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Perspective

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Combat and the Medical Mindset — The Enduring Effect of Civil War Medical Innovation

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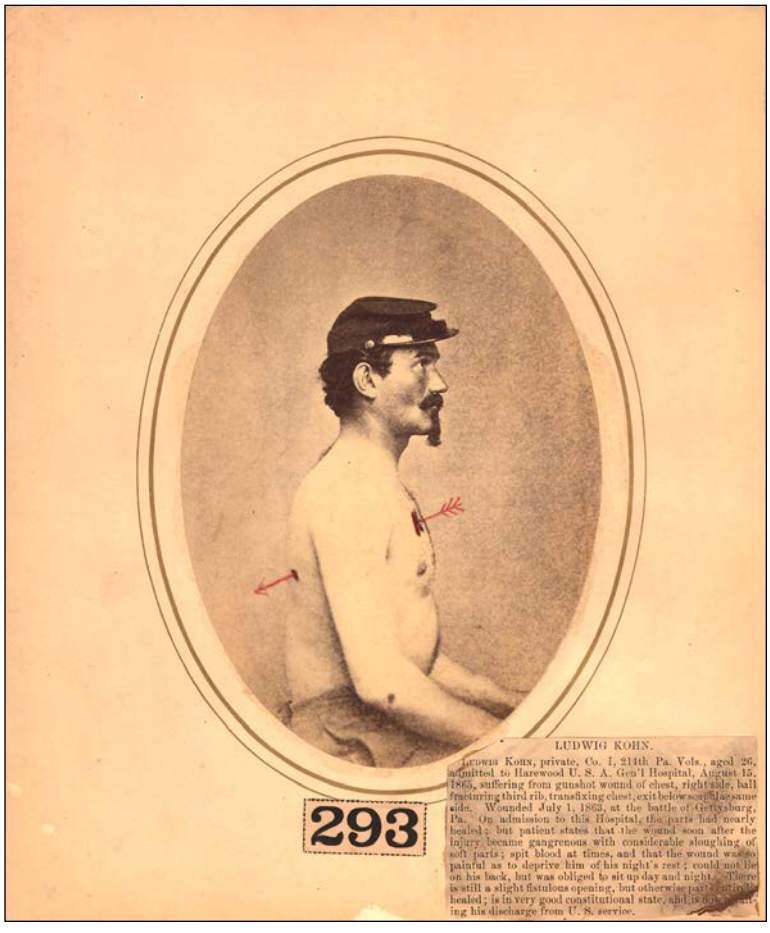
A century and a half ago, the American Civil War (1861–1865) triggered technological and practical advances in medicine, including improvements in surgical tools and techniques, the development of artificial limbs, and new systems of evacuation and hospital care. Yet the war's most important and enduring effects on medicine may have been epistemological: ways of teaching, learning, and thinking about medicine changed drastically during the war and in the years that followed.[1]

More than 12,000 physicians served as medical officers during the Civil War. All told, they treated nearly half a million wounds (see photos) and more than 7 million cases of disease. As the Confederate surgeon Edwin Samuel Gaillard recognized in 1868, "Few, perhaps, appreciate the fact that the war has been of incalculable advantage to the physician, for it has afforded a school in which, during a few years, he has learned those great lessons which a life time would have been powerless to impart."[2] These physicians' experiences shaped not only their own postwar practices, but American medical practice writ large, because they went on to serve as medical school professors and deans, authors and editors at medical journals, and other important contributors to the medical community. Medical practice evolved as changes that were forged in the crucible of combat took hold and spread in the postwar years. Some of these developments have continued to influence advances to the present day.

Before the war, medical practitioners in post-Jacksonian America ran the gamut from virtually untrained charlatans to highly educated experts, with countless apprentice-trained practitioners in between. Some doctors embraced the emerging principles of scientific medicine, but most insisted on rigid adherence to the methods of earlier masters. A revolution of sorts had taken place in the field of surgery with the introduction of ether and chloroform anesthesia in the 1840s, but Louis Pasteur

A slide show is available at NEJM.org



Civil War Wound Card 293.

Wound card showing the gunshot wound of Private Ludwig Kohn, part of a series of photographic cards made at the behest of Surgeon General William Hammond for inclusion in the Medical and Surgical History of the War of the Rebellion. The text reads, "Ludwig Kohn, private, Co. I, 214th Pa. Vols., aged 26, admitted to Harewood U.S.A. Gen'l Hospital, August 15, 1865, suffering from gunshot wound of chest, right side, ball fracturing third rib, transfixing chest, exit below scapulae same side. Wounded July 1, 1863, at the battle of Gettysburg, Pa. On admission to this Hospital, the parts had nearly healed; but patient states that the wound soon after the injury became gangrenous with considerable sloughing of soft parts; spit blood at times, and that the wound was so painful as to deprive him of his night's rest, could not lie on his back, but was obliged to sit up day and night. There is still a slight fistulous opening, but otherwise parts entirely healed; is in very good constitutional state, and is now awaiting his discharge from U. S. service." For additional images, see slide show, available with the full text of this article at NEJM.org.

had not yet developed his germ theory, and aseptic surgical practice was still years away. Civil War doctors tended to have one foot in the past and one in the future.

When the U.S. Army began recruiting doctors to support the expanding military effort, the qualification standards were nominal. The state authorities that were responsible for filling the ranks of their regiments often appointed surgeons and assistant surgeons who had neither a medical degree nor any legitimate medical experience; certainly, many lacked even the most fundamental knowledge of combat medicine. In 1862, a brash new Army surgeon general, William Hammond, implemented rigorous examinations for all regular Army medical officers, emphasizing public health, hygiene, and surgery. Hammond's efforts improved the quality of medical officers throughout the Army, and the elevated standards raised expectations of the medical profession long after the war ended.

Hammond himself embodied a significant change in military thinking. A 33-year-old surgeon with limited Army experience, he was the first surgeon general appointed on the basis of merit rather than seniority. He had served well on the western frontier in the decade before the Civil War and had been recognized by the American Medical Association for his research on health and hygiene, but he had resigned from the Army in 1860 to take a professorship at the University of Maryland. After the war broke out, Hammond returned to the Army as a mere assistant surgeon, but he had powerful allies who lobbied for his appointment to the surgeon general post when it became vacant a year later. Secretary of War Edwin Stanton acquiesced despite his reservations about the young doctor, whom many senior officers viewed as arrogant and presumptuous. An ambitious and progressive thinker, Hammond fought for resources, tackled problems head on, and planned for a future beyond the war; innovative medical officers thrived under his leadership.

Standards of care rose steadily as Hammond pushed for changes

Civil War First Aid Station.

Wounded Union soldiers at an aid station near Marye's Heights, Fredericksburg, after the Battle of Spotsylvania, 1864. For additional images, see slide show, available at NEJM.org.

throughout the medical department. With his support, Major Jonathan Letterman of the Union Army implemented a brilliantly efficient system of evacuation and echeloned medical care, which is still the model used by armed forces worldwide 150 years later. The Army's experiments in hospital architecture contributed greatly to civilian medicine for the next half-century, as techniques for improved ventilation and designation of wards according to disease types were adopted by institutions such as Johns Hopkins Hospital, which John Shaw Billings designed on the basis of his experience with hospital construction during the war.

A strong advocate of scientific medicine, Hammond shook the foundation of the therapeutic tradition when he removed calomel and tartar emetic — frequently prescribed medicines made from mercury and antimony — from the formulary because of emerging evidence of their inefficacy. Such controversial steps caused both military and civilian physicians to reexamine long-standing medical practices and opened a dialogue about standards of medical care.

In addition, Hammond launched an initiative — the Army Medical Museum — that would, in tandem with the Library of the Surgeon General's Office (predecessor of the National Library of Medicine), play a key role in the work of medical professionals, scholars, educators, and others. In May 1862, he directed medical officers in the field to "collect and to forward to the Office of the Surgeon General all specimens of morbid anatomy, surgical or medical, which may be regarded as valuable; together with projectiles and foreign bodies removed; and such other matter as may prove of interest in the study of military medicine and surgery. These objects should be accompanied by short explanatory notes."[3] In response, surgeons began sending such specimens, as well as durable medical equipment, preoperative and postoperative photographs, and medical illustrations of wounded soldiers. These materials formed the basis of both the Army Medical Museum and the *Medical and Surgical History of the War of the Rebellion*, published between 1870 and 1883.

Major John Hill Brinton, the museum's first curator, recalled in 1914 that the museum and the history were meant "not for the collection of curiosities, but for the accumulation of objects and data of lasting scientific significance, which might in the future, serve to instruct generations of students, and thus in time be productive of real use."[4] Brinton advanced the view of the Civil War — and arguably other wars — as a "natural experiment" that allowed large amounts of medical information to be amassed, and he, like Hammond, evinced an appreciation for collected data and pathological specimens as underpinnings for medical science. That vision would eventually be realized: the very existence of the museum's collection and its extensive documentation — combined with similar large-scale epidemiologic studies of the day, such as the 1850 Shattuck Report of sanitary conditions in Massachusetts, which became a blueprint for future public health efforts — helped to establish the basis of medical and public health sciences as we understand them today.[5] The original museum collection still exists, now housed in the National Museum of Health and Medicine, a unit of U.S. Army Medical Research and Materiel Command (Silver Spring, MD).

Thus, the changes driven and implemented by Hammond and his

U.S. National Library of Medicine

contemporaries reached well beyond the Civil War years and have influenced principles and practices of American medicine to the present day. These changes were scientific, procedural, and administrative in character, but perhaps most important, they marked the start of a transformation in the way doctors, patients, and the public thought about the practice of medicine.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Progress and Hurdles for Follow-on Biologics

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In March 2015, the Food and Drug Administration (FDA) approved filgrastim-sndz (Zarxio), Sandoz's version of the leukocyte growth factor Neupogen, an Amgen drug indicated for conditions including neutropenia in patients with nonmyeloid cancers and for stem-cell harvesting. Filgrastim-sndz is a follow-on biologic, a version of a protein-based drug made by a different manufacturer but approved for the same clinical indications; it was the first product in the United States authorized through the new regulatory pathway for follow-on biologics.

Biologics have provided major advances in the treatment of cancer, rheumatologic disease, and other conditions. Though they account for less than 1% of all prescriptions dispensed in the United States, expenditures on them amount to 28% of prescription-drug spending, and both their use and their cost are forecast to grow sharply. Payers have responded by imposing greater patient cost-sharing obligations and increased preauthorization requirements or have refused to cover certain biologics — moves that can result in substantial burdens for patients with chronic diseases.[1] Yet some of these drugs, such as filgrastim, have been on the market for decades and have no active-ingredient patents remaining to block competition from other manufacturers.

When market-exclusivity protections end for small-molecule drugs, interchangeable generics are approved through an abbreviated FDA pathway created by the 1984 Hatch–Waxman Act, which leads to major price reductions. A similar regulatory pathway for follow-on biologics did not exist until Congress passed the Biologics Price Competition and Innovation Act (BPCIA) as part of the Affordable Care Act in 2010. This pathway permits approval of follow-on biologics based on solid evidence of structural similarity, with only small confirmatory clinical trials — much smaller than the trials traditionally required for approving new drugs.

Two types of follow-on biologics can emerge from this pathway: biosimilars, products with no clinically meaningful structural differences from a brand-name biologic; and interchangeables, biosimilars that can be safely substituted for the original — a higher regulatory standard. Because the FDA has not yet clarified the level of evidence required for the interchangeable designation, most products initially approved under the BPCIA will be biosimilars, as filgrastim-sndz is. Other follow-on biologics being considered by the FDA include versions of infliximab (Remicade, first approved in 1998), pegfilgrastim (Neulasta, 2002), and epoetin alfa (Epogen, 1989). By contrast, follow-on biologic alternatives to several brand-name large-molecule drugs have been in use in Europe for years, although they are not automatically considered interchangeable.

The introduction of generic versions of small-molecule drugs can reduce prices by 90% from the brand-name version, which has saved U.S. consumers more