Milestones in PSP research during 50 years

I am delighted by being with you all and particularly with many friends I have known for many years as we sought to understand the disease we know as progressive supranuclear palsy.

The organizers have asked me to begin this international Movement Disorder symposium by discussing the milestones that now lead us to conclude it is a proteinopathy, and a universal and sporadic 4R taupathy with multiple phenotypes which is transmissible to mice and perhaps between humans.

We agree, I think, that PSP was probably first described by Charles Dickens, a literary master of medical illnesses, in 1857, while on a walking tour in southern England with his friend Wilke Collins, where he observed; “a chilled, slow, earthy, fixed man. A cadaverous man of measured speech. A man who seemed as unable to wink, as if his eyelids had been nailed to his forehead. A man whose eyes—two spots of fire—had no more motion than if they had been connected with the back of his skull by screws driven through them, and riveted and bolted outside among his gray hair. He had come in and shut the door, and he now sat down. He did not bend himself to sit as other people do, but seemed to sink bolt upright, as if in water, until the chair stopped him.”

100 years later, in 1955, in Toronto Canada, neurologist Clifford Richardson began our present journey of research and understanding of PSP when he recognized a similar illness in a successful business executive who was his good friend. As Richardson puzzled about is features of progressive supranuclear palsy of gaze and bulbar muscles, axial dystonia, gait impairment and dementia he identified 3 other patients with similar symptoms and he realized then their illnesses must be an unrecognized neurodegenerative syndrome.

He resisted opinions by neuropathologist colleagues that it was a variant of post encephalitic parkinsonism, and in 1962 he asked Jerzy Olszewski, the new professor of neuropathology at the Banting Institute and me as his resident to examine seven cases which he had identified.

We found the histopathology of neurofibrillary degeneration and gliosis in brain stem and subcortical nuclei was quite as distinctive as the clinical syndrome, but we could not be certain if it was a primary neurodegenerative disease like Alzheimer’s disease was assumed to be, or a noninflammatory infection akin to scrapie and kuru which were just then beginning to be described.

Interest in progressive supranuclear palsy has expanded since our description in 1964, and during the past 45 years its features have been vigorously investigated by an increasing number of
neuroscientists using new biological techniques and studies that are facilitated by internet communication and international meetings.

By 2014 we have learned PSP is a 4R tauopathy. Richardson’s syndrome, as he originally described in 1963 is its principal manifestation but PSP disease also includes diverse phenotypes of parkinsonism, corticobasal degeneration, pure akinesia with gait freezing, frontotemporal dementia and progressive nonfluent aphasia. Furthermore we have learned Richardson’s syndrome is not unique to PSP disease, and it occurs also in the ALS/Parkinsonism-dementia of Guam and in Guadeloupean parkinsonism.

As multiple system atrophy and corticobasal degeneration have been defined and studied in similar fashion to PSP, and as they are compared with the classical neurodegenerations of Parkinson’s disease, Alzheimer’s disease and ALS remarkable similarities are now recognized between them. All are featured by an abnormal and spreading protein that is specific to the neurodegeneration and accumulates in nerve cells and glia. Although some neurodegenerations are due to identified gene mutations, the majority are sporadic without obvious inheritance or family predisposition. Except for the 3 and 4R tauopathy of post encephalitic parkinsonism that followed epidemic lethargica, and subacute sclerosing panencephalitis that is sometimes a sequel of measles, and the spongiform encephalopathy of kuru which came after single feasts during mortuary cannibalism, there is no obvious preceding cause of these sporadic proteinopathies. Their onset is silent and asymptomatic, and it is not known if environmental exposure is single and isolated, or repeated and cumulative. It is not certain to what extent the pathogenesis may relate to genetic predisposition or protection.

On Guam, a tropical island in the Western Pacific, the ALS/Parkinsonism-dementia complex has held my interest for 32 years. It is a geographic isolate of a familial and long latency polyproteinopathy which includes all the immunohistochemical proteins of all the major universal neurodegenerations. Its phenotypes are as diverse as its abnormal proteins, and include classical ALS, PD, atypical parkinsonism with PSP and CBD, and Alzheimer-type dementia. During the past 50 years, this single disease has slowly declined by its principal phenotypes of ALS and PDC, and its age in onset has steadily increased. In 2010, classical ALS which was 100 times more common than elsewhere in 1953, no longer occurs on the island. Parkinsonism with dementia is uncommon and only 29 cases older than 70 were recently identified in a 2003 community survey of elderly Guamanians.

The remarkable decline and disappearance of ALS/PDC in this distant place gives me hope that related and universal proteinopathies could end in the same way. But we must first identify its environmental cause and that remains our intention.

The challenge to Neurology in years ahead is to understand why abnormal proteins form, how they are acquired, and how each adversely affects the nervous system. We need to learn about their spread, and why the same protein can give rise to different phenotypes, and different proteins can cause the same phenotype. These will be new milestones as we will learn about
protein metabolism and understand how we can influence and modify their abnormalities to prevent neurodegeneration.

In 1964, we were not certain if PSP was a classical neurodegeneration and akin to Alzheimer’s disease, or an infection due to a slow latent and temperate virus akin to scrapie. And we were aware of its similarities to post encephalitic parkinsonism. 45 years later we are still not certain. But we have learned that PSP and other neurodegenerations are due to the accumulation of abnormal proteins in the nervous system, and we are optimistic that future advances in understanding protein metabolism will give knowledge of pathogenesis and methods of cure.

I thank the Movement Disorders Society for making this meeting possible. And I congratulate the Dr. Hoglinger and his organizers for bringing together foremost authorities of PSP from all countries to know just where we are and how to move forward with others organizations like the Tau Consortium and CurePSP which have similar interests.

During 50 years we have made great progress in understanding PSP and other neurodegenerative diseases. We are not at an end or even the beginning of an end, but we are now at the end of a beginning to find their cause and their cure. I’m confident we will.

Thank you.

John Steele MD, FRCP©, FACP
Neurologist