NEUROSCIENCE

New Guidelines Aim to Improve Studies of Traumatic Brain Injury

It's still dark outside as neurosurgeon Geoffrey Manley greets a visitor in the lobby of San Francisco General Hospital. "It's been a busy night," Manley says. An overnight rain has made the roads slick. "We just got a guy who was ejected from the back seat of a car," Manley says. "He wasn't wearing a seat belt."

The U.S. Centers for Disease Control and Prevention estimates that 1.7 million Americans suffer a traumatic brain injury (TBI) each year in car accidents, falls, or other mishaps. Unfortunately, the doctors who treat them have limited options. Despite promising leads from animal research, dozens of drugs intended to protect the brain after injury have failed in clinical trials.

Manley thinks part of the problem is an outdated system used to classify TBI patients for trials. (For a perspective on obstacles to drug development, see the 14 April issue of *Science Translational Medicine*). Manley has been a leading force in an initiative to improve the way TBI patients are characterized for clinical trials and other studies. A rough draft of new guidelines was released on 1 April by one of the project's sponsors, the National Institute of Neurological Disorders and Stroke,* and they will be described in detail later this year in a special issue of the *Archives of Physical Medicine and Rehabilitation*. Manley, who co-directs the Brain and Spinal Injury Center at the University of California, San Francisco, recently received a $4.1 million Grand Opportunities Grant from NINDS to study at four U.S. medical centers whether it's feasible to collect up to 500 pieces of information on individual TBI patients and to standardize brain scans and other measurements so they can be compared across centers. If it succeeds, the project's leaders hope the methodology will be widely adopted.

One of the primary tools now used to assess TBI patients, the Glasgow Coma Scale (GCS), has been in use since the 1970s. It rates patients' eye movements, limb movements, and speech. Scores range from 3 (comatose) to 15 (fully awake and responsive). Doctors describe patients' injuries as mild (13 or above), moderate (9 to 12), or severe (8 or below), and researchers use these groupings in clinical trials and observational studies. Sorting patients by their GCS scores makes sense when you're triaging patients in the emergency room at 3:00 a.m., says Manley, but it's an awfully coarse tool for research: "We're taking one of the most complex, heterogeneous disorders in the most complex organ in body and dumbing it down to mild, moderate, and severe."

Two people with the same GCS score can have very different brain injuries, Manley says. One patient, for example, might have a subdural hematoma, an expanding pool of blood between the protective layers surrounding the brain, whereas another might suffer from diffuse axonal injury: extensive damage to the white matter tracts that convey signals from one brain region to another. Grouping together two such patients in a drug trial may dilute any therapeutic effects, because a drug that helps patients with subdural hematoma would likely have a mechanism very different from one that helps patients with diffuse axonal injury.

Several types of TBI can easily be distinguished by CT scans, which have become routine in the decades since the GCS was developed. Although the scans are often used to diagnose patients in the hospital, they're rarely used to sort patients for clinical trials or other studies, says Manley, who would like to change that. This can be tough to do retrospectively, but part of the goal of his pilot study is to standardize CT scans and other measurements taken shortly after an injury so that they can be used to sort patients for research.

Deciding which data are most useful for characterizing patients is one goal of the NINDS "common data elements" project, which is also sponsored by four other agencies, including branches of the Department of Defense and the Department of Veterans Affairs, whose interest in TBI has surged with the tide of soldiers returning home from Iraq and Afghanistan with head injuries. The first draft contains checklists for collecting several categories of patient information, from demographic details to neurological symptoms and CT results.

Andrew Maas, a neurosurgeon at University Hospital Antwerp in Belgium, helped draft the new guidelines and hopes they can be applied globally to make it easier to compare findings across studies. He and colleagues recently analyzed data sets for 11 large TBI observational studies and clinical trials in Europe and North America. It was far more work than his team imagined because the studies differed in which variables they measured, how they measured them, and how they were coded in their database. "It took 10 person-years just to transform the data into a format we could work with," he says.

Still, the utility of the guidelines will depend on how they're used, says John Whyte of Moss Rehab, a rehabilitation center in Elkin Park, Pennsylvania. There needs to be a balance between standardizing data collection and bogging down researchers with long lists of data elements that may or may not be relevant for a given study, Whyte says.

Meanwhile, as Manley leads a cluster of medical residents on rounds, each patient they visit illustrates how a life can be altered in an instant by a fall, a crash, or even a punch to the head. Some are likely to recover; others aren't. For all of them, better science can't come soon enough. **–GREG MILLER**

A good outcome. Linda Sparks of Huntington Beach, California, holds a photograph of herself unconscious in the hospital with a TBI caused by a car accident.

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*www.nindscommondataelements.org/TBI.aspx

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