Featured Report

The Myth of the Medical Breakthrough: Smallpox, Vaccination, and Jenner Reconsidered

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ABSTRACT

A discussion of the particulars leading to the eradication of smallpox is pertinent to both investigators and the public as the clamor for more "breakthroughs" intensifies. The rational allocation of biomedical research funds is increasingly threatened by disease-advocacy groups and congressional earmarking. An overly simplistic view of how advances truly occur promises only to stunt the growth of researchers and research areas not capable of immediate great breakthroughs. The authors review the contributions of Jenner and his countless predecessors to give a more accurate account of how "overnight medical breakthroughs" truly occur—through years of work conducted by many people, often across several continents.

In the public eye, few achievements are regarded with such excitement and awe as the medical breakthrough. Developments such as the discovery of penicillin and the eradication of polio and smallpox have each become a great story built around a singular hero. Edward Jenner, for example, is credited with discovering a means of safely conferring immunity to smallpox. The success of vaccination and subsequent eradication of this disease elevated Jenner to a status in medical history that is rivaled by few.

However, the story of the eradication of smallpox does not start or end with the work of Jenner. Men such as Benjamin Jesty and Reverend Cotton Mather as well as unnamed physicians from tenth century China to eighteenth century Turkey also made critical contributions to the crowning achievement. Inoculation to prevent smallpox was commonplace in Europe for generations prior to Jenner's work. Jenner himself was inoculated as a child. In fact, vaccination with cowpox matter was documented in England over 20 years prior to Jenner's work.

The authors' review of primary and secondary sources indicates that although Jenner's contribution was significant, it was only one of many. It is extremely rare that a single individual or experiment generates a quantum leap in understanding; this "lone genius" paradigm is potentially injurious to the research process. Wildly unrealistic expectations can only yield unsuccessful scientific investigation, but small steps by investigators supported by an informed public can build toward a giant leap, as the story of smallpox eradication clearly demonstrates.

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> *"...in science credit goes to the man who convinces the world, not the man to whom the idea first occurs."*
>
> *Francis Galton*

Major scientific advances often come to be associated with a single researcher, such as Salk or Fleming, who is considered responsible for the "breakthrough." However, actual examples of the lone genius phenomenon, in which an investigator single-handedly resolves a large problem, are few and far between. Much more commonly, developments represent the culmination of decades, if not centuries of work, conducted by hundreds of persons, complete with false starts, wild claims, and bitter rivalries. The breakthrough is really the latest in a series of small incremental advances, perhaps the one that has finally reached clinical relevance. Yet once a breakthrough is proclaimed, and the attendant hero identified, the work of the many others falls into distant shadow, far away from the adoring view of the public.

This phenomenon is particularly important to consider now, as the sciences and scientific funding come under closer scrutiny. Disease-specific interest groups have had great success swaying public opinion, and research dollars, in their favor. In this environment, it is increasingly important to convey an accurate perception of how successful biomedical research occurs. The public is enamored with the idea of the "breakthrough"; a search for this word in the Nexus database yielded 1096 media citings over the past 2 years. A climate of unrealistic expectations by patients and the general public alike has developed. As such, research that does not overtly go for the "home run" may be hampered and even endangered.

In this light, it is instructive to consider the breakthrough work of Edward Jenner, who is broadly credited for developing the vaccine that ultimately led to the erad-

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ication of smallpox. As such, this is perhaps the greatest public health achievement recorded; Jenner's stature as a scientist and benefactor of mankind is surpassed by few. But the history of smallpox prevention did not begin or end with Jenner (Table 1). Indeed, effective inoculation against smallpox had gone on for centuries before his time, across many continents, incorporating varying approaches. One could even suggest that control of smallpox would have occurred had Edward Jenner never been born. Yet 200 years later, Jenner is the individual uniquely identified not only with smallpox vaccination but with the development of vaccination in general.

Appreciation of what Jenner did and did not achieve is revealing for its applicability to the current races for medical breakthroughs in diseases such as cancer and acquired immunodeficiency syndrome (AIDS). The smallpox story is one of many heroes, each contributing a crucial element to the crowning achievement—the eradication of smallpox. Reviewing their historic roles is important for understanding the collaborative nature of research and tempering current expectations of researchers toiling to improve the lot of those with AIDS, cancer, and other diseases.

EARLY INOCULATION

Early in recorded history, a critical observation was made—people who survived smallpox were immune to subsequent infections with the disease. As early as 430 B.C., survivors of smallpox were called upon to nurse the afflicted.[1,2] In the 10th century, the Chinese endeavored to transfer the infection to susceptible individuals with the goal of rendering them immune. They observed that "...the opening of pustules of one who has the small pox ripe upon them and drying up the Matter with a little Cotton... and afterwards put it up the nostrils of those they would infect" could transmit the virus and sometimes immunity.[3,4] The Chinese text known as the Great Herbal of 1597 described an interesting alternative, which conjured images of modalities practiced years later. It suggested placement of "...powdered cow ice...into the nose of a child."[5] The substance "cow ice" was not characterized.

In India, it was noted that the case:fatality rate was lower in some epidemics than in others, probably owing to variation in virulence of the virus. However, infection during any epidemic still conferred lasting protection. It is believed that the Indian population exploited this observation as early as the 17th or 18th century.[6,7] During the "milder disease" outbreaks, pox-laden blankets were collected and susceptible children were wrapped in them with the intention of transmitting mild disease.[6,7]

Another means of transmitting smallpox from person to person is referred to as *inoculation*, derived from the Latin *inoculare*, meaning "to graft." The terms inoculation and variolation, often used interchangeably, refer to the subcutaneous instillation of smallpox virus into nonimmune individuals. The inoculator utilized "...a lancet wet with fresh matter taken from a ripe pustule of some person who has had a favorable kind of smallpox....to make an incision in the forearm of a child."[8] A local skin lesion would usually arise after 3 days and develop into a large, erythematous pustular lesion with satellite lesions over the next 4 or 5 days. Fever and constitutional symptoms would often accompany these lesions.

Table 1. Important Dates in the History of Smallpox and Its Demise

Date	*Event*
430 B.C.	Thucydides chronicles Athens besieged by plague, possibly smallpox
300 A.D.	Earliest reported Chinese description of smallpox
679 A.D.	Earliest specific European references to smallpox epidemic
Tenth century	Chinese physicians inoculate smallpox intranasally to bolster immunity
1701	Chinese practice of subcutaneous inoculation relayed to Royal Society; generates meager interest
1716	Lady Mary Wortley Montagu witnesses inoculation while living in Turkey; has her children inoculated
1721	Lady Montagu introduces inoculation in England; generates interest among upper class, but well-publicized early fatalities sharply limit growth
1721	Smallpox epidemic strikes Boston; Cotton Mather initiates controversial inoculation program
1757	Edward Jenner is inoculated (8 years old)
1774	Benjamin Jesty vaccinates his children with cowpox, and subsequently confirms their immunity by exposing them to smallpox
1775	George Washington orders all troops inoculated
1796	Edward Jenner vaccinates James Phipps with cowpox matter
1798	Jenner publishes his findings in "An Inquiry into the Causes and Effects of Variolae Vacciniae."
1800	Waterhouse uses Jenner vaccine in the United States
1880	Pasteur initiates anthrax, rabies vaccines
1967	World Health Organization begins global initiative for the eradication of smallpox
1977	Ali Mao Malin is last human to contract naturally acquired smallpox
1979	WHO's Global Commission for the Certification of Smallpox Eradication decrees smallpox has been eradicated

The practice of inoculation seems to have arisen independently when the people of various countries were faced with the threat of an epidemic. It is likely that inoculation had been practiced in Africa, India, and China prior to the seventeenth century.[9-13] In India, members of the Brahman caste performed inoculation in conjunction with a religious cult of the smallpox deity.[10,11] The "...priests traversed the country in the spring of every year and the virus was introduced by scarification in the arm...moistened with the water of the Ganges."[12]

Inoculation was not without its attendant risks, however. There were concerns that recipients might develop disseminated smallpox and spread it to others.[14,15] Transmission of other diseases, such as syphilis, via the bloodborne route also was a concern.[7]

INOCULATION IN EIGHTEENTH CENTURY EUROPE

Eighteenth century Europeans were eager to learn about and adopt innovative ideas, especially from other cultures.[1] Although the earliest recorded use of variolation in Europe was in seventeenth century Denmark, it was in Turkey that the influential minds of Europe first witnessed inoculation and eventually recommended its use throughout Europe.[2] The Turks attributed this innovation to the Circassians, "...whose women were reported to be very beautiful and...sold for slaves by the poorer sort...(it was thought) necessary that all their females should have the small pox in their infancy because the distemper can spoil a face at any time, and the expense of a polite education might....be thrown away."[16]

The idea was presented to the Royal Society of London in 1714, when the physicians Jacob Pylarini and Emanuale Timoni independently sent letters from Constantinople.[13,14] The presentation was greeted with little more than a passing interest, however, as London physicians were wary of risking their reputations on such an unconventional idea.[14]

It would be 20 years before inoculation was tested in England. Lady Mary Wortley Montagu (1689-1762) lived in Turkey with her husband, the ambassador Edward Wortley Montagu.[14] It was there that Lady Montagu first witnessed inoculation, in 1716, and subsequently had her son inoculated. It is thought that her dedication to preventing the disease grew from the fact that her own once beautiful face had been disfigured by smallpox.[3,17] Two years later, having returned to England, Lady Montagu had her daughter inoculated during a smallpox epidemic, under the scrutiny of the Royal Society's Physicians.[13] The inoculation was considered successful when the child developed a limited number of lesions and did not contract overwhelming disease.

Hans Sloane, physician to the king and prominent member of the Royal Society, recognized the significance of this experience and played a major role in promoting the subsequent study of the technique.[4] Under the direction of Sloane, the procedure was tested on six condemned prisoners who were promised amnesty if they survived.[14] They all survived; one of them was even exposed to patients with active smallpox to demonstrate immunity. After seeing 10 orphans in St. James parish successfully inoculated, the Princess of Wales had her own two children inoculated.[2] Although this and many other early inoculations were apparently successful, reports of sporadic inoculation-related deaths sharply limited acceptance of the practice.[13,18]

THE NEW WORLD

Under the guidance of Dr. Zabdiel Boylston (1679-1766) and the Reverend Cotton Mather (1663-1728), variolation caught on much more rapidly in the colonies. Mather, a venerable leader of the Puritan church, is probably better remembered for compounding the hysteria surrounding the notorious Salem, Massachusetts, witchcraft trials.[19]

A graduate of Harvard College, Mather was extremely interested in science and medicine.[20] In 1706, he learned of variolation from Onesimus, a slave who had been inoculated in Africa as a child.[9] Several years later, the ever-curious Mather read Timoni's reports on the inoculation experience in Constantinople in the Royal Society's Philosophic Transactions. The Reverend later wrote a letter to Dr. John Woodward (1665-1728) of the Royal Society, stating that if his community were threatened by smallpox, he would ask the local physicians to introduce a program of inoculation.[1,20]

In 1721, a ship carried persons sick with smallpox into Boston from the West Indies, starting an epidemic that was to become Boston's worst in the eighteenth century. As he had planned, Mather wrote a "cautious and appeasing letter, which contained abstracts of the Timoni and Pylarini articles and urged...Boston physicians to practice variolation immediately."[14]

Boylston was the only physician Cotton Mather was able to persuade to initiate an inoculation program. They began inoculating volunteers throughout Boston, transferring inoculum from the lesions of infected individuals to incisions on the arms of susceptible people. Boylston's colleagues in the medical community spoke against this practice on both religious and medical grounds. Boston's most prominent physicians expressed concern about inoculation contributing to spread rather than containment of the disease, referring to reports of inoculation-related deaths from Europe. They also stated that it was not man's place to interfere with the Lord's "providence"

in these matters.[20] Interestingly, it was the leading clerical figures of the city who spoke out in defense of Boylston and the practice of inoculation. They rallied around this medical innovation, stating that it was no more sacrilegious than any other invasive medical procedure. The physicians took their struggle to the town's governing body, the Selectmen. Dubious about the idea of intentionally exposing citizens to a potentially fatal disease, they reprimanded Boylston and proceeded to outlaw the procedure.[20]

With Mather's support, Boylston worked in contempt of the Selectman and continued his inoculation practice. As the disease spread, however, so did the controversy surrounding Mather. At the height of the epidemic, a bomb was thrown into his home.[20] Mather sought to defend the practice in scientific terms. However, many of the earliest reports about inoculation were published by the practitioners themselves, who had a financial stake in the matter.[21]

To make their point, Mather and Boylston used a statistical approach to compare the mortality of smallpox infection contracted naturally with that contracted by inoculation. This may have been the first time that comparative analysis was used to examine a medical intervention. During the great epidemic of 1721, approximately half of Boston's 12,000 citizens contracted smallpox (5889 cases). The case:fatality rate was 14%. In contrast, Boylston and Mather reported a mortality rate among inoculated individuals of approximately 2% (6/300 patients).[20] Assuming that all susceptible people in Boston had contracted the disease, they calculated that a mandatory inoculation program could have reduced the fatality rate from 14% to 2%, saving 726 lives. In addition, smallpox acquired through inoculation was noted to be much less severe than naturally acquired disease.

Subsequent reports confirmed that the mortality rate of inoculation was not insignificant—approximately 2%.[22,23] Throughout the colonies, many prominent figures continued to criticize inoculation and its practitioners harshly on religious grounds as well as scientific. Edmund Massey's 1730 publication, "A Sermon against the Dangerous and Sinful Practice of Inoculation," contains insight into the thinking of the time.[25] He quoted Job 2:7, "So went Satan forth from the presence of the Lord, and smote Job with sore boils...." Massey felt this action was analogous to inoculation, and went on to implicate Satan as the first practitioner of inoculation.[24]

Massey argued that Job had achieved spiritual enlightenment by enduring the trials of his suffering. He continued, "Men cannot be sure of themselves until they have been proved...diseases are sent, if not for the trial of our faith, then for the punishment of our sins.... There is no thing so universally dreaded, as the disease which this strange method of practice pretends to exclude. But...the fear of it is a happy restraint upon many people...to keep themselves in temperance and sobriety."[24]

Word of the Boston Experiment Spreads

The adoption of variolation throughout Europe can be directly traced to the efforts of Cotton Mather during the Boston smallpox epidemic of 1721. Although British physicians had been loathe to inoculate after the well-publicized demise of some recipients, Mather and Boylston's data were influential. Inoculation was subsequently adopted in England, and it was later said that without the New England evidence the practice of inoculation would not have been reinstituted.[20] The idea of inoculation spread from England throughout Western Europe.

In 1757, an 8-year-old boy was inoculated in Gloucester; he was one of thousands inoculated that year. The procedure was effective, as he developed a mild case of smallpox and was subsequently immune to the disease. His name was Edward Jenner.[2]

By the end of the eighteenth century, there were many practitioners of inoculation in Europe, and this likely decreased morbidity and mortality considerably. In addition, the concept of bolstering immunity to prevent the spread of disease helped to lay a foundation that would greatly facilitate the subsequent adoption of vaccination.[1]

VACCINATION: A NEW IDEA?

Cowpox is a self-limited, pastoral disease contracted via direct contact with lesions on the cow. People who contracted cowpox were noted to be immune to smallpox. It is impossible to determine when this protective phenomenon was first recognized, but a statement issued by the Jennerian Society in 1805 indicated that it was the "...common opinion of the country ever since (the 1750s)...that persons who had gone through the Cow Pox naturally...were insusceptible of the Small Pox."[17] In other parts of the world, however, this phenomenon was recognized far earlier. It has been described that certain tribes of Indian shepherds, for example, were convinced of the protective effect of cowpox "...since the earliest recollection of man."[12]

The first man credited for applying this hypothesis to clinical practice was a farmer named Benjamin Jesty. In 1774, Jesty's community of Downshay was confronted with reports of smallpox in the area. Jesty noticed that two of his milkmaids who had previously suffered cowpox did not contract smallpox despite close contact with known patients. Since he had already suffered cowpox and believed that he also was immune, he decided to transmit cowpox to his family. A neighboring farmer, Mr. Elford of Chittenhall, had several affected cows, which Jesty used to vaccinate his wife and two sons. In 1789, the Jesty boys were inoculated as part of a community-wide variolation program. They were the only children who did not acquire self-limited smallpox from this procedure. Later, Jesty exposed his children to a smallpox

patient to prove their immunity. He also vaccinated other people in the community.[17]

On May 14, 1796, Edward Jenner performed his first vaccination, introducing material from a cowpox vesicle on Sarah Nelmes, a milkmaid, into the arm of a boy named James Phipps. On July 1, 1796, he inoculated the boy with smallpox. Smallpox did not develop.[25] In 1798, Jenner published "An Inquiry into the Causes and Effects of the Variolae Vacciniae," a disease discovered in some of the western counties of England, particularly Gloucestershire, and known by the name of "The Cow Pox."[7]

From a commercial perspective, the publication was an immediate success; however, from a scientific perspective it initiated a lengthy and vigorous debate. Jenner believed in *vaccination*, a term he coined, and was willing to dedicate his career and his fortune to promoting its use. In 1798, he journeyed to London to convince his colleagues of the vaccine's ability to confer immunity without the attendant risk of disseminated disease or systemic systems. Many prominent physicians opposed this practice. Professional jealousy, financial considerations, and apprehension about risking their reputations by performing untested procedures all played a role.[14]

Despite the objections of the medical establishment, vaccination rapidly became more widespread. However, it was reported that over two-thirds of recipients experienced generalized eruptions, in marked contrast to Jenner's early reports of cowpox vaccination. Jenner attributed this phenomenon to contamination of lymph, the substance used for vaccination, with smallpox virus.[14]

Lymph was propagated by extracting material from a vaccinated individual's pustule to use on subsequent patients. This arm-to-arm passage was periodically supplemented with cowpox material whenever an active case of this rare disease was discovered. Jenner used and distributed vaccine from his original stock until the 1840s. It is not clear if any action was taken to minimize use of contaminated lymph; in fact some documents described vaccination with Jenner's lymph as having a quantity of pustules and mortality rate similar to that seen previously in variolation.[15,26]

Over 100,000 people were vaccinated by 1801, and Jenner subsequently petitioned the House of Parliament for recognition of his claim to discovery of vaccination and recompense. The House of Commons, after hearing the results of a special committee's inquiry, issued a statement that "The whole of oral depositions, as well as the written documents from abroad, are uniform and decisive in favor of Dr. Jenner's claim to Originality."[27] Jenner was awarded grants totaling £30,000.[7]

During the committee's deliberations, it was pointed out by some that inoculation had been practiced "...in some dairies previous to Dr. Jenner's experiments." In an 1805 publication, Jenner's nephew George replied that "...if a person makes a discovery calculated to ameliorate the sufferings of his fellow creatures, and withholds its benefits from the world, certainly he cannot claim that reward which would otherwise be due his merit."[28]

Later that year, Benjamin Jesty petitioned the newly formed Jennerian Society for recognition of his contribution. After hearing his evidence, the Society recognized Benjamin Jesty as the first person to "...personally institute...the vaccine pock inoculation,...(and) provide decisive proofs of the permanent anti-variolous effects of the Cow Pock."[17] He was brought to London, where he sat for an official portrait and was given a nominal reward. Disliking London, Jesty returned to his farm a few days later.

The first vaccination in the United States was performed in 1800 by Benjamin Waterhouse (1754–1846) on his son, Daniel.[29] Waterhouse then wrote to President Thomas Jefferson (1743–1826) and asked him to sponsor the distribution of vaccine to the southern states. Jefferson, who had been variolated himself at the age of 23 years, had his family and neighbors vaccinated. He quickly became a fervent proponent of vaccination, and wrote a letter to Jenner thanking him for his work.[14] Congress established the National Vaccine Agency, in 1813, and named Dr. James Smith (d. 1841) as its director. However, reports of vaccine contamination with smallpox, and concerns about the duration of its protective effect led Congress to eliminate funding for the Agency in 1822.[14]

FURTHER DEVELOPMENTS IN VACCINATION

Prominent philosophers, such as Robert Thomas Malthus (1766–1834), questioned the utility of smallpox prevention. He hailed the disease as an agent of population control, particularly among the overcrowded lower class.[30] Antivaccination groups proliferated, but these vocal minorities were unable to halt the rapid adoption of the idea. By 1821, vaccination was required by law in Bavaria, Norway, Sweden, and Denmark. In 1853, England rendered primary vaccination of infants compulsory, with a penalty of 20 shillings for noncompliance.[31]

Although there was widespread use of vaccination in the early nineteenth century, the lymph being used was far from ideal. A questionable duration of immunity, contamination and decomposition of the lymph, and shortage of cowpox matter all plagued early practitioners.

In spite of excellent compliance with vaccination in some European countries, pandemics occurred in 1824 and 1837. These outbreaks were notable for an unusually high incidence of illness, albeit mild, in vaccinated adults. Acting on the hypothesis that vaccine-induced immunity wanes over years, several German teams instituted a mandatory revaccination program in the 1830s. Within a year of this initiative, a sustained decrease in the incidence of smallpox was realized.[1]

About 1850, a British physician named Cheyne added glycerol to cowpox lymph and found that it prevented decomposition without decreasing efficacy. The pro-

longed storage time enabled physicians to cease arm-to-arm passage of vaccine, dramatically decreasing the potential for contamination. The newer formulation of vaccine also enabled worldwide distribution for the first time, as the shelf-life no longer precluded long-distance shipping.

By the middle of the twentieth century, smallpox was a rarity in industrialized nations. The development of a freeze-dried vaccine, which remained stable for much longer periods at ambient temperature, was a crucial step in the quest for smallpox eradication. Leslie Collier (b. 1921) developed a method for mass production of freeze-dried vaccine in the early 1950s.[1] It is interesting to note that the virus used by the World Health Organization (WHO) to eradicate smallpox in the twentieth century was actually vaccinia virus, which is distinct from both cowpox and smallpox virus. Its origin is unclear.[32,33]

In 1967, the WHO began the global initiative for the eradication of smallpox. Under the guidance of D. H. Henderson, the WHO recruited thousands of health care providers to organize a comprehensive network for efficient reporting and containment of outbreaks and distribution of vaccine. On October 26, 1977, the last naturally occurring case of smallpox was reported, and on December 9, 1979, the WHO's Global Commission for the Certification of Smallpox Eradication decreed that smallpox had been eradicated.

CONCLUSION

Is Edward Jenner deservedly a hero? People had been injecting smallpox-infected matter subcutaneously to prevent disease for centuries before Jenner's time. This was crucial, as it laid a foundation for rapid acceptance of Jenner's subsequent recommendations for vaccination (with cowpox-infected matter). Even cowpox matter had been used and tested prior to Jenner's initial experiment. In fact, it is a distinct possibility that Jenner and his colleagues were mistakenly using smallpox matter for many early "vaccinations."

The recognition of these facts should not diminish our view of Jenner's accomplishments. His relentless promotion of vaccination changed the way medicine was practiced. Reexamination of the historic context of his work demonstrates that Jenner's contribution was indeed a vital step toward the elimination of smallpox. However, it is equally clear that his work was one of countless vital steps and not the singular, crucial one. Yes, Edward Jenner is indeed a hero; yet he is one of many.

If history reflects breakthrough after breakthrough, however, then this is what the public comes to expect. Wildly unrealistic expectations lead to a profound misunderstanding of successful scientific investigation. A breakthrough most often is a result of countless small steps, rather than a giant dramatic leap. Smallpox is one example of this; perhaps AIDS will be another. But we will have to wait and hope for progress, one step at a time.

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