

***Primum non nocere: a call for balance when reporting on
chronic traumatic encephalopathy***

Stewart, W^{1,2}, Allinson, K³, Al-Sarraj, S⁴, Bachmeir, C^{5,6,7}, Barlow, K⁸, Belli, A⁹, Burns, M¹⁰, Carson, A¹¹, Crawford, F^{5,6,12}, Dams-O'Connor, K¹³, Diaz-Arrastia, R¹⁴, Dixon, CE^{15,16}, Edlow, BL^{17,18}, Ferguson, S^{5,6,12}, Fischl, B¹⁸, Folkerth, RD¹⁹, Gentleman, S²⁰, Giza, CC^{21,22}, Grady, MS²³, Helmy, A²⁴, Herceg, M^{25,26}, Holton, JL²⁷, Howell, D^{28,29}, Hutchinson, P²⁴, Iacono, D^{30,31}, Iglesias, JE^{32,33}, Ikonovic, MD³⁴, Johnson, VE²³, Keene, CD³⁵, Kofler, JK³⁶, Koliatsos, V^{37,38}, Lee, EB³⁹, Levin, H⁴⁰, Lifshitz, J^{41,42,43}, Ling, H²⁷, Loane, DJ^{44,45,46,47}, Love, S⁴⁸, Maas, AIR⁴⁹, Marklund, N⁵⁰, Master, CL^{51,52}, McElvenny, DM⁵³, Meaney, DF^{23,54}, Menon, DK^{55,56}, Montine, TJ⁵⁷, Mouzon, B^{5,6,12}, Mufson, EJ⁵⁸, Ojo, JO^{5,6,12}, Prins, M^{15,16}, Revesz, T²⁷, Ritchie, CW⁵⁹, Smith, C^{60,61}, Sylvester, R⁶², Tang, CY⁶³, Trojanowski, JQ^{64,65,66}, Urankar, K⁴⁸, Vink, R⁶⁷, Wellington, C⁶⁸, Wilde, EA^{69,70}, Wilson, L⁷¹, Yeates, K⁷², Smith, DH²³

¹Department of Neuropathology, Queen Elizabeth University Hospital, Glasgow, UK

²Institute of Neuroscience and Psychology, University of Glasgow, Glasgow, UK

³Department of Pathology, Cambridge University Hospitals NHS Foundation Trust, Cambridge Biomedical Campus, Cambridge, UK

⁴The Institute of Psychiatry Psychology and Neurosciences, Kings College London

⁵Roskamp Institute, Sarasota, Florida, USA

⁶The Open University, Milton Keynes, UK

⁷Bay Pines VA Healthcare System, Florida, USA

⁸Child Health Research Centre, Faculty of Medicine, The University of Queensland, Australia

⁹Institute of Inflammation and Ageing, University of Birmingham, UK

¹⁰Georgetown University Medical Center, Washington DC, USA

¹¹Centre for Clinical Brain Sciences, University of Edinburgh, UK

¹²James A. Haley Veterans' Hospital, Tampa, Florida, USA

¹³Department of Rehabilitation Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, USA

¹⁴Department of Neurology and Center for Brain Injury and Repair, University of Pennsylvania Perelman School of Medicine, Philadelphia, USA

¹⁵Department of Neurological Surgery, Brain Trauma Research Center, University of Pittsburgh, Pittsburgh, USA

¹⁶Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, USA

¹⁷Center for Neurotechnology and Neurorecovery, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, USA

¹⁸Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Charlestown, USA

¹⁹City of New York Office of the Chief Medical Examiner, and New York University School of Medicine, New York, USA

²⁰Division of Brain Sciences, Department of Medicine, Imperial College London, UK

²¹UCLA Steve Tisch BrainSPORT Program, USA

- ²²Departments of Pediatrics and Neurosurgery, David Geffen School of Medicine and UCLA Mattel Children's Hospital, University of California, Los Angeles, California, USA
- ²³Department of Neurosurgery, Penn Center for Brain Injury and Repair, Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA.
- ²⁴Division of Neurosurgery, Department of Clinical Neurosciences, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK
- ²⁵Department of Physical Medicine and Rehabilitation, Phelps Hospital Northwell Health, New York, USA
- ²⁶School of Public Health, New York Medical College, New York, USA
- ²⁷Queen Square Brain Bank for Neurological Disorders, UCL Queen Square Institute of Neurology, London, UK
- ²⁸Sports Medicine Center, Children's Hospital Colorado, USA
- ²⁹Department of Orthopedics, School of Medicine, University of Colorado Anschutz Medical Campus, USA
- ³⁰Neuropathology Research, Biomedical Research Institute of New Jersey (BRInj), Cedar Knolls, NJ, USA
- ³¹Atlantic Neuroscience Institute, Atlantic Health System, NJ, USA
- ³²Centre for Medical Image Computing, Department of Medical Physics and Biomedical Engineering, University College London, UK
- ³³Computer Science and Artificial Intelligence Laboratory, Massachusetts Institute of Technology, USA
- ³⁴Departments of Neurology and Psychiatry, University of Pittsburgh, Pittsburgh, USA
- ³⁵Department of Pathology, University of Washington, Seattle, USA
- ³⁶Department of Pathology, Division of Neuropathology, UPMC Presbyterian Hospital, Pittsburgh, USA
- ³⁷Departments of Pathology, Neurology, and Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, USA
- ³⁸Neuropsychiatry Program, Sheppard and Enoch Pratt Hospital, Baltimore, USA
- ³⁹Translational Neuropathology Research Laboratories, Division of Neuropathology, Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, USA
- ⁴⁰Department of Physical Medicine & Rehabilitation, Baylor College of Medicine, Houston, USA
- ⁴¹Barrow Neurological Institute at Phoenix Children's Hospital, Phoenix, USA
- ⁴²University of Arizona College of Medicine Phoenix, 42283, Child Health, Phoenix, USA
- ⁴³Phoenix Veteran Affairs Healthcare System, Phoenix, USA
- ⁴⁴Department of Anesthesiology, University of Maryland School of Medicine, Baltimore, USA
- ⁴⁵Shock Trauma and Anesthesiology Research (STAR) Center, University of Maryland School of Medicine, Baltimore, USA.
- ⁴⁶School of Biochemistry and Immunology, Trinity College Dublin, Ireland.
- ⁴⁷Trinity Biomedical Sciences Institute, Trinity College Dublin, Ireland
- ⁴⁸Dementia Research Group, Institute of Clinical Neurosciences, School of Clinical Sciences, University of Bristol, Bristol, UK
- ⁴⁹Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium

⁵⁰Skane University Hospital, Department of Clinical Sciences Lund, Neurosurgery, Lund University, Lund, Sweden

⁵¹Center for Injury Research and Prevention, The Children's Hospital of Philadelphia, USA

⁵²Division of Orthopedic Surgery, The Children's Hospital of Philadelphia, Philadelphia, USA

⁵³Research Division, Institute of Occupational Medicine, Edinburgh, UK.

⁵⁴Department of Bioengineering, University of Pennsylvania, Philadelphia, USA

⁵⁵NIHR Global Health Research Group on Neurotrauma, University of Cambridge, Cambridge, UK

⁵⁶Division of Anaesthesia, Department of Medicine, University of Cambridge, Cambridge, UK

⁵⁷Department of Pathology, Stanford University, Stanford, CA, USA.

⁵⁸Barrow Neurological Institute, Depts of Neurobiology and Neurology, Phoenix, USA

⁵⁹Centre for Dementia Prevention Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK

⁶⁰Academic Neuropathology, University of Edinburgh, Edinburgh, UK.

⁶¹Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK.

⁶²Homerton University Hospital NHS Trust, National Hospital of Neurology and Neurosurgery, University College London, London, UK

⁶³Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, USA

⁶⁴Department of Pathology and Laboratory Medicine, Institute on Aging, and Center for Neurodegenerative Disease Research, Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA.

⁶⁵Institute on Aging, University of Pennsylvania, Philadelphia, USA.

⁶⁶Center for Neurodegenerative Disease Research, Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA

⁶⁷Health Sciences, University of South Australia, Adelaide, Australia

⁶⁸Department of Pathology and Laboratory Medicine, Djavad Mowafaghian Centre for Brain Health, International Collaboration on Repair Discoveries, School of Biomedical Engineering, University of British Columbia, Canada

⁶⁹Department of Neurology. University of Utah, Salt Lake City, USA

⁷⁰Michael DeBakey VA Medical Center and Baylor College of Medicine, Houston, USA.

⁷¹Division of Psychology, University of Stirling, Stirling, UK

⁷² Department of Psychology, Alberta Children's Hospital Research Institute, & Hotchkiss Brain Institute, University of Calgary, Canada.

Corresponding Author: Dr William Stewart, MBChB, Ph.D, FRCPath.
Department of Neuropathology
Queen Elizabeth University Hospital
1345 Govan Rd
Glasgow G51 4TF, UK.

Email: William.Stewart@glasgow.ac.uk

Tel: +44 (0)141 354 9535

As clinicians and researchers in traumatic brain injury and neurodegeneration we are concerned by the tone of reporting on chronic traumatic encephalopathy (CTE) that has developed in the past decade, highlighted in a recent article in the New York Times¹. Misleading reporting can have unintended, negative consequences and we call for balance from the medical and scientific communities and the media when communicating on issues related to CTE.

Contrary to common perception, the clinical syndrome of CTE has not yet been fully defined², its prevalence is unknown and the neuropathological diagnostic criteria are no more than preliminary³. Crucially, we have incomplete understanding of the extent or distribution of pathology required to produce neurological dysfunction or to distinguish disease from normality, with the neuropathologic changes of CTE reported in apparently asymptomatic individuals^{4,5}. Finally, although commonly quoted, there remains no consensus agreement on staging the severity of CTE pathology. In short, a single focus of the pathology implicated in CTE is not yet sufficient evidence to define disease.

Recognizing limitations of the diagnostic process in human pathology, pathologists are careful to note that they are merely providing an opinion; acknowledging that another pathologist might reasonably reach a different conclusion on the same case⁶. In diagnoses where the criteria for assessment and reporting are established by broad consensus, the expectation is that variance in opinion is minimised. At this time, however, while CTE diagnostic criteria remain far from established, it is to be expected that there will be discordance in opinions on individual cases¹.

Unfortunately, the uncertainties around the clinical syndrome and the pathological definition of CTE are not acknowledged adequately in much of the current research literature or related media reporting, which at times has resembled 'science by press conference'⁷. Too often an inaccurate impression is portrayed that CTE is clinically defined, its prevalence is high and pathology evaluation is a simple 'positive' or 'negative' decision. This distorted reporting on CTE may have dire consequences. Specifically, individuals with potentially treatable conditions, such as depression or post-traumatic stress disorder, might make decisions on their future based on a misplaced belief that their symptoms inevitably herald an untreatable, degenerative brain disease culminating in dementia.

We propose that the principle of 'first, to do no harm' is employed when communicating on CTE, whatever the platform. In particular, the many remaining uncertainties should always be acknowledged. Otherwise, there is a distinct risk of doing very real harm.

References

- 1 Belson, K (2018). 'Doctors Said Hockey Enforcer Todd Ewen Did Not Have C.T.E. But He Did.' *The New York Times*, 12/01
<https://www.nytimes.com/2018/11/30/sports/hockey/todd-ewen-cte-hockey.html?smtyp=cur&smid=tw-nytsports>
- 2 Wilson, L, Stewart, W, Dams-O'Connor, K, et al (2017). The chronic and evolving neurological consequences of traumatic brain injury. *Lancet Neurol*, 16, 813-825
- 3 McKee, A, Cairns, NJ, Dickson, DW, et al (2016). The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathol*, 131, 75-86
- 4 Ling, H, Holton, JL, Shaw, K et al (2015). Histological evidence of chronic traumatic encephalopathy in a large series of neurodegenerative diseases. *Acta Neuropathol.*, 130, 891-893
- 5 Noy, S, Krawitz, S, Del Bigio, MR (2016). Chronic traumatic encephalopathy-like abnormalities in a routine neuropathology service. *J Neuropath Exp Neur*, 75, 1145-1154
- 6 Manion, E, Cohen, MB, Weydert, J (2008). Mandatory second opinion in surgical pathology referral material: clinical consequences of major disagreements. *Am J Surg Pathol*, 32, 732-737
- 7 Moore, A (2006). Bad science in the headlines. Who takes responsibility when science is distorted in the mass media? *EMBO Rep*, 7, 1193-1196