CHAMPIONS OF TRANSLATION

William Heberden and reverse translation

Elazer R. Edelman[1,2]* and Kelly LaMarco[3]

Beginning with the 18th-century physician-scientist William Heberden, the elder, *Science Translational Medicine* introduces a new article series about historical figures whose transformational contributions to science, medicine, and society remain relevant today.

> *Experience may, in politics and morality, be called the teacher of fools; but in the study of nature, there is no other guide to true knowledge.*
>
> ~William Heberden, the elder

Many view the practice of medicine before anesthesia, surgery, and synthetic pharmacology as consisting of bleedings, healing waters, and mysterious herbal mixtures. Even in their own time, practitioners of old were depicted by cartoonists as barely trained self-appointed barbers, quacks, or witch doctors, and we continue to embrace these caricatures. Today's professionals identify instead with physicians who embrace evidence-based practice, scientists who seek to understand mechanisms of disease, and innovators who develop therapies and interventions based on a fundamental understanding of pathophysiology and mode of action. Our role models are those who integrate these features in their scientific perspective, engineering approaches, and medical practices, and we embrace the notion that the emergence of these heroes is a modern event. Thus, we might be surprised to learn how long ago such personae were embodied and celebrated.

For this reason, *Science Translational Medicine* initiates a "Champions of Translation" series to celebrate historical figures who transformed science and medicine and whose impact remains relevant today. We begin with the English physician William Heberden, the elder (1710–1801), a master of translational science who embodied all of the elements biomedical scientists respect and pursue today. He not only spent a lifetime recording intricate observations of diseases at his patients' bedsides—earning him the title "father of clinical observation" of the 18th century—he also influenced generations that came after him. In many respects, he heralded modern concepts of medicine as a scientific art form.

Heberden remains acclaimed for his description of angina pectoris (the first person to do so) and for defining the osteoarthritis nodes that still carry his name. But few are aware that he was the first to recognize the distinction between smallpox and chicken pox and that he inspired his student Edward Jenner—later called the "father of immunology"—to engage in smallpox inoculations en route to the first smallpox vaccine (*1*). Furthermore, Heberden's greatest impact on medicine was achieved through education and information sharing. In addition to his copious documentation of clinical observations, he spurred the establishment of a forum for medical professionals to share and discuss their findings with their peers called "Medical Transactions of the Royal College." He also worked to translate the smallpox vaccine to the masses in the American colonies through an inoculation education program. Here, we highlight his varied contributions—as a physician, scientist, educator, author, and humanitarian—to modern translational medicine.

PATH TO ENLIGHTENMENT

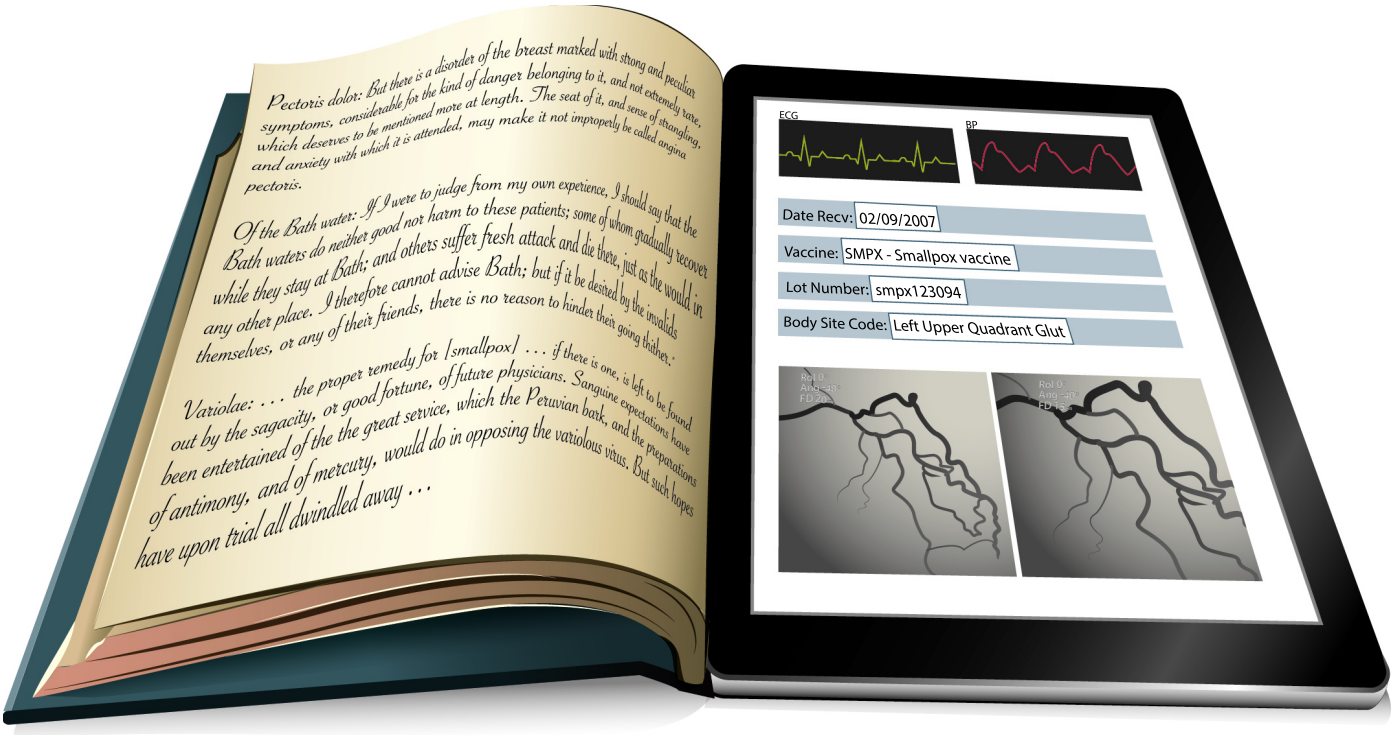
Our knowledge of Heberden's life derives principally from the biography (*2*) penned by his relative of five generations later, Ernest Heberden, who obviously never met Heberden, the elder. Born in London in 1710 at the dawn of the Age of Enlightenment, William Heberden became a scholar of this cultural movement, celebrating the power of reason to transform tradition into scientific legacy. At St. John's University, Cambridge, he studied Classics as well as Greek and Hebrew literature, and as an undergraduate, he authored a paper for a literary society on "A Letter from Cleander to Alexias on Hippocrates and the State of Physic in Greece." The letter notes that Hippocrates' native island of Cos "afforded him a singular advantage" because it housed a temple devoted to Aesculapius (Greek god of medicine, healing, rejuvenation, and physicians) that was "full of votive tablets, on which were registered many cures, and the means by which they were effected; all of which he diligently studied and transcribed." This paper foreshadowed not only Heberden's later activities and interests but also his belief in the potency of life-long learning and celebration of the intellectual basis of medicine. After receiving a Bachelor of Arts degree in 1728, Heberden continued his university studies for another 11 years, receiving his medical degree in 1739. He was then a man of extensive and expansive education and training, a far cry from the images we hold of "quacks" of his day.

Enlightenment's focus on reason aligned with Heberden's philosophy about the practice of medicine, which was based on facts, observation, and learning from experience. The movement coincided with the Scientific Revolution, and philosophers and writers challenged society to rethink ideas based on faith, tradition, and superstition and replace these with knowledge gained through intellectual pursuits. In England, the movement flourished first among scholars, and Heberden became a senior statesman in the medical science realm. Early in his career, he began keeping concise but precise notes of his clinical observations and supporting these observations with empirical evidence. Through his experiences, he debunked as medical myths traditions with no objective support, such as bathing in the famed waters of Bath; in his writings (*3*), Heberden chastised physicians whose practices "had afforded them frequent opportunities of observing the effects of the Bath waters" for not reporting their observations to the public (*4*). Thus, he extended experimentalism, making the clinic his laboratory, the analysis of precisely documented observations his science, and the communication of his ideas and observations his mode of impact. In 1766, Heberden convinced the Royal College of Physicians to publish clinical accounts and notes, as he did in *Commentaries on the History and Cure of Disease* (*3*), a book that documents a lifetime of bedside observations that is still in print to this day. *Commentaries* was originally written in Latin and later translated by Heberden's son and physician, William Heberden, the younger.

FROM COMMENTARIES TO COMPUTERS

Heberden's lifetime of clinical observations fit into one publication. Today, in the information age, biomedicine relies on

[1]Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, MA 02139, USA. [2]Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA. [3]*Science Translational Medicine*, American Association for the Advancement of Science, Washington, DC 20005, USA.
*Corresponding author. E-mail: ere@mit.edu



Bench and bedside: Translating patient data. Turning the page from notepad to iPad. (**Left**) Heberden's notes: selected patient symptoms, therapies, and treatment responses [from *Commentaries* (*3*)]. (**Right**) E-notes: At the bench and bedside, physician-scientists gather and share patient data electronically.

terabytes of data, computational modeling, data sharing, and digital medicine. Physicians and scientists are working to develop data networks that integrate biomedical research on human disease with clinical data from individual patients in order to produce a new taxonomy of disease that drives diagnoses and treatments tailored to the needs of individual patients (www.nih.gov/precisionmedicine).

Heberden's focus on information sharing and approach to treatment based on clinical observations also link him with the modern biomedical research community and the practice of evidence-based medicine. *Commentaries* represents a precursor to emerging meta-analyses of electronic medical records and the current movement to share genomic, clinical-trial, and other crowd-sourced patient data. In Heberden's day, travel was difficult, so medical care often was delivered remotely; a physician frequently learned of a patient's symptoms through letters, which made patients and caregivers instrumental participants in the practice of medicine, much like modern citizen scientists. Today, access to high-quality, cost-effective medicine also occurs remotely through digital medical devices and the delivery of services via telemedicine (*5*).

SMALLPOX AS A MODEL DISEASE

The compilation of case studies in *Commentaries* allowed Heberden to cull seemingly disparate observations into a coherent whole and to separate similar diseases into distinct entities. He distinguished between chicken pox and smallpox on the basis of observations of the diseases' symptoms and lesions (and thus that varicella and variola are distinct viruses). He also argued from clinical observations that those who had chicken pox were granted immunity from ever contracting the disease again (*3*), setting the intellectual stage for Jenner's smallpox vaccine in 1796.

The history of vaccination shows Heberden at his best; he defined the disease, presaged vaccination, and served as a mentor to Jenner. Years before Jenner developed the world's first vaccine, Heberden embraced a controversial intervention called variolation—intentionally inoculating a person with a mild form of the smallpox virus—in order to make immunization mainstream, and he disseminated the smallpox vaccine with fervor and personal funds. With his friend Benjamin Franklin, who had lost a 4-year-old son to smallpox, Heberden drafted simple instructions for performing self-inoculation and the inoculation of children and then paid for printing "a very large impression" of the pamphlet to be distributed for free in the American colonies. In the pamphlet's introduction (*6*), Heberden wrote that "many lives would be saved if all who are desirous of being inoculated could easily be furnished with the means of having it done. This consideration has engaged me to draw up a few short and plain instructions, by which any person may be enabled to perform the operation in a tolerable manner, and to conduct the patient through the distemper in those places where it is not easy to procure the assistance of physicians and surgeons … and this practice has so greatly the advantage over every other way of communicating the smallpox, that it would be better to have inoculation performed by anybody … than to suffer this disease to come on in the common way, though assisted with all the helps which art can afford."

In fact, General George Washington's order for mandatory smallpox inoculation of Continental-Army recruits immediately upon enlistment—the first army in

the world with a smallpox-prevention program—might have been an important factor in reversing the fortunes of the American colonial army and in their eventual victory for independence (*7*).

CAUSE AND CELEBRITY

Heberden's writings reveal that he practiced medicine as a physician-investigator (*3*) who assessed and treated patients as individual cases but also regarded each one as a source of medical information. To this end, he closely observed patients, recorded his observations in detail, and synthesized this information so that each medical experience could benefit future patients and physicians. This view of medicine foreshadows that of today's proponents of integrating patient information so as to advance our understanding of human pathophysiology and to create a learning health care system (*8*).

However, Heberden's personality is difficult to decipher from his own writings or from books and manuscripts written about him. We know his areas of interests were broad and that he was a premier observer, a driver of data sharing, and a colleague who inspired other experimental scientists to investigate his clinical observations (reverse translation). His contributions suggest that he embodied the "renaissance" physician-scientist. In the collective spirit of William Osler, James B. Herrick, Albert Schweitzer, and Mary Ellen Avery (*9*), Heberden was at once a gifted physician, scientist, teacher, author, and humanitarian. Still, Heberden is not as well known as the aforementioned personalities, even though he possessed all the qualities of a premier physician-scientist.

Our culture celebrates cult figures as our own living superheros, bigger-than-life individuals who epitomize a movement or the culture of the times in which they live: U.S. President Abraham Lincoln, physicist Albert Einstein, activist Susan B. Anthony, sports figures Babe Didrikson Zaharias and Hank Aaron, and the 14th Dalai Lama, Tenzin Gyatso. We honor Heberden not as a superhero teeming with presence, personality, or power but rather for his work as a champion who promoted a perspective on medical science that celebrates evidence as a means to translation. History has incorporated his philosophy into the evidence-based medicine credo, memorializing his views as our standard in a manner truest to his personal decorum. Indeed, Heberden voluntarily receded early from medicine, before his "presence of thought, judgment, and recollection were impaired." In a letter to a friend, he wrote that "it is more desirable for a man to do this a little too soon, than a little too late; for the chief danger is on the side of not doing it soon enough" (*10*).

It is important for today's physician-scientists to know Heberden's story because it reminds us that we are all part of a much bigger narrative that extends before and beyond our time. Reading chapters about people who lived out the passions of their times and made lasting contributions can help today's physician-scientists to stage and direct their own passions as they write their chapters in the age of information. In *Leaves of Grass*, poet Walt Whitman wrote about his forerunners, "I dare not proceed till I respectfully credit what you have left.… I regard it all intently a long while.… Then I take my place for good with my own day." Today, physicians and researchers can learn from Heberden's inspiration of experimental science spurred by an observation in the clinic—a rich path to new insights in human biology.

REFERENCES AND NOTES

1. J. B. Herrick, William Heberden, in *Society of Medical History of Chicago, Bulletin and Correspondence*, vol IV. M. Fishbein, Ed. (Special Collections Research Center, University of Chicago Library, Chicago, 1928), pp. 30–40.
2. E. Heberden, *William Heberden: Physician of the Age of Reason* (Royal Society of Medicine Press, London, 1989).
3. W. Heberden, *Commentaries on the History and Cures of Diseases* (Wells and Lilly, Boston, 1818).
4. From William Heberden's *Commentaries on the History and Cures of Diseases* (*3*), on the Bath waters: "Few medicines have been more repeatedly tried under the inspection of such numerous and able judges; and yet we have had in the present age a dispute between those who by their experience and sagacity were best qualified to decide this question, in which one side asserted that paralytic patients were cured, and the other that they were killed by the use of these waters. Such contrary decisions, so disreputable to physicians, and so perplexing to the sick, could never have happened after so long a trial, if a very small part of these, whose practice had afforded them frequent opportunities of observing the effects of the Bath waters, had told the public what in their judgment was to be hoped or feared from them. It is probable that in some cases it would have been almost unanimously determined they do no good; in others, that they do no harm, though it might be doubtful that they be of much use; in a third sort they would be generally condemned; and in a fourth class of disease, some might judge them to be beneficial, and others detrimental."
5. S. R. Steinhubl, E. D. Muse, E. J. Topol, The emerging field of mobile health. *Sci. Transl. Med.* **7**, 283rv3 (2015).
6. From Heberden's introduction in *Benjamin Franklin and William Heberden's pamphlet, Some Account Of the Success of Inoculation for the Small-Pox in England and America: Together with Plain Instructions, By which any Person may be enabled to perform the Operation, and conduct the Patient through the Distemper* (Straham, London, 1759); available at http://pds.lib.harvard.edu/pds/view/7336204.
7. U.S. military and vaccine history (www.historyofvaccines.org/content/articles/us-military-and-vaccine-history), and George Washington's Mount Vernon, Small pox (www.mountvernon.org/educational-resources/encyclopedia/smallpox).
8. C. P. Friedman, A. K. Wong, D. Blumenthal, Achieving a nationwide learning health system. *Sci. Transl. Med.* **2**, 57cm29 (2010).
9. W. Osler (1849-1919), Canadian physician, medical educator, and founding professor of Johns Hopkins Hospital, www.medicalarchives.jhmi.edu/osler/biography.htm; James B. Herrick (1861–1954), American physician credited with one of the first descriptions of sickle-cell disease and symptoms of myocardial infarction, http://en.wikipedia.org/wiki/James_B._Herrick; Albert Schweitzer (1875–1965), German and later French physician, medical missionary, and winner of the Nobel peace prize, www.nobelprize.org/nobel_prizes/peace/laureates/1952/schweitzer-bio.html; Mary Ellen Avery (1927–2011), pediatrician, scientist, educator, improved access to care for premature infants, www.nlm.nih.gov/changingthefaceofmedicine/physicians/biography_17.html.
10. E. Heberden, William Heberden the elder (1710–1801): Aspects of his London practice. *Med. Hist.* **30**, 303–321 (1986).

Funding: E.R.E. is supported in part by a grant from the U.S. National Institutes of Health (R01 GM 49039).

10.1126/scitranslmed.aaa2250

Citation: E. R. Edelman, K. LaMarco, William Heberden and reverse translation. *Sci. Transl. Med.* **7**, 287fs20 (2015).

Science Translational Medicine

William Heberden and reverse translation

Elazer R. Edelman and Kelly LaMarco

Sci Transl Med **7**, 287fs20287fs20.
DOI: 10.1126/scitranslmed.aaa2250