CLEMENTS-MANN LECTURE– APRIL 22, 2013/final

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(Obviously not a finished product but enough for an oral presentation)

My thanks to the NFID, to Gregg and to Bruce, for the honor of presenting the Mary Lou Clements-Mann lecture. This year, we celebrate the world's 35th year without smallpox – a pestilence which throughout history had been unrivaled in its destructive force. Despite this, the decision in 1966 of the World Health Assembly to mount a serious eradication effort passed with a margin of only 2 votes. Why was this? Many doubted that it was logistically feasible; others argued that eradication of any disease was impossible. Three previous eradication campaigns had failed; malaria eradication, the largest and most costly was then in its 11th year and was proving to be far more difficult than any had imagined. Its demise was only a matter of time. Confidence in WHO, in public health expertise, and in the concept of eradication had been shaken.

The smallpox program was launched in 1967 with a 10 year time target which called for the last case to occur by the end of December 1976. Health staff from some 72 different countries were to take part in the program. A considerable number who provided key leadership were under the age of 40. They proved to be unusually creative, dedicated, willing to endure long weeks in difficult field conditions. As WHO Director General Mahler said: "They did not know that the task was impossible". And the target was missed -- but by only 9 months and 26 days. The potential for application of new ideas and the power of public health caused many to alter their own career directions and, for this, the field of infectious disease prevention profited enormously. Mary Lou Clements was one whose life and career were shaped by that program. Her inspiration and contributions in the field of vaccines are celebrated with this lecture.

For me, Mary Lou was a colleague, a friend, a leader and a creator. Our first meeting was early in 1975. She had just joined WHO and was en route to the Eradication Program in India. She came highly recommended by faculty of the London School where she had just received her Diploma in Tropical Medicine; this was subsequent to 3 years of internal medicine residency.

The 1974-75 smallpox year proved ultimately, to be the critical one for the program. Only 4 countries remained endemic – India, Pakistan, Bangladesh, and Ethiopia. India was, far and away, the most formidable. Major epidemics were raging across northern India. In 1974, 188,000 cases had been reported–perhaps 800,000 had actually occurred; 130,000 local staff were engaged in search and containment. We were desperate for senior staff. The time was critical – full activity had to be sustained despite unbearable summer temperatures, primitive accommodations and dawn to dusk work. Some questioned the feasibility of a woman being able to provide leadership at this time in a country with an all male hierarchy. ML was unfazed but feisty, as always. Her energy, friendly good humor, and ready willingness to work long hours under impossibly difficult conditions were inspirational. On August 15, 1975 Prime Minister Indira Ghandi announced that three months had passed without a known case. Certification would require 2 more years. ML continued throughout this period and subsequently arrived in Baltimore just in time to enroll as an MPH student. Her primary interests in immunization and

infectious disease prevention continued as she worked with Mike Levine at Maryland for 6 years before returning to Hopkins in 1985 as Director of a new Hopkins University Center of Immunization Research. She compiled a remarkable record of accomplishment as she built an internationally distinguished program.

Applicable lessons from the program

I was asked specifically, to take up two subjects in this lecture: 1) lessons from the smallpox program and 2) prospects for the eradication of other human diseases. Many illustrative lessons derived from the smallpox program. Much has been written about the importance of continuing research and dialogue between the field and the laboratory; of the need for understanding, involvement and support from village worker level to highest authorities; of the potential of enthusiastic, young staff; of the importance of management and quality control; and the critical need for sustained support by international agencies and other donors.

But let me take up the question of two specific components that I believe were pivotal in the program. One was the surveillance-containment strategy, an epidemiological approach to disease control and elimination, and the second, the provision of a reliable and stable single dose vaccine. The potential applicability of each merits serious consideration as one weighs various eradication options.

Surveillance – containment

To understand the anatomy of the smallpox eradication program, there is need to understand some elements of its history.

SLIDE 2 A token WHO smallpox eradication effort first began in 1959 at the instigation of the Soviet Union and the approval of the World Health Assembly. However, few resources were provided, voluntary donations were scant – its headquarters staff consisted of one medical officer.

After 7 years and continuing complaints by several countries that more was not being done, the Assembly asked that Director General Candau prepare a comprehensive 10 year eradication plan, including estimated costs. The report was to be discussed and voted on at the 1966 Assembly. If the report was rejected, smallpox eradication would be abandoned. Actually, such an outcome was not unwelcome to Candau. At the time, virtually all possible resources and efforts of WHO were consumed by the decade-old malaria eradication effort. It was failing. Candau had no confidence that smallpox eradication would fare better. He was reasonably confident, however, that the delegates would abandon the smallpox initiative when they realized that substantially more financial resources would be needed and that each country would have to increase its financial contribution. As it turned out, the Assembly, after 3 days of debate, approved the plan but by a margin of only 2 votes.

SLIDE 3 Candau's report called for a two part program. First was a vaccination campaign intended to reach 80% vaccination immunity in the population. It called for use of the comparatively new freeze-dried vaccine and stipulated that it must meet international standards. Second –and to be undertaken at the same time-- was the establishment of a surveillance program. In brief, it called for obtaining a

weekly report of smallpox cases from all health units and, in response, a "two or three day intensive mass program of vaccination in the immediate area".

Reporting of cases in the 1960s was considered to be so incomplete as to be worthless – so stated a 1964 Expert Committee. Later studies were to show that substantially less than 1% of cases were being reported in 1966. Epidemiological information was minimal. In endemic areas, health authorities responded to outbreaks utilizing such vaccine as they had – most of which was sub-standard. Success was measured in terms of the number of vaccinations performed.

SLIDE 4 The concept of disease "surveillance and containment" was an important one. As you may recall, it was first introduced at CDC by Alex Langmuir after his arrival in 1949. It was first applied to coping with malaria and in 1955, to poliomyelitis when the Cutter poliovaccine catastrophe occurred. Thereafter, surveillance was progressively expanded to include other infectious diseases, beginning with hepatitis and influenza. The principal elements were the systematic weekly collection of reports of cases, epidemiological analyses, and reports to responsible health officials for action. My position during the 5 years preceding assignment to WHO had been as Director of Alex's Surveillance Section at CDC. In February 1966, I was asked to come to Geneva for a week to work with WHO staff in drafting the Director General's report for the World Health Assembly. That surveillance and containment was specified as a uniquely new and significant component was no accident.

Eastern Nigeria provided the first demonstration after the intensified eradication program began that the surveillance-containment strategy could be more efficacious than expected. Bill Foege with local Nigerian staff found that smallpox was much less contagious than many believed. Comparatively limited containment measures to contain reported outbreaks could dramatically hasten smallpox elimination over a large geographic area. This was confirmed about the same time in field studies in Pakistan by Tom Mack and a group from the University of Maryland. Supportive studies in India followed soon after.

Surveillance data served to monitor progress in the program, to identify groups or areas at special risk, to focus efforts of the vaccination program, to redirect strategies. It demonstrated its value where ever it was used. As we were to discover, however, traditional health authorities regularly resisted diverting even a few staff from mass vaccination to work in small containment teams.

Eventually, we adopted the slogan "Target Zero" for the program hoping to shift attention to progress in reducing the numbers of cases rather than progress in vaccinating ever larger numbers. For this, we even got some help from Snoopy with the help of Charley Schulz. SLIDE 5. To our surprise, a remarkable number of countries became smallpox free even before a functional surveillance-containment program could be established. Provision of potent, stable vaccine was what was needed. Whatever the case, the surveillance containment programs proved to be invaluable in certification activities to document that at least two years had elapsed without cases.

Smallpox vaccine

The critical role of potent and stable vaccine has largely been overlooked. Many, including myself, have cited the efficacy of surveillance-containment as being the critical element in transforming control efforts into a feasible eradication campaign. Surveillance-containment did play an important role. However, as I have reviewed the evolution of the program, I realize that, even more important, was the provision of ample supplies of a fully antigenic, heat-stable vaccine. Smallpox vaccine, as you know, has a long history dating back more than 200 years. It has been accepted as an effective preventative measure from the time of its discovery; its use steadily spread around the world. Effective, widespread use was limited, however, due to its loss of potency in ambient temperatures. In the 1950s, a practical solution to the problem was found -- the vital development that made eradication a plausible reality.

A very brief history. Smallpox vaccine, as you will recall, was our first vaccine and the stimulus for Pasteur and others to develop other vaccines. It was in 1796 that Edward Jenner took pustular material from a cowpox lesion on the hand of milkmaid Sarah Nelms and scratched it into the arm of 8 year old Jimmy Phipps. Six weeks later, he inoculated Phipps with smallpox virus. Phipps was protected. The cowpox virus or some variant of it was called vaccinia. Jenner showed that pustular material from a vaccination pustule could be transferred to others who, in turn, would be protected. For the next 70 years, protection was effected primarily by arm-to-arm transfer of the virus. Unfortunately, syphilis and hepatitis B as well were occasionally transmitted with the virus.

SLIDE 6 LIQUID VACCINE In the 1860s, scientists demonstrated that it was possible to grow the vaccinia virus on the flank of a calf and distribute it in containers. The vaccine virus was viable for only a matter of days at ambient temperatures. But smallpox was such a major problem that production centers were set-up in many cities, including some in developing countries– the manufacturing facilities consisting of little more than a stable and a cow. In many areas, the vaccine was put in capillary tubes; in some, the cows were walked from house to house by the vaccinator. Such remained the practice until methods for drying the vaccine pulp came into use during the 20th century.

SLIDE 7 MAP 1900 World-wide except for Sweden and Australia

SLIDE 8 MAP 1958 Europe, North Africa—smallpox-free despite use of a liquid vaccine

SLIDE 9 LESLIE COLLIER – Developed the methods for commercial production for a stable vaccine which remained potent for at least 3 months at 37 degrees C.

SLIDE 10 Vaccine crisis See slide

We were concerned about vaccine quality but laboratories in Canada and the Netherlands volunteered to test samples of vaccine. As we soon discovered, most of the vaccine was grossly unsatisfactory; half the lots were of low potency; some contained no detectable virus at all; and many had large numbers of bacteria. Russian, U.S. and French vaccines were satisfactory but, otherwise, not more than 10% of the vaccine in used in endemic countries met acceptable standards.

It took 3 years before sufficient vaccine for all programs became available.

This was achieved as quickly as it was because of the use of a remarkable new device for vaccination called the bifurcated needle invented in 1964 by a Wyeth scientist, Ben Rubin.

SLIDE 11 BIFurcated needle From the time of the first vaccinations, vaccine had been inoculated by scratching or pressing vaccine through a drop of vaccine on the skin. In contrast, the bifurcated needle was dipped into the vaccine suspension; a very small amount was held by capillarity between the two prongs; 15 rapid punctures within a small area guaranteed a successful take. A 0.25 ml. vial of vaccine was required for 25 vaccinations using conventional methods. Use of the needle effectively quadrupled our vaccine supply and eased a serious shortage

SLIDE 12 MAP 1958 BEFORE THE initial GLOBAL PROGRAM REPEAT

SLIDE 13 MAP 1967 Smallpox free before the 1967 campaign began -- Most of Latin America, CHINA, Thailand, Burma, half of the countries in the CDC West and Central African program. No surveillance-containment utilized.

SLIDE 14 MAP 1970

CDC CENTRAL/ WEST AFRICA were free but also EAST Africa where we had not had the manpower or time to set up surveillance-containment.

SLIDE 15 MAP 1972 Africa is Free except Ethiopia and Botswanaajor campaigns in India, Pakistan, Bangladesh followed. Here the emphasis was primarily on case search and containment as a supplement to the routine reports from health units

SLIDE 16 ALI MAALIN –October 26 1977

The point to be made is that there were many health service resources in place than we had thought but this was obscured by the fact that liquid or comparatively impotent vaccine was being used. Once potent, heat-stable vaccine was available and began to be used by existing health staff, smallpox incidence dropped dramatically.

Prospects for the Eradication of Other Diseases

As we look to the future and the prospects for eradication of other diseases, it is difficult for me to forget the hostile climate toward the concept of eradication which prevailed during the late 1960s and 1970s. There were good reasons: an 11 year old collapsing malaria eradication effort had already expended 2 billion dollars; more than 600 WHO malaria posts and 27% of all funds at WHO's disposal were devoted to malaria. Three 3 years later, UNICEF and USAID withdrew all support. Confidence in WHO and international programs was at a low ebb. In this milieu, the success of the smallpox eradication program came as a stunning surprise. It came at a time when Rene Dubos and others asserted that it was untenable to believe that a single organism could be extracted from the complex ecological world in which it had evolved.

In September 1980, only 3 months after the declaration of smallpox eradication, a meeting was convened at the Fogarty Center with the theme: "What next do we eradicate?" Measles, tuberculosis, urban rabies, poverty, hunger, and others were suggested. Frank Fenner and I provided the opening presentation. It was difficult not to join in the wave of ebullient optimism that was palpable at the meeting. The global eradication of man's most devastating pestilence had been achieved in just 10 years and at a total cost in international assistance of less than $100 million ($300 million in today's dollars); a disease that infected 10 million people each year and killing 2 million was no more; WHO had demonstrated its worth in bringing the nations of the world together in common cause. More than 700

international staff had experienced an appreciation of how much could be achieved with how little, given dedication, imagination and persistence. What next, indeed!

For those of us who had struggled personally with the array of challenges that had been faced – and, indeed, instances when a fatal setback appeared imminent. We succeeded but just barely. And yet this disease was intrinsically easier than it would be for any other entity. We had been combatting a disease that was greatly feared by all, that was well-known and recognized by villagers, that had no sub-clinical cases to silently spread infection. Moreover, it was not very contagious -- one patient seldom infected more than 2 to 4 others. Our principal weapon was an extremely inexpensive vaccine costing 2 cents per dose, that protected for decades with a single, simple inoculation, that could withstand 37° C. temperatures for at least a month and that produced a visible pustule if vaccination was successful.

Civil conflicts had presented serious problems and personal risk. Civil wars occurred in Nigeria, Pakistan, Zaire, Sudan, and Ethiopia. Floods and famines regularly produced hundreds of thousands of refugees and consequent spread of smallpox. Several specific instances are still fresh in my mind when major, all but fatal problems were averted by fortuitous circumstances beyond our control such as changes in governments. Smallpox eradication succeeded but just barely.

At the first eradication meeting, Fenner and I stated *"...there is no other disease which possesses so many characteristics favorable to eradication or for which* we now have available, effective, simple and inexpensive measures for prevention or treatment".

Eight years later, in 1988, at the Talloires Conference, a program for polio eradication was being ardently advocated. Reluctantly, I accepted to join in the proposal but only on condition that a vigorous research program be supported to develop a far more antigenic and heat-stable vaccine. That was agreed to by both WHO and UNICEF as global polio eradication began. Nothing was subsequently done to make that a reality.

Meanwhile, as smallpox eradication was being certified, many former staff joined a new WHO campaign, the "Expanded Program of Immunization". This had been launched in 1974 during the course of the smallpox eradication program as we looked beyond the immediate horizons to using approaches and techniques from smallpox in the administration of other vaccines. Initially, these included measles and polio along with DTP (diphtheria, tetanus, pertussis) vaccine and BCG. Its remarkable success has hopefully laid to rest the regrettable belief that funds for public health programs can only be raised under the banner of eradication.

Finally, a belated salute to the two individuals most responsible for the pivotal contributions: Leslie Collier, for perfecting the methods needed for making a commercial-scale, potent freeze-dried vaccine to Alex Langmuir who was the creator of the concept of surveillance-containment, and to the 780 international staff from some 72 countries who did the impossible. Among them were ML Clements and indeed, a number who are here today at this meeting.

The Clements-Mann Lecture

Eradication of Disease through Vaccination

35th Anniversary of the last case of smallpox

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April 22, 2013

1

Smallpox eradication – at birth

- 1959 USSR proposes global smallpox eradication
- 1960-1966
  - Budget – $160,000 per year (average)
  - One medical officer in Geneva; 4 assigned to contries
- 1965 Director-General to prepare 10 year plan

2

Program strategy

Director General's Report to the World Health Assembly –May, 1966

- Vaccination
  - Target: 80% of population
  - Vaccine
    - Freeze-dried, stable for 30 days at 37° C.
    - Quality control by WHO standards
- Surveillance
  - To begin at the same time as vaccination program
  - Weekly case reports from all health centers
  - Containment of outbreaks to the extent possible

3

Surveillance-containment

- Concept of Surveillance – Alex Langmuir, 1949
  - Inspiration – Wm. Farr, U.K. Registrar General's Office
- Application – U.S. malaria, polio, measles, hepatitis
- Application – Global program
  - 1966 Bill Foege and CDC team in Eastern Nigeria
  - 1966-67 Tom Mack, et al in Pakistan
  - 1967 Rao in Madras, India
  - 1967 Morris in Brazil

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5

"Liquid" vaccine

- Vaccine pulp – beginning material
  - Calf, sheep, water buffalo
    - Shaved, scarified, vaccinia suspension applied
    - Sacrificed at 5 to 7 days; lymph scraped off
- Liquid vaccine
  - Put in capillary tubes and sealed
  - Stability limited to a few days
  - Universally used from 1860s until replaced by dried vaccine nearly a century later
- Early dried vaccine –1920-1970
  - France for its colonies or former colonies

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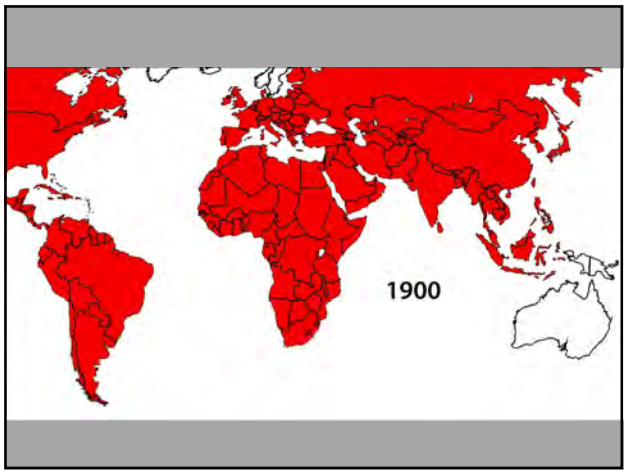

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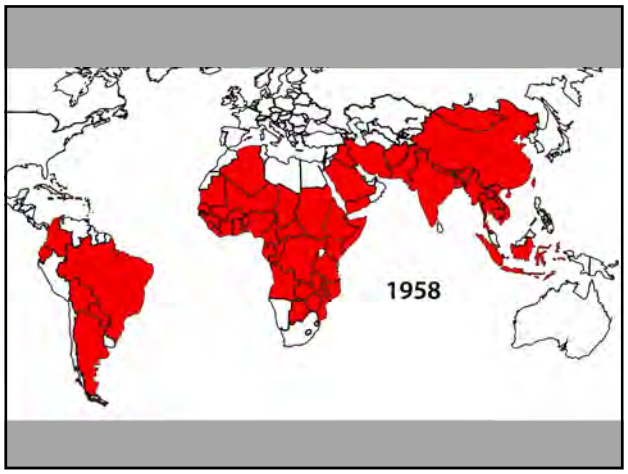

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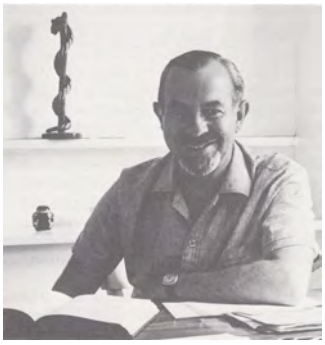
Dr. Leslie Collier
Lister Institute, U.K.

Developed a practical industrial method for freeze-drying vaccine and designed the necessary equipment

UNICEF furnished equipment
WHO began vaccine testing and training in 1968.



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The Freeze-dried vaccine crisis 1967

- Quantity needed per year -- ~ 350 million doses
  - U.S. and USSR –committed to 75 million doses
  - Balance expected from 59 active national producers
- International testing labs – Netherlands, Canada
  - Approximately 10% of vaccine in use met standards
- Production manual written – 22 labs visited
  - By 1972, 41 labs producing potent and stable vaccine

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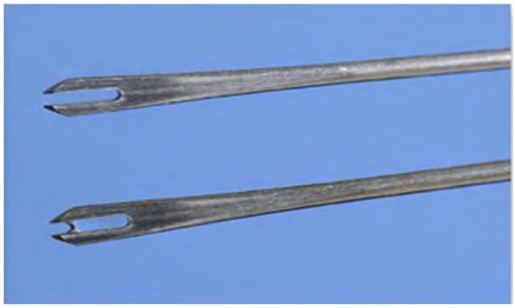

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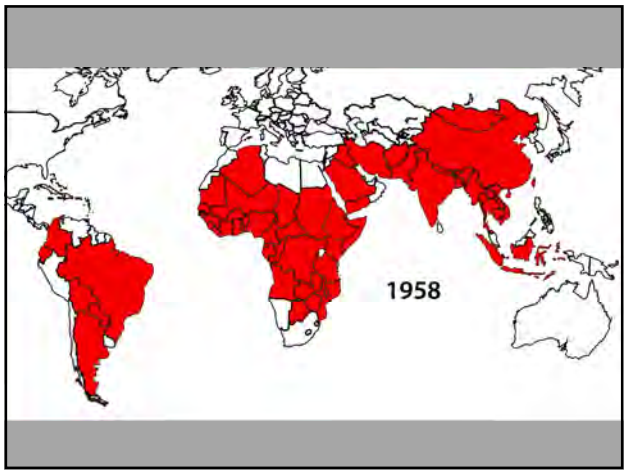

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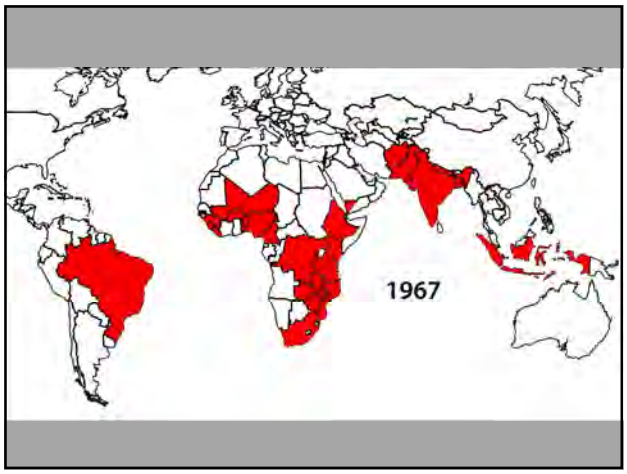

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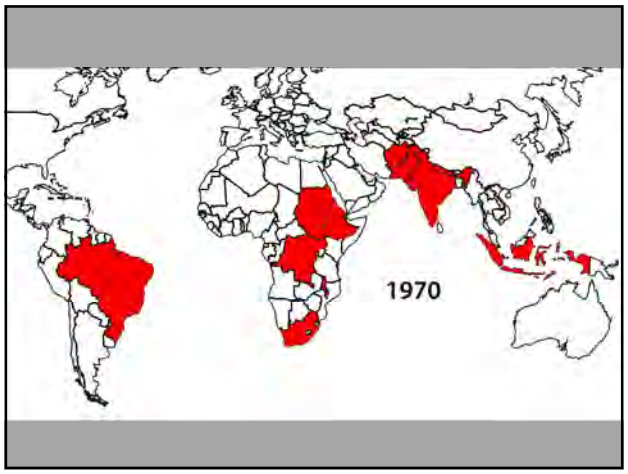

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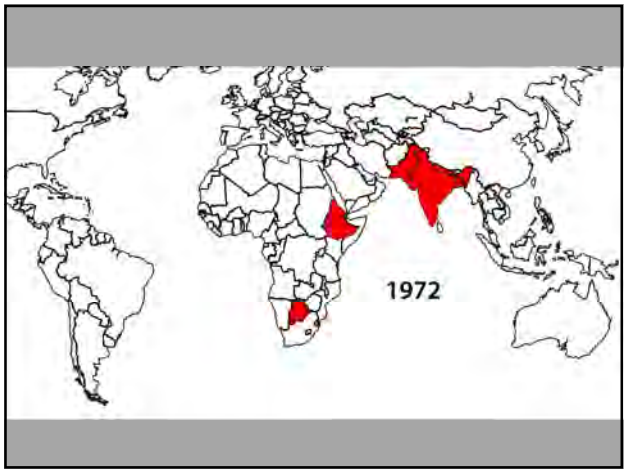

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Ali Maalin - 26 October 1977

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