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## *Annotations*

# Vaccine advances

Like many other fields of medicine, that of immunisation is advancing rapidly. Long standing vaccines are being improved and entirely new vaccines made by exploiting recombinant DNA technology, controlled gene expression, and synthetic peptide chemistry. It is now often a straightforward matter, by use of monoclonal antibodies, to identify and purify the protein antigens of complex micro-organisms. These antigens can be examined for their capacity to induce immunity, and by genetic analysis the gene coding for antigens found to be protective can be identified. Such genes can be transferred into bacteria, yeasts, or mammalian cells to produce large amounts of the corresponding antigen in culture, from which it can be purified for use as an inactivated vaccine. Genetic engineering can also be used to prepare, for use as live vaccine, variants of a pathogen that express its protective antigens but not its virulence factors. The *practice* of immunisation is also benefiting—from improved epidemiological techniques and from a growing understanding of how high immunisation rates can be secured, both in the Third World and in countries such as our own, where the population may fail to perceive the benefits of immunisation or be influenced unduly by the fear of side effects.

Killed, whole bacterial preparations, such as typhoid and cholera vaccines, often cause unpleasant pyrexial side effects, and the degree of immunity they elicit is incomplete. Consequently, there is much interest in developing live vaccines, which may prove to be free from side effects yet capable of inducing a degree of humoral, secretory, and cellular immunity similar to that which follows natural infection. The first promising application of this approach in human medicine (live veterinary vaccines against *Escherichia coli* have been in use for some years) is live typhoid vaccine.[1] It is prepared from a stable variant capable of multiplying for only a few generations in the intestine, a degree of growth sufficient to immunise without causing illness. Clinical studies suggest this vaccine to be safe and effective in countries where typhoid is endemic, although its value in developed countries has yet to be established. Parallel work is in progress with the aim of preparing vaccines against dysentery, cholera, and other bacterial intestinal infections.[2 3]

Of particular current interest are new whooping cough vaccines, prepared from purified fractions of this complex bacterium. An important component is the major toxin of the organism, lymphocytosis promoting factor, which can now successfully be 'toxoided'—that is, chemically detoxified while retaining immunogenicity. Such 'acellular' vaccines are already under clinical trial in Japan and Sweden and the early results suggest that they are markedly less reactive than the traditional whole bacterial vaccines used in those countries.[4] Clinical evaluation of similar vaccines is expected to begin soon in the United Kingdom.

Other approaches in the bacterial vaccine field concern the use of microbial polysaccharides. The recently introduced vaccines against meningococci,[5] pneumococci,[6] and *Haemophilus influenzae* type b[7] consist of highly purified preparations of the capsular polysaccharide antigens of these bacteria. The antigens are of known chemical structure, and the potency and purity of the vaccines are controlled by testing their physicochemical properties. Of these vaccines, only the pneumococcal preparation is at present licensed in the UK, but they are used widely in the United States and elsewhere, even though the corresponding infections in man are relatively uncommon. The vaccines have an important drawback—their poor or absent immunogenicity in children under about 2 years of age, the age group mainly affected by bacterial meningitis. Additionally, the meningococcus group B capsular polysaccharide is non-immunogenic in man, whereas about 65% of meningococcal meningitis in the UK is caused by group B organisms. Both problems are being approached by linking the carbohydrate antigens to a protein carrier such as diphtheria toxoid,[8] which may cause the body to deal with the antigen as if it were a foreign protein, to which young infants as well as adults readily produce an immune response.

In the virus vaccine field there is much interest in the herpes virus group (herpes simplex types 1 and 2; Epstein-Barr virus; cytomegalovirus; varicella zoster). Live, attenuated varicella vaccines, first developed in Japan, are now under study in the UK. They appear to be protective and may prove sufficiently safe for use in children with leukaemia who are at special risk from this infection.[9 10] A protective antigen has been purified from Epstein-

Barr virus by Professor Epstein's group in Bristol[11] and is likely to come into clinical trial soon. This is of major interest owing to its potential for preventing cancers—Burkitt's lymphoma in Africa and the very common post-cricoid carcinoma of southern China, both of which are associated with Epstein-Barr virus infection.

The hepatitis B vaccine used at present is prepared in a manner not widely different from that used for the earliest vaccine, smallpox. It is derived from the blood of carriers of the virus but, unlike smallpox vaccine, it is meticulously purified and inactivated. A more advanced preparation, a cloned surface antigen (HBsAG) of the virus expressed in yeasts is likely soon to be available.[12] The coding sequence of HBsAG has also been inserted into the vaccinia virus genome.[13] Rabbits vaccinated with such virus produced antibodies to HBsAG. Such a vaccine could be an effective and economical means of preventing hepatitis B and other infections, as a number of different protective antigens could be added to the vaccine virus by means of genetic engineering. The potential side effects of vaccinia, however, may preclude its use in man. Hepatitis A vaccines are also under development; live attenuated variants have been prepared by virus passage in cell culture,[14] and recombinant DNA procedures are being used to prepare inactivated antigens. Other virus vaccine developments for the future include improved poliovaccines. The live preparations now available carry a remote risk of inducing paralysis in recipients, and safer and more effective vaccines are in prospect based on a detailed knowledge of the genetic structure of the virus.[15] A live, oral rotavirus vaccine, using a rotavirus isolated from calves, has also been developed and is currently under clinical trial in the UK. The calf virus, attenuated by passage in tissue culture, appears capable of replicating in the intestine and inducing immunity to human rotavirus diarrhoea.[16]

In many developed countries vaccine acceptance rates are much higher than in the UK. The strong interest of American paediatricians in immunisation is probably a major factor in the successful programmes of that country, and it is therefore encouraging to see a growing interest among British paediatricians. The British Paediatric Association has recently established a group, which is working in liaison with the Department of Health and Social Security and Scottish Home and Health Joint Committee on Vaccination and Immunisation. In a number of health districts paediatricians are running immunisation clinics on the Harringay model of the late Dr W B Marshall. Children with possible contraindications to a vaccine may be referred by general practitioners and others and in most cases immunisation can be successfully completed. Such developments must complement the technical advances. As the whooping cough episode has shown, the practical realities of delivering vaccines and of convincing the public—and possibly the medical profession—of their value can outweigh the scientific realities on which immunisation is based.

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