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Acceptance of the Howland Award

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President Dorfman, Dr. Silver, and friends: In looking over the list of 29 awardees, I feel most humble. The recipients were uniformly people of quality, quality in its classic Greek sense—knowing how to live with grace, intelligence, bravery, and mercy. In honoring me here, I hope you also feel the kinship we all have in better serving the needs of children. This is and should be our common goal regardless of our rank or our age. I happily served on our Council and then as your president two years ago (17), and I am keenly aware that each year the one chosen for the Howland Award is selected from a large and equally deserving group of people.

The award gives me a final opportunity to pay tribute to those who were my teachers. They include students, residents, fellows, and faculty members who were my colleagues over the years, but especially three teachers who had a critical influence on my life and work: Drs. Edward Shaw at the University of California in San Francisco, Grover Powers of Yale, and Joseph Smadel of the Army Medical Research and Graduate School at Walter Reed Medical Center. These three men, of totally different temperaments, were at once very demanding of excellence for themselves and for those to whom they felt responsible. They gave of themselves freely in time and in affection, providing models of commitment in all that is best in our field. Let me urge you then to go as they did, to be both demanding and generous. These two qualities, above all others, are needed as we strive to improve the life of children now and in generations to come.

Dr. E. B. Shaw (Fig. 1) introduced me to the ravages of poliomyelitis during my medical school and internship training in San Francisco. He was and is still a model of a careful, precise, and inspired clinician and healer.

Dr. Grover Powers (Fig. 2), who was then late in his career, was my chief during my last year of training at Yale. It was during that year that I became engaged to a fellow senior resident in pediatrics. It seemed quite natural to me to ask him first for her hand in marriage, even before I asked her father. Powers became my inspiration in my efforts to try to humanize hospital and outpatient care for the sick child.

Dr. Joseph Smadel (Fig. 3) introduced me to the pox viruses and urged me to take another look at the well-trodden field of smallpox. Helpful in his own way was the senior virologist who urged me instead to get involved in another, more fruitful field. He said, "Poliomyelitis is where the money is. Smallpox leaves no room for further work. It was well studied in the 1920's." He strengthened my resolve to reexamine current concepts in the field of smallpox and vaccination, the subject which was to occupy me for the next 30 years, until global eradication succeeded in 1977.

VACCINATION AGAINST SMALLPOX AND ITS COMPLICATIONS

In 1948, I had been working with vaccinia-variola group of viruses for a couple of years and had become quite aware of the many serious complications of smallpox vaccination, when, in one of those brief but important moments in one's life, I presented a child with eczema vaccinatum to Grover Powers (Fig. 4). I, who had just spent a period of intensive research on smallpox while in the Army, pointed out fairly blithely that occasional serious complications were bound to occur with any procedure we performed in medicine and that "this is a risk we have to take." Dr. Powers looked very sad. Those of you who remember Powers know just how sad he could look. He looked at me; he looked at the baby; finally, pointing to the patient, he said: "Who has to take? Who asked him?" It was a moment that has not been forgotten, and the incident led to my increased interest in learning more about the reasons that some individuals developed such severe complications after smallpox vaccination. As time went on, it became my view that the risk of a child in this country of contracting smallpox from an accidental importation of the disease was much smaller than the known risk of universal and routine vaccination and so I concentrated on reducing this risk (15).

In the 1950's and 1960's, eczema vaccinatum was a common occurrence in eczematous children and adults from accidental contact with a child who had been recently vaccinated against smallpox. We developed and then studied the use of an attenuated live vaccinia strain (CVI-78) in over one thousand children suffering from eczema who received elective vaccination with this sterile, freeze-dried vaccine. It did not produce a single case of eczema vaccinatum and conferred antibody protection against subsequent exposure to standard vaccine and to vaccinated siblings and other children. Children vaccinated with the CVI-78 strain had an exceedingly mild, local, and systemic response and no complications (21).

The worst, and happily, rarest complication of smallpox vaccination was progressive vaccinia or vaccinia gangrenosa in immunologic-deficient individuals (Fig. 5). In children, this complication was poorly understood, and it was not recognized that it was an instance of a deficiency of antibody-producing plasma cells and/or small lymphocytes capable of producing delayed hypersensitivity responses. We had previously shown in rabbits that delayed hypersensitivity was a principal defense in localization of primary vaccination and against spread of vaccinia virus to distant sites. We had found that greatly diminished redness on the third or fourth day (postvaccination) was indicative of a deficient small lymphocyte-transmitted response and that vaccinations were then likely to be large; in the absence of any erythema, progressive disease and necrosis was likely to occur (13). We also saw children known to have exceedingly low levels of gamma globulin due to plasma cell deficiency who had been routinely vaccinated in infancy but had not developed any complication. Among fifteen such boys, there was not a single case of vaccinia gangrenosa, but all had histories of enormous and hyperactive delayed hypersensitivity responses resulting from an intact small lymphocyte system. This alone was able to arrest vaccine introduced to the skin by multiple pressure techniques. None of these children had measurable antibody, but they reacted to intradermal injection of killed vaccinia virus with a marked erythematous response. On the other hand, children who had plasma cells but lacked small lymphocytes, either transiently due to intercurrent virus infection or due to a congenital defect, developed a progressive disease.

In the course of our studies of vaccinia necrosum, we encountered children whose lesions were progressive locally but did not disseminate widely. Surprisingly, two such children were shown

Fig. 1. Dr. E. B. Shaw.

Fig. 2. Dr. Grover Powers.

to have levels of neutralizing antibody in their sera usually consistent with healing vaccinia. We then discovered that these children lacked specific and general cell-mediated immune function; they were incapable of containing vaccinia virus locally but prevented distant spread by virtue of neutralizing antibody. From these observations, two important generalizations emerged: (1) vaccinia necrosum in these patients was curable by surgical excision and thiosemicarbazone therapy, techniques subsequently utilized successfully by others for similar patients; and (2) the Robert Good two-component scheme of immunologic development appeared valid. These children had split immunologic functions and represented loss of the thymic limb of the immune system. Simultaneously, Nezeloff was describing such children in France, and the syndrome now bears his name (Fig. 6). Finally, in combined defects, when neither the lymphocytes nor the plasma cells was present in sufficient number, a progressive vaccinia necrosum occurred which, if not treated effectively, in time would cause truly horrible lesions and death (Fig. 7). Although antibody therapy alone did little good, passive transfer of sensitized lymphocytes from adult donors was able to cause local transfer of delayed hypersensitivity and arrest the lesions (Fig. 8) (8).

Although these early transfer experiments were gratifying, we were unaware that we had caused the very first cases of graft-*versus*-host disease in man (10). In time, it was shown that even a single blood transfusion to the tolerant child caused fatal graft-*versus*-host disease at a time when the vaccinia virus had totally disappeared (9). We had "cured" the patient of vaccinia only to lose him to graft-*versus*-host disease. Although it was possible to develop temporary, local, or systemic delayed hypersensitivity with the administration of white blood cells from highly immunized donors, human graft-*versus*-host reaction would follow.

Subsequently, we found that we could treat adults suffering from a lymphoma or other neoplasm (Fig. 9) who were partially immunosuppressed either from their disease or from their therapy, with an anti-viral drug, Marboran B-thiosemicarbazone (1), supplemented by large amounts of vaccinia immune globulin first produced by us in 1951 from the serum of recently revaccinated army and air force recruits. These patients uniformly did well. Thus, in a completely fortuitous way, we began to understand immunologic mechanisms in vaccinia of antibody-producing plasma cells and the small lymphocyte-produced delayed hypersensitivity reaction and to show how very important and beneficial delayed hypersensitivity is in vaccination. At the same time, effective therapy sometimes produced a different fatal disease in the tolerant host. I raise these matters only to point out that a very simple question of how to deal with a few dozen cases of vaccinia gangrenosa which were referred to us over the years as examples of an exceptionally rare complication of a common, ubiquitous, immunization procedure made us understand: (1) that antibody alone was a marker rather than giving any information *per se* about immunity as we had believed since the early days of immunization against rabies, diphtheria, and tetanus; (2) that delayed hypersensitivity (commonly regarded as an unfavorable body response to something unknown) in fact was beneficial, and, in the case of vaccinia gangrenosa, life-saving. Indeed, one could predict the course of that disease simply by noting whether there was an inflammatory response typical of delayed hypersensitivity around the edge of lesions (Fig. 10). We now have a much better

Fig. 3. Dr. Joseph Smadel.

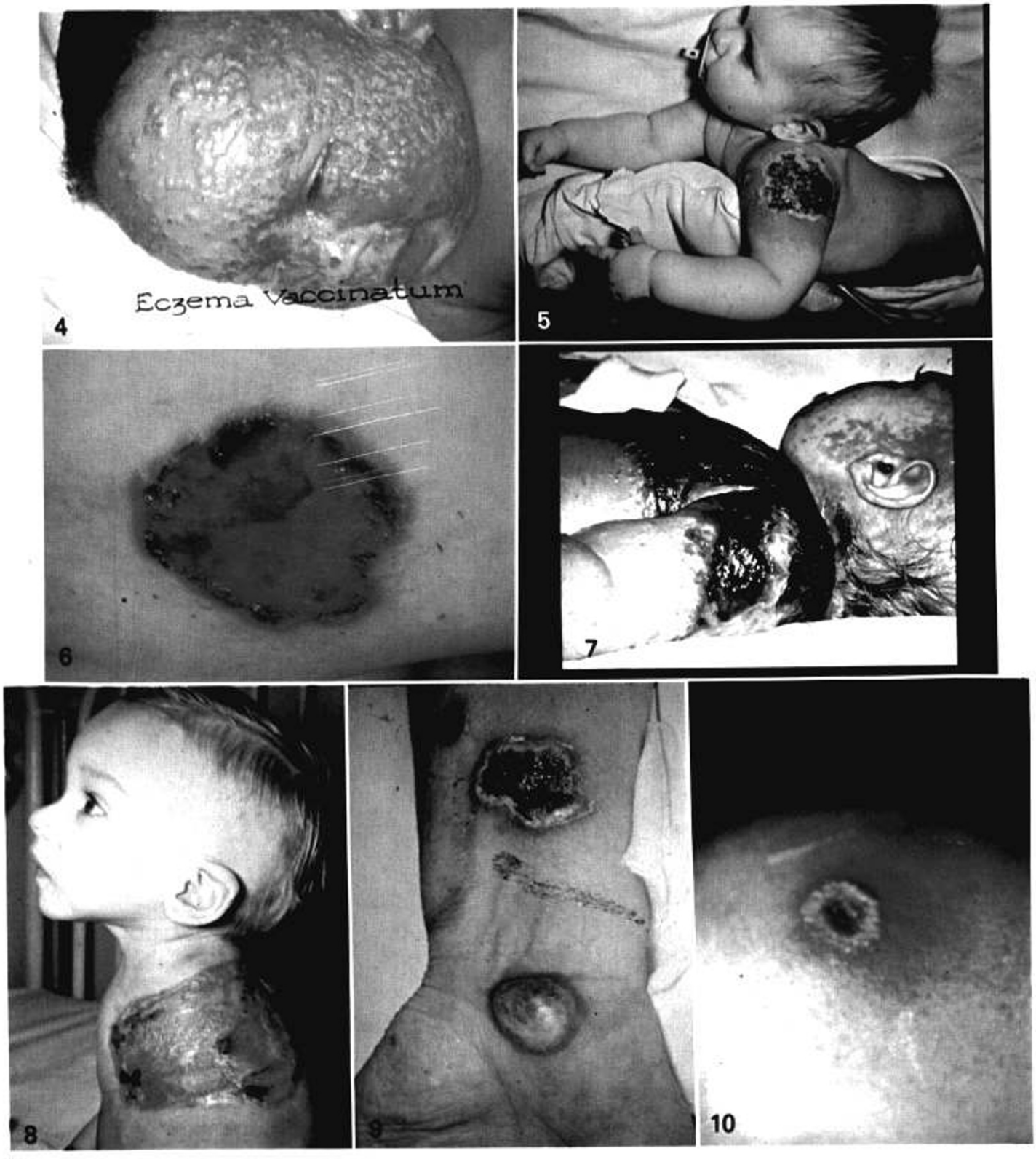


Fig. 4. Eczema vaccinatum.
Fig. 5. Vaccinia gangrenosa (Progressive vaccinia).
Fig. 6. Vaccinia necrosum curable by surgical excision and thiosemicarbazone therapy.
Fig. 7. Progressive vaccinia necrosum.
Fig. 8. Delayed hypersensitivity arrests lesions.
Fig. 9. Vacinia necrosum in lymphoma patient.
Fig. 10. Delayed hypersensitivity marked by inflammatory response around edge of lesions.

understanding of the very broad implications of many of these concepts based on the study of a rare complication of a standard pediatric procedure which is now happily discontinued for children.

For a considerable period, it was widely, and wrongly, thought that our freedom from smallpox since the 1940's was due to population or "herd" immunity. In fact, although our babies were well protected (they were unlikely to come in contact with chance

importation), solid protection against infections only lasts about 3 years. Despite this, nobody had ever suggested a 3-year schedule for reimmunization for our people as a whole. Exposure to smallpox 16 years after immunization produces the same incidence, although not the fatality rate, in vaccinated as well as unvaccinated individuals. Our adult population could be said to have been well vaccinated but not well immunized. We had simply been lucky to have so very few importations in part because the world reservoir was shrinking fast.

At the 1964 meeting of our Society in Philadelphia, I described the results of a national survey of 20,000 physicians as to the complications of vaccination and proposed that the time had come to discontinue routine universal vaccination of American children because the danger of the procedure at that time far outweighed the risk of exposure to smallpox (14).A lively and at times emotional debate followed. Only Margaret Smith supported our stand, but in 1971, only 7 years later, routine vaccination was stopped in this country (16, 22).

SMALLPOX ERADICATION

For over 30 years, most of the papers I presented at these meetings and those of the Society for Pediatric Research have dealt with smallpox, its eradication, and the serious complications of smallpox vaccination which we have studied. For over a decade, our Pediatric Department in Denver served as a national referral center for life-threatening complications, whereas our smallpox studies were carried out at a branch laboratory of the Department of Pediatrics of the University of Colorado located in Madras, India, and sponsored by the World Health Organization (WHO), the government of India, and the state of Madras. Over the years, many students, fellows, and faculty members went to the smallpox hospital in Mandras where we always had many cases of smallpox in the early spring months. I saw well over 10,000 cases during these years; one-third of them died of the disease.

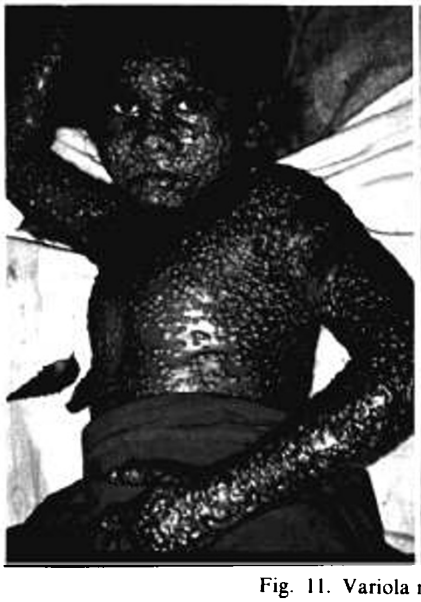
Smallpox occurred in two forms: variola major (Fig. 11) which had a mortality of 30%, and alastrim, the minor form (Fig. 12),with a mortality of only 1%. The vast majority of epidemics seen in this century in the Americas and Europe have been due to variola minor. In the United States, there were perhaps 50,000 such cases in 1930, but with widespread vaccination in infancy, smallpox began to decrease. The United States had its last case of smallpox in 1949.

In 1958, the Tenth Anniversary Session of the WHO was held in Minneapolis, and it was a milestone for those few of us who had been working towards worldwide eradication of smallpox. At this meeting, the USSR proposed and the USA, through Dr. Joseph A. Smadel, seconded a resolution that the "WHO should institute a plan aimed at worldwide eradication of smallpox" (2). I was a junior member of the United States team under Smadel, and I assume that it was he who suggested that I be appointed to the first Expert Committee on Smallpox Eradication at the WHO.

By 1958, both North America and Europe were free of endemic smallpox, and as many countries in Central and South America and several in Asia were smallpox free due to intensive vaccination campaigns. Mainland China had eradicated smallpox without any international aid and was then not a member of WHO. In South America, alastrim (variola minor) remained with a focus primarily in Brazil.

When I set up a smallpox research laboratory in the smallpox hospital in Madras, India, in 1952, it became posible to maintain a year-round facility in a hospital full of patients suffering primarily from smallpox and cholera in a facility where we could count on at least 500 hospitalized patients each spring and where with Professor Allan Downie of Liverpool, Dr. Gordon Meiklejohn of Denver, and other colleagues, students, and technicians,

Fig. 13. Aggressive crow.



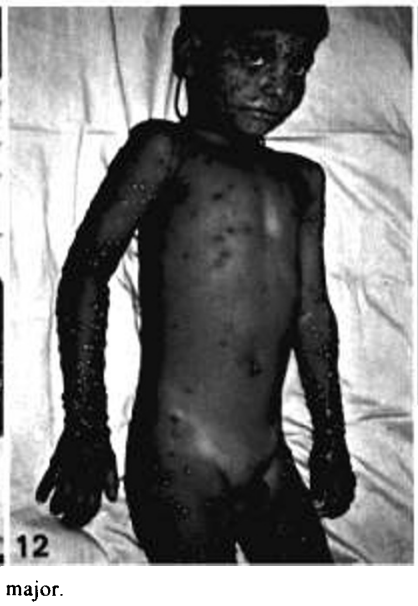


Fig. 11. Variola major.
Fig. 12. Variola minor or alastrim.
Fig. 14. Three or four simultaneous primary vaccinations in infant for longer lasting immunity.

we would study smallpox patients and their contacts until the disease was virtually eradicated, despite occasional importations in the state, just a few years later, and well in advance of the worldwide effort. It was possible here to show that bringing the most modern techniques to bear along with a good understanding of methods of transmission, this disease could indeed be wiped out.

We first showed that the use of vaccinia hyperimmune gamma globulin could prevent smallpox in intimately exposed, unimmunized family contacts of a patient, in newborn infants, and in pregnant women who had a high risk of contracting the hemorrhagic form of the disease. The hyperimmune gamma globulin was prepared from the plasma of recently vaccinated air force recruits; this special product later was licensed for use in this country. In accordance with Indian law, all family contacts received routine vaccination regardless of the period of possible incubation of the disease. One-half of the study group of 695 contacts received serum albumin, whereas the other one-half received vaccinia immune gamma globulin. There were four times as many cases of smallpox in the control group. These findings were particularly important because among newborn infants, all of whose mothers died of the hemorrhagic form of the disease, a virtually 100% mortality rate was prevented. Only three of nine such treated newborns developed smallpox, and these were very mild cases of the disease (13, 19, 20).

Clinical evidence suggested that a smallpox patient is not highly infectious in the 3- or 4-day febrile pre-eruptive period of the disease and that the virus was first discharged from mouth lesions, generally on days 6 to 9 (6). Contrary to what I had been taught, smallpox simply did not sweep through a population, even one that was relatively susceptible, as does measles or varicella, and acted in a much more random fashion. This led us to sample air in the vicinity of smallpox patients by taking measured air samples in and around the smallpox wards where we never had less than 30 or 40 patients (5, 24). Surprisingly, virus was recovered on only one occasion by the air sampling device, although large volumes of air were sampled in close proximity to patients at various stages of the disease. Initially, the volumes of air collected were on the order of 20 liters. Eventually, in desperation, we assayed as many as 18,000 liters, all with negative results. Although the sampling was not 100% efficient, it was sufficiently efficient so that in a 30-min run even a single pox forming unit of virus per liter should have been detected. With the exception of intimate family contacts, smallpox tended to be carried only small distances and then in a manner more like dust-borne streptococcus than by aerosol. In other studies, several plates of Petri dishes located where contaminated blankets were shaken yielded plenty of virus, whereas concurrent air sampling in the same vicinity did not.

In Madras, I was constantly enraged by the aggressive crows (Fig. 13) who flew in and out of the wards and ate the dried scabs on the blankets of our patients, and, on occasion, even attacked the patients themselves. I would have loved to have shown that these birds were an important cause of the spread of virus in the community, but marking them, as I did, I found their range of flight surrounding the hospital to be small, no more than 40 or 50 feet, and although they were mechanical carriers of the virus in an unchanged form, there was no evidence that they caused smallpox to spread. Nonetheless, we did get the wards crow-proofed by screening.

In terms of eradication strategy, one study from the Madras laboratory resulted in an influential contribution. It dealt with a comparison of freeze-dried vaccine and fresh Indian buffalo calf lymph in revaccination against smallpox (11). In periods during the year when there was a low incidence of the disease, we would invariably trace an outbreak, no matter how small, to an individual who might have an exceedingly mild case, and that person, often a young adult who had been vaccinated in childhood and now had mild modified disease, was able to transmit the virulent disease to the unprotected. The agent used routinely for vaccination in Madras was liquid buffalo calf lymph. This gave a high take rate in primary vaccination, but successful takes on revaccination amounted to less than 7.5% when the calf lymph was not kept cool during use of each multidose vial. By comparing this material, even when cooled in wet ice, to a potent freeze-dried vaccine given to patients admitted to our smallpox hospital for ailments other than smallpox, we could show that: (1) using buffalo lymph stored in wet ice, the percentage of successful revaccination takes in people previously vaccinated was raised from less than 7.5 to 27%; (2) the successful take rates for the freeze-dried vaccine done at the same time on the opposite arm was 64%; and (3) freeze-dried vaccine used in both arms produced successful revaccinations in 83% (Table 1). This indicated that in tropical climates the liquid lymph was not sufficiently potent for successful revaccination to maintain immunity. This led to the adoption of the freeze-dried vaccine, which was eventually the only preparation used in the worldwide eradication campaign. Incidentally, I remember presenting the results of this study at Atlantic City in what was the shortest paper on record; it was given in just under one min.

Of interest was the observation that the common Indian custom of using 3 or 4 simultaneously primary vaccinations in infants led to far greater and long-lasting immunity than occured when only one insertion was made (Fig. 14). A study of 2000 previously immunized individuals who, despite vaccination, subsequently developed smallpox, showed that there were 13 times as many cases of smallpox in children having only one primary vaccination scar than if they had four scars (12).

We also showed that levels of antibodies in newborn babies of vaccinated mothers were equal to the levels of their mothers in 50% of the cases, but two or three times higher in the other one-half, showing that the placenta could be a concentrating organ in passive antibody transfer. This correlated with attack rates in infancy (18).

We did a considerable amount of work on hemorrhagic smallpox, the universally fatal form, which was commonly seen in pregnant women. This turned out to be always accompanied by massive and continuous viremia, and the bleeding was due to disseminated intravascular clotting (4, 23, 25).

A number of approaches successfully used during the past few years in the eradication of smallpox in Africa had been described in detail by the Royal Commission on Vaccination almost 75 years earlier in 1896, but had been forgotten or not believed (3, 7,

Table 1. *Revaccination against smallpox. Comparison of Dried Vaccine with Fresh Buffalo Calf Lymph, Madras, 1960*

	Revaccination take rate (%)
Liquid calf lymph (not kept in wet ice)	7.5
Simultaneous vaccination on opposite arms	
Liquid calf lymph (kept in wet ice)	27.0
Freeze-dried vaccine	64.0
Freeze-dried vaccine alone on both arms	83.0

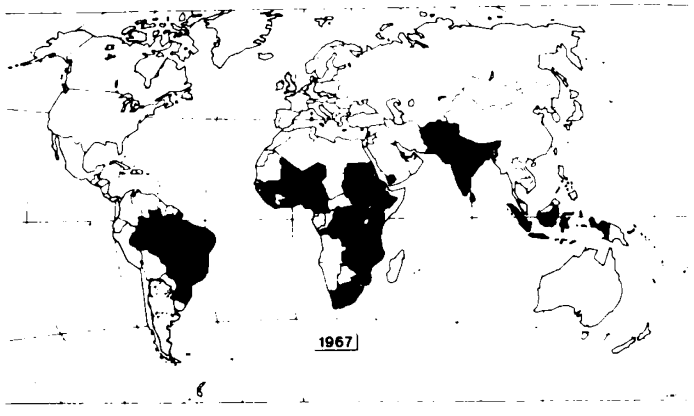


Fig. 15. Endemic smallpox distribution (1967) (global eradication effort initiated by WHO).

26). Indeed, to this day, we tend to ignore vast segments of the world's scientific literature either because it was not published in this country or is considered outdated. The "older" literature, to which our residents sometimes refer, usually implies that a paper was published more than 10 years ago.

In1967, the World Health Organization initiated its global eradication effort, which was directed from Geneva, used all our best technical and logistic knowledge in one international effort under the leadership of D. A. Henderson, and had a 10-year target date (Fig. 15). This unique international effort involved an international team of over 600 health officials and at its peak, between 150,000 and 200,000 health workers. At the time the eradication program was initiated, endemic smallpox still remained in some 30 countries, and 12 others had experienced importations (Fig. 16). In a single year, there had been at least 215 million cases (Fig. 17). By 1972 (Fig. 18), that number had dropped to about 13,000, and by 1977, endemic smallpox was essentially eradicated.

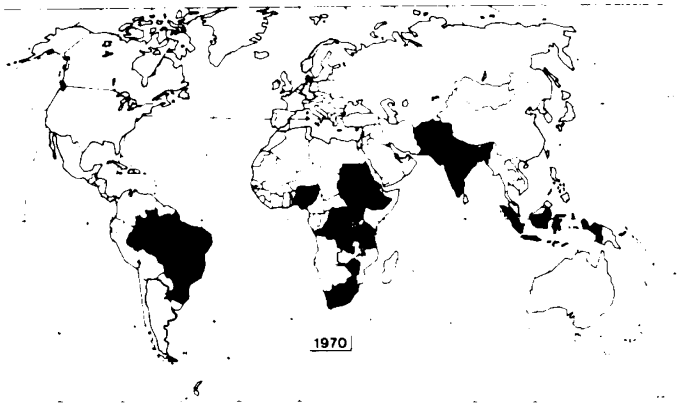


Fig. 16. Endemic smallpox distribution (1970).

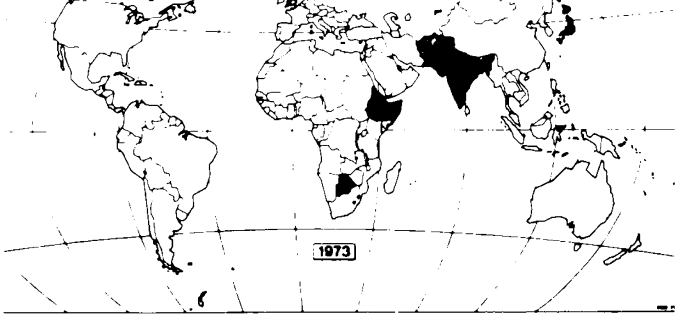


Fig. 17. Endemic smallpox distribution (1973).

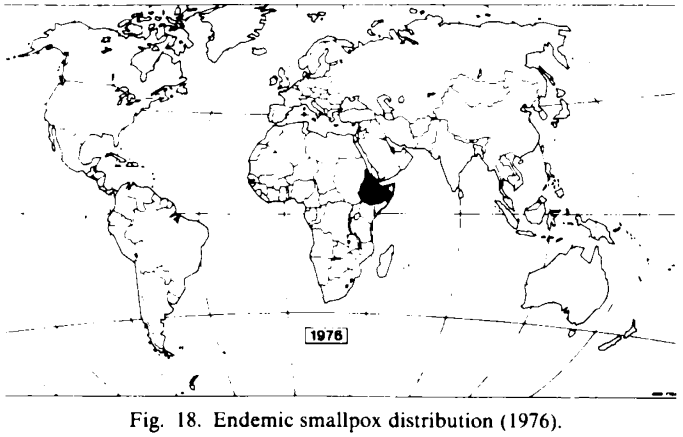


Fig. 18. Endemic smallpox distribution (1976).

The recent report of possible smallpox in a traveller who returned to Italy from Indonesia was not confirmed; it was varicella. Between 50 and 70 reports of suspected cases of smallpox are received by World Health Organization each year, all of which have turned out to be false, principally chicken pox. Smallpox virus now remains locked in about six or seven deep freezes in laboratories where it is preserved for scientific reasons, or, I suspect, for nostalgia. Because man is the only host of the disease, the only threat of the virus, therefore, remains in these few laboratories. It is my hope that even those stored strains of variola major will be destroyed because the minor strain will suffice for research, and there are so many other nondangerous pox viruses with which we can play.

CONCLUSION

In closing, let me point out that Howland, like Osler, was a Hopkins star. Let us recall with Osler that, "the great possession of any university is its great names. It is not the pride, pomp, and circumstances of an institution which brings honor, nor its wealth, nor the number of its schools, not the students that throng its halls, but the men and women who've trodden in its service the thorny road through toil, even through hate, to the serene abode of fame, climbing like stars to their appointed height." We do honor to Howland by loyally supporting the next generation of teachers of pediatrics at all academic levels in the eternal continuum of the university.

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