The roots of evidence-based medicine

Drs Lind, Louis, and Semmelweis laid the groundwork for evidence-based medicine in the 18th and 19th centuries.

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In 1996 Dr D.L. Sackett and colleagues published a landmark article that established the core principles of evidence-based medicine (EBM), which they defined as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."[1] The modern history of clinical trials began in the 1940s, when the Medical Research Council in the UK conducted two clinical studies involving treatment against tuberculosis and the common cold.[2] Some consider this the beginning of evidence-based medicine, but in fact EBM's roots stretch far back to an earlier era. Three pioneering physicians from the 18th and 19th centuries—Drs James Lind, Pierre Louis, and Ignaz Semmelweis—laid the groundwork for this important clinical tool.

Dr James Lind (1716–1794)

In the 18th century scurvy was a major problem, causing the deaths of thousands of seamen on the high seas. By that time there was good evidence that the disease could be prevented by consumption of fresh fruits and vegetables. Nevertheless the British Admiralty had not yet instituted a supply of lemon juice on board ships for long voyages and many men continued to perish from scurvy.[3]

In 1747 Dr James Lind (**Figure 1**), a naval surgeon on board HMS *Salisbury,* carried out an experiment to find a cure for this disease. He divided 12 men with scurvy into six pairs, giving each pair different additions to their regular diet. Dr Lind made the cases "as similar as I could have them. They all had putrid gums, the spots and lassitude with weakness of their knees."[4] The six pairs received cider, seawater, elixir of vitriol, vinegar, a purgative mixture, and oranges and lemons. Because of food scarcity this last pair was only treated for 6 days as opposed to 14 days for the others. The results revealed some improvement in the pair given cider but dramatic recovery in the pair given citrus fruit. Dr Lind noted "the most sudden and visible good effects were perceived from the use of oranges and lemons."[4] Although the numbers used were small, this study was randomized and controlled with a specific treatment time. Within the limits of his situation Dr Lind had demonstrated the power of clinical trials.

Figure 1. Dr James Lind, a British naval surgeon who discovered a cure for scurvy.

However, Dr Lind's thinking was dominated by the current theory of disease and he failed to understand the implications of his own experiment. In his famous paper from 1753 there was a disconnect between the clarity of his findings and the murkiness of his conclusions.[5] He still did not appreciate the prime importance of fresh fruit in the prevention of scurvy. This does not detract from the importance and originality of his study, which paved the way for Dr Gilbert Blane to eventually encourage the Admiralty to order a ration of lemon juice for all sailors. From that day in 1796 the incidence of scurvy in the Royal Navy dropped dramatically.

Dr Pierre-Charles-Alexandre Louis (1787–1872)

In the 18th century bloodletting was especially popular in Europe and the United States, where it was standard therapy for numerous conditions. Dr Pierre Louis (**Figure 2**) was a French physician who wanted to analyze the efficacy of bloodletting in the treatment of acute pneumonia.[6]

In order to put his study into context we must first look at the main par-

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Figure 2. Dr Pierre Louis, a French physician who used statistical methods to analyze the efficacy of bloodletting in the treatment of acute pneumonia.

adigm of disease at the time. For almost 2000 years—since the era of Hippocrates—the major disease concept was the theory of the four humors: blood, phlegm, black bile, and yellow bile.[7] The central idea was that each humor was related to one of the four basic elements (air, water, earth, fire), was centred in a particular organ (brain, lungs, spleen, gall bladder), and was associated with a certain personality type (sanguine, phlegmatic, melancholic, choleric). In this model being ill meant having an imbalance of the four humors, and since blood was the dominant humor an ill person was perceived as having an excess of blood. Treatment involved removing this excess and restoring a healthy balance through bloodletting, or venesection.

In his paper from 1836[8] Dr Pierre Louis examined the clinical course and outcomes of 77 patients with acute pneumonia taken from his own and hospital records. He compared the results in patients treated with bloodletting in the early phase with those treated in the late phase of the illness. In his conclusions he did not condemn bloodletting but concluded that the effect of this procedure "was actually much less than has been commonly believed."

The scientific accuracy of Dr Pierre Louis's methods was mixed. On the positive side he believed in the value of statistical analysis to study the effectiveness of different treatments using comparable groups of patients. On the negative side he used a retrospective study with no control group, his allocation of treatment was not randomized, and his results were open to differing interpretations.

However, Dr Pierre Louis made an important attempt to answer a clinical question through scientific analysis and thereby helped open the door to evidence-based medicine. For his meticulous work and major influence he has rightly been considered one of the fathers of epidemiology.

Dr Ignaz Semmelweis (1818–1865)

Dr Ignaz Semmelweis (**Figure 3**) received his MD in Vienna, and in 1846 he started working at the Vienna General Hospital, one of the major obstetric facilities in Europe.[9] Soon after arriving he made some startling observations regarding maternal and infant mortality. He noticed that there were fewer deaths among women who delivered at home rather than at the hospital, and the babies in hospital often died of the same disease as their mothers. He also noted a much higher mortality among mothers delivered at the First Clinic compared with those at the Second Clinic. For example, in the years 1840, 1841, and 1842, the maternal mortality at the First compared with the Second Clinic was 9.5% vs 2.6%, 7.8% vs 3.5%, 15.8% vs 7.5%, respectively. Autopsy examination revealed that these women and children had died of an overwhelming infection known as postpartum or puerperal fever.[10]

Figure 3. Dr Ignaz Semmelweis, a Hungarian physician who discovered that the incidence of puerperal fever could be drastically cut by the practice of hand washing in obstetrical clinics.

Dr Semmelweis then made a determined effort to see what was different about the two clinics and find a reason for this difference in mortality. He was able to quickly eliminate several possible factors such as the socioeconomic status of the women at the clinics, the physical locations of the mothers in the clinics, and the birthing positions of the mothers in labor. Then for a while he was stymied in his quest until a colleague, Professor Jakob Kolletschka, cut himself with a scalpel while performing an autopsy and soon died of an overwhelming infection proven at postmortem as identical to postpartum fever.

Dr Semmelweis then looked more closely at the practices in the two clinics and realized some important differences. Whereas the First Clinic with the high mortality was used by physicians and medical students, the Second Clinic with the low mortality was used only by midwives. Furthermore, while it was common practice for the doctors and students to go directly from autopsy room to delivery room and perform examinations on laboring women, the midwives never performed autopsies at all.[10]

This observation struck Dr Semmelweis like a thunderbolt as he realized the doctors and students were probably carrying "cadaverous particles" from the autopsied patients and introducing them directly into the laboring women by their vaginal examinations. With this finding in mind he instituted the practice of hand washing with chlorinated lime solution by anyone who performed an autopsy before examining any laboring women. Almost immediately the mortality rate of the First Clinic dropped down to that of the Second Clinic.

One would like to report that the maternal mortality remained at the low level thereafter. However, Dr Semmelweis had a serious personality conflict with his immediate supervisor, Dr Johann Klein, and he was not reappointed to the hospital. Dr Semmelweis left Vienna for Budapest and the mortality rate at the First Clinic in the Vienna General Hospital rose once again.[10]

In truth Dr Semmelweis had not instituted a controlled study but by chance had come upon an inadvertent experiment with a "control" group at one clinic and a "treatment" group at the other clinic. With his astute observation and inquiring mind he was able to establish an important cause of human disease and institute a change in hospital practice that brought about a significant reduction in mortality.

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My main working relations with him were specifically based on shared interests in the history of medicine, in our respect and support of the BC First Nations (which honored him with characteristic dignity at his death), in advocating humanitarian medicine, and in strengthening international scientific relations, in all of which his judgment, advice, and action remained most profound, humanistic, practical, and productive. His latest service was in helping me found the International Association for Humanitarian Medicine, which proudly published his last book, *Old Endeavour,* on his 93rd birthday.

Bill will be much missed by many persons in different parts of the world, and his steady friendship and intellectual stimulation will be long remembered by those who were fortunate to have him as a friend.

—S. William A. Gunn, FRCSC
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