SMALLPOX – VIROLOGICAL PROBLEMS (1)
NICD – DEC. 1966 INDIA

Privileged and honored to speak to you tonite on the subject of smallpox, a subject of deep interest to us all.

~~My concern for the past 11 years has been principally for the virus diseases and other disease entities for which we have immunizing agents. My career was inaugurated~~ at the C-D-C – in Atlanta ~~by the Cutter vaccine incident in 1955 ( ) and then oral poliovaccine testing and problems followed by measles vaccine testing and application have followed in this brief span.~~ 4 yrs ago ~~With measles vaccine safely launched, we turned our attention, in part, to smallpox vaccine, the oldest of immunizing agents, with the result, as you know, that now I am no longer a practicing epidemiologist, an amateur virologist but more correctly, I suppose, a professional administrator.~~

I am ~~doubly~~ particularly pleased to ~~be with you tonite for~~ talk ~~with~~ before a distinguished group of microbiologists for you must know, in preface, that I do not qualify myself as a ~~microbi~~ virologist but as an epidemiologist with an interest but not an expertise in virology. The importance of virology per se to ~~the epidemiologist~~ epidemiology and, conversely, of ~~the~~ epidemiology to virology is all too frequently forgotten. Often each works on his separate problems with all too little interchange of ideas. My great friend and mentor, Dr. Karl Meyer of the Hooper Foundation and now Prof. Emeritus of the U. of Cal. always insisted that there really was only one way to do good epidemiology & good virology. ~~Take your~~ This was to assess your problems in the field, refer them to the laboratory, take them back to the field, etc. At the C-D-C – in Atlanta where I was privileged to work for the past 11 years, ~~I can only say that our most productive findings derived from this approach.~~ this was a basic ~~principle of~~ tenant of our whole philosophy of work and accounts, I believe, in major portion for what success we have realized. ~~The fact that Dr. Meyer's guiding spirit accounts for the development of~~

~~CDC may~~

This evening, therefore, I should like to talk briefly about smallpox and its virological problems primarily from the vantage point of an epidemiologist.

The topic of Smallpox – in 1966 a resurgence of interest and concern.

1966 W-H-A – voted money, for the first time, $\$2.4 \times 10^6$ to assist the various countries in eradication and produced a 10 year intensive program. Voluntary contrib. and Bilateral assistance was also sought in addition.

As you may know, smallpox, once world-wide it was) in South America confined, to Brazil c̄ scattered cases only in ~~neighboring~~ bordering areas to Africa south of the Sahara and to 6 countries in Asia ~~Afghan, Nepal, Pakistan, India~~ Burma and Indonesia, but almost 75% of the total cases occur in the Asian countries, the majority of these are of India.

Thro vacc. programs vast areas of the world have become free of the disease.

Europe, N.A., C.A., most of S.A., North Africa, Middle Eastern countries, Japan, mainland China, Taiwan, P.I., Viet Nam, Cambodia, Laos, Thailand and this year Burma nearly so. ~~Many of these countries c less advanced~~ A majority of these countries have neither adequately developed health services, ~~trained~~ few trained personnel, and limited expertise, ~~less well developed health services, etc. than may be found in India.~~ Quite clearly the job can be done.

in 1967 Programs ~~this year~~ to be launched in Brazil and neighboring countries, 23 countries in Africa, and programs are to be stepped up in several countries in Asia. The response to the W.H. Assembly's request has been truly gratifying. USSR has donated 75 × 10⁶ doses of vaccine to WHO and is expected to continue providing vaccine to a number of Asian countries, US has expanded help to W. + C. Africa ~~too~~ ~~...~~ Vaccine has been offered by additional donor countries.

All of this puts a new focus and interest in smallpox and suddenly makes us all more acutely aware of the very great deal we know and don't know. In fact, as Dr. Murthy noted to me last week, we really know more about polio and measles for example, diseases for which virological techniques only recently intro. than for smallpox – for which viral techniques have been known for a long time.

Story of additivity – 3 virologists – Benenson, Smadel, Warren – one ?, one Na⁺ good, one Na⁺ no good

But ~~first~~ let me speak elementary on the subject of vaccination

Simplest form – the application of a quantum of vaccinia virus ~~(dermally adapted) sufficient to~~ into the epidermal layers of the skin in sufficient quantity to ~~induce~~ permit growth; a lesion is produced and a C.F. HI + Neut AB response is obtained ~~of C.F., H.I. + Neut AB~~

Objective – prevent smallpox.

Most people assume this is a perfectly straight forward ~~situation~~ interaction phenomenon – well described + well understood – we don't have to go far before we realize how pitifully little we really know.

~~1) Vaccine efficacy – never been controlled study of smallpox vaccine~~

To begin at the last portion of this definition —

1. Efficacy of vaccine —

Nobody been a controlled study of vaccination — efficacy must be guessed at in retrospect. When intro. — control trial unknown; later, ethically couldn't do.

WHO Expert Com. (really Dixon) — ~~p~~ 1° vaccination

at 1 yr.	99.9 %
at 3 yr.	99.5 %
at 10 yrs.	87.5 %
at 20 yrs.	50 %

if so, one of best vaccines — prob. only slightly less effective than Y.F. vaccine.

Of cases observed by Dr. Rao in Madras and elsewhere in India, comp. few c vaccination scars who have spox. Emphasize vaccination scars — ? how often can one get a "vaccination-like" scar c the rotary lancet + 2° infection.

Further — as to be pointed out — many strains of vaccinia — hard to know how far one can extrapolate in a situation where various strains used.

2. Antibody response —

Following vaccination — ↑ titer of C.F., H.I. + Neut. Ab.

C.F. — transient response — say no more.

1° response — H.I. > Neut. (in our lab.) esp. in adults.

~~p~~ a few yrs. H.I. Antibody fades + Neut. Ab persists.

(As groups in Madras showed: If HI was high, neut was high — but may have good neut in absence of detectable HI titer).

Revac. — ~~Like~~ H.I. + Neut. tend to behave differently — may have little or no HI. but good neut response. In fact, unlike measles vac. ( ), spox produces a remarkable booster response. Demonstrated in those 20 yrs.+ vac. c little or no Ab. (different as night + day

Concl.:

1) HI ≠ Neut c spox (contrary to such as measles) — using HI only studies need to critically evaluated.

~~2) [illegible]~~

2) Raises ? of desirability of vac. + revac. for long lasting immunity (return to efficacy studies — ? those vac. vs. those vac. + revac.)

Reverted to use — study of ~~cell~~ meaning of neut Ab c protection — see polio, measles, influenza, other viral agents — YES. If shown, permit ~~comparative studies of various strains, elevate of protection~~, etc.

3. <u>Lesion</u> -

1° lesion - comparatively straightforward problem. Intravenous vaccinia.

Revac. - a problem - ~~[illegible]~~ ; is a problem to appraise - not clear cut as 1°

Attempted correlation of neut. AB + existence of lesion - frankly, not too successful. (Tissue AB vs. circulating AB - perhaps not surprising there is a problem).

Indian, c̄ sharp neut AB ↑ and no cutaneous lesion - even a few with lesions and no ↑ in AB. Cross-correlated in various ways but to little avail.

Appears that greater amt. of virus needed for revac. than 1° vac. - ? how much more.

Again, most studies focus on cutaneous response - do this right?

Must know more re: neut. AB.

4. <u>Application</u> -

How many insertions? Here again, much controversy in Revacs. [argued that more tissue in which virus grows, the better the protection]

1. At CDC. - study of 1 and 2 vaccinations c̄ MP c̄ high titer vaccine could detect no difference ~~[illegible]~~ in AB + little difference in cutaneous response.

2. Madras studies in 1960 showed

<u>Years</u>	<u>90% neut.</u>	<u>80% neut.</u>
1	65	90
2	73	88
3	71	86
4	71	85

3. <u>Rao</u>

	<u>No.</u>	<u>Confluent cases (%)</u>	Overall <u>C.F.R.</u> (%)
1	61	11.5	0
2	184	23.9	3.7
3	51	10.5	2.0
4	246	14.2	0.8

Suggests some differences. -

May be a resolution - by 2 vaccinations 2x amt. of virus. If vaccine of less than optimum potency, may be useful.

note 1×10^8/ml. may $< 1 \times 10^6$

in other words 1/100 the amt. of vaccine desired.

Threshold.

Vaccinia
5. Virus

a. Multiplicity of Strains—

From Jenner's time, strain has been propogated on a whole variety of animals, in eggs, tissue culture, etc. Vaccine production now of a "seed" virus; recent concept. As anyone aware, virus changes progressively with continued passage on one or another medium. In the '30's Thomas Rivers, for example, adapted vaccinia to growth on egg + with prog. passage, got attenuation - so much, in fact, it was ineffective as an immunizing agent. Dutch strain obviously highly encephalitogenic.

At present, work only begun to purify and characterize the multitude of strains in existence, and to evaluate their safety and their efficacy.

~~optimal~~ b. Production –

Science and an art. No 2 producers actually produce vaccine in an identical manner. While at CDC, sent virologist to 2 prod. labs. – each different & rather curious practices at dif. stages. Query – always done it this way – not about to change. Titers $> 1 \times 10^9$/ml. consistently – dictated

At same time – many labs. & difficulty achieving this titer.

~~optimal~~ c. Standards – minimum stds. developed & a great help. ~~lyophil~~

~~Principle on~~ ~~lyophil.~~ freeze dried vaccine.

~~lyophil. vaccine~~ ~~37°C. g. 30 days < 1.0 log~~

Titer of $> 1 \times 10^8$ = @ 1/10 this, a sl. decline in efficacy progressively ↑ – extra vaccine for safety.

37°C g 30 days – < 1 log decrease.

Moisture content < 1% –

Japan Med. Sci Biol. 18: 249-265, 1965

	Moisture (%)	after 6 months at 45°C. No trypsin	Trypsin
5% peptone dried	1.1	6.8	7.5
	2.0	6.5	7.3
	3.0	6.7	8.0
8% glutamate	1.1	7.2	7.7
	3.2	6.8	7.8
	4.3	6.4	7.5

? meaning in terms of "takes"

d. Method of production –

i) Only vaccine in which standards permit bacteria in final product. spec. < 500 orgs./ml.

ii) ? Why not use new techniques – e.g. tissue culture. – excellent idea but,

a) ? what tissue cultures all live – chick embryo tc. (used in part in a way) in USA – dog kidney approved – now under heavy fire oncogenic viruses – problem.

b) Stability + potency – ↓ stable ; many few & switch from the tried and true to a new live – ? what is its field efficacy.

I have raised tonight & am sure more questions than I have answered. If you now have the sense that we have about as much specific information, with respect to smallpox, as the clinician who diagnosed typhoid by standing at the entry to the room and ~~smelling~~ sniffing & detected a "watery" odor — then I feel that I & my team may have made a point.

I submit however that there is, ~~however~~, a key — a single series of studies which could do more to clarify this process than any other high powered studies involving electron microscopy, RNA ~~or DNA~~ analysis or what have you.

If we could verify that in this disease, that neut. AB is highly significantly correlated with protection (as it is in most other virus diseases), a whole new realm of studies would become possible —

Strains could be compared re: efficacy
Duration of protection could be assessed
The ? of multiple vaccine applications could be appraised
The titers requisite for successful revac. could, for the first time, be objectively determined.
Rel. levels of com. protection requisite to terminate transmission could be appraised.
The question of whether 1 or 2 separate races should be employed for protection could be answered.

~~The problem is one major~~

As an epidemiologist, I refer to you this problem. ~~It is a study pot~~ There are other problems no ~~doubt~~ question only some of which I have touched upon. While the herpesviruses, rubella, varicella, the oncogenic viruses, etc. appear to represent bright new vistas, I submit to you this antigen, the variola virus, ~~which~~, contrary to what you may have thought, is really the prize of them all.