International traumatic brain injury research: an *annus mirabilis?*

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In the history of science, the term *annus mirabilis*, Latin for extraordinary or miraculous year, refers to several years since 1666, including 1905, when a patent clerk in Bern, Switzerland, published four papers that revolutionised our understanding of the physical world.[1] With no resources and few scientific contacts, within 12 months, Albert Einstein published papers related to the photoelectric effect, the Brownian motion of particles showing the link between molecular motion and heat, the theory of special relativity, and the mass-energy equivalence ($E=mc^2$). For more than a century, many scientists have sought to achieve even a fraction of this productivity and transformational success.

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In 2011, the International Initiative for Traumatic Brain Injury Research (InTBIR) was formed with ambitions that might approach those for a new *annus mirabilis*. As a cooperative effort, the European Commission, the Canadian Institute for Health Research, and the US National Institutes of Health united with the mission of "working together to improve outcomes and lessen the global burden of traumatic brain injury (TBI) by 2020". One of the foundational studies of InTBIR is the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) project. In a study reported in *The Lancet Neurology*, Ewout Steyerberg and colleagues aimed to characterise patients with TBI in Europe.[2] With data from 4559 patients enrolled in a core study (in which patients were prospectively enrolled and followed up throughout their hospital stays and rehabilitation) and data from another 22 849 cases collected in a registry study (in which patients' hospitalisation was characterised from medical records after they have been discharged), the CENTER-TBI group reports their attempt to shed new light on a disorder that affects 50 million people each year and over half of the world's population over the lifespan.[3] This Article contains a wealth of information that informs both the readership of *The Lancet Neurology* and the entire field of neurotrauma on issues such as the predominance of patients with mild TBI (as measured by the Glasgow Coma Scale [GCS] score—more than 95% of patients discharged from the emergency room or admitted to the ward), the disposition of patients within the health-care system (hospital and intensive care unit admission and discharge), demographics, comorbidities, use of anticoagulants as a predisposing injury factor, the contribution of alcohol consumption to the circumstances around the event, the advanced age of the cohort (median age 50 years [IQR 30–66] in the core study), and many others. Perhaps the most intriguing finding is that patients who were characterised with moderate (GCS 9–12) or severe TBI (GCS <9) had similarly poor neurological outcomes after injury based on Glasgow Outcome Scale Extended scores, casting further doubts on the utility of this time-honoured injury severity score when used alone to adequately stratify patients into clinical trials and to prognosticate for patients, caregivers, and policy makers. Indeed, the findings place the traditional classifications of mild, moderate, and severe TBI in jeopardy.

However, this study has several substantial limitations. Although the study included many patients, they were all seen at clinical centres that were capable of doing such research in 18 European countries and Israel. Because of the overwhelming scope of TBI as a public health problem, patients are cared for in many hospitals, clinics, rehabilitation centres, and other places. As the authors of this manuscript have previously recognised, major variations in practices and outcomes exist between centres,[4] thereby making extrapolations about outcomes and other aspects of this study challenging across the continent. Similarly, within each clinical centre, patients in the core cohort represented a fraction of those cared for at these institutions. Although the registry cohort somewhat compensates for this shortcoming, the study design complicates the interpretation of the imaging findings, biomarker data, and other variables that were obtained in only a subset of patients, given the selection bias that is inherent in undertaking such a monumental task.

These limitations aside, the authors should be congratulated on completing the difficult task of studying a dauntingly large cohort across so many European centres and revealing potentially groundbreaking and provocative findings that can be tested in other populations. Rather than a single genius such as Albert Einstein developing thought experiments, the field of TBI will

probably require many groups to collaborate to achieve the ambitious goals outlined by the InTBIR investigators. We anticipate that the CENTER-TBI efforts will be combined with those of ongoing studies, including the Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) study[5], the Italian Creactive study, several Canadian studies of mild TBI in children, along with many other clinical and research efforts worldwide to generate data that will help us understand how to care for the myriad external injuries that can occur so commonly to the most complicated organ in the human body. Perhaps the foresight of the InTBIR organisers has launched a wonderful decade, or *mirum decennium*, for TBI.

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PMK reports a stipend from the Society of Critical Care Medicine as editor-in-chief of the journal *Pediatric Critical Care Medicine*, which published the Guidelines for the Management of Severe TBI in Children in 2019, on which he was the first author. MJB declares no competing interests.

1 Renn J, Hoffman D. 1905—a miraculous year. *J Phys B: At Mol Ot Phys* 2005; **38:** S437–48.
2 Steyerberg EW, Weigers E, Sewalt C, et al. The contemporary landscape of traumatic brain injury in Europe: case-mix, care pathways, and outcomes from the CENTER-TBI study. *Lancet Neurol* 2019; **18:** 923–34.
3 Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol* 2017; **16:** 987–1048.
4 Lingsma HF, Roozenbeek B, Perel P, Roberts I, Maas AI, Steyerberg EW. Between-centre differences and treatment effects in randomized controlled trials: a case study in traumatic brain injury. *Trials* 2011; **12:** 201.
5 Manley GT, Maas AI. Traumatic brain injury: an international knowledge-based approach. *JAMA* 2013; **310:** 473–74.

Antithrombotics and bleeding risk: paradoxical findings

Published **Online**
August 7, 2019
http://dx.doi.org/10.1016/S1474-4422(19)30280-7

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Can an antithrombotic drug prevent bleeding? For cerebral cavernous malformations (CCMs), a study in *The Lancet Neurology* by Susanna Zuurbier and colleagues[1] suggests that, paradoxically, it might.

CCMs, also called cavernous angiomas or cavernomas, are small vascular lesions that are detected in up to 0·2% of the general population[2] and can cause focal neurological deficits or seizures. Clinicians typically avoid antithrombotics in these patients because CCMs are prone to bleeding, with an approximate risk of bleeding of 0·8–1·6% per year for asymptomatic lesions and 3·6–6·2% per year for symptomatic lesions, depending on location.[3] However, avoiding antithrombotics is becoming increasingly difficult because of expanding indications for their use and an ageing population.[4]

In this cohort study, systematic review, and meta-analysis, the authors used data from the Scottish Audit of Intracranial Vascular Malformations and the published literature to establish whether antithrombotic use was associated with new focal neurological deficits or bleeding.[1] Patients were identified by screening of all radiology reports within a defined geographical area (Scotland, UK) for diagnosed CCMs. Active surveillance was then used to identify patients who had either new episodes of documented bleeding or new focal neurological deficits in the absence of new bleeding, as well as treatment with antithrombotics.

Despite the widely held clinical concern that antithrombotic drugs could increase the risk of bleeding, the findings from the study suggested the opposite. There were fewer episodes of new bleeding or new focal neurological deficits over a mean follow-up of 11·6 years in the patients given antithrombotics (one [2%] of 61 patients) than in those who did not take antithrombotics (29 [12%] of 239).

The adjusted hazard ratio (HR) of 0·12 (95% CI 0·02–0·88) was remarkably low, given that HRs that small are rarely seen in clinical research. In secondary prevention trials, for example, aspirin prevents recurrent stroke with an HR of 0·83.[5] Therefore, potential sources of bias should be considered. The most plausible source of bias could be confounding by indication. That is, if clinicians mostly use antithrombotics in patients at lower risk for haemorrhage, but not in patients at higher risk, then a spurious association might be detected between antithrombotic use and lower recurrence of haemorrhages. To mitigate this risk for bias, the authors adjusted for type of presentation and brainstem location,[3] the two factors that influence bleeding risk that would also be known to the treating clinician and might have