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New Trends and Developments in Vaccines

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Preface

It was not too long ago that many physicians and biomedical scientists felt that the era of 'vaccines' for protecting mankind against infectious disease was coming to an end. During the 1940s and 50s the widespread use of newly developed antibiotics and antimicrobial chemotherapeutic agents suggested a new era in medicine, i.e. the control and eventual elimination of all infectious diseases, at least those caused by bacteria, by chemical means. The magic 'bullet' proposed by Paul Ehrlich in the early 1900s seemed to be the method of choice for controling infection. However, it is now quite evident that those high expectations were unwarranted. Although many acute infections, especially those caused by pyogenic cocci, have been controlled by antibiotics, it is quite evident that infectious diseases, even those caused by bacteria, still are a major problem. Thus, the old 'standby' of preventative vaccination is making a strong comeback, not only for viral but also for bacterial infections. However, except for a relatively small number of viral diseases and those bacterial diseases due to toxin elaborated by microorganisms rather than invasion and replication of the microbe *per se*, preventative vaccination still has not fulfilled the expectations of their proponents.

There has been a recent resurgence of interest concerning all aspects of vaccines, not only their preparation and administration, but also the nature and mechanism of the host immune response to the constituent microorganisms and their products. A number of recent symposia, conferences, and scientific sessions at national and international meetings have been devoted to the subject of vaccines. This volume is an outgrowth of an international meeting held in Brussels, Belgium under the sponsorship of the Robert S. First Co. At the Conference a number of presentations were made in attempts to answer some of the vital questions concerning the value of various vaccines for bacterial, viral, parasitic and fungal infections, as well as newer developments in this ares. Both fundamental and clinical aspects of vaccine development, use, and applications were discussed. A number of participants were then asked to contribute chapters to this volume. In addition other investigators actively participating in either development or use of newer vaccines for a variety of purposes were also asked to contribute to this volume. No attempt was made to cover completely every aspect of vaccines, either

historical or prospectives for the future. It is anticipated that further conferences as well as publications dealing with this rapidly re-emerging area of microbial immunology and preventative medicine will, within the next few years, permit the realization of many hopes by biomedical scientists that infectious diseases can be controlled by appropriate immunological 'engineering,' i.e. administration of effective and safe vaccines.

The editors are grateful to contributors to this volume who obviously gave of their time and effort in preparing manuscripts. The editors are also grateful to the staff of MTP Press for their forebearance and assistance. We also wish to acknowledge the excellent assistant of Ms. Leony Mills, Albert Einstein Medical Center, Philadelphia, Penna. for various editorial aspects in preparing this volume.

Herman Friedman
Alister Voller
January 1978

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1
Vaccines: general background and introduction

H. FRIEDMAN AND A. VOLLER

It has only been about a century since the definitive discovery that infectious diseases were caused by micro-organisms. At about the same time it was shown categorically that many of these infections could be prevented by administering properly prepared and utilized vaccines. Once such observations were accepted by the biomedical community, the pendulum swung from a general attitude of scepticism to the belief that it was necessary only to identify the appropriate micro-organism, prepare the corresponding vaccine, inject this material on to individuals and a wide variety of diseases could be prevented, ameliorated or cured.

Obviously this concept was quite simplistic, especially since the mechanism of the host–parasite relationship in terms of infectious agents was not completely understood, either at the end of the last century or even today. Vaccines *per se* are used to confer immunity by stimulating a complex series of events culminating in development of specific lymphoid cells and their products which can interact with the infectious agents. Thus the purpose of immunization is to stimulate a specific immunological response to a microbial agent or antigens, with the expectation that this will result in humoral factors (i.e., protective antibodies) in the blood or development of cell-mediated immunity. While such protection may diminish with time, sufficient residual immunity usually remains, so that the individual is expected to respond to future exposure to the same antigenic stimulus with a rapid return of the immune response, because of heightened reactivity of the antibody forming phagocytic and/or other cell classes within the immune system.

Presumably the concept of immunity to what are now known to be infectious diseases was understood by ancient civilizations many thousands of years ago, even though the cause or even nature of such diseases was not

known. It is usually assumed that modern 'vaccination' began with the observations and reports of Jenner at the end of the eighteenth century that smallpox could be prevented by first 'vaccinating' individuals with cowpox, similar to the natural situation in which milkmaids acquired cowpox in nature. However, it is acknowledged that such prevention of infection by exposing individuals to attenuated infectious agents was known at least a thousand years earlier. Apparently the Chinese were aware that smallpox could be prevented by exposure to mild cases. This information appears to have been brought back to Europe by travellers and adventurers such as Marco Polo. Nevertheless, it is conceded that the modern era of vaccination began only 100 years ago. The first 'golden era' of immunology developed rapidly at the end of the last century and the beginning of the present one, when immunity was first studied in terms of mechanisms whereby individuals can be made resistant to infections by administration of certain vaccines. It is now widely recognized that, after most infectious diseases, immunity is generally acquired and that similar forms of immunity may be induced by administration of appropriately prepared 'vaccines' derived from inactivated or live micro-organisms of modified (i.e., attenuated) disease producing potential. Thus the purpose of immunization, at least in terms of infectious diseases, is to provoke a specific immunological response to a selected agent or antigen, with the expectation that this would result in humoral (i.e., antibody) protective factors in the blood. While such protection may diminish with time, sufficient residual immunity remains, so that a heightened and more rapid immune response occurs upon a subsequent exposure to the same micro-organism.

It became quite clear at the beginning of this century that cellular aspects of immunity were also involved in protection and/or defence from microbial infection. Phagocytic activity, considered to reflect mainly a non-specific phenomenon, was thought by some of the earliest immunologists to be more important than humoral immunity in protection against infectious agents. Furthermore, in many cases humoral antibody was thought to function mainly by enhancing phagocytosis by macrophages. Other cells involved in what is now considered 'classic' cell-mediated immunity may also be stimulated by infectious disease agents, and vaccines can mimic the effects of such infections. Indeed during the last few decades interest in the role of cell-mediated immunity, especially that involving specifically sensitized T-lymphocytes, has increased in almost an explosive manner in many areas of basic and applied immunology.

For those diseases in which the role and manner of the immune responses are clearly defined, methods for prevention of infection have been readily devised by developing vaccines which are generally considered safe and effective. It has been widely acknowledged that, with adequate immunization programmes, marked reduction or elimination of such previously common diseases as smallpox, measles, diphtheria, tetanus, poliomyelitis and scarlet fever can be achieved. However, many infectious diseases present special problems

which have impeded development of effective vaccines. One such example is infection with *Salmonella* bacteria; the *Salmonella* group of organisms is composed of a multiplicity of antigenic variants or strains numbering hundreds. Furthermore, among the respiratory diseases, the 'cold' viruses and pneumococci present a similar problem. Recovery from infection of any one type of organism generally leaves the individual vulnerable to others.

It should be noted that antigen–antibody reactions involved in microbial infections are not well understood in most cases. The immune response to some antigens may be absent, or meagre. In addition, pathogenesis in many diseases induced by some bacteria is often poorly understood. The presence of micro-organisms or their antigen may sometimes be advantageous or part of a complex cycle in the evolution of the disease syndrome in question. In some situations the exact host relationship to the presumed offending organism may be so obscure that factors which determine infection and/or resistance remain undefined. In this regard, the role of cell-mediated immunity, as well as factors derived of T-lymphocytes and macrophages in controlling or preventing infectious diseases, (either in individuals who have been actively exposed to micro-organisms or been treated with a vaccine) is essentially unknown. Despite these problems, marked advances concerning the use of vaccines in preventing microbial infections have been made over the past few decades. It should be noted, however, that during a period of two decades or so, shortly after the development of 'chemotherapeutic' agents and antibiotics, it was felt by many that infectious diseases could be controlled chemically rather than immunologically. This obviously has not occurred. Although some of the major acute infections of man have been readily controlled by antibiotic treatment, infections are still a major problem in human medicine. It has been estimated that at least 70% of all patient visits to physicians are due to an infection. In the USA alone, it has been estimated that over 100 000 individuals die per year because of hospital-acquired infections. Thus the advantage of preventive immunization, for controlling both acute and chronic infections of man by a wide variety of micro-organisms, is once again being seriously considered.

Recent events during the last few years have focused attention on vaccines for preventing important infections. A polyvalent pneumococcal polysaccharide vaccine, based on careful isolation and identification of polysaccharides associated with certain strains of pneumococci, has recently been approved for widespread use in the USA and elsewhere. The eradication of smallpox as an infection in man has been proclaimed by world health organizations. On the other hand, an attempt to 'prevent' a suspected pandemic of influenza, i.e., the Swine Flu Programme, brought attention to the difficulties not only in developing an effective and safe vaccine for a common upper respiratory virus infection, but also the difficulties in predicting in advance which strain of virus may be prevalent in the next epidemic, and whether or not such an epidemic would indeed occur. Some of the

dangers involved in vaccine administration, especially vaccines prepared from biologically active substrates such as eggs, were pointed out by the influenza virus programme in the USA. On the other hand, the tremendous success achieved in eradicating polio by means not only of a killed vaccine, but also a 'live' vaccine, has brought the scientific community and the lay public to a level of expectation which has not been realized in other areas of medicine.

Many of the advances in preparing effective vaccines have been achieved with viruses and toxic products from micro-organisms. These advances have been achieved mainly because of knowledge of the antigens involved. However, further achievements in the area of effective vaccines will also depend upon increased understanding of the immune response mechanisms and requirements for inducing effective immunity to certain micro-organisms. It is widely accepted that certain forms of antigen are more effective than others and that there are differences in the protective immune response based not only upon the antigen used, but its route and dose of administration, the immune status of the host, etc. An understanding of the antigenic nature of the micro-organism (be it a bacterium, a virus, or a protozoan) is also essential. Much knowledge must also be gained concerning many areas of microbial immunology and the host–parasite relationship. However, based on successes achieved to date with certain vaccines, it seems likely that even greater successes will be apparent in future years.

This volume is based generally on the proceedings of a conference on the topic of New Trends and Developments in Vaccines, sponsored by the Robert S. First Co. and held in Brussels, Belgium. A number of investigators who presented scientific papers were invited to review their work for this volume. In addition, other chapters were solicited from well-known bioscientists who have made major contributions in the field of vaccines. It is apparent from the presentations at the meeting and chapters submitted for this volume that most of the successful vaccines to date have been those derived from either inactivated or attenuated virus preparations. This is not surprising since the initial vaccine developed for man almost a hundred years ago was also for a virus infection, i.e., rabies. Bacterial vaccines also have been used extensively over the last half-century or so. As stated earlier, many of these vaccines, especially those developed for cholera, salmonella (i.e., typhoid fever) etc., have had only limited effectiveness. Newer types of bacterial vaccines are dependent upon identification of the protective antigen on the micro-organism. In this regard, a number of newer vaccines have been recently developed, including a pneumococcal vaccine, as well as vaccines for meningococci. However, since many of the newer developments deal with vaccines for viral infections, a number of chapters deal with such vaccines, i.e., rubella, measles, polio, influenza, hepatitis and herpes viruses. The important role of vaccines in protecting children from infectious diseases is properly emphasized. However we are made aware that the effects of

vaccination (e.g. against whooping cough) are difficult to estimate and the risks have to be carefully weighed against the benefits. Developments in the area of vaccination against dental infections, as well as veterinary vaccines for parasitic diseases, and allergies are also described.

It is anticipated that much further work will be performed in the area of microbial vaccines, especially because of the serious limitations of chemotherapeutic agents not only for microbial infections but obviously also for parasitic and viral infections. This is evident from the renewed interest in the current status and prospects for improved microbial vaccines as reviewed in a number of other recent symposia, conferences and publications. It is anticipated that in the near future much more information will be available, not only concerning the basic immune response mechanism in infectious diseases, but also the mechanism whereby effective and safe microbial vaccines influence the immune response.

2
New developments in vaccines

W. HENNESSEN

Developments are based on past experience and lead to the future. With vaccines, success in the past will show what can be expected for the future. This paper tries to demonstrate what factors are to be considered for a reliable prediction for developments in vaccines. The factors studied are:

feasibility of manufacture of vaccines
quality requirements
target populations
epidemiological considerations
costs
consequences

FEASIBILITY OF MANUFACTURE OF VACCINES

It seems safe to say that, in a decade or less, it will be possible to offer vaccines against all infectious diseases caused by viruses or bacteria. Antiparasite vaccines, perhaps even certain antitumour vaccines, will also be available. Some may regard such a plain statement as sensational, some as natural progress. In figures it looks explosive (Figure 1); on this diagram the number of antigens from which the vaccines are produced is tabulated for the period from 1950 to 1985. It does not contain all the combined vaccines which can be made out of these antigens. It shows that before 1960 there were ten antigens developed for vaccine production: diphtheria; vaccinia; tetanus; rabies (?); pertussis; influenza; typhoid (?); poliomyelitis (Salk); BCG; measles (inactivated). A number of them were not yet as effective as required today.

Between 1970 and 1975 certain other vaccines were developed (see Table 1). The steep increase of antigens for vaccines will take place during the

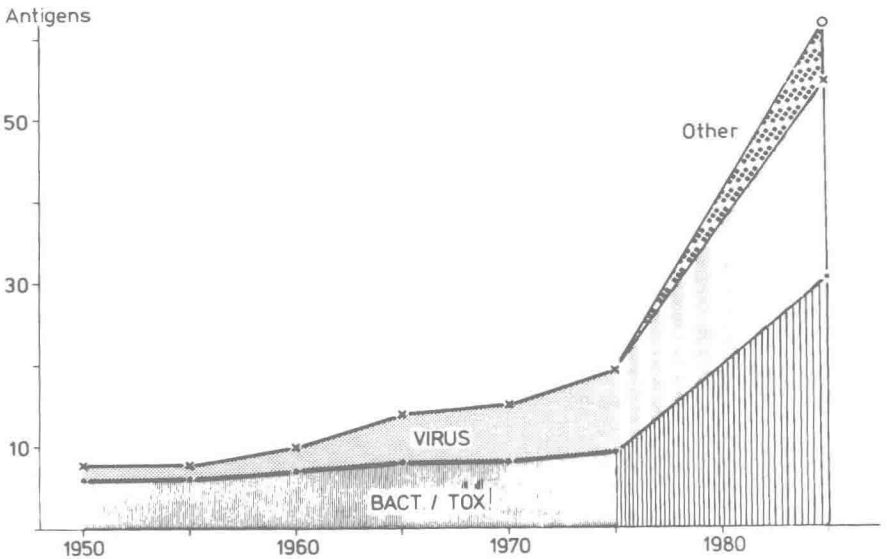

Figure 1 Human vaccines, 1950–85

Table 1 New vaccines, 1970–75

Vaccinees	*Bacteria/Toxoids*	*Virus*
Children	Meningococci A, C	Rubella Mumps Poliomyelitis HDC
Adults		Rabies HDC

next 10–15 years. With more than double the number of antigens it will be possible to cover all infectious diseases caused by bacteria and viruses and more. These new developments are listed in Table 2. It goes without saying that, as in the past, existing vaccines will be improved, be it for better compatibility or better efficacy. Such improvements require an increasing integration of biophysical, biochemical and microbial technology into vaccine manufacture. One example may demonstrate what is meant here. Some viral vaccines (influenza-inactivated, rabies-inactivated, others to come) in routine production were only made possible by the use of centrifuges which were developed for space research. Some enthusiasts for space-labs still expect vaccine manufacture to be carried out in space to achieve more purity for the products. From what has been shown so far it is self-evident that future vaccine production, or at least the know-how, can only be found in highly industrialized areas.

Although it would go far beyond the scope of this paper to describe just