BBS 2711
Virology

Virus Vaccines

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Virus Vaccines

First vaccine developed by Jenner in late 1700's against smallpox virus

Smallpox:

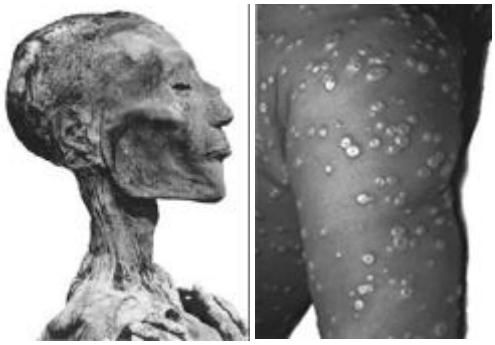
has been known for many centuries.

The characteristic "pocks" produced by variola (smallpox) virus gave their name to all forms of infectious disease:

"a dose of the pox".

Has even been used as a form of abuse

“a pox on your house!”



Smallpox:

first appeared in China and the Far East at least 2000 years ago.

The Pharaoh Ramses V died of smallpox in 1157 B.C.

Smallpox:

reached Europe in 710 A.D. and was transferred to America by Hernando Cortez in 1520.
3,500,000 Aztecs died in the next 2 years.

Smallpox:

reached plague proportions in the cities of 18th century Europe and was a highly feared scourge.

Smallpox:

killed five reigning European monarchs during the 18th century.

Smallpox:

has now been eradicated.
The last naturally occurring outbreak was in Somalia on 26th October 1977.

Birth of Vaccination

On 14th May 1796, **Edward Jenner** used cowpox-infected material obtained from the hand of Sarah Nemes, a milkmaid from his home village of Berkley in Gloucestershire to successfully vaccinate 8 year old James Phipps.

On 1st July 1796, Jenner challenged the boy by deliberately inoculating him with material from a real case of smallpox !
He did not become infected !!!

"Modern" vaccines

INACTIVATED under conditions that retain immunogenic properties

ATTENUATED virulent organism weakened by growth in unnatural host

- **immunity to reinfection usually life-long**
- **mostly IgG/IgA neutralization**

For vaccination, principle objective is to elicit antibodies of correct class - then CMI

object is to

PROTECT AGAINST DISEASE not PREVENT INFECTION

What is required of an immune response to vaccine candidates for protection?

not same for all diseases
e.g. systemic versus mucosal infections

- activation of antigen-presenting cells

- activation of both T and B cells - memory on challenge

- generation of Th and Tc cells to multiple epitopes
MHC polymorphism

- persistence of antigen
dendritic follicular cells in lymphoid tissue

- sub-clinical infection extremely effective
induces life-long immunity

Immune Response to Virus Infection

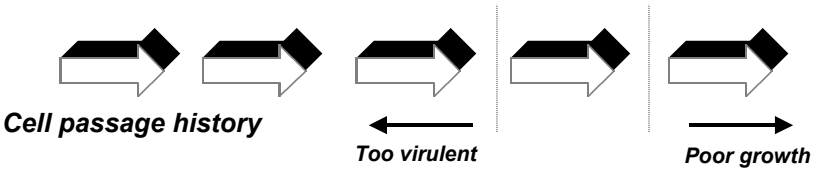
Both antibody and CMI responses normally involved in protection

antibody targets virion and the infected cell (with complement)

CMI (cytotoxic T cells) target the infected cell

Live vaccines are derived empirically by serial passage in cultured cells of non-human origin

monitored for
1. loss of virulence
2. retention of growth potential



phenotypic characters defining attenuation:
- temperature sensitivity
- small plaque morphology

problem of reversion

- "genetic surgery" is possible
e.g. poliovirus

- some inactivated vaccines also effective

e.g. rabies - 100% fatal to 100% preventable

- valid reasons for not producing live vaccines

- inability to grow in TC

- unusual virulence

- oncogenicity

- ability to establish persistence

There are three basic types of vaccine:

1) Sub-unit Vaccines

The newest type; completely safe, except for rare adverse reactions. Unfortunately, they also tend to be the least effective.

Problems:

(Relatively) poor antigenicity (especially short peptides)
Vaccine delivery (carriers/adjuvants needed)

a) Synthetic Vaccines

Not very effective. Great potential. None currently in use.

b) Recombinant Vaccines

Better than above - some success:
HBV - now produced in yeast.

c) Virus Vectors

The idea is to utilize a well-understood, attenuated virus to present antigens to immune system, most effective approach e.g:

- **Vaccinia Virus**
- **Attenuated polioviruses**
- **Retroviruses (gene therapy)**

Hard to produce, safe???, none successful yet - lots of trials underway.

2) Inactivated Vaccines

Method of production - exposure to denaturing agent, heat, phenol - results in loss of infectivity without loss of antigenicity.

Advantages:

- **Better immunogens than synthetic. Stable.**
- **Little or no risk (if properly inactivated)**

Disadvantages:

- **Not possible for all viruses; denaturation may lead to loss of antigenicity, e.g. measles, RSV**
- **Not as effective at preventing infection as live viruses (mucosal immunity - IgA).**
- **May not protect for a long period ?**

3) Live Virus Vaccines

The use of virus with reduced pathogenicity to provide immune response without disease.

- **naturally occurring virus (e.g. cowpox) or**
- **attenuated (oral poliovirus vaccine, OPV).**

Advantages:

- **Good immunogens**
- **Induce long-lived, appropriate immunity**

Disadvantages:

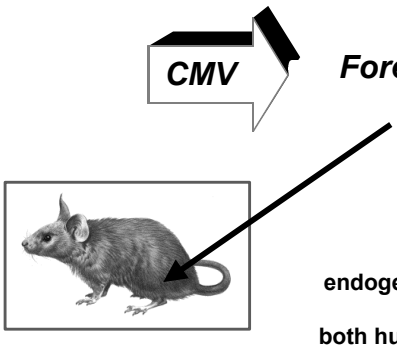
- **Unstable: biochemically (live virus) and genetically (reversion to virulence)- infant shedding of polio virus.**
- **Not possible to produce in all cases - trial and error black box !**
- **Contamination possible (SV40)**
- **Inappropriate vaccination e.g. immunocompromised hosts / rubella in pregnancy may lead to disease.**

The Future?

- **Synthetic peptides**
- **DNA vaccines**
- **Improved adjuvants, liposomes, ISCOMS etc**
- **Edible vaccines?**

Naked Nucleic Acid Vaccines

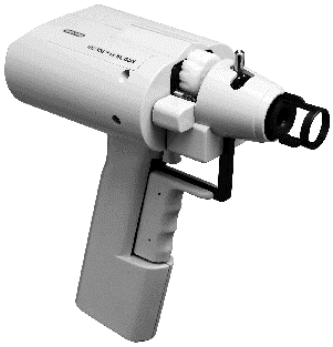
Direct injection of expression plasmids encoding foreign genes under the control of a strong promoter (usually the early CMV promoter)

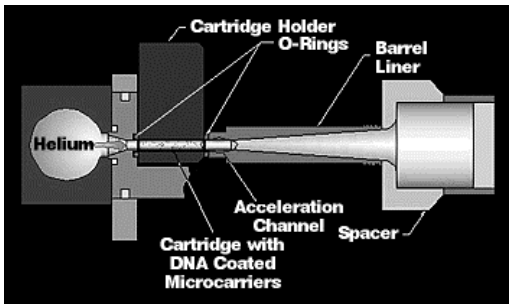


endogenous expression of foreign gene in skeletal muscle
both humoral and CMI responses elicited

Gene Gun delivery of plasmid vectors

Bombardment of exposed skin with DNA coated on gold particles provides improved uptake of plasmids and presentation of expressed antigen - involves local dendritic cells





Commercial development

POWDERJECT