ON VACCINES AND VACCINATION

BASIC CONCEPTS AND RECENT DEVELOPMENTS

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'THE ideal vaccine is one that confers full life-long protection to a vaccinated individual, against a particular disease, causes no harmful local or systemic reaction upon its exhibition and administration and is given in one small single dose, preferably by mouth' (Vella, 1963. *J. Hyg.(Lond.)*).

Introduction

The prevention of disease by vaccines has always been the subject of close study by the Armed Forces Medical Services; of great value in the prophylaxis of bacterial diseases, vaccines are at present our best means of defence against the viral diseases in which field chemotherapy still lags far behind.

It is therefore to be desired that the service medical officer should be aware of the present day evolutionary trends towards more effective, more sophisticated and safer vaccines and the same applies mutatis mutandis to the civilian practitioner.

The medical officer needs to know the answers to such questions as:

Which vaccine to give; When to give it and when not to give it; How to give it; What untoward reactions might ensue as an immediate (fatal anaphylaxis) or delayed (possibly subacute sclerosing panencephalitis (S.S.P.E.)) result of vaccination and How to deal effectively with these emergencies and disabilities?

He should make himself familiar with the possible hazards that might arise from his intervention upon the administration of these agents, and thus be in a position to prevent and/or nullify any mishaps to his patients. As of yore 'Primum non nocere' must be his watchword; in the medical (biological) world every individual is 'an island unto himself or herself', and what is good for one individual is not necessarily equally good for the next person waiting his turn in the queue of vaccinees.

Vaccines available

Vaccines come in four main forms:

- a. Dead (inactivated) vaccines—suspensions of organisms which have been killed/preserved by physical and/or chemical means such as heat, formalin, phenol, mercurials, hydrogen peroxide, ultraviolet rays, methylene blue and photodynamic action, gamma-rays irradiation, Beta-propio-lactone, and others.
- b. Live (attenuated) vaccines—containing organisms which are not pathogenic for man:

The organisms may be mutants found by chance as with El Tor cholera vibrio from water sources and used in certain studies in India or,

mutants induced/elected by artificial means, for example, B.C.G. tubercle bacilli of bovine origin, tamed down by several years subculturing on glycerol bile potato medium; a method adopted by the two French workers Calmette and Guérin. This is

in contrast to the Vole bacillus vaccine advocated by Wells; this mammalian mycobacterium does not require the long artificial subculturing treatment accorded to B.C.G. as by its very nature it is only very slightly pathogenic for man or,

hybrids, that is to say strains produced as a result of mating two strains or species of micro-organisms as the progeny of mating *Shigella* organisms with *Escherichia* strains to produce a bacillary dysentery vaccine, currently being investigated by some workers in the United States of America.

c. Fractions (sub-unit vaccines) of organisms containing as far as possible the antigenic components which give protection, lessen untoward reactions, are non-infectious and hence completely safe. These may be extracts of the constituents of the organism as the lipopolysaccharides of *Salmonella* bacilli or units from the body of the organism as with cell walls from tubercle bacilli and haemagglutinin antigen from influenza viruses.

d. Toxoids—toxic substances, extruded during the growth and possibly lysis of micro-organisms, which are rendered non-toxic as in Tetanus toxoid, Diphtheria toxoid and Cholera toxoid. The explanation of the phenomenon which takes place has not yet been clearly elucidated, but it may be that under the action of formalin (the chemical agent commonly used to treat the toxins to produce formal toxoids) the spatial configuration of the toxin molecule is altered so as to render it harmless to the body but at the same time the molecule retains enough of its original characteristics to induce in the human or animal body the corresponding specific protective antibody (antitoxin).

The efficacy of dead (inactivated) vaccines depend to a great extent on the amount by weight of the appropriate antigenic constituents. A series of injections is almost always to be recommended, though the protective value of a single dose of typhoid (South America) has been reported and a single dose of cholera is acceptable for the purpose of international certification by the World Health Organisation (W.H.O.).

Moreover booster doses are often required at suitable intervals to top up the basal immunity established by the primary course of vaccination. The resulting immunity may often be gauged by detecting and measuring the titre of the evoked antibodies (it is a wise precaution to test for serum antibodies after a course of pre-exposure rabies vaccination to check the effects of this prophylactic measure, if the primary course of injections proves unsuccessful more booster doses would be indicated); one must not lose sight of the fact that serum antibodies are not the total final result of vaccination, as cell-mediated immunity may also be involved though this unfortunately has not been in the past taken into account to any extent.

The potency, effectiveness and duration of immunity of vaccines are considerably enhanced by additive substances called adjuvants such as absorbed Tetanus toxoid (Tet Vacc, PTAH) utilising aluminium hydroxide or phosphate. Mineral oils or vegetable oils are also possible as influenza vaccines with adjuvants producing a stable water-in-oil emulsion which gives a better response than plain saline influenza vaccine. It has been recommended that adjuvants should preferably be such as to be metabolised by the human body. Unfortunately some vaccines with adjuvants may produce more untoward reaction in patients than the corresponding simple 'plain' vaccine, and thus are liable to prove unpopular both with the patient and the physician. In days gone by the danger of 'provocation poliomyelitis' was also considered a disadvantage but with the advent

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of easy-to-administer oral polio vaccines and the high percentage of the population immunised against polio this is no longer considered to be a contra-indication to the use of adjuvanted vaccines.

In the triple vaccine Diphtheria-Tetanus-Pertussis (D.T.P.) the pertussis component is considered to act as a 'biological' adjuvant; but even so in some countries this vaccine is being produced with a mineral adjuvant and will no doubt in due course be adopted in this country as well. On the whole adjuvanted vaccines are superior to plain vaccines and hence their use should be encouraged whenever they are specially indicated.

As stated above micro-organisms in attenuated vaccines are still viable, and in fact they must be capable of multiplying to some extent in the human body. This is essential for their efficacy and they are tailor-made by the manufacturer with this end in view. As a corollary to this, taking the numbers of micro-organisms inoculated as the criterion of efficacy, one can usually effect protection using a live attenuated vaccine with a lesser number of micro-organisms than the corresponding vaccine utilising micro-organisms. This offers some advantages not the least being that the smaller the amount of extraneous non-micro-organismal foreign matter, necessarily contained in most commercially available vaccines, that are injected into a vaccinee the less are the chances of untoward reactions and incidental mishaps occurring. Note that the producer of live vaccines has to steer a course between the pristine virulent fully pathogenic micro-organisms which would undoubtedly give a good immunological response (indeed such a vaccine would produce a specific 'natural' disease process, followed by the expected natural body response) but this would be too dangerous to be approved by the licensing authorities, and the fully attenuated, feeble and weakened micro-organisms, on the other hand, which would be completely safe but in the long drawn out process of attenuation may have suffered so much change that such a vaccine would prove of little, if any, use as an immunogenic agent.

In between these two extremes is the ideal attenuated vaccine, constituted of micro-organisms which are just pathogenic enough to gain a foothold and multiply in the human body, and which have retained as much as possible their valuable antigenic factors unchanged; and yet at the same time are sufficiently domesticated as to offer no real hazards to the defences of a normal individual (one cannot cater for all the human race, some individuals do have an idiosyncratic deficiency in their immunological mechanism). If possible once introduced these organisms should stay put inside that human body, or at least if able to leave the body of the vaccinee then they should retain their stable attenuated state and not be capable of reverting to their original sin of virulence which could well prove epidemiologically disastrous to the community.

Another useful effect of locally instilled live attenuated (viral) vaccines is the possible production by the sensitised stimulated cells of the non-specific antiviral substance Interferon which affords blanket protection against all viral would-be invaders albeit for a limited period of time; still even this may be useful against an accidental exposure of the weak, elderly and chronically sick persons or an unavoidable exposure of the physician and other busy personal in an acute localised epidemic as an influenza outbreak in an institution, or nursing home or a hospital.

In general 'live' vaccines, no matter what their degree of attenuation is, should not be inoculated into individuals with a 'suspect' immunological mechanism, this includes:

Natural impairment such as occurs in leukaemias, lymphomas, malignant diseases, history of familial or personnel allergy, hypo- and dys-gamma globulinaemia and artificial impairment produced by therapy with corticosteroids, irradiation, alkylating drugs and anti-metabolites.

Moreover the physician should be very wary indeed whenever he is called upon to vaccinate female patients of child-bearing age who may be pregnant.

The administration of a blood transfusion or blood products such as gamma-globulin may interfere with the 'take' of an attenuated vaccine; in much the same way maternal antibodies may interfere with vaccine administered to the newly born.

Techniques of vaccination

Vaccines may be injected into the skin or deeply into the tissues as in the multiple pressure method of smallpox, subcutaneous yellow fever vaccine, and intra-muscular anthrax vaccine.

Vaccines may also be introduced or so placed so as to act on the surface of tissues, for example; anti-diphtheria lozenges to act on the throat; oral typhoid, cholera, and dysentery vaccines to act on the intestinal mucosa; aerosol immunization against influenza to act on nasal mucosa; nasal drop instillation against Rubella, and even conjunctival instillation in Rubella has been tried!

It was the Army Medical Service, during the period when Almroth Wright was Professor of Pathology (Army Medical School, Netley) which introduced vaccines against typhoid; details of the first two anti-typhoid inoculations in humans, published

(Courtesy of the Wellcome Trustees)

Almroth Wright (1861-1947)

As Professor of Army Pathology, Royal Victoria Hospital Medical School, introduced Typhoid Vaccines. An enthusiastic exponent of Vaccine prophylaxis and Vaccine therapy.

'The physician of the future will take upon himself the role of an immunizer'.

in medical literature are recorded in the issue of the *Lancet* for 19 September 1896. The Army Medical Service scored another first in this country with the production, and use in the forces, of the intradermal T.A.B. and T.A.B.T. vaccines. For the intradermal technique of inoculation claims have been made that it causes less reactions than a subcutaneous injection; indeed one published series reports only 49 reactions after the issue of 7.5 million doses of intradermal T.A.B./T.A.B.T. produced by the Army's own vaccine laboratories.

It is of interest to record that B.C.G. had been given subcutaneously in the past, and indeed Calmette vaccinated infants against tuberculosis by giving 3 *oral* doses of his attenuated B.C.G. vaccine. However the usual practice of injecting B.C.G. vaccine is an intradermal inoculation by means of a syringe and appropriate needle. Various appliances have been proposed and are now available for the performance of this technique—thus the Heaf Gun originally designed for tuberculin skin testing may be utilised as an instrument for the intradermal introduction of B.C.G., as well as more elaborate apparatus (Jet gun: Needle-less injector) which emit a constant dose of the vaccine as a spray under pressure, such as the Ped-O-Jet, Dermo-Jet and Intra-Jet. In certain situations requisition of one of these handy gadgets may be advantageous, such as for example in firms with a large number of employees, and again in big schools where to the advantage of not having to charge a separate syringe per vaccine is added the non-appearance of the all too familiar and rather dreaded needle and syringe.

The W.H.O. also speaks very highly of a bifurcated needle—a forked-needle with 2 prongs—for use in the multi-pressure or multi-puncture technique in smallpox vaccination.

Rationale of vaccination

To keep abreast of modern developments in the vaccine world one must take cognizance of the great advances being achieved in the rapidly expanding discipline of immunology and at least have some basic acquaintance with terminology currently in vogue.

Thus when vaccines made up of suspensions of bacteria are introduced into man, antibodies belonging to the class of globulins known as IgM (Immunoglobulin M) are produced early and in good amounts depending on the efficacy of the stimulating agents and the reactivity of the individual concerned. These IgM's circulate round in the blood stream dealing with the foreign particulate invaders.

In response to soluble non-particulate foreign matter, to persistent antigenic stimulus, and appearing at a slightly later date, another immunoglobulin called IgG (Immunoglobulin G) is produced; IgG (M.W.160,000) consists of a smaller molecule than IgM (M.W.900,000) and so diffuses easily out of the vascular system to inactivate the foreign substances wherever they can be got at.

The importance of immune antibodies (IgA—Immunoglobulins A) produced locally in nasal secretions and alimentary tract secretions is now the subject of great interest and intense experimental work both in the laboratory and in the field; thus alimentary tract produced IgA (copro-antibody) may be 100-1000 times more useful to the patient than the IgA circulating in the blood stream for the purpose of defence against intestinal pathogenic micro-organisms; in addition this IgA appears not to be destroyed by intestinal enzymes.

In all fairness one must place on record that attempts to produce local tissue immunity as a means of protecting indirectly the whole body against invasion by organisms dates to the years before I was born, but as has happened in other instances in the history of medicine, this knowledge is made to appear as if it has been recently discovered as of now. In this connection lessons in bacteriology given to me as a fourth year medical student in the 1940's, remarking on the experimental work and theoretical applications reported by Besredka twenty years previously on the possibility of immunising animals by giving orally cultures of typhoid and dysentery bacilli, are still fresh in my memory and come readily to mind on reading of the present attempts to immunise people by giving oral doses of typhoid cholera or dysentery bacilli.

Closely related to, and only recently separated from IgA are the IgE's (Immunoglobulins E); these globulins (reagins) have a strong affinity for tissue surfaces and are responsible for the hypersensitivity reactions of the immediate type such as anaphylaxis, urticaria, skin-test reactions. It is to be noted that these IgE's have nothing to do with the so called 'reaginic' antibodies met with in the non-specific serologic tests for syphilis; the use of the term 'reagins' for the latter purpose is misleading, causes confusion and should be dropped.

Conclusion

It is fitting to conclude this paper which it is hoped may be read with ease, interest and profit in conjunction with Her Majesty's Stationery Office publication JSP311 (1968) Memorandum on Immunological Procedures, 4th Edition, by referring to Edward

Edward Jenner (1749-1823)

The Gloucestershire physician who pioneered the practice of vaccination.

'I selected a healthy boy, about eight years old, for the purpose of inoculation for the Cow Pox. The matter was taken from a sore on the hand of a dairy maid, who was infected by her master's cows'.

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Louis Pasteur (1822-1895)

The French chemist who founded the science of vaccine production.

'A method the fruitfulness of which inspires me with boundless anticipations'.

Jenner (1789). He of course first founded the practice of vaccination by inoculating against smallpox using cowpox (vaccine) material taken from a dairy-maid; previously variolation was in vogue i.e. the practice of inoculation using material from lesions of very mild cases of smallpox. One can hardly fully realise in our days the good luck story, in the then pock-marked world, which underlies that familiar nursery rhyme, as the pretty farmer's daughter with a clear complexion and without a visible blemish on her smooth rosy cheeks consciously sings "My Face is my Fortune, Sir".

Nearly a century passed before the greatest of them all Louis Pasteur arrived on the scene (1880) and first protected fowls against chicken cholera (*Pasteurella septica*) by means of an old fortuitously attenuated broth culture which he apparently had laid aside on going on his holidays. After Jenner he named his suspensions 'vaccine' and since then by general agreement all these products, (constituted of attenuated or inactivated micro-organisms or their antigenic products and components) which are administered to our patients in order to immunise them, have been called *Vaccines* and the process *Vaccination*.