CONTROL OF VIRUS DISEASES

FORTY-FIFTH SYMPOSIUM OF
THE SOCIETY FOR GENERAL MICROBIOLOGY
HELD AT
THE UNIVERSITY OF WARWICK
APRIL 1990

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EDITED BY

N. J. DIMMOCK, P. D. GRIFFITHS

AND C. R. MADELEY

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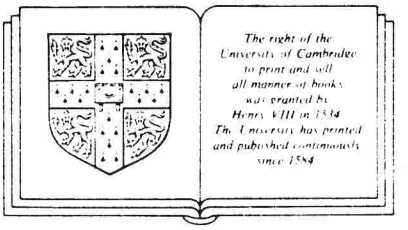

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EDITORS' PREFACE

The current AIDS pandemic has brought home only too clearly the realization that past successes in vaccination have more to do with serendipity than a real understanding of the basis of immune responses to virus infections. While we know that protection against infection requires activation of a particular part or parts of the immune system, each infection is unique and each must be understood before rational intervention is possible. Without such understanding, introduction of new vaccines is often a leap in the dark with sometimes unfortunate consequences of which the inactivated measles and respiratory syncytial virus vaccines are obvious examples. Study of infection is not a simple matter: animal model systems can be used but close parallels with the human infection are not always available. In the end, we must have detailed knowledge of the human immune responses, and this is only obtained with immense difficulty. Finally, even supposing that we have arrived at this advanced state of knowledge, we do not yet know how to stimulate specifically each part of the immune system. Much is being done to fill these gaps in our knowledge and to provide vaccines which are urgently needed.

The following chapters are based on a Symposium organized to address these formidable problems. It begins with an assessment of the effectiveness of current conventional vaccines and continues with a forward look at the ways in which the problems of immunization are being tackled. Presentation of antigen, new adjuvants, factors influencing the uptake of vaccine by the man or woman in the street, advantages and drawbacks of modern molecular technologies to immunization are amongst the topics covered by leading exponents in the field.

The second part of the book deals with chemotherapy, so successful against bacterial infections, but only rarely effective against viruses. Using empirical screening procedures, industry has been searching diligently for the past three decades for antivirals, yet today there is only one unequivocally effective compound (Acyclovir) on the market. Knowledge of viruses at the molecular level has been steadily increasing over this period and we now know that viruses are recalcitrant to chemotherapy because they have few gene products, and most of these are too similar to those of the cell to provide differential toxicity. However, unique viral functions, potential targets for chemotherapy, have been discovered and the recent explosion of knowledge about virus structure and virus–cell interactions at the molecular level, based primarily on recombinant DNA technology, has reinforced hopes of rational progress in chemotherapy. Again, the AIDS pandemic has brought unprecedented finance, manpower and determination to bear on solving the problems associated with HIV and these

efforts will have far-reaching beneficial consequences for all virus infections. This section of the volume starts with a discussion of the current philosophy and practice of chemotherapy and then examines a number of individual virus systems where progress is being made.

This book, the parent Symposium and discussions during the Meeting in April 1990 at the University of Warwick focus attention on a vitally important area of human disease. In particular, we hope it will be useful to the new generation of virologists and if it encourages them to help solve the problems of controlling virus infections we shall count it a success.

N. J. Dimmock
P. D. Griffiths
C. R. Madeley
April 1990

CONTENTS

PART I: IMMUNISATION

CONVENTIONAL VIRAL VACCINES AND THEIR INFLUENCE ON THE EPIDEMIOLOGY OF DISEASE

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There are some general principles that apply to most virus vaccines used in the prevention of human disease. Vaccination (or natural infection) does not always result in total immunity against a subsequent exposure to the wild virus. Even when vaccine-induced resistance does not totally block infection, but only serves to limit the multiplication of wild virus within the individual, it prevents spread to the target organs where the severe pathological damage occurs. Thus, wild poliovirus may replicate in the gut of a vaccinated person, but it will be prevented from invading the brain and spinal cord.

In many instances a number of susceptibles in a population may fail to be covered by vaccine, yet the herd immunity based on proper immunisation of a significant number of other susceptibles may serve to break the chain of transmission to a degree that wild virus no longer is able to sustain endemic circulation in the population.

Killed-virus vaccines prepared from whole virions generally elicit circulating antibody against the coat proteins of the virus. For some diseases, killed-virus vaccines or viral subunit vaccines are currently the only ones licensed.

Attenuated live-virus vaccines have the advantage of behaving like the natural infection in their effect on immunity. They multiply in the host and not only stimulate production of long-lasting humoral antibody but also induce cellular immunity and resistance at the portal of entry. However, some disadvantages, particularly that of genetic mutability, are associated with live attenuated vaccines.

Until recent years, virus strains suitable for live-virus vaccines were developed chiefly by selecting naturally attenuated strains or by cultivating the virus serially in various hosts and cell cultures in the hope of deriving an attenuated strain. The search for such strains is now being approached by laboratory manipulations aimed at specific genetic alterations in the virus. Newer vaccines and vaccine candidates (derived from deletion or other mutants, from reassortants, or from genetic recombinants) none the less must go through most of the same processes of development and demon-

stration of efficacy and safety – including examination of their epidemiological effects – that were requisite to the development of conventional viral vaccines.

One fact cannot be overemphasised. An effective vaccine does not protect against disease until it is administered at the proper time and in the proper dosage and potency to the proper target population. With the introduction of a new vaccine, there often follows not only a marked decrease in incidence of the target disease, but also a significant change in its epidemiology, brought about by the new age-distribution of susceptibles in the population. Some examples are described in this article, which is concerned with the conventional vaccines that have been used throughout the world.

HISTORY

As with history in general, the history of vaccines needs to be re-examined and updated. My task is to look back to see what has been successful. The present vaccines consist either of infectious, living, attenuated viruses or of non-infectious killed viruses or subviral antigens. When we look at the record, it is the live vaccines with which the greatest successes have been achieved in controlling diseases around the world. Examples are smallpox, yellow fever, poliomyelitis, measles, mumps, and rubella.

The chronological course of the development of vaccines for virus diseases of humans is shown in Table 1. One of the greatest triumphs of mankind has been the purposeful eradication of smallpox from the world's population. Almost 200 years ago, Jenner noted that cowpox conferred immunity against smallpox. This observation led him to inoculate material from the cowpox lesions as a means of protecting persons against smallpox, and the first successful vaccine came into use. More recent dramatic results of widespread vaccination can be seen in the rapid decreases, in the United States, of cases of four viral diseases that had previously been common in childhood (Fig. 1).

CURRENT ERA

The viral vaccines now in use are listed in Table 2. Those in the top section of the table are recommended for the general public, whereas those in the lower section are recommended only for special populations. However, there are some general principles that apply to most virus vaccines used in the prevention of human disease. Vaccination (or recovery from natural infection) does not always result in total immunity against a subsequent exposure to the wild virus. This situation holds true for diseases for which successful control measures are available, including polio, smallpox, influenza, rubella, measles, mumps, and adenovirus infections. But the replication of the wild virus, if it occurs, is markedly restricted. The restriction

Table 1. *Chronology of virus vaccines*

Year	Type of vaccine
1721	Variolation
1798	Smallpox attenuated
1885	Rabies attenuated and inactivated
1936	Yellow fever attenuated
1940s	Influenza inactivated (and later subviral)
1955	Poliomyelitis inactivated
1960	Poliomyelitis attenuated
1960s	Measles inactivated (no longer used)
	Measles attenuated
	Mumps attenuated
	Rubella attenuated
1970s	Japanese encephalitis inactivated
1980s	Japanese encephalitis attenuated
	Varicella attenuated
1982	Hepatitis B subviral particles
1986	Hepatitis B recombinant

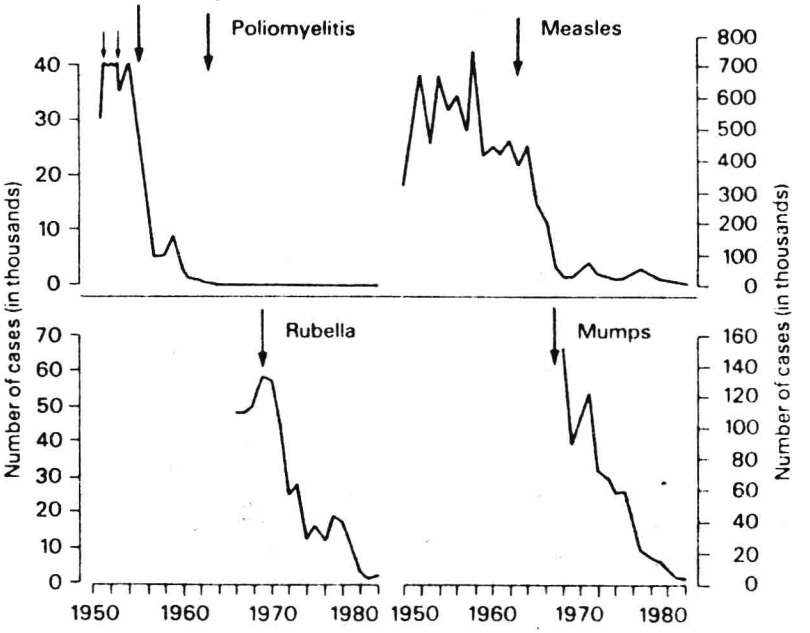

Fig. 1. Record of the decrease in cases of poliomyelitis, rubella, measles, and mumps in the USA following widespread administration of vaccines. Numbers of cases are indicated in thousands.

of replication thus not only can prevent spread of virus within the community but also can prevent, within the infected individual, spread of virus to target organs where the severe pathologic damage is done. (For example,

Table 2. *Principal vaccines used in prevention of virus diseases*

Disease	Source of vaccine	Vaccine virus	Route
Immunization recommended for everyone			
Poliomyelitis	Monkey kidney cells, human diploid cells	Live attenuated	Oral
		Killed	Subcutaneous
Measles	Chick embryo cells	Live attenuated	Subcutaneous
Mumps	Chick embryo cells	Live attenuated	Subcutaneous
Rubella	Human diploid cells	Live attenuated	Subcutaneous
Hepatitis type B	Purified HBsAg from human plasma	Killed, subunit	Subcutaneous
	Recombinant HBsAg from yeast	Subunit	Subcutaneous
Immunization recommended only under certain conditions (epidemics, exposure, travel, military)			
Smallpox	Lymph from calf or sheep	Live vaccinia	Intradermal
Yellow fever	Chick embryo	Live attenuated	Subcutaneous
Influenza	Chick embryo	Killed, subunit	Subcutaneous
Rabies	Human diploid cells	Killed	Subcutaneous
Adenovirus	Human diploid cells	Live attenuated	Oral
Japanese B encephalitis	Hamster kidney cells	Killed	Subcutaneous
Varicella	Human diploid cells	Live attenuated	Subcutaneous

polio and measles viruses may be prevented from invading the brain and spinal cord; rubella virus may be prevented from infecting the embryo.)

Killed-virus vaccines

Those prepared from whole virions generally stimulate the development of circulating antibody against the coat proteins of the virus, conferring some degree of resistance. For some diseases, killed-virus or subunit vaccines are currently the only ones licensed. However, some caveats are associated with them:

1. Since virulent strains often have been the ones chosen as source material for vaccine, extreme care is required in the manufacture of these vaccines to make certain that no residual live virulent virus is present in the vaccine.
2. The immunity conferred may be relatively short-lived, and therefore booster doses may be necessary. The use of killed-virus vaccines not only involves the logistical problem of repeatedly reaching the persons in need of immunisation but also has caused concern about the possible induction of hypersensitivity.
3. Sometimes protection conferred by parenteral administration of killed-virus vaccine is limited. In these instances, even when the vaccine stimulates circulating antibody (IgM, IgG) to satisfactory levels, local resistance (IgA) is not induced adequately at the natural portal of entry or the primary site of multiplication of the wild virus – for example, the nasopharynx for respiratory viruses, and the alimentary tract for poliovirus.

Attenuated live-virus vaccines

These have the advantage of behaving like the natural virus. They multiply in the host and tend to stimulate production of longer-lasting humoral antibody and also to induce cellular immunity and resistance at the portal of entry. However, some problems are associated with live attenuated vaccines:

1. There may be a risk that the vaccine virus reverts to greater virulence during its multiplication in the vaccinee. Although reversion of conventional vaccines has not proved to be a major problem in practice, its potential exists. Long-term monitoring of vaccine programmes should be required.
2. Unrecognised adventitious agents latently infecting the culture substrate (eggs, primary cell cultures) may enter the vaccine stocks. Viruses found in vaccines have included avian leukosis virus, simian papovavirus SV40, and simian cytomegalovirus. The problem of adventitious contaminants

has been circumvented through the use of pretested normal cells serially propagated in culture as substrates for cultivation of vaccine viruses. Vaccines prepared in such cultures have been in use for years and have been safely administered to many millions of persons.

3. The storage constraints and limited shelf-life of live attenuated vaccines present problems, but these can be overcome in some cases by extraordinary efforts to maintain the 'cold chain' of refrigeration even under difficult field conditions, and also by the use of viral stabilisers (e.g. molar $MgCl_2$ for polio vaccine).

SMALLPOX

Control of smallpox by deliberate infection with material from lesions of mild cases of the disease was practised for centuries. This process, called variolation, was dangerous but it decreased the disastrous effects of major epidemics, in some instances variolation reduced the case-fatality rate from 25% to 1%. Then Jenner introduced the first live attenuated vaccine in 1798. Almost two centuries later, WHO introduced a worldwide campaign to eradicate smallpox. Epidemiological features of the disease made it feasible to attempt total eradication. At that time, in 1967, there were 33 countries with endemic smallpox, 10 to 15 million cases per year. The programme has been a huge success, with the last naturally infected victim diagnosed in Somalia in 1977. A new concept of disease eradication by a co-ordinated global vaccination strategy came into being. Furthermore, with the eradication of the disease, it is no longer necessary to spend large sums and effort on a vaccination programme.

The following epidemiological features made smallpox amenable to total eradication, there was no known non-human reservoir; there was one stable serotype; there was an effective vaccine; since there were no subclinical cases, asymptomatic carriage of the virus did not occur; the patient's contacts could be readily identified, and thus specifically targeted control measures could be instituted quickly to interrupt the cycle of transmission.

In view of the current investigations of vaccinia virus as a vector for introducing immunising genes of other viruses into susceptible persons, a word of caution has been raised. Smallpox vaccination is associated with a definite, measurable risk. In the USA, the risk of death from all complications was 1 per million for primary vaccinees and 0.1 per million for revaccinees. For children under 1 year of age, the risk of death was 5 per million primary vaccinations. Among primary vaccinees, the combined incidence of post-vaccinal encephalitis and vaccinia necrosum was 3.8 per million in persons of all ages. Even in revaccinees, these two complications occurred, at a rate of 0.7 per million.

Since strict and effective barriers had been maintained against imported smallpox cases for many years, routine vaccination of children was discon-