

Not Official.

THERAPEUTIC AGENTS OF MICROBIAL ORIGIN.

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THERAPEUTIC SERA.

Syn.—ANTITOXINS, OR ANTI-SERA.

These are obtained by treating an animal with subcutaneous or intravenous injections of increasing doses of (a) bacterial toxins, (b) bacterial cultures, living or killed, (c) a combination of a and b, then bleeding the animal, allowing the blood to coagulate, drawing off the serum and bottling this in the fluid state or after drying *in vacuo*; all these operations being carried out under the strictest aseptic precautions. To the fluid serum a small quantity of an antiseptic is usually added, and each bottle or vial generally contains a single dose only. The dried serum should be in the form of thin scales or fine powder, otherwise it is difficult to dissolve; for use each gramme (corresponding to about 10 c.c. of fluid serum) of the solid is dissolved in 5 to 10 c.c. of cool Distilled Water (not above 40° C. = 104° F.), previously sterilised by boiling.

Two classes of anti-sera may be distinguished: one prepared by method a, with bacterial toxins, to which the term 'antitoxin' is alone strictly applicable (*e.g.*, diphtheria and tetanus antitoxins), the other prepared by method b, and termed anti-microbial, or simply anti-sera (*e.g.*, anti-streptococcic, anti-plague, and anti-pneumonic sera).

The last named are much less potent than the antitoxins, and attempts have been made to reinforce their action by the simultaneous injection of fresh normal serum, but without much success.

It is customary in some instances to employ several strains of the organism in the preparation of the serum; such sera are termed 'polyvalent.' The subject of serum treatment is fully dealt with in Hewlett's 'Serum Therapy.'

The therapeutic sera in most instances retain their activity for several weeks at least if kept in a cool, dark place—preferably an ice-safe: diphtheria and tetanus antitoxins probably for nearly a year, the anti-microbial sera for a much shorter period. They should not be administered with any other substance, must not be heated, and a bottle of the fluid having once been opened, any fluid not used at the time should be discarded. The dried products are preferable in hot climates.

The dose of therapeutic sera corresponds usually to 5 to 20 c.c. of the fluid serum, according to the activity, which is estimated by ascertaining the amount of serum required to neutralise a given amount of toxin or culture. The dose depends on the gravity of the disease and not on the age of the patient. Symptomatic treatment on general principles should be employed in addition to the anti-serum.

The therapeutic sera are administered by subcutaneous injection, in the abdomen or between the scapulae, the skin having been previously disinfected with an antiseptic lotion and the syringe by boiling for five minutes. Or, if an immediate effect be desired, by intravenous injection into a superficial vein, the serum being warmed by standing the bottle in warm Water (35° to 40° C. = 95° to 104° F.) and strained through a piece of fine muslin, sterilised by boiling, if there be any deposit. Care must be taken that no air is injected. Intra-muscular injections are more quickly absorbed than subcutaneous ones. Early treatment is of the utmost importance.

Some clinicians assert that antitoxins and anti-sera exert their action when

administered by the mouth or rectum. Hewlett, however, was unable to detect any absorption of tetanus antitoxin when given in this way to rabbits, and Sternberg similarly no absorption of diphtheria antitoxin.—*Wien. klin. Wochr.* 1908, p. 709.

The therapeutic sera are specific, e.g., diphtheria antitoxin is of use only in diphtheria; carefully administered they are harmless, but cutaneous eruptions or joint pains may follow, for the treatment of which Calcium Chloride is of service.

A second injection of serum at an interval of 10 to 40 days after the first one may be followed by immediate and serious symptoms ('supersensitisation,' *see* Goodall, *Jour. of Hyg.* vii. 1907, p. 607). But the continuous use of a serum for some days does not produce this effect.

The anti-sera may be used as prophylactics (dose 10 to 20 c.c. subcutaneously), but the immunity produced does not last longer than three weeks.

DIPHTHERIA ANTITOXIN.—Anti-diphtheritic serum is official in the *Ph. Ger.* Both a liquid and a solid antitoxin are described, the former as a yellowish, transparent fluid, having the odour of the preservative agent, and with at most a slight sediment, the latter is a yellowish-white powder, or yellow transparent lamellae, which, by the addition of 10 parts of Water, dissolves to a liquid corresponding in colour and general appearance to the liquid diphtheria antitoxin.

The sizes of the liquid diphtheria antitoxin mostly used are No. 0, 200 immunisation units; No. 1, 500 to 600 immunisation units; No. 2, 1000 immunisation units; No. 3, 1500 immunisation units.

The solid diphtheria antitoxin is required to contain at least 5000 immunisation units per gramme.

The *Ph. Ger.* also stipulates that antitoxin, with marked permanent turbidity or thick deposit, as well as serum of a prohibited test-number, is not permitted to be sold in pharmacy.

It should be protected from the light and stored in a cool place.

The therapeutic value is reckoned in Ehrlich units, 1 unit being that amount of serum which will completely neutralise about 100 lethal doses of toxin in a medium-sized guinea-pig.

The method of standardisation is a very exact one, devised by Ehrlich, but is too complicated to explain here. The different makes are of different strengths, i.e., contain a variable number of units in a given volume. The dosage is always referred to in units.

The dosage varies with the severity of the attack, and with the lapse of time after the onset before treatment is commenced. In a mild case, coming under observation on the first day, a single dose of 4000 units may suffice, but is best repeated on the next day. In severe cases the 4000 units should be repeated every 4 hours for 3 or 4 doses, and repeated the next day if necessary. In bad cases, coming under observation late, 8000 to 30,000 units have been recommended, followed by smaller doses, every 3 or 4 hours. In such cases Cairns considers that valuable time is saved by giving the primary dose intravenously. If there be a reasonable suspicion that the case is diphtheritic no time should be lost in giving antitoxin. The guide to the administration of subsequent doses is the general condition and the appearance of the membrane; this when the patient is fully under the influence of antitoxin appears to melt away.

The prophylactic dose should not be less than 500 units.

Several preparations by different makers can be obtained.

Diphtheria antitoxin, *re* the intravenous injection, even in cases other than laryngeal, it seems difficult to say (*L. '04, ii. 1776*) of an individual patient that a better result was obtained by this method than might have followed subcutaneous injection.

TETANUS ANTITOXIN.—If the case be seen immediately upon the development of the premonitory symptoms (stiffness, etc., of the facial muscles), 25 to 30 c.c. of the serum may be injected subcutaneously, followed by an injection of 10 c.c. every 8 hours as long as the symptoms last. If any time has elapsed since the development of the premonitory symptoms, 10 c.c. should be administered intravenously and 20 c.c. subcutaneously, followed by 10 c.c.

subcutaneously every 8 hours as before. But if the case has lasted any length of time, and especially if spasms have already occurred, no time should be lost in giving the antitoxin by cerebral or spinous inoculation (*see infra*).

Dried and pulverised tetanus antitoxin has been recommended as a dressing for wounds soiled with earth, etc.

For prophylactic use 3 doses of 10 c.c. should be injected at intervals of a fortnight.

In veterinary practice, 20 to 40 c.c. may be injected every 12 to 24 hours, but unless the animal be a valuable one the cost of the treatment is prohibitive.

Since Tetanus Toxin becomes fixed in the cells of the central nervous system, and antitoxin is but slowly absorbed from the subcutaneous tissues, it is desirable, in order to obtain a maximum and rapid response, to inject the antitoxin so that it may at once come in contact with the nerve tissues. This may be done by (a) intra-cerebral, into the cerebral hemispheres, (b) intra-ventricular, into the lateral ventricles, (c) intra-spinous, by lumbar puncture, inoculation. A primary dose of 5 c.c. of tetanus antitoxin of double strength (*i.e.*, 1 gramme of the solid dissolved in 5 c.c. of Water) may thus be administered, subsequent doses being given subcutaneously. As tetanus toxin is absorbed along the nerve trunks, antitoxin may be injected in addition into nerves if the site of the wound permit.

A method given by Roux and Borrel.—*T.G.* '98, 773.

A method given by Semple.—*B.M.J.* '99, i. 10.

10 c.c. doses, given intradurally in a case of tetanus, were followed by recovery.—*B.M.J.* '04, ii. 1696.

ANTI-VENENE.—An antitoxin prepared by the injection of snake venom. A separate serum is required for every venom, so that this antitoxin must have a limited use. That prepared by Calmette, of Lille, is mainly antidotal for the venom of the cobra. At least 30 to 40 c.c. should be injected at the earliest possible moment; if any interval has elapsed since the bite, 10 c.c. should be given intravenously in addition.

Antivenomous sera have been shown (*L.* '04, ii. 1277) to be markedly if not absolutely specific, even between the venoms of species of the same genus. The only sera at present in practical use are Calmette's and one prepared at the Pasteur Institute of India with pure cobra venom. Both are specific for cobra venom. The neutralising power is low, and 300 to 400 c.c. may be necessary even when given intravenously, and 10 or 20 times this amount if given subcutaneously.

ANTI-STREPTOCOCCIC SERUM.—The dose is 10 to 20 c.c. every 12 or 24 hours. Some Continental authorities regard this amount as much too small, and administer 50 to 150 c.c. for a dose.

N.B.—Streptococcic serum rapidly diminishes in strength with age, and should not be kept.

Is of especial value in erysipelas. Some cases of septicæmia react well to it, in others apparently similar it has little effect. Cases of septicæmia may be due to a variety of organisms, but it is only in pure streptococcic infections that the serum can be expected to have any effect. Even in streptococcic infections it is not always efficacious; there seem to be many varieties of streptococci, and a serum prepared with one variety may have little or no antidotal action towards another variety. The serum should be a 'polyvalent' one, *i.e.*, prepared with several varieties or strains.

The use of a serum prepared from a horse which has been immunised against a variety of strains has been recommended (*L.* '04, ii. 1829); the commencing dose being at least 20 c.c., and repeated, if necessary, at least every 24 hours. Useless to persist in the administration of any particular serum unless its beneficial action is almost immediately apparent.

The serum is innocuous if carefully prepared and injected with due precaution. (2) It must be administered early in the disease, and in large doses—20 c.c.—twice in 24 hours in severe cases. (3) If administered early and in large doses, definite improvement is observed in a considerable proportion of cases.—*B.M.J.* '05, i. 584.

The most rational method of dosage (*L.* '04, ii. 1832) would seem to be that of a large injection on the first occasion, followed by smaller doses as case may require. More uniform results are obtained with polyvalent sera.

In a simple septicæmia or sapsræma good results can be obtained with the anti-streptococcic serum.—*L.* '04, ii. 1213.

Fenwick recommends rectal injections of polyvalent anti-streptococcic serum in gonorrhœa, gonorrhœal pyæmia, rheumatism and hæmorrhagic purpura.—*B.M.J.* '06, i. 979.

A prophylactic injection recommended by Cheyne previous to operations about mouth and throat.

ANTI-ANTHRAX SERUM.—Prepared by immunising asses with killed and living cultures of *B. anthracis*. Sclavo's is that generally employed, dose 50 c.c.

A successful case, *B.M.J.* '05, ii. 118.

ANTI-PNEUMOCOCCIC SERUM.—The dose is 20 to 30 c.c. subcutaneously twice daily until the crisis. If the case be seen *early*, this serum may be very useful in the case of debilitated, aged, or alcoholic patients. Pane's serum seems to be the most potent.

Washbourn, *B.M.J.* '97, i. 510; ii. 1849; and Eyre, *ib.* '99, ii. 1247; Wilson, *Jour. Amer. Med. Assoc.* 1900 (Sep.), 595; Tyler, *ib.* 1901 (June), 1540.

ANTI-PLAGUE SERUM.—Yersin's serum is that generally employed. Calmette recommends 20 c.c. intravenously to be given immediately, followed by two subcutaneous doses of at least 40 c.c. each during the first 24 hours, and subsequently 10 to 40 c.c. daily, according to the condition of the patient. Choksy and also Cairns recommend still larger doses (60, 80, 100, 200 c.c.). The prophylactic dose is 10 c.c. subcutaneously.

Calmette, *Ann. de l'Inst. Pasteur*, xiii. '99, 865; Cairns, *L.* '03, i. 1287.

ANTI-TYPHOID SERUM.—No satisfactory serum seems to have been prepared as yet. The sera on the market are anti-microbial; dose 10 to 20 c.c. Chantemesse has prepared a serum, the use of which he claims gives good results.

Chantemesse, *La Presse Méd.* '02, No. 103, 122; *Trans. XIV. Internat. Congress Hygiene*; Macfadyen, *B.M.J.* '03, i. 681.

Anti-typhoid serum is stated (*B.M.J.* '04, ii. 1269) to exercise a specific action on the diseases of the organism. If the nervous system is deeply poisoned, the benefit is much smaller, and failures occur. In the treatment of a large number of cases during several years, Chantemesse shows a mortality of 4 p.c., and claims (*B.M.J.* '04, ii. 1449) to have produced a serum with which remarkable success is stated to have been obtained. The serum is given in small doses (4 to 5 m.), and Wright believes that it contains a *toxin* and is in reality a *vaccine* (Chantemesse agrees with this view). In the case of typhoid fever (*B.M.J.* '04, ii. 1449), the serum of a horse, after repeated inoculations with the virus, though possessed of anti-bacterial properties, is found to be practically devoid of any antitoxic value.

ANTI-TYPHOID EXTRACT OF JEZ.—Prepared from the tissues of immunised rabbits. Dose, 2 drms., by the mouth every 1 to 2 hours until temperature becomes remittant.

See *B.M.J.E.* '01, i. 51; '02, i. 27.

ANTI-TUBERCLE SERUM.—Paquin and Maragliano have each prepared an anti-tubercle serum.

Dr. Marmorek has obtained a new tuberculous serum by growing the young bacilli in a medium consisting of leucotoxic calf serum and Glycerin liver bouillon. In pulmonary tuberculosis he claims, by the use of this antitoxin, to have produced amelioration, and even definite cures. In pleurisy there was a rapid diminution of the effusion.—*B.M.J.* '03, ii. 1434, '06, i. 340; *L.* '03, ii. 1470, 1642, 1746.

Not very favourably reported on.—*B.M.J.* '01, ii. 1621; *L.* '03, ii. 1695.

The dose for rather chronic cases is ordinarily 5 c.c., whilst in acute cases, such as meningitis, as much as from 20 to 30 c.c. in divided doses may be given every day for 4 or 5 days, the dose being then gradually diminished. The serum when given in carefully graduated doses, with proper precautions and in suitable cases, does no harm. Experience tends to show that the serum does produce a specific antitoxic effect.—*L.* '04, i. 859, 979; *B.M.J.* '04, i. 749, 857.

The treatment has so far proved rather disappointing (*L.* '04, ii. 1827), Marmorek's serum proving no more successful in active and progressive cases than other sera. The method of administration recommended in the *Edinburgh Medical Journal*, 1905, 213, is 3 c.c. injected on the first day, 4 c.c. on the second, 5 c.c. on the third day, no injections for the next three days, 5 c.c. on the seventh, 6 c.c. on the eighth, 7 c.c. on the ninth, and 8 c.c. on the tenth day. This completes the first series, and an interval of eight to ten days is allowed. Then 8 c.c., and in another series of eight injections the amount is raised to 20 c.c. Another interval, and then a further series of injections similar to the latter.

An interesting and instructive lecture on Antitoxins was delivered by Professor R. Tanner Hewlett at an evening meeting of the Pharmaceutical Society, and is duly reported in the *P.J.* '04, ii. 888; and *C.D.* '04, ii. 975.

An interesting *résumé* of the tuberculins and anti-tuberculous sera is given (*L.* '05, i. 923), the conclusion being that, judging from evidence, the use of tuberculins materially improves the results of treatment, and it would seem quite justifiable to supplement sanatorium methods with this specific one.

The method now recommended by Marmorek is the injection of 5 c.c. every other day for 3 weeks, followed by a clear 3 weeks' interval, after which the injections are repeated as before. The site of injection is preferably the abdominal walls or thighs, and should be varied as much as possible.

(1) The beneficial effects of the serum are most marked in the 'surgical' forms of the disease.

(2) No objectionable features whatsoever follow the injections.

(3) The pyrexia is diminished, though the fall in temperature is sometimes preceded by an initial rise.

(4) Pain in the 'surgical' forms is almost invariably alleviated.

(5) The amount of sputum in pulmonary tuberculosis is rapidly diminished.

(6) The general health rapidly improves and the patient gains in weight.—*L.* '05, ii. 760.

Cases on record (*L.* '05, ii. 603) which would seem to show that it undoubtedly exerts a neutralising effect on the tuberculosis toxin. In all cases in which the serum may be tried it is advisable not to push it unduly, and sufficient intervals should be allowed between the injections.

A valuable paper (*L.* '05, i. 928), by H. Batty Shaw, on the treatment of tuberculosis of the lungs by means of tuberculin and other bacterial derivatives. A history of the different tuberculins is given and their respective doses. Dr. Marmorek's serum is again referred to, and a review of the work of various experimenters is recorded. The general conclusion seems to be that, judging from the evidence, it would seem that the use of the tuberculins materially improves the results of treatment. Tuberculin treatment is of little use alone, but may be justifiable to supplement the ordinary treatment by sanatorium methods.

Many anti-tuberculous serums have been produced and others have attracted some attention. The results so far achieved have been inconclusive and, for the most part, disappointing.—*B.M.J.* '05, i. 1393.

SERUM FOR HAY FEVER.—Dunbar, by injecting horses with the toxin extracted from the pollen of various *Graminaceae*, has obtained an anti-serum which is stated entirely to allay the troublesome symptoms of hay fever. The fluid serum is applied frequently to the eyes, a solid powder to the nose. The remedy is sold under the name of 'Pollantin.'

A lengthy paper appears in the *American Journal of Pharmacy*, 1905, 335, giving a *résumé* of this suggested remedy for hay fever. The substance is prepared in powder and in liquid form. The method of using is as follows:—

(1) Pour about a third of the contents of the serum-phial into the accompanying empty glass-phial, provided with a dropping pipette. The phial with dropper is

sent out in a small wooden case, and should be carried in the pocket as nearly as possible in the upright position.

(2) The method to employ in using liquid Pollantin is as follows: (a) For the eye. Bring, by means of the pipette, one drop to the outer angle of the eye, and, drawing down the lower lid with the finger, allow the drop to come into contact with the mucous membrane. A pleasantly cool sensation felt in the eye shows that the instillation has been properly carried out.

(b) For the nose. With the head bent somewhat backwards, insert the point of the pipette about $\frac{1}{2}$ inch into each nostril, and express one or two drops of Pollantin into each. Care must be taken to keep the pipette squeezed so long as it is within the nose, otherwise the Pollantin will be drawn back into the pipette again. After Pollantin has been introduced into one nostril the other must be kept closed while the serum is snuffed up from the one treated, tapping the while on the outside of that nostril with the finger.

(3) The pipette, together with the india-rubber head, should be thoroughly cleansed at least once daily, and kept for one minute in boiling Water.

The powder is obtained (*A.J.P.* '05, 335) by completely drying the serum *in vacuo* at 45° C. (113° F.) and mixing it with sterilised Milk Sugar. It forms a yellowish and almost colourless powder. This should be snuffed into the nostrils or blown in with an insuffiator, and can be dusted upon the conjunctiva with a camel's-hair brush.

The method of using the powder:—(1) A portion of the pulverised Pollantin as large as a lentil is dropped into the little scoop attached to the stopper of the bottle. The scoop is then held under one of the nostrils, the other nostril being compressed and occluded by the finger. The powder is then snuffed into the open nostril, the snuffing being repeated several times, during which the ala of the nostril is lightly tapped with the finger to distribute the powder over as much of the mucous membrane as possible. (2) If the powder is also to be used for the eyes, the accompanying camel's-hair brush is lightly dipped into it, the brush being then gently applied to the inner surface of the attached lower lid, or a small quantity of the powder may be shaken upon it from the brush. With each new bottle of the powder a new brush should also be brought into use.

Distressing symptoms following the use of 'Pollantin'; giddiness, tinnitus, vertigo and vomiting.—*L.* '05, ii. 130.

Semon, *B.M.J.* '03, i. 713; '04, i. 1168.

CANCER SERUM.—Various sera have been prepared for malignant growths. A recent one is that of Schmidt, but reports of its use are not encouraging.—*L.* '03, ii. 1374; *B.M.J.* '04, i. 299.

Doyen has reported the discovery of a micrococcus (*M. neoformans*) in cancerous tumours, and with the organism has prepared an anti-serum. The results of the inquiry at the Pasteur Institute and elsewhere are to establish that the *M. neoformans* does sometimes exist in cancerous tumours. Dudgeon finds that it is almost identical with *M. pyogenes albus* (*Jour. Hyg.* vii. '07, 13). As regards the serum, the tumours have diminished in size; but as to whether the serum can prevent recurrence, requires some years to answer.—*B.M.J.* '04, ii. 1712; *L.* '04, ii. 1799.

It is stated (*B.M.J.* '05, ii. 211) that during the five months in which all the cases which M. Doyen has wished to show have been examined, no single case of amelioration has been seen. Records of a further series of cases treated with the serum also appear in *L.* '06, i. 955, 1188, but in no case was any benefit seen.

NORMAL SERUM FOR ALIMENTATION.—Normal horse serum, heated to 60° C. (140° F.) for half an hour, may be used (a) to replace for a short time, or (b) to supplement, gastric or rectal feeding in cases of vomiting, obstruction, etc. For (a) children, 30 to 50 c.c., adults 100 to 150 c.c., for (b) 20 to 40 c.c. should be given subcutaneously daily.

Many other anti-sera have been prepared, but are of doubtful value and are not on the market (*e.g.*, cholera, dysentery, hydrophobia, leprosy, scarlatina, syphilis, whooping-cough, etc.).

Serum injections, *e.g.*, horse serum and diphtheria antitoxin, sometimes produce good effects in many diseases, *e.g.*, arthritis, gonorrhoea arthritis, asthma, broncho-pneumonia.

TUBERCULIN PREPARATIONS.

A.—KOCH'S ORIGINAL TUBERCULIN.—Prepared by boiling, concentrating, and filtering three-months-old Glycerin broth cultures of the tubercle bacillus.

An amber-coloured, syrupy fluid, with a characteristic odour. Gives the reactions for Glycerin and for albumoses.

The maximum initial dose should not exceed 0.001 c.c. and is administered by subcutaneous injection. The injection is followed in tubercular subjects by a rise of temperature of 2° to 5° F., and constitutional disturbance more or less severe. The dose must not be repeated until the reaction produced by the preceding one has completely passed off. The same dose is administered until it is followed by only a slight reaction; a larger amount may then be given, increasing by 0.001 c.c. until 0.005 is reached, then by 0.002 c.c. and so on.—Watson Cheyne, *Med. Chirurg. Trans.* 1891.

Goetsch considers that it is undesirable to obtain a reaction, and therefore commences with very small doses, 0.00001 to 0.0001 gramme; if even the former produces reaction, treatment is commenced with the *new* tuberculin 0.001 increasing to 0.1 milligramme. When this is reached treatment is continued with the old tuberculin, commencing with 0.0001 to 0.001 gramme.

For diagnostic purposes the initial dose should not exceed 0.005 c.c., which, if no reaction is produced, may be followed by 0.01 c.c. and 0.02 c.c. Tuberculin for diagnostic purposes has been applied to the skin after scarification (Von Pirquet's cutaneous reaction). Precipitated with Alcohol and the precipitate dissolved forms the solution used in Calmette's ophthalmic-reaction.

(For the diagnosis of tuberculosis in cattle the dose is 0.1 c.c. to 0.2 c.c.)

For the commencement of treatment a 1 p.c. solution is a convenient dilution, later on a 10 p.c. solution. The dilutions should be made with a $\frac{1}{2}$ p.c. aqueous solution of Carbolic Acid, and only so much prepared as can be used in a few days. Now almost discarded for treatment, *new tuberculin*, TR, being used at present.

Tuberculinum Kochi is included in the *Ph. Ger.* It is described as a clear, light brown fluid, possessing a pleasant aromatic odour. It is readily miscible with Water. It contains in addition to the active constituents about 40 parts of Glycerin in 100 parts, as well as the constituents of the bouillon, but no antiseptic.

It is put up in flasks bearing an official leaden seal, and only the undiluted preparation is allowed to be held in stock. The dilutions recommended by the physician are directed in all cases to be freshly prepared, and sterilised Distilled Water or, still better, a 0.5 p.c. Carbolic Solution to be used in the preparation thereof. It must be kept in a cool place and protected from the light.

The tuberculins possess distinct value as a specific means of treatment. An interesting and encouraging account of the results which have followed the use of the original tuberculin of Koch was given (*B.M.J.* '05, i. 1393) by Professor McCall Anderson in an address at the annual meeting of the Dermatological Society of Great Britain and Ireland. The treatment extends over a period of six or more months. Beginning with an initial dose of from a $\frac{1}{2}$ to a $\frac{1}{4}$ c.c. of a 1 in 1000 solution, the amount is gradually increased, according to the constitutional reaction obtained, up to as much as 1 c.c. of pure tuberculin. The injections are repeated every third or fourth day. Old tuberculin is still a valuable remedy, capable of producing satisfactory and even brilliant results.

Old tuberculin is not trustworthy in intra-ocular tuberculosis, and frequently did much harm. Useful as a means of diagnosis in intra-ocular tuberculosis, but useless in treatment.—*B.M.J.* '05, ii. 432.

Not necessary to employ tuberculin in gradually increased doses when using it for diagnostic purposes. Procedure consisted in administering the minimal dose of $\frac{1}{10}$ milligramme of Koch's old tuberculin in adults and $\frac{1}{100}$ milligramme in children, repeating the injection if necessary after an interval of 3 or 4 days.—*L.* '05, ii. 1203.

B.—KOCH'S NEW TUBERCULIN.—There are three varieties, termed respectively A., O., and R. Tuberculin R. or T.R. is the only one of therapeutic value.

It is prepared by triturating and emulsifying virulent tubercle bacilli with Distilled Water and centrifugalising. The fluid contains 2 milligrammes of solid matter per c.c. (not 10 milligrammes as formerly stated, *B.M.J.* '08, i. 463).

The fluid is administered by subcutaneous injection after diluting with sterile 20 p.c. Glycerin Solution. The preliminary doses should correspond to not more than $\frac{1}{500}$ of a milligramme of solid matter, i.e., 0.5 c.c. of a dilution of 1:500. The doses now recommended are usually $\frac{1}{10000}$ to $\frac{1}{2000}$ milligramme administered every 10 to 14 days and controlled by opsonic determinations.

The impossibility of limiting the reactive energy of tuberculin to the skin prevents, in many cases, the utilisation of specific properties in the treatment of lupus vulgaris.—*B.M.J.* '05, i. 689.

The results gained by injections of Tuberculin T.R. are at least as good as those by any other method. It is not assumed that in Tuberculin T.R. a perfect remedy for tuberculosis of the urinary system exists, but for vesical tuberculosis it seems the best remedy at our disposal.—*L.* '05, ii. 1769; *B.M.J.* '05, ii. 1587.

Tuberculin R given in doses of about $\frac{1}{1000}$ milligramme at intervals determined by estimations of the opsonic power of the blood is a most valuable weapon in the fight against pulmonary tuberculosis.—*B.M.J.* '06, ii. 18.

Latham has adduced clinical and bacteriological evidence that Tuberculin R and bacterial vaccines produce their therapeutic effects when administered by the mouth.—*Proc. Roy. Soc. Med.* i. '08, Med. Sec. 195.

REFERENCES.—*L.* '97, ii. 568, 600, 704, 1488; '98 ii. 194; *B.M.J.* '97, ii. 207; '98, i. 357; '98, ii. 77; *B.M.J.E.* '97, ii. 19, 27, 31, 55, 103; '98, i. 47, 55; *T.G.* '97, 850; '98, 400; *Pr.* lix. 399. Oxy Tuberculin.—*L.* '98, i. 179; *B.M.J.E.* '98, ii. 27.

OPSONINS.

Great interest has been aroused by the discovery of the significance attached to the opsonic power of the blood and the value of estimations of the opsonic index in the diagnosis and treatment of tuberculosis and other infections. The term 'opsonin' was invented by Wright and is derived from a classical word which means 'to cater or prepare victuals for,' and it apparently prepares the bacteria for ingestion by the phagocytes. Opsonins are described (*L.* '05, ii. 1917; *B.M.J.* '05, ii. 342) as substances contained in the serum or plasma of blood which possess the power of so modifying various kinds of bacteria as to render them an easier prey to the attacks of leucocytes.

This opsonic power is found in the blood of both healthy and diseased persons, but differs in degree, an essential difference being that whereas the degree is held to be approximately the same in normal healthy persons, wide variations are found amongst those who are diseased. The process of determining the opsonic index of the blood in tuberculosis is briefly outlined (*B.M.J.* '05, ii. 172) as follows:—Equal quantities of the patient's serum, an emulsion of tubercle bacilli (or other organisms), and leucocytes (washed in a solution of $\frac{1}{2}$ p.c. Sodium Citrate in normal salt), are taken in a capillary pipette and incubated together for 15 minutes, after which films are made of the mixture and stained in a modified way for tubercle bacilli, etc.; the number of tubercle bacilli (or other organisms) ingested by 50 polynuclear white corpuscles is counted, and the figure thus obtained is compared with a standard similarly obtained, but using the serum of a healthy person. The former figure divided by the latter gives the 'opsonic index.' A series of experiments on the 'opsonin' treatment of tuberculous patients were undertaken at the London Hospital Medical College, and the results are recorded in the *L.* '05, ii. 1603.

An address on the opsonic theory and its practical application to medicine and surgery is reported in the *B.M.J.* '06, ii. 16, and gives a very lucid and up-to-date review of the present knowledge of this subject. (See also *Practitioner*, May 1908, Wright and others.)

VACCINES.

Vaccines are used either for prevention or prophylaxis, or for the treatment of chronic or sub-acute infections. For the latter, cultures of the organism corresponding to, and preferably isolated from, the infection, are sterilised by

heat and standardised as to the number of organisms they contain in a given volume, from which the dose is calculated. For tuberculous infection Tuberculin R is used (*see above*).

GLYCERINATED VACCINE LYMPH is prepared by mixing calf lymph with 50 p.c. of Glycerin and storing for three months; this destroys all extraneous organisms. A preparation in which the extraneous organisms are killed with Chloroform is also prepared (Green's method). (Prophylactic.)

LEPROLIN.—A toxin of the cultivation of the *Bacillus lepræ*. It is stated (*B.M.J.* '05, i. 699) to have given good results in the treatment of leprosy.

By incubating leprosy tissue in salt solution Deycke obtains a growth of an acid-fast streptothrix. A fatty substance extracted from this (termed Nastin) used for the treatment of leprosy.—*B.M.J.* '08, i. 802.

STAPHYLOCOCCIC VACCINE is prepared from cultures of the *S. pyogenes*, *aureus* and *albus* (dose 100-1000 millions). Valuable in chronic staphylococci infections, *e.g.*, acne, furunculosis, sycosis, etc.—*B.M.J.* '04, i. 1075.

CHOLERA VACCINE is prepared from virulent cultures of the cholera spirillum. Dose, 1 c.c. (Wright and Bruce, *B.M.J.* '93, i. 227). (Prophylactic.)

TYPHOID VACCINE is prepared from virulent cultures of the *Bacillus typhosus* (Wright and Semple, *B.M.J.* '97, 256; Wright and Leishman, *ib.* '00, i. 122). (Prophylactic.)

PLAGUE VACCINE is prepared from cultures of the *Bacillus pestis* (*B.M.J.* '97, i. 1057 and 1461). (Prophylactic.)

Streptococci (dose, 20-60 millions), Pneumococci (dose, 10-50 millions), Gonococci (dose, 100-500 millions), Malta fever, *Bacillus coli* (dose, 5-15 millions), and other vaccines have been used with success in the corresponding chronic or sub-acute infections. Vaccine treatment should be controlled by opsonic determinations.

ANTI-RABIC INOCULATION.—The Pasteur system of inoculation as practised for bites of rabid animals. Emulsions of spinal cord of rabbits dried for periods varying from 14 to 3 days and injected subcutaneously. The treatment must be carried out at an Institute (*e.g.*, Pasteur Institute, Rue Dutot, Paris; Pasteur Institute, Lille). (Useless for treatment of disease when declared.)

Some of the anti-sera (diphtheria, tetanus, plague, and streptococcus) may be employed as prophylactics, but their protective power is transient (three weeks), whereas the vaccines protect for at least many months.

COLEY'S FLUID.

A fluid prepared by cultivating the streptococcus of erysipelas and the *Bacillus prodigiosus* in broth, and heating to 58° C. (136·4° F.) for one hour.

It has been used in the treatment of malignant growths, especially sarcomata. The dose to commence with is $\frac{1}{4}$ to 1 minim, administered by injection in the neighbourhood of the tumour. The dose is gradually increased, the guide being the amount of reaction produced.

MALLEIN.

Prepared by boiling and concentrating broth cultures of the glanders bacillus. Employed for the diagnosis of glanders in animals. The requisite dose is injected subcutaneously in the neck. In a glandered animal a large swelling forms at the seat of inoculation, any local lesion becomes enlarged, and the temperature rises at least 2·5° F. above the normal. It is of no therapeutic value.

DE BACKER'S FLUID.

Pure cultures of yeast stored under pressure in syphon-like vessels provided with hollow needles by means of which the dose is injected.

Has been used in the treatment of tuberculosis and cancer.—*B.M.J.* '97, ii. 802.