Neurology Practice in India: At Crossroads

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Some 350 years ago, Thomas Willis coined the term Neurology to describe the then-nascent science that studied what we know today as the nervous system.[1] Since then, several eminent physician scientists in England, France, Italy, and several other prestigious universities in mainland Europe and later the New World had enriched the neurosciences.[2] The practice of neurology today is on the threshold of an exciting new era. The progress in basic sciences, allied specialties, imaging, neurobiology, neurophysiology, genetics, neurochemistry, and several other branches of science have made this possible. Neurology had progressed from understanding of how progressive neurological disorders manifest their symptoms to their precise diagnosis and finally potential remedies. Much of this progress had evolved in the past 10 years and even more exciting progress is awaiting us. Inevitably, these progresses have brought in their share of ethical dilemma too. How do these developments influence the environment, biological systems, and the human kind at large. His Highness the 13th Dalai Lama was referring to this dilemma when he stated that:

> *"Today, humanity is at a critical crossroad. The radical advances that took place in neuroscience and particularly in genetics … have led to a new era in human history."*[3]

Let me try to illustrate this with a couple of examples. In 1962, Luft *et al*. had for the first time described "a disease that was not according to the books" – characterized by highest metabolic rate, profuse perspiration, heat intolerance, resting tachycardia, and muscle weakness.[4] This disorder later known as Luft's disease is the first mitochondrial disorder to be described. Today, we are aware of several neurodegenerative disorders attributed to mitochondrial genetic disorders. So far, there is no permanent cure for this group of disorders that people inherit from their mothers. Nevertheless, progress in reproductive medicine and embryology has made it possible to do mitochondrial gene replacement in the ovum from a healthy donor so that the disorders related to defective mitochondrial genes will not be transferred from the mother to the baby. The mitochondrial gene replacement can be carried out before or after *in vitro* fertilization. The first baby with successful mitochondrial gene transfer was born to a woman who had Leigh syndrome. This technique popularly known as a three-parent baby had opened much ethical debate. There are ethical concerns about germ cell modifications and eugenics. There are concerns regarding the safety of the

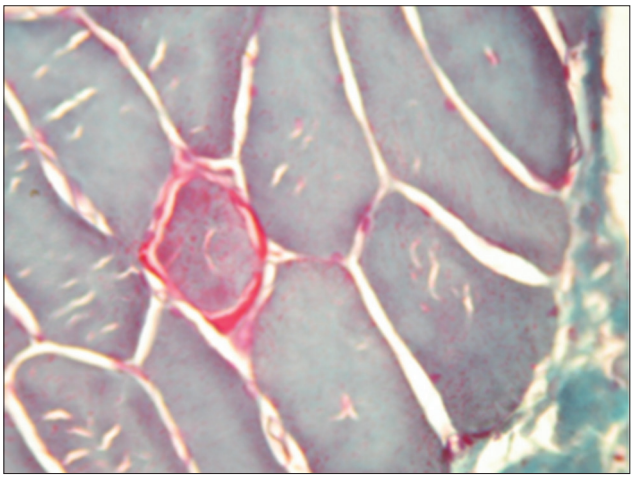

Figure 1: Gomori Trichrome staining of muscle biopsy showing aggregation of abnormal mitochondria in red color along the periphery of muscle fibers in a case of mitochondrial disorder

Figure 2: Dr. Nikolaus Friedreich who described Friedreich's ataxia for the first time

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Figure 3: Prof. Andrew Barbeau and Claude St. Jean: A doctor–patient relationship that flourished to extensive research

procedure and the nuances of the parental rights of the donor. The UK Human Fertilization and Embryology Authority was established way back in 1990 to govern the practices in reproductive medicine. The UK parliament had passed the law on October 29, 2015, that legalized mitochondrial transfer therapy for selected disorders.[5] Following on the approval from the UK government, mitochondrial replacement therapy had been implemented for the prevention of myoclonic epilepsy with ragged red fibers (MERRF).[6] MERRF is a rare disorder that affects one in 5000 live-born babies. It manifests as myoclonus, muscular weakness, and later on, long-tract signs are added. Typically, the condition is diagnosed from muscle biopsy and special stains that demonstrate accumulation of abnormal mitochondria as red spots on special staining [Figure 1].

Nikolaus Friedreich first described his eponymous ataxia in a series of papers, published between 1863 and 1876, on nine members of three families who developed ataxia, dysarthria, sensory loss, muscle weakness, scoliosis, foot deformity, and cardiac symptoms at the onset of puberty[7] [Figure 2]. The clinical condition is relentlessly progressive, and most of the affected persons become wheelchair bound by the third decade of life. The condition remained a clinical curiosity and typical "examination case" for several decades. Claude Saint Jean (1952–2006) was one of the victims of this condition [Figure 3]. He was diagnosed Friedreich's ataxia (FA) at the age of 15 years. After overcoming the initial frustration and anger, he focused all his energy to encourage doctors and scientists to undertake research into the cause and possible treatment of FA. During his lifetime, he had raised over 6 million dollars to support research and demonstrated extraordinary courage and drive to find the cause of the disease and possibly a cure.[8] He had encouraged Prof. Andre Barbeau who was then researching on Parkinson's disease at McGill University to set up a research team to carry out extensive research into FA [Figure 3]. More than 240 scientists from over 40 institutions in 8 countries had participated in this mammoth research over 10 years and brought out 148 publications. At the end of 10-year research, Dr. Barbeau had written that.

> "The last 10 years have indeed seen important strides taken in the definition and nosography of the hereditary ataxias and the characterization of a number of new entities. Biochemically, the principal leads uncovered during the initial prospective survey, have been pursued to great detail. Unfortunately no clear-cut constant and severe enzyme block in the principal metabolic pathways has yet been identified, despite intensive studies."[9]

The next milestone in the research on FA is its familial and clinical characterization by Professor Harding.[10] She had brought out the criteria for early diagnosis of FA. Thus, the 1970s and 1980s were the decades of nosological characterization, yet the precise cause was eluding. These were people who had walked ahead of time, since science had not matured enough to identify the cellular mechanisms of many neurodegenerative disorders including FA. It unfortunates that we lost Professor Barbeau soon after this decade of research on FA and Professor A. Harding who was also researching on the genetics of FA quite early in her life. It was in 1996 that the scientists in the Valencia University in Spain had found out that intronic GAA triplet repeat expansion is the cause of FA.[11] The potential treatment of FA that Claude St. Jude was hoping was not even at horizon and remained a wish even as late as 2005. In 2012, a paper was published in science that a programmable dual RNA-guided DNA endonuclease can alter the genomic DNA.[12] This team had shown that it is possible to make targeted cuts in genomic DNA with appropriate "scissors" – CRISPR-CAS systems. Science accepted this paper within 2 weeks of submission. This landmark paper demonstrated an incredibly precise and quick yet inexpensive method to alter the genomic DNA at points of interest. Several teams have subsequently improved upon this technique to alter the genomic DNA that could ultimately overcome the defects in several neurodegenerative disorders. A report in 2017 showed that in mouse models of FA, it is possible to delete the GAA repeats in the human frataxin gene with the help of CRSPR-CAS-9 system.[13] A more recent paper had shown that such gene therapy fully reversed the FA changes in mouse models.[14] It appears that a specific curative genetic therapy is round the corner for FA and several other genetic disorders. CRISPR technology had been further expanded to develop a chain reaction that would convert heterozygous to homozygous mutations.[15] This technology had been popularly known as gene drive and some scientists consider them to be the extinction invention.[16] A research laboratory in the UK had shown this year that it is possible to eliminate a population

of *Anopheles gambiae* mosquitos in six generations by applying gene drive.[17]

The progress in molecular biology, biotechnology, genetics, and neurobiology in the past 10 years had been amazing. We are almost at the threshold of conquering many degenerative disorders and infections of the nervous system with the help of these progresses. Nevertheless, progress always comes with ethical dilemmas too. I would like to quote Dalai Lama again.

> "*Our knowledge of the human brain and body at the cellular and genetic level with the consequent technological possibilities offered for genetic manipulation has reached a state that the ethical challenges of these scientific advances are enormous*."[3]

The national academies of science, engineering and medicine in the USA have laid down certain governing principles so that genome editing would applied with due care to promote well being. It should uphold principles of responsible science, respect to persons, distributive justice and promote transnational cooperation.[18] They have recommended that germline editing requires further understanding, clinical research only for compelling purposes, and not for enhancement purposes. Transparency, public discussion, and policy debates are essential in this field.

While rapid progress is happening in technology-driven neurosciences, there are serious issues with public health aspect in India. A typical example is rabies. Clinical rabies is known to humankind for long and is 100% fatal yet almost always a preventable condition. Half of all deaths due to rabies in the world happen in India. In India, about 20,000 people die of rabies every year and this number is likely to be higher if we include the neuroparalytic variant also.[19] The incidence of rabies has not decreased in India in the recent past. More than 95% of infection is due to dog bite, and the casualties are mostly children. Our neighboring country Sri Lanka had effectively eliminated rabies by universalizing postexposure prophylaxis and reduction in the number of stray dogs.[20] The World Health Organization (WHO) has initiated the "United against rabies collaboration: a global catalytic platform to achieve zero human rabies death by 2030-popularly known as "zero by 30." Dog sterilization, dog immunization, public cooperation, and postexposure prophylaxis to every dog bite are the cornerstones for rabies eradication.[21]

Stroke is one of the most important causes of death or disability in India and other low-income countries. The incidence of stroke in high-income countries had decreased from 163 to 94/100,000 population between 1979 and 2008. In contrast, during the same period, the incidence in low-middle-income countries including India had increased from 56 to 117/100,000 population.[22] Stroke in low-middle-income countries is characterized by younger age and higher mortality risk. The important risk factors are obesity, tobacco use, diabetes, high blood pressure, and dyslipidemia. An integrated stroke management policy that includes prehospital care, acute management, and follow-up with emphasis on secondary prophylaxis has been initiated in India.[23] The Government of India had initiated a national program on prevention and control of diabetes, cardiovascular diseases, and stroke in early 2008. This pilot program aimed to prevent or control noncommunicable diseases (NCDs), facilitate early detection of NCDs, and promote awareness on lifestyle changes and capacity building of health systems to tackle NCDs. Unfortunately, we have not progressed much on these coveted goals. One of the important areas is attention to mild hypertension. The risk of stroke increases by 44% when the blood pressure is in the range 120–129/80–84 mm and by 95% when the blood pressure is between 130–139 and 85–89 mm of mercury.[24] The data from the USA show that the incidence of stroke had reduced between 1972 and 2008 when the mean arterial blood pressure had reduced from 129-mm mercury to 122-mm mercury. These figures indicate that even a small drop in systolic blood pressure could be associated with substantial decrease in stroke incidence although it is likely that other factors also would have influenced the decrease in the stroke during this period. The WHO had recognized the public health priority of managing high blood pressure and made it the world health day theme in 2013.

Are we sufficiently equipped to handle these demands? The medical training that leads to a final certification as a neurologist in India involves a 6-year initial MBBS course, then a 3-year residency in internal medicine or pediatrics, and a final 3-year residency in Neurology. Nowadays, one could go for a postdoctoral fellowship in epilepsy, stroke, or other subspecialties within neurology. Altogether, a person spends about 12–14 years of training before he qualifies to practice neurology independently. Over the years, we have produced doctors with exceptional clinical skills who have also shown extraordinary adaptability and energy. Our doctors have demonstrated the adaptability to practice in small setups such as primary health center as well as large corporate hospitals. They can work for several hours at a stretch and still have the energy to see more patients if required. Nevertheless, the medical educational programs in India have provided little opportunity for interdisciplinary interactions with professionals in other fields and research experience. Research funding is difficult to obtain as funding is always scarce. There are few institutions dedicated to research such as the National Institute of Neurological Disorders and Stroke or National Institutes of Health in the USA. Nevertheless, we have demonstrated that we can rise to the occasion. The Nipah encephalitis in Kerala is a success story. A person with features of encephalitis was admitted to a general hospital in North Kerala, and the neurologist who attended to him had suspected Nipah encephalitis within 12 h of admission and the blood samples confirmed the diagnosis in 24 h. The epidemic affected 19 persons within that period and 17 of them succumbed to the illness which included Mrs. Lini Puthusserry, a nurse who had attended to the first case in that epidemic. The WHO Director for health workforce

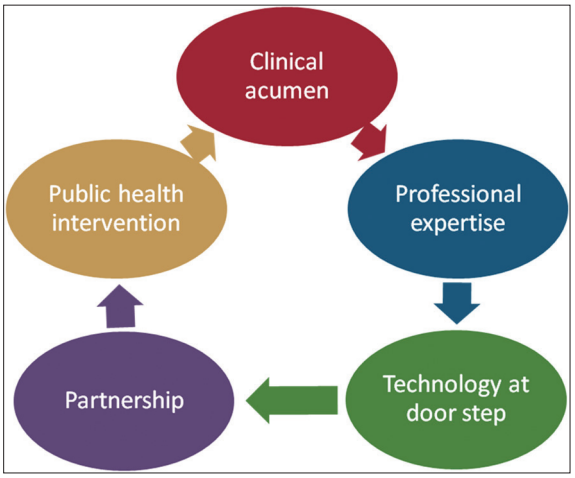

Figure 4: The synchronization between clinical expertise, laboratory services, partnership, and public health

Figure 5: Millennium development goals for the Indian Academy of Neurology

had commented on the sacrificial service of this nurse. The Kerala State public health department also swung in to action immediately, and deployed its professionals to contain the epidemic and bury the deceased as per international standards. They carried out large scale screening for infection. The clinical acumen of the neurologist and the availability of technology at doorstep (to carry out the laboratory tests), partnership between institutions, government and nongovernmental level, and prompt public health response enabled the state to contain the epidemic [Figure 4]. The synchronization of clinical acumen, professional expertise, technology at doorstep, effective partnership, and prompt public health intervention made it possible to control the encephalitis from becoming a catastrophic epidemic in Kerala state. What are the Millennium development goals for the Indian Academy of Neurology [Figure 5]. The academy is committed to promote skills and training and establish standards of care. It needs to maintain a public health perspective and enhance its partnerships. Let me conclude this oration with a famous quote from Helen Keller:

"*Alone we can do little, together we can do so much*."

Helen Keller was born with visual and auditory handicap, what we now call multiple handicaps. Even today, multiple handicaps are extremely challenging to handle. Helen Keller with the help of her teachers and subsequently the public had overcome those handicaps and lived a successful career where she proved that we can overcome insurmountable problems collective efforts. I wish all success to the Indian Academy of Neurology.

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Conflicts of interest

There are no conflicts of interest.

References

1. Available from: http://www.science.jrank.org/pages/10242/Mind-Thomas-Willis-Birth-Neurology.html">Mind-Thomas-WillisAndTheBirthOfNeurology. [Last accessed on 2018 Dec 12].
2. Gardner-Thorpe C. A short history of neurology. Brain 2000;123:2573-5.
3. Gyatso T. The Dalai Lama Science at the Crossroads. Available from: https://www.dalailama.com/messages/buddhism/science-at-the-crossroads. [Last accessed on 2018 Dec 12].
4. Luft R, Ikkos D, Palmieri G, Ernster L, Afzelius B. A case of severe hypermetabolism of nonthyroid origin with a defect in the maintenance of mitochondrial respiratory control: A correlated clinical, biochemical, and morphological study. J Clin Invest 1962;41:1776-804.
5. Castro RJ. Mitochondrial replacement therapy: The UK and US regulatory landscapes. J Law Biosci 2016;3:726-35.
6. Hamzelou J. First UK Three-Parent Babies could be Born this Year. Available from: https://www.newscientist.com/article/2160120-first-uk-three-parent-babies-could-be-born-this-year/. [Last accessed on 2018 Dec 12].
7. Schulz JB, Pandolfo M 150 years of Friedreich ataxia: From its discovery to therapy. J Neurochem 2013;126 Suppl 1:1-3.
8. Available from: http://www.canadianataxiaconference.com/claudestjean/. [last accessed on 2018 Dec 12].
9. Barbeau A. The Quebec cooperative study of Friedreich's ataxia: 1974-1984-10 years of research. Can J Neurol Sci 1984;11:646-60.
10. Harding AE. Friedreich's ataxia: A clinical and genetic study of 90 families with an analysis of early diagnostic criteria and intrafamilial clustering of clinical features. Brain 1981;104:589-620.
11. Campuzano V, Montermini L, Moltò MD, Pianese L, Cossée M, Cavalcanti F, *et al.* Friedreich's ataxia: Autosomal recessive disease caused by an intronic GAA triplet repeat expansion. Science 1996;271:1423-7.
12. Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. Science 2012;337:816-21.
13. Ouellet DL, Cherif K, Rousseau J, Tremblay JP. Deletion of the GAA repeats from the human frataxin gene using the CRISPR-cas9 system in YG8R-derived cells and mouse models of Friedreich ataxia. Gene Ther 2017;24:265-74.
14. Piguet F, de Montigny C, Vaucamps N, Reutenauer L, Eisenmann A, Puccio H. Rapid and complete reversal of sensory ataxia by gene therapy in a novel model of Friedreich ataxia. Mol Ther 2018;26:1940-52.
15. Gantz VM, Bier E. Genome editing. The mutagenic chain reaction: A method for converting heterozygous to homozygous mutations. Science 2015;348:442-4.
16. Regalado A. The extinction invention. Technol Rev 2016;119:54-9.
17. Kyrou K, Hammond AM, Galizi R, Kranjc N, Burt A, Beaghton AK, *et al.* A CRISPR-cas9 gene drive targeting doublesex causes complete population suppression in caged *Anopheles gambiae* mosquitoes. Nat Biotechnol 2018;36:1062-6.
18. National Academies of Sciences, Engineering, and Medicine, National Academy of Medicine, National Academy of Sciences, Committee on Human Gene Editing: Scientific, Medical, and Ethical Considerations. Human Genome Editing: Science, Ethics, and Governance. Washington (DC): National Academies Press (US); 2017.
19. Kole AK, Roy R, Kole DC. Human rabies in India: A problem needing

more attention. Bull World Health Organ 2014;92:230.
20. Karunanayake D, Matsumoto T, Wimalaratne O, Nanayakkara S, Perera D, Nishizono A, *et al.* Twelve years of rabies surveillance in Sri Lanka, 1999-2010. PLoS Negl Trop Dis 2014;8:e3205.
21. United Against Rabies Launches Global Plan to Achieve Zero Rabies Human Deaths. Available from: http://www.who.int/rabies/news/RUA-Rabies-launch-plan-achieve-zero-rabies-human-deaths-2030/en/. [Last accessed on 2018 Dec 12].
22. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: A systematic review. Lancet Neurol 2009;8:355-69.
23. Pandian JD, William AG, Kate MP, Norrving B, Mensah GA, Davis S, *et al.* Strategies to improve stroke care services in low- and middle-income countries: A systematic review. Neuroepidemiology 2017;49:45-61.
24. Huang Y, Cai X, Li Y, Su L, Mai W, Wang S, *et al.* Prehypertension and the risk of stroke: A meta-analysis. Neurology 2014;82:1153-61.