THE USE OF SPECIFIC PROPHYLACTIC MEASURES IN THE CONTROL OF ACUTE INFECTIOUS DISEASES.

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Excluding such procedures as the addition of the appropriate vitamins to the dietary for the prevention of scurvy, rickets or beri beri, and omitting, more questionably, the quinine prophylaxis of malaria, the term "specific prophylactic measures" is synonymous with artificial immunisation against certain of the major acute specific infectious diseases. Since the last war the number of diseases potentially preventable by immunisation has increased, notable additions being diphtheria, scarlet fever and epidemic typhus, while advances in the technique of production of antigens and antisera have made the means of defence much more effective and much less exceptionable upon the score of undesirable reactions of one kind or another.

Active and Passive Immunity. Active immunity implies the presence in the tissues of specific antibodies sufficient to overcome the clinical effect of invasion by the specific antigen. It is acquired slowly or relatively slowly and is lost still more slowly, but never entirely; and is capable of being restored quickly at least to its original level by a further specific stimulus.

Active immunisation is thus a long-term policy preferably carried out well in advance of expected or potential risks.

Except for the temporary maternally transmitted immunity of infants to a number of the common specific infectious diseases, passive immunity is always artificial.

Although quickly conferred by the injection of the appropriate antiserum derived from human or animal active immunes it is completely lost in from two or three weeks. Passive immunisation is thus an emergency measure to be employed for the immediate protection of known contacts or others temporarily at risk. It may sometimes be combined with or followed by active immunisation.

Antigens and Antisera. In human prophylaxis a living antigen is very rarely employed; if so, it is always attenuated, usually by passage. The antigen may be a vaccine, which is a suspension of the killed bodies of the specific organism; an endo- or exotoxin derived from the organisms; or a toxoid which is a toxin filtrate treated with formaldehyde and heat. The advantage of toxoid over toxin is that the former, while completely non-toxic, retains unimpaired its antigenic value.*

Very great advances have been made in recent years in the preparation of vaccines. The selection of the appropriate strain; its growth upon the most suitable medium; and its garnering when in the correct antigenic (smooth) phase are now recognised as of the utmost importance if effective antibody response is to be obtained. The use of the chorio-allantoic membrane of the developing chick-embryo as a medium for the propagation of viruses is increasing and satisfactory immunity upon an experimental scale has been recorded in the case of vaccinia virus (Stevenson & Butler (1939)) and a louse-typhus vaccine (Cox (1940)), so produced. Apart from ease of production in quantity, the method has the merit of yielding an antigen free from extraneous organisms, which, of course, is not true of ordinary calf lymph.

Primary and Secondary Stimuli. Vaccinia is a clinical entity immunologically equivalent to an attack of smallpox. Successful vaccination provides solid immunity against smallpox for a number of years. It is thus a valid "one shot" procedure, but to produce satisfactory immunity with prophylactic vaccines, toxins or toxoids more than one inoculation is required, unless it is a question of restoring immunity which has waned. The first injection is a primary stimulus (Glenny and Südmersen); the antigenic response thereto must be increased by a secondary stimulus preferably at an interval of not less than two, or better, four weeks or even more.

* A notable exception is the toxoid produced from scarlet fever toxin. Conversion destroys its antigenic value. (See the Dicks' monograph *Scarlet Fever*, Chicago, 1938, p. 87.)

Antisera. Nearly all are produced from horses; although human immune (convalescent) serum has been employed in the attempted prophylaxis of a number of infectious diseases, the only really consistent successes have been obtained in the case of measles.

Reactions. The foreign proteins contained in antigens and antisera are liable to provoke reactions which in sensitive subjects may be severe. Preliminary intradermal tests, to which further reference is made later, may give timely warning of their probable occurrence and thus show the necessity for caution in injection of the prophylactic.

Serum reactions. The process of protein digestion now so largely employed in the preparation of sera ensures the removal of practically all foreign proteins leaving only pseudo-globulins to which the antibodies adhere. A prophylactic dose of such a serum is contained in a very small volume, which for this purpose it is never necessary to inject intravenously. Hence, serum phenomena are most uncommon and nearly always of trifling severity. Except in the case of antitetanic and anti-gas gangrene sera, serum prophylaxis is rarely sufficiently urgent to call for the injection of known or potential allergics without a prior intradermal sensitivity test. If this is positive the prophylactic dose should be diluted with normal saline and injected subcutaneously. Because sensitivity tests are not infallible, and the very rare natural hypersensitive cannot be detected prior to the explosion of an anaphylactoid reaction, which even an intradermal test may provoke, adrenalin should always be at hand for immediate use when animal serum is injected in any dose by any route.

SPECIFIC PROPHYLACTIC MEASURES.

It is not possible to deal at any length with the available specific prophylactic measures, but an attempt has been made to indicate current practice. References are given to some of the more important recent papers. The diseases for the control of which specific methods are discussed are grouped as follows:—

Group I. Inhalation Diseases. (a) diphtheria, (b) scarlet fever, (c) whooping cough, (d) measles, (e) smallpox.

Group II. Ingestion Diseases. (a) enteric fevers, (b) cholera.

Group III. Inoculation Diseases. (a) tetanus, (b) typhus fevers.

Needless to say this grouping is somewhat artificial; some diseases may fall into more than one category. Thus, non-respiratory types of diphtheria and scarlet fever occur and epidemic typhus is believed to be contracted occasionally by inhalation of the dried excreta of the Rickettsia-infected louse.

GROUP I.

(a) **Diphtheria; Active Immunisation.** That diphtheria is preventable by mass immunisation there is abundant evidence to prove (Harries (1939)); that so far it has not been prevented in this country is a reproach which at long last more active steps are now being taken to remove.

Diphtheria is most fatal among the pre-school group and active immunisation should be commenced from nine to twelve months of age to ensure protection during the ages of maximum fatality and to secure immunity at the age of maximum exposure, i.e., at school entry. Immunisation of school children alone has no effect upon local prevalence; at least a third of the pre-school group must also be protected (Godfrey (1932)). Prophylactics consist of toxoid, either alone as formol-toxoid (F.T.); combined with alum as alum-precipitated toxoid (A.P.T.); or with antitoxin as toxoid-antitoxin floccules (T.A.F.). All three possess high antigenic value. In Canada F.T. is used extensively (Fitzgerald, Fraser *et al.* (1938)). In this country A.P.T. is most generally used for children under eight years of age among whom it causes very few reactions, and T.A.F. for older children and adults, reactions at any age being rare. The most usual doses of A.P.T. are 0.2 or 0.1 c.cm. and 0.5 c.cm. injected intramuscularly at an interval of four weeks. T.A.F. is given in three doses of 1 c.cm. at intervals of not less than two weeks. In clinics pre-Schick testing of young children is usually omitted; in older children and adults tests are desirable not only because many are already immune, but because the pseudo + positive reading is an indication of protein sensitivity and dictates modification of dosage. Where feasible, post-Schick testing of a proportion of the immunised three months later is desirable as a check upon results.

Passive Immunisation. From 1,000 to 2,000 units of diphtheria antitoxin will protect contacts for from two to three weeks. Since active immunisation produces no negative phase it may be commenced simultaneously.

(b) **Scarlet Fever ; Active Immunisation.** The syndrome "scarlet fever" caused by the erythrogenic toxin produced by strains of beta-hæmolytic streptococci has long been very mild in this country and, for the present at least, active immunisation is called for chiefly in residential schools and for the protection of nurses in fever hospitals. Pre-Dick testing is necessary, the smallest reaction being read as positive. As pseudo-reactions very rarely occur and do not reliably forecast reactors to the prophylactic, control injections are usually omitted.

The Dick test represents a skin test dose of toxin (s.t.d.) and the prophylactic consists of multiple s.t.d. Commonly five weekly injections are made subcutaneously. The scales of dosage vary.

The Dicks' (1938) scale is as follows :—

(i) 650, (ii) 2,500, (iii) 10,000, (iv) 30,000, (v) 100,000 s.t.d.

Reductions of dosage are made if the Dick test has been very markedly positive in order to minimise reactions—which are frequently troublesome and sometimes severe.

Post-Dick tests are made two weeks after the last dose : if positive the last dose is repeated. The Dicks' claim that 90 per cent. thus immunised are protected for several years.

Passive Immunisation. The injection of 3,000 U.S.A. units of scarlet fever antitoxin will protect contacts for ten to fourteen days ; rarely longer.

(c) **Whooping Cough.** Although regarded lightly by the public, the gravity of whooping cough needs no emphasis here. Fortunately, there is satisfactory evidence to show that, thanks largely to the work of Gardner (1936) of Oxford and Sauer (1939) of the U.S.A., *H. pertussis* (Bordet-Gengou) vaccines as now prepared are of real value in the prevention or mitigation of an attack, provided that the immunisation-exposure interval is adequate. Sauer thinks that this should be from two or three months ; others consider that a shorter interval is sufficient. The periodicity of epidemics is sufficiently regular to be forecast ; hence immunisation upon a large scale is preferably carried out towards the end of the inter-epidemic phase and particularly among infants of six months upwards. Sauer believes that a high aggregate of organisms, 80,000 million or more spread over three doses, is requisite ; Maclean (1940) prefers a fifth of this total distributed over four doses.

Despite the difference in dosage both observers report satisfactory result in controlled series of cases. Sauer makes three increasing weekly injections "just under the skin" ; Maclean divides his four doses equally, but stresses the importance of correct spacing : a week separates the first two doses, then at least a month between the second and third, and third and fourth. (For details, see the original papers.) Sauer and Maclean prefer "straight" vaccines, but Joslin and Christensen (1940) advocate a formalinised (detoxified) soluble toxic substance derived from the organisms.

Passive Immunisation. In general, the results of the sero-prophylaxis are equivocal. Maclean advises that very young infants exposed to the disease should be isolated and injected with convalescent serum.

Whooping cough and diphtheria prophylaxis is sometimes combined. Dosage of the vaccine varies, but, large or small, it is important that a month should separate the two doses containing both vaccine and A.P.T.

(d) **Measles—Active Immunisation.** Using a virus propagated on chick-embryos tentative claims have recently been made by Stokes and Rake (1940) for successful active immunisation, but so far on a small experimental scale.

Passive Immunisation. Pooled serum, convalescent or adult immune, placental extract (immune globulins) and parental whole blood are all of proven value for the sero-attenuation or sero-prevention of the disease. "Convalescent" is more potent than adult-immune serum ; parental whole blood (intramuscular) is very suitable for familial contacts ; placental extract, while readily obtainable, tends to give rise to reactions. Immune sera should ordinarily be reserved for children under five or even under three years of age. If the exposed child is delicate, temporary prevention is indicated ; if robust, an attenuated attack, conferring lasting

immunity, is to be preferred. For prevention, injection must be made within the first five days of exposure : for attenuation, between the sixth and ninth days. Half the " preventive " dose injected within the first five days will attenuate (Gunn).

The following scale for children under five years is suitable.

	Days after Exposure.		
	. 1 — 5		6 — 9
	<i>Prevention.</i>	<i>Attenuation.</i>	<i>Attenuation.</i>
Convalescent serum	5 c.cm.	2.5 c.cm.	5 c.cm.
Adult	10 c.cm.	5 c.cm.	10 c.cm.

*Double the doses for children over five years.**

Placental Extract (Immune Globulin). For children up to two years of age the dose advised is 2 c.cm. This dose is increased by 0.25 c.cm. per year of age up to a maximum of 4.0 c.cm.

(d) *Smallpox*. It is unnecessary to emphasise the importance of vaccination or re-vaccination for troops proceeding to countries where *variola major* is endemic ; the tragedy of the objector to vaccination infected with the virus of classical smallpox was witnessed all too frequently by those who served in the East during the last war. Nor is it necessary to describe the standard scratch method of vaccination enjoined upon public vaccinators by the Order of 1929. (Elastoplast, incidentally, is now the accepted dressing.)

Although it is true that the foveated scar provides easily read proof of successful vaccination, there is no doubt that the elimination of an open wound and the chances of superimposed sepsis would remove a major objection of the public to the process. Attention is therefore drawn to the intradermal method successfully practised by Pierce (1937) in the Port of Liverpool, because of its economy and simplicity. Nevertheless, exception has been taken to the intradermal insertion of calf lymph because it is not free from extraneous organisms.

The use of " lymph " grown in chick embryos, already referred to, would remove this objection, especially as the virus so produced has shown no increase of neurotropic affinity (Stevenson and Butler).

GROUP II.

(a) *Enteric Fevers* (Typhoid and paratyphoids A. B. and C.)

Active Immunisation. During the last few years the well-known T.A.B. vaccine has been improved as the result of the work of A. Felix on the flagellar, somatic and vi-agglutinins of *Bact. typhi* ; and of Perry, Findlay and Bensted (1933), who have rejuvenated the original Rawlings strain (Bensted, 1941), following the observation of Grinnell (1932) that the strain had reverted to a rough phase unsuited to making potent vaccines. The current vaccine used in the Army is rich in the vi-antigens of T.A.B. & C. and there is evidence that immunity is greater and more lasting than that obtained with the old type. Felix (1941) and Felix, Rainsford and Stokes (1941) have recently substituted alcohol for phenol as a preservative and claim that whereas phenol tends to destroy vi-antigens, alcohol not only leaves them unimpaired, but lessens the severity of reactions. Further, they show that if the intervals between injections of the new vaccine are increased from one to two or three weeks, satisfactory antigenic response is obtained from smaller doses. The full account of this important chapter in immunology should be sought in the papers cited.

Passive Immunisation. It has been suggested that contacts of typhoid (*not* paratyphoid) fever should be temporarily protected by an injection of Felix's vi- (antityphoid) serum.

* For fuller discussion, see " Clinical Practice in Infectious Diseases " (Harries and Mitman), 1940, p. 214-216.

(b) **Cholera.** From a considerable experience of the treatment of cholera in the last war, I concluded that patients who had been inoculated with two doses of cholera vaccine within six months, if infected, suffered a mitigated attack from which they usually recovered. Immunity is only valid for about six months, at the end of which a further dose is necessary to restore it. (Cholera vaccine combined with T.A.B., formerly known as T.A.B.C., is now termed T.A.B.Chol. to distinguish it from the enteric group vaccine T.A.B.C.)

GROUP III.

(a) **Tetanus. Active Immunisation** is usually carried out by two 1 c.cm. doses of tetanus toxoid at an interval of six weeks, although Marvell and Parish (1940) have adduced evidence to show that the antigenic response is better if two or three months separate the doses. They also prefer intramuscular to the usual subcutaneous injection, using the short fine Shick type of needle which can be inserted to the full extent into the arm at an angle of about 45 degrees.

Tetanus toxoid may be combined with T.A.B. (T.A.B.T.) (Ramon, 1937). It is claimed that the antigenic response to the tetanus toxoid is improved by the combination. Two injections T.A.B.T. are made at an interval of at least a month.

Passive Immunisation. The routine injection of casualties with tetanus antitoxin is familiar; a dose of 3,000 International units is now recommended.

(b) **Epidemic (louse) Typhus.** The introduction of typhus into the country during the war is a possibility, although during the last war it remained exempt. If introduced, the conditions of shelter life are obviously favourable to the spread of a louse-borne infection. Several rickettsia vaccines have been prepared of which Weigl's consisting of the triturated bodies of infected lice has been used upon a large scale in Eastern Europe. Durand's vaccine (Durand and Giroud (1940)) consists of formalised rickettsiae grown in mouse lung; of this five weekly injections are necessary. More recent is Cox's vaccine (chick-embryo (Cox 1940)) given in three doses of 1 c.cm., of which favourable reports have been published. It may be added that systematic lousing is *essential* for the control of typhus; vaccine prophylaxis is an additional precaution *only*.

Passive Immunisation. Convalescent serum has been employed in the protection of immediate contacts with doubtful results.

References.

- BENSTED, H. J. (1941) J.R. Inst. Publ. Hlth. **4**. 7.
 DURAND, P., and GIROUD, P. (1940) Arch. Inst. Pasteur, Tunis. **29**. 24.
 COX, H. R. (1940) Publ. Hlth. Repts. Wash. **55**. 110.
 DICK, G. F., and DICK, G. H. (1938) Scarlet Fever, Chicago, p. 86 *et seq.*
 FITZGERALD, J. G., FRASER, D. T., MCKINNON, N.E., and ROSS, M. A. (1938) Lancet **i**. 391.
 FELIX, A. (1941) Brit. Med. J. **1**. 1391.
 FELIX, A., RAINSFORD, S. G., and STOKES, E. J. (1941) Brit. Med. J. **1**. 435.
 GODFREY, E. S., Jun. (1932) Amer. J. Publ. Hlth. **22**. 237.
 GARDNER, A. D. (1936) Proc. Roy. Soc. Med. **29**. 1273.
 GRINNELL, F. B. (1932) J. Exp. Med. **56**. 907.
 HARRIES, E. H. R. (1939) Lancet **i**. 45.
 JOSLIN, C. L., and CHRISTENSEN, T. A. (1940) Amer. J. Dis. Childr. **60**. 1269.
 MARVELL, D. M., and PARISH, H. J. (1940) Brit. Med. J. **2**. 891.
 MACLEAN, I. H. (1940) Proc. Roy. Soc. Med. **33**. 425.
 PERRY, H. M., FINDLAY, H. T., and BENSTED, H. J. (1933) Jour. R. Army Med. Cps. **60**. 241.
 PIERCE, E. R. (1937) Brit. Med. Journ. **1**. 1066.
 SAUER, L. W. (1939) Journ. Amer. Med. Assoc. **112**. 305.
 STEVENSON, W. D. H., and BUTLER, G. G. (1939). Min. Hlth. Repts. on Publ. Hlth. and Med. Subj. No. 87.
 STOKES, J., and RAKE G. (1940) Science **92**, Supplement, p. 10.