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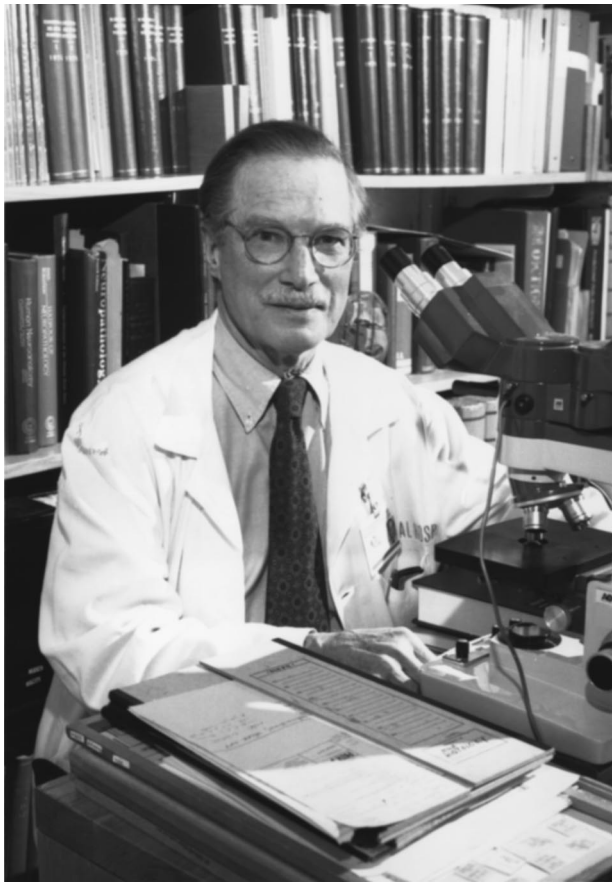
Obituary

Edward Peirson Richardson Jr (1918–1998) and the discovery of PML



Dr Edward Peirson Richardson Jr, neuropathologist and neurologist at the Massachusetts General Hospital who in 1958 co-authored the paper describing progressive multifocal leukoencephalopathy, died in Boston on November 30, 1998.

Dr Richardson was born on April 3, 1918 to a family with deep roots in the Boston medical community. He attended Harvard College (1939) and Harvard Medical School (1943 A). Following a medical internship at the Massachusetts General Hospital (MGH), he served as a neuropsychiatrist with the US Army until 1946, when he returned to MGH to study psychiatry and neurology under Stanley Cobb. From 1947–1949 he obtained additional neurology training at Queen Square and psychiatry training at the Maudsley Hospital in London.

Returning to MGH in 1949, Dr Richardson began a career in neurology and neuropathology at MGH and Harvard Medical School, working in the neuropathology laboratory at MGH with Charles S Kubik. After taking over the direction of the laboratory in 1951, he led it to international recognition, working side by side with a long line of illustrious professors of neurology and pathology, including Raymond D Adams, C Miller Fisher, Benjamin Castleman and Robert E Scully. Dr Richardson became Professor of Neuropathology at Harvard Medical School in 1974 and was appointed Bullard Professor of Neuropathology in 1984.

Dr Richardson was a gentleman whose impeccably polite, encouraging demeanor was seen in his interpersonal relations with everyone. The breadth of his interests in neuropathology was extraordinary, and he contributed papers encompassing almost every category of neurological disease. Also remarkable were his careful analyses of hundreds of MGH Case Records, or 'CPCs' which appeared over the years in the New England Journal of Medicine. All of his writings were characterized by precise wording and clear syntax, exhaustive surveys of the literature and meticulous study of the case material. One of the exciting moments of his career involved the description of progressive multifocal leukoencephalopathy (PML).

Discovery of PML

In 1953, an elderly woman with chronic lymphatic leukemia was admitted to the medical service of the MGH with a rapidly evolving left hemiparesis. The interpretation of the neurological disorder gave rise to a sharp divergence of opinion between the medical service, who favored focal leukemic infiltration of the brain, and the neurological consultants, Dr Raymond D Adams and Dr Maurice Victor, who thought that this was extremely unlikely and that the case was unique in their experience. The patient received a short course of radiation therapy to the brain without effect, and when she died 4 months later, Dr Richardson examined her brain. In a 1994 lecture (Richardson, 1994) he recalled:

> 'One thing was certain–there was no kind of leukemic infiltration of the brain. Instead, there was a diffuse destructive process involving

> mainly the central white matter of the brain asymmetrically. There was an indication that the disorder was fundamentally demyelinative, and that there were lesions of varying size . . . It seemed to me that the case somehow belonged in the large category of subacute primary demyelinative disease, with aspects suggestive both of multiple sclerosis and disseminated encephalomyelitis. But what really caught my attention was the presence, within the demyelinative foci, of gigantic astrocytes with bizarre nuclear configurations and unequivocal mitotic figures, some multipolar, such as are seen in malignant neoplastic cells. What I was seeing, I thought, was an unusual demyelinative disease in which the reactive astrocytes were turning into glioblastoma multiforme, right before my very eyes!'

He put this case aside. Three years later, another elderly woman with chronic lymphatic leukemia in remission was admitted to the MGH with a rapidly evolving neurological syndrome. Examination of her brain at autopsy revealed lesions that were identical to those of the earlier case. Dr Richardson, together with Dr Karl-Erik Åström and Dr Elliott Mancall, embarked on a detailed clinical and pathological analysis of the two cases. A third case was soon contributed from Emory University.

> '[As] we worked on these cases together, we became aware of another and more constant cellular change, consisting of the presence of prominent round nuclei which stained deeply with hematoxylin and presented a smudgy appearance because of the effacement of the chromatin pattern. We called these the 'dark cells' and . . . decided that they must be oligodendrocytes that were undergoing a pathologic change that was unfamiliar to us from previous experience.'

In 1958, the journal *Brain* published the landmark paper that was the first to recognize the clinical and neuropathological features of the condition they named progressive multifocal leukoencephalopathy (PML) (Åström *et al.*, 1958). Soon, additional cases began to appear in the literature. Dr Byron Waksman suggested to Dr Richardson the possibility that PML was the result of a viral infection in immunocompromised patients. One day shortly thereafter, Dr Richardson happened upon a picture showing the cytopathological effects of a virus which looked exactly like the diseased oligondendrocytes in PML. He put together additional cases and sent a paper to the New England Journal of Medicine proposing the virological hypothesis. The paper was accepted with the editorial instruction that 'The section regarding etiologic considerations adds little to the paper and the theories proposed are at best rather tenuous hypotheses. It would be better to eliminate this section . . .' Dr Richardson recalled that 'I naturally could not bring myself to eliminate these considerations entirely – but I did cut my statements to the bare-bones minimum.' The paper appeared in 1961 (Richardson, 1961). The subsequent detection of virus particles in PML oligodendrocytes by electron microscopy in 1965 by Gabriele Zu Rhein and others, and the isolation of a novel papovavirus, named JC virus, in 1971 by Billie Padgett and Duard Walker are well known chapters in the discovery of this 'modern' disease. The elucidation of this important condition – the first to link demyelination with an infectious cause – began, however, with the careful clinicopathological observations of Drs Richardson, Åström and Mancall.

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