19 infected patients while restructuring neurological clinical services and approaches to clinical training (Waldman et al *Neurology* 2020; 94:1-6. doi:10.1212/WNL.00000000000009519).

The pandemic necessitated rapid transitions in models of neurology care delivery, the retraining of providers, and the revisiting of conversations on allocation of scarce resources. These transitions have been with an eye to sustainability for when the pandemic surge gives way to a steady volume of COVID-19 infected patients, all in the setting of a burden of neurological disease that does not subside even in the face of a pandemic.

By mid-March, our outpatient clinical visits began to transition from in person to telemedicine care. Staff education for telehealth was deployed within days, covering topics ranging from scheduling of visits to equipment setup and billing. Over the past six weeks, the number of telemedicine visits have grown exponentially, from only a handful of visits per week before the pandemic, to hundreds per day. Faculty, residents, and fellows have utilized multiple party teleconferencing options to ensure trainee clinical exposure and care delivery.

The pandemic also affected procedural care delivery, initially requiring the rescheduling of non-urgent EEG, EMG and nerve conduction studies, lumbar punctures as well as planned admissions to our epilepsy monitoring units. In the ambulatory infusion center, processes from scheduling, to screening, to administration of medications were refined to mitigate exposure risk to patients and clinic staff alike.

In the hospital, resident staffing of our neurological services was reduced to half-staffing levels, akin to what is used annually over the winter holiday period. This change allowed for the continuation of clinical activities in balance with needs for social distancing on the wards and mitigation of exposure risk within the residency. Schedules for attending back-up were made to ensure faculty coverage of the inpatient services in the event of illness or deployment elsewhere within the health system. Faculty and fellows volunteered to backfill residents and faculty in the event of illness or deployment elsewhere in the medical system.

In collaboration with the emergency room and inpatient services, in-person consultations were limited to emergent and urgent clinical questions (e.g. acute stroke) and performed by single residents with consultant faculty rather than whole teams. Non-urgent questions were addressed by telephone conversation and telemedicine visits either within the hospital or by arranged outpatient telemedicine visits. In addition, daily multi-disciplinary care and discharge coordination rounds were restructured utilizing teleconferencing rather than in person meetings of case managers, nurses, pharmacists, therapists, and physician teams.

In preparation for a potential surge in patients requiring mechanical ventilation, our dedicated 24 bed neurocritical care unit (NCCU) at Johns Hopkins Hospital was divided into a 16 bed COVID-19 positive critical care unit and an 8 bed COVID-19 negative critical care unit for neurosciences, surgical, and medical ICU patients. The 6 bed intermediate care unit (IMC) was transitioned to an ancillary critical care unit. The NCCU at our Bayview medical center campus, with 8 NCCU and 6 IMC beds, was transitioned to a COVID-19 negative critical care unit for neurosciences as well as surgical and medical ICU over-flow patients.

This restructuring necessitated the creation of two additional physician teams to deliver care within the two new critical care areas. Nursing staff in our 6 bed neurosciences IMC were trained for critical care delivery under the supervision of a critical care nurse. NCCU nursing schedules were restructured from staffing for a single unit, to staffing for four. A day-night float system was developed for physician staffing of the four NCCUs. Critical care faculty, fellows, and advanced practice providers; anesthesia, medicine,

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neurology, and neurosurgery housestaff; and faculty and fellow volunteers from the departments of neurology and neurosurgery came together to form these teams. Initially, a pulmonary critical care faculty member, fellow, and an internal medicine resident joined the NCCU COVID-19 positive team to train our neurosciences providers in the institutional best practices for the treatment of COVID-19 infection.

To prepare these neurology volunteers, neurocritical care faculty organized a lecture series on airway management and mechanical ventilation, cardiovascular emergencies, and sepsis. In addition, residents led a neurology-specific “tips and tricks” for use of the inpatient electronic health record system for our outpatient providers to use in preparation for possible inpatient deployment. This training was in addition to weekly departmental and divisional virtual meetings for discussion of responses to the pandemic and next directions.

Faculty and fellow volunteers took on day-shift responsibilities in our JH Bayview NCCU. This allowed for hands-on training beside a neurocritical care faculty member in the management not only of neurocritical care patients but also medical and surgical ICU over-flow patients. This also ensured that the NCCU teams were able to follow a day-night float schedule while developing a cohort of neurologists to augment NCCU staffing going forward through the pandemic.

Mindful of the experiences of colleagues elsewhere, our neurocritical care physician and nursing leadership have been early participants in institutional and state-wide initiatives to address anticipated scarcity of resources due to the pandemic. This process is based on a project which used a state-wide public engagement process to develop a framework for disaster resource allocation of mechanical ventilation (Daugherty Biddison et al 2019 Chest. 155(4):848-854. <https://doi.org/10.1016/j.chest.2018.09.025>).

We are, however, only in the first phase of this pandemic. As the initial surge passes, we must be mindful to employ models for sustainable care delivery, both in the inpatient and outpatient settings. This entails training of providers to meet care needs (e.g. intensive care) as well as the resumption of outpatient care, particularly rescheduled procedures, in a manner that is safe for patients, clinic staff, and providers. An added unknown is the consequence of deferred care on the burden of neurological disease. There have been concerns that patients are not presenting for acute neurological care out of fear of COVID-19 infection. This could lead to an unanticipated surge of inpatients with neurological disease as public concerns for a COVID-19 surge passes. Also, as the summer fast approaches, academic neurology departments will need to navigate the logistics of residents and fellows transitioning into and out of institutions in an era of quarantines of out-of-state arrivals and the changing landscape of medical student education.

The challenges of the COVID-19 pandemic provide opportunities for improvement in clinical care delivery. For example, in our early experience, patients have regularly voiced satisfaction with telemedicine services, particularly for clinical follow-up. Now is the time to assess if such anecdotal reports are reflective of general perceptions of telemedicine to inform future clinical practice and care reimbursement. This also prompts us to explore telemedicine technologies in the performance of the neurological examination and monitoring.

The COVID-19 pandemic has necessitated rapid changes in methods of care delivery, team structures, and training. As we go forward, neurologists will need to continue to be prepared, flexible, and creative to address clinical needs as they arise. We must continue to evaluate these responses to refine the care we provide in this time of pandemic and after.

Research Recommendations and Funding Opportunities to address the COVID-19 Pandemic Emergency

By Walter Royal

This article provides a brief overview of information for researcher who have had their research impacted by the COVID-19 pandemic and discusses opportunities for COVID-19-related funding.

As a result of the pandemic, there has been a need for a major shift in focus among the research community to protect research personnel and study subjects from infection and to contribute to the development of effective approaches to diagnosing, treating and preventing community spread of infection. Unlike other pandemics of recent decades, the urgency has called on physicians and other clinically trained individuals involved in research to suspend their research activities and direct their efforts to patient care, both in-person and using virtual approaches. Also, many institutions have restricted research activities so that they occur only at levels necessary to protect vital research resources. The impact on currently funded research has been swift and dramatic and has led to extensions and redirecting of currently funded research, opportunities to recoup losses, including those due to supplies donated to individuals working in the clinical setting where there have been shortages, flexibility with grant-associated deadlines and new funding opportunities.

The NIH has released the specific guidelines for funded researchers for addressing delays and interruptions (see: <https://grants.nih.gov/policy/natural-disasters/corona-virus.htm>), several which are highlighted below and can be applied to research that receives funding support from other entities:

Human subject research and clinical trials: Funding recipients are encouraged to contact study-associated IRB's and to follow local institutional guidelines that may limit study visits and governmental and institutional policies regarding numbers of persons who may be present in an area.

Application deadlines: All non-AIDS applications with due dates between March 9 and May 1, 2020 that were submitted late were accepted through May 1. It is expected that such submissions were to be reviewed in the August or October 2020 council round, but this was guaranteed. There has been no change in the due dates for AIDS applications, which include the May 7, 2020 due date. Any further delay requests need to be accompanied by a correspondence for the applicant's institution and will be considered on a case-by-case basis.

Pre-award costs and post-award reporting: For entities performing research related to or affected by COVID-19, following the provision of appropriated documentation, specific flexibilities in allowing pre-award costs and extension of post-award financial and other reporting may be granted. It can be expected that late reporting will result in delayed issuing of awards.

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Research Recommendations and Funding Opportunities to address the COVID-19 Pandemic Emergency

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Research opportunities for addressing the COVID-19 pandemic

In response to the emergency, on March 6, 2020 the Coronavirus Preparedness and Response Supplemental Appropriations Act, 2020, which provides \$8.3 billion in emergency funding for federal agencies to respond to the coronavirus outbreak, was signed into law. This bill is not to be confused with the Coronavirus Aid, Relief, and Economic Security (CARES) Act, which provides over 2 trillion to the American public for economic relief and was signed into law on March 27th, 2020. U.S. funding agencies have released announcements describing opportunities to apply for new awards and for supplemental and competitive revisions to existing grants. Due to ongoing changes in the status of the pandemic and developments related to research needs, such funding opportunities can be expected to change over time. There is a growing list of opportunities for funding offered by U.S. and international agencies to support projects of regional or global impact. The following are some that are likely to be of interest members to the ISNV research community:

National Institutes of Health: <https://grants.nih.gov/policy/natural-disasters/corona-virus.htm>

Department of Defense: <https://www.grants.gov/web/grants/view-opportunity.html?oppld=326034>

National Science Foundation: <https://www.nsf.gov/pubs/2020/nsf20052/nsf20052.jsp>

Co-Creation Hub: <https://cchubnigeria.com/call-for-projects-funding-and-design-support-for-COVID-19-projects/>

Australian Government: Medical Research Future Fund: <https://www.health.gov.au/news/research-funding-for-COVID-19-treatments>

UK Research and Innovation: COVID-19 Call: <https://www.ukri.org/funding/funding-opportunities/ukri-open-call-for-research-and-innovation-ideas-to-address-COVID-19/>

California Institute for Regenerative Medicine: <https://www.cirm.ca.gov/about-cirm/newsroom/press-releases/03272020/stem-cell-agency-board-approves-5-million-emergency>

Canadian Institute of Health Research: <https://cihr-irsc.gc.ca/e/51917.html>

There will certainly be questions about situations and opportunities that cannot be addressed by the information provided above. Therefore, researchers should not hesitate to contact the respective agency.

COVID-19 Quick Links

Stay current. Stay informed.

Sources for epidemiologic data:

CDC: <https://www.cdc.gov/coronavirus/2019-ncov/index.html>

WHO: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>

JHU: <https://coronavirus.jhu.edu/>

Open sources for coronavirus research publications

NEJM: <https://www.nejm.org/coronavirus>

JAMA: <https://jamanetwork.com/journals/jama/pages/coronavirus-alert>

Open access to media and news coverage:

New York Times: <https://www.nytimes.com/2020/04/28/us/coronavirus-updates.html>

Washington Post: <https://www.washingtonpost.com/world/2020/04/28/coronavirus-latest-news/>

Coronavirus neuro-focused research: suggestions

By Bruce Brew

In the space of a few weeks since the conception of this special newsletter we have gone from a suspicion of direct brain involvement by COVID-19 to near certainty. Such is the pace of this virus and that of the global research community. COVID-19 infection is not just leading to a non-specific encephalopathy that is seen in many seriously ill patients but rather to a form of encephalitis. It is timely then as a Society that we shape the relevant research questions to expedite discovery to ultimately improve patient care. Knowledge is power but focused and relevant knowledge is even more power.

To this end, I have the following questions. These are meant really to serve as a framework for more critical discussion to facilitate targeted research. It is certainly not meant to be exclusionary. The timing and precise nature of brain involvement are of paramount importance. Given that ACE2 expression in the brain is relatively low as opposed to the expression on blood vessels including those in the brain, is the primary process vascular? Or is brain ACE2 expression upregulated by the increasing cytokine levels as patients become sicker? Is the portal of entry into the brain via the systemic circulation and crossing the blood brain barrier (likely impaired from endothelial cell infection), or via meningeal infection first or via the olfactory nerve? Does anosmia increase the risk of brain involvement? Is brain infection a multi-step process akin to progressive multifocal leukoencephalopathy (PML) where perhaps there is a permissive setting eg as indicated by anosmia or blood brain barrier damage which then has to be “fueled” by cytokine-mediated upregulated brain ACE2 expression? Which parts of the brain are infected – the brainstem especially the cardiorespiratory center in the medulla? Why is CSF so often PCR negative at least from current reports – is it just an issue of PCR sensitivity or is it a reflection of trans-neuronal spread as suggested by animal models?

Cell culture and animal models along with human autopsy studies should be able to address these issues to a large extent. However, there will be the usual problems of translatability to humans and autopsy selection bias towards the sickest patients that will mean in vivo studies will be essential.

In the acute setting, these will be challenging in design as they must not compromise patient care by the demands of extra research investigations and they must minimize risk to researchers. Virtual assessments will help but of more practical importance will be the standardization of data that are already being routinely collected as part of routine care. This essentially will place no burden on the front-line staff nor the safety of researchers – there will just be a need for some agreed minimum data set which can be collected and entered into a database. Such data will also capture pre-existing neurological co-morbidities and their therapies to better understand the potential bi-directional influence of COVID-19 infection. Efforts are already afoot internationally to agree on a minimum data set. These should be expedited and ideally harmonized as much as possible among countries.

In the long-term recovery phase, when patients are no longer shedding virus, assessments will provide a unique opportunity to better understand the disease. More detailed examinations and investigations, especially MRI brain scans, will be possible. CSF studies though scientifically desirable will be clinically hard to justify.

Research in both settings should endeavor where possible to distinguish between non-specific neurological consequences of systemic infection and those that are more indicative of direct brain involvement. Such distinction is critical as it influences patient management: direct involvement means that brain-specific interventions are required not just systemic measures. For example, headache and myalgias are non-specific occurring not infrequently in systemic infection. Similarly, the development of neuropathy and myopathy in ill patients will have to be distinguished if possible from critical illness neuromyopathy. Even acute hemorrhagic necrotizing encephalopathy is non-specific. Perhaps most importantly, detailed attention will need to be given to the potential confounding effects of hypoxic brain damage on the neurological consequences of COVID-19 infection. On the other hand, direct brain involvement will require not only that a potential drug be able to cross the blood brain barrier but also that it is effective in the cell type supporting infection – this appears to be the neuron.

This is a unique time in history, not only for knowledge but for its direct practical implementation into improved patient care. As a Society we have the opportunity to make a valued contribution.