Seminar

University of Colorado

The history of smallpox is a fascinating story of one of the major infectious diseases of man. It is as old as antiquity and as new as tomorrow. In this interesting seminar by a senior medical student of the University of Colorado School of Medicine, a brief historical review is presented, and our knowledge about the disease brought up to date. Of particular interest is the report of the successful chemoprophylaxis of the disease in a recent controlled study in Madras, India.

This review of the history of smallpox should serve as a reminder of what could happen again if preventive vaccination should fall into disrepute.

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History of Smallpox and Its Prevention

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Smallpox is an acute, communicable, viral disease characterized by severe constitutional symptoms and a single crop of skin lesions all proceeding at the same rate over a period of approximately three to ten days, through macular, papular, vesicular, and pustular stages. At the present time, vaccination is the chief means of control of the disease whereas, previously, inoculation (variolation) was the principle method of prevention. Vaccination has eradicated the disease from most areas, so that it is no longer the threat that it was formerly when it was endemic over much of the earth and often assumed epidemic and pandemic proportions. At that time, it had a morbidity rate of 25% and a case fatality rate of 20% to 80%.

The purpose of this paper is to present a brief history of smallpox and to discuss its control, first by inoculation and then by vaccination. A brief biography of Edward Jenner is included since he was chiefly

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responsible for the development of the process of vaccination.

Suggestions from the ancient literature indicate that smallpox may have begun in Eastern Asia. It was known to the Chinese for at least 2,000 years, on the basis of its mention in sacred Sanskrit writings, and it would appear to have been present in India for thousands of years. The disease was not described in other parts of the world until much later. Note was made of it in Syria in 302 AD, and an epidemic is thought to have occurred among Arabic troops during the Elephant War of 569 AD. Spread to Egypt is believed to have taken place in 572 AD. However, some historians have concluded that smallpox occurred in Egypt much earlier, since the mummified head of Rameses V, 1160 BC, shows that he possibly had smallpox.

In 622 AD, the disease was spread by the Arabsians eastward into Asia Minor as Mohamet and his followers set out, sword in hand, to propagate his religion. In the sixth century, the Arabs carried the disease to North Africa where they fought many wars. From there it appears to have spread southward across Africa, although it may have been present prior to that time in the central areas of Africa. In 731 AD, the Moors
crossed the Pyrenees and brought the disease to France. Smallpox probably reached Spain in 710 AD after its soldiers returned from a war in North Africa. Early in the seventh century the Persian armies brought smallpox to the Holy Land, as well as to Italy as they invaded the Holy Roman Empire. In the 10th and 11th centuries the crusaders helped to spread the disease widely throughout Europe.

There is confusion about the first appearance of smallpox in the British Isles. Creighton is doubtful of its existence before the 16th century, but McVail feels that, since smallpox was known to be present in Europe in the seventh century, it was probably also present in Britain at that time.6 Dixon states that there is good evidence that smallpox was prevalent in Ireland as early as 675 AD, although the clinical description of the disease was not a good one.6

During the 16th century smallpox was brought to the New World by the Spanish. In 1507, fifteen years after Columbus’s famous voyage, an epidemic in the West Indies exterminated whole tribes. The disappearance of the Lucayan Indians is chiefly ascribed to smallpox. It was first described in Mexico in 1520, where it is estimated that it caused the death of 3.5 million people within a few years. Brazil had its first epidemic in 1563. From there the disease spread across South America. Early in the 17th century the disease appeared in that part of the North American continent destined to be the American Colonies where it was brought by travelers from Central America, Negro slaves from Africa, or travelers from Europe.20 Smallpox was probably first brought to Australia in the late 1700’s; in 1789, one year after settlement by the English, an extensive epidemic of a disease believed to be smallpox broke out amongst the native aboriginal inhabitants. By the 18th century the disease was widespread over the whole world.

The derivations of the various terms used to indicate the disease are of interest. Variola, the generic term for the disease, is a word which was first used by Mariam, Bishop of Avenches in 569 AD but we do not know whether it was actually applied to smallpox since we do not have an accompanying clinical description of the epidemic which occurred in Italy and France at the time.21 Constantinius, who, in the ninth century, translated some of the Arabic medical work into Latin, was the first to use the term “variola” for the disease described by Rhazes. Variola is derived from the Latin varius meaning “spotted” or varus meaning “pimple.” In Latin pocca, which gave rise to “pock,” refers to a “bag” or “pouch.”

In the year 907 Princess Alfreda, daughter of Alfred the Great, contracted and recovered from smallpox. In 961 her grandson died from a malady which was called by the physician-in-charge variolas sine poecas. This was the first time the words “variola” and “pock” were used in connection with the same disease.5

In Latin writings smallpox was sometimes described as variola minuta, the pustules being small as compared with boils or with the bubos of true plague. Creighton points out that 16th century descriptions in French of les pocs might refer to la petite verole, which meant smallpox, or to the great pox, referring to syphilis. Similarly, in the English literature “pox” referred both to smallpox and to syphilis. In later years when syphilis became more prevalent, the word “small” was added to the word “pox” to differentiate more clearly the two diseases.5 In the past 200 years various authors have used the term, “the red death” as the term for smallpox.6

In the early 1900’s a mild form of smallpox which differed from the better known major form and occurred in previously unexposed and unvaccinated individuals was described. The terms “variola major” and “variola minor” seem to have been used first in an Annual Report of the Ministry of Health in England. Other synonyms for variola minor are “mild,” “atypical,” “subtoxic,” or “parasmallpox.” In South Africa it was called amass, and in Brazil it had the name alastrum.5

The first clinical description of smallpox by a medical writer is that of Rhazes, an
Arabian physician to the hospital of Bagdad, who died in 930 AD. A few years before his
death he wrote a treatise usually spoken of
by its Latin title, De Variolis et Morbillis
Commentarius. Rhazes believed smallpox
was a process natural to children because
“the blood is like new wine and must ferment.” He felt every man is born liable
to it. Issac, about the same era, thought the
disease was inevitable and resulted from a
process of putrification of the child from the
retention of menstrual flow during preg-
nancy.5 Dixon points out that with the
prevalence of many diseases at that time, it is
not too difficult to appreciate that certain of
them would be regarded as inevitable and al-
most physiological.5

It is interesting that smallpox is ap-
parently not mentioned in the Old and New
Testaments or in the early Greek and Roman
literature. Hippocrates makes no mention of
this disease. However, later Greek and
Roman scholars began to contribute to the
writing about smallpox. Rhazes mentions
that Galen was familiar with the disease.5
Translation of Rhazes’ work reveals that
at times he confused measles with smallpox,
while translations of the Greek and Latin
literature show that confusion existed be-
 tween smallpox and numerous diseases in-
cluding chicken pox, measles, impetigo,
scabies, the plague, and syphilis.5

The modern period in the history of small-
pox began in the 17th century; it was during
this time that the nature of the disease be-
came more clearly understood and the
methods of prevention were developed. In
the early and mid-1600’s smallpox was men-
tioned with increasing frequency in the
domestic and medical records. For example,
in 1641 in England, it was recorded in the
minutes of both Houses of Parliament that
attendance was very poor because of the
presence of smallpox.5 In 1649 health
officials recorded an epidemic in London in
which 1,190 deaths occurred.5 In the latter
half of the same century an increasing
number of epidemics was noted, as well as an
awareness that disfigurement could be
prominent and the death rate significant. In

1802, a total of 45,000 cases were recorded
in Britain. Lord Macaulay, in his History of
England, noted that during the reign of
William and Mary, “This disease was one
of the most terrible of all ministers of death.
The havoc of the plague had been far more
rapid, but the plague had visited our shores
only once or twice within living memory;
and the smallpox was always present, filling
our churchyards with corpses.”20

White has described smallpox in the
American colonies during the 1700’s. He
states that the disease came in cycles, mov-
ing from one part of the country to another
and leaving devastation in its track with
death of the most susceptible. Those who
survived had a life-long immunity. The dis-
ease might recede and be absent until a new
and unprotected population grew up. Then,
after a lapse of years, smallpox came again
to plague the colonists. Thirteen epidemics
were recorded in the Boston medical litera-
ture between 1650 and 1800. In an epidemic
in 1752, six-thousand inhabitants out of a
population of 16,000 were thought to have
had the disease.20

In 1754 in Europe one out of every ten
deaths was attributed to smallpox. Germany
recorded 65,000 cases in 1796 and Prussia
40,000 cases in 1803. The statistics for India
at this time are not available, but it has been
estimated that at times the incidence of
smallpox reached hundreds of thousands
per year.20

During the 17th century many unsuccess-
ful measures were used in treatment. These
included blood-letting, purging, ointments,
salves, herbs, and witchcraft.5 Toward the
end of that century a controversy arose
about the treatment to be used when Syden-
ham, a popular and influential physician,
sponsored a regimen limited to cooling of the
body. Sydenham’s major contribution was
the concept that no major treatment should
be attempted and be expected to be effective,
especially in those cases where discrete le-
sions were present.12

This was not Sydenham’s only contribu-
tion to smallpox. He is credited with being
one of the first physicians to elaborate the

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true nature of the disease. He differentiated smallpox from other exanthemata and advised various prophylactic measures including strict isolation of cases.\(^\text{12}\) Another very important advance in our knowledge came in the 17th century when von Helmont and Boerhaave described smallpox as an infectious disease and related its mode of contagion.\(^\text{20}\)

Information about the nature of smallpox has grown enormously, especially in the last 80 years. Credit for describing certain inclusion bodies found in affected cells is given to Guarnieri who reported them in 1886, although he may not have been the first to do so. Pascher later described the so-called elementary bodies of which the Guarnieri bodies consist.\(^\text{19}\) At the turn of that century the infectious agent was found to be submicroscopic and filterable and was classified as a virus. In the 1930's the smallpox virus was grown in tissue culture.\(^\text{8}\) Much of the biophysical, biochemical, and electronmicrographic characteristics of this virus have since been described. Clear and concise clinical descriptions have been provided.

A brief discussion of the natural course of smallpox has been presented. Now the story behind the measures used to bring this disease under control will be given.

The process of inoculation, the first artificial means of protection against smallpox, dates back almost as far as knowledge of the disease itself. The first actual description of this procedure was recorded by the Chinese about 590 AD during the Sung Dynasty although it had been done for many years before this. Much of our knowledge of the practices of the Chinese came from the 18th century writings of the Jesuits in Peking, China. The technique of inoculation involved nasal implantation of a small pledget of rolled cotton, containing dried scabs which had fallen off from various pustules.\(^\text{13}\)

The practice of inoculation had also been known in India since ancient times. It was carried out in Hindustan by Brahman priests, who traversed the country every year at the close of the cool season and before the period of great heat. These priests required those individuals desiring inoculation to undergo a preparatory dietetic treatment, involving mainly abstinence from milk and fish for one week's time. Pledgets of cotton, having been soaked in matter from smallpox lesions and then stored for one year, were inoculated into approximately 15 one-half inch parallel incisions in the skin. The wound was then sprinkled with water from the Ganges River and wrapped for 24 hours. Religious incantations were repeated while the procedure was carried out.\(^\text{12}\) It is difficult to tell how long inoculation has been carried out in Africa but there is evidence that it was done there more than a thousand years ago. The practice still continues among certain tribes in eastern and central Africa. From central and eastern Africa inoculation probably spread to Egypt and Asia Minor.\(^\text{14}\)

On the European continent one of the earliest reports was that of Marius, Bishop of Avenches, who described it in the sixth century. Inoculation was also practiced in the School of Salerno in the 10th and 11th centuries.\(^\text{14}\)

The first truly authentic reports of the practice of inoculation in Europe came from Vollgnad of Breslau in 1671 and Schultz of Thorn in 1677.\(^\text{14}\) Inoculation became a popular procedure in northern Greece and the Caucasian provinces of the Ottoman Empire sometime in the late 1600's. A Greek physician, Emanuel Timoni, studied the procedure in Turkey and published his work regarding it. A letter containing this information was sent to the Royal Society of England in 1714. An Italian physician, Giocomo Pylarino, published his studies on inoculation in 1716. The Greek method, as described by Timoni and similarly by Pylarino, involved collecting the contents of a pustule on the 12th or 13th day of the disease from a donor with discrete smallpox lesions. This material was then mixed with the blood which exuded from several small wounds made by abrading the skin of the recipient with a triangular lancet. The ancient Hindu method from India was seemingly less traumatic than this.\(^\text{11}\)
One of the most interesting stories concerning inoculation deals with its establishment in England by Lady Mary Wortley Montagu in the 1720's. The process of inoculation, however, actually preceded Lady Montagu in England by Timoni's letter in 1714 and by its mention in a book by a Scottish physician, Kennedy, in 1716. Nevertheless, the credit for disseminating information about the procedure rightfully belongs to Lady Montagu. She learned of inoculation while living in Constantinople with her husband, the English ambassador to the area. Lady Montagu in a letter, dated April 1, 1717, to Sarah Criswell, a friend in England, wrote: "Apropos of distemper, I am going to tell you a thing that I am sure will make you wish yourself here. The smallpox, so fatal and so general among us, is here rendered entirely harmless by the invention of ingrafting, which is the term they give it." Lady Montagu goes on to describe the method (the Greek method) of inoculation in the letter. She ends with "There is no example of anyone that has died in it; and you may believe I am very well satisfied of the safety of this experiment, since I intend to try it on my dear little son." Miss Criswell, who died of smallpox in 1726, may never have seen the letter.

Lady Montagu submitted her five-year-old son to inoculation by a Greek female inoculator under the supervision of Charles Maitland, surgeon to the embassy. In 1721 she returned to England where she also had her daughter inoculated by Maitland. Lady Montagu, particularly through her friend, Princess Caroline, began to interest the royalty in inoculation. Sir Hans Sloane, in conjunction with Maitland, carried out successful inoculations on six prisoners at Newgate Prison. For partaking in the investigation, the prisoners won their freedom. Through the influence of Lady Montagu, King George I subsequently permitted the inoculation of two of his granddaughters and, later, other members of his family. After the court accepted the practice, inoculation became quite popular and well established in England.5

Another interesting story concerns inoculation as carried out in America. This procedure was first advocated in the colonies by Reverend Cotton Mather. He became acquainted with inoculation by reading the works of Timoni and of Pylarino. Actually, Mather may have been aware of the procedure even before this, for in 1706 some of his parishioners made him a present of a Negro slave. Mather asked if he had ever had smallpox, whereupon the slave answered both yes and no. He stated that he had undergone an operation which gave him something of the smallpox and would forever preserve him from it. The slave then described the method of the operation.5

In April, 1721, at the start of Boston's sixth smallpox epidemic, Mather wrote an "Address to the Physicians of Boston," recommending inoculation. But only one physician, Zabdiel Boylston, took up the suggestion. In June, 1721, Boylston inoculated his 13-year-old son and two Negro servants with complete success. Later he used it for some of his private patients.18

Boylston and Mather did not go unopposed. The clergy, other physicians, and politicians presented sermons and pamphlets against inoculation for personal, political, selfish, and religious reasons. In 1722 after the sixth Boston epidemic ended, the selectmen of Boston made Boylston promise to stop inoculating the populace.16

However, Boylston retained his interest in the subject, and in 1724 he visited England and reported his results in a pamphlet titled, Historical Account of Smallpox Inoculation in New England. In it he stated that 286 people were inoculated in Boston with six deaths (1/47). He also stated that in a recent epidemic involving 6,000 people, over 800 died (1/7).16

In 1730 the seventh Boston smallpox epidemic occurred. Boylston was invited to present the data in his pamphlet throughout New England and to re-establish inoculation. By 1750 inoculation was becoming increasingly more popular. In that year Dr. Adam Thompson made a significant contribution when he published his 17-year experience
with inoculation. He presented his work entitled, “The Preparation of the Body for Smallpox” to the Academy of Philadelphia, and his method was adopted throughout the colonies. It involved a light nonstimulating diet, the administration of mercury and antimony compounds, and moderate bleeding and purging for two weeks. This was followed by inoculation on the leg.

Benjamin Franklin, who lost a son in 1736 in a Philadelphia epidemic, became a strong advocate of inoculation. In 1754 Franklin described the success of inoculation in England and America in a preface to a book on the subject by William Withering.5

The ability of inoculation to alter the course of the disease was probably instrumental in affecting the history of the colonies. An episode is described by Bern¬
stein.2 In June, 1766, the colonial troops, only a small number having been inoculated, were unable to capture Quebec, because, out of 10,000 men in Washington’s army, only 5,000 were fit for duty, mainly as a result of smallpox, which was prevalent at that time. The British troops, having been well inoculated, were relatively unaffected by the disease. Although greatly outnumbered, the British forces were intact and were able to hold off the colonists until reinforcements arrived. Bernstein states that “it can hardly be an exaggeration to say that smallpox was one of the main causes for the preservation of Canada for the British Empire.” 2 In 1776 General Washington, conferring with his medical officers, ordered his whole army inoculated.16 By this time, ten years after Boylston’s death at 87, inoculation was in general use in the American colonies.5

In other areas of Europe inoculation was accepted more slowly. In France only sporadic trials had been carried out. In 1726 Voltaire while in exile in England championed inoculation in his homeland but with little success. Finally, about 1750, Charles Marie de la Condamine and Theodore Tronchin, separately, were able to establish the procedure in France.16 Tronchin began inoculation in the Netherlands in 1748. By 1754 inoculation was being carried out in Sweden, Denmark, and Germany.16

Even though the procedure had been introduced into these countries, all did not always go smoothly. Between 1730 and 1760 opposition to inoculation grew, particularly in England. Physicians had modified the method of Timoni and made deeper incisions. They would “slash through the skin in several places, until a bit of fat was exposed. Then they would affix to each wound for twenty-four hours a pledget of cotton soaked in pustular matter.” In addition, inoculation was being administered more and more by charlatans and quacks.12 The result of all this was to increase both the morbidity and mortality and smallpox began once again to increase. The claim of the “anti-inoculationists” was that inoculation was becoming a means of spreading the disease rather than preventing it. There was documented evidence that inoculated people had even been the source of epidemics.16

The acceptance of inoculation again increased when a new method of carrying it out was introduced by several individuals. The first of these was a physician, Kirkpatrick, from South Carolina, who on the advice of a British surgeon, Mowbray, published a description of a new method of inoculation. Kirkpatrick wrote that “the smallest violation of the surface of the skin, just stained with blood, was sufficient entrance for the variolous matter to be passed by arm-to-arm transfer.” He also advocated strict isolation of the subjects after inoculation. After this there were only slight eruptions and a subsequent reduction in mortality to about 1%.11 Kirkpatrick traveled to England and there published his work. In 1763, Gatti, a Greek physician, added support to the work of Kirkpatrick by reporting a similar successful new method for inoculation.

The leading proponents for a new method of inoculation were two English physicians, Daniel Sutton and Thomas Dimsdale.7 Sutton actually developed his method as a modification of one his father, Robert Sutton, a physician, had previously worked out and had used without a death. Sutton combined

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his technique, which used variolous matter from early vesicles to decrease contamination, with light inoculation, arm-to-arm passage, and no postinoculation treatment at the site. To popularize the method, he provided his patients with a “secret” antidote to ward off ill effects. Later he described the antidote’s contents as calomel, tartar emetic, and jalap. Between 1764 and 1766 he inoculated almost 14,000 people and assisted in 6,000 more. He published a book entitled, *The Inoculator or Suttonian System of Inoculation.*

Baron Thomas Dimsdale was Sutton’s chief rival. Dimsdale published his work on inoculation in 1767. His method was very similar to Sutton’s. He placed great emphasis on taking the virus from a primary vesicle on the arm of a donor who had just been inoculated. He avoided frankly pustular lesions.

In 1768 Dimsdale was invited to inoculate the Empress of Russia, Catherine III, after Sutton had declined because of the risk involved. The inoculation of the Empress, as well as other members of her family, was successful. For his effort Dimsdale was paid the equivalent of $12,000 and an annuity of $500.

Because of the work of Kirkpatrick, Gatti, Sutton, and Dimsdale, the usefulness of inoculation was more widely accepted. The Royal College of Physicians sanctioned inoculation, describing it as “highly salutary to the human race.” The method generally became known as the Suttonian method. In 1775, Maty and Lettsom emphasized the importance of segregation after inoculation and advocated the early inoculation of infants.

With improvement in technique the death rate as a consequence of inoculation fell to 1 in 300, and its ability to produce protection became obvious. However, inoculation did not by itself control smallpox. Carrying it out was generally an expensive and time consuming operation and many of those who could afford it including members of the royal family did not take advantage of it. Most artisans and the poor, in spite of certain well-meaning attempts to give them the benefit of inoculation, could not afford the time or the money to have it done for themselves or their children.

By 1780 it became clear that inoculation was not adequately controlling the incidence of smallpox. The number of epidemics was, in fact, again on the increase. The time was ripe, therefore, for a completely new and more effective method of control. The new method was vaccination, established, and popularized by Edward Jenner.

Edward Jenner was born on May 17, 1749, in Berkeley, Gloucestershire County, England, the third son of Reverend Stephen Jenner. At the age of five he lost his father and mother. According to Drewitt, he was brought up with “affectionate care and judicious guidance” by his eldest brother, the Reverend Stephen Jenner, Jr. Another of his older brothers was the Reverend Henry Jenner. At the age of eight Edward was inoculated with smallpox. He had a fairly severe attack requiring months for complete recovery. Shortly thereafter he began primary school at Notten-under-edge where he remained for several years. He was then sent to school at Cirencester, where he took his first interest in natural history.

At 13 Jenner went to Sodbury, England, to study pharmacy and surgery under Daniel Ludlow. In 1770 at the age of 20 he went to London to complete his medical studies at St. George’s Hospital under the guidance of John Hunter, who became Jenner’s hero and life-long friend. Aside from medicine, Hunter and Jenner spent a great deal of time studying natural history, especially the process of hibernation.

In 1771, Captain Cook returned from his successful voyage to South America. Sir Joseph Banks, botanist for the expedition, had brought back a cargo of natural history treasures, including a mass of new dried and pressed plants. Jenner was asked to prepare and arrange Banks’ specimens. Jenner did this with such skill that he was offered the appointment as naturalist to Cook’s next expedition to sail in 1772. Jenner declined this, as well as an offer from Hunter to assist in the teaching of anatomy.
Instead, in 1773, Jenner began his medical practice in Berkeley. He shared the house of an elder brother. Baron, Jenner’s biographer, described him as “an excellent surgeon with great knowledge and dexterity.” Although his practice was rapidly increasing, he found time to join a small musical club, where he played violin and flute, and to write some poetry, a fashion of the day. Also much time was spent enjoying and studying nature, mainly bird migrations, the habits of the cuckoo, and hibernation, in the beautiful countryside surrounding his home.5

In 1783 his nephew, Henry Jenner, became his apprentice and helped him with his practice. One of Jenner’s medical interests was angina pectoris, a condition suffered by John Hunter. Through these years in Berkeley, Jenner and Hunter kept up a stream of correspondence about medicine and, especially, about natural history.6

Jenner’s fame as a naturalist is based on his careful observations of the habits of the cuckoo, a bird native to his home. Hunter was very interested in this work and presented Jenner’s study on the cuckoo to the Royal Society in London. Sir Joseph Banks was then its president. This work was accepted and won for Jenner the Fellowship of the Royal Society, a considerable honor, which perhaps was in part due to the powerful support of Hunter.9

In 1788 Jenner married Miss Catherine Kingscote. Their marriage was a very happy, compatible one, productive of three children, two boys and a girl.5

In 1792 Jenner obtained the MD degree at St. Andrew’s Hospital in London. He declined to apply for the Royal College of Physicians because of their requirement of proficiency in Latin.5 The next year, John Hunter died during an attack of chest pain, probably from a heart attack. Soon after Hunter’s death, Jenner put aside his studies on natural history and devoted a great deal of his time to his observations on cowpox and smallpox.9

Jenner’s attention to the relation of cowpox to smallpox had begun in 1762 during his medical apprenticeship in Sodbury. A country woman came to seek advice. The subject of smallpox was mentioned in her presence. She immediately stated, “I cannot take that disease, for I have had cowpox.”18 This knowledge was apparently not followed up until 1788, when Jenner began to make observations of cowpox eruptions on the hands of milkmaids.16 In 1791 Jenner started seriously collecting notes of cases of cowpoxed milkers who were said to have resisted smallpox inoculations. For years Jenner discussed these observations only with a close friend, Dr. Edward Gardner. But in 1796, Jenner wrote his first paper on the subject, dealing with the clinical description of both animal and human cowpox.5

On May 14, 1796, Jenner performed his first vaccination upon a country boy, James Phipps. He used matter obtained from a pustule on the hands of a milkmaid named Sarah Nelmes.18 The Suttonian method of inoculation was used for the vaccination. Six weeks later on July 1, 1796, Jenner inoculated Phipps with pus from a case of smallpox. This inoculation failed to take, indicating to Jenner the boy’s immunity to smallpox. Another of the successful series of vaccinations was carried out on a milkmaid, Mary James. On the test inoculation, smallpox was inoculated into Mary and into her unprotected brother. She showed no reaction while the brother developed the usual smallpox inoculation lesions.18

Jenner decided to publish his observations on vaccination, a term coined by him from variolae vaccinae, meaning smallpox of the cow.5 A member of the Royal Society, Jenner naturally assumed that this important contribution would immediately be published. But it was rejected with a note that if he valued his reputation already established by his paper on the cuckoo, he had better not promulgate such ideas as the use of cowpox for the prevention of smallpox.16 The basis for the attitude of the Society was the “lack of adequate proof.”5

In 1798 Jenner published the material himself. The title of the work was “An Inquiry into the Causes and Effects of the
Variola Vaccine, A Disease Discovered in Some of the Western Counties of England, Particularly Gloucestershire, and Known by the Name of Cow-pox."* In this paper Jenner states that "morbid matter of various kinds, when absorbed into the system, may produce effects in some degree similar to cow-pox; but what renders the cow-pox virus so extremely singular is that the person who has been thus affected is forever after secure from the infection of the smallpox; neither exposure to the variolous effluvia nor the insertion of the matter into the skin, producing this distemper." 8 Jenner included the case histories of 23 patients, who were successfully vaccinated, and four colored plates illustrating the vaccination lesions.16 Since inoculation had a specific meaning, it was used to describe the technique utilizing smallpox virus while vaccination was the descriptive term when cowpox was used. Actually both are forms of inoculation.5

It is important to point out that Jenner did not actually originate the process of vaccination. A number of other people had apparently practiced it in one form or another at earlier dates. There are suggestions in ancient Hindu writings dating back to 1500 BC that material from smallpox lesions was passed through calves and then used for inoculation.16 Fewster, an English physician in the early 1700's, presented a paper on "Cowpox and Its Ability to Prevent Smallpox" to the London Medical Society, but it was neither published nor followed up. In 1769 Bose in Germany noted a similar relationship.5 Five years later Ben Jesty, a dairy farmer in Dorset, England, alarmed by an epidemic of smallpox, remembered that some dairymaids, who had had the cowpox, had attended smallpox patients without getting the disease. He decided to deliberately inoculate his wife and three children with cowpox during the epidemic. None contracted smallpox. Jesty also failed to follow up his discovery.16

Jenner was the first to carry out observations and experiments on the protec-

* Cited by Dixon.8

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After publication of the famous "Inquiry . . .," Jenner waited three months with vaccine material to see if anybody would repeat his experiment. He was disappointed and surprised that the profession did not jump at his discovery. Finally Jenner received word that Cline, a surgeon and personal friend, had vaccinated a boy with vaccine sent by Jenner for the purpose of "counter-irritation" in the treatment of a diseased hip. Cline was surprised to find that variolation of this boy was subsequently unsuccessful. Joseph Lister, who consulted on the case, confirmed Cline's findings.16

The second to confirm Jenner's results was Dr. George Pearson, one of the most prominent physicians of the day in London, who successfully vaccinated large numbers of persons over a six-month period. Leikind points out that Pearson's zeal in studying vaccination was based on exploiting the matter for his own advantage.16 Dr. William Woodville vaccinated several hundred children in the outpatient department at the London Smallpox Hospital. He was surprised to find that over half had a more generalized eruption, different from that found by Jenner and more closely allied to the lesions of variolation. Woodville published these observations in 1800. A few years later he realized that his cowpox vaccine had undoubtedly been contaminated with smallpox and that this was the cause of the generalized eruption.8 Further confirmation of Jenner's work came from Marshall who vaccinated 423 patients and reported the results of his work.8

Between 1799 and 1804 opposition both to vaccination and to Jenner's original work began to arise. Much of the criticism came from laymen. Some felt that it was not logical that one disease should protect against an entirely different one. Others, including many clergy, felt that smallpox was an act of
God, and vaccination was therefore sacrilegious. From physicians came other criticisms. Many with vested interests in variolation opposed vaccination. Reports of failures of vaccination to protect against smallpox for any significant length of time were appearing with increasing frequency. Ingenhouz and Sims criticized the accuracy of Jenner's work and, therefore, were skeptical of vaccination until adequate proof was presented. Pearson, and even Woodville, having confirmed the success of vaccination itself, were personally critical of Jenner and his scientific method. Woodville and Pearson started a vaccination practice in London, which became known as the Vaccine-Pock Institution. Jenner, who expected the directorship of this institution, was instead offered the title of "extra consulting physician." Drs. Ben Moseley and William Rowley opposed the process of vaccination per se for still another reason. They were among the first to call attention to the fact that vaccination could be a means of transmitting other diseases. Adenitis, erysipelas, syphilis, leprosy, and tetanus were all implicated. Moseley also pointed out that in an occasional instance a properly vaccinated person might develop generalized progressive vaccine vesicles and go on to die. Acland found rare cases of children who developed convulsions after vaccination. A surgeon, John Birch, presented an interesting criticism of vaccination. He believed vaccination was effective, but he objected to its use; he pointed out that smallpox was an important method of decreasing the population, particularly in large and poor families.

By 1804 failures among the first group of persons to be vaccinated were beginning to be noted. These had apparently had several years of protection against smallpox when they again became susceptible to the disease. Over the next few years it became apparent that "everlasting protection" as put forth by Jenner did not occur and that revaccination would be necessary.

Jenner was personally quite sensitive about criticism of his work, especially about failures in protection. He took it as a personal affront to his integrity. He published his second major work, "Further Observation on the Variolae Vaccine or Cow-pox," in 1799. In this he discussed the reasons for failures occurring a short time after vaccination. He blamed failure on the "ignorance and carelessness" of the vaccinator or on vaccination with what he called "spurious" or false cowpox virus rather than the "true" virus. In 1800 Jenner published his third major article, "A Continuation of the Facts and Observations Relative to the Variolae Vaccine, or Cow-pox." In it he announced that thousands had been successfully vaccinated. He also continued to counterattack those who criticized vaccination.

By 1802 despite criticism by some, there had been extensive acknowledgment of the value of vaccination. Physicians, as well as the royalty and nobility of Britain accepted the procedure and many themselves were vaccinated. The Duke of York ordered the English Army vaccinated. Credit was mainly given to Jenner, but Woodville and Pearson were also recognized for their contributions.

In March of 1802 Jenner presented a petition for compensation to the House of Commons in behalf of himself. He claimed "first, the utility of the discovery itself; secondly, the right of himself to claim the discovery; and third, the advantage in point of medical practice and pecuniary emolument which he had derived from it." The last point emphasized that he had not kept the discovery secret and thereby benefited, but had disclosed it to the world. It is interesting that Woodville, a former critic, spoke in Jenner's behalf. By a slim majority Jenner was awarded the equivalent of $38,000. A few years later he was awarded $76,000.

Soon after general acceptance of vaccination, it became evident that the individual doctor could not be relied upon to provide his own supplies of vaccine. In 1803 the Royal Jennerian Institute was founded with Jenner as its first president. In 1808 the London Vaccine Institute was established.
In 1815 Jenner retired, at least to a certain extent, from public life. He returned with his wife, who was dying of consumption, to Berkeley. In his last years, he once again practiced general medicine and renewed his study of nature. Throughout this time he kept up a steady correspondence with those continuing the work on vaccination.9

In 1820 he suffered from what was most probably a stroke. By 1823 almost all of Jenner’s supporters were convinced that the immunity of vaccination was only short lived, and revaccination was necessary. Jenner’s views, however, remained unchanged. On Jan 14, 1823, Jenner wrote, “My opinion of vaccination is precisely as it was when I first proclaimed the discovery. It is not in the least strengthened by any event that has happened, for it could gain no strength; it is not in the least weakened, for if the failures you speak of had not happened, the truth of my assertions respecting those coincidences which occasioned them would not have been made out.”5

During the latter years of his life Jenner was honored by many people and many nations. In 1821 he was made Physician Extraordinary to His Majesty King George IV. He was awarded an LLD by Harvard University and an Honorary Doctorate of Medicine by Oxford University. He was also honored by Napoleon and by the Empress of Russia.9 On Jan 26, 1823, Jenner, at the age of 73, suffered a second stroke and died 24 hours later.

Robinson, a medical historian, has described Jenner as “a skilled observer, a successful experimentalist, a very practical man, but no thinker, as far as basic ideas or philosophies are concerned.” This, however, he states, is not so important for men of far greater genius have done far less for human happiness than this man, Edward Jenner.”17

Two years after Jenner published his “Inquiry . . .,” Dr. Benjamin Waterhouse set out to establish vaccination in America. Dr. Waterhouse, the Professor of the Theory and Practice of Physic at Harvard Medical School, received a copy of the “Inquiry . . .” from Dr. John Lettsom, a friend in England. In July, 1800, having obtained vaccine from England, Waterhouse vaccinated his five-year-old son, Daniel, and six domestics in his household. The lesions which appeared were exactly as those described by Jenner. A few weeks later, those vaccinated were sent to a smallpox hospital, where they were inoculated with smallpox virus. All proved resistant.16 News of Waterhouse’s success and enthusiasm spread. Soon he was deluged by patients seeking vaccination and by physicians requesting the vaccine, which Waterhouse termed the “kine-pox.”16

Vaccination was spread to Philadelphia by Dr. John Coxe, to New York by Dr. Valentine Seamen, and to Baltimore by Dr. James Smith. From these centers it was sent across America.5

Opposition to vaccination arose in America just as it did in England for many of the same reasons. Massachusetts, especially, was slow to accept vaccination. Waterhouse, however, was eager to establish it in his home state. Perhaps he was too eager. In 1812 for a number of reasons, including political ones, jealousy, and a controversy over fees and profits, Waterhouse was dismissed from his professorship at Harvard. But being a gifted, scientific man, he continued to carry on his crusade.5

Waterhouse, interestingly enough, received great support from Thomas Jefferson. He had written to President John Adams for support but was rebuffed. He then wrote to Jefferson, a candidate for the Presidency, who wrote back high praise and an offer of assistance. Jefferson helped spread vaccination throughout Virginia and other parts of the United States. He also played a role in introducing vaccination amongst the Indians. A tribe of Indians was visiting Washington, DC. Jefferson sent for the chief, Little Turtle, to whom he communicated the fact that the Great Spirit had recently made a gift to the white men in showing them how to preserve themselves from the smallpox. The chief and several of his warriors accepted vaccinations.16

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Waterhouse and Jenner, although they never met, became close friends through correspondence. Waterhouse was termed by many the "Jenner of the New World." He was appointed by the President as Federal Vaccine Agent in the National Vaccine Institute. When Waterhouse died at 92 in 1846, vaccination was well established in America.16

At the turn of the 18th century vaccination spread not only to America but to all parts of the world. In 1799, Pearson, who had been a critic of Jenner, sent vaccine to more than a hundred physicians all over the continent of Europe. From Europe vaccination spread to Russia. The Empress of Russia, very enthusiastic about the practice, decreed that the first child vaccinated should be named "Vaccinnoff." Vaccine reached India through the British ambassador in Constantinople via a ship which was partly paid for by money donated by Jenner. Spain, still a great colonial power, was desirous of extending the benefits of vaccination to South and Central America. The king ordered three frigates to make the voyage. On one, 22 unvaccinated children were placed. Two were vaccinated before the voyage began and two other children were vaccinated arm-to-arm each week. Thus a living chain of virus was carried over the ocean to Caracas, Venezuela. There the expedition split, one party spreading vaccination across South America, the other to Central America. Part of the South American expedition picked up 26 additional unvaccinated children to continue propagating the virus and went on around the world to the Philippine Islands, Macao, and Canton. From Canton it was carried into the interior of China.16

The legislative history of vaccination is a long and involved one. In 1803, Sweden established an ordinance on its statute books regulating the practice of vaccination. Bavaria made vaccination for children compulsory in 1807, and Denmark did so in 1810. England and the United States did not pass similar legislation for almost 50 years after vaccination was introduced. In 1840 England passed its first compulsory law for the vaccination of children, but its enforcement by fine or imprisonment did not come until 1853. By 1842 in England variolation was declared a felony by law.14 The first compulsory law in America was passed in 1855 but was not strictly enforced until 1872. Needless to say, legislation regulating vaccination was criticized over the years for various reasons by layman and physician alike. In one form or another vaccination laws have been modified to meet the needs of the time or the desires of the people.16

The criticism of Jenner and the process of vaccination must be viewed in relation to the results obtained from the procedure. Since 1904 variola major has never produced a significant epidemic in Great Britain. In no year has there been over 100 deaths. Between 1920 and 1935 there were about 5,000 to 10,000 annual cases of variola minor in England; only a few cases of variola major were reported. Since 1935 the incidence of variola minor has fallen to almost zero, with less than 30 cases annually of either type of smallpox reported in England since 1950.5,22

Since the turn of the century, there has also been a similar marked improvement in the morbidity and mortality statistics for the United States. Whereas thousands of cases occurred in the first decades of this century, less than fifty-five cases of smallpox have been reported annually in recent years and most of these have been single, isolated cases of variola minor. During this latter period, no deaths from smallpox itself have been reported, only those secondary to vaccination.5,22

At present, the main reservoirs of smallpox in the world are in India, Pakistan, Burma, and to some extent in Vietnam and Cambodia. All these areas are foci of variola major. From time to time epidemics have flared up in Indonesia and Thailand. In recent years in Africa, especially the Congo, Nigeria, and Tanganyika, there have been sporadic epidemics of variola minor and major. In the Americas, Mexico had been one of the last reservoirs of variola major on the North American continent but

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is now free of smallpox. Venezuela, Colombia, Brazil, Bolivia, Peru, and Paraguay remain as foci of variola minor in South America although extensive vaccination programs have recently been instrumental in decreasing the incidence of this disease. Recently an epidemic in Stockholm from a single imported unrecognized case resulted in 21 other cases.

Through vaccination and rigid quarantine regulations, smallpox has largely been controlled in many areas of the world. The discovery of vaccination led in part to a new science, immunology, and established a principle which had led to the immunization of man against many other diseases.

A review of the history of smallpox would not be complete without mention of two exciting new developments. The first is the worldwide eradication program being carried out by the World Health Organization. The other is the controlled study, recently carried out in Madras, India, of the chemoprophylaxis of smallpox with N-methylsatin β-thiosemicarbazone. In this study the administration of this drug during the incubation period to intimate contacts of smallpox patients resulted in a 94% decrease in the number of cases of the disease which subsequently occurred. The drug exerted its prophylactic effect regardless of the vaccination status of the contact and was much more effective than vaccination alone in the protection of persons who had been in intimate contact with smallpox infection.

It is entirely fitting that the first successful attempt at chemoprophylaxis of a major virus disease affecting man should have been directed against smallpox, one of the first specific diseases known to man.

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REFERENCES


