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Virus Disease Eradication: Lessons still not Learned
Joseph E. Smadel Lecture
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For myself, as for so many others, Joe Smadel was a towering figure amidst what seemed then, and even now, to have been an unprecedented galaxy of infectious disease warriors – Ted Woodward, Colin McLeod, Albert Sabin, Geoffrey Edsall, Fred Robbins,, Alex Langmuir and John Enders are only a few who come immediately to mind.

However, from my vantage point, as someone beginning his public health career, Joe Smadel was one of the most intriguing and challenging—contentious, never hesitating to speak his mind and fond of deflating balloons. He was a counterpart to my long-time boss and mentor— Alex Langmuir— and the two were not infrequently on opposite sides of issues. There were many of us who attended meetings of lesser personal interest if we knew that either Joe or Alex would be there and especially if both were expected. Thus, you will appreciate my apprehension about the challenge of endeavoring to capture in a paper something of the essence of what Joe Smadel might bring to the subject of eradication—skepticism, feistiness, insight, and a dollop of iconoclasm. For a proper Joseph Smadel lecture, provocative ideas are appropriate, I believe, and these I shall endeavor to offer this morning.

A notable adventure that Smadel launched me on bears recounting as it bore with it the seeds of important future developments. In 1961 a new strain of cholera, called el Tor, emerged from Indonesia and spread to several Asian ports. The Philippines experienced one of the earliest outbreaks. It was widely speculated that this was the first stage of yet another pandemic of cholera. There was widespread concern. I was then responsible for surveillance at CDC; Smadel was at NIH. He called and asked that I go to the Philippines on behalf of NIH, specifically to assess the prospects for doing a cholera vaccine trial using the new strain. It was a curious request as CDC and NIH seldom cooperated in studies but one did not argue with Joe Smadel. In his briefing, I was chagrined by his repeated injunctions that I was to undertake no epidemiological studies. Smadel was not then an enthusiast for epidemiology.

I departed for the Philippines with a stop en route at NAMRU 2, then in Taiwan, where Bob Phillips was beginning to explore the potential for IV fluids in the treatment of cholera. I offer this aside for historical context.

My arrival in the Philippines in early 1962, with NAMRU's Craig Wallace, was what one expects in field epidemiology. One arrives after the peak of the epidemic, determines that the epidemic is well under control or perhaps over, and declare victory. Whatever, it was clear that a vaccine trial was not on but the potential for epidemiological studies to chart the course of a new possibly pandemic strain in virgin territory was irresistible. Alex Langmuir agreed to support further studies and, to undertake these, a young EIS officer was recruited—specifically, Henry Mosley who, until then, had never seen a case of cholera. Nevertheless, Henry engineered a magnificent series of studies that are still being cited. Three years later, with Smadel's blessing, he was named Head of Epidemiological Studies at the SEATO Cholera Research Laboratory in Dacca and later, he served as Director of the ICDDR. Ultimately, the genesis of all this was a telephone call from Joe Smadel. It was only of many such initiatives he launched.

But to the theme of this lecture – “Lessons Still Unlearned from the Eradication Programs”. The concept of totally eradicating a disease has been a siren song – for some, transcending reason and assuming the characteristics of a cause where the goal assumes the characteristics of a crusade to discover the Holy Grail, an effort not readily challenged by practical experience and reality. This is not a new phenomenon, as I will note. The fact, however, is that only one disease has been successfully eradicated; four others have failed; and two that are currently being pursued, are encountering heavy weather. One might assume that the lessons learned from the smallpox program would find application and some have. However, certain recent events have once again altered the calculus about the feasibility of eradication and, to date, this has been blithely and studiously ignored. The threat of a deliberate release of whatever agent might be on the eradication agenda is now seen to pose a serious threat and will continue to do so as far into the future as we can presently foresee. For smallpox, this means there is not only a need for eternal vigilance but it implies the need for stocking of vaccines and needles and sustaining a manufacturing base should more vaccine be needed. For the polio campaign, these problems, as they pertain to the post eradication era, have yet to be seriously

addressed. Little thought has been given to the implications they might have for other prospective eradication campaigns. When the problems and costs of undertaking such activities are fully taken into account, they quickly lay to rest any impetus to existing or prospective eradication campaigns.

The acceptance of eradication by the World Health Assembly occurred on 8 May 1980. It is appropriate today to pause to note that the last naturally occurring case of smallpox, Ali Maalin, became ill exactly 25 years ago in Merka, Somalia on 26 October 1977. The 1980 Assembly recommended that routine vaccination cease everywhere and, within three years, all countries had done so. Vaccine manufacture also ceased

A WHO expert committee was established to oversee a variety of follow-on activities to assure that rumored cases were properly investigated and to provide general oversight as various activities wrapped up. A concerted global effort was made by WHO to identify all laboratories that might have strains of smallpox virus -- of 823 identified virology laboratories and 75 indicated that they had strains of the virus. The Organization was spurred on by repeated demands from many recently endemic countries to take action to request that all laboratories destroy their stocks or transfer them to a WHO Reference Laboratory -- either the one at CDC or the Institute of Viral Preparations in Moscow. By 1983, all had given formal assurances to WHO that they had done so. Would that it had been possible to confirm this but, realistically, an effort to search REVCO's and other freezers across the world for tiny ampoules possibly containing smallpox virus was simply not feasible. Bottom line, however, is that there were probably very few laboratories indeed by 1983 that retained smallpox virus.

Beginning in 1990, a U.S.-led initiative proposed that the remaining stocks of smallpox virus be destroyed. A WHO expert committee determined that, so far as was known, no research utilizing variola virus had been conducted for nearly 10 years and none were able to identify a possible use for the virus. To preserve genetic information, the Committee arranged for cloned libraries of smallpox virus to be preserved and, later, supported an initiative to map the genomes of representative strains. Meanwhile, five major professional organizations, specifically solicited as to their views about destroying the smallpox virus, all agreed that this was a desirable action to take. However, in 1996, on the eve of a decision by the WHO Executive Board to recommend destruction of the

virus, the U.S. wavered and later reversed its position. Subsequently, it persuaded the World Health Assembly that it was crucial to retain smallpox virus indefinitely to permit research studies on antiviral compounds and new vaccines. These studies were essential, it was said, because no one could say where smallpox virus might still reside or whether someone might, at some time release the virus.

Whether right or wrong, this decision implicitly introduced a new dimension into the question of the policies and programs that would need to be in place after the natural circulation of any virus had been confirmed. In brief, it was now acknowledged that although global eradication of a *disease* might be possible, certainty regarding eradication of the virus itself would never be possible. Therefore, plans have had to be made to anticipate the recurrence of an eradicated virus, either naturally or by artificial release. For smallpox, I believe it is entirely possible that, if we had a reasonably safe vaccine, we might well resume a universal vaccination program, much as what we have today for diphtheria, tetanus, measles, rubella and several other diseases. We could not afford to do otherwise. Thus, it is obvious that the projected savings in vaccine and vaccination to be expected as a result of vaccination have to be substantially discounted from projected cost-benefit equations. To date, this is not a subject that has been broached.

POWER POINT PRESENTATION HERE-----

Today, the question first has to be asked seriously as to when, of if, polio itself can be eradicated. This is now in doubt because of the two most recently discovered problems that some individuals can excrete poliovirus for 10 years or more and that the oral vaccine strains can revert to a level of virulence and contagiousness indistinguishable from wild strains. Certainly, the concept of doing away with poliomyelitis for all time is an attractive one and has been pursued by dedicated people from around the world for the past 17 years. The progress made is impressive and the number of endemic countries is down to only 7 or so but those seven comprise nearly two billion in population and have numerous difficult problems. Tens of thousands, perhaps hundreds of thousands have been spared the crippling effects of paralytic disease. This is certainly a positive.

Expenditures, however, are approaching \$2 billion and there is evident fatigue both on the part of donors and of now non-endemic countries who are being asked to sustain an array of special activities until the entire world can become free. But even in

the now unlikely circumstance that polio is eradicated, what difference will it make? Look to the smallpox experience and recognize that eternal vigilance will be mandatory and that vaccination will need to continue, perhaps forever, unless we are to be prepared to mount a population wide revaccination program should the disease reemerge. That has difficult implications. To counter epidemic polio again would require enormous quantities of OPV to contain it. Note that one can't contain polio like one can smallpox. Is anyone prepared pay the costs to store hundreds of millions of doses of OPV, if indeed long-term storage is possible, in fact? Is someone prepared to pay the costs of sustaining a very large manufacturing capability for the long term future? Why are we not now reshaping the polio program, as it is apparent we must, to provide for a long-term vaccination effort, just as we now deal with other vaccine preventable diseases. Note that the same problems noted for polio would apply were we to consider such as measles or rubella eradication. In brief, much as I once questioned it, I believe Rene Dubos had it right.

Why is it important to critically examine the eradication issues? Eradication programs are far more costly than those for control. They have another and less well-known problem in that, to date, with the exception of the smallpox program, every other program directorate stopped or markedly reduced research investments for the disease in the belief that the solutions to the problem were in hand and that all possible resources should be applied to their application. Both malaria and, until recently, the polio program have fallen victim to this problem.

With concerns about national security, with a growing recognition that new and emerging diseases are of more than academic concern, I believe we have an opportunity now to seriously ask the question "What are the most critical disease challenges that should be able to be controlled and what research is needed to determine how best to do this?"

My candidates for an enhanced effort are measles, HIV/AIDS, TB and Malaria – not one of these I would propose be a candidate for eradication.

We should, instead, decide now to eradicate one thing – the word, "eradication".