

Failure of viral vaccines

Annual Dinner Meeting

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Following a generous introduction such as you have accorded me I am somewhat at a loss for words. I feel a bit like the two cows observing a milk truck emblazoned with the words Pasteurized-Homogenized-Vitamin enriched. One turned to the other and said - It makes one feel a bit inadequate, doesn't it!

Although I received none of my residence training here, I do feel almost as though I had been part of this department. My internship and residency was at the Mary Imogene Bassett Hospital and there the three people who played the most important roles in shaping my own future were Dr. James Bordley, who had become physician in chief after many years here in the Department of Medicine, and Drs. Campbell and Mary Goodwin, who themselves had spent many years on this faculty of the Department of Pediatrics. Cam and Mary Goodwin deliberately set out to interrelate curative and preventive services for Cooperstown and its surrounding area. They considered that all of the children in the area were their responsibility. Thus, in addition to providing inpatient and outpatient care, Cam Goodwin served as school physician and part-time health officer. Mary braced herself with a variety of projects concerned with remedial efforts in regard to learning disorders and in endeavoring to extend social services throughout the community. They considered the community to be their patient and it mattered naught whether the individuals were in the hospital or at home. To work with them as a house officer was a remarkable experience. It was perceptibly so different to think and act in terms of a population of healthy children rather than individual sick patients presenting themselves for care. I wish I could report that they had successfully implanted this approach but - alas - it was a concept too far in advance of its time - and as at so many edifices of sickness care, the focus gradually reverted to the sick patient and the clinical staff largely retreated from the community and behind the walls. But it was a lesson, a demonstration of a different approach to pediatrics and to health care - and one I could never forget.

The lessons were not unrelated to what we were to learn in the course of vaccination programs in other countries and in the U.S.

As I contemplated what I might possibly say which would be of interest to a distinguished audience such as this - now well-wined and well-dined and I suspect, acutely afflicted with post-prandial fatigue, I decided that perhaps all of you - and no less I - had respectively heard quite enough and talked quite enough about the smallpox eradication program. Thus, tonight I would like to depart from a well-trodden path and reflect briefly with you on the history of several virus vaccines and of our efforts - and notable failures - to employ them wisely in the prevention of disease. With smallpox vaccine and smallpox, I have more than passing familiarity. But my baptism into public health occurred at a memorable time - June 1955 at CDC when we were then rudely learning that batches of Jonas Salk's inactivated polio vaccine were better described as "dead, deader and deadest" rather than simply inactivated. That was the year, if you will recall, of the Cutter incident. Not so many years later, we were embroiled in the tidal wave of enthusiasm for Albert Sabin's oral vaccine, an enthusiasm which it was necessary to temper by pointing out (never to Albert's satisfaction) that it was not without some risk - like any other vaccine. And, finally, with Alex Langmuir, I joined in confidently forecasting the imminent eradication of measles in the U.S. - only to be proven so very wrong by more than a decade. It is important, however, to note that for each of these three diseases - and for rubella - we now have excellent vaccines conferring long lasting protection - for none of these diseases are there known animal reservoirs and in none does a protracted carrier state in man assume epidemiological significance. In theory, each of these diseases could be eradicated. But, even today, in the United States, three of the four disease still persist.

As one stands apart from the situation, one inevitably must ask why. Today in glass vials reside vaccines which can provide 95%+ protection against these diseases for very long periods - perhaps decades. The recipients we can readily identify. The delivery system consists of **what** we proudly declaim to be the best medical system in the world. The end result - far less than any of us could reasonably expect it to be - far less than the promise implicit.

In the interests of countering post-prandial fatigue let me tonight try to be provocative and, in course, irreverent and try to identify problems and culprits as I have seen them and perhaps from all of this - some lessons. My entree into the field was 1955 - a year marked by the end of the so-called "Francis field trials" of the Salk vaccine - a vaccine and a development for which credit more properly should have been accorded the Hopkins team of David Bodian, Howard Howe, Isabel Morgan, and Kenneth Maxey and, at Harvard, John ^{Enders} ~~Landin~~. It was the Hopkins team which had identified that there were three types of polio virus which caused disease, demonstrated that an inactivated vaccine and serum antibody protected against poliomyelitis and laid the extensive basic groundwork of understanding necessary for the production of the so-called Salk polio vaccine. John Enders building on George Gey's work here at Hopkins added the dimension of virus growth in tissue culture. The vaccine which was ultimately used in the trials was developed fully by an ex-influenza biologist who killed the virus by formalin much like he did influenza, made a series of wrong assumptions regarding inactivation but, with the benefit of the March of Dimes Public Relations Department became the well-known Jonas Salk. A harsh judgment perhaps but not so wide of the mark, I believe. My mentor, Alex Langmuir, insisted that we all appreciate the realities of Public Relations, that we try to understand the science of what really happened but that we should always keep in mind that "the public gods have feet of clay." One must regard all after dinner speakers in this light.

At CDC we promoted this inactivated polio vaccine with enthusiasm. But the vaccine itself was a problem. Because it was not sufficiently dead in its debut, it was made "deader" through a more elaborate filtration process - resulting in a vaccine which produced a far lower level of protection than the field trials promised. Failures were frequent - much more was promised than we could deliver. A notable lesson neither appreciated nor learned by the National Foundation but a lesson we should keep in mind for the future.

A remarkable episode of this period is one which I still find difficult to forget. I apologize for recounting it but it occurred - it was reality - and it cast a long shadow. In 1956, a polio outbreak occurred in Kentucky - 12 cases in a moderate sized mining town. One of our CDC

staff went to investigate and decided that a mass immunization campaign was urgently needed. At that time we at CDC had no resources to obtain vaccine - our medical officer approached one of the mine owners who agreed to purchase the vaccine and the supplies required. Local groups volunteered to provide publicity and to man vaccination stations. Within two days, all was organized and the first of a series of meetings throughout the town was convened. At the first of these, the representative of the local medical society avowed this to be the first step toward socialized medicine, insisted that all vaccine be administered in private physicians offices and insisted that the mass campaign be cancelled. Unbelievably, he carried the day - and who else was there to perform the sophisticated medical procedure of vaccination? The epidemic continued. As I was to learn, private physicians concerned with private patients and, I regret to say, private income were then far more prevalent than the Cam and Mary Goodwin's who worried about populations of children.

Eventually the scientific community solved Jonas's problem of making a good, reliable killed vaccine and when applied, reasonably widely, transmission of polio was interrupted. Tom ^{CR:IN} ~~Chen~~, a classic study in Des Moines, Iowa, in 1959, demonstrated conclusively that transmission could be interrupted by the killed vaccine. Subsequent observation in the Scandanavian countries and the Netherlands have confirmed this. This was surprising, for if you will recall, numerous studies had showed that killed vaccine had little effect on either the duration or titer of ~~interstitial~~ ^{INT: CR:IN} excretion of polio virus. The prevailing wisdom had been that each individual was protected by serum antibody but that the circulation of polio virus in the community via the fecal-oral route was not affected. The Des Moines results made no sense. However, as Dave Bodian so beautifully demonstrated, killed vaccine did interrupt pharyngeal excretion. The Des Moines experience suggested that by eliminating pharyngeal transmission, a balance in the ecology of polio virus transmission was altered. Data subsequently made available from the Porkow Downs Laboratory support the view that perhaps poliomyelitis is not primarily transmitted by the fecal-oral route but by the aerosol route. In brief, it would seem that the killed vaccine (let us not refer to it as Salk vaccine) was far more effective in conferring a herd immunity than we had believed. However, by 1960 Albert Sabin, Hilary Koprowski and

Harold Cox were vociferously advocating their respective oral live vaccines. Regrettable was the fact, in retrospect, that we never did and don't now fully understand the basic mechanics of polio epidemiology, of transmission of the virus and of the effects of a vaccine on the process. That we must understand the epidemiology and mechanisms of virus transmission for disease control is an all too apparent lesson still to be learned.

Oral polio vaccine appeared on the scene with a well-orchestrated choir of trumpets and domestic oratory worthy of William Jennings Bryan. For anyone interested or even willing to examine the relative merits of inactivated and live oral polio vaccines under different circumstances, it was an impossible period. One was either "for" or "against" the inactive or live vaccines. (Note that I do not refer to the oral vaccine as "Sabin vaccine" as, again, so much of the basic research - the strains themselves - were not Sabin's anymore than the inactivated vaccine was Salk's - beware the myth of public relations.) In every country, amazingly rigid evangelical stances were taken - scientific debate was all but suppressed as the two orators - Salk and Sabin - and their disciples vied for dominance much as, say, Muslim and Christian had done centuries before. It was and is as vivid a lesson in the perils of orthodox belief applied to science as exists in our time.

Two drops of vaccine on a lump of sugar - so simple, so easy, so painless - and so began the mass campaign to eradicate poliomyelitis. Albert's proposal to vaccinate all of America on a given weekend was rejected as unworkable at the highest levels of government but only by the narrowest of margins. However, city-wide, even state-wide campaigns - "Sabin on Sunday" programs - were all the rage of the early '60's. There was a wonderfully naive belief that one could readily and simply mobilize the host of voluntary and charitable organizations and "voila" the community could be vaccinated in a matter of days. Medical societies with Rotary Clubs and others took a lead role, either voluntarily or involuntarily. Many, in fact most, insisted that a physician be in attendance at each vaccination center to oversee vaccine administration. Exactly what they oversaw or what profound medical decisions had to be made was never clear - nevertheless, at most vaccination stations it was decreed mandatory

that a physician be in attendance. An important precedent was established, however, as never again did we have comparable titanic struggles with local medical societies over vaccination in clinics as contrasted to private offices. The results were dramatic - in city after city, the number of doses of vaccine administered exceeded the total target population of children. The responsible voluntary groups were exultant. It was a real triumph.

To us it seemed simply too good to be true and so we set in motion sample surveys to assess what, in fact, had been achieved. The results were monotonously uniform. In the suburbs, in the middle and upper income groups, 85 to 90% were vaccinated. In the inner cities, perhaps 40% and yet, it was here, that polio epidemics customarily began and spread in concentric waves to the suburbs. It was an all too vivid lesson that some sort of comprehensive plan for marketing the vaccine was required - much more was needed than simply good will, good intentions and enthusiastic volunteers.

A number of approaches to mass vaccination were evaluated. In 1962 in Atlanta we undertook a classic experiment, never published I regret to say, the results of which reverberated throughout the subsequent smallpox eradication program. We took six lower socioeconomic census tracts for study. All were subjected to intensive city-wide radio-TV-press publicity urging all to attend vaccination clinics at their local health center or physicians office. In two census tracts, nothing more was done. In two census tracts, block leaders were painstakingly identified, asked to compile lists of all under five years of age and asked to take or be sure that all so identified were taken to the local health centers or physicians office. In the final two census tracts, we used what we called the Baltimore system. During a year spent in Baltimore, I had been impressed by the attractant force of a "Good Humor" truck in our neighborhood. For these two tracts, we leased Ford vans with loud speakers and proceeded slowly along the street vaccinating as we went. At the end of two weeks, an alternate house survey was conducted throughout the 6 census tracts. Intensive publicity alone had resulted in 70% of those under 5 years receiving vaccine. The block leaders had improved this to 72%. In the areas where we had used the "Good Humor" van - the Baltimore approach,

85% had been vaccinated. The lesson we drew from this was that a vaccine, a preventive measure, to be given to an otherwise well child had to be marketed in a different way than one administered medical care to a sick child. People will seek out a physician to minister a broken leg or a pharmacy to buy aspirin for a headache (and for this a clinic, a medical center meets a need) but prevention - a vaccine - to be given to a perfectly well-child needs a component of marketing more like one needs to sell Coca-Cola or ice cream. One needs to "sell" it, to make it convenient to the consumer.

And, so it was when we moved on to the smallpox eradication campaign and began to develop smallpox vaccination programs that these were conducted by mobile units and mobile workers moving from village to village, in some areas from house to house - vaccine administration in clinics contributed little. Remembering only too well the disastrous voluntary mass polio programs in which a large and critical segment of the population was never vaccinated, we built in an assessment scheme to confirm that the coverage was what the total numbers vaccinated suggested it to be.

One could recite a litany of catastrophic experiences with the health centers in the developing world. I need recount only one in 1972. The area was northwest Iran - West Azerbaijan - then in the grip of a smallpox epidemic and WHO's widely touted example of a model primary health care scheme. I visited a health center - quite recently built, amply staffed, equipped with electricity and refrigeration. I asked the director of the health center as to what method he was using to make sure that all those seen at the health center had been vaccinated. He looked at me with astonishment - "vaccination," he said - "with all of these sick people, we don't have time to vaccinate!" An echo of this experience is recounted by McDaniel and his colleagues in the October 1975 issue of Pediatrics. A survey of 813 patients regularly being seen by 13 Idaho physicians revealed that by the age of 2 years, only 44% of the children had received the recommended immunizations. It has been said that it is an axiom that "operations or service" drives out "research" and, as a corollary, that "sickness care" drives out "prevention." It was true in Iran - I'm afraid it may be no less true throughout the United States.

From the earliest days of the polio vaccination program, surveillance had been essential. It had been started to document the magnitude and cause of the debacle associated with Jonas Salk's not quite dead polio vaccine. It confirmed and was used to characterize our problem areas, one problem group - for, in a sense, every case of poliomyelitis which occurred was a failure of the vaccination program. By studying the failures by area, by age group and other characteristics, it was possible to focus attention on those most in need - the high risk group. Numbers of vaccinations performed were counted but our focus was on number of cases. If poliomyelitis incidence didn't fall, there was little comfort in having vaccinated however many 'X' millions.

This was ultimately the key to smallpox eradication. Until 1967 when we began the intensified global campaign, progress had been measured entirely in terms of the hundreds of millions vaccinated. So little attention had been paid to the reporting of cases - to the surveillance of smallpox - that it took us almost two years to be certain which countries were endemic and which were only experiencing occasional importations of smallpox from endemic countries. Surveys eventually showed that only about 1% of all cases were actually reported in 1967 - that instead of the 131,000 officially reported cases, the true number was in the range of 10 to 15 million cases. Surveillance soon revealed that the vaccine conferred protection not for just one to three years but rather conferred protection to 90% of those vaccinated for as long as 20 years. The program shifted to primary vaccination - the operational slogan "get a scar on every arm" - don't concern yourself with revaccination. One further illustration of the value of surveillance may be offered. An extraordinarily elaborate program had been developed in Afghanistan employing female U.S. Peace Corps volunteers to vaccinate women in Pradesh. Surveillance soon revealed that it was rare to ever find a case in an adult woman (they had all had the disease in childhood and had died or were immune). The whole apparatus was dissolved. And, finally, through attempts to stop smallpox spread, it soon became apparent that our energies were more properly devoted to finding cases and containing outbreaks than to mass vaccination. The disease rarely spread so rapidly or widely as conventional wisdom or the textbooks suggested. The end result you know - 10 years,

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9 months and 26 days after the program began, a 26 year old cook in Merka, Somalia developed smallpox - except for two laboratory associated cases in Birmingham, England, he was the last.

Meanwhile, in the United States, a measles eradication program had been launched in October 1966, 4 months before the global smallpox campaign began. Remarkable progress was made. Cases decreased from 450,000 per year to 32,000 in 1972.1 But then the incidence stalled. Except in a few states (Maryland was an exception), the focus of attention was almost wholly on the numbers of vaccinations performed. Not until late 1975 when CDC smallpox veterans returned to take charge was there once again an emphasis placed on surveillance - on an assessment of why cases were occurring and among which groups. It soon became clear that much more rigorous efforts had to be made to protect children in schools - measles was not like smallpox. It spread far more rapidly. Containment such as was practiced with smallpox was not feasible. The curve of measles incidence has again resumed a downward trend. Through the first 10 weeks of this year, only 2300 cases have been detected - 1/2 of the total recorded last year. Maryland has recorded only 5 cases. We are rapidly approaching that point where transmission will cease. I believe this could happen as early as 15 months hence - but fully 10 years after we should have reached this point. It has not been a distinguished performance.

Meanwhile poliomyelitis incidence has plummeted2 - since 1969, the number of recorded paralytic cases has been in the range of 5 to 30 cases. Let us look at these cases~~y~~. Discuss subclinical infection but continuing transmission stopped sometime prior to 1970. Unfortunately, we cannot cease vaccination as we did with smallpox because of the risk - and occurrence - of importations. Most such importations come from Mexico where the volume of traffic is greatest. It is perhaps time to query whether we might not support a program in Mexico as defense for ourselves. Interestingly, the geographical pattern of polio is remarkably similar to that of smallpox in 1966 - at low or zero incidence throughout most of Europe and North America but heavily endemic in most other countries. Smallpox in the U.S. in the 1940's largely derived from importation from Mexico.

Lastly, let me mention rubella. Only 15 years ago, a major epidemic of rubella swept the U.S. - 20,000 infants were born with congenital rubella and large numbers of women had spontaneous or therapeutic abortions. Since 1969 we have had an effective vaccine - now usually administered as a bivalent or trivalent vaccine with measles and mumps. Rubella incidence has tended to parallel that of measles - so far this year 1800 cases have been reported, 3 cases of the rubella syndrome. But last year, 70% of the recorded cases were among those 15 years of age and older. There is a reservoir of susceptibles in young adults - perhaps 20% - but rubella spreads less effectively than measles and I personally am optimistic that with the present program, the ecological balance could be nearing the point where transmission may cease.

Thus, of the four virus diseases, we have effectively succeeded in breaking transmission with two but two still remain. This is a dismal performance considering the effectiveness of the vaccines and the degree of protection they confer. The vaccines represent a powerful weapon - the failures fundamentally lie not with the vaccines but with ourselves and our system. With other vaccines for such as hepatitis, rotavirus and others now foreseen, we need to assess why our poor performance and the lessons so far learned.

Briefly, it seems to me that vaccines and perhaps more generically - "prevention" needs to be marketed aggressively as one would market Coca-Cola. How else can we reach a population of otherwise healthy young people and persuade them to submit to a procedure. We need the medical community to do this but we need more. Secondly, each case which does occur needs to be investigated to determine the epidemiological behavior of the disease and to measure the characteristics of our failures so that the marketing and application can be specifically targetted to the need. In brief, we need epidemiological surveillance. Finally, it is possible that some day there might be a shift in the practice of medicine and pediatrics from that of caring for sick people to the philosophy embodied in Cam and Mary Goodwin's practice of pediatrics in Cooperstown - of treating populations.

To bring the subject back to Hopkins, may I ask a simple question - "Is every child who enters the outpatient clinic or the wards of Johns Hopkins Hospital checked as a matter of routine to assure that he is fully vaccinated?"