

## Smallpox - some unknown heroes in smallpox eradication

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### *Disappearance of smallpox*

On May 8, 1980 the 33rd World Health Assembly formally declared that 'the world and all its people have won freedom from smallpox'. In May, 1996 the 49th World Health Assembly adopted a resolution recommending that 'remaining stocks of variola virus, including all smallpox viruses, viral genomic DNA, clinical specimens and other materials containing variola virus should be destroyed on 30 June 1999 . . .'

The apparent eradication of smallpox represents one of the most important and most valuable contributions of medicine during the long centuries that the virus plagued humanity. Millions died or were crippled by the disease and the fall of a number of societies including both the Inca and Aztec civilizations are usually attributed to smallpox epidemics.

### *Who deserves the credit?*

In the west and in most formal western medical historical accounts, the major credit for the eradication of smallpox is given to Edward Jenner, an English physician. Such a conclusion is not correct, not even accurate with respect to England. History records that almost 80 years before Jenner advocated vaccination, Lady Mary Wortley Montague introduced into England inoculation against the disease using direct material from smallpox lesions. Even her introduction came very late in history. It is usually overlooked that variolation (direct introduction of smallpox virus-containing material to induce or increase immunity) antedated the birth of Christ and the Christian era. The use of variolation antedated Montague and Jenner by several thousand years.

The Chinese applied powdered old pox crusts to the nostrils. In India, the Brahmins inoculated dried pox crusts directly into the skin. The Persians ingested dried pox crusts. In Europe, fluid from the lesions of mild cases was injected directly into the skin. Jenner himself had been a variolater for many years before he introduced vaccination (inoculation of humans with the lesions of cowpox). Jenner should be - and is - given credit for showing that cowpox vaccine could be used in series by arm to arm passage and for publicising the use of cowpox (vaccination) as a safe and effective alternative to smallpox inoculation (variolation).

However, it should be emphasized that the introduction of new approaches to the prevention or management or treatment of a given disease involves nothing short of heroism on the part of the experimental subjects who subject themselves to the new approach before its safety and benefit are known. If the treatment turns out to be safe and effective, the physician who introduces it is afforded hero status. If the treatment is ineffective or harmful it is erased from medical history with little or no mention of those who were harmed. So it was with vaccination for smallpox.

We were able to obtain an early essay by Jenner. This document identifies by name many of those subjects who were first vaccinated and then exposed to material from smallpox lesions, i.e., who were subjects of an experiment by Jenner whose hope was to prove the effectiveness of vaccination. We will give the names of some of these heroes in a moment. It is often forgotten that almost 200 years elapsed from the introduction of vaccination to the eradication of smallpox. We will provide a description of the masses of Indian villagers and public health workers who played a major role in the eradication of smallpox in India. The ordinary villagers and the public health workers were also heroes.

### *Epidemiology of smallpox*

Before describing these heroic deeds it is useful to review some aspects of the biology and epidemiology of smallpox. One major mystery is the widely variable mortality from naturally occurring smallpox. Here is an example. In British India, between 1926 and 1930, there were 979,738 cases of smallpox with a mortality of 42.3 percent. In contrast, between 1921 and 1930, 381,800 cases were reported in the United States with a mortality of 0.9 percent. The mechanism(s) for this huge difference is usually stated to be variola major versus variola minor, a meaningless distinction which, in fact, tells us nothing about the mechanism which would explain the difference.

The relevance here is that variolation in a high mortality area might well be more dangerous than in a low mortality area. It appears that major outbreaks of smallpox were usually accompanied by a sharp increase in population-corrected mortality. The reason (mechanisms) for this is not known.

It also appears that the mere processing of smallpox material led to a decrease in virulence and in mortality. Although accurate data are not available, this led to the widespread use of variolation, particularly since accurate epidemiologic records of morbidity and mortality from variolation were not kept.

It is also of interest that attenuation of a variola virus isolated in Cologne, Germany in 1890 and subjected to serial animal passage led to an attenuated smallpox vaccine that became the source for clinically administered smallpox vaccines. Thus, ultimately, all vaccinations became variolation, although the generic term 'vaccination' persists.

### *Unsung heroes in Jenner's experiment*

And now to a description of some of the unsung heroes of the original experiments of Edward Jenner. To qualify for inclusion in this series, a subject was not only inoculated with vaccinia virus but was then deliberately injected with material from patients with clinically diagnosed active smallpox.

The first recorded experimental subject was an adult woman only identified as 'Mrs. H. \_\_\_\_\_'. Her age is not known. She was inoculated in 1778 after she gave a history of having had cowpox. Thus she was exposed to smallpox without the protection of vaccination. In 1791 an adult woman, Mary Barge, was vaccinated and then injected with smallpox. In 1792 an adult woman, Sarah Portlock, was injected with smallpox, having stated she had had cowpox 27 years previously. At the time she was deliberately inoculated with smallpox she was nursing her infant.

During 1792 an adult male, William Stichcomb, was injected with cowpox followed by smallpox. During 1795 Joseph Merret and William Smith, male adults, were put through this same sequence. Also in that same year certain events occurred which provided insight into the mind of Edward Jenner and his approach to his experimental subjects. Eight women, 'paupers from the village of Tortworth', were put through the sequence. Only one of the women is identified by name, Hester Wakely. Jenner was pleased that none of these women contracted the disease since, as he noted, '... many of these poor women were at the same time in a state of pregnancy.' We presume Jenner, describing the women as 'poor', was referring to their economic status rather than to their bad luck at being selected as his experimental subjects.

Thus, in Jenner's time, prisoners, the poor and children were frequently the 'uninformed' subjects of medical experiments. The same holds true today in our society (examples will be described in a future paper).

In Jenner's experiments, children played a part. We do not know which year this happened but Jenner exposed a five year old, William Summers, a seven year old, J. Barge, another five year old, John Baker and an eight year old, William Pead, to the sequence of cowpox and smallpox

inoculation.

In 1796 an eight year old boy, James Phipps, was put through the sequence. James Phipps became the subject of a myth that he was the first human to be vaccinated with cowpox against smallpox. James Phipps received his vaccination from material taken from a milkmaid. Sarah Nelmes (age unknown) was also put through the sequence in 1796. The year of experimentation was not given for three adult males, John Phillips, Thomas Pearce and James Coles.

Since Jenner could not have known in advance that cowpox vaccination would be effective in preventing smallpox, the conclusion is inescapable. He experimented on unknowing children, pregnant women and the poor. Had prisoners been available to him they doubtless would have been included. The experiment worked and Jenner became an immortal. The subjects of his experiments, the true heroes 200 years ago, have remained essentially unknown until now.

### *Unknown Indian heroes*

Let us turn now to India for another series of unknown heroes.

During the 19th century, smallpox was unbelievably devastating in India. So prevalent was the disease that there arose a saying: 'Never count children as permanent members of the family until they have had and have recovered from smallpox.'

When an effective vaccine became available during the British occupation, the order of introduction of its use was dictated by social position and class. Jennerian vaccine was first made available to the rich and powerful among the British in India. Then the vaccine was provided to Brahmins and to upper class Indians. Next came poor Europeans, especially soldiers and sailors. Finally, it was the lower class Indians who received effective and relatively safe vaccine. Often, interestingly, the motive was to protect the British from exposure to the disease.

Finally, it should be emphasised that there was a religious and social basis in India for using variolation rather than vaccination. There were special practitioners known as 'tikadars' who practiced variolation, long before vaccination was discovered and became available. This was a form of medical treatment sought after and paid for by the people themselves. There are no precise epidemiologic data but it has been estimated that the mortality from immunologic variolation was between 0.5 to 1.5 percent.

In the absence of accurate data it will never be known how many humans died because of the use of variolation rather than vaccination. In 1831, W. Cameron, a British superintendent-general dubbed variolation a 'murderous trade' and called its suppression 'indispensable to the interests of humanity.' It is not recorded that he personally intervened to make safe vaccination freely available to the masses of Indian people.

In any case, there are data to show that in India, between 1868 and 1877, there were 1.44 million deaths. Between 1878 and 1887, there were an additional 1.46 million deaths. In the next decade, 1888-1897, mortality fell to 0.96 million, and between **1898-1907**, to 0.83 million. The fall in mortality may have been partially related to increasing numbers of those immunised by more effective vaccination practices.

At any rate, by 1971, despite extensive programs of immunization, it became increasingly apparent that mass vaccination did not eliminate smallpox in India and, indeed, in the entire subcontinent of Asia. It became apparent that a program to eliminate smallpox must include the elements of 'surveillance and containment'.

Beginning in 1973, a new strategy was developed. In India, all health care workers, one week per month, would visit every village in India and later every house to find cases. Villagers were mobilised to help in finding cases and to enforce strict isolation of cases. Teams of health care workers would visit every village and finally every house during one week each month finding cases.

Rigid control measures were adopted. House guards were posted at each infected house on a twenty-four-hour a day schedule. Vaccination teams were formed and all visitors were vaccinated. Vaccination teams were organised and were made to live in each infected village, searching and vaccinating in a wide radius around the village.

The Indian model worked and produced dramatic results. The Indian approach was adapted for use in Pakistan, Nepal and Bangladesh. Two years later, using the approach of local vaccination, local control and local surveillance, the last case of smallpox was reported in India in June 1975. Similar success, using the same approach, was achieved in the entire subcontinent.

The public health workers and the villagers throughout India were, of course, heroes in the eradication of smallpox. In order to accomplish this, it was necessary to educate and energise broad masses of Indian people.

The education and energising of broad masses can generally serve as a model for improving health care outcomes. A similar approach, aimed at rheumatic fever, has been instituted in two French Caribbean islands. A ten year program targeted the public and health care workers for education concerning rheumatic fever and its relation to previous benign streptococcal infection. This has led to progressive decreases in the frequency of rheumatic fever, acute glomerulonephritis and rheumatic myocarditis.

### *'The unenlightened poor'*

There is a school of thought in Western medicine which holds that the poor and the uneducated are not capable of exercising autonomy as patients due to their unenlightened state. Indeed, some who hold such views have expressed the opinion that 'medical care should be withheld from the

impoverished in order to control the problem of overpopulation. The Indian experience with smallpox and the Caribbean experience with rheumatic fever reveal the error of these views.

One major lesson to be derived from the eradication of smallpox involves the indispensable role of patients and the public in medical progress. It is lay people who provide the base for the testing of new approaches in medicine.

When the new approach succeeds, all benefit. When the new approach results in net harm, lay people are the ones left injured or dead. Given the critically important role of non-physicians, it is surprising that so little is done to recognise their indispensable contributions in, say, clinical trials. The least that could be done is to define the risks and benefits of a given approach as accurately as possible to individual participants. They should be provided, when possible, with the opportunity to participate or not participate. Society needs a system by which it acknowledges the contribution of lay participants to medical advances.

Although considerable progress has been made since the time of Jenner in protecting the rights of non-physicians with respect to participation in experiments, much remains to be done. For example, an official agency of the US government states that experiments on patients in the intensive care unit can be performed without the permission of the patient, the patient's family or indeed of any non-physician. Whence comes this right for physicians to act as demi-gods? Where is the evidence that intensive care physicians or physician-investigators are particularly skilled at making societal decisions in the intensive care unit? The government position simply assumes that physicians are demi-gods or, at least, super human.

Another major lesson of smallpox eradication involves the contribution to medical care that can be provided by the poor and uneducated. The 'poor' are not dehumanised and the 'uneducated' are not uneducable. Rather, the evidence shows that mobilisation of broad segments of society improves medical outcome for every one.

Mobilising and educating the poor and handicapped touches on another important social issue. If the world is in fact overpopulated, what is the justification for improving the quantity - the lifespan - of masses of people?

We, physicians, are not demi-Gods. In western society, there is growing support for measures to control population growth by limiting medical care to specific population groups or, in some cases, by ending life involuntarily. In one western country, approximately one percent of all deaths occur because physicians or health care givers decide to end the life of the patient - without consulting the patient, the family or any designated societal group.

Here, in the United States, we have a candidate for the presidency who advocates denial of health care to

individuals attaining a certain age, having stated - paraphrasing - 'the old have a duty to die.' How will he behave when he reaches that particular age? Will he voluntarily exclude himself from medical treatment? A European group of physicians indirectly advocates withholding medical care from the poor and the uneducated, at least in particular circumstances.

The problem of dealing with a growing overpopulation is, of course, not a 'medical' problem. It is not a question which physicians are especially qualified to address. We should limit our role as physicians to improving, as best we can, the quality of life or the quantity of life, or both, of individual patients and of groups of patients. We should concede to society the authority to deal with broader and more complex issues like excess population.

In our roles as physicians, we should provide care to the rich, the poor, and those in between. We should provide care to the educated and the uneducated.

We should provide care to the good, the bad, and the majority who are somewhere in between. If and when society decides we should do otherwise, it will be a challenge for each of us to decide whether to accept or reject that societal judgment in carrying out our professional duties.

In closing, and returning to our subject of smallpox, a cautionary note. Viruses are particularly resilient organisms. It is not unthinkable that there may be a resurgence of the disease. In that event, how will our principles -- societal and professional -- serve and guide us?

We invite and welcome observations from as many Indian colleagues as possible since your experience with many of these questions is much closer and more direct than ours.

(Dedicated to the memory of Rahima Banu, a 3 year old Bengali girl who, on 16 October 1975, was the last recorded victim of small pox in Asia.)

## From the World Wide Web...

### Placebo.. .

1. R Harold Parmalee wrote:

A young woman was admitted with undiagnosed abdominal pain. She received parenteral narcotics for pain control. After a few days of tests and consultations, it was decided that she "had no organic cause" of her symptoms. A pain specialist was consulted and prescribed normal saline injections to replace her narcotics. The pain responded and she was discharged three days later.

Are placebos always unethical?

Is deception necessary for a placebo to be effective?

It is often claimed that the placebo effect is responsible for 30% or more of the effectiveness of such standard treatments as antibiotics for infection, anti-depressants for depression, analgesics for pain control, etc. Is there an ethical mandate to inform patients of this medical opinion? If we don't, are we being deceptive?

2. In my practice of family medicine I find that over time, I feel obligated to at least plant seeds with as many patients as possible that there is such a thing as a placebo response and that it may account for an indeterminate but sometimes substantial amount of the healing that occurs following the use of medications and visits to the physician. I especially bring this up when patients and I are puzzling out why something did or didn't work when we have used a trial of medication-as a way of narrowing down the diagnosis. When patients seem especially "tilted" toward alternative/complementary medicine beliefs, mind-body interests, etc. I am more likely to raise this theme explicitly sooner, but I try to find ways to mention it to patients generally over the course of a number of visits. I guess this means 1) I feel some ethical obligation to disclose my reliance upon placebo response as a part of my armamentarium and 2) that I am quite confident that the response will NOT be diminished (and might even be enhanced) because it is frankly disclosed, at least in general— keeping in mind that it would be unwise to disclose one's beliefs in some particular settings around a specific therapy.

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