LEAGUE OF NATIONS

HANDBOOK

of

INFECTIOUS DISEASES

with

NOTES ON PROPHYLAXIS, SERUM TREATMENT AND VACCINATION

GENEVA, 1945

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HANDBOOK OF INFECTIOUS DISEASES

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NOTES ON PROPHYLAXIS, SERUM TREATMENT AND VACCINATION

by the Staff of the Cantacuzène Institute,

under the direction of

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Dedicated to the memory of

Professor J. CANTACUZÈNE

Member of the Health Committee
of the League of Nations

PREFACE

The danger from infectious diseases increases considerably as the result of war and migrations caused by the war. Every recent addition to scientific knowledge concerning methods of combating these diseases is therefore of special interest now to health administrations and to physicians in the civil and military health services. War conditions have in recent years greatly hampered the dissemination from one country to another of information concerning new scientific discoveries and in certain countries have made it difficult, if not impossible, to publish up-to-date medical books containing accounts of these discoveries.

The need for placing in the hands of physicians in a condensed and handy form modern scientific facts relating to infectious diseases, their diagnosis, treatment and prevention, already recognised at the beginning of the war by the League of Nations Health Section, has now become much more acute. It was therefore with gratitude that the Secretariat agreed to publish, in both English and French, this *Handbook* prepared by Professors Ionescu-Mihăești and M. Ciucă, Directors of the Cantacuzène Institute in Bucharest, and their colleagues of that Institute.

The authors give the reader the benefit of first-hand experience gained during the first and second World Wars, not only of the common communicable diseases of Western Europe, but of several of the pestilential diseases which have prevailed in Roumania and the neighbouring countries during the last thirty years.

Their first manual of infectious diseases was issued at the request of the Roumanian authorities in 1915. In 1939, a similar request resulted in the publication of a more comprehensive volume. On the exhaustion of the first, a revised and augmented second edition was issued in January 1944. The present volume is not a mere translation of

this second Roumanian edition, but includes, besides many additions and corrections, new chapters on the sulphonamides, penicillin, etc.

Although the principal authors of this *Handbook* are members of technical committees of the League of Nations Health Organisation, and often base their opinions on official reports of that Organisation, both the merit and the responsibility appertaining to these opinions rest of course with them, as no League body has had an opportunity of discussing or endorsing the contents of the *Handbook*.

The Health Section.

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INFECTIOUS AND PARASITIC DISEASES OF MAN

Part I

INFECTIOUS AND PARASITIC DISEASES OF MAN

CHAPTER I

INFECTIONS DUE TO BACTERIA

ERYSIPELAS

Detailed international nomenclature (1938) : No. **11.**[1] [2]

Latin	= Erysipelas.	Ital.	= Erisipela, Risipola (v) [3].
French	= Erysipèle.	Roum.	= Erizipel.
German	= Erysipel, Rose (v).	Span.	= Erisipela.

An acute, infectious, febrile disease, characterised by an extensive inflammation of the skin and mucous membranes.

Etiological agent : Streptococcus hæmolyticus (*Streptococcus pyogenes haemolyticus*, Fehleisen, 1882).

Incubation : 3 to 6 days.

Direct contagion : Pathological exudates from the patient.

Indirect contagion : Contaminated clothing and fomites.

Portal of entry : The skin or mucous membranes ; open wounds.

Localisations : Generally confined to the erysipelas plaque ; spreads to the lymphatics and regional lymph glands. Sometimes septicæmia.

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[1] This number makes it possible to find the names of the disease in any of the European languages in the " Polyglot Glossary of Communicable Diseases " which forms the 3rd number of volume **10** of the *Bulletin of the Health Organisation* of the League of Nations, 1943/44.

[2] Numbers and letters are those adopted for the Detailed International List of Causes of Death by the 5th Revision Conference in 1938. Letters between brackets indicate supplementary subdivisions introduced for the use of the " Polyglot Glossary... ".

[3] Vulgar name.

Latent streptococcus infections are very apt to occur (J. Bordet).

Symptoms : Rigors, high temperature. *Erysipelas plaque* (red, hot to the touch, with raised edges, spreading). Enlargement of the regional lymph glands. Local or remote complications, suppuration, cellulitis, gangrene, etc.

Prognosis : As a rule favourable.

Channel of elimination : Open focus.

Resistance of the germ outside the body : In the pathological exudates (pus and blood), the streptococcus resists desiccation for several days. Killed speedily by 1‰ sublimate, 5% carbolic acid or by boiling.

Laboratory diagnosis : Identification of streptococcus in vesicles (erysipelas bullosum) or in other pathological exudates (wounds, abscesses, etc.). In case of septicæmia : blood culture.

Treatment : *Anti-streptococcus polyvalent serum*, administered subcutaneously, 100 to 200 cc. Repeat the dose on succeeding days if necessary. In serious cases, by intravenous injection (p. 254).

In the case of erysipelas migrans or in cases of relapse, also treat with *antistreptococcus vaccine* (p. 239).

Sulphonamides alone or combined with serum treatment (p. 282). Avoid toxic accidents : agranulocytosis, hematuria.

Prophylaxis : Isolation of the patient ; disinfection of pathological exudates, contaminated clothing and fomites.

SCARLET FEVER

Detailed international nomenclature (1938) : No. **8.**

Latin	= Febris scarlatinosa, Scarlatina, Febris rubra.	German	= Scharlach.
		Ital.	= Scarlattina.
		Roum.	= Scarlatină.
French	= Scarlatine.	Span.	= Escarlatina.

A contagious, acute, febrile disease ; with characteristic sore throat and toxic eruption. Desquamation during convalescence.

Etiological agent : Streptococcus hæmolyticus (*Streptococcus scarlatinae*, Dick, 1923-1924), regarded by the great majority of authorities as an etiological agent ; found in 99% of cases of scarlatinal sore throat.

Incubation : Generally 2 to 5 days, rarely up to 8 days.

Direct contagion : The most common ; through exudate from the throat or by scales contaminated therewith. Convalescents, if germ-carriers, are also contagious.

Indirect contagion : Fomites and clothing contaminated by the patient's sputum, scales, urine, etc. The disease may be transmitted by the patient's contacts.

Predisposing causes : Infancy and early childhood ; a cold and damp climate, etc., by affecting the state of the mucous membranes, facilitates the invasion of the body by the germs.

Portal of entry : The nose and throat. In exceptional cases, an operation wound or the female genitalia (surgical or puerperal scarlet fever).

Localisation : The tonsils constitute the main reservoir of infection (scarlatinal tonsillitis) whence the streptococcus may also invade the circulation (septicæmia).

Symptoms : *Invasion period :* 24 to 36 hours ; an abrupt onset, rigors, fever, vomiting, sore throat.

Eruption period : 6 to 8 days, redness of the throat, scarlatinal eruption, fever usually continuous.

Desquamation period : 1 to 5 weeks.

Clinical forms ; atypical, septic, malignant, hypertoxic. Sometimes a relapse about the 18th or 21st day : more rarely a reinfection (5%).

Complications : ulcerative necrotic tonsillitis, otitis, phlegmonous adenitis, nephritis, endocarditis, etc.

Prognosis : Variable, directly related to the clinical form and its complications.

Channels of elimination of the germ : By the secretions of the nose and throat and the scales contaminated with these secretions. The streptococcus is also eliminated in the patient's urine and the pus of suppurating complications.

Resistance of the germ outside the body : In the pathological exudates (pus and blood), the streptococcus resists desiccation for several days.

Laboratory diagnosis : Isolation of the streptococcus hæmolyticus in the exudate from the tonsils (on culture media containing blood).

Extinction phenomenon (SCHULTZ-CHARLTON) (p. 208).

DICK Test (p. 207).

Treatment : Serum : (a) *serum from a convalescent* 20 to 60 cc. (p. 266) ; (b) Dick's *antitoxic serum*, 50 to 200 cc. repeated until disappearance of toxic phenomena ; by intravenous, intramuscular or subcutaneous injection according to the gravity of the case (p. 249) ; (c) *Immunotransfusion*, preferably from a donor convalescent from scarlet fever or from an adult previously vaccinated (p. 269).

Associate sulphonamides in complications (p. 282).

Rest in bed, adequate diet. Symptomatic treatment, disinfection of mouth, throat and nose.

Prophylaxis : Compulsory notification of the disease. Isolation of patient until termination of desquamation and disappearance of the hæmolytic streptococcus (negative cultures). Clinical and bacteriological control of contacts for 8 days following notification of case. Disinfection of pathological exudates and contaminated fomites. Final disinfection of dwelling.

Preventive vaccination (p. 225) of contacts showing a positive reaction to Dick's test (p. 207) with toxin or anatoxin, and particularly children. *Serum prophylaxis* (serum from a convalescent).

PUERPERAL SEPSIS
(Puerperal Fever)

Detailed international nomenclature (1938) : No. **147.**

Latin = Sepsis puerperalis, Septicemia puerperalis.
French = Fièvre puerpérale. Infection puerpérale.
German = Kindbettfieber.
Ital. = Febbre puerperale.
Roum. = Infecție puerperală.
Span. = Fiebre de leche.

An acute, microbic infection complicating child-birth.

Etiological agents : In order of frequency : Streptococcus pyogenes hæmolyticus, anaerobic streptococci, colon bacillus, gonococcus, anaerobic microbes ; very rarely, staphylococcus or pneumococcus.

Origin of infection : *Endogenous :* transfer of germs from latent foci as a result of the trauma of delivery. *Exogenous :* insufficient asepsis, unsterilised instruments and dressings.

Predisposing causes : General ill health of the woman : deficiency diseases, chronic diseases, syphilis, malaria, tuberculosis, etc., premature rupture of the membranes. Retention of fragment of the placenta, etc.

Incubation : Generally 5 days, sometimes more. In very acute cases, 24 hours.

Portal of entry : The placental wound (lack of mucous in the uterine cavity, dilated and open blood-vessels and lymphatics).

Localisations : See portal of entry. Blood (septicæmia).

Symptoms : High temperature, rapid pulse, bad general condition.

1. *Putrid or septic endometritis :* pains, absence of involution of the uterus, diminished, discoloured and fetid discharges.

2. *Septicæmia-thrombophlebitis :* repeated rigors, rapid pulse, myalgia, sometimes petechiæ.

3. *Parametritis-peritonitis :* pain in the genitalia, temperature curve of abcess formation, discrepancy between pulse and temperature, tympanitis.

Prognosis : Serious.

Channels of elimination of germs : Uterine discharges, urine.

Resistance of germs outside the body : Varying according to the species of germ concerned.

Laboratory diagnosis : 1. Bacteriological examination, both direct and after cultures (aerobic and anaerobic) from discharges and uterine secretions, taken from the cervix.

2. Cultures (aerobic and anaerobic) from the urine taken aseptically. Examination of urinary sediment (albumin, granular cylinders) must not be overlooked.

3. Repeated blood counts and blood cultures.

Treatment : Early serum treatment corresponding to the causal germ (anti-streptococcus serum, antiperitonitis serum or a combination of both (pp. 254 and 262). Repeated *immuno-transfusions* (p. 269).

Vaccination treatment with stock vaccine or with auto-vaccine (p. 239). Local dressings with streptococcal *filtrates* (p. 241) or polymicrobic bouillon-vaccine (DELBET) (p. 241).

Sulphonamides alone or in combination (p. 282). The necessary gynæcological treatment (drainage, curettage, etc., hysterectomy).

Prophylaxis : Careful disinfection of pathological exudates and contaminated fomites and clothing. Avoid contact with carriers of streptococci (latent or visible infection).

ACUTE RHEUMATIC FEVER

Detailed international nomenclature (1938) : No. **58.**

Latin = Rheumatismus articulorum acutus, Febris rheumatica.
French = Rhumatisme articulaire aigu.
German = Akuter fieberhafter Gelenkrheumatismus.
Ital. = Reumatismo articolare acuto febbrile.
Roum. = Reumatism polyarticular acut febril.
Span. = Reumatismo articular agudo febril.

An infectious, febrile disease, characterised by multiple arthritis often complicated by cardiac lesions.

Etiological agent : Not yet determined (streptococcus, *Streptococcus viridans* (?)).

Probable origin of the infection : sore throat and inflammatory dental foci.

Incubation : 1 to 3 weeks (?).

Direct contagion : Some authorities hold that contagion is possible through secretions from the patient's nose and throat.

Indirect contagion : (?).

Predisposing causes : An arthritic temperament ; deficient hygiene and diet, overwork, cold and damp climate, etc. Age : childhood (?).

Portal of entry : Nose, throat and tonsils.

Localisations : A marked predilection for the serous membranes, above all the serous membranes of the joints, the endocardium, the pericardium and pleura, etc.

Symptoms : The disease is nearly always preceded by *sore throat.*

The *temperature* rises gradually. An abrupt rise is rare. The temperature curve is irregular.

The joints are attacked one after another. When a new joint is affected the attack on the one previously affected begins to subside. Each new attack upon a joint is accompanied by a fresh rise in temperature. The joint attacked is extremely painful especially during movement, but there is never any suppuration. Characteristic pallor ; profuse sweating.

Complications : Heart affections appear between the 6th and 15th day of the illness. Valvular endocarditis (mitral) is the most frequent. Lesions are permanent. Sometimes rheumatic pleurisy occurs. Frequent relapses.

Prognosis : Serious, especially on account of cardiac lesions. Rheumatism is the cause of the majority of heart affections

Channels of elimination : Probably the secretions of the nose and throat.

Resistance of the germ outside the body : (?).

Laboratory diagnosis : Our present knowledge of the disease does not permit of this.

Treatment : Large doses of sodium salicylate. Local applications to relieve pain.

Prophylaxis : Disinfection of the nose and throat. Possible removal of enlarged tonsils in the case of children.

Hygiene of dwelling and of diet. Avoid overstrain and damp dwellings. Systematic treatment of affections of the teeth and tonsils.

PNEUMONIA AND OTHER INFECTIONS DUE TO PNEUMOCOCCI

True pneumonia, an infectious disease following a well-defined course, characterised by an acute inflammation of one or more lobes of the lungs and by its abrupt termination in a crisis. Other pneumococcus infections : peritonitis, meningitis, otitis, mastoiditis, pericarditis, endocarditis, pleurisy, etc. Pneumococcus septicæmia.

Of these infections, pneumococcus meningitis, a very serious illness with a high rate of fatality, has of recent years greatly benefited by the administration of certain sulphonamides, a treatment which is almost specific for this disease.

Biological agent : Pneumococcus (*Diplococcus pneumoniae* Pasteur, Chamberland, Roux, 1881, Talamon, 1883), lanceolated, capsulated diplococcus. Several quite distinct serological types (I to XXX).

LOBAR PNEUMONIA

Detailed international nomenclature (1938) : No. **108.**

Latin = Pneumonia crouposa, P. fibrinosa, P. duplex, P. lobaris, P. bilateralis.
French = Pneumonie.
German = Lobäre Lungenentzündung.
Ital. = Polmonite lobare.
Roum. = Pneumonie lobară.
Span. = Pneumonia lobar.

Etiological agent : The immunological types most frequently encountered are : I, II, III.

Incubation : 2 to 6 days.

Direct contagion : Possible by means of the sputum and purulent exudates of the patient. Under certain conditions, epidemic foci may appear.

Indirect contagion : Probable : inhalation of dust or dried sputum ; fomites and clothing soiled by pneumococcic exudates.

Predisposing causes : Chills, overstrain, injuries, etc.

Portal of entry : The air passages.

Localisation : The pulmonary tissue.

Symptoms : Sudden onset, pain in the side, rigor, high temperature (F. 102°-104° - C. 39°-40°), abdominal pains, difficult breathing, cough painful from the beginning, the sputum stained with blood (red-currant jelly), viscous, towards the end purulent ; discrepancy between pulse and breathing (pulse rate 100, respiration 30 to 70 per minute), labial herpes.

The illness lasts from 7 to 9 days. At the crisis, an abrupt fall in the temperature, usually followed by a definite improvement in the general condition and a rapid recovery. Exceptional types : atypical, mild, or prolonged ending fatally.

Prognosis : Dependent upon the clinical type, serious in the case of old persons and alcoholics.

Channels of elimination : By the sputum and exudates from the nose and throat.

Resistance of the germ outside the body : Pneumococci continue to live for weeks in dust and in dried sputum. Sun and heat kill them speedily.

Laboratory diagnosis : Identification of the germ in the sputum and test for distension of the capsule (NEUFELD'S test) to ascertain the type. Inoculation of mice with sputum or suspected material. Isolation and determination of the serological type.

Treatment : *Chemical : Sulphonamides* alone or in combination with specific treatment (sera) give remarkable results in all pneumococcus infections (p. 283).

Serum treatment with monovalent serum, or polyvalent if it has not been possible to ascertain the type (p. 255).

Vaccine treatment in cases which do not clear up, in chronic cases, broncho-pneumonia, pulmonary abscess, etc. (p. 239).

Prophylaxis : Avoid cold and possible contamination.

STAPHYLOCOCCUS INFECTIONS

Detailed international nomenclature (1938) : No. **24 b.**

Under this head are grouped diseases due to localisations of the staphylococcus in different tissues or viscera : acne, ordinary boils, carbuncles, sycosis, meningitis, pulmonary abscess, staphylococcus pleurisy, endocarditis, pericarditis, otitis, mastoiditis, arthritis, abscess of the liver, various abscesses, perinephretic abscesses, osteomyelitis, etc., septicæmia and pyemia.

Etiological agent : Staphylococcus (*Staphylococcus aureus, albus, citreus,* Rosenbach, 1884). A very common germ abundant on the skin.

Portal of entry : Usually skin and mucous membranes.

Localisations : See above.

Symptoms : Dependent on the part affected and the anatomical characteristics of that part.

Prognosis : According to the particular case ; favourable in the case of local infections of the skin, serious in the case of carbuncle (especially on the upper lip) on the face, and in cases of localisation in the viscera ; always serious with diabetic patients ; staphylococcemia is always very grave.

Channels of elimination : From the lesions (pus, sputum, urine, etc.).

Resistance of the germ outside the body : Well marked ; it resists heat and desiccation relatively well.

Laboratory diagnosis : Identification of the staphylococcus in pathological exudates by direct examination. Blood culture in case of septicæmia.

Treatment : Variable according to clinical types and localisation. *Vaccine treatment* with staphylococcus anatoxin (p. 238) or antistaphylococcus vaccine (p. 237) alone, in combination or alternately. Antistaphylococcus *bacteriophage* by the mouth and in and around the foci (p. 245). Sulphonamides (p. 283) alone or combined with other treatments give good results. *Penicillin* has a very marked abiotic action on this germ (p. 288). In case of septicæmia, antistaphylococcus serum (p. 251) combined with vaccine and chemical treatment.

INFECTIOUS GRANULOMA

Detailed international nomenclature (1938) : part of No. **44 d.**

Latin = Granuloma infectiosum.
French = Bothryomycome (Papillome inflammatoire, Granulome infectieux).
German = Infektiöses Granulom.
Ital. = Botriomicosi.
Roum. = Botriomicom, Granulom infectios.

Benign wart-like (or pediculate) tumours of infectious origin.

Etiological agent : Pyogenic germs ; the most probable, staphylococcus aureus.

Incubation : Several weeks.

Direct contagion : Possible.

Indirect contagion : Through a foreign body.

Portal of entry : A septic puncture, penetration of a foreign body, a crack or cut.

Localisation : Usually on uncovered parts exposed to injuries : hands, cheeks, eyelids, the scalp, lips, mucous membranes of the mouth, etc.

Symptoms : Pediculate tumours varying in size from a pea to a small hazel-nut. Round or egg-shaped in form, bright red or violet in colour, with a mammillated or smooth

surface, sometimes ulcerated. They are not painful and may be the seat of bleeding.

Prognosis : Benign.

Channels of elimination : Ulcerations on the surface of the tumour.

Resistance of the germ outside the body : That of pyogenic cocci.

Laboratory diagnosis : Biopsy, if the diagnosis is uncertain.

Treatment : Excision of the tumour. Electro-coagulation. General treatment with staphylococcus anatoxin (p. 238).

Prophylaxis : Avoid trauma.

CEREBRO-SPINAL MENINGITIS
(Meningococcal Meningitis)

Detailed international nomenclature (1938) : No. **6.**

Latin = Meningitis cerebrospinalis epidemica, M. meningococcica.
French = Méningite cérébro-spinale épidémique (Meningococcie).
German = Übertragbare Genickstarre, Epidemische cerebrospinal Meningitis.
Ital. = Meningite cerebrospinale epidemica.
Roum. = Meningită cerebro-spinală epidemică.
Span. = Meningitis cerebro-espinal epidemica, Meningitis meningocócica.

An acute, infectious, specific, often epidemic, disease, characterised by inflammation of the nose and throat and a purulent inflammation of the meninges.

Etiological agent : The meningococcus (*Neisseria meningitidis* Weichselbaum, 1887). Coffee-bean-shaped diplococcus, 4 types, differing in their antigenic characteristics (Types I and III epidemic).

Incubation : 2 to 7 days.

Direct contagion : Droplets from the mouth, nose and throat emitted by a patient with meningococcal rhinopharyngitis or by a healthy germ-carrier.

Indirect contagion : Possible, by fomites and contaminated clothing (less important owing to fragility of the germ).

Predisposing causes : Age (children, adolescents), damp and cold seasons (common sore throats facilitate the entry of the meningococcus).

Portal of entry : Nose and throat.

Localisations : Nose and throat, meninges, the cerebro-spinal fluid. More rarely : arthritis, pericarditis, cerebral abcesses. The skin (petechiæ). Meningococcemia.

Symptoms : Sudden onset with high temperature, headache, stiffness of the neck, contraction of the muscles, Kernig's and Brudzinski's signs, photophobia, strabismus, convulsions, delirium, vomiting, constipation, vaso-motor disturbances, sometimes a semi-comatose condition, a purpuric eruption (petechiæ). Intense leucocytosis. The disease may last for from 2 to 20 days in its acute form and for several months in chronic forms with relapses and cachexia.

Complications : Inflammation of other serous membranes : arthritis, pericarditis, otitis, orchiepididymites, etc. Meningococcæmia.

Prognosis : Serious, especially in infants ; much more favourable since the use of serum treatment and treatment with sulphonamides.

Channels of elimination : Nose and throat.

Resistance of the germ outside the body : Fragile, sensitive to variations of temperature, lives from 2 to 3 days in secretion from the throat protected by the mucus. For the same period, fomites and soiled clothing are contagious (indirect contagion). Resistance is less in the cerebro-spinal fluid removed by puncture.

Laboratory diagnosis : Lumbar puncture and subsequent examination of the fluid are essential in every acute case of meningitis.

1. Identification of germ in the cerebro-spinal fluid by direct examination or after centrifugalisation. Culture of the cerebro-spinal fluid and of the nose and throat secretions. Blood culture in case of septicæmia. Identification of the type by means of monovalent antimeningococcus serums.

2. Trace healthy carriers by cultures of nose and throat secretions.

Treatment : *Serum treatment :* from the outset of the malady with antimeningococcus serum (p. 255) by intraspinal and intravenous injection, until the cerebro-spinal fluid becomes clear and the leucocytes and germs have disappeared.

It is advisable to repeat the bacteriological examinations to anticipate relapses.

In case of *serous meningitis*, suspend serum treatment (p. 195). In septicæmic types, administer serum both by intravenous and intramuscular injection (p. 188).

Vaccine treatment in chronic and prolonged types and in their complications (p. 239).

Chemical treatment : always combine treatment with sulphonamides (p. 283).

Prophylaxis : Notification of the disease and isolation of the patient. Search for healthy carriers. Disinfection of throat, tonsils and nasal cavities of patients and healthy carriers by painting, gargling and nasal instillation. Disinfection of fomites and clothing with antiseptic solutions.

GONORRHŒA, GLEET

Detailed international nomenclature (1938) : No. **25.**

Latin = Urethritis gonorrhoica.
French = Blennorragie.
German = Gonorrhoe, Tripper (v).
Ital. = Blenorragia.
Roum. = Blenoragie, Uretrită blenoragică
Span. = Blenorragia, Gonococia.

An infectious, specific venereal disease, characterised by acute inflammation of the urethral, vulvar, vaginal or conjunctival (new-born infants) mucous membranes.

Etiological agent : Gonococcus (*Neisseria gonorrhoae*, Neisser, 1879). Coffee-bean-shaped diplococcus.

Incubation : 36 hours to 5 days.

Direct contagion : By contact with an infected mucous membrane ; generally as a result of sexual relations. *Ophthalmia of new-born infants*, as the child passes through the contaminated vagina.

Very important part played by chronic forms in the transmission of this disease.

Indirect contagion : Contaminated toilet articles.

Portal of entry : Genital or ocular mucous membranes, as a rule.

Localisations : Urethra, vulva, vagina, cervix of the uterus, rectum, conjunctivæ.

Symptoms : Purulent secretion, greenish yellow in colour, continuous or intermittent, sometimes slightly blood-stained. Urination and erection painful.

Complications : The infection may spread along the mucosæ : orchiepididymitis, salpingitis, endometritis, cystitis, pyelitis, pyelonephritis, etc. Sometimes infection becomes general : septicæmia. Articular (mono-articular) and endo-pericardial localisations.

Prognosis : Serious owing to complications. Possible sterility. Less serious since use of sulphonamides.

Channels of elimination : By lesions ; mucous secretion in chronic forms.

Resistance of germ outside the body : Little resistance.

Laboratory diagnosis : Identification of gonococcus in pathological exudates (intracellular diplococci). Cultures on special media : flakes (urine) and sperm.

In complications, complement fixation test.

Treatment : Acute forms : sulphonamides (p. 284) and local treatment (potassium permanganate, protargol, oxycyanure of mercury, etc.). In chronic forms and complications, vaccine treatment together with auto-vaccine (p. 239). Penicillin, particularly in sulphonamid-resistant cases.

Prophylaxis : 1. Avoid intercourse with suspected cases. 2. Anti-venereal measures (tracing and treatment of germ-carriers ; education of public).

WHOOPING-COUGH (PERTUSSIS)

Detailed international nomenclature (1938) : No. **9.**

Latin = Tussis convulsiva.
French = Coqueluche.
German = Keuchhusten.
Ital. = Tosse convulsiva, Tosse ferina, Pertosse.
Roum. = Tuse convulsiva, Tuse măgărească.
Span. = Tos ferina.

An infectious, communicable and epidemic disease characterised by fits of a characteristic form of coughing.

Etiological agent : Bordet-Gengou's coccobacillus (*Hemophilus pertussis*, Bordet-Gengou 1906).

Incubation : Variable, 2 to 12 days.

Direct contagion : Especially during the first weeks of the malady, by droplets of saliva ejected in speaking or during fits of coughing.

Indirect contagion : Rare ; fomites and contaminated clothing.

Predisposing causes : Age (children), damp and cold seasons.

Portal of entry : Upper air passages.

Localisations : Respiratory mucous membranes (larynx, trachea, bronchial tubes).

Symptoms : First period (15 days) : cold in the head, conjunctivitis, slight cough, temperature F.100.4° (C.38°), insomnia, lack of appetite. Second period (2 weeks to

2 months) : no fever, frequent coughing, especially at night, spasmodic, suffocating and in recurrent fits, followed by expectoration and very often by vomiting. During a fit of coughing, the face becomes congested, the eyes bloodshot and watering.

Prognosis : Reserved owing to complications.

Channels of elimination : Respiratory passages.

Resistance of the germ outside the body : Very little resistance.

Laboratory diagnosis : During the first weeks, direct identification of germ or cultures on Bordet-Gengou's medium (MADSEN's method).

Treatment : Symptomatic. Well-aired room. Early *vaccine treatment* (p. 240). Change of air (altitude).

Prophylaxis : (*a*) Compulsory notification of disease. (*b*) Isolation of patient until coughing fits cease. (*c*) Isolation of suspects for 15 days. (*d*) Disinfection of patient's room, fomites and clothing.

SOFT CHANCRE

Detailed international nomenclature (1938) : No. **44 a (a).**

Latin = Ulcus molle.
French = Chancre mou, chancrelle.
German = Weicher Schanker, Ulcus molle.
Ital. = Cancro molle.
Roum. = Sancărul moale.
Span. = Chancrillo, Chancro simple.

A specific, infectious, communicable, localised venereal disease, characterised by an ulceration of the skin of the external genital organs, more rarely of the mucous membranes.

Etiological agent : The chancre streptobacillus (*Hemophilus ducreyi*, Ducrey, 1889), a small coccobacillus, with a clear centre.

Incubation : 2 to 5 days.

Direct contagion : Nearly always by sexual contact.

Indirect contagion : Accidentally by a septic puncture (midwives, doctors), from a toilet article, or contaminated hands.

Portal of entry : Abrasion of the skin or mucous membranes.

Localisations : Usually, the genital organs or perineal region.

Symptoms : A deep ulceration with sharp, undermined edges, bordered by a fine red circle. Bottom irregular, ash-coloured, granular, covered with pus. Base *soft*, inflamed. Lesion painful. Sometimes a tendency to rapid extension, phagedenism. The ulceration is often accompanied by adenitis almost always tending to suppurate.

Prognosis : Not a serious disease, but one of long duration.

Channels of elimination : By the local lesion.

Resistance of the germ outside the body : Very little resistance, but may subsist in latent form on the mucous membranes (vagina).

Laboratory diagnosis :

1. Identification of germ in secretion obtained from the edge of the ulceration.

2. Positive auto-inoculation with a small quantity of pus under the skin.

3. Ito-Reenstierna's *intradermal test* (p. 210). The intradermal injection of the patient with a killed streptobacillary antigen (0.2 cc. of the carbolised germ suspension) produces an erythematous papular reaction after 24 or 48 hours. The positive reaction persists, even after the chancre is cured (p. 211).

4. Complement fixation test (a method used only exceptionally).

Treatment : *Of the chancre :* physical cauterisation (by thermo- or galvano-cautery) or chemical cauterisation (silver nitrate, a solution of alcohol saturated with carbolic acid, 40% solution of chloride of zinc). Disinfectants, application of iodoform powder. *Of the bubo :* electro-coagulation ; discharge by puncture.

Vaccine treatment : with a suspension of dead streptobacilli.

Protein treatment (intramuscular injections of milk or intravenous injections of anti-typho-paratyphoid vaccine (0.05 cc. diluted in 5 cc. of physiological saline). The doses to be increased according to the temperature reaction.

Prophylaxis : Individual prophylaxis and anti-venereal campaign.

PLAGUE

Detailed international nomenclature (1938) : No. **3.**

Latin	= Pestis.	Ital.	= Peste.
French	= Peste.	Roum.	= Ciumă.
German	= Pest.	Span.	= Peste.

An infectious, specific, epidemic disease generally characterised by a rapid development and a very grave prognosis. Endemic foci.

Etiological agent : The plague coccobacillus (*Pasteurella pestis*, Yersin, 1894). An important reservoir of the virus exists among certain species of rodents : rats, tarabagan (*Arctomys bobac*), spermophile (*Citillus citillus*), *Guttatus guttatus*, etc. Sub-acute and chronic forms.

Incubation : 2 to 7 days. Usually 5 days.

Direct contagion : Frequent ; the rule in the pneumonic form by droplets of expectoration. Pus from suppurating and open lymph glands (bubonic form).

Indirect contagion : Fleas, rats or other rodents, vectors of the virus. An epizootic among rats always precedes a human epidemic. More rarely by contaminated clothing.

Portal of entry : The skin, mucous membranes and air passages.

Localisations : 1. Lymph glands (*bubonic plague*) ; 2. Lungs (*pneumonic plague*) ; 3. Blood (*septicæmic plague*).

Symptoms : 1. *Bubonic plague :* rigors, violent headache, vomiting, high temperature, asthenia, very painful plague bubo (armpit, groin, neck, etc.). Duration 2 to 3 weeks.

2. *Pneumonic plague :* symptoms of pneumonia or broncho-pneumonia and phenomena connoting serious infection ; fatal ending in 2 to 3 days.

3. *Septicæmic plague :* violent headache, delirium, toxic dyspnea. Duration 2 to 3 days. Bleeding in various parts (black plague) with fatal consequences.

Prognosis : As a rule very grave. Mortality 50-60% in case of bubonic plague, exceeds 90% in the other forms.

Channels of elimination : Suppurating lymph glands, respiratory passages, blood.

Resistance of germ outside the body : Dwelling and articles (fomites, clothing, etc.) contaminated by the patient or by plague-infested rats.

The germ is *very resistant* : in dried blood or pus survives for several months. In endemic areas, rats and rodents in general constitute the reservoir of the virus.

Laboratory diagnosis : Puncture of the lymph gland, with direct identification of germ and cultures. Blood-culture in case of septicæmia. Identification of germ in sputum (plague pneumonia). Test of pathogenicity of germ by inoculation of guinea-pigs. Sero-agglutination.

Treatment : *Anti-plague serum* (p. 257) : results variable.

Sulphonamides have been tried alone or in combination with specific serum treatment in experimental plague (guinea-pigs, rats and mice) and in actual cases among human beings (p. 284) with encouraging results (J. A. Carman, 1938 ; H. S. Vine, 1938 ; Harry Schütze, 1939 ; Paul Durand, 1939 ; G. & M. Girard, 1940).

Prophylaxis : Speedy and accurate bacteriological diagnosis. Immediate notification of case and isolation until completely recovered (*i.e.*, until bacteriological tests have proved repeatedly negative). Ascertainment of origin of epidemic (systematic examination of rodents). Trace latent forms and convalescents and isolate them.

Thorough deratisation and disinfection of premises which may harbour rodents.

Disinfection of patient's room with formalin, of the dwelling in general, fomites, etc., with antiseptics, by steaming or by fire, etc.

Preventive immunisation with anti-plague vaccine of H. SCHÜTZE (p. 216) or with anti-plague serum in case of urgency (p. 257).

TULAREMIA [1]

(Deer-fly fever, Pahvant Valley plague, Rabbit fever)

Detailed international nomenclature (1938) : No. **26 (b).**

Latin	= Tularaemia.	German	= Tularämie.
French	= Tularémie, Maladie de Francis, Fièvre des lièvres.	Ital.	= Tularemia.
		Roum.	= Tularemie.
		Span.	= Tularemia.

A specific infection, communicated to man by sick rodents (hares, wild rabbits, squirrels, etc.) ; development sub-acute and prolonged, characterised by a bad general condition and specific enlargement of lymph glands (where the germ is present).

Etiological agent : *Pasteurella tularensis*, McCoy, Chapin, 1910, a very small micro-organism, polymorphous, mobile.

Incubation : Generally 3 days ; may vary from 14 hours to 10 days.

Direct contagion : Handling of infected animals, their skins or viscera (hares, squirrels, rats, etc.). Laboratory infections very frequent and usually severe.

Indirect contagion : Bites of blood-sucking insects. which are vectors of the germ *(Chrysops discalis, Stomoxys calcitrans, Dermacentor andersoni, D. occidentalis)*. Infected water (KARPOV & ANTONOV, 1936).

[1] From Tulare, a place in California near which the first cases were observed.

Portal of entry : Skin, conjunctiva, air passages, digestive tract.

Localisations : Skin, conjunctiva, lymph glands, nodules in the viscera.

Symptoms : High temperature, headaches, rigors, marked asthenia, ulcerations of the skin and conjunctiva, pronounced swelling of the glands. More rarely meningeal, pulmonary, etc. symptoms.

Clinical forms : Ulcero-glandular form : pustule followed by ulcerations, at the portal of entry ; pronounced swelling, with suppuration, of the regional lymph glands. This inflammation abates gradually, but the glands remain hard and enlarged for from 2 to 3 months.

Oculo-glandular form : conjunctival œdema and papules on the conjunctiva of the lower lid, followed by small ulcerations of the palpebral conjunctiva, inflammation of the preauricular, submaxillary, cervical and parotidian glands.

" Typhoid " form : fever is the dominant symptom. Differential diagnosis with typhoid fever.

Glandular form : identical with the ulcero-glandular form, save for the initial lesion which is not present.

Pulmonary form : symptoms of pulmonary and pleural localisations (pneumonia, broncho-pneumonia, pleurisy).

Prognosis : Benign as a rule. Very long convalescence. Fatality up to 4%.

Channels of elimination : Open infectious foci.

Resistance of germ outside the body : Resistant to desiccation ; readily destroyed by boiling.

Laboratory diagnosis : *Intradermal-* and *skin-reaction* obtained by means of an antigen consisting of an emulsion of killed bacilli (*Tularine*, p. 209) ; *sero-agglutination ;* inoculation of guinea-pigs.

Diagnosis of probability : Recent handling of sick animals (game), or bites of insects, ticks, flies, etc.

Treatment : Symptomatic, rest in bed. Anti-tularemia serum should be tried (Foshay, 1933, in United States, and Ohara, 1933, in Japan).

FOSHAY has obtained good results with *vaccination* with his detoxified antigen (p. 209).

Prophylaxis : Avoid contact with infected game ; very careful handling, etc. If possible destroy sick animals.

BRUCELLOSIS, UNDULANT FEVER
(Malta fever, Bang's disease Abortus fever.)

Detailed international nomenclature (1938) : No. **5.**

Latin = Brucellosis, Febris undulans, Febris abortus.
French = Brucelloses, Fièvre ondulante ; Fièvre de Malte ; Avortement épizootique (vet.) ; Maladie de Bang.
German = Brucellose ; Maltafieber, Mittelmeerfieber ; Bangsche Krankheit, Seuchenhaftes Verkalben (vet.).
Ital. = Febbre ondulante, Brucellosi ; Febbre di Malta ; Infezione da Bacillus abortus.
Roum. = Febră ondulantă, Bruceloză ; Melitococie, Infecţie prin B. melitensis ; Boala lui Bang, Infecţie prin B. abortus.
Span. = Fiebre ondulante, Brucelosis ; Fiebre de Malta ; Fiebre mediterranea ; Infección por el Bacillus abortus.

Infectious diseases caused by germs of the *Brucella* group, usually transmitted to man by the consumption of milk or milk products obtained from sick animals, or by contact with sick animals. They are characterised by an irregular fever of varying duration and a hepato-splenic syndrome.

Etiological agents : Malta fever : *Brucella melitensis*, Bruce, 1887 ; Bang's disease (Abortus fever) : *Br. abortus*, Bang 1897 ; *Br. suis* Traum, 1914 derived from pigs. Minute non-motile non-sporulating organisms.

Incubation : 2 to 3 weeks in the infection due to *Br. melitensis* (melitococcia, Mediterranean fever, Malta fever) ;

2 to 10 weeks and more in infections due to *Br. abortus* (Abortus fever) or to *Br. suis*.

Direct contagion : Is the cause of more than half the cases of infection. The passing of contagion from one person to another is rare, but not impossible in the case of melitococcus infection. Laboratory infection is common with *Br. melitensis*.

Indirect contagion : Contaminated and inadequately sterilised food (milk, cream, butter, etc.).

Portal of entry : Digestive tract, conjunctiva, genital mucous membranes (this is exceptional in the case of man, but the rule in the case of animals), broken (or even unbroken) skin.

Localisations : Septicæmia ; the blood-forming organs, the genital organs (especially in the case of animals) and viscera in general.

Symptoms : Malta fever and Abortus fever differ in their epidemiological characteristics : Malta fever is comparatively common in the Mediterranean basin (rearing of sheep and goats), although not confined there ; Abortus fever, which is connected with epizootic abortion among cows and sows, is sporadic all over the world.

These are diseases of long duration, frequent in men between 15 and 40. The onset presents no special features : rigors and fever, headache, sweating, transient or abiding muscular and articular pains.

In *Malta fever*, the fever is undulant (feverish periods of 10 to 12 days with a temperature up to F. 104° (40° C.) followed by periods of 6 to 8 days without fever). This type of fever may last for months or even years ; on an average 3 to 5 months. In chronic cases, the temperature remains between F. 98.6° and 100.4° (37°-38° C.). Any organ may be the seat of localisation : liver, spleen, muscles, joints, kidneys, heart, lungs, central nervous system, genitals, peripheral nerves, etc., hæmorrhagic or sudaminal eruptions of the skin. Acute malignant forms are common.

In *Abortus fever*, the undulant type of fever is uncommon. As a rule, irregular remittent fever, with daily oscillations, especially in the evening, is more frequent.

Prognosis : As a rule favourable : reserved in cases of acute melitococcus infection and of visceral localisations.

Channels of elimination : Urine, sputum in cases of pulmonary abscess. (In the case of animals, genital organs, mammary gland.)

Resistance of the germ outside the body : Survives for a long time in pathological exudates if shaded from light. Survives in butter, milk and milk products which have not undergone acid fermentation.

Laboratory diagnosis : Blood culture at the height of the fever ; positive in 60 to 70% of cases of Malta fever, but only in 5-10% of cases of Bang's disease. Identification of organism in any suspected product, urine, abscess, fæces.

Blood picture : Anæmia, leucopenia and mononucleosis.

Agglutination test (the test is regarded as positive when the serum agglutinates at 1 : 100).

Intradermal test : injection of 0.05 cc. of *Brucellin, Melitin, Abortin* (microbic filtrates or vaccines) gives rise to an erythematous infiltration after 6 to 8 hours ; this infiltration persists for 48 hours if test is positive (p. 208).

Treatment : Trivalent *stock vaccine* or auto-vaccine (Melitin, Abortin or Endoprotein). Progressive increase of doses.

Chemical treatment : Sulphonamides (p. 284) or neo-arsphenamin.

Give also symptomatic treatment.

Prophylaxis : Compulsory notification of human cases and of epizootic foci.

Human : personal hygiene and disinfection of exposed skin surfaces. Boil or pasteurise milk and derivatives ; preferably use buttermilk or curded milk, etc. Preventive vaccination gives immunity for more than 3 years.

Veterinary : disinfection of pathological exudates. Trace infected animals and slaughter them if they are few in an otherwise clean region. If *Br. abortus* infection is widespread, slaughtering is ruled out by economic considerations.

TYPHOID FEVER

Detailed international nomenclature (1938) : No. **1.**

Latin = Typhus abdominalis, Febris typhoidea, Ileotyphus.
French = Fièvre typhoïde.
German = Typhus, Typhus addominalis, Unterleibstyphus, Darmtyphus.
Ital. = Febbre tifoidea, Tifo addominale.
Roum. = Febră tifoidă.
Span. = Fiebre tifoidea, Tifus abdominal.

A specific infectious, febrile disease characterised by a state of lethargy (typhoid state), intestinal symptoms, a lenticular eruption, hypertrophy of the spleen and a cyclic course.

Etiological agent : Typhoid bacillus *(Eberthella typhi*, Eberth, 1880). A bacillus of the *Salmonella* group.

Incubation : 6 to 14 days, sometimes longer.

Direct contagion : Characteristic feature, the successive appearance of cases. Is due to direct contact with the patient and his excretions, to contact with a healthy carrier or with a convalescent from typhoid fever.

Indirect contagion : Water and contaminated food (milk, vegetables, etc.). Flies carrying the infection. Contaminated fomites and clothing.
Water-borne epidemics are characterised by their sudden outbreak, with a great number of cases in a limited area (connected with the contaminated water supply).

Predisposing causes : Season (summer, autumn), rain' overcrowding, digestive disorders.

Portal of entry : The digestive tract.

Localisations : At the outset, a septicæmic phase ; next, secondary localisations in the intestinal lymphatic system, the gall-bladder and the bile-ducts (main reservoir of the virus).

Complications : Local pyogenic foci (abscesses, osteo-periostitis, arthritis, meningitis, etc.).

Symptoms : Gradual onset, followed by a stationary period with a sustained elevation of temperature, headache, sleepiness, delirium, nose-bleeding, hypertrophy of the spleen, lenticular pink spots, digestive disturbances, loss of appetite, tongue dry and furred, abdominal meteorism, the iliac fossæ sensitive to pressure, diarrhœa or constipation, rumbling in the bowels. Pulse, slow, weak and dicrotic. The malady lasts 4 to 5 weeks.

Prognosis : Reserved, depending on the severity of the disease and possible complications. (Average fatality 10%.)

Channels of elimination : Digestive tract (vomit, fæces), urinary passages (urine) and suppurating lesions.

Resistance of germ outside the body : Fairly resistant in urine and excreta ; may persist for weeks in contaminated water or ice and for 2 to 3 months in the ground or in latrines.

Laboratory diagnosis : Blood culture positive during the first ten days of disease (in 90% of cases). Identification of the germ in fæces, urine, bile (tracing of healthy carriers).

Widal's serum test as from the second week. The test will be confirmed by positive blood culture or by *qualitative serum diagnostic test.*

Treatment : *Symptomatic :* antipyretics and heart tonics.

In serious and toxic forms *anti-typhoid serum* (p. 264) or serum *from a convalescent* (p. 266) (rapid and marked detoxication).

In case of intestinal hæmorrhage or perforation, antiperitonitis serum (p. 262).

Vaccine treatment : (p. 215) with increasing doses in prolonged forms of the disease or in case of relapses or complications. *Auto-vaccination* with sensitised vaccine is preferable.

Anti-typhoid bacteriophage by the mouth (p. 246).

Special diet.

Prophylaxis : Compulsory notification. Isolation of patient. Ascertain origin of first case. Trace carriers, keep them under observation and vaccinate them.

Keep contacts under observation for 12 days (the period of incubation).

Thorough disinfection of stools by means of carbolic acid 2%, creolin, quick lime, etc. Boil clothing and disinfect contaminated fomites with antiseptic solutions : sublimate at 1‰ or carbolic acid at 2%. Boil water, avoid uncooked food, wash and disinfect hands, especially before meals.

Preventive vaccination of everyone in the epidemic zone with anti-typho-paratyphoid vaccine (vaccine TAB, p. 215).

PARATYPHOID FEVERS
(Para A, B, C, etc.)

Detailed international nomenclature (1938) : No. **2.**

Latin = Paratyphus, Febris paratyphoidea.
Fr. = Fièvres paratyphoïdes.
Ger. = Paratyphus.
Ital. = Febbri paratifoidi.
Roum. = Febre paratifoide. Paratifus.
Span. = Fiebres paratifoideas.

Toxic infections of alimentary origin, septicæmic in type, caused by germs of the *Salmonella* group and characterised by gastro-intestinal disturbances, generally fever, and sometimes jaundice.

Etiological agents : 1. B. paratyphoid A. (*Salmonella paratyphi* A. Kayser, 1902).

2. B. paratyphoid B. (*Salmonella schottmuelleri*, Achard & Bensaude, 1895).

3. B. paratyphoid C. (*Salmonella hirschfeldii*, Weil. 1917, Hirschfeld, 1919).

Incubation : Very variable ; on an average 8 to 10 days, sometimes less.

Direct contagion : Contact with a patient or germ-carrier,

Indirect contagion : Water and particularly contaminated foodstuffs, milk, vegetables, etc.

Predisposing causes : Season (summer, autumn), fatigue, gastro-intestinal disorders, general and individual bad hygienic conditions.

Portal of entry : Digestive tract.

Localisations : Similar to those of typhoid fever.

Symptoms : The disease may develop in two ways : the *gastro-enteritic* form, with a very short period of incubation, after absorption of contaminated food ; the *septicæmic form*, which is the most frequent, presenting the appearance and symptoms of typhoid fever.

Duration : the milder clinical forms run their course in 12 to 15 days ; serious forms may last for 40 days or longer (paratyphoid A).

Prognosis : Variable, in general more favourable than in typhoid fever.

Channels of elimination : Digestive tract, by vomit, fæces and urine.

Resistance of germ outside the body : Fairly resistant in infected foodstuffs (meat, tinned food, cream, cakes, etc.) contaminated by a carrier or by flies.

Laboratory diagnosis : *Blood-culture* for the first 10 days of the disease. Identification of the bacillus in stools (tracing of carriers) and in suspected foodstuffs.

Serum diagnosis : See typhoid fever.

Treatment : Symptomatic. *Vaccine treatment.*

Prophylaxis : Notification of disease. Discovery of cases by bacteriological examination. Ascertainment of origin of epidemic. Trace germ-carriers and keep them under observation, likewise convalescents until germs disappear from fæces.

If possible, especially in summer, avoid consumption of preserved or tainted meat.

Personal hygiene.

Preventive vaccination with TAB vaccine (p. 215) of persons in epidemic foci.

FOOD-POISONING

(Due to germs of the Salmonella group.)

Latin	= Intoxicatio alimentis.	Ital.	= Intossicazioni alimentari.
French	= Intoxications alimentaires.	Roum.	= Intoxicatii alimentare.
German	= Nahrungsmittelvergiftung.	Span.	= Intoxicación alimenticia.

Any pathological condition due to the absorption of tainted food. Food-poisonings of an infectious type are usually caused by certain species of the Salmonella group which are pathogenic for man and animals.

Etiological agents : *Toxic* type of food-poisoning : *Salmonella enteritidis*, Gärtner, 1888, *S. Aertrycke*, De Nobele, 1898, *S. Derby*, *S. New-Port*, Schütze, 1920, *S. Stanley*, etc.

Septicæmic type : *S. suipestifer*, *S. paratyphi B* and *S. paratyphi A*.

Motile, non-sporulating bacilli capable of living under both ærobic and anærobic conditions.

Incubation : Short, 30 minutes to 3 days.

Direct contagion : Rare and only occurs in cases of poisonings caused by paratyphoid bacilli excreted by diseased persons or by germ-carriers.

Indirect contagion : More frequent ; by absorption of foodstuffs obtained from diseased animals or of contaminated foodstuffs. Tainted tinned food.

Portal of entry : Digestive tract.

Localisations : Digestive tract.

Symptoms : Intense headache, followed by an intestinal syndrome, nausea, vomiting, diarrhœa—sometimes resembling that of dysentery—intestinal and abdominal pains, fever. In fatal cases, restlessness, cramps, coma. In slight cases, the symptoms disappear in 6 or 7 days.

Prognosis : Usually serious.

Channels of elimination : Vomit, stools, urine.

Resistance of germs outside the body : Prolonged in tainted foodstuffs.

Laboratory diagnosis : Identification of germs in suspected foodstuffs, in vomit and in fæces ; blood culture and identification of germs by specific sera.

Animal inoculation with pathological material or with the isolated germ to test pathogenicity.

Treatment : Symptomatic.

Prophylaxis : In general, careful handling of all food.

Medical inspection of personnel of restaurants, pastry-shops, etc. Bacteriological examination of milk and milk products.

Among food-poisonings of bacteriological origin, cases have been observed of poisoning due to consumption of preserved foods contaminated by certain strains of staphylococci (enterotoxin).

COLIBACILLOSIS

Detailed international nomenclature (1938) : No. **24 d.**

Latin	= Colibacillosis disseminata.	Ital.	= Colibacillosi.
French	= Colibacilloses.	Roum.	= Colibacilloză.
German	= Colisepsis.	Span.	= Colibacilosis.

General or localised infections (urinary tract, gall bladder and bile ducts, genital organs), etc., generally of intestinal origin, characterised by toxic and infectious phenomena and symptoms varying according to the region affected.

Etiological agent : Colibacillus (*Escherichia coli*, Escherich 1885) ; varieties : *Coli communior*, Durham, 1900 ; *Coli aerogenes*, Escherich 1885 ; *B. acidi lactici*, Huepe, 1884 ; *B. cloacae*, Jordan, 1890.

Motile short rods or bipolar staining cocco-bacilli. Germs producing a neurotropic exotoxin (neurotoxin) and viscerotropic endotoxins.

Incubation : Variable.

Direct contagion : Auto-infection.

Indirect contagion : Exogenous infections.

Portal of entry : *Exogenous :* digestive tract (water and food contaminated by excreta), lesions of the skin or mucous membranes (defloration colibacillosis), puerperal fever, accidental infections from the use of a catheter or surgical intervention in the urinary passages, digestive tract, etc.

Endogenous : any obstruction of the intestinal tract (constipation, spasms of the colon, megacolon, constricting bands of scar tissue, strangulated hernia, compresion due to pregnancy, etc.), chronic intestinal lesions (ulcerations, enteritis, enterocolitis, gastro-enteritis, etc.). *Appendicitis*, infections of the gall-bladder due to the presence of gall-stones, etc.

Any of these causes may lead to colibacillary septicæmia, either latent or febrile.

Localisations : Usually the urinary and genito-urinary passages (pyelonephritis, pyelitis, cystitis, orchitis, etc.) secondary to calculi, strictures, angular bends, etc. ; liver (infectious colibacillary jaundice), more rarely, lungs, pleura, heart, meninges, joints, etc.

Symptoms : Acute or sub-acute febrile course ; or chronic and sub-febrile, with periods of acute fever.

Local symptoms : various according to seat of infection and of toxic disturbances due to *viscerotoxin* (gastro-intestinal disorders, jaundice, anæmia) and to *neurotoxin* (*vagotonic and sympatheticotonic disorders :* sensation of fatigue, incapacity to work, headache, profuse sweating, precordial pain and oppression, involuntary muscular contractions, nystagmus, etc.) ; *nervous disorders :* paresis, paralysis ; *mental disorders :* insomnia or excessive somnolence, neurasthenia or melancholia, nervous depression, suicidal tendencies, dementia.

Prognosis : Generally favourable, if the infection is treated.

Channels of elimination : Urine, bile, fæces.

Resistance of germ outside the body : Saprophyte of the intestines of man and of animals. Its presence in water, milk or food indicates that they have been contaminated by fæcal matter.

Laboratory diagnosis : Identification of the germ in febrile forms by blood culture. In chronic forms, bacteriological examination of urine.

Treatment : Suppression of causes of general infection. Correction of malformations constituting the cause of localisations in the genito-urinary system (calculi, angular bends of the ureter, strictures, etc.).

An antiputrefactive and antifermentative diet. A diet acidifying the urine (ketogenic regimen) alternating with an alkalising diet.

Disinfection of the intestines and urinary passages : benzonaphtol, urotropin, *sulphonamides* (sulphaguanidine).

In chronic affections, anticolibacillary *bacteriophage* (p. 245) ; prolonged vaccine treatment with auto- or stock vaccine (p. 240). *Serum treatment* (p. 260) should be used in acute, toxic, and serious forms, also to supplement surgical treatment.

Prophylaxis : General hygiene. Eliminate predisposing causes.

BACILLARY DYSENTERY

Detailed international nomenclature (1938) : No. **27 a.**

Lat. = Dysenteria bacillaris.	Ital. = Dissenteria bacillare.
Fr. = Dysenterie bacillaire.	Roum. = Disenteria bacilară.
Ger. = Bazilläre Ruhr.	Span. = Disentería bacilar.

An acute, epidemic, infectious disease, characterised by inflammatory and ulcerating lesions of the large intestine.

Etiological agents : Germs of the dysenteric group : *Shigella dysenteriae*, Shiga-Kruse, 1898 ; *Bact. ambiguum*,

Schmitz, *Shigella paradysenteriae*, Flexner, 1900; *Y, Hiss, Strong, Sonne* [1] bacilli and local atypical strains.

Incubation : 2 to 8 days; usually 4 to 6.

Direct contagion : Contact with pathological material from patients (infrequent).

Indirect contagion : Articles soiled by the stools of the patient (clothing, food, crockery, etc.). Important part played by flies in the dissemination of the disease. The rôle of water is uncertain.

Portal of entry : Digestive tract.

Localisations : Mucous membranes of the large intestine.

Symptoms : Abdominal pains along the large intestine, diarrhœa, stools containing mucus or mucus and blood, frequent (20 to 100 per day), tenesmus, dehydration of the body. Moderate temperature, F. 100.4° (C. 38°). The illness lasts from 7 to 15 days.

Prognosis : Serious, for untreated cases, especially in children.

Channel of elimination : The intestine (fæces).

Resistance of germ outside the body : The germ subsists on food and vegetables contaminated by infected fæces.

Laboratory diagnosis : Identification of germ during the first days of disease. Cultures of stools on selective media. Identification by specific sera. Serum test for specific agglutinins (in prolonged forms of the disease and especially the *Kruse-Sonne* type).

Treatment : Early polyvalent antidysenteric *serum treatment*, until disappearance of acute symptoms : tenesmus, diarrhœa, fever (p. 258).

Chemical treatment : sulphonamides, sulphaguanidine (p. 284).

Symptomatic treatment.

Antidysenteric bacteriophage by the mouth (p. 246).

[1] The *B. sonnei* infection is known as Dysentery "E" in Centra Europe.

Prophylaxis : Compulsory notification of the disease. Isolation of patients. Disinfection of stools and soiled fomites. Boil water, avoid uncooked food that is likely to be contaminated. Search for and supervise healthy dysentery carriers.

Preventive vaccination with stock vaccine is said to give satisfactory results.

ACUTE PERITONITIS

Detailed international nomenclature (1938) : No. **129.**

Latin = Peritonitis acuta.
French = Péritonite aiguë.
German = Bauchfellentzündung.
Ital. = Paritonite.
Roum. = Peritonita acută.
Span. = Peritonitis.

Acute inflammation of the peritoneal serous membrane, caused by a variety of germs.

Etiological agents : Numerous species of aerobic and anaerobic germs may be responsible for this disease. According to WEINBERG & LAGUIÈRE, up to 1935, 44 aerobic species and 32 anaerobic species had been isolated in cases of appendicular peritonitis.

The most usual species of aerobic germs :

Escherichia coli, Escherich, 1885.
Streptococcus faecalis, Thiercelin 1902.
Staphylococcus aureus, Rosenbach, 1884.
Diplococcus pneumoniae, Pasteur, Chamberland, Roux, 1881 ; Talamon, 1883.

The most usual species of anaerobic germs :

Clostridium histolyticum (B. histolyticus).
Clostridium novyi (B. oedematiens).
Fusobacterium plauti-vincenti, 1896.
Clostridium sporogenes, Metchnikoff, 1908.
B. ramosus, Veillon & Zuber, 1898.
Bacterioides funduliformis, Halle, 1898.

Incubation : Variable. As a rule, very short.

Direct contagion : Auto-infection.

Indirect contagion : Penetrating wound of the peritoneum.

Portal of entry : The blood-stream during or following a streptococcus tonsillitis, erysipelas, pneumonia, pneumonoccal arthritis, etc.

Penetrating wounds of the abdomen and septic wounds resulting from an operation.

By extension to the serous membrane of various inflammatory conditions of the stomach or intestines or as a result of the perforation of these organs (perforation of a gastric ulcer, typhoid, tuberculous, dysenteric, appendicular, etc., ulcerations).

Female genital organs, during childbirth, menstruation, abortion or by extension of an inflammatory process (endometritis, metritis, parametritis).

Abscesses of the liver, suppurating hydatid cysts, ulcerations of the bile ducts, rupture of the gall-bladder with gall-stones, abscess of the spleen, infarct of the spleen, nephritis, suppurating pyelitis, infections of the umbilical wound, extra-uterine gestation, abscess of the psoas, caries of the vertebræ, purulent pleurisy, etc.

Symptoms : *Generalised and localised peritonitis.*

General : modification of temperature (fever and rigors or sub-normal temperature at the time of perforation) ; *accelerated pulse : discrepancy between pulse and temperature, modification of rhythm of breathing* without pulmonary lesions, *facies peritonealis.*

Local : pain, sometimes like a stab with a knife, meteorism, persistent tenseness of the abdominal muscles ; vomiting, hiccup, constipation or diarrhœa, paralysis of the bladder, etc.

Prognosis : Variable according to the clinical form and the nature of the germ ; as a rule serious.

Channels of elimination : Variable according to the clinical form.

Resistance of germs outside the body : See the relevant chapter for each particular germ.

Laboratory diagnosis : Blood culture. Identification of germs by direct examination and by cultures of the peritoneal exudate collected at the time of operation.

Treatment : Surgical. *Antiperitonitis serum treatment :* before, during and after operation, directly into the peritoneum and by injections (p. 262). Heart tonics, diuretics, etc.

Prophylaxis : Prevent possible causes.

BOTULISM

Detailed international nomenclature (1938) : No. (in part) **177.**

Latin, German = Botulismus. French = Botulisme. Ital., Roum., Span. = Botulism.

A very serious food-poisoning caused by the consumption of preserved food containing a toxin produced by *Clostridium botulinum*.

Etiological agent : *Clostridium botulinum*, Van Ermenghem, 1896. A motile, spore-bearing, very resistant and strictly anærobic bacillus. It secretes a very powerful neurotropic exotoxin. Several types, of which A and B are pathogenic for man.

Incubation : 2 hours to 3 days.

Direct contagion : Exceptional, laboratory toxi-infections.

Indirect contagion : Consumption of tainted and especially contaminated preserved foods (of animal or vegetable origin).

Portal of entry : Digestive tract. The bacterial toxin contained in the food consumed resists the action of the digestive enzymes.

Localisations : A strictly neurotropic exotoxin. The germ may be discovered in the contents of the intestines ; *post mortem*, in the liver and spleen.

Symptoms : Headache, feeling of fatigue, somnolence, muscular weakness ; frequently nausea, vomiting, constipation. Disorders of the eyes : ptosis of the eyelids, diplopia, excessive dilatation or contraction of the pupils. Inflammation of the mucous membrane of the mouth and suppression of the flow of saliva. Dryness of the throat, dysphagia, aphonia. Sometimes paralysis of the extremities. Death may supervene at the end of the first or second week as a result of paralysis of the heart or of the respiratory muscles (intoxication of the parasympathetic system).

Pathognomonic signs : the patient retains complete consciousness and sensibility throughout the course of the disease.

Prognosis : Grave.

Channel of elimination : The intestine.

Resistance of germ outside the body : Very great. Saprophyte of the intestine of domestic animals (horses, pigs, cattle), exceptional in case of human beings ; it may contaminate foods of vegetable origin (beans, peas, olives) or of animal origin (meat, ham, cheese) by its spores. The preserving of such products in closed tins produces the conditions of anærobiosis favourable to the growth of the germ and to the production of the toxin.

Laboratory diagnosis : Identification of toxin in suspected foodstuffs, animal inoculation (hypodermically and by mouth). Isolation of the germ (preserved food, vomit or fæces.)

Identification of antitoxin in the body.

Treatment : *Specific serum treatment*, large doses by intravenous and intraspinal injections, with usual precautions (p. 252). Combine with symptomatic drug treatment.

Prophylaxis : Health legislation for the supervision of manufacture of preserved foods. Bacteriological examination of suspected preserved foods.

GAS GANGRENE

Detailed international nomenclature (1938) : No. **24 c.**

Latin	= Gangraena aerogenes, G. emphysematosa.	Ger.	= Gasödem, Gasbrand.
		Ital.	= Cangrena gassosa.
		Roum.	= Gangrenă gazoasă.
Fr.	= Gangrène gazeuse.	Span.	= Gangrena gaseosa.

Gas gangrene is a serious infection, caused by the contamination of wounds with combinations of anaerobic and aerobic germs and generally characterised by a rapidly extending œdema, necrosis of the tissues and the formation of gas.

Etiological agents : A. Various anaerobic organisms, of marked and well-defined pathogenicity :

1. *Clostridium perfringens*, syn. *B. Welchii*, Welch & Nuttal, 1892.

2. *Clostridium septicum*, syn. *Vibrion septique*, Pasteur & Joubert, 1877.

3. *Clostridium novyi*, syn. *B. oedematiens*, Weinberg & Séguin, 1915.

4. *Clostridium histolyticum*, syn. *B. histolyticus*, Weinberg & Séguin, 1916.

5. *Clostridium fallax*, syn. *B. fallax*, Weinberg & Séguin, 1915.

6. *Bacillus gigas*, Zeissler & Rassenfeld, 1929.

B. Organisms of less pathogenicity :

1. *Clostridium sporogenes*, syn. *B. sporogenes*, Metchnikoff, 1908.

2. *Clostridium parasporogenes*, MacIntosh, 1919.

3. *Clostridium bifermentans*, syn. *B. bifermentans*, Tissier & Martelly, 1902.

4. *Clostridium aerofoetidum*, syn. *B. aerofoetidus*, Weinberg & Séguin, 1916.

5. *Clostridium tertium*, syn. *B. tertius*, Henry, 1916.

6. *Clostridium multifermentans*, syn. *B. multifermentans tenalbus*, Stoddard, 1919.

C. Aerobic organisms associated with the anaerobics: streptococci, staphylococci, proteus, colibacilli, b. diphteroid, etc.

Incubation : From the infliction of the wound, 6 hours to 5 days.

Direct contagion : Result of accident.

Indirect contagion : Contamination of lacerated wounds with earth, dust and dirty foreign bodies.

Causes promoting contagion : Crushed tissues, foreign bodies, fatigue, shock, post-hæmorrhagic anæmia.

Portal of entry : Lacerated war or accidental wounds with crushed tissues.

Localisations : Any wounded region.

Symptoms : Evil-smelling wound, massive œdema, sometimes hard as wood, crepitating (presence of gas), extending rapidly (bronzed wounds). Myolysis, extending without regard for anatomical obstacles. Blood-stained serous discharge from the wound. Fever varying according to the type of germs present, and to the presence or absence of germs in the circulation. Pronounced intoxication; sometimes jaundice, hemoglobinuria.

Prognosis : Very serious in untreated cases. Fatality 40 to 60%, may reach 100% according to N. GULEKE.

Channels of elimination : Exudates from the infected wounds.

Resistance of the germs outside the body : The spores very resistant to desiccation, in manure or manured soil.

Laboratory diagnosis : Examine smears of pus and serous discharge from deep in the necrotic tissues for presence of bacilli; these are sometimes sporulated, and Gram-positive. Take cultures on suitable media and identify germs by means of specific sera. If need be, inoculate animals (mice, guinea-pigs, etc.).

Treatment : Wound to be kept wide open and perfectly drained, repeated aeration with hot air and oxygen. In the case of wounds complicated by fractures, surgical operation. Antisepsis.

Polyvalent anti-gangrene serum administered in large doses, preferably by intravenous injection (especially in case of patients suffering from shock), daily until local and general symptoms have ceased (p. 261). Early antigangrene serum treatment considerably reduces fatality.

Sulphonamides (p. 285) and *penicillin* (p. 289) applied locally.

Prophylaxis : Clean the wound and remove all foreign bodies, particularly earth and remains of clothing. Keep wound wide open and well drained. Specific serum in preventive doses.

TETANUS (LOCK-JAW)

Detailed international nomenclature (1938) : No. **12.**

Latin = Tetanus.	Ital. = Tetano.
Fr. = Tétanos.	Roum. = Tetanos, Falcărită.
Ger. = Wundstarrkrampf.	Span. = Tetanos.

A specific toxi-infectious disease, characterised by a general hyperexcitability and spasmodic muscular contractions.

Etiological agent : Tetanus bacillus (*Clostridium tetani*, Nicolaier, 1884), motile, sporulated and anærobic.

Incubation : 4 to 20 days on the average, occasionally longer (up to 10 years).

Direct contagion : Unknown.

Indirect contagion : Manure, garden soil, manured soil, dust, foreign bodies contaminated by tetanus spores.

Portal of entry : A lacerated wound (with necrotic tissues) or a surgical wound (operation on the intestine).

Localisations : At the portal of entry, the germ produces a toxin which penetrates the nervous system.

Symptoms : Acute or sub-acute neuro-intoxication.

Localised tetanus : regional contracture, the localisation depending on the portal of entry.

Generalised tetanus : temperature F. 102°-104° (C. 39°-40°). Stiffness of the neck. Violent local pains, increased during spasmodic contractions. Trismus, risus sardonicus. Opisthotonos, pleurothotonos, emprosthotonos, according to the type of contracture.

Prognosis : In general, very serious in acute tetanus. Favourable in the sub-acute form or the slowly incubating form.

Channel of elimination : Purulent exudate at the portal of entry.

Resistance of the germ outside the body : The germ is habitually present in the digestive tract of ruminants and horses ; the spores, which are very resistant, may persist for years in manure, arable land, dust, etc. ; they are destroyed by damp heat at F. 248° (C. 120°).

Laboratory diagnosis : Identification of germ by anaerobic cultures of pus. Inoculation of mice or guinea-pigs with suspect pus.

Treatment : Specific anti-toxic *serum treatment*, large doses, administered from the outset by intra-muscular, intravenous and intraspinal injection, combined with *active vaccination with tetanic anatoxin*, until complete recovery (p. 223).

Symptomatic medicinal treatment is indispensable : anti-spasmodics (bromide, chloral enemas, etc.).

Prophylaxis : *Preventive vaccination with tetanus anatoxin*, in 3 injections of 1 cc., 2 cc., and 2 cc., at intervals of 30 and 8 days (p. 223).

Immediate sero-vaccination in the case of a suspected wound : simultaneous injections of serum and anatoxin (p. 250). Drainage and rigorous antisepsis of the wound.

ANTHRAX, MALIGNANT PUSTULE

Detailed international nomenclature (1938) : No. **7.**

Latin = Anthrax contagiosus.
French = Pustule maligne, charbon.
Germ. = Milzbrand, Pustula maligna.
Ital. = Carbonchio, Pustola maligna.
Roum. = Infecția cărbunoasă, Anthrax, Cărbune, Pustulă malignă.
Span. = Carbón, Pústula maligna.

An infectious disease common to man and animals, occurring in man in either a cutaneous (malignant pustule), pulmonary, intestinal or septicæmic form, according to the portal of entry.

Etiological agent : *Bacillus anthracis* (Davaine, 1864). An non-motile, sporulated rod.

Incubation : 1 to 3 days.

Direct contagion : Handling of meat, skins, furs from diseased animals, consumption of infected, insufficiently cooked meat (intestinal anthrax) ; inhalation of dust containing spores (wool-sorters' disease—pulmonary anthrax).

Indirect contagion : Articles contaminated by infectious materials, earth containing spores (" champs maudits "), etc.

Portals of entry : Skin, conjunctiva (malignant pustule), mucous membranes of the respiratory passages (pulmonary anthrax), the digestive tract (intestinal anthrax).

Localisations : The original lesion and septicæmia.

Symptoms : *Malignant pustule* (usually situated on the exposed parts), a pustule with a hæmorrhagic centre (blackish), surrounded by a zone of yellow vesicles ; localised indurated œdema, lymphangitis with local adenitis and infiltration of the tissues surrounding the lymph glands, fever. Sometimes the generalised infection ensues. Duration : depends on the treatment, 7 to 10 days on an average.

Pulmonary anthrax : Rigors, dyspnea, headache, vomiting, sometimes delirium, catarrh and œdema of the upper respiratory passages, broncho-pneumonic foci, bloody, frothy sputum, œdema of the lungs. Death in 3 to 5 days.

Intestinal anthrax : Abdominal pains, fever, rigors, meteorism, watery and later bloody stools, peritoneal reactions. Agglomeration of the intestinal loops about the portal of entry. Septicæmia. Death ensues in 3 to 9 days.

Prognosis : Serious in case of malignant pustule and very grave in the pulmonary and intestinal forms.

Channels of elimination : Open lesions.

Resistance of germ outside body : The spores survive for years on the surface of the ground, on fodder, in furs and skins of animals which have died of anthrax.

Laboratory diagnosis : Identification of germ in pathological exudates and cultures. Blood cultures.

Post mortem : bacteriological examination of smears from the spleen, the bone marrow and culture of blood from the heart.

Ascoli test.

Treatment : Specific serum treatment with *anti-anthrax serum* in large and repeated doses (p. 257). Medicinal and symptomatic treatment.

Prophylaxis : Compulsory notification of case. Isolation of patient. In case of an epidemic, ascertain origin. Disinfection and measures of personal hygiene. Measures by the veterinary authorities. Anti-anthrax *vaccination* of animals.

ASIATIC CHOLERA

Detailed international nomenclature (1938) : No. **4.**

Latin	= Cholera asiatica.	Ital.	= Colera.
French	= Cholera asiatique.	Roum.	= Holeră.
German	= Asiatische Cholera.	Span.	= Cólera asiatico.

A highly epidemic, specific, acute toxi-infection characterised by a very serious gastro-intestinal syndrome, rapid in development and with a high fatality rate.

Etiological agent : The cholera vibrio (*vibrio coma*, Koch 1884), motile, monotrichous (single flagellum).

Incubation : A few hours to 5 days.

Direct contagion : From a patient, a convalescent or a germ-carrier (the proportion of healthy carriers is large—hence their epidemiological importance in the dissemination of the disease).

Indirect contagion : Water (springs, wells, streams, etc.) contaminated with excreta of patients (a sudden, mass epidemic). Contaminated food ; contaminated fomites, clothing and articles. Rôle of flies in contamination of food.

Predisposing causes : Rainy seasons, overcrowding, gastro-intestinal disorders due to unsuitable diet, cachexia.

Portal of entry : Digestive tract.

Localisation : The small intestine.

Symptoms : Diarrhœa, *stools at first feculent, later liquid and rice-water*, headache, painful cramps in the pit of the stomach, tenesmus, vomiting, muscular cramps, giddiness, rapid dehydration, cyanosis, algid condition, loss of voice, small pulse, characteristic facies. *Fulminating* forms run their course in a few hours, *severe* in 2 to 3 days, *normal* in 7 to 10 days ; very mild cases may completely recover in a day or two.

Prognosis : Very grave. Fatality above 40%.

Channels of elimination : The intestine ; rarely vomit.

Resistance of germ outside the body : It may survive for more than a month in water polluted with choleraic excrements (particularly warm sea-water), also on damp earth. Much less resistant on soiled clothing, especially if the excrements have dried. Very sensitive to disinfectants.

Laboratory diagnosis : Identification of germs in rice-water stools in hanging drops and stained smears. Cultures of suspect stools in peptonised water and isolation on alkalinised agar. Identification of cholerigenous vibrios by agglutination with specific immune sera and PFEIFFER'S phenomenon.

Treatment : An-ticholera *bacteriophage* by the mouth from the onset of the disease (?).

Intravenous injections of hypertonic saline solution heated to F. 98.4° (C. 37°). Stimulating beverages, heart tonics.

Prophylaxis : Compulsory immediate notification of case. Isolation of patients and germ-carriers. Periodical bacteriological examination of stools of carriers. Immediate ascertainment of origin of first case.

General preventive vaccination with anti-cholera vaccine (FERRANT, HAFFKINE, KOLLE) (p. 215).

Rigorous personal hygiene, wash hands and disinfect them after each suspect contact, especially before meals.

Boil water and food.

Disinfect house, latrines with carbolic acid at 3 to 5%, quick lime, hypochlorite (Javel) solution, etc. Repeated bacteriological examination of springs, wells or other water supply, etc.

SYPHILIS

Detailed international nomenclature (1938) : No. **30.**

Latin, German = Syphilis, Lues.
French = Syphilis.
Ital. = Sifilide, Lue.
Roum., Span. = Sifilis.

A specific infectious, communicable disease, venereal in the vast majority of cases, slow in development and of long duration, characterised by very varied symptoms, alternating with periods of latent infection.

Etiological agent : The syphilis spirochete (*Treponema pallidum*, Schaudinn & Hoffmann, 1905), a motile, filiform micro-organism with very fine, regular, undulations. Does not stain well with aniline dyes.

Incubation : 21 to 25 days after inoculation.

Direct contagion : Contact with lesions containing treponemata, usually by sexual intercourse. As a result of an accident during examination of the vagina, a prick during an operation, a post-mortem or blood transfusion, a bite, etc. (extra-genital contamination).

Indirect contagion : Instruments, crockery, toilet articles, cigarette-holders, etc.

Portal of entry : Contaminated wounds, etc. ; abraded (but sometimes even unbroken) skin and mucous membranes.

Localisation : May be anywhere (viscera, the central nervous system, bones, etc.).

Symptoms : 1. *Primary stage. Syphilitic chancre*, usually single. A round circumscribed ulcer, with *indurated* base, without pain or suppuration, accompanied by enlargement of the regional lymph-glands which are hard and painless and remain so even after the healing of the chancre.

2. *Secondary stage.* Septicæmic phase, 2 to 4 weeks after appearance of the chancre, characterised by *general symptoms :* fever of intermittent, continuous or irregular type ; intense headache, neuralgia, pains in the bones, arthralgia, moderate anæmia, enlargement of all lymph glands, physical and mental depression, latent or acute meningitis, paralysis, etc., and *local symptoms* of the skin and mucous membranes ; erythematous syphilides, roseola, papulo-pustular syphilides, syphilides of the mucous membranes *(mucous patches)*, baldness, in patches or widespread, onychia, pigmentation, depigmentation, etc., periostitis, iritis, keratitis, deafness, etc.

After a variable period, the secondary lesions heal without leaving scars.

3. *Tertiary stage.* Characterised by tumour-like lesions with a tendency to break down and confined to a few regional foci : *syphilitic gummata, arterial lesions*, paralysis, monoplegia, hemiplegia, etc., *lesions of the viscera.*

4. *Quaternary stage or parasyphilis :* tabes, general paralysis.

Clinical forms : congenital syphilis, early hereditary syphilis, late hereditary syphilis, dystrophic hereditary syphilis (not communicable).

Channels of elimination : Any open lesion (in the primary and secondary stages), all body fluids (semen, milk, blood).

Prognosis : Grave in untreated infections.

Resistance of germ outside the body : Very fragile, little resistance to desiccation and antiseptics.

Laboratory diagnosis : Identification of germ in the serous discharge collected at the edge of lesions or in fluid from lymph glands, obtained by puncture (examined with ultramicroscope).

Smears of serous discharge, after fixation and special staining (when the patient is at a distance from the laboratory).

Sero-diagnosis by complement-fixation (BORDET-WASSERMANN method) and by *flocculation* tests (SACHS-GEORGI, MEINICKE, KAHN, etc.) as from 14th day of disease. In secondary stage tests are almost always positive ; finally, in tertiary stage, tests are positive in 50 to 70 % of cases. Repeat the test 7 to 15 days after administration of an anti-syphilis drug (*reactivation*).

Repeated serum tests make it possible to check the efficacy of the treatment.

Treatment : Three classic drugs : arsenic, mercury and bismuth (iodine as an adjuvant) form the basis of all anti-syphilitic treatment. This must begin early and be intense, prolonged and repeated, and must be mixed and adapted to the individual case by the simultaneous or successive employment of several drugs. In the primary and secondary stages, penicillin may replace other drugs.

In nervous syphilis, stovarsol, *malaria therapy*.

Prophylaxis : Sexual hygiene : application of a calomel ointment at latest 3 hours after suspect sexual intercourse, or an injection of neo-salvarsan within 18 to 20 hours. Anti-venereal propaganda campaign ; tracing and treatment of patients with open lesions.

WEIL'S DISEASE, SPIROCHÆTAL JAUNDICE

Detailed international nomenclature (1938) : No. **32 a.**

Latin = Icterus haemorrhagicus (spirochetosus), Icterus infectiosus, Morbus Weilii, Spirochaetosis ictero hemorrhagica.

French = Spirochétose ictéro-hémorragique.

German = Weil'sche Krankheit, Übertragbare Gelbsucht.
Ital. = Leptospirosi, Spirochetosi ittero-emorragica, Morbo di Weil, Ittero infettivo.
Roum. = Spirochetoza ictero-hemoragică, Boala lui Weil.
Span. = Espiroquetosis icterohemorrágica, Enfermedad de Weil, Ictericia epidemica.

An acute, infectious and sometimes epidemic disease, characterised by fever, jaundice, enlargement of the spleen and liver, and a tendency to hæmorrhage.

Etiological agent : *Leptospira ictero-hemorrhagiae*, Inada-Ido, 1915 ; a spirochete with numerous close undulations, mobile, with hook-like extremities.

Incubation : 6 to 10 days.

Direct contagion : Unknown.

Indirect contagion : Urine and excrements of infected rats, and water or food contaminated by them. Rôle of dog as reservoir of virus (?).

Portal of entry : Abraded or even undamaged skin ; mucous membranes, while bathing.

Localisations : Liver, kidneys; to a less degree any other vascular organ.

Symptoms : Sudden onset : rigors, very high temperature, rapid pulse, prostration, violent pains in the limbs, digestive disorders, sometimes meningeal reaction. After 3 to 7 days, jaundice accompanied by hematuria, bleeding of the gums, etc. and temperature falls by *lysis*. The jaundice lasts for from 4 to 7 days and is followed by a short period of remission of from 4 to 7 days followed by a relapse. Jaundice may be absent in 60% of cases.

Prognosis : Sometimes fairly serious.

Channel of elimination : Urine.

Resistance of germ outside the body : The germ may survive in polluted water and remain latent in the sewer rat.

Laboratory diagnosis : Identification of leptospira in the blood and in the cerebro-spinal fluid during the first 6 days ; later (after the 10th day) in the urine. Inoculation of

guinea-pigs with urinary sediment. Blood picture : anæmia ; the number of red blood cells per c.c. may fall to 2,000,000.

Cultures on appropriate media.

Sero-agglutination.

Treatment : *Serum treatment* with serum of a convalescent or specific serum. Symptomatic : stimulants, heart tonics, lumbar puncture in case of meningeal symptoms. Neosalvarsan, results doubtful. Penicillin.

Prophylaxis : Notification of case and isolation of patient. Deratisation of dwelling. Sanitation. Hygienic measures in pig slaughterhouses. Chlorination of water in public bathing-places.

Preventive *vaccination* (practised in Japan with carbolised vaccine).

Hygienic precautions among miners and navvies.

MUD-FEVER, MUD FIELD FEVER

Infection with Leptospira grippo-typhosa.

Detailed international nomenclature (1938) : No. **32 b (d).**

Latin = Leptospirosis grippo-typhosa.
French = Fièvre des marais. Infection à Leptospira grippo-typhosa.
German = Feldfieber, Schlammfieber, Erntefieber, Sumpffieber, Möhrfieber.
Ital. = Leptospirosi da L. grippotyphosa.
Roum. = Febra de câmp, Leptospiroza gripo-tifică.

An infectious, epidemic, febrile disease, characterised by mild jaundice and asthenia.

Etiological agent : *Leptospira grippo-typhosa*, a micro-organism morphologically very like *Leptospira icterohemorrhagiae.*

Incubation : 8 to 10 days.

Direct contagion : Unknown.

Indirect contagion : Probably excreta of infected rodents.

Portal of entry : Skin.

Localisation : Liver, kidneys, blood (septicæmia).

Symptoms : Sudden onset, fever, myalgia especially in the limbs, digestive disorders, mild jaundice. After 4 to 6 days of the disease, a remission of 4 to 10 days followed by a febrile relapse which lasts from 1 to 5 days. Long convalescence.

Prognosis : Comparatively benign.

Channel of elimination : Urine (?).

Resistance of germ outside the body : Rodents constitute the reservoir of the virus.

Laboratory diagnosis : Identification of leptospira in blood during first 2 days of disease. Sero-agglutination.

Treatment : Symptomatic.

Prophylaxis : Isolation of patients, deratisation of dwelling. Trace and destroy epizootic centre (infected rodents).

RELAPSING FEVER [1]

Detailed international nomenclature (1938) : No. **31 a.**

Latin = Typhus recurrens, Spirochetosis obermeieri.
French = Fièvre récurrente (à poux) (Typhus récurrent).
German = Rückfallfieber.
Ital. = Febbre ricorrente (da pidocchi).
Roum. = Febra recurentă (cu căpuşe).
Span. = Fiebre (Tifus) recurrente (de Obermeier).

An acute infectious disease, characterised by alternating febrile and non-febrile periods, each lasting 5 to 7 days.

Under certain conditions may assume epidemic character (explosive outbreak).

[1] In Spain, Africa and America, relapsing fevers are found caused by *Sp. duttoni* ; these are endemo-sporadic (non-epidemic) and with a low fatality rate ; they are transmitted by ticks *(Ornithodorus)*.

Etiological agent : Relapsing fever spirochete (*Borrelia recurrentis*, Obermeier, 1873) ; 5 to 7 spiral turns, mobile.

Incubation : 5 to 8 days (extreme limits 1 to 16 days).

Direct contagion : Unknown.

Indirect contagion : Wounds, scratches contaminated by excreta of infected lice (*Pediculus vestimenti* or *corporis*). The louse becomes infective 6 days after absorbing blood of a patient.

Portal of entry : Skin, scratches and abrasions of the skin, conjunctiva.

Localisations : Blood, during the feverish period ; the blood-forming organs, the spleen.

Symptoms : Rigors, vomiting, temperature F. 102°-104° (C. 39°-40°), rapid pulse, laboured breathing, furred tongue, thirst, enlarged and tender liver and spleen. Sometimes mild jaundice. About the fifth night, the symptoms become more pronounced, the temperature rises (F. 104.2°-104.4° — C. 40.1°-40.2°), delirium, profuse sweating, crisis and remission. After 7 to 8 days, a relapse with less pronounced symptoms. Rarely—in grave cases—extreme asthenia, a typhoid condition and complications : bronchitis, pneumonia, pleurisy, profuse diarrhœa, intense jaundice, hæmorrhages ; death follows. Usually 2 or 3 attacks, rarely more, followed by remission.

Prognosis : Usually favourable in the case of treated patients. Reserved in case of debilitated persons. The disease produces debility.

Channel of elimination : Blood.

Resistance of germ outside the body : Lice [1] constitute the reservoir of the virus.

Laboratory diagnosis : Identification of germ in the blood during attacks. Examination of fresh samples and of stained smears. Inoculation of animals.

Sero-agglutination.

[1] Ticks for Tick fever due to *Sp. duttoni.*

Treatment : Arsenobenzol by intravenous injection ; tartro-bismuthates of Na and K ; emetic, penicillin.

Prophylaxis : Same as for exanthematic typhus ; notification of case ; delousing of patient and contacts (p. 169).

VINCENT'S ANGINA, TRENCH MOUTH
(Spirochætal stomatitis.)

Detailed international nomenclature (1938) : No. **32 b(a).**

Latin = Angina vincenti.
French = Angine de Vincent, Angine ulcéro-membraneuse.
German = Plaut-Vincentsche Angina, Geschwürige Mandelentzündung nach Plaut-Vincent.
Ital. = Angina fuso-spirillare di Vincent.
Roum. = Angina lui Vincent, Angina ulcero-membranoasă.
Span. = Angina de Vincent, Angina ulceromembranosa fusoespirilar.

An acute, specific infection, due to a fuso-spirillary association. Sporadic, rarely epidemic, affecting the mucous membrane of the pharynx and tonsils, characterised by false membranes and ulcero-necrotic lesions.

Etiological agents : A fuso-spirillary combination (*Fusobacterium plauti-vincenti*, Vincent, 1896, and *Borrelia vincenti (Treponema Vincenti)* (1896-1898).

A bacterial association usual in affections of the teeth and mucous membrane of the mouth.

Incubation : Variable.

Direct contagion : From a patient or germ-carrier. Sometimes auto-infection, promoted by a loss of superficial layers of the mucous membrane.

Indirect contagion : Contaminated articles (faulty asepsis in mouth operations).

Predisposing causes : Bad condition of the teeth, lesions of the gums, cachexia.

Portal of entry : Mucous membrane of the tonsils.

Localisation : Tonsils, the uvula, the soft palate, sometimes the mucous membranes of the mouth.

Symptoms : Insidious onset, temperature slight, bad general condition, regional lymph glands painful. Fœtid breath. Sore throat. Pseudo-membranous exudate from the tonsils resembling diphtheritic false membranes. If detached, the false membrane leaves a more or less deep ulceration. Often a very marked toxic condition.

Prognosis : As a rule not serious.

Channels of elimination : Saliva, local exudate.

Resistance of germs outside the body : The germs are normally found in the mouth, as saprophytes; their development may be stimulated by dental caries, the retention of remains of food in the mouth and generally faulty oral hygiene.

Laboratory diagnosis : Identification of the fuso-spirillary combination on smears of false membranes. Cultures on selective media (possible association with the diphtheria bacillus).

Treatment : Arsenobenzol, local and by intravenous injection. Vitamin C.

Prophylaxis : General hygiene. Hygiene of the mouth and treatment of decayed teeth.

FUSO-SPIRILLARY INFECTIONS

The fuso-spirillary combination may produce a variety of local infections, promoted by cachexia, chronic toxemia or by vitamin deficiencies.

I. The Skin.

1. *Phagædenic ulcer* in hot countries. A type of local skin infection, promoted by trauma and abrasions. Infection : exogenous or by contamination of an abrasion with infected saliva.

2. *Hospital gangrene*, formerly very common among war-wounded.

II. Mucous Membranes.

1. *Ulcerative stomatitis*, by communication of the infection from a bad tooth to the cheek or tongue.

2. *Noma :* a gangrenous form of stomatitis ; a serious condition, producing severe toxæmia and resulting often in mutilation.

3. *Pyorrhœa alveolaris :* A fuso-spirillary combination is often found, but its etiological rôle is doubtful.

III. Respiratory Organs.

1. *Laryngitis :* serious owing to suffocation as a result of inflammation.

2. *Putrid hæmorrhagic bronchitis.*

3. *Pulmonary abscess and gangrene.*

4. *Putrid pleurisy.*

IV. Digestive Tract.

1. *Fuso-spirillary enterocolitis :* an acute catarrhal affection, resembling dysentery. Sometimes chronic and fetid.

2. *Fuso-spirillary appendicitis, etc.*

Laboratory diagnosis : Identification of fuso-spirillary combination in smears taken from pathological products (exudate, expectorations, etc.).

Treatment : Symptomatic. General tonics. Arsenobenzol by intravenous injection. Personal hygiene. In pulmonary forms emetine hydrochloride (Theohari).

SWINE ERYSIPELAS

Detailed international nomenclature (1938) : part of No. **26 c.**

Latin = Erysipelas suis. Ital. = Mal rosso dei suini.
French = Rouget. Roum. = Rujet.
German = Rotlauf.

A septicæmic disease in pigs, transmissible to man, characterised by an acute inflammatory focus at the portal of entry and a reaction of the regional lymph glands.

Etiological agent : *Erysipelothrix rhusiopathiae*, Pasteur & Lhuillier, 1882.

Incubation : 1 to 3 days, rarely 4-5 days.

Direct contagion : Contact with diseased pigs or handling of meat from pigs. Butchers, cooks, housewives and veterinary surgeons are especially exposed to infection.

Indirect contagion : Articles and instruments used for cutting up diseased animals.

Portal of entry : Any skin abrasion, especially on the hands.

Localisations : Site of inoculation, regional lymph glands, sometimes the intestine.

Symptoms : A bluish swelling at the portal of entry (usually the hand) with the sensation of a sting. The infected hand becomes unusable. No suppuration, no fever, often inflammation of the regional lymph glands.
Slow evolution (several weeks).

Prognosis : Favourable, thanks to serum treatment.

Channels of elimination : Open lesions.

Resistance of germ outside the body : In general, resistant. Destroyed by boiling. In salted meat, a culture of the germ can still be obtained after one month ; in smoked ham, a culture has been taken after three months.

Laboratory diagnosis : Identification of germ by direct microscopic examination and by cultures of the serous discharge from the original lesion. Inoculation of pigeons and mice.

Treatment : Specific, with anti-swine erysipelas serum.

Prophylaxis : Avoid handling of meat of diseased animals Personal hygiene.
Sero-vaccination of susceptible animals.

TUBERCULOSIS
(Phthisis)

Detailed international nomenclature (1938) : Nos. **13-22.**

Latin = Tuberculosis.
French = Tuberculose, phtisie (v.) bacillose.
German = Tuberkulose, Schwindsucht (v.).
Ital. = Tuberculosis, Tisi (v.), Consunzione (v.).
Roum. = Tuberculoza, Ftizie (v.).
Span. = Tuberculosis, Consunción.

A specific infectious disease which may affect all organs and tissues, but most frequently the lungs, causing inflammatory lesions which tend either towards the formation of tubercles and fibrosis or towards caseous degeneration.

Etiological agent : The tubercle bacillus (*Mycobacterium tuberculosis* var. *hominis*, Koch, 1882), acid-fast, non-motile, asporous. The *bovine* (frequently) and the *avian* (exceptionally) varieties are also pathogenic for man.

Incubation : Some weeks to some years.

Direct contagion : Droplets ejected by a patient with open pulmonary lesions, when coughing, sneezing or speaking.

Indirect contagion : By inhalation of bacillus-carrying dust floating in the atmosphere of the dwelling ; from articles contaminated by bacillus-carrying droplets or expectorations. Food contaminated with the human or animal varieties of the germ (milk, butter, cheese, etc.).

Contagion is particularly serious in the case of children and adolescents. It may have serious consequences in the case of adults also, especially if they escaped a primary infection during childhood.

Portal of entry : In order of frequency : upper respiratory passages, mucous membrane of the pharynx, the intestinal or any other mucous membranes, or any break in the skin.

Localisations : The lungs are the organs most frequently affected ; next come localisations in the lymph glands, the

bones, the mucous membranes and the viscera (tuberculosis of isolated viscera or generalised—miliary—tuberculosis). Meningitis is often the final form in children.

Symptoms : A prolonged symptom-free period may follow infection. The first lesion will often pass unnoticed ; the infection may remain latent for a long period, for years and even for life. Only the calcified scar of the primary lesion and sensitiveness to tuberculin betray the existence of the infection ; this is the case with 60 to 80% of adults.[1] It also happens that periods of illness alternate with periods of apparently good health.

When the disease makes itself apparent, the symptoms are *general* (mainly toxic) : fever, loss of appetite, emaciation, weakness, night sweats, cachexia ; and *local*, varying according to the organ affected. In tuberculosis of the lungs, the main symptoms are coughing, expectoration and hemoptysis. Nevertheless, even tuberculosis of the lungs may, at first, develop for some time without symptoms.

The development and duration of the disease vary according to the clinical form : from a few weeks in acute forms—acute *miliary* tuberculosis (especially frequent in children), *caseous pneumonia* and *broncho-pneumonia* (in both children and adults)—to months and years in the chronic forms—tuberculosis of the *bones*, *lymph glands*, *joints* and *peritoneum* (these forms are especially frequent in childhood) and *fibro-caseous tuberculosis* of the lungs (the most frequent form in adults).

Prognosis : Varies according to the clinical form and the promptness and efficacy of treatment.

Channels of elimination : Expectorations, urine, fæces, pus, etc.

Resistance of germ outside the body : Koch's bacillus resists desiccation ; it is found living after some weeks in dried sputum, especially in houses and in the dark. In direct

[1] The proportion may vary greatly according to the country, the region, the social class and the period.

sunlight in houses and particularly in direct sunlight out of doors, it survives for a much shorter period.

Laboratory diagnosis : Identification of bacillus in sputum, pus, pleural or peritoneal fluid, cerebro-spinal fluid, urine, fæces, contents of stomach, etc. ; its presence establishes the existence of an active tuberculous lesion.

The existence of the *infection* (which is not the same thing as the active *disease*) is shown by a reaction to tuberculin : *skin test* (VON PIRQUET), *intradermal test* (MANTOUX) (p. 202).

Clinical diagnosis : Based on general and local symptoms, auscultation signs, and the X-ray picture which is indispensable especially in pulmonary tuberculosis in the early stages, when even important lesions may escape auscultation. Often, the nature of the infection can only be ascertained by bacteriological examination, which is very useful even in the early stages.

Treatment : Cases which are not too advanced are curable. The basis of any treatment of tuberculosis is rest and diet : rest, fresh-air treatment, proper diet, favourable climate. Rest of the affected lung by collapse treatment (intra- or extra-pleural *pneumothorax*, *thoracoplasty*, *phrenicectomy*) for pulmonary tuberculosis, local immobilisation for bone or joint tuberculosis (a very effective treatment). Natural sun treatment by the sea or in the mountains and artificial sun treatment (ultra-violet rays) are the most valuable aids to the treatment of surgical and skin cases. *Treatment with tuberculin* (p. 242), *methylic antigen* (p. 243) and treatment with gold salts (the indications are more limited) may also sometimes be valuable.

Prophylaxis : Cases of tuberculosis are discovered with the aid of *dispensaries*, centres for the diagnosis and supervision of patients and their contacts. Latterly, the activities of dispensaries have been supplemented by periodical examinations, especially radiological examinations, of groups and classes—army units, schools, factories, etc.—even whole populations have been systematically examined by radiophotography.

An infectious case of tuberculosis should be *isolated*, at any stage of the disease, in a hospital, hospital-sanatorium or

tuberculosis section of a general hospital. *This is the basis of all anti-tuberculosis prophylaxis.* In curable cases, *treatment* should preferably be given in a *sanatorium* or in the home of the patient. In the latter case, the members of the household must be protected by active supervision, for which the visiting-nurse of the anti-tuberculosis dispensary should preferably be responsible.

Preventive vaccination with *B.C.G.* (CALMETTE-GUÉRIN vaccine) of newly born infants and children or susceptible (anergic) young adults (who do not react to tuberculin) imparts a considerably increased resistance to tuberculosis infection ; this leads to a marked diminution in the tuberculosis morbidity and mortality rates, which are particularly high at these ages (p. 226).

LEPROSY

Detailed international nomenclature (1938) : No. **23.**

Latin = Lepra, Elephantiasis Graecorum.
French = Lèpre.
German = Lepra, Aussatz.
Ital. = Lebbra.
Roum. = Lepra.
Span. = Lepra.

A chronic, infectious disease, developing very slowly and irregularly.

Etiological agent : The leprosy bacillus (*Mycobacterium leprae*, Hansen, 1874) ; a bacillus resembling that of tuberculosis, acid-resistant, abundant in lesions.

Incubation : Very variable, from 3 to 5 years, sometimes perhaps a few months or, on the other hand, it may exceed 10 years.

Direct contagion : Promoted by lack of hygiene, promiscuity and prolonged contact.

Indirect contagion : Possible, by articles in common use, clothing, insects.

Portal of entry : Not yet determined. The nasal mucous membrane (initial persistent rhinitis) and the skin have been regarded as possible portals of entry.

Localisations : Skin (tubercular leprosy), nervous system (anæsthetic leprosy).

Symptoms : *Period of invasion :* emaciation, apathy, anæmia, somnolence, rheumatoid pains (arthralgia, backache, neuralgia), digestive disorders (coated tongue, lack of appetite, dyspepsia, diarrhœa).

Cessation of perspiration or fits of sweating, itching, a tingling sensation, a sensation of cold. Intermittent fever, up to F.104°-106° (C.40°-41°). Earthy coloration of skin of extremities, chronic *rhinitis.*

Period of macular eruption : appearance in crops at irregular intervals of maculæ (leprides) of varying colour and dimensions, hard, affecting the face, the extremities, the extensor surfaces of the limbs, the buttocks or the back. The blotches are erythematous and pigmented at first, itching or painful, subsequently *anæsthetic* (loss of sensation of temperature and pain). They are isolated or collected in patches, resembling erysipelas or polymorphous erythema.

Clinical forms : nodular or *tubercular,* characterised by the appearance of quasi-symmetrical leprosy tubercles *(lepromata),* either following a slow and partial transformation of the erythematous and pigmented leprides, or in crops. The tubercles may be hypodermic, perceptible to the touch, resembling separate nodules or form an infiltrated plaque which may ulcerate.

The localisation of the lepromata produces a characteristic appearance *(facies leonina)* ; they may also affect the mucous membranes : *rhinitis* discharging leprosy bacilli is very frequent.

Nervous leprosy (maculo-anæsthetic or tropho-necrotic), characterised by the proliferative infiltration of certain nerves, anæsthesia, trophic disorders of the skin, muscles and skeleton. According to the predominant phenomena, the disease may assume a macular, lazarine or mutilating form.

The two varieties may exist in combination in differing degrees : *mixed or complete leprosy.*

Prognosis : Grave.

Channels of elimination : Nasal mucus, even in the absence of rhinitis, saliva, sweat, squamæ, sputum, milk, fæces, etc.

Resistance of germ outside the body : Not determined experimentally as the germ cannot be cultivated. Probably a resistant germ (contamination by articles from leprous households).

Laboratory diagnosis : Identification of the Hansen bacillus by smears of the nasal mucus or by biopsy.

Treatment : Chaulmoogra oil and its derivatives. Arsenobenzol alternating with Chaulmoogra. Treatment must be started early and must be intense and prolonged ; it must be repeated and adapted to each patient.

Initial treatment : the series of injections to be repeated throughout a year, with some days of rest between them, until clinical and humoral signs have disappeared.

Consolidation treatment : 4 series per year, for 4 to 5 years.

As a further precaution : 2 series per year for 15 to 20 years.

Effective treatment involves the simultaneous or successive use of several drugs. It also includes proper dietary and vitamins.

Prophylaxis : Compulsory notification. Isolation of any patient with open lesions.

GLANDERS
(including Farcy)

Detailed international nomenclature (1938) : No. **26 a.**

Latin = Malleus.
French = Morve, farcin.
German = Rotz, Malleus.
Italian = Morva, Farcine, Cimurro.
Roum. = Morvă, Rapciugă.
Span. = Muerne, Farcin, Lamparones.

An acute infectious disease (usually of equine origin), characterised by high fever, pustulo-ulcerous eruptions of the skin and mucous membranes and of certain organs. Fatal as a rule.

Etiological agent : The glanders bacillus (Pfeifferella *(Malleomyces) mallei*, Löffler, 1886), non-motile and asporous.

Incubation : 3 to 5 days, rarely up to 2 weeks.

Direct contagion : Contact with sick animals with open lesions (horses, mules, donkeys) ; cohabitation with a person suffering from the disease.

Indirect contagion : Handling of contaminated articles, etc. Laboratory or *post-mortem* contamination.

Portal of entry : Skin and injured mucous membranes.

Localisation : Skin, subcutaneous connective tissue, muscles, bones, lymph glands, liver, spleen, kidneys, lungs, etc.

Symptoms : *Acute form :* begins with general symptoms or with a small swelling and lymphangitis at the portal of entry, fever and pains in the joints. Vesico-pustular eruption with œdema of the affected part ; vesicular pustules on the face and body ; ulcers of the phagedenic or gangrenous type, with no tendency to heal. Pustulo-ulcerative lesions on the nasal mucous membrane with purulent discharge ; lesions of the conjunctiva and buccal mucous membranes ; glanders broncho-pneumonia. Superficial, muscular or periarticular abscesses. In acute skin-glanders (farcy), the only lesions are multiple abscesses, superficial or deep ; pustulo-ulcerative lesions appear towards the end.

Chronic form : characterised only by nasal lesions, which may last for years but which always have a fatal termination following an acute attack. In chronic glanders, multiple abscesses, which ulcerate or become fistulous, and a glanderous lymphangitis are observed ; there is also suppuration of the bones, especially of the tibia. The disease may last for months or years and end fatally, but an apparent or even definite recovery is not entirely out of the question. The latent form of glanders is very rare.

Prognosis : Very grave in the acute form and serious in the chronic form.

Channels of elimination : Open foci of the skin, the nasal mucous membrane, etc., expectorations, etc.

Resistance of germ outside the body : A very fragile germ ; easily destroyed in 2 to 3 days by desiccation and sunlight. In moist pathological products, may resist for 15 to 30 days.

Laboratory diagnosis : Identification of germ in lesions not yet open by direct microscopic examination and by cultures. Verification of species by peritoneal inoculation of a male guinea-pig. *Sero-agglutination* positive at 1:500.

Skin test with mallein by scarification of the skin of the forearm ; reaction to be read after 24 hours. *Intradermal test* with mallein.

Treatment : Stimulating drugs, general tonics. Try sulphonamides. In chronic forms, specific *vaccine treatment* with a suspension of killed germs has been tried.

Prophylaxis : Search for the disease among animals by means of allergic and serological tests. Slaughtering of diseased and infective animals. Thorough disinfection of stables and all contaminated articles.

Prevent contamination of human beings by measures of personal hygiene in the case of all persons attending diseased animals.

Compulsory notification of case and thorough disinfection during the course of the disease.

DIPHTHERIA
(Malignant angina (v))

Detailed international nomenclature (1938) : No. **10.**

Latin = Diphtheria.
French = Diphtérie (Angine à fausses membranes [v]).
German = Diphterie, Halsbräune (v).
Italian = Difterite, Angina difterica.
Rouman. = Difterie, Angina difterică.
Spanish = Difteria, Angina lardacea.

A specific, acute, infectious disease, characterised by the local appearance of false membranes and general toxæmia.

Etiological agent : Diphtheria bacillus (*Corynebacterium diphteriae*, Löffler, 1884). A motile germ, with metachromatic corpuscles (Babes-Ernst). Three types : *gravis*, *mitis* and *intermedius*, with different degrees of pathogenicity. A powerful exotoxin.

Incubation : 2 to 5 days, sometimes more.

Direct contagion : From a patient, a convalescent or a germ-carrier.

Indirect contagion : From any article contaminated with the pathological products of the patient.

Portal of entry : Tonsils, mucous membranes of the nose or mouth ; rarely, wounds or other mucous membranes.

Localisation : At the portal of entry. The toxin is diffusible.

Symptoms : Pallor, moderate temperature, vomiting, sore throat, false membranes, sometimes late paralysis.

Clinical forms : diphtheria of the throat, nose or larynx (croup), tracheo-bronchial diphtheria.

More or less marked general toxæmia, manifested by visceral disorders (supraenals, heart, nervous system, etc.).

Malignant, hypertoxic diphtheria : from the outset, alarming symptoms : excessive pallor, marked hypertrophy of the submaxillary lymph glands (proconsular neck), greyish false membranes over the whole of the back of the throat, fetid breath, nose-bleeding, bleeding of the gums and lips, vomiting of blood, ecchymoses of the skin. Cylindruria, azotemia, myocardial symptoms. Rapid evolution in 4 to 5 days. Combination with other germs increases the malignity of disease.

Prognosis : Grave in cases not treated with the specific serum and in the malignant, hypertoxic form. Favourable in cases treated from the outset with serum.

Channels of elimination : False membranes and exudate from the nose and throat.

Resistance of germ outside the body : On any contaminated article (bedding, clothing, fomites, etc.) the germ may persist for months if protected from light and desiccation.

Laboratory diagnosis : Identification of germ in false membranes by direct examination under the microscope and cultures on selective identification media.

Treatment : *Specific antitoxic serum treatment.* 10,000 to 100,000 antitoxin units according to the clinical form and time of administration, and even more (500,000) in hypertoxic malignant forms, until the general symptoms and the false membranes have disappeared. As the serum neutralises only the toxin which is still free (not yet fixed in the body), treatment must be begun early, in adequate quantities and administered by subcutaneous, intramuscular or intravenous injection, according to the time of administration and the clinical form (p. 247).

Combine specific *vaccine treatment* with the anatoxin (p. 221). Vitamins C and B, epinephrin and strychnine are useful adjuvants.

In case of croup, intubation should be performed.

Prophylaxis : Compulsory notification of cases. Isolation of patients.

Compulsory *immunisation* of children (1 to 4 years) with diphtheria anatoxin (p. 221).

Identify susceptible children by SCHICK testing (p. 204) and inoculate them with anatoxin.

If there be risk of infection, immunise immediately all contacts with a positive SCHICK test by injecting 1,000 units of antitoxin and maintain this passively acquired immunity by anatoxin vaccination.

Disinfect pathological products and contaminated fomites and clothing.

TABLE RECAPITULATING [1] THE EXANTHEMATIC FEVERS (RICKETTSIOSES), GROUPED ACCORDING TO VECTORS

Disease	Etiological agent	Reservoir of virus	Vectors	Infection in guinea-pigs		Weil-Felix test		
				apparent (disease)	inapparent	OX_{19}	OX_2	XK
1. *Exanthematic Typhus* (epidemic, historical).	*Rickettsia prowazeki* (da Rocha-Lima, 1916).	Man	Louse *(Pediculus corporis).*	+	+	+++	±	—
Brill's disease.	*Rickettsia prowazeki*	Man	Louse *(Pediculus corporis).*	+	+	+++	+	—
2. *Trench Fever* (Five-day fever, Volhynia fever).	*Rickettsia quintana* (*Rickettsia pediculi.* Töpfer, 1916).	Man	Louse *(Pediculus corporis).*	—	—	—	—	—
3. *Murine Typhus* (endemic). Hone's disease (benign endemic Australian T.), Urban tropical typhus (Shop T. of Malaya), Toulon ship typhus, Indian typhus, etc.	*Rickettsia mooseri* (Monteiro, 1931).	Rats	Fleas	+ Scrotal reaction	+	++	+	—
(3-1) Intermediate Form *Tabardillo* (Mexican typhus), Manchurian fever (Manchurian typhus).	*Rickettsia mooseri.*	Rats, occasionally man	Fleas and occasionally *lice.*	+ Scrotal reaction	+	++	+	—
4. « *Boutonneuse Fever* » (exanthematous, Marseilles fever).	*Rickettsia conori* (Brumpt, 1932).	Dogs, wild and domestic rodents.	Dog tick *(Rhipicephalus sanguineus).*	+ Scrotal reaction	+	++	+ late	±
Kenya tick-bite fever.	»	Rat	Ticks	+ Scrotal reaction	+	±	+ late	±
South-African tick-bite fever.	»	Wild rodents	Ticks	+ Scrotal reaction	+	+	+ late	+ late
Indian tick typhus (Megaw).	?	?	?	+ Scrotal reaction	+	—	—	+
5. *Rocky Mountain Spotted Fever.*	*Rickettsia rickettsi* (Wolbach, 1919).	Rodents	Ticks : *(Dermacentor Andersoni).*	+ Scrotal reaction	±	++	+	±
São Paulo Typhus.	*Rickettsia braziliensis* (Monteiro, 1931).	»	Ticks : *(Amblyomma cajennense).*	+ Rare scrotal reaction	— ?	++	±	—
6. *Japanese River Fever* (Tsutsugamushi).	*Rickettsia orientalis.*	Wild rodents, field rats, birds (?)	Mites *(Trombicula akamushi).*	—	+			
Mite fever of Sumatra.	»	Rat	Mites					
Scrub typhus of Malaya	»	?	»			—±	—	+++
Indian typhus "XK type".	?	?	»					
Queensland coastal fever.	?	?	»					
Scharabeule (U.S.S.R.).	?	?	?					

[1] Tables for a *detailed* comparison between the various types of typhus, with regard to their epidemiological, clinical, immunological and experimental characters, will be found in the *Epidemiological Report* of the L.o.N. 1936, pp. 125-133.

RICKETTSIOSES, TYPHUS AND TYPHUS-LIKE DISEASES

Latin	=	Rickettsiosis.
French	=	Fièvres exanthématiques, rickettsioses.
German	=	Rickettsiosen.
Italian	=	Rickettsiosi, Tifo e tifopetecchialesimili.
Roumanian	=	Rickettsioze.
Spanish	=	Rickettsiosís.

Historic (louse-borne) exanthematic typhus, Endemic or murine exanthematic typhus, Trench fever, Boutonneuse fever, Rocky Mountain spotted fever, Japanese river fever (Tsutsugamushi), etc. :

These are diseases in which the etiological agent belongs to the *Rickettsia* group.

Common characteristics : Similar clinical symptoms : fever, a more or less pronounced typhoid condition, generally a petechial eruption.

The etiological agents are related by their morphological and biological characteristics.

Transmission by insect vectors : *lice*, *fleas* or arachnoids : *ticks* or other *acarinæ*.

As a result of these affections, the serum of patients acquires the property of specifically agglutinating the *Proteus* (OX_{19}, OX_2, XK) (test of WEIL-FELIX) and homologous Rickettsiæ.

For further details, see inset Synoptic Table.

EPIDEMIC LOUSE-BORNE TYPHUS FEVER, EXANTHEMATIC TYPHUS

Detailed international nomenclature (1938) : No. **39 a.**

Latin	=	Typhus exanthematicus, T. petechialis.
French	=	Typhus exanthématique historique (épidémique, européen, à poux, du Vieux-Monde).
German	=	Flecktyphus, Petechialtyphus, Fleckfieber, Epidemisches Fleckfieber.

Italian = Tifo petecchiale, Tifo esantematico.
Rouman. = Tifosul exantematic.
Spanish = Tifus petequial, Tifus exantematico, Tifo europeo, Fiebre petequial.

A specific, acute, infectious and epidemic disease, characterised by a sudden onset, marked nervous symptoms, a typhoid condition, a petechial eruption and usually terminating with a crisis.

Etiological agent : *Rickettsia prowazeki*, a pleomorphic germ, of extremely small dimensions, not yet classified, staining by special methods. A parasite of the living cell : the vascular endothelium, the serous membranes, etc. Only cultivable in the presence of living cells.

Incubation : Extreme limits 6 to 20 days ; on the average 8 to 14 days.

Direct contagion : From one person to another, does not exist. Is conveyed by lice.

Indirect contagion : From the excreta of infected lice (*Pediculus corporis*, sometimes also *Pediculus capitis*). Lice which have bitten a case of typhus become infective 6 to 7 days after absorption of the blood. Then the intestinal content of the insect is very rich in the virus. The transmission of the infection is effected by the excreta of such lice entering the skin through the abrasions caused by scratching.

Laboratory infections are very common, through the mucous membranes and conjunctivæ, during handling of the virus.

Portal of entry : Skin and mucous membranes.

Localisations : A septicæmic disease : the blood is infectious throughout the course of the disease and the early days of convalescence. Perivascular nodules (Fraenckel, 1914).

Symptoms : Sudden onset, rigors, fever, intense headache, congestion of the face ; congestion of the conjunctivæ of the eye-balls without watering or nasal catarrh (except as an early symptom in cases of laboratory infection through the nose). The following day, an appearance of

intense toxæmia. Between the fourth and seventh days of the disease, sudden appearance of the eruption all over the body except the face and neck : isolated red blotches, of an ecchymotic tint or having appearance of petechiæ. Prostration, delirium, collapse. About the 14th or 15th day, as a rule, defervescence and disappearance of the torpor. A long convalescence, debility and asthenia. Very complete and prolonged immunity follows.

In serious forms, nervous symptoms (bulbar phenomena) predominate. Death may supervene between the 9th and 12th days.

In mild forms, symptoms are less pronounced and sometimes even there is no eruption. Diagnosis is possible only by the WEIL-FELIX serum test.

In certain cases, the infection is inapparent.

Prognosis : Variable, favourable in the case of children, fatality increases with age. It varies according to local endemic conditions and the absence or presence of regional immunity. On the average about 10% ; it may reach 35 or 40% (Roumania, winter of 1916/17).

Channel of elimination : The blood is virulent.

Resistance of germ outside the body : In fæces of the vector, probably prolonged at a low temperature.

Laboratory diagnosis : The WEIL-FELIX test applied after the first week. Agglutination of *Proteus OX*[19], with serum of the patient at 1:100 is regarded as positive. A simplified and rapid test (KUDICKE-STEUER) may be used for communities.

Treatment : General, symptomatic. *Serum of a convalescent* administered in large quantities and from the outset gives excellent results.

Prophylaxis : Compulsory notification of disease. Isolation of patient after he and his effects have been rigorously and completely deloused. All contacts must be kept under supervision for 15 days. In case of an epidemic, collective delousing of lice-infested communities.

Preventive vaccination of medical and auxiliary personnel (p. 218). In zones much infested with the disease,

preventive serum prophylaxis with serum from a convalescent (p. 267).

The *Health Committee of the League of Nations* has adopted the following conclusions reached by a Committee of Experts (which met from February 8th to 10th, 1937), with regard to the different methods of vaccination proposed :

" (1) Living virus-vaccines confer early protection either by premunition alone, or by premunition followed by immunity ;

" (2) Living virus-vaccines, when they induce infection, confer *greater*, and hence *wider*, protection—*i.e.*, protection applying to a greater number of strains or species—than that which can be conferred by the same viruses when killed."

The experts were of opinion that these specific methods of prevention usefully supplemented the classical methods, without however suppressing them.

On the basis of these conclusions, the following measures were recommended :

" I. *Measures recommended in the Case of a Threatened Epidemic.*

" In the event of a threatened epidemic, and without awaiting the appearance of the first cases, the following measures should be taken :

" *(a)* Organisation and operation of a systematic and periodic delousing service among the troops and civilian population, including refugees and the floating population . . . "

This service (shower bath, after lathering the body with soap and rubbing it with insecticide ointment, and passing the clothes through the sterilisers) should be staffed with personnel specially trained in advance.[1]

[1] The functions of this service and the training of its staff are made very much simpler by the adoption of the newer method of delousing both body and clothing by insufflation under the clothing (without undressing) of a powder containing 10% D.D.T.

" *(b)* Organisation of a vigilant service for the early detection of typhus cases.

" *(c)* Preparation of a plan for the isolation of patients, including their conveyance in vehicles easy to delouse, and their treatment in hospital. Arrangements must be made for the extension of hospital premises according to requirements.

" *(d)* Preparation of plans for the isolation of infected localities (sanitary cordon, food supply of the population isolated, etc.).

" *(e)* Formation of stocks of serum of immunised animals. Organisation of a service for obtaining serum from convalescents and storage of all necessary material for that purpose.

"*(f)* Vaccination with a killed vaccine of all the medical, sanitary and auxiliary staff." (See below.)

" II. *Measures recommended in the Case of an Epidemic.*

" In the case of an epidemic, it will be necessary :

" To intensify measures of delousing and detection ;

" To apply measures for the isolation of patients and typhus foci ;

" To collect and use the serum of convalescents.

" In addition to these measures, the following will be necessary :

" *(a)* The immediate use of the serum of convalescents or of serum in stock, which is strongly recommended as a preventive measure, in the first place, for the health and administrative personnel in contact with patients, with the exception of persons already immunised with killed vaccine for more than one month and less than twelve months, and, in the second place, for persons having already come into contact with patients.

" *(b)* The mass vaccination of the military and civilian population of infected localities.

" As killed vaccines cannot at present be produced in large quantities, use may be made of living virus-vaccines . . . . " but their preparation requires a technique and a rigorous supervision which in practice are not often available.

Anti-exanthematic vaccines [1] : Vaccines prepared with killed or with living germs are used :

A. *Killed vaccines :*

WEIGL's and COX's [2] *vaccines* (CASTAÑEDA-DURAND), *mouse's lung vaccine* (p. 219), GIROUD's *rabbit's lung vaccine.*

B. *Living virus-vaccines :*

BLANC's *virus-vaccine*, LAIGRET's *virus-vaccine* (p. 218).

TRENCH FEVER

Detailed international nomenclature (1938) : No. **39 c (a).**

Latin	=	Febris Wolhynica, Rickettsiosi quintana, Febris neuralgica periodica.
French	=	Fièvre des tranchées, Fièvre de Wolhynie, Fièvre de 5 jours.
German	=	Fünftagefieber, Wolhynisches Fieber, Schützengräberfieber.
Italian	=	Febbre quintane, Febbre volinica, Febbra della trincee.
Roumanian	=	Febra de cinci zile, Febra de tranşee.
Spanish	=	Fiebre de cinco dies, Fiebre de las trincheras.

A specific, acute and epidemic disease observed among soldiers in war-time, more rarely among civilians, characterised by a sudden onset, a recurrent type of fever and a Rubella-like exanthem.

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[1] *Cf.* BIRAUD, Y. : « The Present Menace of Exanthematic Typhus » (*Bull. Health Org.* L.o.N., Vol. **10**, No. 1, 1943/44).

[2] Harald R. Cox.

Etiological agent : *Rickettsia quintana (= Rickettsia pediculi)*, a pleomorphous micro-organism, not yet classified, of extremely small dimensions.

Incubation : 8 to 20 days.

Direct contagion : No case has been observed.

Indirect contagion : Infected lice *(Pediculus capitis* or *vestimenti)*. Inoculation with the excreta or contents of an infected louse results from scratching. Lice are infective for at least three weeks after biting an infected person.

Portal of entry : Skin (lesions due to scratching).

Localisations : A septicæmic disease; the virus is in the circulating blood for the whole duration of the disease and for three months afterwards or even longer (Bacot).

Symptoms : Sudden onset, headache, pains in the lower limbs (tibias), orbital pains, nystagmus, giddiness, sweating, enlargement of the spleen and a maculo-papular exanthem on the chest, back and abdomen. The exanthem may disappear after 24 hours or even earlier. Fever of a recurrent type with frequent relapses. The first access of fever (3 days) is followed by a 5-day period without fever, then follows a further access of fever for 3 days with a new period without fever and so on. There will be from 3 to 7 accesses of fever at fairly regular intervals. The disease lasts for from 5 to 6 weeks.

Prognosis : Favourable.

Channels of elimination : Blood, urine.

Resistance of germ outside the body : More resistant than other Rickettsiæ. After 4 months, the dried excreta of lice are still infectious.

Laboratory diagnosis : ?

Treatment : General, symptomatic.

Prophylaxis : Compulsory notification of disease. Delouse and isolate patient. Disinfect clothing and fomites. Persons who have been in contact with patient must also be deloused and kept under observation for 15 days.

ENDEMIC, BENIGN TYPHUS

Murine, Flea-borne Typhus, Tabardillo [1].

Detailed international nomenclature (1938) : No. **39 b (a)**.

Latin = Typhus endemicus benignus, T. endemicus murinus.
French = Typhus endémique bénin (Murin), Fièvre nautique de Toulon, Typhus mexicain [1].
German = Rattenfleckfieber, Muriner Flecktyphus.
Ital. = Tifo endemico benigno, Tifo murino, Dermotifo sporadico (di Catania).
Roum. = Tifos exantematic endemic, Tifos murin, Tifos exantematic al lumii noui.
Span. = Tifo endemigo benigno, Tabardillo [1], Tifo mejicano [1], Pinareño (Cuba).

An acute endemic infectious disease characterised by a sudden onset, symptoms of general infection, a maculo-papular exanthem and a bucco-pharyngeal eruption.

Etiological agent : *Rickettsia mooseri*, a pleomorphous micro-organism of extremely small dimensions. A parasite of the living cell (endothelium, etc.).

Incubation : 6o to 20 days.

Direct contagion : No case has been observed.

Indirect contagion : The fleas of infected rats. Urine and excreta of infected rats ; sometimes lice [1].

Portal of entry : Skin, conjunctivæ.

Localisations : A septicæmic infection.

Symptoms : Sudden onset, symptoms of general infection about 3rd or 4th day of fever, successive crops of spots, first on the body, then the face, limbs, the palms of the hands and the soles of the feet. Bucco-pharyngeal and

[1] In Mexico, in other Central-American countries and in China, typhus is transmitted sometimes by fleas and sometimes by lice. The virus may therefore in these countries present the characteristics either of the murine type or of the classic type or it may present intermediate characteristics.

conjunctival eruption. The fever lasts for 10 days. Sudden or gradual defervescence. A long period of asthenia. A state of immunity to the murine virus *(Rick. mooseri)* and also to the epidemic virus *(Rick. prowazeki)* follows.

Ambulant clinical forms with attenuated symptoms. More rarely serious forms, with prostration and delirium.

Prognosis : As a rule favourable in the case of persons belonging to endemic regions. Fatal cases among immigrants and old persons occur.

Channels of elimination : In man, the blood. In rats, urine and fæces.

Resistance of virus outside the body : Persists in the rat and in that of the vectors, lice and fleas of rats. Survives for a long time in the dried excrement of fleas, etc.

Laboratory diagnosis : By WEIL-FELIX test as from the second week. The sero-agglutination of *Proteus* OX^{19} at 1:100 or more is regarded as positive.

Treatment : General, symptomatic.

Prophylaxis : Compulsory notification of disease. Disinfestation and isolation of patient ; disinfection of clothing and fomites. The same precautions in case of persons who have been in contact with patient ; they must also be kept under observation for 15 days.

Deratisation. In case of epidemic waves and for suspects, employ preventive vaccination (p. 218).

BOUTONNEUSE FEVER

Exanthematous Marseilles Fever.

Detailed international nomenclature (1938) : No. **39 b (ca).**

Latin = Febris exanthematosa mediterranea, Febris verrucosa mediterranea.

French = Fièvre boutonneuse, Fièvre exanthématique du littoral méditerranéen, Maladie de Conor et Bruch.

German = Beulenfieber, Exanthematisches Zeckenfieber.
Ital. = Febbre bottonosa, Febbre di Marsiglia, Tifo da zecche minore, Dermotifo benigno.
Roum. = Febra butonoasă.
Span. = Fiebre botonosa, Fiebre exantematica mediterranea (de Olmer).

A specific acute, infectious disease, endemic on the shores of the Mediterranean, characterised by a sudden onset, a sore at point of inoculation (the black spot — *tache noire*), eruption on the skin and mucous membranes of the mouth and throat, maculo-papular exanthem, etc.

Etiological agent : According to most authorities : *Rickettsia conori.*

Incubation : 5 to 7 days, rarely up to 20 days.

Direct contagion : No case has been observed.

Indirect contagion : By the bite of an infected dog-tick *(Rhipicephalus sanguineus).*

Portal of entry : Skin, conjunctivæ.

Localisation : A septicæmic infection.

Symptoms : Sudden onset, rigors, fever, stiffness and soreness of muscles, insomnia, headache, arthralgia, myalgia, constipation or diarrhœa, vomiting, reddish-brown sore *(tache noire)* at the point of inoculation with corresponding swelling of the lymph glands. After 3 to 4 days of fever, a general maculo-papular and sometimes petechial eruption. After 10 to 12 days, the temperature falls *in lysis* and the patient begins to recover.

Prognosis : Favourable ; rather more serious in aged persons.

Channel of elimination : Blood.

Resistance of the virus outside the body : In the vector, *Rhipicephalus sanguineus,* which is infective for several months. Hereditary transmission of the infection among ticks. Dogs and domestic and wild rodents constitute the probable reservoirs of the virus.

Laboratory diagnosis : Positive reaction to Weil-Felix test but only during convalescence.

Treatment : General, symptomatic.

Prophylaxis : Disinfection of clothing and fomites of patient. Destruction of ticks on infected dogs.

TRACHOMA [1]

Detailed international nomenclature (1938) : No. **88 (a).**

Latin = Conjunctivitis granulosa, s. trachomatosa.
French = Trachome, Conjonctivite granuleuse.
German = Bläschenkatarrh, Körnerkrankheit, Aegyptische Augenentzündung, Trachom.
Ital. = Tracoma, Congiuntivite tracomatosa.
Roum. = Conjunctivita granuloasă (Trachom).
Span. = Tracoma, Conjunctivitis tracomatosa.

A specific, contagious chronic disease of the conjunctivæ, characterised by the appearance of hypertrophic granulations followed by cicatricial contractions of the eyelids.

Etiological agent : Accepted by the majority of authorities : *Rickettsia trachomatosis* v. Prowazek, idem Halberstädter & Busacca (1933) ; Cuénod & Nataf (1930); Foley & Parrot (1937), etc. A filterable virus (?) (Nicolle, Cuénod & Blaizot).

Incubation : 8 to 10 days in case of natural infection, 3 to 7 days in case of experimental infection.

Direct contagion : Somewhat rare. Special susceptibility of children (below 5 years : 58.7%).

Indirect contagion : Articles soiled with lacrymal secretions and perhaps nasal secretions. Flies, lice (?).

Portal of entry : Conjunctivæ.

Localisations : Lymphatic follicles of the conjunctivæ.

Symptoms : According to McCollan and Cornet, there are 5 stages in the evolution of the disease : 1st stage, *latent* trachoma ; 2nd, conjunctival lesions with hypertrophy of the follicles and infiltrations of the mucous membrane, the

[1] From the Greek : rough, uneven. (Localised Rickettsiosis ?)

periphery of the cornea being also affected ; 3rd, appearance of pannus and of follicular marginal keratitis ; 4th, commencement of scarring ; 5th, formation of scars around the conjunctivæ of the tarsus and opacification of the cornea.

Prognosis : Varies with the time at which treatment is begun. Generalised trachoma can rarely be cured without serious complications affecting the eyes. If treatment is applied in good time, cicatrisation and cure result without complications in 95% of cases. No period of immunity follows.

Channels of elimination : Conjunctival, lacrymal and probably nasal secretions.

Persistence of the virus outside the body : Destroyed by heat at 113°-122°F. (45-50°C.) in ½ an hour (JULIANELLE, HARRISSON & MORISS) ; at ordinary room temperature in 24 hours ; at 32°F. (0°C.), still pathogenic after 8 days. Cannot be preserved in glycerine.

Laboratory diagnosis : Identification of PROWAZEK-HALBERSTÄDTER *bodies* in the epithelial cells, obtaining them by means of scraping the diseased conjunctivæ ; this should particularly be done at the outset of the disease.

Treatment : Medicamental : sulphate of copper 2%, nitrate of silver 1%, etc. Physical therapy : scraping, brushing the diseased conjunctivæ, diathermy, etc., surgical treatment for intractable scars.

Prophylaxis : Diagnosis and isolation of cases. Measures of personal hygiene, etc.

CHAPTER II

INFECTIONS CAUSED BY FILTER-PASSING VIRUSES

(Virus Diseases)

1. General Febrile Diseases

With a pustular eruption : Smallpox, varioloid, alastrim, cowpox, chicken-pox, shingles.

With a vesicular eruption : Herpes.

With a maculo-papular eruption : Measles, German measles, fourth disease, fifth disease.

Of a septicæmic character : Dengue, yellow fever, sandfly fever.

POX DISEASES

Caused by related filter-passing viruses, characterised by vesiculo-pustular eruptions of the skin, often associated with a pronounced epithelial proliferation.

Epidemic (except shingles) and highly contagious.

An infection with one of these viruses in some cases confers immunity from the others.

(1) *Smallpox.*
(2) *Cowpox.*
(3) *Sheep-pox* (Variole des ovidés, Clavelée).
(4) *Goat-pox* (Variole caprine — variole des chèvres).
(5) *Horse-pox* (Vaccine des solipèdes — stomatite pustuleuse des chevaux (?)).
(6) *Swine-pox* (Variole des porcs — tavelle ; tavellure).
(7) *Bird-pox* (Varioles aviaires).

SMALLPOX (HUMAN)

Detailed international nomenclature (1938) : No. **34 a.**

Latin	= Variola.	Ital.	= Vaiuolo.
French	= Variole humaine, petite vérole (v).	Roum.	= Vărsat.
		Span.	= Viruela.
German	= Pocken, Blättern (v).		

An eruptive, endemo-epidemic, highly contagious disease, transmissible by inoculation, characterised by an exanthem of a vesiculo-pustular type.

Etiological agent : A filterable virus (CASAGRANDI, 1908) maintains vitality in glycerine. It can be cultivated on the chorio-allantoid membranes of a chick embryo and in tissue cultures *in vitro*.

Dimensions : 125-175 mμ. Elementary corpuscles described by PASCHEN. By passage through other animal species, cowpox virus is obtained by mutation. Cross immunity.

Incubation : 10 to 15 days, latent.

Direct contagion : Contact with a diseased person or with infected products : expectorations, saliva, etc., or even with persons in a state of latent infection.

Indirect contagion : Contaminated articles ; third persons who have been in contact with patients ; insects (flies).

Portals of entry : The air passages (nose and throat) ; entry also possible by the digestive tract.

Localisations : A general septicæmic infection, localised in cells of organs derived from the ectoblast and mesoblast. Presence of characteristic formations (cellular inclusions) in the epithelial cells : *Guarnieri bodies* (which, according to HERZBERG, are composed of an agglomeration of elementary bodies enveloped in a capsule).

Symptoms : *Period of invasion :* 3 to 4 days. Sudden onset, violent rigor, temperature (104°F.—40°C.), headache

and backache, vomiting, very intense stiffness and soreness of the muscles, congested condition of mucous membranes and a prodromal rash, often with a tendency to hæmorrhage.

Period of eruption: Cyclic (duration 3 days), characterised by appearance of an *exanthem* (umbilicated variolar pustules), which begins on the face and spreads rapidly (in 48 hours), and of a *enanthem.*

The smallpox exanthem is at first *macular,* but soon becomes *papular* and towards the 3rd day consists of *vesiculated papules.* The transformation of these into *pustules* marks the beginning (about the 4th day) of the *period of suppuration. The scars which result persist for life.*

Duration of the disease: 30 to 40 days. Permanent *immunity* follows.

Prognosis : Variable. Fatality usually from 20 to 30%, sometimes rises to 90%.

Channels of elimination of virus : The content of the pustules.

Persistence of the virus outside the body : Very resistant to desiccation (persists for a long time in dwellings, on all contaminated articles, etc.).

Laboratory diagnosis : (1) Examination of patient's blood : leucocytosis with mononucleosis and myelocytosis. (2) Inoculation with contents of pustules of rabbits or guinea-pigs through the skin or cornea — PAUL'S *test.* Important in time of epidemic.

Treatment : Symptomatic. Curative : the serum of a convalescent may be tried (p. 266).

Prophylaxis : Immediate compulsory notification of case. Isolation of patient. Disinfection of clothing and fomites. Members of the household and especially those suspected of having been infected should be isolated. Ascertain origin of epidemic.

Compulsory vaccination against smallpox of all new-born children, usually between the 3rd and 12th months. Revaccination of children between 7 and 8 years and of recruits (21 years). In the case of an epidemic, the revaccination *en masse* of the whole population in epidemic zones is resorted to.

Duration of immunity conferred by vaccination : 5 to 7 years. There are exceptions. Compulsory anti-smallpox vaccination in a country is usually followed, in normal times, by the disappearance of the disease (p. 229).

VARIOLOID

Detailed international nomenclature (1938) : No. **34 b.**

An atypical form of smallpox in which the papules do not reach the stage of suppuration. There may be practically no eruption and the disease may be confined to the appearance of a rash.

This form of the disease usually occurs in the case of persons vaccinated in infancy and in whom the degree of immunity has since considerably diminished.

ALASTRIM

Detailed international nomenclature (1938) : No. **34 b.**

A mild form of smallpox, the existence of which has been observed in America and Africa, likewise in England and Switzerland.

The disease begins with fever (102°-104°F. = 39°-40°C.), headache, sore throat ; there is no prodromal *rash ;* the eruption consists of small *papules* which become transformed into *vesicles* containing a milky fluid. They do not leave scars. The virus of cowpox (Jenner's vaccine) gives immunity to alastrim. Alastrim does not confer immunity to smallpox.

COWPOX

Detailed international nomenclature (1938) : No. **38 f.**

Latin	= Vaccinia.	Ital.	= Vaiuolo vaccino.
French	= Vaccine.	Roum.	= Vaccina.
German	= Kuhpocken.	Span.	=

An infectious, communicable disease in cattle, characterised by a pustular eruption. Transmissible to man, who acquires immunity to both cowpox and smallpox.

Etiological agent : A filterable virus, closely related to the smallpox virus, preservable in glycerine, can be cultivated on chorio-allantoid membranes.

Dimensions : 125-175 mμ (Elford & Andrewes, 1932). Identification after staining in the form of elementary bodies.

Incubation : 6 to 7 days in cases of natural infection, 3 to 4 days in case of inoculation with vaccine.

Direct contagion : Contact with infected animals.

Indirect contagion : Through persons attending diseased animals (*e.g.*, through the contaminated hands of persons who milk cows, etc.).

Portal of entry : Through breaks in the skin or through mucous membranes, conjunctivæ, etc.

Localisations : As in smallpox (*cf.* Smallpox, p. 96).

Symptoms : An eruption of *non*-umbilicated vesicular pustules surrounded by a red areola, on the udder of a milch cow. The eruption may sometimes be general. The pustules ulcerate and dry up in about 2 weeks after their appearance.

Prognosis : Generally benign when the eruption affects only the skin. Eye accidents serious.

Complications : Appearance of accessory eruptive elements, caused by secondary inoculations resulting from scratching and by contamination of the vaccine lymph used. Accidental inoculations of the conjunctivæ, etc.

Treatment : Not important in view of benign course of disease. For complications : symptomatic treatment.

Prophylaxis : Previous *vaccination* of persons who attend and milk the cows (p. 229).

CHICKEN-POX

Detailed international nomenclature (1938) : No. **38 e.**

Latin	= Varicella.	Ital.	= Cristalli, Raviglioni, Varicella.
French	= Varicelle.		
German	= Windpocken, Varizellen.	Roum.	= Vărsat de Vânt.
		Span.	= Varicela.

An acute, eruptive, infectious disease affecting mainly infants, characterised by slight fever and a polymorphous vesicular eruption appearing in successive waves.

Etiological agent : A filterable virus. In the contents of vesicles, PASCHEN has found *elementary bodies* (identity of the virus with that of shingles).

Incubation : 2 to 3 weeks.

Direct contagion : From the patient—highly contagious.

Indirect contagion : Articles contaminated with the discharge from the vesicles or the saliva of patients.

Portal of entry : The air passages (nose and throat), etc.

Localisations : A septicæmic disease, with localisations in the skin.

Symptoms : *Period of invasion :* debility, fatigue, stiffness and soreness of muscles, moderate fever.

Period of eruption : successive and irregular eruptions of spots which become successively *macular*, *papular* and *vesicular* without *suppuration*.

General condition good. Duration : 1 week. The disease is followed by a condition of permanent immunity.

Prognosis : Favourable, a very mild disease, complications are rare.

Channel of elimination : The skin eruption.

Resistance of virus outside the body : Small. But little vitality, so that germ-carriers are infectious for a very short time.

Laboratory diagnosis : PAUL'S test gives negative results in chicken-pox (no specific lesions on the cornea of rabbits).

Treatment : Symptomatic.

Prophylaxis : Isolation in home until cured. Disinfection. Serum treatment with serum of a convalescent may be applied as a preventive measure.

SHINGLES

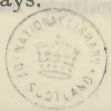
Detailed international nomenclature (1938) : No. **38c.**

Latin	= Herpes zoster, Zona.	Ital.	= Erpete zoster, Zona.
French	= Zona.	Roum.	= Zona.
German	= Zoster, Gürtelrose.	Span.	= Zona, Herpes Zoster.

A specific acute, infectious disease, characterised by a vesicular eruption, affecting the area of skin corresponding to one or more nerves, generally accompanied by violent neuralgic pains.

Etiological agent : A filter-passing virus related to that of chicken-pox ; also, in the view of some authorities, to the herpes virus. Elementary bodies have been observed in the content of vesicles (PASCHEN, 1933). Dimensions not yet ascertained. Cannot be preserved. DE CASTRO TEIXEIRA claims to have cultivated it (in 1936) on the chorio-allantoid membranes of a chick embryo.

Incubation : 12 to 15 days.



Direct contagion : Probably by contact with sufferers from shingles.

Indirect contagion : ?

Portal of entry : Not known.

Localisations : A neurotropic virus. Causes lesions of the skin and nervous tissue.

Symptoms : An acute infection, characterised by a vesicular eruption and by pains about the roots of one or more spinal nerves or about a sensory cranial nerve. The eruption which takes the form of successive crops has three phases : macular, vesicular and scabby. The pain, which is very acute, resembles that from a burn and is both superficial and deep. Duration : 2 to 3 weeks.

Prognosis : Favourable. Temporary immunity follows.

Channels of elimination : Lesions of the skin.

Resistance of virus outside the body : Very small.

Laboratory diagnosis : Not resorted to in practice. Intranuclear inclusions : LIPSCHÜTZ acidophil zosteroid bodies ; PASCHEN : elementary bodies in the contents of vesicles. The histopathological lesions of the skin are characteristic : infiltration of the dermis and " swelling degeneration " of the epithelium (UNNA).

Treatment : Sterilised inert powders to prevent septic suppuration of vesicles. Anti-neuralgic treatment. Ultra-short-wave treatment. Serum from a convalescent.

Prophylaxis : Avoidance of contact with sufferers from shingles.

* * *

Symptomatic Shingles : In the course of various intoxications (arsenic, bismuth, mercury, potassium iodide, ergot, morphine, in diabetes, gout and eclampsia), the appearance of symptomatic shingles have been observed of which the most frequent type is *arsenical symptomatic shingles.*

HERPES

Detailed international nomenclature (1938) : part of No. **153.**

Latin = Herpes simplex, H. menstrualis, labialis, prenuptialis.
French = Herpès, H. simple, H. fébrile ou idiopathique, Bouton de fièvre.
German = Bläschenausschlag.
Ital. = Erpete.
Roum. = Spuzeala, Herpes.
Span. =

An infectious disease of the skin and mucous membranes, characterised by the appearance of small vesicles coalesced in patches on a red base.

Etiological agent : A filterable virus (Doerr, 1920), also ultra-filterable (Levaditi & Nicolau, 1923). Can be preserved in glycerine and can be cultivated on tissue cultures and on the chorio-allantoid membrane of a chick embryo. Dimensions : 100-150 mμ (Elford, Perdrau & Smith, 1933) — 100 to 300 mμ (Levaditi, Paic & Krasnoff, 1936).

Incubation : ?

Direct contagion : From a patient or carrier. A saprophytic virus of the mucous membrane of the mouth and genital organs, becomes pathogenic under certain conditions : traumatism, intoxications, infections, a special physiological condition *(catamenial H.). Genital H.* is also transmissible by sexual intercourse.

Indirect contagion : Contaminated articles, saliva (Flügge's " droplets ").

Portal of entry : Mucous membranes of the mouth or genital organs, conjunctivæ and cornea.

Localisations : Skin and mucous membranes. An epitheliotropic and neurotropic virus. Intranuclear oxyphilous inclusions.

Symptoms : An eruption of vesicles coalesced in patches, varying in number, on an erythematous base. Course :

macules, vesicles, desiccation, scabs—heals without leaving scars. Fever, neuralgia, stiffness and soreness of muscles.

Prognosis : A mild disease ; no immunity.

Channels of elimination : Lesions of the skin (liquid from the vesicles).

Persistence of virus outside the body : Is a saprophyte.

Laboratory diagnosis : Experimental inoculation of rabbits; not much resorted to in ordinary practice.

Intranuclear oxyphilous inclusions : in the epithelium of the cornea of an inoculated rabbit. (LIPSCHÜTZ, 1921, LEVADITI, HARVIER & NICOLAU, 1921, etc.). LÖWENSTEIN *bodies* in the cytoplasm of epithelial cells of vesicles in case of man.

Treatment : Inert sterilised powders to accelerate desiccation of vesicles.

Prophylaxis : Personal hygiene. Occasional small epidemics in barracks.

MEASLES

Detailed international nomenclature (1938) : No. **35.**

Latin	= Morbilli.	Ital.	= Morbillo.
Fr.	= Rougeole.	Roum.	= Pojar, Cori.
Germ.	= Masern, Morbilli.	Span.	= Sarampión, Rugeola.

A specific, eruptive, infectious, epidemic disease, characterised by catarrh of the eyes and upper air passages, followed by a characteristic exanthem. Affects children more particularly.

Etiological agent : The *measles virus* would appear to be filterable. The results of attempts made to cultivate it on cultures of tissue (DEGKWITZ, 1925) and on chorio-allantoid membrane (WENCKEBACH & KUNERT, 1937) are doubtful.

Incubation : 10 to 14 days.

Direct contagion : Projection of droplets of secretions of nose and throat during fits of coughing or sneezing. *Contagiousness very marked* during catarrhal phase of the disease ; diminishes until it ceases altogether at the end of the eruptive phase.

Indirect contagion : Possible but rare.

Portal of entry : Nose and throat, tonsils, probably conjunctivæ.

Localisations : Blood, nasal secretions and expectorations.

Symptoms : *Period of invasion*, 2 to 3 days. The first day intense catarrh of the eyes and nose ; temperature 99.5-100°F. (37.5-37.8°C.). The next day, the catarrh extends to the larynx, hoarseness and cough. Appearance of " KÖPLIK *spots* " (small white or bluish-white spots of 1 mm. diameter on the mucous membrane of the mouth, tongue and lips). Sometimes erythemato-pultaceous stomatitis. As a rule, the mouth eruption precedes the characteristic exanthem by 36 to 48 hours.

The *skin eruption* appears on the 3rd or 4th day, usually in the night. The temperature increases when the eruption appears and reaches 102-104°F. (39-40°C.) or even more. The eruption, which consists of pink smooth papules, at first isolated and later more or less coalescing, begins behind the ears and on the forehead, rapidly spreading to the cheeks, lower part of the face, neck, trunk, upper limbs, etc. In 4 to 5 days, the eruption commences to fade, beginning with the regions where it first appeared.

Desquamation towards the 6th or 7th day.

Total duration of the disease depends on possible complications.

Complications : The most frequent are : *Broncho-pneumonia* generally appearing after the period of eruption, and *suppurating otitis*.

In many cases measles leaves a somewhat pronounced susceptibility to tuberculous infection.

Prognosis : Variable in different countries. Immunity follows.

Channels of elimination : Nose, throat, conjunctivæ.

Resistance of virus outside the body : Very little resistance. Rapidly rendered harmless by air, light and desiccation.

Diagnosis : Exclusively clinical, based on the presence of " Köplik *spots* ", the catarrh of the nose and eyes and the characteristic eruption. Diagnosis by differentiation from other eruptive diseases : scarlet fever, German measles, smallpox during the period of the rash, rose-rash. A characteristic of measles is the disappearance of skin sensitiveness to tuberculin (anergy) especially during the first days.

Treatment : Disinfection of nose and throat. Serum treatment with *convalescents' serum* (up to 100-150 cc. in serious cases)—whole blood of a relation or other person who has had measles may also be used (p. 267).

It is claimed that the administration of pyramidon in repeated small doses during the invasion period renders the disease abortive.

In the Army : isolation for 10 to 12 days in the infirmary of soldiers who have been in contact with patients ; patients to be sent to hospital.

Serum-prophylaxis with serum of a convalescent in case of persons who have been in contact with the patient (serum to be taken between the 7th and 9th days after the fall of the temperature). The sooner the serum is administered after the contact with infection, the more effective it will be. Administered 7 days after contact, it will no longer prevent the disease but will render it milder.

MacKhann & Chu recommend the use of immune globulins from the placenta, especially in the case of debilitated children (p. 235).

Preventive vaccination by "*morbillation*" *(rougeolisation)* is no longer used. *Sero-vaccination :* serum of a convalescent, followed—24 hours later—by an injection with the blood of a measles patient. Disease slight and subsequent immunity.

GERMAN MEASLES

Detailed international nomenclature (1938) : No. **38 d.**

Latin	= Rubella, Rubeola.	Ital.	= Rosolia.
French	= Rubéole.	Roum.	= Rubeola.
German	= Röteln.	Span.	= Rubéola.

An acute, infectious disease characterised by a general swelling of the lymph glands, fever and exanthem. Confused by some authorities with " fourth disease ".

Etiological agent : Presumed to be a filterable virus.

Incubation : 14 to 23 days. In case of an epidemic, usually 14 days.

Direct contagion : During period of invasion and during premonitory symptoms and eruption. Possibility continues for a further 7 or 8 days afterwards.

Indirect contagion : Unlikely, owing to fragility of virus outside the body.

Portal of entry : Tonsils and mucous membranes of the nose and pharynx.

Localisations : Lymph glands.

Symptoms : As a rule, the infection is extremely benign. Usually invasion proceeds without premonitory symptoms, sometimes slight headache, stiffness and soreness of the muscles, catarrh of the eyes, nose and pharynx, fever preceding or accompanying the eruption. An eruption of the measles or scarlet fever type, persists for 2 or 3 days ; swelling of the lymph glands is always present ; scaly desquamation sometimes absent.

Prognosis : Very mild disease. Prolonged immunity follows.

Channels of elimination : Secretions of nose and throat

Resistance of virus outside the body : Very little.

Laboratory diagnosis : A somewhat characteristic blood picture. At the outset hyperleucocytosis which rapidly diminishes ; reaches lowest limit on 3rd day of eruption.

Then follows eosinophilia, lymphocytosis (lymphocytes and lymphoblasts) and plasmocytes.

Treatment : Symptomatic.

Prophylaxis : Compulsory notification. Isolation of patient. Measures of personal and general hygiene, especially in communities.

FOURTH DISEASE

Detailed international nomenclature (1938) : No. **44 d (e).**

Latin = Rubeola scarlatinosa.
French = Quatrième maladie, Rubéole scarlatiniforme.
Germ. = Vierte Krankheit.
Ital. = Quarta malattia.
Roum. = Maladia patrulea.
Span. = Cuarta enfermedad, cuarta erupción.

Some authorities describe by these names a clinical syndrome which resembles German measles but which they distinguish from it ; this syndrome is said to be due to a specific infection caused by a filter-passing virus. The negative results of experimental attempts to transmit these diseases to animals make it impossible at present to reach any definite conclusions.

FIFTH DISEASE

Detailed international nomenclature (1938) : part of No. **38 f.**

Latin = Erythema infectiosum (annulare).
French = Cinquième maladie, Mégalérythème épidémique.
German = Ringelröteln.
Ital. = Eritema infettivo, Quinta malattia.
Roum. = Maladia cincilea.
Span. = Quinta enfermedad.

German authorities have described under the name of Ringelröteln (1889) or *Erythema infectiosum* (1899) an

affection which, clinically and epidemiologically, much resembles German measles. So far as our knowledge extends at present, it would seem to be due to a mere variant of the filterable virus which, presumably, constitutes the etiological agent in German measles.

DENGUE

Detailed international nomenclature (1938) : No. **38 f (a).**

Latin = Febris dengue.
French = Dengue.
German = Denguefieber, Siebentagefieber.
Ital. = Dengue, Febbra dei sette giorni.
Roum. = Denga.
Span. = Fiebre dengue.

A specific, infectious, epidemic disease of tropical and sub-tropical countries, distinguished by a characteristic temperature curve, an eruption of the measles type and rheumatoid pains.

Etiological agent : A filterable virus (Ashborn & Craig, 1907) the dimensions of which have not yet been ascertained (by ultrafiltration, ultra-centrifugalisation, etc.).

Incubation : Variable, as a rule 5 to 9 days. From 3 to 8 in experimental infections.

Direct contagion : Not yet established.

Indirect contagion : Bite of the *Aëdes aegypti* mosquito *(Stegomyia fasciata)* and *Aëdes albopictus* mosquito ; they are infective 8 to 14 days after absorption of blood containing the virus.

Portal of entry : Skin.

Localisations : The virus is found in the circulation until the 5th day of the disease.

Symptoms : Sudden onset ; febrile period (101.3 to 104°F. —38.5-40°C.), lasting for 2 to 3 days with intense headache, lumbar pains, pains in the joints and muscles, insomnia,

marked asthenia and gastro-intestinal disorders. A rash in 50% of cases. Short period of remission. Towards the 4th to 7th day, a recrudescence of fever and subjective symptoms. A rash resembling measles or nettle-rash in 16% of cases.

The pulse and temperature do not correspond : *bradycardia*. Duration of disease : 12 to 14 days.

Prognosis : Favourable. Fatality nil. Sometimes rather lengthy convalescence : loss of appetite, debility, insomnia, etc., especially among Europeans.

Immunity lasts for 10 to 12 months.

Channels of elimination of virus : Not known.

Resistance of virus outside the body : Dried blood containing the virus preserves it for a very long time : 200-250 days. Destroyed by bile, glycerol, phenol, etc.

Laboratory diagnosis : Transmissible to man by experimental inoculation with blood containing the virus. Leucopenia—neutropenia. Guinea-pigs sometimes, and the lower monkeys, develop latent infections followed by immunity after inoculation with the virus.

Treatment : Symptomatic.

Prophylaxis : Protect patients from mosquito bites in order to avert extension of the epidemic. Individual protection against mosquitoes. Mechanical protection of dwellings. Improvement of sanitary conditions of infected areas.

YELLOW FEVER

Detailed international nomenclature (1938) : No. **38 a.**

Latin	= Febris flava, F. biliosa.	Ital.	= Febbra gialla.
		Roum.	= Febra galbenă.
French	= Fièvre jaune.	Span.	= Fiebra amarilla.
German	= Gelbfieber.		Vómito negro (v).

An acute, infectious, epidemic, septicæmic disease peculiar to man, with lesions of the liver and kidneys (jaundice and albuminuria) and foci of degeneration in various other

organs. Geographically limited to certain sectors of the globe. Probably originated in West Africa. Endemic zones : America (the north of South America) and Africa (West Africa).

Etiological agent : The *pantropic* filterable virus *(virus amaril)* (Reed, Carroll & Agramonte, 1900, Stokes, Bauer & Hudson, 1928), transmissible to monkeys *(Macacus rhesus & M. sinicus)* aut. cit. : a *viscerotropic virus ;* and to white mice (Theiler) in which, by passages through the brain, it becomes a *fixed, neurotropic virus ;* also pathogenic for guinea-pigs. Dimensions : 18 to 27 mμ (Findlay & Broem, 1933 ; Bauer & Hughes, 1935). It is cultivated exclusively in the presence of living cells (Haagen, 1932-1934) and on the chorio-allantoid membrane of a chick embryo (Ellemdorff & Smith, 1937).

The dried and frozen virus, kept in a frigorific vacuum (17.6°F. — 8°C.) retains its virulence for more than 3 years (Russell, 1932).

Incubation : 3 to 6 days (from the bite to appearance of first symptoms).

Direct contagion : No case of direct communication from one person to another is known. By experimental inoculation with blood of a patient (during first 3 days of disease) or by accidental puncture with a contaminated needle (doctor or nurse).

Indirect contagion : By the bite of the vector insect.

Transmitting species : (1) African : *Aëdes aegypti* (*Stegomyia fasciata*), *A. luteocephalus, A. stokesi, A. apicoargenteus, A. vittatus, A. africanus, A. simpsoni.*

(2) Brazilian : *Aëdes scapularis, A. fluviatilis, A. taeniorhynchus,* etc.

The time required for the mosquito to become infective after absorbing blood containing the virus varies according to the prevailing temperature :

At 98.4°F. (37°C.) after 4 days.
At 73.4°F. (23°C.) » 11 days.
At 69.8°F. (21°C.) » 18 days. (Davin, 1931).

The virus persists in the body of the mosquito for its whole life. It is not transmitted to descendants. The cycles : man-mosquito-man or monkey-mosquito-monkey are essential.

Portal of entry : Skin, by a bite of the vector. Experimentally, also by the nasal mucous membrane (R. DOERR).

Localisations : In the circulating blood—degenerative visceral lesions : mainly liver and kidneys.

Symptoms : About the 5th day following the infecting bite, sudden onset, violent rigor, headache, fever (103°-104°F. — 39.5°-40°C.). Characteristic congested facies (mahogany red, " yellow fever mask "), congested eyes, sometimes slight jaundice, furred tongue. The patient complains of severe pains : backache and epigastric pains followed by nausea and vomiting. From the outset there is albuminuria. At the beginning the pulse corresponds to the temperature but tends rapidly to become slow.

Convalescence begins about the 3rd or 4th day of the disease in mild forms, but usually, after a short remission, the disease continues to develop as from the 5th day : coffee-coloured hematemesis *(vomito negro)*, jaundice and intense albuminuria (the hepato-renal stage). Various hæmorrhages : nose-bleeding, intestinal hæmorrhages, hæmorrhages from the uterus and miscarriage in case of pregnant women. Oliguria : bile-stained urine. Anuria. Asthenia : collapse, stupor. *Spleen not enlarged.*

Prognosis : Mortality variable according to severity of epidemic : from 5 to 57% (MANSON). In children, the disease is much less serious than in adults : complete recovery in 60% of cases between the 6th and 10th days of disease.

There are also latent forms of the disease (especially among children and negroes) ; there are likewise cases which, after a non-febrile phase about the 4th day recover completely (a lengthy convalescence).

Channels of elimination of virus : The virus exists in the blood and in all pathological products containing blood.

Persistence of virus outside the body : In the body of the vector. In the body of monkeys (permanent reservoir of virus ?).

Laboratory diagnosis : By inoculation (with whole blood or serum) of receptive animals : monkeys, mice, etc. Retrospective : by ascertaining neutralising power of serum upon the virus (THEILER'S *sero-protection test*).

Post-mortem : By histological examination of characteristic lesions of liver and kidneys. In epidemic zones, with the aid of the viscerotome (RICKARD) a small piece of liver is removed (without a complete autopsy). Existence of foci of characteristic necrosis.

Treatment : General, medicinal. *Specific serum treatment :* immune serum of horse or monkey.

Prophylaxis : By *preventive vaccination* (HINDLE, 1929) with vaccines prepared in various ways,—attenuation by chemical substances (phenol, formaline, methylene blue, etc.) or by adaptation of the virus to mice (SAWYER, KITCHEN & LLOYD, 1932) (SELLARDS & LAIGRET, 1932), very encouraging results would seem to have been obtained. The attenuated strain 17D of the Rockefeller Institute of New York, originally cultivated on tissue cultures and then on chicken embryos—employed at first with a human serum base and later, in 1942, with a water base (to avoid cases of jaundice due to the serum)—has been applied with success since 1937 to several million inhabitants of South America and United States soldiers. The immunity resulting from subcutaneous inoculation persists for four years and probably much longer. At the Pasteur Institute, Paris, STEFANOPOULO (1943) employs a viscerotropic virus cultivated on tissues of a chicken embryo until complete attenuation results when it is reactivated by several passages through mice. Doses : 5,000 to 50,000 M.L.D.s for mice administered subcutaneously to man.

In French West Africa, M. PELTIER (1941) vaccinates by scarification of the skin with a neurotropic yellow-fever virus (brains of mice) associated with Jenner's vaccine virus.

Rigorous isolation of patient under a mosquito net. Individual measures of protection against mosquito bites. Mechanical measures for protection of dwellings and particularly anti-larval measures around them.

SANDFLY FEVER
(Pappataci Fever)

Detailed international nomenclature (1938) : No. **38 f (b).**

Latin = Febris pappataci, F. phlebotomorum.
French = Fièvre à pappataci, Fièvre à phlébotomes, Fièvre de trois jours.
German = Pappatacifieber, Phlebotomusfieber, Dreitagefieber, Sommerfieber.
Italian = Febbre da papataci, Febbre dei tre giorni, Febbre da canapa.
Roumanian = Febra de trei zile.
Spanish = Fiebre de pappataci, Fiebre de tres dias.

A specific, infectious, epidemic disease of the Mediterranean area and the Near and Middle East, characterised by fever of short duration and symptoms of general infection.

Etiological agent : A filterable virus (Doerr & Roux, 1908).

Incubation : Generally short, 3-8 days. Occasionally less (24 hours).

Direct contagion : Unknown.

Indirect contagion : The bite of infected insects, generally *Phlebotomus papatasi* Scopoli : infective about 7 days after absorption of blood containing the virus.

Portal of entry : Skin.

Localisations : The blood is virulent for only 24 to 40 hours following the onset of the disease. Spleen (?) Bone marrow (?)

Symptoms : Sudden onset, with shivering and fever, irritability, headache, muscular pains, especially lumbar pains, conjunctival congestion, digestive and urinary disorders ; sometimes vomiting. The patient may have the appearance of being drunk. Sometimes mental confusion or even delirium. Temperature 102°-104° F. (39°-40° C.) the first day, falls the second day, and returns to normal the third day. Bradycardia as soon as the morbid symptoms have disappeared. Sometimes an erythematous rash. Marked asthenia.

Prognosis : Very favourable. Lengthy convalescence. Relapses may occur in cases of convalescents who resume work too soon.

Channels of elimination of virus : Unknown.

Resistance of virus outside the body : The virus is transmitted by the female insect to its descendants (infected eggs) : they constitute a permanent reservoir of the virus in periods between epidemics.

Laboratory diagnosis : The virus can be inoculated experimentally to man, the only higher species known to be receptive at present. Leucopenia, neutropenia. There are no other laboratory tests.

Treatment : Symptomatic.

Prophylaxis : Mosquito nets may be used only to prevent spread of epidemic. They are insufferable in hot weather when their mesh is fine enough to exclude phlebotomes. Measures of personal protection among healthy persons. Mechanical protection of dwellings : sanitation of infected houses : removal and destruction of house refuse, demolition of cracked walls. Fumigation and lime-washing of houses and huts, proper ventilation.

2. Diseases affecting Particular Organs

The respiratory tract : Influenza, Common cold, Psittacosis.

Nervous system : Epidemic encephalitis, Other forms of human encephalitis caused by various viruses, Infantile paralysis, Rabies.

Other organs : Glandular fever, Foot-and-mouth disease, Lymphogranuloma venereum (L. inguinale), Mumps, Venereal warts, Warts, Epidemic hepatitis.

INFLUENZA

Detailed international nomenclature (1938) : No. **33.**

Latin = Influenza.
French = Grippe, Influenza.
German = Epidemische Influenza, Grippe.
Ital. = Influenza.
Roum. = Gripă, Influenţă.
Span. = Influenza, Grippe.

An acute, infectious, epidemic disease, of worldwide distribution, characterised by an acute catarrhal inflammation of the respiratory passages, asthenia and muscular pain. (There is also a similar malady among pigs caused by a kindred virus.)

Etiological agent : A filterable virus, SHOPE, 1931 (Hog flu) ; SMITH, T. C., ANDREWS, H. S., & LAIDLAW, 1932-1933 (human influenza). Dimensions : 80-120 mμ. (ELFORD, ANDREWS & TANG, 1936) can be cultivated on chorio-allantoid membranes (chicken embryo). Associated bacteria : Pfeiffer's coccobacillus *(Hemophilus influenzae)* Streptococci, Pneumococci, *Micrococcus catarrhalis.*

Incubation : 1 to 3 days.

Direct contagion : Extremely contagious by direct contact with the patient (Flügge's droplets—secretions of nose and throat).

Indirect contagion : Clothing and fomites of patient soiled with secretions of nose and throat or expectorations.

Localisations : Respiratory passages, blood and the more vascular organs (lung, etc.).

Symptoms : Acute toxi-infectious fever, with sudden onset, headache, rigors, high temperature, myalgia, loss of appetite, sometimes vomiting and nose bleeding. Characteristic temperature curve (Influenza V curve). Whitish porcelain-like tongue, scanty urine.

Influenza may take a respiratory, nervous or gastro-intestinal form.

Prognosis : Varies with the state of health of the individual, intercurrent disease, the type of epidemic and the gravity of complications.[1] Fatality : very variable—up to 50% in serious epidemic waves.

Channels of elimination : Mainly respiratory passages.

Resistance of virus outside the body : But little resistance. Destroyed at 97°F. (36°C.). In glycerol or kept dry in a refrigerator, retains virulence for several weeks.

[1] Prognosis varies with the germs associated with the influenza virus.

Laboratory diagnosis : The virus may be identified by inoculation of a ferret *(Putorius furo)*. This is an expensive proceeding used only for experimental purposes. It is advisable to identify the associated bacterial species in the pathological products eliminated by the patient (sputum).

Treatment : Symptomatic. Preparations of quinine, aspirin, etc. ; try also serum of a convalescent. For complications due to pneumococcus : sulphonamide preparations.

Prophylaxis : Isolation of patient. Measures of personal hygiene. Gargling with antiseptic solutions. Preventive vaccination with *anti-influenza Tetravaccine* against complications (a vaccine consisting of a mixture of killed Pfeiffer's coccobacilli, streptococci, pneumococci and *Micrococcus catarrhalis* (p. 240). Experiments with specific vaccination with the virus isolated from receptive animals (mouse's lung) have not been conclusive.

COMMON COLD

Detailed international nomenclature (1938) : No. **104 a(a).**

Latin = Rhinitis, Coryza.
French = Coryza, Rhume de cerveau.
German = Erkältungskrankheit, Schnupfen.
Ital. = Corizza, Rafreddore di testa (v).
Roum. = Guturai, Răceală.
Span. = Coriza, Resfriado.

An acute, highly contagious disease, chiefly characterised by an abundant secretion from the nose and throat.

Etiological agent : A filterable virus, transmissible from person to person (Kruse, 1914) ; to the chimpanzee (Dochez, Shibley & Mills, 1929-1930) ; to the hedgehog (Edwards, 1934) ; to the ferret *(Putorius furo)* (Noble & Brainard, 1935). Can be cultivated on Maitland's medium (tissue of chicken embryo)—Dochez, Mills & Kneeland (1931) and on the chorio-allantoid membrane (Hyde & Chapman, 1937).

Incubation : 24 to 48 hours in disease experimentally communicated to man (nasal instillation of filtrate) ; sometimes more : 70 hours.

Direct contagion : Contact with patient (or Flügge's droplets)—cold and damp weather favours the appearance of epidemics.

Indirect contagion : By soiled handkerchiefs or any contaminated article, sometimes also by food.

Portal of entry : Mainly mucous membranes of nose and pharynx.

Localisation : Nose and pharynx.

Symptoms : Signs of acute catarrh of the mucous membranes of the nose and pharynx and sometimes of the conjunctivæ. Abundant watery nasal secretion—moderate fever. Sometimes leucopenia. Complicated frequently by trachitis or bronchitis caused by associated germs : pneumococci, streptococci, etc. Duration of disease : 5 to 7 days.

Prognosis : Favourable. Temporary immunity.

Channels of elimination of virus : Secretions of nose and throat. Sputum.

Resistance of virus outside the body : The filtrate is infective for 18 to 20 hours. Inactivated by heating to 140°F. (60°C.) (Olitsky & MacCartney, 1932). The virus with gum arabic added and then dried retains its virulence.

Laboratory diagnosis : Not employed.

Treatment : Symptomatic.

Prophylaxis : General hygiene. *Tetravaccine* used to protect from the more frequent complications (p. 240).

PSITTACOSIS

Detailed international nomenclature (1938) : No. **44 d(d).**

Latin = Psittacosis.
French = Psittacose, Maladie des perroquets.
German = Papageikrankheit.

Ital. = Psittacosi.
Roum. = Psitacoză.
Span. = Psitacose.

An infectious disease of psittacidæ (parrots), transmissible to man, with a course resembling that of typhoid fever with pulmonary complications.

Etiological agent : A filterable virus (BEDSON, WESTERN & SIMPSON, 1930) ; dimensions : 220-330 mμ (LEVINTHAL) —resists desiccation. The virus in a phosphate buffer solution [pH 7.6 at + 6°C. (42°F.)] retains its virulence for 55 days (BEDSON). If formalin is added (1 to 2 p. 1000), it retains its antigenic power but loses its virulence (BEDSON).

Incubation : 8 to 14 days. Occasionally less : 4 to 6 days (LEVY SIMPSON).

Direct contagion : By a bite, or by the ejection of droplets of saliva, from a diseased parrot ; a parrot which is a carrier of the virus may present a normal appearance. Direct contamination—from a person suffering from the disease—is possible. Laboratory infections are very frequent.

Indirect contagion : Contaminated dust.

Portal of entry : Digestive tract and upper air passages.

Localisations : Lungs. The blood is infective particularly during the first week.

Symptoms : The onset is marked by general indisposition, stiffness and soreness of the muscles, intense headache, backache, nausea. The temperature rapidly rises to 102°-104° F. (39°-40°C.) A typhoid condition, extreme prostration, mental confusion or continuous delirium. The temperature persists at a high level : 104°-106°F. (40°-41° C.), with no marked fall in the mornings. Intense intoxication, extreme pallor (WELTMANN)—*Pink spots* observed by HUTCHINSON, ROWLANDS & LEVY SIMPSON, between the 7th and 13th days, on the thorax, the abdomen and the back. No enlargement of the spleen (GUNTHER, 1930). Constipation. Scanty dark albuminous urine. Pulmonary symptoms from the outset and sometimes between the 7th and 11th

days. Abundant expectoration. Transient foci of congestion, forming successively and tending towards hepatisation. Nervous disorders, carphology and muscular jerks. Death ensues in the 2nd or 3rd week.

In cases evolving towards recovery, the symptoms diminish, usually between the 8th and 10th days. Convalescence is always very long.

Prognosis : In serious forms always very grave. Slight forms are recorded, especially among children and young persons.

Death rate is in general high : 20 to 45%.

Channel of elimination of virus : Sputum.

Resistance of virus outside the body : Considerable in dust contaminated with expectoration or excreta (diseased birds).

Laboratory diagnosis : Intraperitoneal inoculation of mice with sputum or blood (during first 2 weeks of disease)—or with pathological products obtained at the post-mortem examination. The appearance of the lungs recalls that observed in influenza. (Desquamative hæmorrhagic vesicular pneumonia.) In the parrot, the characteristic lesion is in the liver : there are irregularly distributed zones of necrosis with acidophil degeneration of the cytoplasm and shrinking of the cells.

Elementary bodies, round or slightly oval, are found in the reticulo-endothelial cells, which are sometimes completely blocked with them ; stained by Giemsa on smears of organs (*Rickettsia psittaci*—Lillie, 1930)—Evolutionary cycle (?) (Bedson & Bland, 1932).

Treatment : Serum of convalescent ; symptomatic.

Prophylaxis : Immediate notification of suspected cases and isolation of patients. Measures of disinfection and personal hygiene among contacts.

Experiments with preventive vaccination (Rivers & Schwenker), by intramuscular injections of non-attenuated virus have not been conclusive.

The formalinised virus used by Bedson seems to have given better results.

Rigorous veterinary control of imported parrots.

ACUTE INFECTIOUS ENCEPHALITIS
(Epidemic, lethargic)

Detailed international nomenclature (1938) : No. **37 a.**

Latin = Encephalitis lethargica acuta.
French = Encephalite épidémique aiguë (dite léthargique), Maladie de von Economo.
German = Economo'sche Krankheit, Epidemische Gehirnentzündung.
Ital. = Encefalite letargica acuta.
Roum. = Encefalită letargică, Maladia lui v. Economo.
Span. = Encefalitis letargica aguda.

An infectious (occasionally epidemic) disease, characterised by encephalitic phenomena with a tendency to lethargy.

Etiological agent : Believed to be a filterable virus with neurotropic characteristics. With regard to its identity, there are three hypotheses : 1. Levaditi & Harvier (1920) and Doerr & Schnabel (1921), etc., believe that it is a special strain of *herpes virus (Herpes-encephalitis virus)* with particularly pronounced neurotropic tendencies, to which rabbits are receptive. The only apes which are receptive are the *Cercopithecus callitrix* and the *Cebus olivaceus.*

2. The second hypothesis, which is supported by Austrian authorities, is that it is identical with the *influenza virus.* The localisation in the encephalon, and especially in the grey matter of the mesocephalon, is similar to that of some strains of treponemata which, in a limited number of cases, display a tendency to invade the central nervous system (general paralysis of the insane or tabes).

3. Finally, according to the third hypothesis (Jahnel, 1939), the specific virus of this disease has not yet been identified.

According to authorities who have experimented with what they believe to be the specific virus, it is destroyed

by heating for 60 minutes to 131°-158°F. (55°-70°C.) When desiccated at 67° F. (22°C.), it retains its virulence for at least 44 days. It resists post-mortem autolysis for 24 to 48 hours. It can be kept in a 50% solution of glycerol for a year. It resists antiseptics such as menthol, salol, boric acid, phenol 1% (for 3 days). Very sensitive to potassium permanganate (2‰).

Incubation : On the average 9 days ; extremes : 4 to 15 days.

Direct contagion : Appears to be relatively rare ; by secretions of nose and throat, saliva, etc., especially during the catarrhal period.

Indirect contagion : Articles contaminated with saliva, etc.

Portal of entry : Upper respiratory passages (nose and throat).

Localisations : The central nervous system. Small dispersed zones of polio-encephalitis affecting the whole nervous system, more particularly localised in the grey matter of the mesocephalon (VON ECONOMO, 1917), the *locus niger*, the nuclei of the third pair of cranial nerves, the interpeduncular space around the aqueduct of Sylvius and the floor of the 4th ventricle.

Symptoms : Usually an insidious onset, with headache, lack of appetite, drowsiness. Later : toxi-infectious phenomena (temperature 102°-104°F. (39°-40°C.), rigors, vomiting), herpes of the lips or face, tonsillitis, rhinopharyngitis, copious sweating, a petechial, measles- or scarlet-fever-like exanthem. Somnolence or hypersomnia, paralysis of the eyes (ophtalmoplegia). Sometimes : paralysis of the facial, trigeminal, glosso-pharyngeal, hypoglossal and spinal nerves (Parkinson's facies).

Myoclonic, algic and choreic forms are also recorded.

Duration of disease : 4 to 10 weeks.

Complete recovery rare. Usually sequelæ : mental disorders, parkinsonism, etc.

Prognosis : Serious owing to sequelæ and high rate of mortality : 22-48.3%.

Channels of elimination : Saliva, secretions of nose and throat.

Resistance of virus outside the body : 2 weeks in water ; up to 3 months in milk.

Laboratory diagnosis : Examination of cerebro-spinal fluid : lymphocytosis at outset of disease ; hyperglycorrhachia. Characteristic histo-pathological lesions, especially in the mesocephalon.

Treatment : Symptomatic. Treatment with sulphonamides has been tried (Ionescu-Sisesti). Try also serum of convalescent.

Prophylaxis : Preventive vaccination has not been tried. Isolation of patient and of suspected cases. Personal hygiene ; gargling with antiseptic solutions.

1. OTHER FORMS OF HUMAN ENCEPHALITIS CAUSED BY FILTERABLE VIRUSES OTHER THAN THAT OF LETHARGIC ENCEPHALITIS

Detailed international nomenclature (1938) : part of No. **37.**

Japanese encephalatis : (type *B* [1]). As early as 1871, the occurrence of summer outbreaks of encephalitis in Japan was reported. In 1924 (July-August), there was a widespread epidemic in 43 of the 47 provinces, with 6,949 cases and 4,164 deaths. The virus, which was identified by Takaki (1925), who inoculated rabbits with it, and subsequently studied by Hayashi (1934), imparts the disease to monkeys *(Macacus cyclopis)* by intercranial inoculation with emulsion of the infected human brain.

In 1936, other Japanese investigators also transmitted the human disease to white mice.

The symptomatology of the natural infection in man differs markedly from that of von Economo's disease : there is a febrile onset, a sudden appearance of meningitic and encephalitic phenomena and an absence of parkinsonian sequelæ. The disease attacks, above all, elderly persons (60 to 70%).

[1] Kaneko & Aoki (1928) refer to Japanese encephalitis as follows : Japanese type : type *B*, different from the European type *A*.

This virus is akin to, but not identical with those studied in the United States during the epidemics of encephalitis which occurred in St. Louis, Kansas City, Paris (Illinois) and New York.

The *American encephalitis* (the St. Louis (U.S.A.) encephalitis), described for the first time in 1933, differs from von Economo's disease in respect of the topographical distribution of its histo-pathological lesions, its epidemiological characteristics and its serological reactions (C. Levaditi). It also differs from the Japanese encephalitis (type B)—the cross immunity tests are negative— and from the Australian form.

The virus is pathogenic for monkeys and mice. The dimensions (according to Bauer, Fite & Webster, 1934) are 22-23 mμ. It can be cultivated on chorio-allantoid membrane of a chicken embryo (Harrisson, Moor, 1937).

Australian encephalitis has been observed mainly among children and takes the form of summer epidemics.

2. FORMS OF ENCEPHALITIS CAUSED BY A FILTERABLE VIRUS WHICH OCCUR AMONG ANIMALS AND ARE TRANSMISSIBLE TO MAN

Detailed international nomenclature (1938) : part of No. **37.**

The *American equine encephalo-myelitis,* of which two types have been described—that of the East and that of the West—is, under certain conditions, transmissible to man (to persons living in contact with horses). Several cases have been recorded in the United States during and since the autumn of 1938. The virus isolated in human cases has been identified with that causing the equine disease.

Serological differences have been found between the Californian virus (Western type) and the New Jersey virus (Eastern type).

3. SECONDARY ENCEPHALITIS

(a) *Post-vaccinal Encephalitis and* (b) *Post-infectious Encephalitis.*

(a) *Post-vaccinal encephalitis* (or encephalo-myelitis) [*Det. int. nom.* 1938. No. 195 a] is an affection of the central

nervous system which occurs mainly as a very rare sequel to late primary anti-smallpox vaccination (performed after the age of 2) (McINTOSH, 1912 ; LUCKSCH, 1924 ; BOWDIJK BASTIAANSE, 1925).

Etiological agent : The vaccinal virus (?) or—more probably—a pre-existing encephalitis virus latent until vaccination.

Incubation : 11 to 12 days after Jennerian vaccination. Rarely a shorter period : 5 days. When it occurs after re-vaccination, the incubation period seems to be shorter.

Symptoms : Sudden onset, vomiting, giddiness, headache, often convulsions, *Kernig's* sign (in 50% of cases observed in Holland), *Babinski's* sign (68%). Peripheral paralysis (mono-hemi-paraplegias). Paralysis of the eyes, face, tongue, etc.

Prognosis : Grave. Fatality : 40-50% (Holland, 1925), 46% (British Commission), 35% (German Commission).

Complications : Various : bronchitis, pneumonia, cystitis, etc. Reference has also been made to the generalisation of the vaccinia. PETTE (1929) has noted the appearance of sequels : paresis, modification of the reflexes, foot-clonus, mental disorders and even epileptoid fits. Sometimes relapses occur.

Laboratory diagnosis : No changes in the blood. The cerebro-spinal fluid is *normal* in most cases—or lymphocytosis is found.

From a histopathological standpoint, there is diffuse encephalo-myelitis, with perivascular infiltration, neurological proliferation and foci of demyelinisation.

Localisations : The white matter of the brain, sometimes in the basal ganglia, the internal and external capsules, the mesocephalon, etc.

Treatment : Symptomatic. Vaccination treatment has also been tried with *"vaccineurine"* ; serum treatment (with the serum of animals hyper-immunised against vaccinia). The results have not been conclusive.

Prophylaxis : Up to the present time there is no means of preventing post-vaccinal encephalitis with absolute

certainty (J. P. Bijl, 1938). It is recommended that children should be vaccinated when very young, preferably between 3 and 12 months.[1] Anti-smallpox vaccination should be suspended during encephalitis epidemics.

Avoid the use of strains of lymph associated with encephalitis.

(b) *Encephalitis occurring in the course of general infections.*

1. *Acute disseminated encephalo-myelitis* (Pette & Redlich, 1927). Occurs mainly among persons between 16 and 30 years of age. Clinically, encephalitic symptoms predominate; they take various forms (paralysis, paresthesia, bulbar symptoms, disorders of the eye muscles, etc.). Generally, the temperature rises. Low mortality. Speedy and complete recovery. Rarely sequelæ : Babinski's sign, spasmodic paresis.

2. *Encephalo-myelitis* occurring during :

Measles ; the first symptoms appear between the 3rd and 7th days after the appearance of the exanthem. Mortality : 10-15%.

Smallpox ; considerable analogy with post-vaccinal encephalitis, but spinal symptoms predominate. Cerebral symptoms appear from 1 to 8 days after the smallpox eruption.

Chickenpox ; appears between the 2nd and 8th days after the onset of the disease (rare). Mortality 6 to 10%. Very rarely sequelæ after recovery.

Mumps ; mumps-meningitis and mumps-meningo-encephalitis. The encephalitis appears as a rule 8 to 10 days after the onset of mumps.

* * *

In different countries, cases have been reported of accidents affecting the central nervous system during or after anti-rabies treatment. Such accidents consist mainly of paralyses usually appearing 2 to 4 weeks after commencement of the treatment, never more than 10 days after its termination.

[1] Thus minimising chances of a silent infection by encephalitis virus occurring prior to vaccination.

The *fixed virus* appears to be solely responsible for these complications.

Cases of meningitis, meningo-encephalitis or myelitis have also been observed after anti-yellow-fever vaccination.

COMBY (1921), RICARDO JORGE, BUCHANAN (1927-1930), have reported encephalitis as a complication of influenza, sometimes even in mild cases of that disease.

MALADIE DES PORCHERS
(" Swineherds' Disease ")

Detailed international nomenclature (1938) : under No. **38 f.**

Latin = Meningitis serosa porcinarii.
French = Maladie des porchers.
German = Schweinhirtenkrankheit.
Ital. = Malattia dei giovani porcari.
Roum. = Maladia porcarilor.

BOUCHET (1935) has described a disease prevailing in Savoy and Switzerland which mainly attacks young persons employed in pig-rearing. This disease is characterised by meningitic symptoms and fever. The febrile attacks are usually separated by some days without fever. Recovery invariably follows in 12 to 15 days.

This affection was generally attributed to a *filterable virus* not yet identified. According to researches recently published, mainly by Swiss authors (GSELL & RIMPAU, 1944, RENÉ MACH, 1944, MONGAKOV—quoted by MACH), it appears to be a leptospiral infection, one of the group of benign leptospiroses (*Pomona* strain).

LYMPHOCYTIC CHORIO-MENINGITIS
(Armstrong's Disease)

Detailed international nomenclature (1938) : part of No. **81 b.**

Latin = Meningitis lymphocytaria benigna.
French = Chorio-méningite lymphocytaire, Méningite aiguë aseptique, Maladie d'Armstrong.

German = Akute benigne lymphocytäre Meningitis.
Ital. = Meningite linfocitaria detta benigna.
Roum. = Meningită acută aseptică.

A disease, the virus of which was isolated by CH. ARMSTRONG & R. D. LILLIE, in 1934, in a fatal case, during an encephalitis epidemic in St. Louis (U.S.A.). The affection is characterised clinically by a febrile meningeal reaction with lymphocytosis in the cerebro-spinal fluid, intense headache, vomiting, stiffness of the nape of the neck, etc., accompanied sometimes by catarrh of the upper air passages.

The course of the disease is sometimes benign and complete recovery follows in 1 to 6 weeks. It affects mainly young persons. The cerebro-spinal fluid, which is clear or opalescent, often contains a considerable number of lymphocytes (500 to 1,000 cells or more per c.m.m).

The virus can be cultivated on chorio-allantoid membrane and its dimensions are said to be about 100 mμ (RIVERS, MCNAIR, SCOTT, 1936). Elimination of the virus in the urine may continue after recovery. Experimentally transmissible to monkeys, guinea-pigs and mice : natural infection in mice in captivity has also been described (TRAUB, 1936).

An attack of the disease confers immunity.

INFANTILE PARALYSIS
(Acute Poliomyelitis)

Detailed international nomenclature (1938) : No. **36.**

Latin = Poliomyelitis anterior acuta, Paralysis infantum.
French = Poliomyélite, Paralysie infantile.
German = Heine-Medinsche Krankheit, Epidemische Kinderlähmung, Spinale Kinderlähmung.
Ital. = Poliomielite anteriore acuta, Paralisi infantile.
Roum. = Paralizie infantilă.
Span. = Poliomielitis aguda, Paralisis esencial de la infancia.

An acute, infectious, epidemic disease, affecting mainly the young, characterised by paralysis and ensuing atrophy of the muscles.

Etiological agent : A filterable virus (LANDSTEINER & LEVADITI, 1909; KRUEGER & SCHULTZ, 1928/29) can be kept in a 50% solution of glycerol; can be cultivated in tissue cultures (spinal ganglia) by the method of HARRISSON, BURROWS & CARREL (LEVADITI, 1910). It is highly *neurotropic* and is pathogenic for a very small number of animal species only (man, monkeys). Dimensions: 8 to 10 mμ (ELFORD & GALLOWAY, 1935); it is thus one of the smallest known viruses.

Incubation : 3 to 14 days. On an average 9 to 12 days. In the disease experimentally imparted to monkeys, 5 to 15 days.

Direct contagion : Relatively rare by contact with a patient, more frequent by contact with a germ-carrier.

Indirect contagion : Water, milk; contaminated articles (?). Insects (?). House, school, hospital ward, etc., epidemics.

Portal of entry : Nose and throat, upper air passages, digestive tract. The virus invades the lymphatic spaces surrounding the blood vessels of the central nervous system (*Neuroprobasia :* C. LEVADITI; *Odogenesis* · G. MARINESCO & ST. DRAGANESCO).

Localisations : A highly neurotropic virus, selective affinity for the grey matter of the medulla (anterior horns), of the medulla oblongata and of the brain and spinal ganglia, where the characteristic lesions of this disease are found : neuronophagia and perivascular infiltration.

Symptoms : The prodromal symptoms may pass unnoticed or they may have no apparent connection with the subsequent localisation in the central nervous system. The following have been observed : fever, sore throat, gastro-intestinal disorders (loss of appetite, diarrhœa, vomiting). The period of invasion generally precedes by a short interval only (24 hours) the appearance of paralytic symptoms; it is characterised by a high fever: 102°-104°F. (39°-40°C.), headache, painful stiffness of the neck, backache, general or local hyperæsthenia, sweating and somnolence. The paralysis may come on suddenly or by degrees, begin-

ning with partial paresis which develops into paralysis : mono- para- or tetraplegia. C. LEVADITI mentions the following types of paralysis. Many mild infections show no evidence of involvement of the central nervous system : many such abortive attacks escape recognition altogether.

Spinal forms, the most frequent.

Ascending form (Landry type), one of the most serious and most fatal owing to its final localisation in the medulla oblongata.

Forms affecting the medulla and the pons from the outset (facial, bulbar, etc., paralysis).

Encephalic forms. Ataxic forms. Neuritic forms.

The paralysis sometimes recedes, but it generally persists, at least partially (usually in the muscular groups first attacked).

Prognosis : Variable in different epidemics. Mortality : 8.4 to 42% of paralytic cases ; it is in inverse proportion to the recognised morbidity (American Commission). Many abortive cases.

Channels of elimination : Secretions of nose and throat, digestive tract (fæces).

Persistence of virus outside the body : In a dry state, it keeps its virulence from 20 to 30 days.

Laboratory diagnosis : Inoculation of monkey with filtrates of nasal secretion, of fæces (special method) or, after death, of nervous tissue removed at autopsy. During the invasion period, an examination of the cerebro-spinal fluid shows : constant slight leucocytosis and pleocytosis ; few polymorphs in the early stage ; increased albumin ; presence of globulins. Normal glucose and chlorides preclude a diagnosis of meningitis. If the cerebro-spinal fluid is completely normal, the case cannot be one of poliomyelitis (DRURY & SHADEN, 1939).

Treatment : *Serum treatment :* convalescent serum (p. 267). Immune horse serum obtained by inoculation with virulent nervous tissue taken from infected monkeys (PETTIT'S *method*).

Serum treatment must be applied *early* (during the pre-paralytic period) in order to produce results (p. 265).

Prophylaxis : Immediate compulsory notification of cases of the disease. Isolation of patients [1] ; ascertain origin of first cases ; trace carriers of virus and isolate them. *Measures of personal hygiene*, particularly as regards nose and throat.

Preventive vaccination of children (by BRODIE's method : with formalinized virus ; or KOLMER's method : with virus attenuated by addition of sodium ricinoleate) has not so far given satisfactory results.

As a preventive measure, the serum of convalescents, or even of normal adults, may be administered to children.

RABIES

Detailed international nomenclature (1938) : No. **38 b.**

Latin	= Lyssa humana, Rabies.	Ital.	= Rabbia, Lissa.
		Roum.	= Turbare.
French	= Rage.	Span.	= Rabia, Lyssa.
German	= Tollwut, Hundswut(v), Lyssa.		

A specific, infectious disease of certain animal species (wolf, dog, etc.) transmissible to man, affecting the central nervous system and proving rapidly fatal.

Etiological agent : A filterable virus (PASTEUR, 1880, 1885) (NEGRI, REMLINGER, 1903). *Fixed* virus : 100-150 mμ (GALLOWAY and ELFORD, 1933); can be cultivated in symbiosis with living cells (HARRISSON-CARREL method, LEVADITI, 1914 ; KANAZAWA, 1937, etc.). Transmissible by intracerebral inoculation to dogs, cats, rabbits, guinea-pigs, etc. Cold-blooded animals are completely unreceptive : the virus inoculated into the brain subsists for a long time in a latent condition (disappears after 302 days ; REMLINGER, 1904).

Incubation : In man, 3 to 6 weeks ; in rare cases less : 10 to 12 days ; very occasionally, more than 1 year. The

[1] Without undue hope of arresting an outbreak in this way in view of the large proportion of abortive cases and undetected infections.

duration of the period of incubation depends upon the virulence of the virus and the severity and localisation of the bite.

Direct contagion :

1. The bite of a rabid animal or of one in the incubation stage (seven days before appearance of first symptoms).

2. Any other break in the skin : scratch, bruise, etc., contaminated with the saliva of an infected animal.

Indirect contagion : Exceptional.

Portal of entry : Any break in skin or mucous membranes.

Localisations : Central and peripheric nervous system (especially Ammon's horn and the medulla oblongata).

Symptoms : The premonitory fever, remarked by V. Babeş, in the case of animals, 24 to 48 hours before the appearance of other symptoms, does not always occur in man. An examination of the blood shows a high degree of neutrophil leucocytosis and eosinophilia. The onset of the disease is sudden : insomnia, uneasiness, excitability. Sometimes abnormal sensations (painful itching, pins and needles) around the scar of the bite. After this short preliminary period (10 to 24 hours) bulbar phenomena make their appearance : difficulty in swallowing caused by spasms of the pharynx, difficulty in breathing, hydrophobia and aerophobia, hallucinations of sight and hearing. The condition of hyper-excitability is sometimes evidenced by priapism. Breathing becomes more and more difficult ; it is often of the Cheyne-Stokes type. Towards the end of this period, an abundant flow of saliva marks the beginning of the final paralytic period. The disease runs its course in not more than 1 to 4 days. Death supervenes by asphyxiation and heart failure.

Prognosis : Clinical rabies always ends fatally. Rabies following upon bites on the head, or incubating rapidly (in less than 15 days), may prove fatal, notwithstanding treatment.

Mortality among persons who have been bitten by a rabid animal and have undergone anti-rabies treatment (by one of the various methods) is 0,52% in the case of deep

bites (this figure is based on 9,834 cases) and 0.08% in the case of superficial bites (223,501 cases).

Channel of elimination of virus : The saliva is virulent for 7 days preceding the appearance of morbid symptoms and during the course of the disease.

Resistance of virus outside the body : At a low temperature and in glycerine (ROUX) the virulence persists for a long time. Fragments of brain infected with rabies preserved in a 50% solution of glycerine and at 17.6°F. (—8°C.) have retained their initial virulence for more than 4 to 500 days (SCHWEINBURG). Desiccation at 71.6°F. (22°C.) or heating to 140°F. (60°C.) diminishes the virulence and finally entirely destroys it (depending on the duration of the process).

Laboratory diagnosis : The examination of microscopic preparations taken from the hippocampus major (smears and sections after fixation, rapid inclusion and special stainings) shows characteristic formations *(Negri bodies)*. Experimental inoculation of rabbits, guinea-pigs, mice, etc. The blood-picture and a histopathological examination of the spinal ganglia may afford useful indications.

Treatment : Only possible during incubation and it must be started as soon as possible after the bite. Once the disease has developed, specific treatment is of no avail. It is indispensable to cauterise the wound *directly after the bite* with thermocautory or fuming nitric acid. For anti-rabies treatment, the medulla or brain of a rabbit inoculated with fixed virus (ordinary virus with incubation fixed by repeated passages on rabbits) is employed (PASTEUR, 1884). The methods of vaccination [1] [2] most commonly employed at present are the following :

Method of the Pasteur Institute of Paris : medulla of rabbit with fixed virus, attenuated by desiccation (2 to 4 days).

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[1] MARIE, A. C., REMLINGER, P., & VALLEE, H. Reports to the International Rabies Conference, Paris 1927, L.o.N. doc. *C.H.531(1)*.

[2] MCKENDRICK, H. G. Analytical Reviews of the Reports of Pasteur Institutes on the Results of Vaccination against Rabies in L.o.N. Document *C.H.844*, 1930, and series of the *Bull. Health Org.*, L.o.N., 1, 1932, to 9, 1940.

Babeş-Puscariu method : a suspension of fixed virus (rabbit medulla) heated to 122°, 131°, 140°, 149°F. (50°, 55°, 60°, 65°C.)—with desiccated medulla added.

Högyes method : dilutions of fixed virus.

Various methods : consisting in use of fixed virus attenuated or killed by addition of chemical substances : phenol (FERMI, PUNTONI, SEMPLE), ether (REMLINGER, HEMPT), etc. (p. 235).

Prophylaxis : Compulsory notification of all cases of rabies among domestic animals. Destruction of wandering dogs. Compulsory vaccination of dogs.[1]

GLANDULAR FEVER

(Infectious Mononucleosis)

Detailed international nomenclature (1938) : No. **44 d(b).**

Latin = Lymphoblastosis benigna, Mononucleosis infectiosa.
French = Fièvre ganglionnaire, Mononucléose infectieuse, Angine à monocytes.
German = Drüsenfieber, Pfeiffersche Krankheit.
Ital. = Febbre ghiandolare, Mononucleosi infettiva.
Roum. = Angina monocitară.

A febrile disease characterised by a polyadenitis beginning in the lymph glands of the neck, tonsillitis (sore throat) and hypertrophy of the spleen. Small epidemics especially among adolescents. The disease was described by PFEIFFER in 1881.

Etiological agent : A filterable virus (BLAND, 1931). Can be communicated by inoculation to the lower monkeys *(M. rhesus)*, producing a disease comparable in all respects to that of man.

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[1] GAUTIER, R. "Preventive Vaccination of Dogs against Rabies", *Bull. Health Org.* L.o.N., **9**, 269-326, 1940/41.

Incubation : 2-9 days.

Direct contagion : Contact with a patient.

Indirect contagion : Probable.

Port of entry : Tonsils.

Localisations : Lymphatic glands.

Symptoms : Bad general condition, stubborn constipation, enlargement of the lymph glands, generally the posterior cervical glands, followed by tonsillitis with diphtheroid false membranes. Other lymph glands are progressively affected. Spleen increased in size. As a rule, the disease develops rapidly. Sometimes it may last for several weeks. Nephritis in 6 to 8% of cases. Symptoms of serous meningitis have also been observed.

Three clinical types : *glandular*, *tonsillar* and *febrile*. The fever continues for 7 to 14 days.

Prognosis : Usually favourable.

Channels of elimination of virus : Exudate from tonsils.

Persistence of virus outside the body : (?)

Laboratory diagnosis : Characteristic blood-picture : slight anæmia with leucocytosis which may reach 15,000-50,000 white cells per c.m.m, of which 40 to 90% will belong to the hyaline series—lymphoblasts and plasmocytes.

It has been observed that, towards the end of the 1st and 2nd weeks, there is a positive reaction to the *Bordet-Wassermann test.*

Similarly, there is a high proportion of anti-sheep hæmo-agglutinins (1:64, PAUL & BUNNELL'S test, 1932) and of other hetero-hæmo-agglutinins (for the blood of rabbit, guinea-pig, cattle and pig).

Treatment : Excellent results appear to have been obtained with sulphonamides (M. & B. 693) administered by intramuscular injection (STANNUS & FINDLAY, 1939).

Prophylaxis : Isolation of patients, disinfection and personal hygiene.

FOOT-AND-MOUTH DISEASE

Detailed international nomenclature (1938) : No. **44 d(a).**

Latin = Aphtae epizooticae, Stomatitis aphtosa epidemica.
French = Fièvre aphteuse.
Germ. = Maul- und Klauenseuche.
Ital. = Febbre aftose.
Roum. = Febra aftoasă.

An acute, infectious disease mainly affecting cattle, transmissible to man under certain conditions, characterised by a vesicular eruption of the mucous membranes and skin.

Etiological agent : A filterable virus (LÖFFLER and FROSCH, 1898) ; three immunologically different types : O, A, C. The disease caused by one of these types does not confer immunity to the two others. The virus will pass special filters (LEVADITI, NICOLAU & GALLOWAY, 1926). Dimensions : 8 to 12 mμ (GALLOWAY & ELFORD, 1931) ; 7 to 16 mμ (KRASSNOFF & REINIÉ, 1937) ; 20 to 40 mμ (VON ARDENNE & DYL, 1940) according to direct measurements made with the aid of an electronic microscope.

Incubation : 3 to 7 days under natural conditions. Occasionally more : up to 20 days.

Direct contagion : From a diseased animal. " Man displays a varying degree of susceptibility under natural conditions : at the present time, many conclusive observations establish without doubt that man is susceptible to this disease." (J. VERGE, 1943.)

Indirect contagion : Contaminated fodder, liquids, straw, etc. Man may convey the virus.

Portal of entry : Mucous membrane of the mouth ; breaks in the skin.

Localisations : Man : mouth and limbs. Quadrupeds : mouth and limbs.

Symptoms : A vesicular eruption : isolated vesicles *(aphthae);* duration of disease : 2 to 3 weeks.

Prognosis : Benign in case of man. Adult animals : fatality rate 2 to 3%. Very grave in cases of young animals still fed by their mothers.

Channels of elimination : Liquid from vesicles ; epithelial shreds from *aphthae*, milk and urine.

Resistance of virus away from the body : Can be kept a long time in a solution of glycerine containing phosphate. Resists desiccation for a long time (years). Retains virulence unaffected for 41 days in pure water and for 37 in sea water (J. VERGE). Persists for 60 days on clothing, in fodder, etc.

Laboratory diagnosis : The experimental inoculation of guinea-pigs, calves or pigs is the only means of identifying the foot-and-mouth disease virus in the aphthæ of man. Ascertainment of the neutralising power of the serum of the patient (convalescent).

Treatment : No specific treatment for man. Disinfection of mouth : potassium permanganate at 1/1000, etc. ; cauterisation of lesion with a solution of silver nitrate, etc.

Prophylaxis : Personal hygiene among persons in contact with sick animals. For animals : preventive vaccination.

LYMPHOGRANULOMA VENEREUM ; PORADENITIS (Climatic Bubo)

Detailed international nomenclature (1938) : No. **44 a(b).**

Latin = Lymphogranuloma venereum, Lymphogranuloma inguinale.
French = Maladie de Nicolas-Favre, Lymphogranulomatose inguinale bénigne, Bubon climatique, Esthiomène.
German = Lymphogranuloma inguinale, Klimatische Bubo.
Ital. = Limfogranuloma inguinale, Bubbone climatico, Quarta malattia venerea.
Roum. = A patra maladie venerian, Ulcer venerian adenogen, Poradenolimfită inguinală benignă.
Span. = Limfogranulomatosis inguinal, Enfermedad poradenica, Bubón venereo.

A contagious venereal disease affecting particularly the lymph glands of the groin and iliac region.

Etiological agent : A filterable virus (HELLERSTROM & WASSEN, 1929), cannot be kept in glycerine. Dimensions : 125-175 mμ (MIYAGAWA and collaborators, 1935)—visible in the form of elementary bodies in diseased cells and tissues (MIYAGAWA'S bodies).

Incubation : Variable : 10 to 15 days on the average. May be less, 5 or even 3 days, or longer, up to 3 months.

Direct contagion : By sexual contact. Occasionally by accidental inoculation (doctors and nurses).

Indirect contagion : (?)

Portal of entry : Genital mucous membranes : chancre of ulcerous type, superficial, may often pass unnoticed.

Localisations : The virus has an affinity for lymphatic and reticulo-endothelial tissue (mesoblastosis, reticulo-endotheliosis).

Localisations in the glands, joints, veins, meninges, central nervous system, urethra and bladder ; perimetritis, adnexitis. Vegetating proctitis, elephantiasis and ulcerative lupus of the vulva are due to this virus.

Symptoms : The glandular form in the groin is the most frequent : a swelling of the glands in the groin—on one or both sides—develops between the 2nd and 15th days following the appearance of the chancre. It begins with local pains, rendering walking difficult ; hypertrophy of the glands increases progressively and the tissues around the glands become inflamed ; periadenitis and involvement of the skin. Evolution varies from case to case.

General phenomena : fever, asthenia, headache, loss of appetite, frequently pains in the joints and loins, emaciation. In the mass of glands, which is at first hard, small foci of softening soon appear ; abscesses and fistulæ result. The course of the disease is sub-acute, varying from 2 to 3 weeks to 4 to 5 months or even longer.

The infection gradually spreads and other groups of glands may become affected (in the iliac region, etc.). There

are also generalised glandular forms. Other localisations have their own special symptoms.

Prognosis : In mild forms without complications : favourable. In prolonged cases, the prognosis becomes serious owing to possible complications (proctitis, stricture of the rectum, elephantiasis, etc.).

Channels of elimination : Suppurating lesions.

Resistance of virus away from the body : (?) Rôle of virus carriers (prostitutes).

Laboratory diagnosis : Identification of *Miyagawa* bodies. Inoculation of receptive animals : monkeys, white mice, guinea-pigs.

Biological diagnosis : By *Frei's intradermal test* (p. 211). Histopathological examination (biopsy).

Treatment : *Surgical :* removal of glandular tumours.

Medicinal : Fuadine, Anthiomaline. Recently sulphonamides preparations.

Specific : An anti-lymphogranuloma vaccine, consisting of a suspension of the crushed spleen, liver and mesenteric glands of a monkey inoculated in the peritoneum with the specific virus, in saline solution, inactivated by heat, or serum from a horse hyperimmunised with the same antigen, have been tried with good results.

Prophylaxis : Measures of sexual hygiene as for venereal disease in general.

MUMPS

Detailed international nomenclature (1938) : No. **44 c.**

Latin = Parotitis epidemica, Parotis.
French = Oreillons.
German = Mumps, Ziegenpeter(v).
Ital. = Orecchioni.
Roum. = Oreion.
Span. = Orejones.

An acute, highly contagious, febrile disease, characterised by the inflammation and swelling of the parotid glands.

Etiological agent : A filterable virus (GRANDA, 1908 ; NICOLLE & CONSEIL, 1914 ; WOLLSTEIN, 1916 ; JOHNSON & GOODPASTURE, 1934 ; LEVADITI and collaborators, 1935, etc.). Dimensions : (?)

Incubation : 16 to 21 days ; sometimes 30 days.

Direct contagion : Contact with a patient, especially during the 24 hours preceding the development of fever and the 4 or 5 following days. Contagiousness gradually diminishes and ceases about the 20th day of the disease.

Indirect contagion : Rare,

Portal of entry : Nose and throat ; mouth (Stenson's duct).

Localisations : The salivary glands, particularly the parotids ; the testicles or ovaries. Other localisations : the sub-maxillary, sublingual, mammary and lachrymal glands, the pancreas, the thyroid gland and the kidneys ; also : the serous membranes of the joints, the nervous system, or the respiratory system.

Symptoms : Shivering, pain in the limbs, slight fever ; painful swelling of the salivary glands. According to GREENE & HEEREN, in more than 50% of cases, hypertrophy of the spleen. When the disease is localised in the testicles or ovaries, etc., the fever is higher. Duration of disease : in cases without complications : maximum 10 days. *Orchitis* in 10-40% of cases. Pancreatitis or ovaritis in 5-8%. Thyroiditis or mastitis are rarer.

Epidemics of mumps have been recorded with meningeal and meningo-encephalic complications in 11-27% of cases.

Prognosis : Relatively benign disease. Recovery is followed by lasting immunity. Fatality zero or nearly so : 0.01%. Genital complications may be followed by atrophy of the seminal gland affected ; hence sterility ensues if both testicles or both ovaries have been affected.

Channels of elimination of virus : Secretions of the glands affected.

Resistance of virus away from the body : Little resistance.

Laboratory diagnosis : Not employed.

Blood-picture : Leucopenia, mononucleosis followed by lymphocytosis.

Treatment : Symptomatic. Convalescent serum may be tried owing to its virus-destroying properties.

Prophylaxis : Isolation of patient and of contacts for 21 days. Compulsory notification in many countries. Personal and general hygiene.

VENEREAL WART

(Condyloma acuminatum, Verruca acuminata) — Warts.

Detailed international nomenclature (1938): part of No. **30 dd.** [1]

Latin = Condyloma acuminatum.—Verruca vulgaris.
French = Végétations vénériennes, Condylomes acuminés. —Verrues.
German = Condyloma acuminatum, Feigwarzen.—Warzen.
Ital. = Condilomi acuminati.—Porro.
Roum. = Vegetatii.—Negi.

An infectious, communicable, ubiquitous disease characterised by the appearance of papillomatous proliferations on the skin or mucous membranes *(Condyloma acuminatum)*.

Etiological agent : A filterable virus [1] (Ciuffo, 1907 ; Wille & Kingery, 1919), may be kept in a 50% solution of glycerine, destroyed by heating to 140°F. (60°C.) for one hour.

Incubation : 3 weeks to 8 months ; varies according to the general condition of the individual.

Direct contagion : Contact with a person suffering from the disease.

[1] The classification adopted under No. 30 (syphilis) at the time of the revision of the Nomenclature in 1938 is due to the spirochetic etiology accepted by many authorities following Dreyer and Favre & Civatte, 1919, with regard to venereal warts. Other authorities, including the author of the above description, attribute a common etiology to these growths and to ordinary warts (part of No. 153 of Det. Int. Nom.—1938) which all agree in ascribing to a filterable virus. —Ed.

Indirect contagion : Use of soiled toilet articles.

Portal of entry : Skin or mucous membranes.

Localisations : Glans penis, foreskin, the balanopreputial groove, the genito-crural folds, the scrotum, the vulva, the perineal region, etc.

Symptoms : Growths isolated or in bunches, pink or white, dry or moist.

Prognosis : Cure is often spontaneous.

Channels of elimination of virus : The lesions.

Resistance of virus away from the body : Retains initial virulence for 2 months in a 50% solution of glycerine.

Treatment : *Biological :* Specific vaccine treatment appears to be effective (Biberstein & Stein).

Physical : Surgical removal. Galvanocauterisation, electrocauterisation.

Prophylaxis : Preventive immunisation is possible (Findlay). The serum of patients has virus-destroying properties.

EPIDEMIC HEPATITIS

Detailed international nomenclature (1938) : No. **44 d(g).**

Latin = Hepatitis epidemica.
French = Hépatite épidémique, Ictère épidémique.
German = Epidemische Gelbsucht.
Ital. = Itterizia epidemica.
Roum. = Icter epidemic.
Span. = Ictericia epidemica.

An acute, epidemic disease, characterised by jaundice, asthenia and a prolonged convalescence.

Etiological agent : A filterable virus (Findlay, MacCallum & Murgatroyd, 1939 ; von Bormann, 1940-41 ; Siede & Madling, 1941 ; Siede & Luz, 1943 ; Dressel, Medling & Weineck, 1943 ; Dohmen, 1943, St. Nicolau and collaborators, 1944, etc.). Destroyed by heat ; retains

virulence for 14 days if frozen. Can be inoculated to white mice, canaries, etc. Existence of elementary bodies in the nuclei of hepatic cells and intranuclear inclusions (St. Nicolau and co-workers, 1944).

Incubation : 2-40 days (von Bormann), may even be several months (Kramer & Rewerts).

Direct contagion : Contact with patient, especially at outset of disease ; urine and saliva.

Indirect contagion : Rodents (?) (Iacobi and collaborators).

Causes promoting contagion : Cold season (October-December). Adolescents and young persons are more susceptible.

Portal of entry : Probably mucous membrane of mouth, and digestive tract.

Localisation : Liver.

Symptoms : 2 stages : 1st stage, without jaundice, 4 to 6 days, characterised by a profound deterioration of general condition, oscillating fever, gastro-intestinal disorders. Leucocytosis with monocytosis ; 2nd stage, with jaundice : commences, after a short remission (1 to 3 days), with appearance of jaundice which usually develops without fever. General condition relatively good. Enlarged liver which projects two finger-breadths below the costal margin ; the spleen is palpable. The total number of leucocytes falls to normal, monocytosis persists. The jaundice persists for 2 weeks on the average. Convalescence is lengthy, with asthenia, enlarged liver and spleen, and frequent reappearances of jaundice. Beside the usual form of the disease, abortive forms, without jaundice, have been observed.

Prognosis : Immediate ; favourable ; ultimate (?).

Channels of elimination of virus: Urine, fæces and saliva droplets, the last-named being the chief source of contamination according to British and American authorities.

Resistance of virus away from the body : A somewhat fragile filterable virus, destroyed by heat (Weinecke).

Laboratory diagnosis : The disease has been experimentally communicated to canaries. According to St. Nicolau and collaborators (1944), it is possible, by puncture of the liver and histopathological examination of the fragment removed, to confirm the diagnosis of epidemic hepatitis, if the following *triad of lesions*— "*I.N.K.*"—is found to be present :

1. Nuclear *Inclusions* in the hepatic epithelial cells.
2. Very large *Nucleoli*.
3. Frequent *Karyokineses*.

Treatment : Diet, duodenal intubation ; glucose serum.

Prophylaxis : Avoid physical overstrain, cold, crowds. Avoid exclusive consumption of preserved foods.

CHAPTER III

INFECTIONS CAUSED BY PROTOZOA AND METAZOA

Amœbic dysentery.
Kala Azar, Leishmaniasis.
Malaria.
Taeniasis, Tape-worms.
Hydatid disease.
Ascariasis.
Pin-worms.
Hookworm.
Trichiniasis.
Itch.
Louse infestation (Delousing).

AMŒBIC DYSENTERY

Detailed international nomenclature (1938) : No. **27 b.**

Latin = Dysenteria epidemica.
French = Dysenterie amibienne.
German = Amœbenruhr, Amœbiasis.
Ital. = Dissenteria amebica.
Roum. = Disenteria amœbiană.
Span. = Disentería amebiana.

A parasitic disease affecting the digestive tract (large intestine) characterised by acute attacks followed by periods of remission—tending to become chronic. Endemic in tropics, sporadic in temperate regions.

Etiological agent : *Entamoeba dysenteriae* Councilman & Lafleur, 1893. A hæmatophagous amœba in the vegetative stage. Quadrinucleated cysts.

Incubation : 2-15 weeks or longer.

Direct contagion : Possible.

Indirect contagion : Ingestion of contaminated water or food containing cysts. *Infection through water* is the more important factor. House-flies may convey infection.

Portal of entry : Mouth.

Localisations : Large intestine ; colon and rectum. In the event of complications : liver (abscess), lungs, etc.

Symptoms : *Acute attacks :* pains in abdomen ; soft, mucous and bloody stools, 4-5 at first, later 10-25 per day. Often tenesmus and scanty mucous stools. Fever is slight, except in cases of abscess of the liver (when temperature rises to 100.4°-102°F. (38°-39°C.). When the disease becomes *chronic*, it takes the form of alternate periods of diarrhœa and constipation. Marked emaciation. Duration indefinite.

Complications : Abscess of the liver or lungs ; also peritonitis.

Prognosis : Serious.

Channels of elimination : Fæces, sputum in case of pulmonary abscess.

Resistance of parasite outside the body : In the vegetative stage, the amœba has no resistance outside the body, but the cysts are resistant when dispersed in water-courses, reservoirs and other accumulations of water, or in dust, earth and food polluted by contaminated excreta.

Laboratory diagnosis : 1. *Examination of fæces*, immediately after discharge, at a temperature of 98.6°F. (37°C.). Search for mobile vegetative and hæmatophagous forms and for *minuta* quadrinucleated cysts. In chronic forms of the disease, search must be made for the non-hæmatophagous *minuta* form. *Differential diagnosis :* bacillary dysentery and infestation with *Entamoeba coli*, *Ent. hartmanii*, *Ent. dispar* (identical with the *minuta* form but not pathogenic).

2. Inoculation of receptive animals : young dogs and cats ; intrarectal injections of suspect fæcal matter and occlusion with a plug of collodionised cottonwool.

3. Cultivation on artificial media, to isolate the Entamoeba.

Treatment : Formerly large doses of ipecacuanha powder, which has now been replaced by *emetin* (subcutaneous injections) 0.04-0.08 gm. per day for 8-10 days. *Emetin accumulates in the body. Yatren 105* administered by mouth in pills or by intravenous injections. *Stovarsol* in tablets by the mouth.

Prophylaxis : Trace and treat amœba carriers. Disinfection of fæces of patients. Defæcation restricted to receptacles kept under supervision and periodically disinfected. Purification of water. Avoid uncooked food.

KALA-AZAR, LEISHMANIASIS

Detailed international nomenclature (1938) : No. **29 b(a)** and No. **29 b (b).**

Latin = Kala-azar, Leishmaniosis visceralis.
French = Kala-azar indien (Kala-azar des adultes), Kala-azar infantile, Leishmaniose viscérale des adultes, Leishmaniose infantile.
German = Kala-azar, Tropische fieberhafte Splenomegalie.
Ital. = Kala-azar, Leishmaniosi splenica infantile.
Roum. = Kala-azar, Leishmanioza viscerală a adulţilor şi Leishmanioza infantilă.
Span. = Kala-azar, Leishmaniosis esplénica infantil, Leishmaniosis visceral.

A specific chronic disease, characterised by *irregular intermittent fever*, pronounced anæmia, sometimes by cutaneous and intestinal hæmorrhages, but essentially by *splenomegaly*.

Etiological agent : For the Indian kala-azar : *Leishmania donovani* (Laveran & Mesnil, 1903). For infantile kala-azar : *Leishmania infantum* (Ch. Nicolle, 1908). These protozoa, which are small oval-shaped bodies of $2 \times 4\ \mu$ (*Leishman's* bodies) and are characterised by a nucleus, a blepharoblast and a flagella. They are parasites of the monocytes, macrophages, endothelial cells, etc. In cultures and in the vector insect, the Leishman bodies become transformed into *typical acicular Leptomonas*.

Incubation : Duration variable ; several weeks and more.

Direct contagion : Does not exist.

Indirect contagion : Infection is conveyed by biting insects of the Psychodides family : *Phlebotomus argentipes* (Indian kala-azar) and *Phlebotomus perniciosus*, possibly also *Phlebotomus major*, *Phleb. papatasi* (infantile kala-azar).

In the case of infantile kala-azar, the *dog* is the reservoir of virus.

Portal of entry : Skin.

Localisations : Circulating blood (monocytes, macrophages), vascular endothelium and lymphatic vessels of the spleen, liver, bone-marrow, skin, etc.

In Indian kala-azar there are frequently localisations in the intestine (ulcerations) and the skin (Leishman boils and ulcers).

Symptoms : *Indian kala-azar :* a chronic disease, characterised by an irregular intermittent fever, *resistant to quinine*, hypertrophy of the liver and of the superficial lymph glands and by *splenomegaly*. Presence of intestinal disorders characterised by diarrhœa-like and dysentery-like stools, due to intestinal *ulcerations* which cause copious hæmorrhages. Sometimes Leishman boils (nodules in the skin containing many *Leishmania*) and ulcerations (of the mouth and nose) appear and there is progressive cachexia.

Infantile kala-azar : a chronic disease characterised by an irregular intermittent fever, resistant to quinine, marked anæmia, œdema of the face and limbs, possibly hæmorrhages of the skin, and, above all, *very pronounced splenomegaly*. There are no ulcerations.

Prognosis : Very serious (if untreated, a high fatality rate, up to 50%).

Channel of elimination : The parasite is found in the peripheral and visceral blood.

Resistance of parasite outside the body : The whole life-cycle of *Leishmania* is confined to the mammalian host (Leishman bodies) and the insect vector (Leptomonas forms, which are also to be found in cultures).

Laboratory diagnosis : Identification of Leishmania in the blood and leucocytic formula (pronounced leucopenia). Blood culture on blood-agar.

Puncture of spleen, of superficial lymph glands or of the sternum in order to discover *Leishmania*.

The formalin-gelification test may provide useful indications.

Treatment : Tartar emetic, antimony tartrate and other preparations of antimony ; stibenyl, neostybosan, urea-stibamine, fouadine.

Prophylaxis : Destruction of phlebotomi and of their breeding-places.

Mechanical protection.

Treatment and isolation of patients.

Destruction of wandering dogs and veterinary measures.

MALARIA

Detailed international nomenclature (1938) : No. **28.**

Latin	= Malaria.	Roum.	= Malaria, Paludism, Friguri de baltă.
French	= Paludisme.		
German	= Malaria.	Span.	= Paludismo.
Ital.	= Malaria.		

A specific, infectious disease characterised by intermittent attacks of fever, anæmia and hypertrophy of the spleen. The disease, at first acute, subsequently tends to become chronic with alternating acute attacks and periods of quiescence.

Etiological agent : The malaria hæmatozoon (LAVERAN, 1881) with 4 varieties :

Plasmodium vivax (Grassi & Feletti, 1890), the agent in benign tertian.

Plasmodium falciparum (Welch, 1887), the agent in malignant tertian or " estivo-autumnal " fever.

Plasmodium malariae (Laveran, 1881), the agent in quartan fever.

Plasmodium ovale (Stephens, 1922), found in certain parts of Africa.

Incubation : In the infection due to :

P. vivax : 10-14-17 days.
P. falciparum : 10-14 days.
P. malariae : 18-22 days or longer.
P. ovale : 16-19 days.

In the case of persons contracting the disease in autumn (temperate zone), *prolonged periods of incubation*—several months—are recorded. In the event or reinfection, the incubation period varies according to the degree of immunity acquired.

Direct contagion : Does not occur.

Indirect contagion : By the bite of the *Anopheles* mosquito, which becomes infective 12-15 days (at 77°F.-25°C.) after having bitten a person with malaria. The cycle man-anopheles-man *is essential* for the development of the hæmatozoon, which multiplies asexually in the human blood, but the sexual phase of which and its ensuing multiplication can take place only in the body of the vector.

Portal of entry : Skin by mosquito bite.

Localisations : In the peripheral blood and particularly in the visceral blood of all highly vascular organs : spleen, liver, bone marrow, adrenals, brain, kidneys, etc.

Symptoms : 1. *Acute malaria* (first invasion). The first symptoms of the infection are generally :

A continuous phase of fever, without rigors (2-8 days).

Then follows the acme, a variable period of remittent daily fever (these features are especially pronounced in benign and malignant tertian infections) ; finally, after a period of latency, the typical intermittent fever makes its appearance (remissions of 48 hours in benign tertian, 72 hours in quartan and from 24-48 hours in malignant tertian), characterised by the *malarial attack*, which comprises :

A shivering stage (frigor) which lasts for from 20 to 30 minutes to 1 ½ hours, with a rise in temperature, intense headache, vomiting and intense sensation of cold ; *the hot*

stage (calor) characterised by very high fever (104°F.-40°C. and more), rapid pulse, vomiting, violent headache, delirium, nose-bleeding, diarrhœa, enlarged spleen. This stage lasts for several hours and is followed by a *sweating stage (sudor):* profuse sweating, fall of the temperature, patient is left in an anæmic condition.

2. *Relapses* ensue at varying intervals (after 10-15 days in the first place, then at an interval of several months), the number and character of paroxysms depending on the degree of immunity acquired.

The duration of the infection is from 18 months to 2 years approximately in the case of *P. vivax* infections, one year in the case of infections due to *P. falciparum*, and several years in the case of those due to *P. malariae*. Re-infections are always possible in endemic regions and affect the course of the disease.

3. *Pernicious forms :* these are rarer and are due as a rule to *P. falciparum* infections ; they are characterised by an abrupt onset, with a very high temperature, convulsions, a comatose condition, which is followed by an algid condition or collapse. A fatal termination is frequent.

4. *Black-water fever* is especially frequent in tropical countries. It is generally a consequence of *P. falciparum* infections. In addition to the symptoms above mentioned, hæmoglobinuria, bilious-vomiting, a seriously anæmic condition and prostration are observed. Fatal cases are frequent.

5. *Malarial cachexia*, which is observed, in regions where malaria is highly endemic, in the case of debilitated patients who have suffered from malaria for a number of years, is characterised by intense anæmia, hæmorrhages of the skin and an irregular fever. There is very pronounced enlargement of the spleen with hypertrophy and often cirrhosis of the liver.

Prognosis : Variable according to the species of hæmatozoon, the clinical form and the efficacy of the treatment applied.

Channel of elimination : Parasite of the red blood corpuscles.

Resistance of parasite away from the body : The hæmatozoon has no independent existence outside its human or insect host.

Laboratory diagnosis : Identification of the hæmatozoon in the peripheric blood (puncture of the finger or lobe of ear) and in the bone marrow (sternal puncture). Stained smears.

Treatment : I. *Against fever (Schizontocide) :*

(a) *Quinine by the mouth :* for adults, a daily dose of 1 gm. (15 gr.) of quinine hydrochloride or quinine sulphate repeated for 7-8 days (corresponding quantities for younger age groups).

(b) *Total alkaloids standardised on the basis of the "Totaquina" standard preparation.* Same doses as for quinine.

(c) *Quinine-Urethane :* intravenous or intramuscular injections ; a dose of 0.50 gm. daily for 5 days. Recommended in cases where the stomach will not tolerate quinine or where the patient is in a comatose condition.

(d) *Quinine suppositories or syrups to disguise the bitter taste* for children below 2 years.

(e) *Atebrin* (mepacrine), a synthetic product ; dose for adults : 0.30 gm. per day, to be taken in 3 tablets each of 0.10 gm. after meals for 5-7 days (correspondingly smaller quantities for younger age groups).

II. *Treatment against gametes* always given after the schizontocide treatment.

Plasmoquine (a synthetic product). Plasmoquine treatment, which destroys the gamete, is particularly important as a measure of collective prophylaxis.

Adults : give 0.02 gm. per day, in two doses of 1 tablet of 0.01 gm. after meals for 5 consecutive days (corresponding quantities for younger age groups), beginning 5 days after the schizonticide treatment (quinine or atebrin) and never together with atebrin.

Plasmoquine prophylaxis must be under medical supervision.

III. *Combined treatment.*

Quinine and plasmoquine in the doses indicated above for each of these medicaments, but always with an interval of 5 days between the end of the quinine treatment and the beginning of the plasmoquine treatment.

Atebrin-plasmoquine treatment : the same observation applies.

Prophylaxis : This is directed—

1. Against the *vector insect :*

Mechanical protection for human dwellings : protect windows, doors and all external openings with wire netting, mounted on fixed frames (netting : 15 mesh to an inch).

Individual mechanical protection : gauze mosquito nets.

Measures against adult mosquitoes : insecticidal sprays.

Antilarval measures. Petroleum and derivatives. Paris green, etc.

2. To the protection of *man :*

Drug prophylaxis. Medicinal prophylaxis should be confined to organised groups or communities which lend themselves readily to strict supervision : groups of workers, troops, schools, etc. To be effective, this prophylaxis must be continued for 4 weeks after departure from a malarial zone. Persons who live in such a zone must carry out drug prophylaxis throughout the whole malarial season.

Dosage : *Quinine* (quinine hydrochloride or sulphate) 0.40 gm. (*ca.* 6 gr.) per day (for adults) to be taken in tablets throughout the whole malarial season. For children of 6-9 years : 0.20 gm. (*ca.* 3 gr.) per day.

Atebrin. Adults : 0.20 gm. (2 tablets of 0.10 gm.) per day, twice a week (at 3 days' interval) or a single weekly dose of 0.30 gm. Daily prophylaxis with 0.06 gm. is more difficult to arrange but is to be recommended; 0.1 gm. daily six days a week in common practice of armies in hyperendemic areas.

TAENIASIS, TAPE-WORMS

Detailed international nomenclature (1938) : No. **42 (g)**.

Latin = Taeniasis.
French = Téniasis et Bothriocéphalose (ver solitaire).
German = Taeniasis.
Ital. = Teniasi, Verme solitario.
Roum. = Tenie, Panglică.
Span. = Teniasis.

Parasitic diseases due to the localisation of *Cestodae* in the intestine.

Etiological agents : *Taenia solium* (Linné, 1758), *T. saginata* (Goetze, 1872), *Hymenolepis nana* (von Siebold, 1852), *Dipylidium caninum* (Linné, 1758), *Dyphyllobotrium latum* (Linné, 1758), *Bothriocephalus latus*.

Incubation : 3-12 weeks, according to species.

Direct contagion : Does not exist.

Indirect contagion : By contaminated meat (Taenia), fresh-water fish and caviar (Bothriocephalus), through the agency of various insects or the ingestion of eggs in substances contaminated by excreta (Hymenolepis).

Except in the case last mentioned, man becomes infected by ingesting cysticerci (in larval form) located in the various intermediary hosts :

Taenia solium is found in pigs (the muscles).

Taenia saginata in cattle (the muscles).

In the case of *Hymenolepis*, either man himself (localisation of the cysticercoid in the intestinal *villi*) or insects (fleas or *Tenebrio molitor*) play the part of intermediate host.

Dipylidium caninum is found in the fleas of dogs and men.

In the case of *Diphyllobotrium latum*, in the 1st larval stage, the intermediary host is a *Diaptomus* or *Cyclops* (fresh-water crustaceans), in the 2nd (infective) larval stage, carnivorous fresh-water fish (pike, trout, etc.).

Auto-infestation : Possible in the case of *Taenia* (due to antiperistalsis which leads to *cysticercosis*) but not in the case of the *Bothriocephalus*.

Portal of entry : The mouth.

Habitat : The intestine.

Symptoms : Definite clinical symptoms are very often lacking : they take the form of gastro-intestinal disorders, nausea, vomiting, epigastric and abdominal pains (appendicular, etc., colic), diarrhœa or constipation. Nervous disorders : convulsions (especially in children), gastric disorders, disorders of the organs of sense, especially of the sight, headaches, dizziness, emaciation, anæmia (especially in the case of the Bothriocephalus infection).

Prognosis : Usually favourable.

Channels of elimination : Fæces.

Persistence of parasite outside the body : Adult worms cannot live outside the human intestine.

Laboratory diagnosis : Examination of fæces for worm segments (proglottides) and embryo-containing eggs.

Treatment : Pure and fresh ether extract of *Aspidium filix mas*, followed by purgative salts *(Taenia) ;* thymol. In cases of *Hymenolepis nana* infection, oil of chenopodium gives excellent results (same dosage as in treatment of ascaridiasis).

Prophylaxis : 1. Strict veterinary supervision of meat : destruction of meat containing cysticerci. 2. Pork, beef, and fish should be eaten only after having been properly roasted, boiled, etc.

HYDATID CYSTS, HYDATID DISEASE OF THE LIVER

Detailed international nomenclature (1938) : No. **41.**

Latin = Hydatides (hepatis), Echinococcosis (hepatis).
French = Maladie hydatique, Echinococcose.
German = Echinokokkus (der Leber).
Ital. = Cisti idatica (del fegato).
Roum. = Chist hidatic (al ficatului).
Span. = Quiste hidatidico (del higado).

A verminous disease caused by the localization of the *Taenia echinococcus*, in the larval stage, in the viscera, where it forms the hydatid cyst.

Etiological agent : *Echinococcus granulosus* (Batsch, 1786) —*Taenia echinococcus* (von Siebold, 1855) and also *Echinococcus alveolaris* (Posselt, 1903). The adult is a small cestode (5 mm.), a parasite of the intestine of dogs, cats, etc.

Embryonate eggs ingested by man (and by many domestic animals) hatch out in the intestine and the embryos bore through its wall and find their way into the viscera (liver, etc.) where they lodge and pass into a larval stage which develops very slowly ; in this way the *hydatid cyst* is formed. This reaches a diameter of 5 to 15 cm. and contains innumerable *scolices* which, on release in the viscera, may form a like number of new cysts.

Incubation : One or more years.

Direct contagion : Does not exist.

Indirect contagion : Results from the association of man with dogs and cats ; it is due to the ingestion of embryonate eggs contained in the fæces of an infected animal and spread over either the hair and muzzle of the animal or contaminated objects (food, etc.).

Auto-infestation : Only as a result of rupture of the wall of the hydatid cyst.

Portal of entry : Mouth.

Localisations : Generally the liver and lungs—more rarely brain, kidneys, peritoneum. In the event of the rupture of the original cyst, the released *scolices* cause a *secondary echinococcus infestation* which is often localised in the peritoneum.

Symptoms : These vary according to the part affected : at first frequent outbreaks of urticaria. If the cyst develops freely (as is the case for a cyst in the peritoneum) clinical symptoms are lacking ; otherwise—in the case of cysts in the region of the liver and gall-bladder, lungs, brain, etc.—it may cause serious and sometimes fatal compressions (a tumor syndrome).

Complications : (*a*) rupture of the cyst : generalisation of the disease ;

(*b*) invasion by bacterial germs, characterised by signs of suppuration which may lead to peritonitis and sometimes to the discharge of pus externally.

The parasite may die and become calcified.

Channels of elimination : By vomit (cyst in the liver or lung) or by perforation of the abdominal wall (peritoneum). In the contents of the cyst are found vesicles, scolices or hooklets.

Persistence of parasite outside the body : It cannot live outside the body.

Laboratory diagnosis :

1. Examine blood for *eosinophilia.*
2. Intradermal test (CASONI, BOTTERI) (p. 212).
3. Deviation of complement (WEINBERG-PÂRVU).

X-ray examination is as a rule necessary.

Treatment : Exclusively surgical : complete removal of cyst without damaging its wall (rupture).

Prophylaxis : The human infection is almost always contracted through the agency of a dog (or cat) which becomes infested by eating raw scraps of contaminated butcher's meat (beef, mutton).

1. Destroy all contaminated viscera (town and country slaughter-houses). Never give infested viscera to dogs.

2. Prohibition or strict control of entry of dogs into slaughter-houses.

ASCARIASIS

Detailed international nomenclature (1938) : No. **42 (a).**

Latin	= Ascaridiosis.	Ital.	= Ascaridiosi.
French	= Ascaridiose.	Roum.	= Ascaridioză.
German	= Ascaridiosis.	Span.	= Ascaridiosis.

A widespread parasitic disease caused by the presence of ascarides in the digestive tract.

Etiological agent : *Ascaris lumbricoides* (Linné, 1758), a long cylindrical fusiform worm. Separate sexes (♂ 12-16, ♀ 18-28 cm.). Occasionally : ascarides of dogs *(Toxocara canis)* and of cats *(Toxocara cati).*

Direct contagion : Does not exist.

Indirect contagion : The infestation results solely from the ingestion in contaminated food of embryo-containing ova. (Eggs eliminated in the fæces of the carrier are not at that moment infective. To become so they require 30-40 days incubation in a damp soil during the warm season).

Portal of entry : Mouth.

Localisations : *Adult worm :* in the small intestine. Occasionally *erratic ascarides* may be found which, from the intestine, penetrate into other organs : liver, lungs, pancreas, Wirsung's duct, the common bile duct, appendix (ascaris appendicitis), larynx, trachea, etc.

Course of the infestation : The embryo from an ingested egg, on hatching out in the small intestine, perforates the wall of the intestine and passes through a period of *migration* (parenteral cycle) necessarily involving pauses in the liver and lungs ; the embryo develops and then finds its way to the bronchi, the trachea, pharynx, œsophagus and small intestine, where it becomes adult.

Symptoms : Gastro-intestinal disorders : distentions, nausea, epigastric and abdominal pains ; sometimes diarrhœa, appendicular syndrome. Nervous disorders : convulsions, epileptiform fits, giddiness. Itching of the nose or anus at night.

Prognosis : Favourable.

Channels of elimination : Fæces ; rarely the mouth.

Persistence of parasite outside the body : Neither adult ascarides nor their larvæ can live away from their host ; only their eggs can do so and there the infective embryo is formed.

Laboratory diagnosis : Discovery of eggs in fæces, preferably after administration of a saline or vegetable laxative on the previous evening. Oily purgatives are to be avoided.

Examination of blood to ascertain the leucocyte formula : eosinophilia.

Treatment :

1. Santonica *(Artemisia maritima)* powder combined with calomel.

2. Santonin followed by a saline purgative.

3. Essence of chenopodium, XXXVI-XLV drops, in three doses of XII-XV drops at hourly intervals. Three hours later a saline purgative.

Prophylaxis : Boil or wash thoroughly with boiled water all food (vegetables and fruit) likely to be contaminated by the eggs of ascarides from fæces.

OXYURIS VERMICULARIS
(Pin-Worms, Thread-Worms)

Detailed international nomenclature (1938) : No. 42 (f).

Latin	= Oxyurasis.	Ital.	= Ossiuriosi, Enterobiasi.
French	= Oxyurose.		
German	= Oxyurasis, Madenwurmn.	Roum.	= Oxyuroză.
		Span.	= Oxiurosis.

A verminous disease caused by the development of the *Nematode : Enterobius vermicularis* in the intestine.

Etiological agent : *Enterobius vermicularis* (Linné, 1758) a fusiform worm of small size (♂ 5 mm. ♀ 10 mm.) and white in colour. The embryonate eggs are infective.

Direct contagion : Infested children pass the parasite to persons in charge of them and vice versa.

Indirect contagion : By linen and clothing contaminated by the oxyuris, or by contaminated food. By contact. Numerous cases of contagion in families, boarding-schools or other communities.

Auto-infestation is frequent : embryo-containing and infective eggs dropped by the female worms in the folds of the mucous membrane of the anus, contaminate the hands of infested persons and their linen or clothing.

Portal of entry : Mouth.

Habitat : The thread-worms from ingested eggs at first settle in the distal part of the small intestine, breed there, and then grate to the cæcum, the appendix and the large intestine. The pregnant female finds its way to the rectum and the folds of the mucous membrane of the anus, where it dies after laying its eggs or is carried away with fæces. This cycle takes about 2 weeks. The lodgment of the females in the anal mucous membrane causes an unbearable itching which leads the sufferer to scratch that part—thus the hands and, in particular, the nails become infected. This promotes auto-infestation and the passing of the contagion to other persons.

The stomach, the œsophagus, the nasal passages, frequently the vulva and the vagina may be the seat of erratic thread-worms.

Symptoms : Principal characteristic : very violent *itching* at night, particularly in the evening after going to bed.

Lesions due to scratching ; border of the anus congested, covered with red spots (bites) and with secretions of mucus and blood. Pains and itching in the perianal, perineal and genital regions.

Irregular intestinal disorders. Soft, mucous stools ; nausea, vomiting, loss of appetite.

Nervous disorders : convulsions (in children), giddiness.

Temperamental disorders : genital disorders.

Complications : Thread-worm *appendicitis*.

Prognosis : Generally favourable ; but the infection is obstinate (auto-infestation).

Channel of elimination : Anal mucous membranes, fæces.

Resistance of parasite away from the body : The adult worm cannot live outside the body. Eggs mixed with mucus or fæcal material may survive for some days in soiled articles if dry. In water, the eggs rapidly perish.

Laboratory diagnosis : Search for eggs and adult females : this is done with the aid of a spatula in the folds of the

mucous membrane of the anus; they are difficult to find in fæces.

Examine blood for eosinophilia.

Treatment : Santonin or Santonica in conjunction with calomel—for two or three consecutive days; afterwards give a non-saline purgative.

Or, essence of chenopodium, "Butolan", aluminium acetate.

Gentian violet: 0.15 gm. (*ca.* 2 gr.) for 8 consecutive days; repeat treatment after interval of 7 days.

Ascertain whether eggs are present after the treatment.

Rigorous hygienic measures during treatment to prevent auto-infestation (cleanliness of hands, linen, pyjamas sewn up at night).

Prophylaxis : Cleanliness of hands and nails.

Avoid contact of hands with anus.

Cleanliness of linen. Boiling of infected linen.

Prolonged treatment and supervision of patients.

Avoid contact with patient.

HOOKWORM
(Uncinariasis.)

Detailed international nomenclature (1938) : No. **40.**

Latin = Ankylostomiasis.
French = Ankylostomiase.
German = Wurmkrankheit der Bergleute (v), Hakenwurmkrankheit.
Ital. = Anchilostomiasi, Ipoemia dei minatori (v), Anemia epidemica.
Roum. = Anchilostomiază.
Span. = Anquilostomiasis, Amarellao, Anemia epidemica.

A ubiquitous disease, caused by the presence in the intestine of the nematodes: *Ancylostoma duodenale* and *Necator americanus*, and characterised by a slowly developing and progressive anæmic cachexia and by gastro-intestinal disorders.

Etiological agent : *Ancylostoma duodenale* (Dubini, 1843) (especially in Europe, rarer elsewhere) and *Necator americanus* (W. Stiles, 1902), predominating in tropical and subtropical regions, not found in Europe. These are small worms (♂ 6-8 mm., ♀ 10-12 mm.) with a buccal capsule.

Incubation : 5-6 weeks.

Direct contagion : Does not exist.

Indirect contagion : Adult females attached to the wall of the *small intestine* lay eggs containing 4-8 blastomeres ; from these eggs, which are evacuated in the fæces, *rhabditiform* larvæ are hatched in 48 hours (if conditions of heat and humidity are favourable) ; this is stage I. In stage II, these larvæ become transformed into *filariform strongyloids* which become encysted in their old covering, but remain motile. This stage is the *only infective* one. Contagion takes place :

1. *Through the skin :* the encysted filariform larvæ perforate the skin (of the arms or legs) and travel via the blood vessels or the lymphatics to the right heart and lung capillaries ; thence they pass to the alveoli, the bronchi and trachea ; they are then swallowed and reach the small intestine, where they become adult in 3-4 weeks.

2. *By the mouth :* the infective larvæ perforate the wall of the digestive tract and then follow the same course as under 1.

Auto-infestation : Does not exist.

Portal of entry : Skin or mouth.

Localisation (habitat) : Mature worm : small intestine.

Symptoms : A *chronic* disease, characterised by a progressive anæmia, slight and irregular fever, abdominal and particularly epigastric pains, tympanites, nausea and vomiting, pallor, œdema (of the face and ankles), shortness of breath. Stools sometimes black in colour, sometimes diarrhœa-like.

Before or during the course of the disease, symptoms of dermatitis (due to the penetration of the skin by the larvæ) :

papular and itching eruptions, pustular on the hands, feet and folds in the skin (miners' itch) and pulmonary symptoms : a catarrhal bronchitis (passage of larvæ into the lungs).

Prognosis : Grave, if not treated.

Channels of elimination : Fæces.

Resistance of parasite away from the body : The *mature hookworm* cannot survive outside the body. The *eggs* are spread on the ground with *fæces*. They develop rapidly (24-48 hours) if the atmosphere is sufficiently warm and damp : under such conditions (in tropical regions, or in *mines*, tunnels, quarries, etc., in temperate regions) the larvæ develop in the ground and become infective in 5-6 days.

Laboratory diagnosis : Examination of fæces to find ova of the ankylostoma (by WILLIS' concentration method).

Only stools not more than 24 hours old should be examined.

Differential blood count shows eosinophilia and count of red blood cells shows anæmia.

Examine stools for mature worms after administration of a purgative.

Stool culture.

Treatment : *Thymol* — fast and laxative the previous evening.

For adults : 3-6 gm. (*ca.* 45-90 gr.) to be taken hourly in capsules of 1 gm. (15 gr.). After 4 hours give a dose of purgative salts. Contra-indications : alcohol, ether, chloroform, fats, oils, to be avoided.

Oil of chenopodium :

For adults : XLV drops in three doses of XV drops at hourly intervals. A dose of purgative salts 3 hours afterwards.

Children : two drops per year of age.

Carbon tetrachloride (chemically pure) :

Adults : 3-4 cc.

Children : 0.2 cc. per year of age.

Prophylaxis : Prevent fæcal contamination. Defæcation should be forbidden except in special receptacles ; movable receptacles able to be hermetically closed should be con-

structed and periodically disinfected. Avoid walking unshod on ground fouled with human excrement. Strict supervision of infected communities.

Trace and treat worm carriers until eggs have finally disappeared from their stools.

Supervise drinking-water. Personal hygiene and cleanliness of clothing.

TRICHINIASIS

Detailed international nomenclature (1938) : No. **42 (h)**.

Latin = Trichinosis, Trichinellosis.
German = Trichinosis, Trichinenkrankheit
French = Trichinose.
Ital. = Trichinosi.
Roum. = Trichinoza.
Span. = Triquinosis.

A parasitic disease caused by infestation of the muscles by larvæ of the nematode *Trichinella spiralis*.

Etiological agent : *Trichinella spiralis* (Owen, 1835).

Mature worms : very small (♂ 1.5 mm., ♀ 3-4 mm.) fusiform and elongated.

Larvæ : vermiform ; they migrate and settle between the fibres of the muscles and there form lemon-shaped cysts in which the larvæ can be seen rolled up in spiral form.

Incubation : 2-15 days.

Direct contagion : Does not exist.

Indirect contagion : From infested pork.

Portal of entry : Mouth.

Habitat : *Mature worms :* they emerge from cysts ingested in infected pork. Parasites of the small intestine where they live for 1 or more weeks (7) ; the females give birth to larvæ (not eggs) and then die.

The *larvæ*, which are laid in the sub-mucosa, emigrate (in 7-10 days) via the portal or lymphatic channels and spread throughout the body, establishing themselves in the muscles, where they form cysts (the limbs, the diaphragm, thorax or neck).

Symptoms : *1st Period* (evolution in the intestine). Abdominal pains, nausea, vomiting, frequent stools, either

watery or dysentery-like, progressive rise of temperature (continuous curve), reaching 104°F. (40°C.) or more after 7-8-10 days.

2nd Period : Dissemination of larvæ (as from the 8th day). The temperature continues, pains in the joints and muscles, functional disorders of the various groups of muscles (mastication, swallowing, breathing, the eyes, etc.) from the 8th to 10th days, œdema of the face, eyelids and scrotum.

3rd Period : Encystment of the larvæ (as from the 3rd week, continues for several months). Stupor, cachexia, œdema (abdomen and lower limbs), itching, miliary eruptions, petechiæ, etc. Death may supervene between the 4th and 10th weeks.

Prognosis : Variable according to the intensity of the infestation. If the infestation is inconsiderable, the disease runs its course in 1-2 weeks ; if it is more pronounced, in 7-8 weeks ; if severe, it may take several months.

Channel of elimination : Adults and larvæ in fæces, only during the 1st period.

Resistance of parasite outside the host : Neither the adult nor the larva can survive outside the host. The larvæ are encysted in the muscles of various domestic or wild mammals, especially the *rat*, which constitutes a *reservoir of infection* for the *pig*, whence the human infection comes.

Laboratory diagnosis :

1st Period (intestinal catarrh) :

(a) Examination of fæces to find larvæ and adult worms.

(b) Differential blood count shows very pronounced eosinophilia.

2nd Period (dissemination of larvæ) from 5th to 10th day :

Examine blood for larvæ : to 5-10 cc. of blood 100 cc. of a 3% aqueous solution of acetic acid is added. Centrifugalise and spread the sediment on a slide, stain with Giemsa and examine.

Ascertain the degree of eosinophilia of the blood.

3rd Period (encystment) :

(a) Examine a fragment of muscle taken by biopsy.

(b) Ascertain degree of eosinophilia of the blood.

Treatment : During the first period, irrigation of the stomach, purgatives (calomel, castor oil) and vermifuges (thymol, essence of chenopodium).

During the second period try treatment with "*Fouadine*" by intramuscular injection, adults : 1st day : 3.5 cc., 2nd and 3rd days, 5 cc., then a series of 9 injections of 5 cc. every two days.

There is no specific treatment after the encystment of the larvæ in the muscles.

Prophylaxis : Compulsory supervision of pork.

Inspection of public and private slaughter-houses.

Destruction of pork infested with Trichinellæ.

Destruction of rats.

No raw pork should be consumed ; it should always be cooked.

ITCH, SCABIES

Detailed international nomenclature (1938) : No. **153 (b).**

Latin = Scabies, Acariosis.
French = Gale, Acariose, Sarcoptose.
German = Krätze, Scabies.
Ital. = Scabbia, Rogna (v), Acariosi.
Roum. = Râĭe (v), Scabie.
Span. = Sarna, Roña (v), Acariosis.

A parasitic contagious disease caused by the lodgment in the skin of the itch-mite (*Sarcoptes scabiei*).

Etiological agent : *Sarcoptes scabiei :* an arachnoid arthropod of the order *acarina*, ♀ 350 μ in length, ♂ 225 μ.

Incubation : In summer, the disease begins as early as the third day following contamination ; in winter, it begins 12-14 days after contamination (average 8-10 days).

Direct contagion : Much the most frequent ; by direct contact with a person suffering from scabies.

Indirect contagion : From the sheets of a bed where a case of scabies has slept ; occasionally from his clothing.

Portal of entry : Skin.

Localisation : The sides of fingers, hands, wrists, elbows, knees, armpits, the region around the navel, inner sides of thighs, ankles, buttocks, penis (the back and face remain free).

Symptoms : Very violent itching, especially at night, lesions due to scratching. Presence of *furrows*, several millimetres long (tunnels at the end of which the female mite is found) dug in the skin, and more rarely pearly whiteish *vesicles* contiguous to the furrows. The diagnosis is facilitated by the presence of prurigo lesions in the regions affected ; impetigo and pyodermitis (elbows).

Prognosis : Benign, save in case of complications due to secondary infections (phlegmons).

Channel of elimination : Skin.

Resistance of parasite outside the host : The mite survives for 1-2 days exposed to the air and 10 days in contaminated linen.

Laboratory diagnosis : Find the female mite and eggs by scraping a furrow with the point of a scalpel ; place the products of the scraping between slide and cover slip in 2-3 drops of a 15% solution of potash.

Treatment : Frictional : (1) rub with soft soap and tepid water and bathe (for ½-hour), continuing the rubbing ; (2) rub for ¼-hour with a sulphur solution or pommade (Hardy's pommade) which should be left to act until the following morning ; then give another bath. Repeat the treatment 8 days later. During the first treatment, disinfect fomites, underclothing and bedding (by steaming or boiling). Recently, a simpler method has proved effective in England in 99% of cases : the single application of a 20% emulsion of benzyl benzoate to the whole body except the head, following a hot bath, and *without* disinfection of bedding or clothing (GRAHAM, J. R., 1943).

Prophylaxis : Isolation of patient until completely cured. Disinfect bedding and covers of mattresses and burn straw. Look for other cases in persons living in contact with the patient.

LOUSE INFESTATION, PEDICULOSIS

Detailed international nomenclature (1938) : No. **153 (a)**.

Latin = Pediculatio, Pediculosis capitis, corporis, pubis, Phtiriasis.
French = Pédiculose, Phtiriase.
German = Verlausung, Phtiriasis.
Ital. = Pidocchi, Pediculosi.
Roum. = Pediculoza, Phtiriaza.
Span. = Piojos, Ptiriasis.

Etiological agents : *Pediculus corporis* (body louse) (de Geer, 1778), *Pediculus capitis* (head louse) (de Geer, 1778), *Phtirius pubis* (crab louse) (Redi, 1668).

Evolution : The eggs of all these species hatch out in 5-7 days at a temperature of 89°-95°F. (32°-35°C.). The *larvæ* develop in 15-20 days under normal conditions.

Adults : Length of life : about 40-45 (60) days.

Factors promoting or checking development : heat and damp accelerate development, cold checks it and also the intensity with which they feed (hematophagia).

Desiccation kills lice, as also does light.

Direct infestation : Direct contact with infested persons (this is the case for all kinds of lice). Sexual contact in so far as the crab louse is concerned.

Indirect infestation : Through personal belongings, clothing, etc., through carriers of eggs (nits) or adult lice (of all species). Bedding (for all species), W.C. seats (crab louse).

Habitat : *P. capitis :* lives exclusively in the hair (eggs and adult lice).

Phtirius pubis : groin, pubic region and perineum, occasionally also the armpit, beard, eyebrows and lashes.

Pediculus corporis : the inner surface of underclothing (eggs and adults), especially along seams and the inner surface of clothes. As a rule, they are found on the surface of the skin only when actually feeding. In cases of *massive infestation :* on linen, clothing and also on the skin, especially the armpits, groin, neck, face, etc.

Symptoms : Intense irritation, more acute in the evening and at night (causing irritative papules), lesions due to scratching (shoulders, abdomen, hips and front part of thighs). Brown spots around old lesions due to scratching—sometimes generalised melanoderma (tramps). *Dark, brownish spots* (especially in cases of pediculosis in the groin). Presence of eggs and adult lice.

Resistance of parasite away from the body : It may happen that lice leave an infested person of their own accord and are found on clothing, linen, bedding, seats of railway or other carriages, mattresses, the seats of water-closets (crab lice), but in a dry and hot atmosphere or exposed to light they die rapidly and do not survive lack of nutrition. *In cold weather, they can survive without feeding for 10-14 days* and recover their vitality if returned to normal conditions of development.

Diagnosis : Search for and identify parasites in the parts indicated.

Treatment : See : *Delousing.*

DELOUSING

Individual and Collective Measures :

Men : Ped. capitis. Cut the hair very short ; lather the head vigorously with soft soap.

Ointments : vegetable oils, butter, vaseline, petroleum or a mixture of petroleum and vegetable oils in the proportions of 1:3 or 1:4.

Women : Lather the head vigorously ; apply for 20 minutes a rubber cap containing a pad of petroleum ether.

Repeat process after 8-10 days.

Avoid contact with infested persons.

Phtirius pubis. Shave the hair of the groin, armpits, etc. Prolonged local baths, vigorous lathering.

Apply unguentum hydrargyri or better still, vaseline.

Boil underclothing.

Repeat after 8-10 days.

Change underclothing frequently. Avoid contacts with infested persons.

Pediculus corporis. Shave hair of groin, armpits, etc. (this is not absolutely necessary).

Complete and prolonged bath, vigorous lathering.

Application of vegetable oils, alone or in combination with petroleum (1:5), to groin, chest, armpits, etc.

Repeat after 1 week.

Individual daily inspection of groups (troops, etc.) in order to trace and treat infestations as they occur.

Personal effects (clothes, linen, headgear).

Disinsectisation of these is effected as follows:

(*a*) By *dry heat* (60-80 minutes) at 158°-167°F. (70°-75°C.) or by *damp heat* (steaming) 45 minutes at 212°F. (100°C.) with frequent sudden variations of pressure.

(*b*) By toxic gases: SO^2, chloropicrin, vaporised hydrocyanic acid.

Furs, woollen garments, etc.

(*a*) Use exclusively *dry heat* (delousing oven) 60-80 minutes at 158°-167°F. (70°-75°C.).

(*b*) Delousing with toxic gases: chloropicrin, hydrocyanic acid.

(*c*) *Leather articles* (shoes, etc.): petroleum.

For *mass delousing*, special installations will be used, where bathing, haircutting, etc., and the delousing of personal belongings can be carried out simultaneously. Each operation will be carried out in a special compartment. Such installations will therefore comprise three kinds of special compartments:

A compartment of sterilisers in the centre.

Compartments (infected) for haircutting, undressing, etc.

Compartments for dressing in deloused clothing after delousing and cleaning.

Prophylaxis: Avoid contact with infested persons and articles.

Vigorous daily bodily hygiene.

Frequent changes of underclothing.

Dormitories for groups must be disinfested before use, the premises must be fumigated, the bedding changed, linen disinfested, blankets and floors sprayed with petroleum.

D.D.T., Neocid, Gesarol. A remarkable step forward in the combating of insects and particularly parasites has been achieved by the use of Gesarol [1] and its derivative—Neocid [1]—known in America and England as D.D.T. (Dichlorodiphenyltrichloromethylmethane).

In the combating of lice, excellent experimental results have been obtained by MOOSER and by ROSE, and large-scale success was obtained by American military authorities in North Africa (1942/43) and during the Naples typhus epidemic (1943/44) [2]. The underclothing and clothes of the troops were impregnated with a solution of D.D.T. which effectively prevented infestation. The underclothing and clothes of infested persons were sprayed internally under pressure without their undressing with an inert powder containing 10% of D.D.T., which destroyed all adult lice within a few hours. Nits are not affected, but larvæ which develop from them are killed later by contact with what remains of D.D.T. powder in the clothing. This process has the advantage of requiring no special installation, of being very rapid, effective, and preventing for weeks reinfestation of the sprayed clothing.

In the same way, the walls of dwellings and stables sprayed with an atomiser containing the same substance (Aerosol + D.D.T.) remain toxic for flies and mosquitoes for several weeks.

In America, D.D.T. is also used dissolved in a readily liquefiable gas—*Freon*—which, on volatilisation, facilitates the dispersion of the insecticide.

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[1] Proprietary names given by the GEIGY firm, which discovered the insect-killing properties of D.D.T.

[2] And in 1945 in the process of repatriation of prisoners and deportees from heavily infested German camps.—ED.

CHAPTER IV

INFECTIONS CAUSED BY PATHOGENIC FUNGI

Favus.
Microsporia, small-spored ringworm.
Trichophytosis, large-spored ringworm.
Madura foot (Mycetoma).
Blastomycosis.
Sporotrichosis.

FAVUS

Detailed international nomenclature (1938) : part of No. **43 (c)**

Latin = Tinea favosa. Ital. = Tigna favosa.
French = Favus, Teigne faveuse. Roum. = Favus.
German = Favus, Grind, Erbgrind, Kopfgrind.

Definition : A parasitic disease ; a universal, contagious epidermomycosis frequently found in country districts.

Etiological agent : *Achorion schönleini* (Remak, 1845). A dermatophyte which develops in the hair of the head and body where it is found in the form of spores and mycelium.

Incubation : Variable.

Direct contagion : Contact with a sufferer from the disease.

Indirect contagion : Infected clothing and toilet articles.

Localisations : Usually the scalp. May also become localised in hairless skin, mucous membranes and nails.

Symptoms : Erythematous spots, isolated or grouped in patches or plaques, covered with pityriasic squamæ ; *favus cups* around hair-follicles ; discoloured hairs easily plucked out. Cicatricial *alopecia.*

Prognosis : Recovery is never spontaneous.

Channels of elimination : The lesions.

Resistance of parasite away from the body : Great vitality away from the human body.

Laboratory diagnosis : Microscopic examination of favus cups or of hairs attacked by parasites in a drop of a 40% solution of caustic potash (spores, or short irregular mycelian filaments, with short sporulated lateral branches or favus " tarsi ", contained in the hair, characteristic air bubbles).

Treatment : Temporary depilation by X-rays and daily painting with a 1% solution of iodine in alcohol.

Prophylaxis : Isolation of patient, rigorous disinfection of clothing (headgear) and toilet articles.

MICROSPORIA, SMALL-SPORED RINGWORM

Detailed international nomenclature (1938) : part of No. **43(b)**.

Latin = Microsporia.
French = Microsporie, Teigne microsporique.
German = Mikrosporie.
Ital. = Tigna microsporica.
Roum. = Microsporie.

A parasitic disease ; a contagious epidermomycosis frequent in schools, especially in towns.

Etiological agent : *Microsporum audouini* (Gruby, 1843). A dermatophyte with small, equal, polyhedral spores forming a sheath around the hair.

Incubation : Variable.

Direct contagion : From person to person.

Indirect contagion : Toilet articles.

Portal of entry : Skin.

Localisations : The scalp, very occasionally the hairless skin.

Symptoms : *Dry form :* round or oval, regular pityriasic patches of varying size, clearly defined, covered with fine, grayish adhesive scales, showing hairs broken off at 3-6 mm.

from the base. The hairs can be easily pulled out and their roots are surrounded by a chalky sheath.

Inflammatory form : characterised by zones of a suppurating folliculitis covered with scabs.

Small-spored ringworm on the hairless skin is rarer ; it appears in the form of erythemato-squamate patches slightly raised at the edges and depressed in the centre. Sometimes the lesions are surrounded by a circle of vesicles (trichophytic herpes).

Prognosis : An obstinate infection.

Channels of elimination : The lesions.

Resistance of parasite away from the body : Great vitality away from the body.

Laboratory diagnosis : Examination of hairs in 40 % solution of caustic potash or in lactophenol.

Treatment : Temporary depilation by X-rays, friction with 1% solution of iodine in alcohol.

Prophylaxis : Isolation of patient. Rigorous disinfection of clothes (headgear) and toilet articles.

TRICHOPHYTOSIS, LARGE-SPORED RINGWORM

Detailed international nomenclature (1938) : part of No. **43 (b)**.

Latin = Trichophytosis.
French = Trichophytie, Teigne trichophytique.
German = Trichophytie, Flechten, Flechtengrind.
Ital. = Tigna tricofitica.
Roum. = Trichofiţia.

A parasitic epidermo-mycotic disease, of the *dry* type, causing the hair to fall, frequent in schools, which is spontaneously cured on reaching puberty, or of the *suppurating* type, which occurs more particularly among adults.

Etiological agent : A parasite of the genus *Trichophyton* (Malmstein, 1848).

(1) *Trichophyton endothrix :* typical species : *T. tonsurans* Malmstein 1845.

In Roumania, the *T. violaceum* Bodin 1902 is often found. These are characterised by the presence of uniform spores *inside* the hair.

(2) *T. endo-ectothrix (Ctenomyces)*. A sheath of equal spores surrounding the hair.

Incubation : Variable.

Direct contagion : Person to person.

Indirect contagion : Contaminated articles.

Portal of entry : Skin.

Localisations : Scalp (children), beard, hairless skin and nails (adults).

Symptoms : 1. *In children :*

Ringworm of the scalp : Dry : pink erythematous spots, slightly scaly, spreading rapidly, or isolated spots with diffused edges, pityriasic and scaly ; hairs broken at base.

Suppurating (Kerion Celsi): a deep follicular inflammation with the appearance of a conglomerate folliculitis produced by pyogenic trichophytons, of animal origin. This also begins with erythemato-squamous spots on the surface of which, after 10-15 days, yellowish points of folliculitis appear which combine to form a raised patch, infiltrated at the base and covered with brownish-yellow scabs.

2. *Adults :* usually in the beard, where it takes the form of dispersed, irregular, asymmetric lesions, which almost always leave the moustache unaffected.

(*a*) Dry ringworm takes the form of circinate herpes, or dispersed pityriasic patches, where the hairs are broken off at the base.

(*b*) An appearance of impetigo : the horny layer of the skin is eroded in the affected areas and the exuded serum solidifies in yellow crusts.

(*c*) Trichophytic sycosis : suppurating follicular nodules, dispersed or contiguous (Kerion).

(*d*) On the hairless skin : itching, erythemato-squamous or vesicular lesions of a polymorphous appearance.

Prognosis : The disease terminates spontaneously.

Channels of elimination : The lesions.

Resistance of parasite outside the host : Some species have great vitality outside the host.

Laboratory diagnosis : Examination of hairs and squamæ in a 40% solution of caustic potash or in lactophenol.

Treatment : Temporary depilation by X-rays ; daily rubbings with a 1% solution of iodine in alcohol.

Prophylaxis : Isolation of patient. Rigorous disinfection of clothing (headgear) and toilet articles.

MADURA FOOT (MYCETOMA) and ACTINOMYCOSIS

Detailed international nomenclature (1938) : part of No. **43 (c)**.

Latin = Mycetoma pedis.
French = Mycetomes, Maduromycose (Pied de Madura). Actinomycoses.
Germ. = Madura Fuss.
Ital. = Micetoma.
Roum. = Micetome, Picior de Madura.

Inflammatory tumors, containing *grains*, of varying form, colour and dimensions, and consisting of mycelial filaments. The grains are eliminated by fistulæ.

Cases of mycetoma in which the grains are formed of large septate mycelial filaments, and forming chlamydospores, are known as *maduromycoses*.

Actinomycoses are cases in which the grains are formed of non-septate fine mycelial filaments.

Etiological agents : Many species of parasites (more than 48 different species).

These are : in the case of *maduromycoses* the following genera : *Aspergillus, Penicillium, Glenospora, Madurella, Indiella, Sterigmatocystis*, etc. ; in the case of *actinomycoses*, the following genera: *Actinomyces (Nocardia, Streptothrix)*, etc.

Incubation : Variable ; continues for months and years.

Direct contagion : (?)

Indirect contagion : By the agency of some body causing trauma.

Portal of entry : A break in the skin or mucous membranes.

Localisations : In the case of maduromycosis, mainly the lower limbs.

In the case of actinomycosis, chiefly the neck and face, the pleura and lungs, the inner abdomen, the skin and the brain.

Symptoms : Well-defined, hard nodules from which pus and grains exude by fistulæ.

Prognosis : Serious in the case of maduromycosis, which does not tend to generalise.

Grave in the case of actinomycosis, which may lead to death from cachexia.

Channels of elimination : Fistulæ.

Resistance of parasite outside the body : They can live as saprophytes or as facultative parasites in man, animals, certain plants, earth and water.

Laboratory diagnosis : Discovery of the parasite in the grains.

Treatment : Potassium iodide, Lugol's solution in combination with sodium hyposulphite by intravenous injection, electro-coagulation, X-ray.

Prophylaxis : Good hygienic conditions.

BLASTOMYCOSES

Detailed international nomenclature (1938) : part of No. **43 (c).**

Latin = Blastomycosis. Ital. = Blastomicosi.
French = Blastomycoses. Roum. = Blastomicoze.
German = Blastomykose.

Parasitic diseases caused by *yeast*-like fungi.

Etiological agents : Numerous species of parasite belonging to the genera : *Blastocystis, Blastodendrion, Candida, Geotrichoides, Mycotorula, Mycotoruloides, Redaellia, Torula, Cryptococcus,* etc.

Incubation : Variable.

Direct contagion : (?)

Indirect contagion : By different infected objects.

Portal of entry : A break in the skin or mucous membranes.

Localisations : Skin, mucous membranes, viscera.

Symptoms : In forms affecting the skin, erythemato-vesicular lesions, miliary abscesses, nodules, abscesses of the skin.

In generalised blastomycosis : a septicæmic condition with localisations in the form of tumors and abscesses of the skin, lungs, intestines, joints, bones, muscles, brain and eyes.

Prognosis : As a rule benign.

Channels of elimination : Open lesions.

Resistance of parasites away from the body : They are saprophytes.

Laboratory diagnosis : Identification of the yeasts in the closed lesions by direct examination and by pure cultures.

Treatment : Potassium iodide or Lugol solution (iodine 1 gm., potassium iodide 2 gm., distilled water 100 gm.) associated with a 20% solution of sodium hyposulphite, 1-10 cc. every other day by intravenous injection. Arsenic.

Prophylaxis : Good hygienic conditions.

SPOROTRICHOSIS

Detailed international nomenclature (1938) : part of No. **43 (c).**

Latin = Sporotrichosis. Ital. = Sporotricosi.
French = Sporotrichoses. Roum. = Sporotrichoze.
German = Sporotrichose.

Parasitic diseases (mycoses) with many symptoms of a tuberculous or syphilitic appearance.

Etiological agents : Parasites of the genera : *Sporotrichum* and *Rhinocladium.*

In culture they have the appearance of fibrous and sporulated fungi. In pus or parasitised tissues, they are found in the form of yeast, which may or may not be combined with mycelial filaments.

Incubation : Variable.

Direct contagion : From one person to another or from animal to man.

Indirect contagion : By articles or food contaminated by vegetable debris containing the parasite.

Portal of entry : Broken or unbroken skin and mucous membranes.

Localisations : All tissues : hypodermis, dermis, epidermis, the glands of the skin, bones, joints, muscles, lymph glands, eyes, larynx, tongue, nose, lungs, testicles.

Symptoms : Lesions of the skin : ulcerating or non-ulcerating gummata, simple or multiple abscesses, lymphangitis, chancres. In general an assortment of lesions of varying appearance and age.

On the mucous membranes, erythematous, vegetative, ulcerating, suppurating lesions (in appearance resembling all the varieties of sore throat, stomatitis, glossitis, laryngitis, rhinitis). These lesions are, as a rule, accompanied by gummatous lymphangitis or adenitis.

In the muscles and breast, inflammatory swellings and lesions having the appearance either of abscesses due to pyogenic microbes, of syphilis, tuberculosis, or even of cancer.

The bones are the seat of periostitis and abscesses ; joints may be the seat of lesions resembling white swellings.

In the viscera, orchi-epididymitis, congestion of the lungs, lesions of a tuberculous appearance.

Prognosis : Usually benign.

Channel of elimination : The lesions.

Resistance of parasites away from the body : They are saphrophytes and have great vitality.

Laboratory diagnosis : Essential. Inoculate Sabouraud's glucose agar medium with an abundance of pus or tissues.

Serodiagnosis (WIDAL & ABRAMI).

Complement fixation test.

Direct isolation of the parasites is difficult, as there are but few of them and it is hard to distinguish them from cellular debris.

Inoculation of animals (mice or rats) in exceptional cases.

Treatment : Potassium iodide : 2-6 gm. per diem. Lugol solution (iodine 1 gm., potassium iodide 2 gm., water 100 gm.) is better ; from 1-10 cc. to be administered by intravenous injection every other day, with the addition of a 20% solution of sodium hyposulphite in sufficient quantity to discolour the Lugol solution. The first injections may aggravate the lesions.

Prophylaxis : Good hygienic conditions.

Part II

OUTLINE OF GENERAL AND SPECIAL IMMUNOLOGY

PART II

OUTLINE OF GENERAL AND SPECIAL IMMUNOLOGY

CHAPTER V

BRIEF OBSERVATIONS CONCERNING IMMUNITY AND ITS APPLICATIONS

Some brief observations concerning immunity and its applications.
Titration and standardisation of immune sera and microbic products.
The technique of immune sera injections.
Accidents due to sera and their prevention.

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1. Some Brief Observations concerning Immunity and its Applications

A state of *immunity* or of *specific resistance* to a microbic infection may be produced artificially in a subject:

(a) by progressive inoculation with increasing non-lethal doses of an organism or its toxins against which immunity is sought;

(b) by injection of the blood serum of an animal previously immunised against these microbes or toxins.

By the first method, the subject immunised is induced itself to build up the *specific principles* (antibodies) necessary to provide protection against the microbe or its toxin.

By the second, these *specific principles* are introduced ready-made into the body by means of the injected immune serum.

The first method of immunisation is usually known as *active immunisation* or *preventive vaccination*, the second as *passive immunisation* or *serum prophylaxis*.

The state of immunity or *specific resistance* imparted to the subject by *preventive vaccination* develops progressively and generally lasts for a considerable time, varying

from some months (in the case of vaccination against typhoid and paratyphoid fevers, cholera, etc.) to some years (in the case of anti-smallpox vaccination, for instance).

This condition of immunity is usually permanent when it results from spontaneous recovery from an infectious disease (typhoid fever, exanthematic typhus, etc.).

On the other hand, specific immunity conferred by *serum prophylaxis* is immediate but transitory, only lasting for 2 to 3 weeks and gradually ceasing to operate as the immune serum injected is eliminated.

Prophylactic vaccination is applied in most cases to *prevent* a disease. This method may also be employed during the evolution of certain diseases which have already declared themselves, with a view to inducing a more rapid production of specific antibodies and to stimulating phagocytosis (*vaccine treatment* (WRIGHT)) in the course of typhoid fever, pneumonia, staphylococcus and gonococcus infections, etc).

Immunisation by means of immune sera is employed most often for curative purposes *(serum treatment)*. It represents one of the most important means of specific biological treatment in microbic toxi-infections. But sometimes, if it is desired to secure an immediately effective immunisation, this method is applied for prophylactic purposes (serum prophylaxis). It must, however, be borne in mind that such immunisation is of limited duration and that it is better to supplement it with preventive vaccination (*see* more particularly : sero-vaccination in tetanus, diphtheria, etc.).

There are certain chronic infections (tuberculosis, syphilis, etc.) during the course of which an increased resistance is observable in the body which only persists so long as the *specific antigen* (tubercle bacillus or Schaudinn's treponema) also persists in the body. Once the infection has been cured, no residual immunity persists. This transitory specific resistance is known as *premunition* (*see* tuberculosis premunition by means of B.C.G. vaccine).

Vaccines may be divided into :

1. *Antimicrobic* vaccines, which generally consist of a suspension of microbes in a suitable liquid, either killed by

various physical or chemical agents, or with their virulence attenuated, or with specific immune sera added to them (sensitised vaccines).

2. *Antitoxic* vaccines (that is to say, against the toxins produced by the microbes) consisting of microbic *toxins* or *endotoxins*.

Antitoxic vaccines are of two kinds :

(a) *Vaccines* in which the toxin is incompletely *neutralised* by the corresponding antitoxin (a mixture of toxin and antitoxin) (EHRLICH).

(b) *Vaccines* in which the toxin is *detoxified* by formalin or *anatoxin* (RAMON) (diphtheria, tetanus, etc., anatoxin).

Immune sera are also divided into :

1. *Antimicrobic sera* which are obtained from hyper-immunised animals—*i.e.*, animals to which have been administered progressively increasing quantities of microbes (anti-streptococcus, anti-meningococcus, anti-pneumococcus, anti-anthrax, etc., sera).

2. *Antitoxic sera* from animals which have been immunised with the soluble toxin of certain microbes (anti-diphtheria, anti-tetanus, anti-botulinus, etc., sera).

3. Finally, sera which are both *antitoxic* and *antimicrobic* —*e.g.*, anti-dysentery serum, anti-gas-gangrene serum, etc.).

2. THE TITRATION AND STANDARDISATION OF IMMUNE SERA AND MICROBIC PRODUCTS

As early as 1921, at its second session at Geneva, the Health Committee of the League of Nations considered the question of the standardisation on an international scale of biological products used in therapeutics and prophylaxis.

In order to secure the continuity of this work, the Health Committee decided, in 1924, to set up a *Permanent Commission on Biological Standardisation* whose task it was :

(1) To adopt standard preparations, (2) to select and fix the value of the *international units* best calculated to express the activity of the various biological products

used in therapeutics and for prophylaxis, and (3) to take the necessary steps to ensure that the *standard preparations* of these units adopted by the Commission should also be accepted for international use by the Institutes in the different countries producing such substances.

" The Commission's method of work is founded entirely on international co-operation. When the state of our knowledge concerning a given substance seems to warrant an attempt at standardisation, the Commission entrusts the conduct of the preliminary work to a certain number of official and private laboratories having special experience of this branch of research, the experimental results being co-ordinated at the *Copenhagen Institute* in the case of serological questions and at the *Hampstead Institute* in other cases. "[1]

The Danish State Serum Institute at Copenhagen was entrusted with the conservation of standard preparations and with their preparation and distribution of all sera and bacterial products regarding the titration of which an international agreement existed.

The Hampstead Institute (London) concerned itself with biological products such as *Vitamins* and *Hormones* and certain medicaments in *very general use* such as digitalis and the arsenobenzols.[2]

With regard to anti-diphtheria serum, the International Biological Standardisation Commission recommended that P. Ehrlich's old unit should be adopted as the international unit (I.U.).

The antitoxin content of anti-tetanus serum was expressed in terms of three different units : the German, American and French, each differently defined.

Agreement had first to be reached as to the relative value of these different units, then the definition of the initial value of the old German unit had to be altered in

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[1] GAUTIER R. " The Health Organisation and Biological Standardisation ", *Bull. Health Org.*, L.o.N., 4, No. 3, pp. 491-554, 1935.

[2] The Cantacuzène Institute of Bucharest has adopted the international standards and the titre of its products (sera and vaccines) is expressed in I.U.

order to make it possible to retain this " modified German unit " as the international unit for the measurement of the anti-toxic potency of anti-tetanus serum.

At present, the following ratio has been adopted : 50 American units = 100 new German units (I.U.) = 2,500 French units.

In the following table, we give the list of standard preparations (sera and microbic products) kept at the Danish State Institute of Copenhagen and placed at the disposal of the Serological Institutions of all countries :

Standard serum	*Abbreviation*	*Adopted in*	*International unit in mg.*
Diphtheria antitoxin	DI.	1922	0.0628
Tetanus antitoxin	TE.	1928	0.1547
Anti-dysentery serum (Shiga).	DY.	1928	0.0500
B. perfringens antitoxin . . .	PE.	1931	0.2660
Vibrion septique antitoxin . .	VI.	1934	0.2377
B. œdematiens antitoxin . . .	OE.	1934	0.2681
B. histolyticus antitoxin . . .	HI.	1935	0.3575
Anti-pneumococcus serum Type I	P.A.	1934	0.0886
Anti-pneumococcus serum Type II.	P.B.	1934	0.0894
Staphylococcus antitoxin . .	ST.	1938	0.2376
Diphtheria antitoxin (for flocculation).	DI.F.	1938	Serum 1184
Koch's tuberculin (the old tuberculin)	T.V.	1931	—

3. The Technique of Immune Sera Injections

The administration of a serum by means of injections (subcutaneous, intramuscular, intravenous, intraspinal, etc.) must be accompanied by the strictest possible observance of the principles of asepsis. The syringe and needle must be sterilised by boiling for at least 10 minutes in water to which sodium biborate has preferably been added. A local disinfection (painting with a tincture of iodine and 96° alcohol) is generally sufficient.

The method most employed is *subcutaneous* injection and the favourite place *is under the skin of the side of the abdomen.* For this purpose, a syringe the capacity of which corresponds to the quantity of serum to be injected (20-50 cc.) is used, together with a needle with a long bevel of a total length of 6-8 cm. and a diameter of 0.8-1 mm. Having fixed the needle in the syringe, the contents of one or more phials of the serum to be injected are drawn in. If possible, the serum is first warmed in a water bath to 98.6°F. (37°C.). With the thumb and the first finger of the left hand the skin is raised to form a fold in which the needle is inserted —at a tangent to the surface of the skin—so as to penetrate the layer of cellulo-adipose tissue. The loose network of subcutaneous connective tissue, rich in lymphatic vessels, is very distensible and facilitates the absorption of the liquid injected.

When large quantities of serum (100 to 200 cc. or more) have to be injected, it is advisable to facilitate the dispersal of the liquid by changing from time to time the direction of the needle's point during the injection.

When the condition of the patient requires that the action of the immune serum should be more rapid, *intramuscular* or *intravenous* injections should be employed.

For *intramuscular* injection, the *buttock* is usually the site selected, observing of course all the precautions required by this method of injection.

In order to avoid the sciatic nerve and vessels, the posterior iliac spine and the top of the greater trochanter must first be located. The injection should be made above the line joining these two points, in the upper and external part of the buttock.

After thorough disinfection of the skin, the needle is plunged into the gluteus maximus. The syringe, previously charged with serum, preferably warmed to 96°F. (37°C.), is then adjusted. The injection should be made very slowly.

Intravenous injection of serum is indicated in very serious cases, in infections which develop rapidly (gas-gangrene, streptococcus and pneumococcus infections, anthrax septi-

cæmia, etc.), and whenever specific serum treatment has been delayed. In all cases where immediate specific action is necessary, this method must be used.

To administer the serum by this method, the procedure is as follows :

First select the vein, which must be clearly perceptible to the finger, of large volume and fixed. The veins in front of the elbow joint are best suited for these injections and particularly the median cephalic vein immediately above its junction with the median vein. *Place a constrictive band* around the middle of the upper arm to cause the veins to swell. For this purpose a rubber band or tube 40-50 cm. in length may be used, the ends of which are fixed with a pair of artery forceps. Make sure by feeling the radial pulse that the band is not too tight.

After disinfection of the region (with alcohol or tincture of iodine), the vein is punctured with the needle fixed in the syringe ready filled with the serum to be injected.

For intravenous injections of serum, a needle 4-5 cm. in length with a short bevel and an internal diameter not exceeding 0.6 to 0.8 mm. is generally employed.

The puncture is made obliquely to the surface of the skin and parallel to the direction of the vein. The fact that the needle is in the lumen of the vein can be verified by the few drops of blood which appear in the syringe. Then the elastic band is gently removed, taking care not to move the syringe or alter the angle of the needle. If the needle has been inserted some millimetres into the vein, the removal of the band cannot cause it to slip out.

The serum—previously warmed to 98.6°F. (37°C.)—is injected *very slowly*, the patient being duly watched so that the injection can be stopped at the least sign of intolerance.

As soon as the injection is completed, the needle and syringe are withdrawn together under a pad of cottonwool soaked in alcohol. This pad also serves to maintain a slight pressure (for 1 or 2 minutes) on the puncture left by the needle. In most cases, a dressing is unnecessary.

A precaution, which is *absolutely indispensable* when dealing with a patient to whom heterologous serum has previously been administered (and is therefore in a sensitised condition as regards that serum), and which is advisable in every case of intravenous injection, is to divide up the dose of serum and administer it in several injections at 10- to 15-minute intervals, or else to apply Besredka's *method of desensitisation* (see special chapter: Serum Disease and Anti-anaphylaxis).

Intraspinal injection is employed in cases of infections or toxi-infections localised in the central nervous system (epidemic cerebrospinal meningitis, tetanus, infantile paralysis, etc.).

For this form of injection, the patient must be either *seated* (Figure 1) or *lying on his side* (Figure 2).

In the first case, the patient sits on the side of his bed or on a chair, the back turned towards the operator, elbows on his knees, legs relaxed, the head bent forward as far as possible so as to extend the interspinal spaces of the vertebral column.

This position, which is generally adopted for exploratory lumbar puncture and spinal anæsthesia, is usually impossible in the case of patients suffering from cerebrospinal meningitis or infantile paralysis. Moreover, it sometimes entails a danger of accidents (syncope) as a result of sudden decompression and too rapid a discharge of the cerebrospinal fluid.

The *lateral decubitus* position is better in the great majority of cases and is therefore more advisable. The patient must lie on his side, on a hard and flat surface with his knees drawn up. For an intraspinal puncture it is essential that the patient should be in the correct position. The neck and back must be bent forward as much as possible. It is advisable that an assistant should hold the patient so as to prevent him from moving during the operation. As soon as the position is correct, the puncture is made.

The region must be sufficiently widely disinfected with tincture of iodine. Then the intervertebral space where the needle is to be inserted must be carefully verified—*i.e.*, between the *4th and 5th lumbar vertebræ*. The 4th lumbar

Figure 1. — Site for intraspinal injections, after Donald Core : *The Examination of the Central Nervous System*, 1928, p. 203.

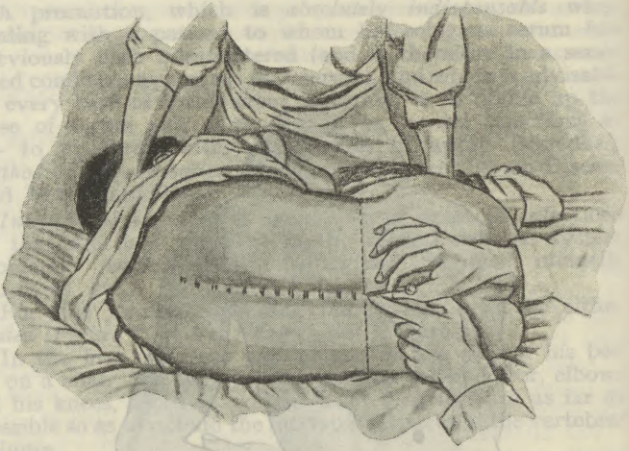


Figure 2. — Intraspinal injection in the recumbent position, after Duplay, Rochard, Demoulin: *Diagnostic chirurgical*, 1921, p. 66.

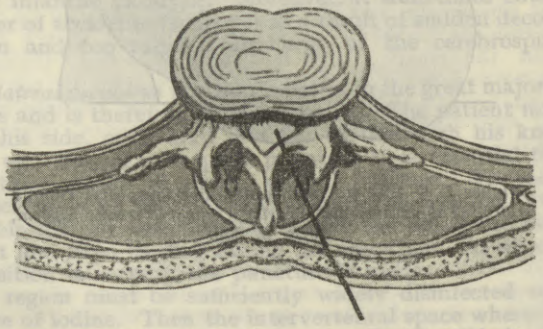


Figure 3. — Intraspinal injection, after Duplay, Rochard, Demoulin: *Diagnostic chirurgical*, 1921, p. 64.

apophysis is on the horizontal line joining the tops of the iliac crests. This apophysis is covered with the forefinger of the left hand—previously disinfected. In the right hand is held, like a pen, the needle fitted with its stylet (8 cm. long and 0.8 mm. in diameter) which will have been carefully sterilised beforehand (boiled for at least 15 minutes) and, with a sharp push, it is inserted in the middle line equidistant from the two apophyses (the 4th and 5th) which define the intervertebral space (Figures 1 and 2). As soon as the skin has been pierced, the needle is pushed slowly deeper, taking care to follow the direction of the middle line while avoiding the spinal apophysis (Figure 3). At a depth of 4 or 5 cm. some resistance is encountered: this is the subflavous ligament. Once this resistance has been overcome, the needle meets the surface of the dura mater. On being driven in a few millimetres, the tip of the needle will be in the dural cul-de-sac. The stylet is withdrawn and the cerebro-spinal fluid begins to flow from the needle. The fluid is collected in a sterilised test tube for subsequent bacteriological and cytological examination. The pressure of the fluid and its macroscopic appearance are observed. Not more than 20 cc. of the fluid in the case of a child, or 30-40 cc. in the case of an adult, must be allowed to escape. The *cerebro-spinal fluid must never be aspirated.* When the requisite quantity of the fluid has been extracted, the syringe filled with the serum to be administered (warmed to 98.6°F.) is carefully adjusted and the piston is very slowly pushed.

When the injection is completed, the patient must be placed in a recumbent position, with the head lower than the rest of the body to facilitate diffusion of the serum in the direction of the cranial meninges. Precautions to avoid anaphylactic accidents due to serum must be taken before every intraspinal injection of serum (see below Serum Disease and Anaphylactic Shock).

4. Accidents due to Serum and Their Prevention

Accidents due to serum, which frequently result from the injection into the human body of a heterologous serum,

may be either immediate (occurring within the first 15 minutes), or delayed, occurring between the 4th and 5th days after the injection. In both cases, there will be local and general symptoms.

Immediate accidents, which are somewhat exceptional in the case of a first injection of serum, generally occur in connection with a re-injection and particularly in cases where several months have elapsed since the first injection.

The general symptoms comprise : tachycardia, rapidity and weakness of the pulse, a lowering of arterial tension, collapse, often accompanied by a generalised scarlet-fever-like rash, with a certain amount of itchiness of the skin, or in other cases by a typical nettlerash. There may be a reaction of the digestive system taking the form of vomiting, diarrhœa, incontinence of fæces, etc., and of the nervous system, taking the form of agitation, convulsions or a state of coma. In some cases, an abundant whiteish, frothy expectoration has been observed, more in the nature of an excessive flow of saliva.

A characteristic of these symptoms is that, *once the crisis has passed—which it almost always does— recovery is just as complete as the appearance of the symptoms is sudden and dramatic.*

As soon as the crisis has passed, the patient can, as a rule, withstand the injection of the serum without difficulty ; in other cases, accidents occur afresh on each occasion that serum is injected.

Fatal accidents are very rare. Péhu & Durand, in a study on serum accidents, analysing all fatal cases mentioned in medical literature, point out that in most of them the post-mortem examination revealed the presence of pre-existing organic lesions : lesions of the liver, kidneys or meninges (co-existence of a tuberculous meningitis together with cerebrospinal meningitis), a fact which much diminishes the responsibility of the serum for the fatal result.

The immediate *local symptoms* appear at the point of injection and consist in : redness, swelling, a sensation of heat, and perhaps patches of nettlerash with mild irritation. *Accidents which occur in the course of repeated intraspinal*

injections, given as treatment for cerebrospinal meningitis and giving rise to serum meningitis, may be regarded as immediate local re-injection phenomena of the same category.

It often happens that, after a number of intraspinal injections, these can no longer be tolerated by the patient. Even during the actual injection, the patient complains of violent lumbar, abdominal or peritoneal pains—pains which are sometimes intolerable and may lead to collapse or even syncope. The face is pale and anxious and the patient complains of constriction in the chest and abdomen ; after the puncture, the pain persists, headache becomes violent and is sometimes accompanied by vomiting ; the pain in the spine reappears and the temperature reaches 102°-104°F. (39°-40°C.).

All these symptoms present the appearance of a recurrence of the meningitis, thus giving a false indication for the continuation of the treatment. If one takes the precaution of examining the cerebrospinal fluid in such a case, one will be struck by the following points : *the fluid is viscous and of a yellow colour, similar to that of the serum injected ; it contains an enormous quantity of albumen and many polymorphonuclear cells in perfect condition ; there are no meningococci and, above all, the quantity of glucose is normal.* All these signs prove that, far from there having been a relapse, the case is one of intolerance of the serum—*a case of serum meningitis—and that the course to be followed is to abstain completely from further serum treatment.*

Of the delayed accidents some may make their appearance between the 4th and 6th days (these occur when not more than 1 to 6 months have elapsed since the first injection), others between the 8th and 20th days (these occur when more than six months have elapsed since the first injection or after a first injection of serum) ; for, unlike immediate accidents, retarded accidents are very frequent even after a first injection.

These accidents are characterised by rashes, more or less discrete, generally resembling nettlerash, the eruption being sometimes generalised and sometimes local (in which case the area affected is usually the site of injection). The erup-

tion may sometimes assume a hæmorrhagic character, but always superficial and transitory, and may be accompanied by swelling of the local lymph glands. Among general symptoms, the following have been observed : fever, vomiting, pains in the joints and muscles, cramps, trismus resembling the beginning of tetanus.

Though sometimes alarming, owing to the disturbances of the circulation which may accompany them, these accidents are rarely serious. Von Pirquet & Schick *state that, after consulting the whole literature on the subject, they do not feel justified in attributing to such accidents a single indisputable case of death.*

Although the causation of these accidents, the *nature of the serum and the quantity injected do not play a predominant part, the method of administration is very important, especially with regard to immediate reactions.* Of all methods, intravenous injection is that which is most liable to cause such accidents ; next comes intraspinal injection ; accidents are, on the whole, rare following intramuscular or subcutaneous injections, which are the usual methods of administration.

The prophylaxis of serum accidents. Since immediate accidents are those which may prove the more serious, it is these which must above all be averted. Their pathogenesis is not yet fully elucidated. They are anaphylactic phenomena in regard to the causation of which several theories have been propounded. According to some authorities, the violent and sudden reactions which characterise them are due to the contact between the antigen and the corresponding antibody, which, by modifying the blood and intracellular colloidal balance, causes disorders throughout all the tissues, but especially in the nervous system, which is particularly sensitive to such modifications.

Other authorities consider that these phenomena are comparable with what occurs in histamine intoxication and hold that anaphylactic accidents are identical with those due to histamine shock. According to Danielopolu, these accidents result from a release of acetylcholin.

However these phenomena are to be explained, the slow desensitisation or anti-anaphylactic method recommended by BESREDKA *is still the most reliable, though not infallible, means of prevention.* This method is based on the assumption that, by introducing the antigen into the body very slowly and in small doses, the antigen-antibody reaction will take place unaccompanied by violent disturbances of the colloidal balance and consequently without violent symptoms of anaphylaxis.

When a subcutaneous injection has to be administered to a patient who has in the past undergone serum treatment or who, there is reason to believe, is likely to be particularly susceptible to anaphylactic reactions, it is advisable to test the degree of susceptibility by an *intradermal injection* of a very small dose of serum (0.1 cc. of a 1:100 dilution) or by the ophthalmic reaction caused by a drop of 1:10 dilution into the conjunctival sac. The way to proceed is as follows :

A subcutaneous injection of 0.25 cc. of serum, either pure or diluted with saline solution, is administered ; three hours later, 1 cc. is injected and, only after a further interval of 3 hours, the therapeutic dose. Of course, this dosage may be modified and the rhythm of administration may be accelerated or retarded according to the known or supposed susceptibility of the patient. Again, as a precaution, the injection may be made in the arm or thigh and a tourniquet applied above the site of injection which can be tightened directly the first signs of intolerance appear.

In the case of an intraspinal injection, the procedure is the same ; if, however, the case is a very serious one which requires extremely urgent treatment, desensitisation may be effected by the intravenous method : first, 1 cc. of a 1 : 10 or 1 : 20 dilution of serum in saline solution is injected ; some minutes later, 2-3 cc. of the same dilution and, finally, 20 or 30 minutes later, the intraspinal injection is administered as slowly as possible.

Intravenous injection is the method involving the greatest danger of accidents and, accordingly, this method must be accompanied by greater precautions ; the procedure is as

follows :

5 cc. of serum are diluted with 500 cc. of saline solution ; 10 cc. of this mixture are injected into the vein, very slowly, taking about 5 minutes ; 15 minutes later 20 cc. of the same dilution. If, 15 minutes later, the patient shows no abnormal symptoms, the remainder of the serum to be injected—20, 50 or 100 cc.—is added to this dilution and administered to the patient. For this purpose, an apparatus employed for the injection of saline solution, or a container suspended at a height sufficient to cause the serum to flow by gravity, is used ; the height must not be too great, and the needle must be sufficiently fine to ensure that the discharge of the whole quantity takes at least half-an-hour to one hour. If need be, the speed can be regulated by a Mohr's forceps fixed to the rubber tube.

To avoid repeated punctures of the vein, which in the case of some patients may be undesirable, the following method may be adopted : the needle connected with the container, holding at first only the physiological saline solution warmed to 98.6°F. (37°C.), is inserted in the vein ; when it has been verified that the flow is operating normally, 1 cc. of serum is added to the contents of the container. If the injection is borne well by the patient, after 10 minutes, 2 cc. of serum are added and again 2 cc. after a further 10 minutes ; if after half-an-hour no accident has occurred, the remainder of the serum may be added, and the injection continued as slowly as possible.

In this way, the injection can be interrupted should any unfavourable symptom supervene. It is as a rule prudent to add to the mixture to be injected 0.25 cc. of adrenalin at 1:1000. Danielopolu recommends that the injection should be preceded by the intravenous injection of 1.5 mgm. of atropin in two doses.

In the event of intolerance (congestion of the face, rigors or dyspnea) the injection will be interrupted and cold compresses applied to the patient's face. If it is a real case of shock, adrenalin, heart tonics and restoratives must be employed. After the disappearance of these symptoms, an attempt may be made to proceed with the injection and this is sometimes successful. Sometimes a more or less

violent rigor, followed by a rise of the temperature, occurs half-an-hour to an hour after the injection.

With regard to *delayed accidents*, adrenalin has been recommended to counteract cardio-vascular disturbances and hypotension; likewise antipyrin, aspirin and sodium salicylate to alleviate articular and muscular pains; calcium chloride is particularly effective against eruptions of the skin and nettlerash. Finally, in the treatment of very obstinate serum reactions with a tendency to become chronic—which, however, are rare—FLANDIN has successfully used injections of horse serum in very small doses (0.10-0.05 cc.).

PAUZAT & LÉVY have successfully used the serum of *convalescents from serum disease*, injecting 10 cc. before the injection of the therapeutic serum. ROBERT treats serum accidents by autohemotherapy, once they have declared themselves. LUMIÈRE advocates as a prophylactic, as well as for treatment, magnesium hyposulphite, of which he injects 10 cc. of a 10% solution, either subcutaneously or intravenously, at the same time as the serum and on the two following days. Adrenalin, the beneficial but ephemeral action of which on anaphylactic accidents is well known, has been successfully replaced by ephredin. P. P. LÉVY recommends the administration of an ephedrin tablet (0.05 gm.) one hour before the injection of the serum and subsequently one tablet every 8 hours for 14 days. For children between 1 and 4 years, he prescribes tablets of 0.01 gm., between 4 and 9 years, of 0.02 gm., and above 9 years, of 0.03 gm. As in the case of salicylate treatment, continuity is a condition *sine qua non* for success.

Antergan, which has recently been adopted for anti-allergic treatment, may also be used.

In order to overcome the meningeal sensitiveness which sometimes makes intraspinal treatment impossible, RAMON and subsequently DELABERT have injected their patients, first subcutaneously and subsequently intrathecally, with the serum of the patients themselves.

As a rule, a milk and vegetable diet, and preferably vegetables only, with an abundance of liquids, both diuretic and laxative, is a valuable adjuvant and should be prescribed for the 8-12 days during which the patient is exposed to the danger of delayed accidents.

One important point to be remembered in order to reduce such accidents to a minimum is that the serum to be injected must not be too fresh. Sera issued for use should have been kept for some months, as the fresher the serum the more frequent and the more severe serum reactions will be. Finally, the removal of non-essential proteins from sera, a practice which has become widely adopted, also contributes to a reduction of the frequency of accidents.

Serious accidents are rare. Delayed and usually benign accidents call for most attention.

At all events—and this is the unanimously accepted view —the fear of such accidents should never prevent a doctor from resorting to serotherapy in cases in which that is the only effective treatment for the disease in question.

CHAPTER VI

BIOLOGICAL DIAGNOSTIC TESTS

Tuberculosis : *Tuberculin tests.*
Diphtheria : *Schick's test ; Moloney's test.*
Scarlet Fever : *Dick's test ; Schultz-Charlton extinction phenomenon.*
Brucellosis : *Burnet's test.*
Tularemia : *Foshay's test.*
Soft Chancre : *Ito-Reenstierna test.*
Poradenitis : *Frei's test.*
Hydatid Disease : *Casoni's test.*

TUBERCULOSIS

Tuberculin Tests

The biological diagnosis of tuberculosis is based on the special sensitiveness (local and general reactions) of infected subjects to tuberculin, and the absence of reaction to it in non-infected men and animals.

The preparation of tuberculin and the discovery of this phenomenon are due to R. Koch.

To obtain tuberculin, cultures of human and bovine bacilli in a glycerinated bouillon (6 to 8 weeks old) are sterilised in an autoclave. The volume of the bouillon is then reduced to one-tenth by evaporation ; the liquid obtained by filtration is *crude tuberculin* A.T. (Koch's " alt Tuberkulin ").

Biological characteristics. Tuberculin is not toxic to normal men or animals ; it is extremely toxic to a tuberculous animal. Tuberculin, when injected intradermally into a tuberculous guinea-pig causes : (1) a *local reaction*—

redness, œdema, swelling, sometimes ecchymosis and even necrosis ; (2) a *general reaction* characterised by fever, toxic symptoms, and finally hypothermia and the death of the animal ; (3) a *focal reaction* with symptoms of congestion around the tuberculous lesions.

Sensitiveness to tuberculin makes its appearance some time after the infection, the degree being in proportion to the infective dose and the virulence of the germ. Killed bacilli produce only a very slight measure of sensitiveness and only when large quantities are injected. The degree of sensitisation increases as the infection develops ; it disappears during the final period of cachexia. The intensity of the reaction varies according to the method of injection of the tuberculin ; it increases progressively according as the injection is cutaneous, subcutaneous, intraperitoneal, intravenous or intracerebral.

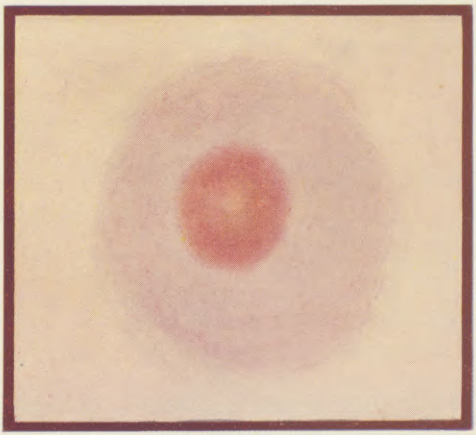
R. Koch, who was the first to study the sensitiveness of man to tuberculin, demonstrated the general and focal reaction ; he advocated the use of tuberculin in the treatment of tuberculosis. Von Pirquet studied the reaction of the skin and advocated its use for diagnostic purposes.

The methods for the use of tuberculin are at present as follows :

Skin test (von Pirquet, 1893). A drop of tuberculin is placed on the skin of the front of the forearm and, with a lancet or with von Pirquet's vaccinostyle, the skin is slightly scarified where the drop has been placed ; contact must be maintained for 10 minutes. On the same forearm, lower down, a similar scarification is made, without the addition of tuberculin (for control).

The *reading of the reaction*, preferably after 48 hours, shows an erythematous patch of varying dimensions and œdema at the spot where the skin was scarified ; the patch subsequently becomes a papula or sometimes a pustule. The reaction lasts for several days.

The intradermal test (Mantoux, 1908) is carried out by injecting strictly within the dermis 0.1-0.2 cc. of a 1 : 10,000 dilution of tuberculin. When the reaction is negative with this dilution, the process is repeated with dilutions of



Positive Intradermal Tuberculin Test
48 hours after the injection of 0.1 cc. of a 1:10,000 dilution of tuberculin.

1 : 1000, 1 : 500 and even 1 : 100, if the reaction remains negative after the previous dilutions. The reaction should preferably be observed after 48 hours. A positive reaction is characterised by a central œdema surrounded by an erythematous zone of at least 5 to 10 mm. in diameter. If this zone is smaller, the reaction is doubtful and the test should be repeated with a stronger concentration of tuberculin.

The local reaction to tuberculin may also be tested by other methods : the rubbing of the skin with a tuberculin ointment (Moro, 1908) or the application of tuberculin under a plaster.

The instillation into the conjunctival sac of a drop of *purified tuberculin* has also been advocated (Wolff Eisner, 1907, Calmette, 1907).

The *skin test* and the *intradermal test* are the methods recommended as preferable for epidemiological investigations.

The general reaction and the focal reaction are provoked by *subcutaneous* injection of tuberculin. This method should be used only in the case of patients with no fever who show no symptoms of congestion and have not recently expectorated blood.

After an injection of a 1 : 1,000,000 dilution of tuberculin, the tuberculous patient will show fever, toxic symptoms, nausea, loss of appetite, headache and symptoms of congestion at the tuberculous foci. This method, which is liable sometimes to cause serious accidents, is only used in exceptional cases.

Interpretation of results. A positive reaction to tuberculin is evidence of an infection with Koch's bacillus and not necessarily of the disease itself. We know, indeed, that the infection is very widespread in European countries, where 50 to 80% of adults (who are clinically normal) react to tuberculin.

Nevertheless, a positive reaction is of real importance in the case of a child, in which the earlier the infection the more serious the prognosis (though it is not always grave). Moreover, valuable conclusions may be drawn from a

comparison between the clinical data and the intensity of the reaction.

A negative reaction makes it possible to rule out a tuberculosis infection and consequently also the tuberculous nature of an affection. But there are always exceptions to be reckoned with : in the case of any recent infection, one may chance upon an ante-allergic period ; during this period it is possible that sensitiveness to tuberculin has not yet developed. In such cases the test should be repeated after an interval with a stronger dose of tuberculin.

Again, in the course of acute and grave tuberculous disease at its penultimate stage, and also when tuberculous persons are suffering from some anergising affection (influenza, measles, typhoid fever, etc.), the reaction may be negative.

The reaction to tuberculin is of real value in epidemiological investigations ; these methods afford us valuable data regarding the distribution and extent of endemic tuberculosis in the locality or region where the investigation is conducted.

DIPHTHERIA

1. Schick Test

It is possible by means of Schick's test (1912) to ascertain which persons are susceptible to diphtheria and which are not. An intradermal injection of 1/50th of the dose of diphtheria toxin fatal to guinea-pigs (M.L.D.) gives rise in the case of receptive persons to the appearance of an erythematous and sometimes inflamed zone around the injection (positive reaction). This reaction is negative in the case of immune persons whose blood contains at least 1/30th of an antitoxin unit per cc. This quantity of antitoxin is sufficient to protect a person from infection.

To carry out this test, a graduated syringe of a capacity of 1 cc., with a stopcock and a fine needle (1.5-2 cm.) of stainless steel with a short bevel, is used ; *the toxin is*

Positive Schick Test:
Upper—after 3 days (72 hours).
Lower—after 14 days.

diluted with GLENNY'S fluid[1] (1/50 of the M.L.D. for a guinea-pig per 0.2 cc.) and *a control dilution of the same toxin*, inactivated by heating to 149°F. (65°C.) for half-an-hour, is prepared. The dilutions of toxin, if kept cool and away from the light, may be used for 30 days.

Technique. Disinfection of skin (inside of forearm) with alcohol-ether; intradermal injection (bevel of the needle uppermost) of 0.2 cc. of the inactivated control dilution of toxin in the left forearm and injection of 0.2 cc. of the dilution of toxin in the right forearm.

First reading of the test, 48 hours later:

(a) A *negative* reaction, characterised by absence of erythema on both forearms, is evidence of the immunity of the person.

(b) A *positive* reaction on the right forearm (injected with toxin) and an absence of reaction on the left forearm (injected with heated toxin) indicate that the person is receptive to diphtheria. The intensity of the reaction is usually indicated and recorded as follows:

A reaction in the form of a rosette with a diameter exceeding 20 mm. is designated by +++;

A reaction 20 mm. in diameter, but without the rosette, is indicated by ++;

A reaction of 12 mm. in diameter by +;

And, a reaction of less than 10 mm. by ±.

(*Medical Research Council*, 1923.)

(c) A *pseudo-reaction* due to protein sensitisation will appear on *both* arms.

There are some persons who, for the first 24-48 hours, react similarly to both the heated and the active toxins; this reaction is known as a "*pseudo-reaction*". It is proteinic in character; it represents the sensitiveness of the body to bacterial proteins. Pseudo-reactions may be met with among persons receptive to diphtheria as well as

[1] 1.5 gm. of a powder composed of: 57 gm. of crystals of biborate of soda, 84 gm. of boric acid and 99 gm. of NaCl well mixed in a mortar are dissolved in 100 cc. of twice-distilled sterilised water. This solution constitutes a buffer fluid with a pH 8.2-8.4.

among those who are not. In order to differentiate those who are in reality susceptible from those who are not, the reactions must be observed a second time 4 to 6 days later; if the reaction phenomena diminish in intensity or disappear on both arms alike, the test is *doubtful.* If the reaction to the toxin persists after 4 to 6 days, whereas the control reaction (to the inactivated toxin) has very much decreased or has disappeared after this lapse of time, the test is regarded as *positive.*

In the case of a *doubtful reaction,* the titration of the antitoxin in the circulating blood can alone indicate with certainty whether the subject is receptive or not.

Avoid performing the Schick test on persons who have within the last few days been injected with normal horse serum (since the horse's blood may contain diphtheria antitoxin) or still more on those who have received anti-diphtheria serum. The circulating antitoxin, by its neutralising action, will cause a false negative reaction. The Schick test constitutes an effective means of checking the efficacy of anti-diphtheria vaccination.

2. Moloney Test

It has been observed in the course of vaccinations with diphtheria anatoxin that adults often show strong local and general reactions, whereas young children do not do so. These reactions are due to the sensitisation of the body of an adult with proteins of the diphtheria bacillus which it harbours either in a latent condition or as the result of a previous diphtheria infection.

In order to ascertain whether this allergic condition is present, Moloney recommends the following test: 0.2 cc. of a 10% dilution of anatoxin in saline solution is injected under the skin of the arm. If, after 2 or 3 days, the local reaction is less than 1 cm. in diameter, the reaction may be regarded as *negative* and vaccination with the recommended doses of anatoxin may be proceeded with. If the local reaction is more intense and is accompanied by general symptoms (extensive inflammation of the arm, a temperature reaching 102°F. (39°C.), etc.) the test must be regarded

Positive Dick Test
after 24 hours.

as *positive* and vaccination must be proceeded with by fractional doses of anatoxin : 0.1, 0.2, 0.3 cc. of 10 or 5% dilutions of anatoxin.

SCARLET FEVER

1. Dick Test

G. & Gl. Dick (1923) recommend the employment of the test bearing their name for epidemiological investigations in regard to scarlet fever. Persons susceptible to scarlet fever show a characteristic erythematous reaction at the place where a given quantity (S.T.D.) of the toxin of hæmolytic streptococci, isolated from scarlet-fever patients, is injected into the dermis. The toxin is obtained by the filtration of 5 to 6 days cultures in bouillon. Each toxin is then titrated by intradermal reaction; the titre of the toxin is expressed in terms of the *skin test dosis* (S.T.D.).

The toxin is diluted so that 0.2 cc. contains *one S.T.D.* Dilutions of the toxin in buffered solution are no longer effective after 30 days.

The test is carried out with a graduated syringe of a capacity of 1 cc. and a needle with a short bevel. The injection—which must be strictly intradermal—of 0.2 cc. of the toxin (1 S.T.D.) is generally carried out on the inner surface of the right forearm ; a control injection with the same dose of inactivated toxin (0.2 cc.) heated for *3 hours to 212°F. (100°C.)* is administered on the inner surface of the left forearm.

The reactions make their appearance 6 to 8 hours after the injection and persist for from 24 to 48 hours. A pigmented zone, sometimes followed by desquamation, marks the area of the reaction.

The reaction is observed after an interval of 12 to 24 hours.

(a) A *positive reaction* is characterised by an erythematous patch of more than 1 cm. in diameter at the place of injection of the toxin and an absence of reaction at the

place of injection of the inactivated toxin. The intensity of the positive reaction is expressed as follows :

(+) 10-19 mm. in diameter.
(++) 20-29 mm.
(+++) 30 mm. and more in diameter.

(b) A *negative reaction* shows no alteration of the skin at the places of injection.

(c) A *combined positive reaction* shows a distinctly greater reaction to the active toxin than to the heated (control) toxin.

2. The Schultz-Charlton Extinction Phenomenon

These authorities in 1918 advocated the following method of diagnosis for distinguishing the scarlet-fever rash from other toxic rashes resembling it. Patients are given an intradermal injection of 0.2 cc. of undiluted serum of a scarlet-fever convalescent or of a 1 : 10 dilution of anti-toxic horse serum. Failing convalescent serum, the normal serum of an adult may be used. Six to eight hours afterwards, the *scarlet-fever rash* fades around the injection. The phenomenon does not occur if the toxic rash is of another kind.

The results of this test are more distinct during the first days of the disease. This *extinction phenomenon* is, in the view of the originators of the method, to be explained by a local neutralisation of the scarlet-fever toxin producing the rash by the antitoxin contained in the serum used.

BRUCELLOSIS

Burnet Test

We are indebted to Etienne Burnet (1922) for the experimental bases of this test. After injecting 2 drops of a suspension of *Brucella melitensis* into the dermis of a convalescent from Malta fever, the author observed the appearance of characteristic phenomena, both local and general. In his subsequent experiments, in order to avoid

the general phenomena, he used germs killed by heat or, better still, filtrates of macerated germs, and obtained identical results.

At the present day, for the preparation of the *antigen (brucellin)*, cultures of different types of *Brucella* in broth are macerated at 98.6°F. (37°C.) for 20 days. These cultures, which are rich in endotoxins, are then passed through a porcelain filter and placed in sealed ampoules.

To carry out the test, 0.05 cc. (one drop) of this filtrate is injected in the dermis of the forearm and, for purposes of control (to reveal proteinic pseudo-reactions) the same quantity of peptonised broth.

If the reaction is positive, 6 to 8 hours after the injection, a reddish œdematous patch is observed; this is slightly painful and persists for 48 hours.

The reaction is *specific*. It begins to become positive from the first days of the disease and remains so for its whole duration and even long after recovery, thus permitting a retrospective diagnosis. It is also very sensitive and enables not only slight cases, but also latent infections, which are somewhat common in these diseases, to be diagnosed.

Taylor, Lisbonne, Vidal & Hazemann have adopted as an antigen, a nucleo-protein, an extract of *Brucella suis* standardised by dilution in a saline solution, slightly alkalinised, so that a test dose of 0.1 cc. contains 0.008 mgm. of nitrogen.

TULAREMIA

Foshay Test

An *intradermal test* carried out by means of a suspension of *Pasteurella tularensis*, advocated by Wherry in 1917, could not be adopted in practice owing to the severe reactions (local ulcerations and necroses, and alarming general symptoms) which accompanied it. We are indebted to Foshay (1932) for a technique which, by detoxifying the germs without depriving them of their antigenic property, has brought this method into current use.

In practice, 0.01 cc. of a suspension of 1,000,000,000

germs per cc. detoxified by the action of nitrous acid, is injected into the dermis of the forearm with the usual precautions. Two days later, a papule, which is sometimes erythematous, with a hard and pale centre and a diameter of 5-6 cm., is observed in patients with this disease. The reaction may persist for 5 days and leave a pigmentation of the skin.

The reaction is observable at an early stage. It begins to become positive as from the 4th day of the disease and persists for more than a year.

In Japan, Ohara has obtained similar results with a suspension of less toxigenic germs killed by heat.

In the U.S.S.R., Volpertz has applied the skin-test with good results with a suspension of *P. tularensis* of 2,000,000,000 per cc. in 3% glycerol, heated for 1 hour to 140°F. (60°C.).

A small superficial scarification is made on the skin of the forearm through 2 drops of this antigen. If the reaction is positive, a local hyperæmia, followed some days later by pigmentation and desquamation, will be observed.

SOFT CHANCRE

Ito-Reenstierna Test

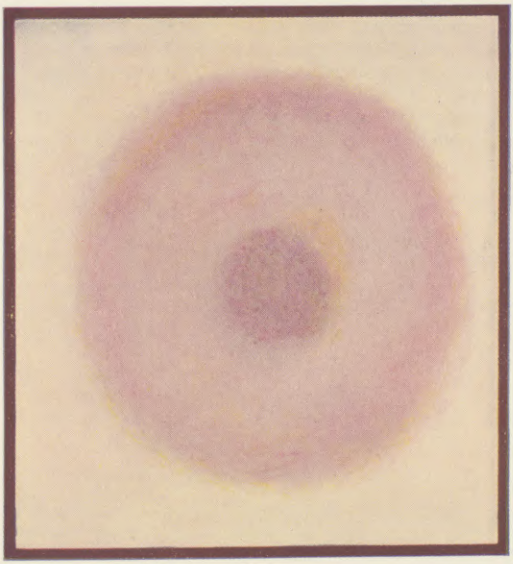
In 1913, Ito showed that an intradermal injection of some drops of a suspension of Ducrey's bacilli caused a local reaction in patients suffering from soft chancre. Ten years later, Reenstierna repeated Ito's experiments and perfected the technique of the intradermal test.

In practice, 0.2 cc. of a suspension of *Hemophilus ducreyi* in a 0.5% phenolated saline solution is injected into the thickness of the dermis with the usual precautions.

After 24 hours, in cases where the test is positive, an erythematous zone will be observed at the point of injection and, the next day, an œdematous patch with, in the centre, a papule which may become a pustule. The reaction persists for about 10 days.

Only reactions the diameter of which exceeds 10 mm. are regarded as positive.

The reaction is specific, very sensitive and begins to become positive about the 8th day of the disease. It remains



Positive Frei Test
after 48 hours.
(Maculo-papular reaction).

positive for more than 10 years after recovery, thus permitting retrospective diagnosis.

The antigen may be replaced by the same quantity of "*Dmelcos*" vaccine ; the reactions are the same.

Teissier, Reilly & Rivalier employ as antigen "*streptobacillin*", an aqueous extract of dried streptobacilli, pulverised after the addition of sea salt, obtained after a contact of 24 hours by centrifuging.

Nicolau & Banci, in their experiments, have used as antigen, "*ducreine*", a toxin obtained from Ducrey's bacilli cultivated in a special liquid medium, macerated for 5 days at laboratory temperature and filtered through a L3 Chamberland filter. Before use, the toxin is tyndalised at 133°F. (56°C.).

PORADENITIS
(Lymphogranuloma inguinale)

Frei Test

Poradenitis is sometimes difficult to diagnose. In 1925, Frei introduced into medical practice a method of diagnosis based on the allergic reaction of the skin of patients, following on an intradermal injection *of a dilution of inactivated pus* extracted from an unbroken lymphogranulomatous suppurating lymph gland. The pus obtained by aseptic puncture, is diluted to 1 : 5 on three successive days. The specificity of this antigen is then tested, first on poradenitis patients known to show a positive reaction, secondly, on patients suffering from other affections of the lymph glands or on healthy persons. The reaction in the case of persons in the two groups last mentioned should be negative. *Frei's intradermal test is the best method* of confirming a diagnosis of poradenitis.

Technique. A strictly intradermal injection of 0.1 to 0.2 cc. of the antigen is administered.

The reaction, which should be read 48 hours later, will be as follows :

A positive reaction is characterised by the appearance of an erythematous nodule 8-20 mm. in diameter : this is what dermatologists call the *papular form of reaction.* There are also other forms of a positive reaction : the *papulo-vesicular form,* the *pustular form,* the *suppurating form*

(the nodule develops into an abscess). The two latter forms, which are more rarely encountered, are regarded as very intense reactions.

The positive reaction persists for 8-10 days, sometimes a month or longer. After its disappearance, a slight desquamation and a permanent pigmented patch will be observed.

When the *reaction is negative*, only the mark of the puncture will be visible. *False reactions* are characterised by the appearance of an erythematous patch without infiltration or a small transitory nodule which disappears within 48 hours after the injection.

The reaction to Frei's intradermal test does not appear before the 10th day of the disease. Sometimes this interval is longer and may reach 60 days.

The allergy of the skin persists for a very long time; HELLERSTROM mentions instances of a positive reaction to Frei's test 31 years after the appearance of the first symptoms of poradenitis.

HYDATID DISEASE

CASONI TEST

Recommended by TROISIER, CASONI (1910-12), GASPERRINI (1919). It consists in the injection into the dermis of the forearm of 0.5 cc. of pure hydatic fluid, recently collected, and, as control, a weak solution of peptone.

If the reaction is *positive*, after 10 to 15 minutes, an elevated white patch (resembling nettlerash) 2 cm. in diameter appears *(immediate reaction)* and, 3 to 12 hours later, an oval erythematous patch, accompanied by œdema of the dermis *(late reaction)*.

Casoni's intradermal test is very sensitive and may be positive in 80% of cases (DEUTSCH, 1924).

Positive Frei Test
after 48 hours.
(Papular reaction, with necrotic centre.)

CHAPTER VII

PREVENTIVE VACCINATION AND VACCINE TREATMENT IN INFECTIOUS DISEASES

1. Preventive Vaccination.

Anti-typhoid and paratyphoid vaccination.
Anti-cholera vaccination.
Vaccination against plague.
Vaccination against exanthematic typhus.
Anti-diphtheria vaccination with anatoxin.
Anti-tetanus vaccination with anatoxin.
Anti-scarlet fever vaccination : with toxin and anatoxin.
Anti-tuberculosis vaccination with B.C.G. (Calmette-Guérin vaccine).
Anti-smallpox vaccination.

2. Anti-rabic Vaccination.

3. Preventive Vaccination against Measles with Immunoglobulin.

* * *

The Chinese had long employed empirical methods of preventive vaccination against infectious diseases.

In 1796, JENNER employed cowpox virus as a preventive of smallpox in man. PASTEUR (1880) laid down the scientific principles of active immunisation by conceiving the earliest methods of attenuating bacteria and viruses by means of physical agents and chemical substances. The results obtained with regard to anti-anthrax vaccination, vaccination against chicken-cholera and against rabies, constitute the experimental bases of the methods of immunisation for the prevention of infections.

Salmon & Theobald Smith (1884-1886) in America, Pfeiffer, Kolle, in Germany, etc., tried different methods of preventive immunisation by the employment of killed germs. Ferran (1885) and Haffkine, after utilising such vaccines (killed germs), found that the antigenic action of killed germs was thermostabile. The immunising properties of the thermostabile somatic antigen of bacteria are now definitely established.

General Technical Principles for the Preparation and Use of Vaccines

1. For the preparation of vaccines from strains of microbes complete in their antigenic composition, recently isolated "S" forms,[1] which have been carefully studied from the standpoint of their antigenic structure, should in general be used.

2. In the case of each microbe or virus, the adequate method of attenuation must be employed. This varies according to the species of microbe and the object in view.

3. As a rule, auto-vaccine treatment is to be preferred to stock vaccines whenever it has been possible to isolate the germ from the patient.

4. The density of the suspension of microbes, which varies according to the species of germ used, is as a rule between 50,000,000 to 1,000,000,000 germs per cc., or more.

5. The administration of the vaccine should be progressive, beginning with doses so small as to cause no reaction. The dose will be increased in accordance with the degree of local and general reaction after the last inoculation. A fresh injection of vaccine must never be administered until the reaction following upon the previous dose has disappeared.

6. The period for which vaccination is to be continued varies and depends upon the course of the infection.

[1] Smooth.

1. PREVENTIVE VACCINATION

Anti-typhoid and Paratyphoid Vaccination

The first trials of preventive vaccination against typhoid fever were carried out by Pfeiffer & Kolle (1896). In 1897, Wright demonstrated the presence of specific antibodies in the blood of vaccinated persons.

The efficacity of *mass* vaccinations, which were carried out during the Spanish-American War and the Boer War, has been amply confirmed in the course of the two world wars.

The anti-typhoid and paratyphoid vaccine generally used is a suspension of 2,000,000,000 germs (typhoid and paratyphoid bacilli) per cc. killed by heat (1 ½ hours at 136°F. (58°C.)).

Selected strains with "*Vi*", "*O*" and "*H*" antigens (virulence antigen, somatic antigen and flagellar antigen) are used for the preparation of the vaccine. It is also well to add local strains of germs recently isolated in epidemic areas.

The T.A.B. vaccine is mainly used preventively; it may also be used for vaccine treatment of typhoid fever, the dosage of course being modified.

Immunity is usually obtained after 3 subcutaneous injections of 0.5 cc., 1 cc. and 1.5 cc. at intervals of 7 days.

Post-vaccination reactions, which are more marked after the first inoculation, consist of slight inflammatory local œdema and sometimes pains which usually disappear 24 to 48 hours later. A slight general reaction (fever, fatigue) accompanies these reactions. They are usually much less intense after the last two inoculations.

The duration of immunity is about 1 year.

A single "repeat" inoculation in the case of persons previously vaccinated is necessary in regions where typhoid is endemic.

Anti-cholera Vaccination

The results of the first attempts at vaccination with living cultures of cholera vibrios (Ferran, 1885, Haffkine, 1892) were not very encouraging. Kolle (1896) for the

first time used as a vaccine a culture of cholera vibrios killed by heat. Trials on a larger scale were undertaken by MURATA in Japan (1904) and by SAVAS in Greece (1914). It was the observations of J. CANTACUZÈNE in Roumania (1913 and 1916), concerning hundreds of thousands of vaccinated persons, which by the "consistency and precision of the results, marked a definite step forward in the epidemiology and prophylaxis of cholera." (TIFFENEAU).

Method of preparation. As a rule about 20 strains of authentic cholera vibrios, which have been recently isolated and the characteristics of which (the fact that they attack hæmoglobin and ferment sugars) correspond to HEIBERG'S Group I and to GARDNER & VENKATRAMAN'S serological group I.

These strains are sown on 5% agar with a pH 8.2, the agar having previously been spread on the inner surface of flasks (with a capacity of 8 litres) and solidified by pouring cold water in the flasks. The germs vibrios are washed off with saline solution after 24 hours of incubation at 98.6°F. (37°C.). The suspension of germs is heated for 1 hour at 131°F. (55°C.). The final dilution of this suspension of germs in a 0.5% phenolated saline solution is effected in such a way as to produce a concentration of 3,000,000,000 germs to the cc.

Method of vaccination. A fairly high degree of immunity is obtained after 2 subcutaneous or intramuscular (preferably in left triceps) inoculations—1 and 2 cc. of the vaccine, administered with an interval of 5-6 days.

After the first injection, a slight local reaction with a slight rise in temperature is observed. There is no, or hardly any, reaction after the second inoculation.

This immunity lasts for about 6 months; after that it is desirable to administer a "repeat" inoculation in order to re-intensify the production of specific antibodies in persons previously vaccinated.

VACCINATION AGAINST PLAGUE

The first attempts at vaccination against plague with old cultures killed at 149°F. (65°C.) were carried out at

Bombay in 1906 by HAFFKINE. Among 151 vaccinated persons, only 2 cases of plague and no deaths were recorded, whereas, among 177 unvaccinated persons, there were 12 cases of plague and 6 deaths. The work was taken up again experimentally in various laboratories in order to ascertain the relative effectiveness of different vaccines prepared with living, attenuated, or sensitised, germs.

To simplify the mass preparation of anti-plague vaccine, a suspension of germs cultivated at 98.6°F. (37°C.) and killed by heating to 132.8°F. (56°C.) for half-an-hour, is used for preventive vaccination against plague. At this temperature, the antigens of the germ's capsules are not altered (SCHÜTZE, 1932, KURAUCHI & HOMMA, 1936).

The method of preparation used at the Cantacuzène Institute is as follows:

48-hours-old cultures on agar with a pH 7.5 at 98.6°F. (37°C.) in Roux flasks; the germs are suspended in saline solution with the aid of glass beads; the suspension of germs is heated to 132.8°F. (56°C.) for half-an-hour, and diluted with a 0.5% phenolated saline solution.

Two subcutaneous injections of 0.5 and 1 cc. respectively of this vaccine are administered with an interval of 8 days. The reactions, both general and local, are very slight.

In time of epidemic, this vaccination must be repeated every six months.

The relative failure of vaccination with killed vaccines as a means of collective prophylaxis in countries where plague is endemic, directed research towards the use of live vaccines. GIRARD & ROBIC in Madagascar, in 1932, found that a strain (E.V.), isolated from a fatal bubonic case in 1926 and subcultured monthly since then on agar, had lost its virulence for the guinea-pig whilst preserving its antigenic properties. The emulsion in saline solution of this germ has been administered with complete success to several million Malagasy.

OTTEN (1936, 1940) has also vaccinated and re-vaccinated several million inhabitants of the endemic plague zones of Java with an avirulent variant of plague bacilli obtained

by dissociation of a local virulent strain (Tjiwidej) maintained for several years in stab cultures in serum agar at 41°F. (5°C.). The quantity of germs injected, irrespective of age, corresponds to 1/50th of a two-days agar slope per cc.

Vaccination against Louse-borne, Exanthematic, Typhus Fever

For this vaccination, vaccines are employed in different countries prepared in accordance with a variety of methods based on the use of either killed germs or attenuated live germs.

Among the vaccines prepared with live attenuated germs, the most widely used are :

Blanc's virus-vaccine : Cultures of *Rickettsia mooseri* in the intestines of rat fleas *(Xenopsylla cheopis)*. The excreta, which are rich in stable virus, are kept in sealed tubes ready for use by a simple extemporised suspension in a buffer solution with a pH of 7.5 with 6.66‰ of ox bile added thereto.

A single inoculation causes a slight or latent infection and confers immunity.

Laigret's virus-vaccine : Murine virus *(Rickettsia mooseri)* cultivated *in vivo* by peritoneal inoculation of mice. The brain is pulverised with 40 cc. of yolk of egg and 12.5 gm. of anhydrous sodium phosphate. After desiccation, the Rickettsia content of the sifted powder is determined ; it is then titrated in mouse-units (the minimum quantity capable of causing paralysis in a mouse). One brain suffices to prepare 1,000 doses of vaccine of a virulence of 200 mouse-units per dose.

A single inoculation causes a slight or latent infection and confers immunity.

The vaccines prepared with killed germs are :

Weigl's vaccine. A suspension in a 0.5% carbolised saline solution of crushed intestines of lice, inoculated 8 days previously by intra-rectal injection with the classic virus.

Method of use and doses : 3 subcutaneous injections, at intervals of 3 to 6 days, of progressive doses of 25, 50 and

100 lice intestines. (Subsequently, Weigl reduced the dosage to a total of 90 lice for the normal vaccination and even less (6) for a slight transitory immunisation.) There is a normal post-vaccination reaction.

Duration of immunity about 6 months.

Cox's vaccine. A suspension of rickettsiæ cultivated in fertile yolk of egg. A 10% dilution of this suspension purified by fractional centrifugalisation and to which 0.4% of phenol and 0.1% of formalin are added constitutes the vaccine.

Method of use and doses : 3 subcutaneous injections, of one cubic centimetre each, at intervals of 7 to 10 days. " Repeat " inoculations every 4 to 6 months.

Mouse lung vaccine [1] (technique used at the Cantacuzène Institute at Bucharest).

I. *Strains of Rickettsia prowazeki :*

(a) Inoculation of a guinea-pig with blood from human typhus cases.

Those guinea-pigs which show fever (above 104°F.-40°C.) are killed between the 3rd and 4th days of the disease.

(b) Infection of lice by the anus : either with defibrinated blood of the infected guinea-pig, or with an emulsion of brain, or with a mixture of brain and defibrinated blood.

The infected lice are fed twice a day on a human being and are in the meantime kept at a temperature of 93.2°F. (34°C.). Seven to eight days after infection, the lice are crushed in a few drops of a mixture of ascitic fluid (1 part) and saline solution (4 parts).

The content in rickettsiæ of the suspension obtained is ascertained (by MACHIAVELLO'S or GIEMSA'S staining methods).

(c) The suspension of rickettsiæ (4 or 5 drops) is instilled into the nostril of white mice previously anæsthetised with a mixture of chloroform and ether. Each mouse receives the equivalent of 2 to 5 infected lice.

[1] Similar techniques are employed at the Pasteur Institutes of Paris and Algiers, for the preparation of vaccine from the lungs of rabbits (GIROUD) and sheep (SERGENT, E.) respectively.

The mice are kept under observation at room temperature. Those which die after 48 to 72 hours are examined and the content in rickettsiæ of the lung lesions is ascertained. Those lungs which are rich in rickettsiæ are crushed in the same mixture : ascitic fluid—saline solution. The suspension is administered to fresh mice by intranasal instillation and so on.

(d) After this first " mouse lung " passage, successive series of fresh mice are infected. After 3 or 4 passages, the animals show broncho-pneumonic lesions 48 to 72 hours after inoculation. The virulence of the germ is as a rule maintained in the course of the ensuing passages.

II. *Preparation of the vaccine.* The lungs of one mouse, infected as described above, are ground up with quartz in 10 cc. of saline solution containing 1/5 of ascitic fluid or human serum and formalin to a concentration of 2 °/₀₀. The suspension of rickettsiæ, having been previously controlled, is kept for 10 days in a refrigerator. Its sterility is once more controlled. The formalin is neutralised by ammonia.

In cold weather, *dog lung* vaccine is also prepared. Small dogs are infected via the trachea ; the infected animals, which are kept at 32°F. (0°C.), develop a rickettsial pneumonia similar to that of the mice. They die after 3 or 4 days. The lungs of an infected dog are ground up with quartz, and then suspended in 2,000 cc. of saline solution formalinised at 2°/₀₀.

As a rule, 1 part of mouse lung vaccine is mixed with 2 parts of dog lung vaccine.

III. *Employment of the vaccine.* The immunisation of human beings is effected by means of 3 inoculations of 0.5 cc., 1 cc. and 1.5 cc. administered subcutaneously at 5-day intervals. The post-vaccination reactions are usually slight.

The immunity conferred by this vaccination is fairly prolonged, but gradually decreases. It is therefore well, in time of epidemics and in the case of medical and auxiliary

personnel who are much exposed to mass contamination, to repeat the vaccination every 4 months.

The suspension of vaccine retains its efficacy for 12 months.

Anti-diphtheria Vaccination with Anatoxin

In 1923, Ramon succeeded in completely detoxifying diphtheria toxin by the action of formalin (3 to 4‰) maintained at a temperature of 102.2°F. (39°C.) for 3 to 4 weeks. *Diphtheria anatoxin (or formol-toxoid) prepared in this way retains its antigenic properties.* Administered to man or animals, it is harmless and confers upon them strong immunity to diphtheria within the 2 months subsequent to vaccination.

The results of many tests carried out in France, Canada and the United States led the Committee of Experts of the League of Nations Health Organisation (1931) to advocate for anti-diphtheria vaccination the use of *anatoxin*, which, in fact, constitutes the most effective vaccine for the prevention of diphtheria. Following a decision of the French Academy of Medicine, vaccination with anatoxin has become compulsory in France. The employment of this method is at the present day compulsory in most civilised countries for all children from 1 to 10 years of age.

Method of preparation. 4‰ of neutral formalin is added to a toxin, the titre of which is at least 20 antigenic units (flocculation units, Lf) per cc. The mixture is kept for 30 days at 103°-104°F. (39.5°-40°C.). Under the combined action of the formalin and heat, the toxin loses its toxicity, while retaining its antigenic properties. The absence of toxicity and the antigenic power of the anatoxin are then tested by the inoculation of guinea-pigs.

Method of vaccination. All children below 12 years and adolescents and young adults with a positive Schick test should be vaccinated as follows : a first inoculation with 0.5 cc. of anatoxin ; 3 weeks later, a second inoculation of 1 cc. ; after a further 2 weeks, a third inoculation of 1.5 cc. Adults sensitive to proteins of the diphtheria bacillus and showing a pseudo-reaction to Schick's test or a positive reaction to Moloney's test should be vaccinated at the same

intervals with small doses : 0.1 to 0.3 cc. of a 1 : 10—1 : 20 dilution of the anatoxin in saline solution.

The results of the immunisation are verified by the application of the Schick test 3 weeks after the last inoculation. The proportion of negative reactions to the test is approximately 96%.

There are practically no post-vaccinal reactions in children up to 12 years of age. About 12 to 15% of adults show reactions (local and general). The disorders observed are not at all serious and do not amount to a contra-indication, even in the case of children suffering from tuberculosis of the bones.

Indications. The greatest number of individuals susceptible to diphtheria are found among children from 1 to 6 years of age, and it is they therefore who will benefit chiefly from immunisation. Moreover, post-vaccine reactions are negligible in this age-group. Children not vaccinated while of pre-school age will be vaccinated on arrival at school. In time of epidemic, or in an endemic zone, a " *repeat* " inoculation of children previously vaccinated is advisable, as also the vaccination of adults with a positive Schick test. There is no negative phase to contra-indicate the application of this method.

In special epidemiological circumstances—enclosed epidemic foci : in boarding-schools, barracks—it is advisable to begin by protecting individuals by an antitoxin injection (1,000 A.U.) until the immunity acquired by vaccination (which begins 7 days later) has become effective.

In Roumania, anti-diphtheria vaccination is compulsory as from the age of 1 year. Children are given a " repeat " inoculation on entering school.

Purified anatoxin. Vaccination with purified anatoxin has been advocated by various authors in order to avert post-vaccination reactions and to simplify the method of vaccination (1 or 2 inoculations only). *Glenny's alum-toxoid*, obtained by precipitation with alum, is absorbed slowly. A single inoculation is said to be sufficient to produce immunity. These statements are not confirmed by all authors. Claus Jensen (1935-1937) purifies anatoxin

by means of aluminium hydrate and at the same time obtains a concentration of anatoxin. One month after a single inoculation with purified anatoxin + $Al(OH)_3$, nasal instillations with purified anatoxin (one per week for 3 weeks) are administered. Children, as well as adults, withstand the immunisation very well. The results are excellent. Trials carried out in Roumania with this method among a group between the ages of 6 and 17 with positive Schick test showed one year later 100% of negative reactions.

Contra-indications to vaccination. Febrile diseases, eruptive fevers, skin infections. Vaccination should be postponed until recovery from the disease.

Duration of immunity. Immunity acquired by vaccination continues for many years (DEBRÉ). It is well to administer a " repeat " inoculation 1 year after vaccination in order to re-stimulate the formation of the antitoxin.

Mixed vaccination. Anti-diphtheria vaccination may be administered together with anti-scarlet-fever, anti-tetanus or anti-typhoid and paratyphoid vaccination, provided that the intervals which are particularly requisite in the case of anti-diphtheria and anti-tetanus vaccination are duly observed.

Antitoxic *immunity* is favourably influenced by inflammatory reactions caused by microbic vaccines.

ANTI-TETANUS VACCINATION WITH ANATOXIN

Tetanus anatoxin is tetanus toxin detoxified by the action of formalin at 4‰ and of heat (102°-104°F.) (39°-40°C.) for 15 to 30 days. While completely atoxic, the anatoxin retains its antigenic properties. The detoxification of the anatoxin is verified by inoculating guinea-pigs or mice with large doses ; a subcutaneous injection of 10 cc. should not provoke any toxic symptoms. Its antigenic power is ascertained by flocculation in the presence of a test serum and is expressed in flocculation units (Lf).

Method of vaccination. For preventive vaccination, an anatoxin of at least 15-20 flocculation units per cc. is used. *A first subcutaneous injection of 1 cc. of anatoxin* is adminis-

tered ; 30 days later, a *second injection of 2 cc.* and 8 days later again, a *third injection of 2 cc.* Between the first two injections, the person will still display a certain receptivity. In the event of a serious wound during this period, a preventive injection of anti-tetanus serum (3,000 I.A.U.) should be administered. Immunity, which becomes effective after the second injection, is considerable after the third and lasts for from 3 to 5 years, according to RAMON. A " repeat " injection 1 to 2 years after vaccination causes the antitoxin titre of the blood to rise once more, sometimes above 20 I.A.U. per cc. (HARTLEY). The immunity acquired seems to be permanent.

In the case of serious wounds suffered by vaccinated persons, a single injection of anatoxin affords protection against infection.

Vaccination in an emergency. In the case of lacerated tetanigenous wounds, with foreign bodies contaminated with soil, dung, etc. (suffered by an unvaccinated person), is advocated the combination of vaccination with anatoxin and serum prophylaxis. Under the immediate protection afforded by the antitoxin, an active immunisation of long duration is thus secured (p. 250). Anti-tetanus vaccination does not cause any local reaction ; in very rare cases, symptoms of sensitisation (to peptones) of no gravity have been observed.

Mixed vaccination. Anti-tetanus vaccination may be combined with diphtheria anatoxin vaccination, or with vaccination with T.A.B. or another vaccine. Its immunising action is stimulated by the mixture with microbic vaccines which cause a local inflammatory reaction. We would recall that, when several vaccinations are combined, it is also essential to observe the 30-day interval between the 1st and 2nd injections of tetanus anatoxin.

In the French and Roumanian armies, combined vaccinations are systematically administered (tetanus anatoxin and T.A.B.). In children, vaccination with the tetanus and diphtheria anatoxins is combined.

Anti-scarlet-fever Vaccination

The investigations of American authors regarding the etiology of scarlet fever and the theory of G. & Gl. Dick concerning the rôle of the *streptococcus hemolyticus* in the pathogenesis of this disease constitute the bases of the methods employed for the prevention of scarlet fever by means of the toxic products of the *streptococcus hemolyticus*. At the present day, either the toxin (filtrates of cultures of the *S. hemolyticus* isolated in scarlet-fever cases) or a partially detoxified formolated toxin is used.

Vaccination with the toxin.

As a rule, children (who are very susceptible to scarlet fever) and adults showing a positive reaction to Dick's test are vaccinated (p. 207). In time of epidemic, the mass vaccination of children who have not had scarlet fever is recommended, regardless of their reaction. As a rule, 5 injections of previously titrated toxin are administered at intervals of 6-7 days.

First	injection :	100 to 200 S.T.D. (skin test doses).
Second	,,	500 to 1,000 S.T.D.
Third	,,	2,500 to 5,000 S.T.D.
Fourth	,,	8,000 to 15,000 S.T.D.
Fifth	,,	15,000 to 30,000 S.T.D.

The post-vaccination reactions consist in a local rash, slight œdema, sometimes a little fever, soreness and stiffness of the muscles, headache and, in very rare cases, a scarlet-fever-like rash.

Some persons are particularly sensitive to the toxin of the streptococcus. In such cases, the doses must be split up, the quantity being reduced to the limit of the individual's tolerance and the number of injections being increased so that a total of 80,000-120,000 S.T.D. will be administered, this quantity being necessary to ensure that vaccination is effective.

Vaccination with Anatoxin.

Preparation. Cultures of *Streptococcus hemolyticus* in Martin's bouillon (containing 2‰ of glucose and 5 to 6 days old) are filtered through Seitz E-K filters. 5‰ of

neutral formalin is added. The mixture is kept at 98.6°F. (37°C.). The (partial) detoxification of the anatoxin is controlled by administering it to persons with a positive Dick test, or to chinchilla rabbits. The post-vaccination reactions are as a rule slighter than those produced by the toxin.

Vaccination. In case of epidemic, all children below 12 years of age and adolescents with a positive Dick test should be vaccinated.

First injection : 0.5 cc.

3 weeks later, second injection : 1 cc.

2-3 weeks later again, third injection : 2 cc.

The local post-vaccinal reactions appear as a rule 8 to 12 hours after the injection and disappear in 24 hours. In a small proportion of cases, local reactions are accompanied by a general reaction (a slight rise of temperature).

Following vaccination with anatoxin, a change in the reaction to the Dick test is observed in 64% of cases (Ramon-Debré). Immunity develops slowly during the 30 days following vaccination and, according to American authorities, lasts for about 1 year.

It is advisable to administer a " repeat " injection of anatoxin 1 year after vaccination to reactivate the immunity acquired.

If indicated by local epidemiological conditions, anti-scarlet-fever vaccination may be combined with anti-diphtheria vaccination or with other vaccines, provided the intervals between injections are duly observed.

So far, the results obtained show that vaccination with the toxin is more satisfactory.

Anti-tuberculosis Vaccination with B.C.G. (Calmette-Guérin Vaccine)

Robert Koch's discovery (1891) that the inoculation of a guinea-pig, previously infected with tuberculosis, with tubercle bacilli, did not cause a progressive infection, but simply an acute local inflammation, followed by a scab which disappeared and the healing of the lesion, led to much research and experiment with regard to the possibility of immunisation against tuberculosis. From all this research

and numerous experiments with vaccination (STRAUSS: vaccination of cattle with human bacilli; KOCH (1904): vaccination of cattle with human and bovine bacilli, attenuated by prolonged cultivation in glycerinated bouillon; S. ARLOING (1906): vaccination with homogenised cultures, etc.), the fact emerges that *an animal, once tuberculised, is more or less unreceptive to a fresh inoculation with tubercle bacilli*. This resistance is greatest in the case of a tuberculous animal—*i.e.*, one infected with virulent germs producing a progressively developing disease. A less degree of resistance is conferred by inoculation with attenuated germs; finally, inoculation with killed germs imparts a very slight measure of resistance.

In 1913, CALMETTE & GUÉRIN found that a strain of bovine tubercle bacilli, cultivated on media containing ox bile, after a number of passages, had lost its virulence for cattle. At the same time, the animals inoculated with this organism had acquired an appreciable measure of resistance to inoculation with virulent germs.

Subsequent experiments on laboratory animals—guinea-pigs, rabbits, monkeys—having confirmed the innocuous character of this vaccine and its powers of immunisation, these authors, in 1921, embarked upon their first experiments in the vaccination of human beings, administering the vaccine by the mouth to new-born infants.

Encouraged by the fact that the method proved harmless and by the first satisfactory results obtained, they, and, following their example, workers in many countries, continued to apply this method and to-day several million children have been vaccinated in this way and observed for a period sufficiently long to enable the results of the method to be assessed.

From all these observations it emerges that:

1. The administration of the vaccine by the mouth and, under certain conditions, subcutaneously or intradermally, is completely innocuous for new-born infants, children, or adults free from tuberculosis.

2. Vaccination imparts an appreciable resistance to tuberculosis. Thus, tuberculosis mortality (which is very high for the first year of life—from 5 to 25% among children

living in a tuberculous environment) has been reduced among vaccinated children to one-fifth or even to one-tenth of the previous rates. Furthermore, with regard to older children up to 10 and even, according to some observers, up to 15 years of age, a much lower mortality and, more especially, a much lower morbidity rate has been noted in contaminated surroundings among vaccinated children than among unvaccinated controls.

In Roumania, where vaccination has been practised since 1926, and where over 1,500,000 children have been vaccinated, the results wholly bear out these statements.

Since the resistance imparted by vaccination is not permanent, it should be repeated at the ages of 1, 2 and 3 years. Persons who have not been vaccinated at birth and who have not in the meantime been infected and *do not therefore react to tuberculin*, may be vaccinated at any age; in that case, however, the vaccine should be administered subcutaneously or intradermally (a method which, moreover, may be applied also in the case of newborn infants). Among persons thus vaccinated, the morbidity rate, when they are exposed to contamination, is much lower than among unvaccinated controls exposed to contamination under the same conditions (HEIMBECK'S investigations concerning hospital nurses at Oslo).

The technique of vaccination. B.C.G. vaccine is a culture of living germs of bovine origin, rendered avirulent by repeated passages on bile media; it must be prepared afresh on each occasion, *as it does not keep for more than 15 days.* It is therefore impossible to accumulate stocks of it.

New-born infants should be vaccinated during the first 10 days of life.

The vaccine is administered by emptying the contents of an ampoule (0.01 gm. of germs in 2 cc. of liquid) in a spoon containing a little tepid milk (98.6°F.-37°C.), which the child is made to ingest before being fed at the breast. With regard to revaccination, this is preferably administered in the morning on an empty stomach before the first meal. A complete vaccination consists of 3 equal doses administered every two days, for instance, the 3rd, 5th and 7th days from birth. *Shake the container well before emptying.*

The ingestion of the vaccine is quite harmless ; it causes no disorders of any kind.

Subcutaneous or intradermal injection is also admissible in the case of new-born infants, but it is more particularly indicated in the case of older children and anergic (susceptible) adults for whom it is the method to be preferred. *A special suspension of vaccine* is used : " S.C. " (subcutaneous) B.C.G., as the dose to be injected must be much smaller (1/50 to 1/20 mgm.).

Administration by scarifications or punctures, a method recently introduced by ROSENTHAL, NÈGRE, WEIL-HALLÉ, is the best method for all ages. The vaccine used is the usual emulsion for administration by the mouth. A drop is placed on the skin, which has previously been cleaned with ether ; through this drop a series of 10 intersecting scarifications are made covering a surface of 0.5 to 2 cm., or alternatively 30-40 punctures with a needle ; the scarifications or punctures must penetrate well into the dermis. After 10-15 minutes, the drop of vaccine may be wiped away and a small sterilised dressing applied. After 15 to 30 days, a slight eruption of small nodules, at first pink, afterwards turning white, occurs. Reaction to tuberculin is positive after 30 to 45 days in about 90% of vaccinated persons.

B.C.G. vaccination is advisable for all new-born infants, but more especially for those living in contact with tuberculous persons. It is also desirable in the case of adolescents and young adults who have not yet been infected (with a negative reaction to tuberculin) and who are exposed to contagion. In all cases, it confers an appreciably increased resistance to tuberculosis, a fact which is borne out by a marked decrease in morbidity and mortality.

ANTI-SMALLPOX VACCINATION

We owe to Edward JENNER (1796) the introduction into medical practice of the method of immunising man against smallpox by inoculating him with lymph obtained from the pustules of calves suffering from cowpox. This was also

the first instance of the use of the method of vaccination against an infectious disease.

JENNER's discovery opened the way to PASTEUR's investigations. The latter, 80 years later (in 1880) established by experiment the basic principles of active immunisation in infections caused by bacteria and viruses.

Anti-smallpox vaccination is effected with the virus of cowpox *(vaccinia)* obtained from calves inoculated for the purpose with that virus; hence the term "vaccination" which is used generally as a synonym for "preventive immunisation". The removal of the pulp of the cowpox pustules is as a rule effected on the 5th day of the eruption. The lymph mixed with glycerine is kept for at least 2 weeks in a refrigerator at 39.2°F. (4°C.). Before use, all lymph is examined with regard to the presence of associated germs and to ascertain its specific activity, by the inoculation of rabbits.

The vaccine must be kept cool and protected from light; it should be used within 15-20 days after its receipt from the laboratory.

In hot countries, dried vaccine is used; desiccation effected under certain conditions does not diminish the activity of the virus.

Method of vaccination. As a rule, vaccination is effected in the region of the deltoid muscles or on the outer side of the thigh (girls). Sterilise the skin (without using antiseptics). A drop of lymph is placed on one to three scarifications made with a lancet; the scarifications, 2 mm. apart, must penetrate only the epidermis (the scarified skin must not bleed). The inoculated surface is left for a few moments to dry. It need not be protected by a dressing except in surroundings particularly favourable to an infection.

The first anti-smallpox vaccination of children is usually effected 3 months or so after birth. The duration of immunity is 5 to 7 years. In time of epidemic, re-vaccination is compulsory before the expiration of this time. In Roumania, anti-smallpox vaccination is compulsory: after birth, at 7 years (on entering school) and at 21 years (calling-up of recruits for military service) (Law of 1875, amended in 1893).

Local complications may arise from an infection caused by associated germs in the vaccination lymph or on the patient's skin. Lesions due to scratching tend to promote associated infections.

General complications. Generalized vaccinia ; appearance of cowpox pustules over the whole surface of the skin, fever, headache, etc.

Cases of post-vaccinal encephalitis have been observed more particularly in countries where primary vaccination is effected later, between the ages of 7 and 21. In spite of the length of time during which vaccination has been practised, there are still problems awaiting solution.

What is the most effective method of vaccination ? The replies to the questionnaire of the International Public Health Office led to the following conclusions :

(a) Primary vaccination may be regarded as effective if there is at least one cowpox pustule at the place of inoculation.

(b) In the case of re-vaccination, the presence of several vesicles or papules, 2-3 days after vaccination, constitutes a sign of immunity.

(c) The intensity of the general reaction is not always related to the number of scarifications.

(d) On the other hand, the local reaction depends on the number and length of scarifications. The size of the pustules is in inverse proportion to their number.

(e) The presence of the cowpox virus in the blood can be demonstrated during the first 10 days of a normal vaccination. It is not found in the cerebrospinal fluid.

If the virus is found in the blood after the 10th day and if its presence is observed in the cerebrospinal fluid, the vaccination is taking an abnormal course.

(f) It is not known how long the virus remains in the organs of vaccinated persons.

(g) It has not yet been possible to establish a definite connection between the virulence of the lymph and the

degree of immunity it confers. Comparative experiments with strains of lymph of different degrees of virulence are necessary with special precautions to avoid errors occasioned by varying dilutions.

(h) The immunity acquired after vaccination is a general immunity.

(i) The duration of immunity varies in individuals and very probably in different races. No dogmatic statement is warranted. The immunity, which is evident during the first years after vaccination, appears to decrease or disappear after one or more decennia. There is no known case of a smallpox infection during the first 5 years following vaccination.

Researches undertaken in Great Britain have established the following facts :

Among persons vaccinated once, the proportion of cases of smallpox, as compared with that among unvaccinated persons, during the first 10 years following vaccination, was 1 : 150, between 10 and 14 years after vaccination 1 : 64, 15 to 20 years after 1 : 6, and from 25 to 30 years after 1 : 5 ½.

Between 30 and 35 years after vaccination, smallpox attacks vaccinated and unvaccinated persons in equal proportions.

2. VACCINATION AGAINST RABIES [1]

The application of anti-rabies treatment to persons bitten by rabid animals is possible only by reason of the relatively long period of incubation of rabies in man (p. 131).

The effectiveness of the treatment therefore depends on the date of commencement of this treatment and on the seriousness of the bite.

Following the first International Rabies Conference (1927), all the Pasteur Institutes adopted the classification of the

[1] With regard to anti-rabies vaccination, we have largely relied on : LÉPINE, P. : *Rage-Virus rabique* in : *Les ultravirus des maladies humaines* by C. Levaditi & P. Lépine, Vol. 1, 1938, pp. 395-488 ; the Rabies Conference organised by the Health Section of the L. of N. (C.H.531, 1927) ; and the [*first*] *Analytical Review of the Results of Anti-rabies Vaccination*, doc. of the L. of N. Health Organisation C.H.844, 1930 ; the subsequent reviews appeared in the *Bulletin of the Health Organisation.*

Paris Pasteur Institute with regard to categories of persons bitten in order of gravity. Another system of classification, which perhaps is better suited to most countries both in Europe and overseas, is the following, which is employed by the Pasteur Institute of Kasauli (reproduced from P. LÉPINE : " Rage-Virus rabique "—in the treatise by C. LAVADITI & P. LÉPINE, p. 475) :

Class I. — Wounds, cuts or abrasions of the skin contaminated with saliva from the rabid animal, without any actual bite.

Class II. — Superficial bites, but few in number and small, on the trunk and limbs, with the exception of the fingers.

Class III. — *(a)* All superficial bites on the fingers ; *(b)* numerous superficial bites anywhere on the body except the head and neck ; *(c)* deep but not large bites anywhere on the body except the head and neck.

Class IV. — *(a)* Deep and large or numerous bites anywhere on the body ; *(b)* all bites or scratches on the head or neck.

There are at present various systems of anti-rabies vaccination all more or less based on the original method conceived by L. PASTEUR.

The principle of Pasteur's classic method consists in the daily injection of the spinal cords of rabbits infected with rabies (the virus being fixed by passage through rabbits), attenuated by desiccation over caustic potash in the dark. Treatment is begun with the less virulent medullas and the treatment is continued with medullas of increasing virulence, concluding with the most virulent. Since 1885—the memorable date of the first application to man of anti-rabies treatment—the original method of treatment has undergone modification, though the principle remains the same.

The technique at present employed at the Paris Pasteur Institute is as follows :

" Rabbits inoculated by intra-cerebral injection with the fixed virus (Pasteur's strain) are bled to death as soon as paralysis has become generalised ; the spinal cords are at once extracted by OSHIDA'S method with a sterilised nickel

stylet inserted in the spinal canal, after the latter has been cut transversely at the two extremities. After extraction, the spinal cords, cut into 2 or 3 sections, are hung by a sterilised thread in Pasteur flasks, the bottom of which is filled with caustic potash. The medullas are dried in a drying-room kept at 71.6°-73.4°F. (22°-23°C.). The cords are thus subjected to attenuation for 2 to 4 days ; they are then fixed at the desired stage by immersion in glycerine and kept in the refrigerator. The cords can be used for fifteen days.

" Persons who have been bitten receive daily a subcutaneous injection of 3 to 4 mm. of cord thoroughly ground in 3 cc. of sterilised water.

		3 cc. (4 mm.) of medulla					3 cc. (4 mm.) of medulla
" *(a)*	1st day	4 days old			14th day	3 days old	
	2nd »	4 » »			15th »	2 » »	
	3rd »	4 » »		*(b)*	16th »	3 » »	
	4th »	4 » »			17th »	3 » »	
	5th »	3 » »			18th »	2 » »	
	6th »	3 » »		*(c)*	19th »	3 » »	
	7th »	4 » »			20th »	2 » »	
	8th »	3 » »		*(d)*	21st »	2 » »	
	9th »	2 » »			22nd »	2 » »	
	10th »	3 » »			23rd »	2 » »	
	11th »	3 » »			24th »	2 » »	
	12th »	2 » »			25th »	2 » »	
	13th »	3 » »					

" The treatment is stopped on the 15th day in mild cases (mere suspicion of contamination or scratches) ; on the 18th day (normal cases) or on the 21st day when there are aggravating factors (bites on bare skin, delay in commencement of treatment, etc.) : the full period of 25 days is reserved for serious cases (deep or numerous bites on uncovered surfaces, bites on the face, a delay of several days in commencement of treatment)."

HÖGYES' *method*. Another method also based on the use of the fixed live virus is HÖGYES' dilution method. It consists

in the use of dilutions of the fixed virus. A virulent emulsion is diluted to the point at which its injection no longer produces rabies. The treatment is begun with inactive dilutions (1 : 10,000—1 : 6,000) and continued with dilutions increasing in virulence until active dilutions are reached (1 : 5,000, 1 : 4,000, 1 : 3,000 .... 1 : 100).

The BABEŞ-PUSCARIU *method.* Emulsions of heated fixed virus.

* * *

A second group of methods consists in the use of fixed virus modified by the addition of chemical substances.

Phenol: FERMI, PUNTONI, SEMPLE, MULFORD.
Ether: REMLINGER, ALIVISATOS, HEMPT.
Formalin: E. PLANTUREUX.
Formalin and phenol: CUMMING.

The methods based on the employment of a fixed virus modified by these chemical substances (especially phenol and ether) in general present the advantage of enabling anti-rabies treatment to be decentralised, since they put at the disposal of doctors a vaccine which can be kept for 2 to 3 months and therefore make possible an immediate application of the treatment to bitten persons remote from the centres of anti-rabies treatment.

3. PREVENTIVE VACCINATION AGAINST MEASLES WITH IMMUNO-GLOBULIN

The difficulties of obtaining large quantities of the serum of measles convalescents led MACKHANN & CHU to use the anti-infectious properties of an extract of globulins from human placenta, since it is well known that new-born infants enjoy effective protection against infectious diseases for the first six months of life.

The extraction of globulins from the human placenta is effected with a 4% saline solution (FREUND).

As a rule, a single intramuscular injection of globulin is administered as soon as possible after contact with a case

of measles. The doses of globulin vary from 3 to 10 cc., according to age, probability of contagion and living conditions.

An injection given during the first two days of the incubation period protects about 64% of children against measles; the remainder may present very slight clinical forms.

If the injection is given between the 5th and 11th days of incubation, the protection against infection is probably less.

After the appearance of the rash, the preventive value is nil.

The preventive efficiency of immuno-globulin, though less than that of convalescent serum, is greater than that of normal adult serum.

The passive immunity acquired after inoculation with immuno-globulin lasts for about three weeks. There is no objection to repeating the dose; immuno-globulin does not induce sensitisation and does not produce allergy.

According to American statistics, local reactions are observable in 5% of cases, a moderate fever in 19% and a high fever (above 102°F. (39° C.)) in 3% of cases.

Indications. Administer the immuno-globulin immediately after the appearance of the first case of measles to all children in the same institution who have not yet had the disease.

Vaccination with immuno-globulin is indispensable in time of epidemic in children's hospitals, crèches, kindergartens, orphanages, etc.

Children below 3 years of age should be inoculated first. Children who have been inoculated with immuno-globulin and who nevertheless develop the disease are just as contagious as those who have not been so inoculated.

4. VACCINE TREATMENT

Vaccines against:

Staphylococcus	**(polyvalent vaccine).**
"	**(anatoxin).**
Streptococcus	**(polyvalent vaccine).**
Pneumococcus	**(polyvalent vaccine).**
Meningococcus	**(polyvalent vaccine).**
Gonococcus	**(polyvalent vaccine).**
H. pertussis	
B. coli	**(polyvalent vaccine).**
Influenza	**(tetra-vaccine).**

* * *

The current practice in vaccine treatment is as a rule to employ a polyvalent stock vaccine. Whenever it is possible to isolate the microbic strain which has infected the patient, it is better to use an auto-vaccine prepared in a similar manner. On the other hand, it is well to combine a stock vaccine with the auto-vaccine when the germ isolated from the patient shows weak antigenic properties.

Infra-reactional doses of the vaccine must always be given; the duration of the vaccine treatment will be dictated by the course of the infection.

* * *

Anti-staphylococcus polyvalent vaccine is a suspension of staphylococci, 1,000,000,000 germs per 1 cc., killed by heat. As a rule, 10 to 20 inoculations are given at intervals of 2 to 4 days, beginning with 0.1-0.2 cc. or even less, according to the intensity of the local and general reactions.

This vaccine is used in cases of carbuncle, acne, sycosis, hydroadenosis, mastitis, whitlow, chalazion, pyodermitis, osteomyelitis, purulent otitis media, etc., and in all other staphylococcus infections.

Staphylococcus anatoxin is the staphylococcus toxin detoxified by the action of formalin (5°/₀₀) at a temperature (100.4°F.-38°C.—for 25 to 30 days).

As a result of the modifications undergone, the toxin loses its hæmolytic and necrotic properties, likewise its lethal toxic effects on rabbits and guinea-pigs : 3 to 4 cc. of the anatoxin injected intravenously should not kill a rabbit.

On the other hand, the anatoxin retains its antigenic properties and, accordingly, its power of immunisation against the staphylococcus and its toxic products. The immunising action of the anatoxin is more rapid and effective than that of the antistaphylococcus vaccine.

In staphylococcus infections, an injection of anatoxin is given every 3-4 days, beginning with a dose of 0.1-0.2 cc. The doses are gradually increased with due regard to the intensity of local and general post-vaccination reactions (pain, œdema, redness, temperature, soreness and stiffness of the muscles, irritation of the kidneys). If the reactions are too severe, the injections must be suspended and resumed when these symptoms have disappeared.

Some patients are particularly sensitive to this anatoxin ; they display local symptoms and an intense general reaction. In such cases, the doses must be reduced, the injections given at longer intervals or even definitely stopped altogether if intolerance is extreme. If the anatoxin is borne well, the doses may be gradually increased to 0.6, 0.8 and even 1 cc. or more.

The indications for treatment with anatoxin are the same as those for antistaphylococcus vaccine.

If the results are unsatisfactory and if relapses occur, it is advisable to supplement the treatment with autovaccine or with a stock vaccine (alternate injections of half-doses).

In cases of staphylococcus septicæmia, it is desirable to combine vaccine treatment (with either anatoxin or vaccine) with serum treatment ; the antitoxic action of the serum will be reinforced by active immunisation.

The practitioner should devote special attention to those patients with lesions of the heart, liver or kidneys, whose infectious condition call for vaccine treatment.

Anti-streptococcus polyvalent vaccine is a suspension of streptococci of various origins, killed by heat, in normal saline. The density of the suspension is 1,000,000,000 germs per cc.

Indications : erysipelas, arthritis, streptococcus abscess and pleurisy and other infections due to this germ.

Vaccine treatment combined with serum treatment in streptococcus septicæmia and puerperal fever.

Ten to twenty inoculations, at intervals of 2 to 4 days, with gradually increased doses of vaccine are administered, beginning with a dose of 0.1-0.2 cc.

Anti-pneumococcus polyvalent vaccine is a suspension of pneumococci of different serological types (types I, II, III, etc.), killed by heat, in normal saline. The density of the vaccine is 1,000,000,000 germs per cc.

Indications : Complications of pneumonia and broncho-pneumonia, arthritis, otitis, conjunctivitis, tonsillitis, pneumococcus peritonitis.

As a rule 12 to 20 successive inoculations are administered at intervals of 2-4 days, beginning with a dose of 0.2 to 0.5 cc.

Anti-meningococcus polyvalent vaccine is a suspension of meningococci (A, B, C, D, or types I, II, III and IV), killed at 130.8°F. (56°C.). The density of the suspension is 1,000,000,000 germs per cc.

Indications : The vaccine is used in cerebrospinal meningitis in combination with serum treatment and sulphonamides, particularly in prolonged forms of the disease, such as meningococcus septicæmia followed by complications in other organs or tissues.

Anti-gonococcus polyvalent vaccine is a suspension of different strains of gonococci in normal saline ; the density of the suspension is 1,000,000,000 germs per cc.

Indications : All forms of gonococcus infection and its complications—acute or chronic urethritis, orchiepididymitis, cystitis, pyelitis, vulvo-vaginitis, metritis and salpingo-ovaritis, ophthalmia, etc.—may be treated with vaccine.

As a rule, 10-12 inoculations are administered at intervals of 2-4 days, beginning with a dose of 0.1-0.2 cc.

Anti-whooping-cough vaccine contains per cc. 500,000,000 *Pasteurellae pertussis* (Bordet-Gengou) of serological type I, killed by formalin.

As a rule, whooping-cough patients are given 10-20 inoculations or more of 1 cc., regardless of the age of the patient. The vaccine is given daily or every other day, until the patient improves.

Anti-B. coli polyvalent vaccine contains 1,000,000,000 germs per cc. made up of many strains of different origin; the suspension of microbes in normal saline is heated for 1 hour to 138°F. (59°C.).

Indications: Enterocolitis, angio-cholecystitis, cystitis, colibacilluria, etc.; in combination with serum treatment in cases of colibacillæmia.

The treatment generally consists of a series of 10-15 injections.

Anti-influenza tetravaccine. In the course of an influenza infection (due to a filter-passing virus), associated infections, caused by the germs common in the respiratory passages (streptococci, pneumococci, Pfeiffer's coccobacilli, etc.), are common.

It is these associated germs which are responsible for the complications—veritable secondary infections—the gravity of which exceeds that of the disease due to the specific virus. The streptococcus is the most commonly found of these germs, then comes the pneumococcus, Pfeiffer's coccobacillus and, lastly, the *Micrococcus catarrhalis*.

Anti-influenza tetravaccine is a suspension in normal saline of germs killed by heat belonging to these four microbic species. The density of the vaccine is 2,000,000,000 germs per cc.

As a rule, an injection of the vaccine is given every 2 to 4 days, beginning with a dose of 0.1-0.2 cc. and the dose is gradually increased with due regard to post-vaccination reactions.

Indications : Preventive vaccination in influenza epidemic areas ; vaccine treatment of complications due to the above-mentioned germs.

* * *

5. MICROBIC FILTRATES

(Polymicrobic bouillon-vaccine, shock treatment.)

Certain microbic infections are amenable to a local treatment with culture filtrates (streptococci, staphylococci, etc.) usually introduced into suppurating wounds.

Particularly in genital infections of women, polymicrobic bouillon-vaccine (staphylococcus, streptococcus, B. pyocyaneus) is given by subcutaneous injection with good results. In the same infections, protein treatment (injection of milk, peptone, etc.), is also employed.

Shock treatment is a recognised therapeutic measure of use in chronic affections, whether of infectious or other origin. In this category are malaria therapy (artificial malaria infection), protein treatment (milk and its derivatives), albumoses and peptones, sodium nucleinate ; suspensions of microbes killed by heat (microbic vaccines, especially T.A.B.), " Omnadin ", colloidal salts, autohemotherapy, etc.

It is generally agreed that the physiological process consists in the stimulation of the body's normal non-specific means of defence.

6. SPECIFIC TREATMENT OF TUBERCULOSIS

Since the first trials of serum treatment for tuberculosis undertaken by Richet & Héricourt (1888), many methods for the preparation of an anti-tuberculosis serum have been proposed, the best known of which are the sera of Maragliano (1895), Marmorek (1913), Vallée (1909), Bruschettini (1913), Jousset (1918), etc. Hitherto, however, serum treatment has not fulfilled the hopes placed

in it (G. CALMETTE) and some authorities now employ it only quite exceptionally (JOUSSET).

Certain methods akin to vaccine treatment, such as treatment with tuberculin, methylic antigen and other similar preparations, play a relatively prominent part in the treatment of tuberculosis.

Tuberculin, which was discovered by R. KOCH in 1891, was recommended by its discoverer for the treatment of tuberculosis. The doses then administered caused serious accidents. The method in the original form advocated by Koch was abandoned for a time. Later, very small gradually increasing doses of tuberculin were given, thus accustoming the body to the remedy, a process of desensitisation.

Below is given the programme of a treatment with tuberculin as indicated by JACQUEROD :

The unpurified tuberculin (Koch's A.T.) is used. *The first dilution of 1 : 100,000* is injected beginning with 0.1 cc., the dose being increased by 0.1 cc. at each injection until it reaches 1 cc.

Then the *second dilution of 1 : 10,000* is administered, proceeding in the same manner and the treatment is continued with stronger and stronger concentrations : 1 : 1,000 ; 1 : 100 ; 1 : 10 and finally with pure tuberculin. Some authorities advocate beginning the treatment with a *dilution of 1 : 1,000,000*

The injections are given subcutaneously at intervals of two or three days. They should never cause a marked rise of temperature. If, following an injection, the temperature should rise by some tenths of a degree, the interval between the injections must be extended and a fresh start made with a dose of the same quantity as that last administered.

Tuberculin treatment should never be applied except to patients without fever, with localised, quiescent or chronic lesions, with a tendency to fibrosis. Apart from tuberculosis of the lungs, the forms of tuberculosis which benefit from tuberculin treatment are chiefly non-pulmonary localised forms, tuberculosis of the bones, the lymph glands, the joints, the skin or the eyes.

Rest cure must be strictly enforced during the tuberculin treatment.

Methylic antigen treatment was introduced by BOQUET & NÈGRE (1927); they utilise the antigenic action of a methylic extract of bacillary bodies, the soluble lipoids of which have previously been extracted by acetone. The action of the methylic antigen differs from that of tuberculin in that there is a total absence of toxicity, even for a tuberculous animal or person.

The indications respecting this treatment are the same as those for tuberculin except that since, even after large doses, local, focal and general reactions are rare, it is possible to utilise it on a wider scale and even in certain febrile forms, as for instance in tuberculous peritonitis.

Methylic antigen is prepared in two forms: diluted and pure. The treatment is begun with a 10% dilution of the antigen, doses of ¼, ½, ¾, 1 and 2 cc. being injected. The injections are given subcutaneously at intervals of 3-4 days, generally 2 per week. Next the pure antigen is administered, the doses being increased at the same rate; when the last dose, 2 cc., is reached, this may be repeated several times in succession.

As a rule, the injections are borne well and do not cause reactions; should the injection be followed by a rise in temperature or a local reaction, the intervals between injections are lengthened and the increase in the doses is slowed down.

A.O. vaccine. The Japanese workers ARIMA, AOYAMA & OHNAVA (1928) have recommended for the prophylaxis and treatment of tuberculosis A.O. vaccine, which is a suspension of tubercle bacilli of human origin, which are selected for their virulence and their antigenic properties and which, after culture on saponin media and maturing in the refrigerator, have lost their acid-fast property and virulence to such a degree that they can no longer be cultivated.

The treatment is given by subcutaneous injections, with gradually increasing doses; the indications are almost the same as for the preceding preparations.

CHAPTER VIII

TREATMENT OF INFECTIOUS DISEASES BY BACTERIOPHAGE (THE LYTIC PRINCIPLE)

The discovery of the phenomenon of the transmissible autolysis of the staphylococcus and colon bacillus (TWORT, 1915) and the demonstration of the presence of a lytic anti-Shiga-bacillus principle in the filtrate of cultures of the fæces of a dysentery convalescent (D'HÉRELLE, 1917), led to the employment, in the treatment of infectious diseases, of bacteriophages the lytic action of which on certain pathogenic germs *in vitro* promised good results.

The therapeutic action of a bacteriophage is due to its particularly complex composition; in a culture lysed by the bacteriophage there are proteins and other constituents of the culture medium, substances resulting from the autolysis of the germ (true antigen rendered soluble), *a specific lytic principle*, various products resulting from the metabolism of the germ, etc.

This complex of factors, and particularly the characteristics of the bacteriophage, must therefore be taken into account in order to apply it effectively within the limits of its therapeutic activities. The effects obtained are difficult to separate : protein shock, an immunising antigenic action, the effect of an anti-virus (BESREDKA), etc. A remarkable critical study of the voluminous data concerning treatment by phage, collected by MONROE EATON & STANHOPE BAYNE, JONES, leads to the following conclusions (which are unanimously accepted) :

(a) The action of the bacteriophage *in vitro* and its action *in vivo* are not comparable ;

(b) It has no effect in cases of septicæmia in man or in experimental septicæmias induced in animals;

(c) Its efficacity varies in local inflammatory processes and in chronic infections (with a tendency to localisations) due to the staphylococcus, the colon bacillus and, more rarely, to the typhoid and dysentery bacilli;

(d) Staphylococcus infections of the skin, suppurating wounds, cases of pyelitis, cystitis, chronic enteritis, etc., benefit by treatment with the specific bacteriophage.

METHOD OF APPLICATION

Anti-staphylococcus Bacteriophage.

Indications: staphylococcus urinary infections, infections of wounds, widespread carbuncle infection, sycosis, etc.

In urinary infections, as a rule, two subcutaneous injections of the anti-staphylococcus bacteriophage (0.5 and 1 cc.) are given at an interval of 48 hours. At the same time, dilutions of the bacteriophage (10 to 20 cc.) are introduced into the bladder. The infection is cured in 3-4 days. In the treatment of wounds, the bacteriophage should be introduced into the wound (pieces of dressing soaked with the lytic principle) and at the same time (1 cc.) injected into the surrounding tissues.

In staphylococcus infections of the skin, focal and perifocal injections of the bacteriophage are given at intervals of 24-48 hours.

Anti-colon Bacillus Bacteriophage.

Indications: pyelonephritis, prostatitis, vesiculitis, cystitis colibacilluria.

As a rule, an attempt is made to isolate the colon bacillus from the urine and to prepare a stock-bacteriophage from this strain. The bacteriophage thus obtained is administered subcutaneously (2 injections at 48 hours interval) and by instillation into the bladder (3 instillations at 5-day intervals). The bacteriophage is also administered by the mouth (3 to 5 cc. in a glass of water on an empty stomach). It is unnecessary to continue bacteriophage treatment by

subcutaneous injection for more than 3 or 4 days. By continuing the treatment in different ways, cures are obtained in 40 to 50% of cases.

Anti-dysentery Bacteriophage.

Bacterial dysentery and other dysentery-like forms of enteritis are susceptible to bacteriophage treatment. There is no contra-indication.

The administration of the lytic principle by the mouth comprises 2 to 3 doses of 5 cc. in a glass of water on an empty stomach.

A dilution of the bacteriophage may also be injected into the intestine; for this purpose a Nelaton's catheter attached to a syringe is used.

The fact that the efficacy of bacteriophage treatment of cases of infection is relatively uncertain is more than counterbalanced by the effective preventive action of the bacteriophage in epidemic foci. The results obtained by German doctors in the last is 1939-45 war are most encouraging in this respect.

Anti-typhoid Bacteriophage.

As a rule, 2 to 3 injections of 0.5, 0.5 and 1 cc. are given at 48-hour intervals.

The results obtained in the treatment of typhoid fever are somewhat dubious.

The lytic principle has also been administered by the mouth, on an empty stomach in the mornings.

CHAPTER IX

SERUM TREATMENT

A. **Antitoxic sera** against:

Diphtheria.
Scarlet fever.
Tetanus.
Staphylococcus infection.
Botulism.
Venoms.

B. **Anti-microbic sera** against:

Streptococcus infections.
Pneumococcus »
Meningococcus »
Plague.
Anthrax.

C. **Anti-microbic and anti-toxic sera** against:

Dysentery.
Colon bacillus infection.
Gangrene.
Peritonitis.
Typhoid.
Cholera.

D. **Serum against poliomyelitis.**

E. **Convalescents' sera.**

A.

Anti-diphtheria Serum and Serum Treatment.

Anti-diphtheria serum is obtained by repeated injections of a horse with filtrates, either toxic or detoxified by formalin, of cultures of the diphtheria bacillus. This serum came into general use as a result of the communication made by ROUX, MARTIN & CHAILLOU to the Budapest Congress

(1894). Anti-diphtheria serum is titrated, the titre being expressed in international antitoxic units (I.A.U.).

This serum has a strictly specific antitoxic action; the sooner it is employed after the onset of an infection the more effective it is.

Method of Use.

Preventive action (serum prophylaxis). By injecting contacts of a patient with 1,000 I.A.U.'s, a *passive immunity* can be imparted to them which lasts for 2 to 3 weeks.

Serum treatment. Anti-diphtheria serum, if injected in time and in sufficient quantities, cures the disease. The intensity of the treatment will depend on how serious a form the disease takes, how soon the treatment is begun and on the antitoxic titre of the serum. Toxic lesions already formed (owing to belated treatment) cannot be altered. Mild cases are cured by the administration of 10,000-20,000 I.A.U.'s.

In more serious cases, if the injection is administered at the outset of the disease, the dose must be increased to 50,000-100,000 I.A.U.'s or even more. The treatment during the following days will depend on the state of intoxication, the course of the fever, the pulse and the general condition of the patient. As a rule, the false membranes become detached 24 to 48 hours after the administration of an adequate dose of serum. The illness must not be regarded as over so long as the fever persists.

In cases of *diphtheritic croup*, 50,000-100,000 I.A.U.'s must be injected and the dose repeated 24 hours later if the symptoms persist.

In very serious cases and especially in cases of malignant diphtheria, it is recommended that serum should be administered by intravenous injection after the anti-anaphylactic method has first been applied (0.5 cc. of serum diluted in 4 cc. of saline solution; one hour later, 5 cc. of undiluted serum; two hours later, the bulk of the serum (p. 197).

In cases of diphtheritic paralysis, American authorities advocate strong doses of serum (100,000 I.A.U.'s, or more).

As a rule, the serum is injected subcutaneously under the skin of the abdomen, except in very grave cases, when intravenous injection is indicated.

Serum accidents (nettlerash, pains in the joints, headache, fever, etc.) of no significance make their appearance some days after the injection and generally disappear without treatment of any kind.

To produce a maximum concentration of specific antibodies in the patient, the necessary quantity of serum should be administered within a period of 48-72 hours and as nearly as possible at the very outset of the disease.

This rule applies to serum treatment in general.

Anti-scarlet-fever Serum and Serum Treatment.

In serious cases of scarlet fever (septic and hypertoxic cases), the serum used for treatment is convalescent serum (p. 266) or antitoxic serum obtained from horses immunised against the toxin of the *Streptococcus hemolyticus (erythrotoxin)*.

Antitoxic serum was brought into use as a result of the researches of American authorities, who regard the scarlet-fever syndrome as an intoxication caused by the soluble toxin of the *Streptococcus hemolyticus*.

As a rule, this serum is obtained by the immunisation of horses with the toxin from original strains—Dick NY[5] and Dochez—and with the toxin produced by strains of *Streptococcus hemolyticus* isolated from local scarlet-fever cases (regional strains).

The antitoxic action of the serum is most marked if the injection is given right at the beginning of the disease. The quantities administered vary according to the gravity of the case and the age of the patient. Normally there is no objection to injecting 50-200 cc. in one dose and repeating the dose, if need be, the following day. Children are given half the doses recommended for adults.

(*See also:* Serum treatment with convalescent sera, p. 266).

Anti-tetanic Serum and Serum Treatment.

Anti-tetanic serum is obtained by immunising horses with means of subcutaneous injections of gradually increased doses of tetanus anatoxin. As soon as a measure of immunity has been acquired, the immunisation is continued by administering the toxin (gradually increased doses).

Antitoxic serum provides a rapid means of preventing tetanus and, combined with tetanus anatoxin, affords the only specific means of treating this disease. The antitoxin content of the serum is measured (by testing on mice or guinea-pigs) and its titre is expressed in I.A.U.'s.

Serum prophylaxis. A subcutaneous injection of 3,000 units confers on the wounded an immediate passive immunity which lasts from 2 to 3 weeks. In order to create a long lasting active immunity and thus to avoid the necessity for repeating the prophylactic serum inoculation, vaccination with anatoxin should be administered at the same time.

Indications: wounds with crushed tissues, lacerated wounds, or wounds contaminated with dust or dung; wounds resulting from punctures (with rusty nails, splinters, bits of glass); war wounds; wounds containing foreign bodies; septic condition of the umbilicus in new-born infants, etc.

Special indications regarding war casualties. The experience of countries whose soldiers have been previously immunised with tetanus anatoxin suggests the following recommendations in case of wounds:

1. A single "repeat" injection: 2 cc. of anatoxin for wounded satisfactorily vaccinated beforehand and who have a simple wound.

2. Unvaccinated wounded, those whose vaccination has been incomplete or doubtful, and those with multiple, lacerated wounds containing foreign bodies, should be treated as follows:

(a) A first injection of anatoxin (1 cc.) and at the same time (in another part) an injection of antitetanic serum: 3,000 antitoxic units.

(b) 10 days later, a second injection of 3,000 I.A.U.'s.

(c) After a further 10 days, an injection of 2 cc. of anatoxin every 7-8 days ; active immunisation should be continued until the wound has healed.

(d) In the event of a new wound, only a single " repeat " injection of 2 cc. of anatoxin need be given.

Treatment of tetanus. In case of infection, the following programme should be followed :

1. A first injection of 2 cc. of anatoxin and at the same time 300,000 antitoxic units (of anti-tetanus serum) by subcutaneous or intravenous injection. The same day 10,000-30,000 I.A.U.'s (10-20 cc. of serum) should be administered by intraspinal injection.

2. After 5 days interval, 2 cc. of tetanus anatoxin.

3. Every 4-6 days, increasing doses of anatoxin (2-6 cc.). The final dose of 6 cc. of anatoxin should be repeated at the same intervals until the patient is cured.

4. Symptomatic anti-spasmodic and hypnotic remedies : subcutaneous and intravenous injections of hypertonic glucose and phosphate serum. *Avoid* injections of normal saline solution.

5. Surgical treatment of wounds is essential : removal of foreign bodies and gangrenous tissues; rigorous disinfection of wound with oxidising substances (H_2O_2-K_2MnO_4, chlorine disinfectants, etc.) ; perfect drainage of the wound.

Observation. If the patient had previously been given horse serum, BESREDKA'S anti-anaphylactic method should first be applied (p. 197).

Serum disease should be treated according to the usual methods : a milk diet, 3-6 gm. of $CaCl^2$ daily, injections of adrenalin.

Anti-staphylococcus Serum and Serum Treatment.

Anti-staphylococcus serum is obtained by immunising horses with staphylococcus anatoxin and toxin (gradually increased doses). The antitoxic value of the serum is expressed in I.A.U.'s.

Indications : Staphylococcus infections and especially threatened or confirmed staphylococcus septicæmia (positive blood culture). The antitoxic efficacy of the serum is dependent on its early administration. In view of the strictly antitoxic properties of this serum, treatment with it should be supplemented by anatoxin or an auto-vaccine, and, in some cases, both (pp. 237, 238) to stimulate active immunity.

Method of treatment.

Immediately after the confirmation of the diagnosis, a first intramuscular injection of 50 to 100 cc. of anti-staphylococcus serum should be administered. If the general condition of the patient is serious, a quantity of 40-50 cc. of the serum should be injected intravenously, after preliminary desensitisation ; the remainder of the dose being administered by intramuscular injection.

The next day 0.2 cc. of anatoxin should be injected subcutaneously.

3rd day of treatment : 100 cc. of serum subcutaneously or in the muscles.

4th day : 0.4 cc. of anatoxin or 0.2 cc. of staphylococcus vaccine.

5th day : a further quantity of 300 cc. of serum.

6th day : 0.6 cc. of anatoxin or 0.3 of vaccine.

The active immunisation should then be continued with increasing doses of anatoxin or vaccine, having due regard to post-vaccination reactions.

Children below 5 years should be given half the doses recommended for adults.

The above programme is subject to modification according to the gravity of the case and the intensity of post-vaccination reactions.

Anti-botulinus Serum and Serum Treatment.

Anti-botulinus serum (KEMPNER 1897, FORSMANN 1915, LENCHS 1910, etc.) is an antitoxic serum obtained from horses immunised with progressive doses of anatoxin and toxin of the *Cl. botulinum*, types A and B.

The polyvalent serum is a mixture of the monovalent sera A and B. The polyvalent serum can also be obtained from the same animal strongly immunised, first, against the A toxin and then, after 1 month's rest, against the B toxin.

The titre of the serum is expressed in I.A.U.'s.

Serum prophylaxis. Persons who have ingested contaminated food and who do not yet show any morbid symptoms should be given a dose of 10 cc. of serum administered by intramuscular injection.

Serum treatment. The efficacy of anti-botulinus serum is dependent on its early administration in large doses (50,000-200,000 I.A.U.'s). The administration of the serum by intravenous injection should be continued on ensuing days until the toxic symptoms disappear.

Anti-venom Serum and Serum Treatment.

CALMETTE (1892-1894) demonstrated the antigenic properties of snake venom by immunising horses against it. The serum obtained has active qualities. The venoms of different species of snakes have specific antigenic properties : an anti-cobra serum, for instance, exercises an intense neutralising effect on cobra venom ; but its action is much less against other venoms (*e.g.*, that of the viper).

In Europe, anti-viper serum is generally used owing to the frequency of viper bites (*Vipera berus, V. ammodytes, V. renardi, V. ursini*).

Method of use : Anti-venom serum, which is employed solely for *curative purposes,* must be administered immediately after the bite. If this is done, the definite neutralising effect of the anti-venom is clearly apparent. In this connection, we would recall the rapidity with which intoxication due to snake venom develops.

If the administration of serum is delayed for some hours, at least 20 cc. of serum must be injected into a vein, after having desensitised the body by means of fractional doses of diluted serum (p. 197).

Indications in case of snake-bite. Immediately after the bite, a tourniquet should be applied above and quite close to the bite. The pressure should be maintained for half-anhour ; the wound should be allowed to bleed and washed copiously with water. A dressing with chloride of lime (2%) or gold chloride (1%) should be applied.

Avoid cauterisation of the wound.

B.

Anti-streptococcus Serum and Serum Treatment.

Polyvalent anti-streptococcus serum is prepared by immunising horses against the most varied strains recently isolated in streptococcus infections (without passage through laboratory animals). The strains are continually renewed as fresh ones are isolated.

Indications : Infections due to streptococci : erysipelas, puerperal fever, streptococcus septicæmia, streptococcus pemphigus ; streptococcus complications of scarlet fever.

Method of use : In general, the injection of strong doses—100-200 cc. daily in the case of adults—is recommended, the dose to be repeated daily until improvement results. Children are give smaller quantities according to age. In cases of septicæmia, the diluted serum should be given intravenously : 80-100 cc. in 300 cc. of normal saline. The injection should be given very slowly, the body having first been desensitised (p. 197) and a subcutaneous injection of serum administered.

In meningeal streptococcal complications, 15 to 40 cc. serum may also be injected by lumbar puncture, after an equal quantity of cerebrospinal fluid has first been extracted.

The efficacity of anti-streptococcus serum treatment (practised in Roumania for nearly forty years) depends upon the promptitude and intensity of its administration ; within 48 hours there should be a fall in the temperature and an improvement in the patient's general condition.

It is essential that sulphonamides should be combined with anti-streptococcus serum treatment (p. 282).

Anti-pneumococcus Serum and Serum Treatment.

The polyvalent serum is a mixture of monovalent sera of types I, II and III, obtained by the immunisation of horses with strains isolated from various pneumococcus infections—lobar pneumonia, broncho-pneumonia, pleurisy, meningitis, pneumococcal septicæmia, etc.

Indications : All the pneumococcus infections above mentioned.

The efficacity of the serum, which varies in different cases, depends first of all on the possibility of using a specific serum—*i.e.*, one corresponding to the type of pneumococcus to which the infection is due.

In the absence of a monospecific serum, the polyvalent serum must be used.

The satisfactory results of anti-pneumococcus serum treatment have been reported by many authorities : F. & F. KLEMPERER, EYRE WASHBURN, NEUFELD & HÄNDEL, AVERY, CHICKERING, COLE, DOCHEZ, M. NICOLLE & TRUCHE, etc.

Method of use : In cases of pneumonia, 80-100 cc. of serum must be injected and the dose repeated on ensuing days.

Intra-pleural injection is used in cases of meta-pneumonic pleurisy, after having extracted the pus and washed out the pleural cavity with normal saline.

The operation should be repeated several days running until the fever has subsided and the local symptoms have improved.

In cases of pneumococcus meningitis, intraspinal injections of the serum (30 to 40 cc. for an adult, 15-20 cc. for a child) should also be administered, 80-100 cc. being also given by intramuscular injection. It is essential that sulphonamides should be combined with serum treatment (p. 283).

Anti-meningococcus Serum and Serum Treatment.

Anti-meningococcus polyvalent serum is composed of : (1) monovalent sera obtained from horses immunised respectively with types A, B, C and D ; (2) a polyvalent

serum obtained by injecting horses with atypical local strains.

The immunisation of horses is effected by the method of M. Amos & M. Wollstein.

The potency of the sera is assessed by the agglutinin reaction, complement fixation and the presence of bacteriotropins.

Anti-meningococcus serum is usually inactivated at 130.8°F. (56°C.) ; no antiseptic substances should be added.

Indications : Epidemic cerebrospinal meningitis and its complications.

Method of use : Intraspinal injections of the serum (30-45 cc. for an adult, 10-20 cc. for a child) are essential. As a rule, these injections are continued daily until the symptoms have disappeared, the cytological characteristics of the cerebrospinal fluid have been modified and the germs have disappeared therefrom (absence of meningococci, tendency to mononucleosis). Each fresh injection is preceded by a physical and cytological examination of the fluid, in order to avoid the danger of serum meningitis. Control punctures should be continued even after the cerebrospinal fluid has become clear ; the treatment should be resumed if the fluid again becomes cloudy and if the meningococcus reappears.

It is essential that the serum should be administered simultaneously by intramuscular and intravenous injection, particularly in cases of meningococcæmia or in order to prevent this complication.

In those cases of meningitis where the normal flow of the cerebrospinal fluid is impeded by adhesions, the serum can be administered in other parts of the spinal canal (dorsal region, cervical region, etc.).

In *meningo-ventriculitis*, the serum may be introduced directly into the lateral ventricle, by puncture at the external angle of the fontanel (still open in the case of infants). In the case of adults, trepanation is necessary 3 cm. in front of the bregma and 3 cm. away from the middle line.

In cases of meningococcæmia, intravenous and intramuscular serum treatment should be combined.

Local applications of the serum will be made in all local complications : ulcer of the cornea, iridocyclitis, arthritis, etc.

Sulphonamide treatment should be combined with serum treatment (p. 283).

Anti-plague Serum and Serum Treatment.

YERSIN, ROUX & BORREL (1896) were the first to immunise a horse against plague, by inoculating it first with killed cultures and afterwards with live cultures of the germ. The serum thus obtained exercised a definitely protective effect in mice experimentally infected. On the other hand, the results of serum treatment in human cases of plague were not very encouraging.

In a plague epidemic at Nhatrang, the fatality rate was 73% among patients inoculated with the serum and 100% among untreated patients (YERSIN, 1899). Official investigations conducted during the ensuing years with regard to the use of anti-plague serum did not lead to any more encouraging conclusions.

Sulphonamide treatment in combination with serum treatment has been recommended in recent years (p. 284).

Anti-anthrax Serum and Serum Treatment.

Anti-anthrax serum is obtained by immunising a horse against different strains of anthrax germs of human or animal origin (horse, ox or pig). The immunisation of animals is begun by intradermal and subcutaneous inoculations of Pasteur's vaccine I and II and continued with inoculations of virulent cultures by intravenous injection.

The preventive and curative action of anti-anthrax serum is now well established.

The *preventive action* of the serum is employed in cases of infective wounds or bites.

Curative action.

Indications: malignant pustule, anthrax septicæmia, pulmonary anthrax, intestinal anthrax.

The effectiveness of the treatment is dependent on the quantity of serum administered, the promptitude with which the treatment is begun and the form of the infection. In the case of malignant pustule (when the infection is recent), a rapid cure follows the injection of a dose of 20-40 cc. of serum. When the infection is several days old and when the local inflammatory zone is larger, an injection of 40 cc. should be administered intravenously.

In serious infections—*septicæmia, pulmonary anthrax, intestinal anthrax*—large doses of serum (100 to 200 cc. daily) should be administered by intravenous injection, after previous desensitisation of the body. The dose should be repeated daily until the fever and œdema have disappeared and the germ is no longer found in the circulation.

As a rule, patients can receive large quantities of serum without ill effects. In some serious cases of septicæmia, the total quantity of serum administered may reach 2 litres.

The effectiveness of the serum treatment is demonstrated by an improvement of the general condition, the fall of the temperature, the disappearance of the local œdema and of the swelling of the regional lymph glands.

Avoid local cauterisations and injections of tincture of iodine in cases in which serum treatment is given.

Note. — *Anti-anthrax vaccination* is practised only for the prevention of anthrax in animals ; it is not applicable to man.

The vaccination of animals is effected with Pasteur's vaccines I and II. The attenuated germs (cultures at 107.6°-109.5°F. (42-43°C.) can be incorporated in lanoline or alum (Ramon & Staub 1936). This latter method, tried in France, entails only a single inoculation.

C.

Anti-dysentery Serum and Serum Treatment.

Anti-dysentery serum was introduced into the treatment of this disease as a result of Todd's (1904) and Rosenthal's (1903-1904) researches. They demonstrated the antigenic properties of the *exotoxin* of Shiga's bacillus. The toxin when injected into the body of an animal stimulates the production of a specific antitoxin.

The results of the investigations of recent years with regard to the antigenic character of the dysentery bacillus have also demonstrated the existence of an *endotoxin* and have at the same time made clear the affinities of these two toxic elements and their rôle in the pathogenesis of dysentery. The *neurotropic* exotoxin (Olitzky & Kligler, Boivin and others) which is of a proteic nature—is produced by the Shiga bacillus (the " *S* " and " *R* " forms) only ; the enterotropic endotoxin, which is of a glucido-lipid nature (Boivin's thermostabile somatic antigen), is also produced by bacilli of the Flexner group, but only by the " *S* " forms of that group.

The knowledge acquired regarding the antigenic properties of germs of the dysentery group has been applied to the preparation of an effective specific serum. The immunisation of horses is effected by means of injections of exotoxin (filtered Shiga cultures), injections of endotoxin and inoculations with young cultures (germs of the Flexner group). The strains of germs used for this purpose belong to the well-known types : Shiga, Flexner, Y, Strong, etc. In some institutes (*e.g.*, Bucharest), regional strains of non-agglutinable dysentery germs are also added.

The antitoxic value of the polyvalent, anti-dysentery serum thus obtained is expressed in I.A.U.'s.

Method of use. In slight or average cases (less than 40 stools per day), 60-100 cc. of serum is administered the first day by subcutaneous injection and the dose is repeated on the second and third days if necessary.

In serious cases, a dose of as much as 100-150 cc. of serum should be injected on the first day and repeated if need be on the following days. Children up to 2 years of age are given half this dose. Anti-dysentery serum has a specific effect in epidemic bacillary dysentery, caused by bacilli of the Shiga-Kruse and Flexner groups and kindred types. It has no effect in amœbic dysentery or in cases of dysentery-like enteritis caused by other species of germs.

The effects of serum treatment, which are dependent on the qualities of the serum and the promptitude of its application, are observable within a few hours of the injection :

the abdominal pains and tenesmus decrease in intensity; the number of stools decreases rapidly; the fæces lose their dysenteric character; the general condition improves and a rapid disintoxication of the patient is observed.

Anti-colon-bacillus Serum and Serum Treatment.

Anti-colon-bacillus serum was introduced into medical practice following the researches of H. VINCENT (1925), who prepared a specific serum against this infection. Other anti-colon-bacillus sera have been prepared by M. WEINBERG (1927), KATZENSTEIN (1927), etc.

Most serological institutes have adopted the method of the preparation of an antitoxic and antimicrobic polyvalent serum. In order to produce this, horses are immunised with *(a)* live germs belonging to numerous native strains of B. coli of different origin; *(b)* the toxic products of these germs: a soluble neurotropic toxin, a soluble enterotropic endotoxin and an insoluble endotoxin.

At the commencement of the immunisation, gradually increased injections of a mixture of toxins are administered, then alternate injections of toxins and live bacilli.

The immunising power of the serum is controlled *in vitro* by its power of agglutination and precipitation and by fixation of the complement, and, *in vivo*, by its antitoxic and anti-infectious qualities.

Method of use. The serum is administered on the basis of a laboratory diagnosis designed to verify that the infection is of colibacillary origin, except in cases of gangrenous appendicitis requiring urgent serum treatment without awaiting such diagnosis.

In cases of B. coli bacilluria, 5 to 6 injections of serum should be administered: 30-40 cc. daily in the case of adults, 5 to 15 cc. in the case of children. The same course will be followed in cases of pyelonephritis and cystitis, in combination with lavages and instillations of serum.

Cases of enterocolitis, of mucous and pseudo-membranous colitis, and of digestive infections due to B. coli, may also be treated with serum on similar lines. Administration of serum by the mouth or rectum is also recommended.

In cases of gangrenous appendicitis, of appendicitis with imminent danger of perforation or of acute generalised peritonitis, the anti-B. coli serum (2 parts) should be mixed with anti-gangrene serum (1 part).

Nervous affections due to B. coli infection accompanied by coli bacilluria (giddiness, impediments of speech, psychological changes, mental confusion, catatonia, delirium, etc.) are also benefited by serum treatment (20-50 cc. daily).

Other complications of a colibacillary nature (abscesses, periostitis, stone in the kidney, hypertrophy of the prostate, urinary infections, etc.) should be similarly treated.

We would here recall that serum treatment is only one method of treating B. coli infections which are also amenable to adequate surgical and medical treatment. Combine treatment with sulphonamides (p. 284).

Anti-gangrene Serum and Serum Treatment.

Gas gangrene, a serious complication more especially of war wounds, is usually due to an association of anaerobic germs and is characterised by the necrosis of the tissues and a marked tendency to rapid extension. Against these germs, which are of many different kinds (p. 55), specific monovalent sera are prepared (in the first place against the most important and most frequently encountered species : *Cl. perfringens, Cl. septicum, Cl. novyi, Cl. histolyticum.* For this purpose, horses are immunised by subcutaneous injections of centrifugalised culture (toxins and microbic bodies). The monovalent serum obtained has a twofold action, antitoxic and anti-microbic.

The antitoxic value of these sera is expressed in I.A.U.'s ; they are titrated according to the method adopted by the International Standardisation Commission.

The proportion of these monovalent sera in the polyvalent anti-gangrene mixture varies in different countries according to the frequency with which infections caused by the various germs are encountered. The proportions of the

monovalent sera contained in the polyvalent mixture of the Cantacuzène Institute are as follows : 40% anti-perfringens serum, 30% vibrion septique serum, 20% anti-œdematiens serum and 10% anti-histolyticus serum.

Method of use. In order to prevent gangrenous complications in the case of serious accidents—lacerated wounds with great destruction of the tissues, contaminated with dung, dust, etc., a subcutaneous injection of 20-40 cc. of polyvalent anti-gangrene serum should be administered together with anti-tetanus serum.

In a case where gangrene is imminent (crushed, swollen wounds, with infiltration, œdema, etc.), pending surgical treatment, a subcutaneous or intramuscular injection of 100 cc. of polyvalent serum should be given. This first dose of serum will as a rule be followed within 24 hours by an improvement in the general and local conditions. In such cases, it is desirable to repeat the dose on the following day.

If the patient's state of intoxication remains unchanged and if there are clear symptoms of gas gangrene and the patient is in a state of shock, 100-200 cc. of polyvalent anti-gangrene serum must at once be administered intravenously and the dose repeated on the following day. Anti-gangrene serum treatment is, however, merely a useful and effective adjuvant to surgical treatment, which must be applied at the earliest possible moment and must be thorough (the wound must be widely opened, cleaned and drained, etc.)

Other indications for anti-gangrene serum treatment : melæna of the new-born, ulcerous colitis accompanied by a general reaction, perforation and hæmorrhage of the intestine during typhoid fever, hypertoxic or gangrenous appendicitis, peritonitis, Ludwig's angina, primary or post-scarlatinal ulcerative-necrotic tonsillitis, malignant diphtheria (in combination with anti-diphtheria serum) complicated by the presence of anaerobes, pulmonary gangrene, noma, etc.

Anti-peritonitis Serum and Serum Treatment.

The researches of Veillon (1898), Weinberg (1924) and Vincent (1925) demonstrated the pathogenic importance

of the various aerobic and anaerobic germs in gangrenous appendicitis (p. 51). In order of frequency, the colon bacillus occupies the first place ; then come the enterococcus, the streptococcus and, lastly, the staphylococcus. Among the many anaerobes isolated in cases of gangrenous appendicitis, the following are most frequently found : *Cl. perfringens*, the vibrion septique, *Cl. histolylicum*, *B. oedematiens*, *B. sporogenes*, *B. ramosus*, *B. fusiformis*, *B. funduliformis*.

The preparation and use of a serum against peritonitis are based, first, on the pathogenic rôle of the germs above mentioned and, secondly, on the Weinberg-Ginsbourg cataxia phenomenon (1925). According to these authorities, a putrid polymicrobic infection may be also combated by employing a monovalent serum corresponding if possible to the species of germ predominating in the infection.

The anti-peritonitis serum prepared at Bucharest is a mixture of therapeutic sera in the following proportions :

	%
Anti-colon-bacillus serum	40
Anti-gangrene polyvalent serum.	30
Anti-enterococcus serum	10
Anti-staphylococcus »	10
Anti-streptococcus »	10

Indications. Anti-peritonitis serum treatment is only a useful complement to surgical treatment in cases of very acute and serious appendicitis, of appendicular peritonitis (with or without perforation), gangrenous appendicitis, generalised peritonitis, appendicitis accompanied by septicæmia and appendicitis accompanied by toxic for hypertoxic phenomena.

Method of use.

Serum prophylaxis with anti-peritonitis serum is recommended in the case of patients who have to undergo a surgical operation affecting the gastro-intestinal tract or the genito-urinary system.

50 cc. of serum should be administered by subcutaneous injection the day before or on the actual day of operation. In the latter case a desensitising injection should be given

two hours before the operation, in the course of which 50 cc. of serum may be administered, partly subcutaneously and partly in the wound.

Curative serum treatment is administered as follows : after the opening of the abdominal cavity, the evacuation of pus and the insertion of drainage tubes in the cavity, the wound and drainage tubes are flooded with serum (60 to 80 cc. for an adult ; 20-50 for a child) and while the patient is under the anæsthetic an injection of 40-100 cc. is given intramuscularly and 25 cc. intravenously. The local application and the injections of serum are repeated whenever the wound is dressed. If the first injection of serum has been given under the anæsthetic, the subsequent intravenous injections will be given after first desensitising the patient.

Anti-typhoid Serum and Serum Treatment.

In 1907, CHANTEMESSE obtained an anti-typhoid serum from horses inoculated by intravenous injection with filtrates of cultures (endotoxins) and live germs.

The serum obtained had bactericidal properties, stimulated phagocytosis and neutralised the microbic endotoxin. The fatality among patients treated with serum was only 4.3% as against 17.5% among controls.

Later, BESREDKA also obtained an anti-endotoxin serum by intravenous injections of germs killed at 140°F. (60°C.). This serum protects a guinea-pig inoculated with typhoid bacilli.

Experiments were resumed as a result of FELIX & PITT'S researches into the antigenic structure of microbic variants. For the preparation of the serum, strains possessing a complete series of antigens—namely, *Vi*, *O* and *H* (live germs)—are now used ; these are administered by intravenous injections alternately with subcutaneous injections of glucido-lipidic antigen. The serum has both antitoxic and anti-microbic properties.

The disintoxicating effect of the serum in serious forms of the disease is manifest.

Anti-cholera Serum and Serum Treatment.

METCHNIKOFF & SALIMBENI, MACFAYDEN, SCHURUPOV have obtained agglutinating and anti-endotoxic sera of high titre from horses immunised with the cholera vibrio.

The results of experiments conducted on laboratory animals are at variance with the failures recorded in the serum treatment of human cases of cholera.

D.

Poliomyelitis Sera and Serum Treatment.

In 1917, PETTIT advocated the preparation of a serum against poliomyelitis obtained by inoculating a horse with virulent nervous tissue from monkeys experimentally infected with the poliomyelitis virus. In 1932, PETTIT obtained an anti-poliomyelitis serum by immunising a chimpanzee in the same manner.

Serum prophylaxis. Prophylactic treatment of children with serum has been advocated in epidemic foci, *the normal serum of adults being used for the purpose ;* this serum neutralises the poliomyelitis virus, very probably as a result of a previous abortive infection.

Curative serum treatment is practised with Pettit's serum or with convalescent serum (p. 267). Pettit's serum (immunised horse-serum), having no effect on lesions already formed, should be administered at the very outset of the disease. [1]

The serum is administered simultaneously by intraspinal injection—20-40 cc. of serum, after having extracted an equal quantity of cerebrospinal fluid—and by intramuscular injection—40-60 cc.

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[1] It is now known that these lesions are already formed when the first symptoms of the disease appear (in the phase wrongly called the " phase of invasion "). This explains the failure of serum as a *curative* agent in the strictly controlled series of cases observed in the United States (cf. *Epidemiological Report*, L.o.N., vol. **14**, 1935, p. 236-239).

The injections are repeated, if need be, on the three following days. If the condition of the patient does not improve, the doses of serum may be increased (all necessary precautions with regard to the desensitisation of the patient should be taken before the intraspinal injection).

E.

Serum Treatment with Convalescent Serum.

In the prophylaxis or treatment of infectious diseases, convalescent serum is employed if no other effective specific serum is available.

The efficacy of convalescent serum is related to the dose and the promptitude with which it is administered.

As a rule, blood is taken from convalescents whose general condition is good and who have no complications. Each serum is examined for sterility and subjected to the Bordet-Wassermann test before a mixture of the sera from several convalescents is prepared.

Convalescent serum is mainly used in the following diseases :

Scarlet fever. Convalescent serum was introduced into the treatment of scarlet fever by WEISSBECKER (1895) and is employed with success in Roumania, particularly in toxic and hypertoxic cases. For this purpose blood is taken from scarlet-fever convalescents (free from suppurating complications) between the 30th and 40th days of the disease. The sera obtained from several patients are mixed and this mixture is heated for 30 minutes to 132.8°F. (56°C.). The serum is kept in a refrigerator.

20 to 100 cc. of serum (according to the seriousness of the case) is injected under the skin or in a vein, and, if necessary, the dose is repeated on the following day.

Whooping-cough. Serum taken during the 3rd and 4th weeks of the disease has a preventive effect. If the serum is administered during the period of incubation, the ensuing attack will be mild (DEBRÉ). Dose : 50 to 100 cc.

Exanthematic typhus. Serum taken 10 to 12 days after the fall of the fever is examined for sterility and power of agglutinating a suspension of Proteus OX_{19} or of *Rickettsia prowazeki*. The administration of large doses of serum—200-400 cc. at least (if possible at the outset of the disease)—is followed by a definite disintoxication and sometimes by a shortening of the duration of the attack.

Measles. Convalescent serum, taken as a rule 7 days after abatement of the fever, has a very definite *preventive action.* Its use during epidemics is essential in children's institutions. If administered during the early days of incubation, it does not prevent the attack, but the clinical form of the disease will usually be mild.

In the absence of convalescent serum, normal adult serum or immunoglobulin is employed (p. 235).

Poliomyelitis. NETTER and LEVADITI in France, FLEXNER and NOGUCHI in America, demonstrated (in 1910) the neutralising action of *convalescent serum* on the poliomyelitis virus (experiments carried out on monkeys).

Following upon these researches, NETTER (1911) advocated the use of convalescent serum in the treatment of poliomyelitis. According to this authority, the intraspinal injection of 10 to 15 cc. of convalescent serum during the preparalytic stage prevents the development of the lesions and accelerates the process of healing. Other practitioners have used larger doses with no untoward effect.

More recent investigations by W. PARK (1931) do not confirm the curative efficacity of convalescent serum.

Only too often the serum is obtained from individuals presenting paralytic sequels of poliomyelitis, although titrations effected at the State Serum Institute, Copenhagen, and the Lister Institute, London, have shown that the number of protective units per cc. of convalescent serum is 1,000-2,000 only in paralytic cases, against 80,000 in non-paralytic ones and 150,000 in abortive cases (JENSEN, C., 1935).

Convalescent serum has the same preventive effects and the same limitations as regards curative efficiency as Pettit's serum, with which it may be combined.

CHAPTER X

TRANSFUSION AND IMMUNO-TRANSFUSION DURING THE COURSE OF INFECTIOUS DISEASES

Transfusion is a process consisting in the introduction of the blood of one person (the *donor*) into the circulation of another person (the *recipient* or *receptor*).

In the course of infectious diseases, blood transfusion is indicated: (1) in cases of peripheral circulatory collapse; (2) in hæmorrhagic complications and in any condition calling for hæmostatic action (hæmoptysis, ulcers, etc.); (3) in cases of dehydration of the body (profuse diarrhœa, uncontrollable vomiting, profuse sweating, etc.); (4) in cases of a breakdown of the body's defence against infection or any form of poisoning.

Contra-indications: œdema of the lungs, infantile bronchopneumonia with extensive lesions, thrombophlebitis, malignant endocarditis, myocarditis, cardiac deficiency, arterial hypertension, renal insufficiency. None of these contra-indications is absolute. Many a patient dies because the doctor hesitates to make a transfusion. If the precautions prescribed below are observed, a transfusion involves no danger. It is nevertheless true that the abuse of this practice might be dangerous. Make sure that the indications are perfectly clear and do not expect the impossible from a transfusion.

The mechanism of the anti-infectious action of blood transfusion is complex and incompletely elucidated. In addition to the general toning up of the body—by the introduction of an extra supply of proteins, hæmoglobin, vitamins, hormones, etc.—there are more direct anti-infectious effects: an increase of phagocytes and of anti-bodies, the non-specific stimulation of the reticulo-

endothelial system and the neutralisation, absorption and dilution of microbic toxins.

Immuno-transfusion. The anti-infectious action of a blood transfusion may be considerably increased if the donor has been previously immunised against the germ in question *(immuno-transfusion)*. Two courses are possible : *(a)* an immuno-transfusion of the blood of a convalescent, or *(b)* an immuno-transfusion of the blood of a donor artificially immunised. Both of these may give excellent results in the treatment of serious infections and cases of septicæmia.

The preparation of artificially immunised donors : (a) systematic vaccination (simple or mixed) one or two months beforehand ; once immunity has been established, it must be maintained by periodically repeating the inoculation with the antigen ; *(b)* a final stimulation of the immunity by an inoculation 6-12 hours before the transfusion (this is useful even if a donor is immune as the result of recovery from the disease) ; *(c)* if the donor is not immune, 100 million killed germs may be injected intravenously or 1,000 million subcutaneously, 4-6 hours before the transfusion. In this way non-specific defensive activity is reinforced. *General rule :* an immuno-transfusion must be administered at the outset of the disease. *Quantity to be transfused : (a)* large or medium transfusions (200-400-500 cc.) when a circulatory collapse has also to be overcome ; *(b)* small transfusions (60-100-200 cc., as a rule repeated) if it is a question of intensifying the body's anti-infectious means of defence ; *(c)* very small transfusions (60 cc. or less) when merely a coagulating effect is aimed at in case of hæmorrhage.

Selection of the donor. In order to avert accidents, it is necessary that the donor should fulfil the following conditions :

1. His blood must be compatible with that of the recipient.

2. He must be in perfect health : free from tuberculosis, malaria, syphilis, from foci of pyogenic infection, anæmia, and hypotension ; individuals in a bad general state of health must also be avoided. Persons with a high blood-pressure may be used if their blood nitrogen is normal.

3. A negative syphilis sero-diagnosis must have been recorded within the last 2 weeks.

4. His weight must be at least 100 to 110 lbs. (45-50 kilos).

5. He must be between 18 and 60 years of age.

6. He must have good veins.

7. Donors should preferably give their blood on an empty stomach (this is not a hard-and-fast rule).

In a case of imminent danger (hæmorrhage), even a donor who does not fulfil these conditions (except the rules as to compatible blood groups, which must always be observed) should be used rather than make no transfusion.

Blood compatibility, blood grouping. As early as 1901 (date of the first work on isoagglutination) LANDSTEINER foresaw the importance that the discovery of blood groups would assume in the practice of transfusion. Only by paying due regard to serological differences in blood can the serious accidents due to incompatibility, formerly so frequent, be avoided. These accidents are the consequence of the reactions between blood-cell antigens and plasma antibodies, reactions which *in vitro* take the form of isoagglutination and isohemolysis. Only the former is used in the usual technique for the identification of groups.

The red blood-cells of man contain principally two antigens (agglutinable and agglutinogenic substances) designated by the letters A and B [1], which are found separately (in subjects belonging to group A or group B, or together (group AB) or which are entirely lacking (group O (zero)).

There are therefore 4 blood groups. In accordance with the decisions of the League of Nations Health Committee (1927), they are designated by the name of the respective antigens: A, B, AB and O (zero). Table I shows the relative prevalence of these 4 groups in certain European countries:

[1] Chemically speaking, these are polysaccharides which impregnate not only the R.B.C.'s but also all cells throughout the system and are likewise found in a state of solution in most of the body fluids and secretions (plasma, blood serum, urine, saliva, etc.).

TABLE I

	O	A	B	AB
	%	%	%	%
Portuguese	38.3	52.5	6.1	3.1
Spaniards	38.6	41.2	8.9	4.3
British	46.4	43.4	7.2	3.1
French	43.2	42.6	11.2	3.0
Germans	38.6	43.9	12.7	4.7
Swedes	37.2	47.8	9.2	3.6
Italians	47.2	38.0	11.0	3.8
Roumanians	34.9	41.3	16.3	7.4
Greeks	31.8	47.2	17.0	4.0
Russians	40.7	31.2	21.8	6.3

The serum of persons belonging to group A contains anti-B antibodies [1]; that of persons belonging to group B, anti-A antibodies; the serum of persons in group O, anti-A and anti-B antibodies; lastly, the serum of persons in group AB contains no isoantibodies. In a healthy body, therefore, the corresponding antigen and antibody never exist together. (LANDSTEINER'S rule.)

TABLE II

Blood group	Antigen	Antibody
A	A	Anti-B
B	B	Anti-A
O	O	Anti-A and Anti-B
AB	AB	No antibodies

The antibodies are also sometimes indicated by the Greek letters α and β (α = anti-A; β = anti-B).

In order to avert any danger from the transfusion, donor and receptor must belong to the same group. There is, however, one remarkable exception to this rule. Owing to the dilution of the blood transfused into the blood-stream of the receptor and the partial neutralisation of the transfused isoantibodies by the antigens dissolved in the plasma of the receptor,

[1] Isohemagglutinins and isohemolysins. The sera of subjects belonging to groups A, B and O are employed as standard sera for the identification of blood groups.

the isoagglutinating and isohemolysing power of the transfused blood is reduced to such an extent that it may practically be ignored. The isoagglutination and isolysis of the injected red cells are therefore alone to be feared (OTTENBERG'S rule, 1911). It follows that *subjects belonging to group O may be employed as universal donors:* their blood can be injected without troubling to ascertain the group of the receptor; this simplifies proceedings very greatly [1]. For the same reasons, subjects belonging to group AB can be given the blood of any donor, regardless of his group (universal receptors).

Figure 4 shows the different transfusions which may be operated (the arrows indicate the direction of the transfusion):

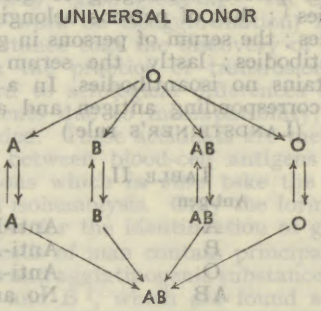


Figure 4.

[1] Nevertheless, it has been sought to explain certain, very rare, accidents which have occurred in the course of transfusions with the blood of a universal donor (group O), by the presence of anti-A and anti-B antibodies. This theory was widely accepted in many countries, but is certainly not in accordance with the facts, for transfusions from one group to another produce identical accidents, with the same frequency. It would seem, on the other hand, that a certain rôle in the pathogenesis of these accidents is to be attributed to the antigenic factor *RH*. We cannot here deal with this as yet incompletely elucidated question. Other antigenic factors (M, N, P, H, etc.) contained in the red cells do not appear to play any part.

Identification of Blood Groups.

Classic method : employ standard sera A and B, provided by an authorised laboratory. Place on a glass slide, marked at the left edge with the letter A and at the right edge with the letter B, a drop of the corresponding standard sera. Extract, by a puncture of the finger or lobe of the ear, one or two drops of blood and dilute in 1 cc. of saline solution. Mix one drop of the red cell suspension thus obtained with serum A and a second drop with serum B. Mix thoroughly by inclining the slide in various directions. After some minutes, examine on a white well-lighted background. If the mixture remains homogeneous, there is no agglutination. If lumps appear (resembling powdered brick), there is agglutination.

There are four possibilities :

TABLE III

Standard Serum A	Standard Serum B	Group to which the unknown subject belongs
—	+	A
+	—	B
+	+	AB
—	—	O

+ = agglutination. — = no agglutination.

In some persons, the red cells containing antigen A (group A or AB) are agglutinated by B sera (anti-A) with much greater difficulty than is normal. Absorption experiments show that, in such cases, it is a question of very slightly different varieties of Antigen A (sub-groups A_2, A_3, A_2B, etc.). Agglutination may be so slight that, on reading the results, there is a danger of wrongly regarding a subject A_2 as belonging to the " universal donor " group (O), or a subject A_2B as belonging to group B. As the anti-A agglutinins of O sera are much more active than those of anti-B sera, it is advisable, in order to avoid the error in question, to supplement the classic method described above by also using a drop of standard serum O. Accordingly, 3 drops of standard sera will be placed on the

slide—from left to right: serum A, serum B and serum O. The following table shows the possible results:

TABLE IV

Standard Serum A	Standard Serum B	Standard Serum O	Group to which the unknown subject belongs
—	+	+	A
+	—	+	B
+	+	+	AB
—	—	—	O

Sera of the A sub-groups may give the following reactions:

—	(+) or	— +	A_2 A_3
—	(+), usually	— +	A_2B

+ = agglutination. (+) = slight agglutination.
— = no agglutination.

For the purposes of transfusion, persons belonging to sub-groups A_2 and A_3 will be regarded as belonging to group A—*i.e.*, they may be given the blood of subjects belonging to groups A and O and may give their blood to any subject belonging to group A. Similarly, subjects of sub-group A_2B will be treated as though they belonged to group AB. In spite of the assertions of some authorities, it has not been proved that the existence of sub-groups is the cause of certain accidents. As regards Antigen B, no sub-groups exist, at least in Europe.

In order to avoid errors which might have serious consequences, it is *indispensable*, in addition to the above-mentioned precautions, also to carry out a counter-check—that is to say, to ascertain the agglutinins of the unknown serum with the aid of A and B standard red cells. On each extremity of a slide marked with the letters A and B, a drop of the unknown serum is placed. The *serum must have previously been inactivated* (by heating for 30 minutes to 132.8° F. (56°C.)), as isoagglutination is much diminished when sera are fresh. Mix with the drop at the end of the

slide marked A a drop of a suspension of A standard red cells (3-1%) ; with the drop at the end marked B a drop of a suspension of B standard red cells.

Below are indicated the four possible results :

TABLE V

A Standard R.B.C.'s	B Standard R.B.C.'s	Group of unknown subject
—	+	A
+	—	B
—	—	AB
+	+	O

+ = agglutination. — = no agglutination.

This counter-check constitutes not only an indispensable means of verifying the grouping previously arrived at with regard to the unknown red cells, but also makes it possible to avoid errors due to weak agglutinogens (A_2, A_3), since agglutinins are always readily ascertainable.

The Technique of Transfusion.

A transfusion is made with blood, either pure, or mixed with substances which prevent its coagulation (stabilised blood). Modern apparatus can, as a rule, be used for either of these proceedings. There are numerous models, with two or three channels ; in the latter case, one of the channels serves to draw in normal saline (which may or may not be citrated) by means of which the syringe and the tubes of the apparatus can readily be rinsed during the actual operation. It also makes it possible to inject the patient with any solution (separately or together with the transfused blood) without interrupting the transfusion.

The transfusion of pure blood. (1) Sterilise the apparatus, syringes, needles, joints and rubber tubes (by boiling for 20 minutes) ; (2) make the donor and receptor lie side by side ; (3) disinfect the parts to be operated upon ; (4) puncture the respective veins of the donor and receptor[1] ; (5) draw the blood of the donor into the syringe and empty

[1] Ways of injection which may be used if the veins generally used cannot be employed : veins of a lower limb, an external jugular vein, the upper *sinus longitudinalis*, the epicranial veins, intra-osseous injection (particularly by puncture of the sternum).

the tubes of air ; (6) adjust the outlet tube to the joint of the receptor's needle ; (7) inject the required quantity of blood ; (8) withdraw the needles and apply a dressing.

Precautions. (a) Lubricate the syringe, tubes, needles, etc. before use with sterilised paraffin oil ; *(b)* always have one or two spare syringes in case the piston should suddenly cease to function properly (apparatus with three tubes make it possible to rinse the syringe without changing it) ; *(c)* transfuse slowly (5 to 10 cc. per minute) but continuously ; any pause promotes the formation of clots ; *(d)* be careful not to push the injection in the wrong direction (from the patient to the donor) ; *(e)* watch the reactions of the patient ; *(f)* after the first 20 cc., stop or considerably slow down the transfusion for a minute or two and observe the patient ; should alarming symptoms appear (disturbances of the circulation and respiration, lumbar pains) stop the transfusion immediately (OEHLECKER's *biological test*) ; *(g)* do not forget continually to control the quantity of blood injected. Control the speed of the injection. Note the total duration of the transfusion.

The transfusion of stabilised blood. This has numerous advantages : the blood is easy to handle, transportable and can be kept ; its quality is guaranteed ; the operator has not to concern himself with the donor ; it is unnecessary for the donor to be present ; the vaselining and paraffining of the apparatus is unnecessary as the blood does not coagulate ; it is possible to inject slowly, even drop by drop *(= blood perfusion)* ; it is possible to administer massive transfusions ; reserves always available ; rapidity of action in case of emergency. In the great majority of cases results are obtained similar to those with pure blood.

Technique. Sterilise and disinfect instruments and the parts to be operated on, as in the case of pure blood ; homogenise the preserved blood by gently turning the receptacle (flask or ampoule) upside down several times ; as the blood has been kept in the refrigerator, it must be warmed to room temperature or a little above (not above 95°F. (35°C.) ; open the flask, insert the aspirating tube, fill the syringe and empty it of air ; puncture the receptor's vein ; adjust the outlet tube to the needle ; inject the required quantity slowly ; withdraw needle ; apply a dressing.

Precautions. Make sure that the preserved blood is not hemolysed (a zone of hemolysis 1-2 cm. in thickness above the layer of red cells is admissible) ; if the flask contains visible clots, it is better not to use it. Make sure that the aspirating tube is provided with a filter which will prevent small clots from passing (a silk sifting-cloth) ; do not omit OEHLECKER's biological test (inject 20 cc. ; pause for 2 minutes ; continue only if there is no reaction). Transfuse slowly (5-10 cc. per minute).

Observations concerning the preparation, conservation and transport of stabilised blood. The anti-coagulant at present most used is sodium citrate ; notwithstanding its anti-coagulation properties, it in no way diminishes the hemostatic action of transfused blood. Post-transfusional shivering is not, as some have supposed, due to it ; on the contrary, during the present war, it has been found that reactions are less frequent with preserved blood. Moreover, far from being harmful, these reactions appear to serve a useful purpose in many cases (they impart a stimulus to the body).

Notwithstanding the merits of sodium citrate, it is probable that, in the future, anti-coagulants of the heparin type will be used.

With the technique now employed, there are no longer any grounds for preferring pure blood to stabilised blood ; moreover, the latter can be injected immediately after it has been taken (fresh stabilised blood).

Hemolysis is the chief alteration in blood which takes place during conservation. It may be considerably retarded by adding glucose and a very little sodium chloride to the citrate. We recommend the following formula :

Twice-distilled water	1,000 gm.
Sodium citrate	5 gm.
Glucose	40 gm.
Sodium chloride	3.5 gm.

Mixed with this solution in equal quantities, blood may be kept for at least 3 weeks at a temperature of 35.6°-40.8°F. (2°-6°C.). By being thus diluted, it does not lose its valuable colloidal properties. It may also be prepared with concentrated solutions so that dilution will be insignificant.

The taking of blood must be effected under rigorously aseptic conditions (bacteriological control). It must be kept at a low temperature during transport and as far as possible shaking and disturbance must be avoided. To this end, boxes with inner casings, fitted with fixed tin containers to hold the flasks, are used. After the containers have been closed, they are entirely surrounded with ice.

Transfusion of Plasma and Serum.

General observations. When transfusion is resorted to to make good massive loss of blood (hæmorrhages, shock, collapse), the introduction of red cells is of less importance, the anoxæmia being due to an insufficient flow of blood which causes the empty heart to contract to no purpose—and not to the lack of red cells. The salutary effect of the transfusion is in this case mainly mechanical. Notwithstanding the little value of transfused red cells in cases of this kind, the introduction of blood into the receptor's vessels cannot be replaced by the injection of artificial serum, since non-colloidal solutions are rapidly eliminated in the tissues and by the kidneys. Unlike saline or sugar (iso- or hypertonic) solutions which only produce a transitory effect and cannot therefore ensure survival, blood serum and plasma can be successfully substituted for blood. As a rule, serum is to be preferred because it does not coagulate.

Plasma and serum can also, in many cases, be substituted for blood in the course of infectious diseases. There is the same enduring replacement of lost fluid, the same yield in proteins and antibodies and the same non-specific stimulative action as with whole blood.

Technique. Identical with that for the transfusion of stabilised blood.

Advantages. These substitutes for blood are not adversely affected by shaking, disturbance, and variations of temperature which are difficult to avoid during transportation. They can be kept practically idefinitely and a low temperature is not essential; there is no need to identify the donors' groups; mixtures of several sera are possible and even to be recommended.

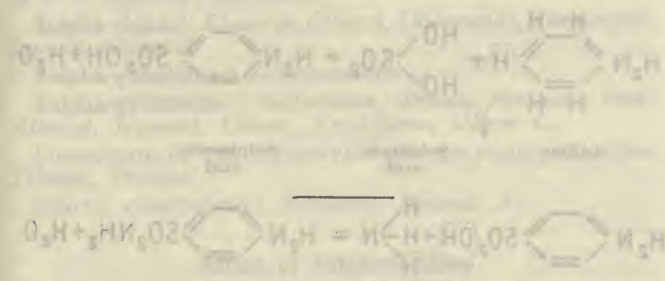
Transfusion accidents. *(a)* Serious accidents, which are always immediate, due to *incompatibility of blood* can be averted by having due regard to the blood-groups. Symptoms of alarm: anxiety, excitement, oppression, dyspnea, redness, pallor, cyanosis of the face, violent lumbar, abdominal or epigastric pains. Disturbances of the circulation (collapse), respiration, or of kidney functions (oliguria, anuria) which ensue, if the transfusion has not been stopped in time, are often followed by death. The cause is hemolysis of the injected red cells[1] (" hemolytic shock "). *Treatment.* Transfuse 200-300 cc. of compatible blood; administer alkaline substances.

(b) As opposed to these serious but avoidable accidents of incompatibility, the transfusion of *compatible blood* is often followed by *slight* disorders, of unknown cause and therefore unavoidable. They usually occur *after the transfusion,* between 15 minutes and 2 or 3 hours afterwards, sometimes more. They disappear *without treatment* within a period varying from a few minutes to a few hours. Symptoms (varying very much in intensity): shivering, hyperthermia, headache, more rarely, nausea, vomiting, nettle-rash, erythema, œdema. The term " shock " often used to

[1] Notwithstanding hemolysis, hemoglobinuria and hemoglobinæmia do not necessarily follow.

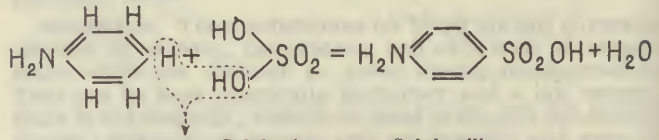
describe these *post-transfusion reactions* tends to confusion and should not be used, as the connection with anaphylactic symptoms is not established and a clear differentiation from hemolytic shock is essential.

Transfusions of plasma and serum may be followed by post-transfusion reactions, but never by hemolytic shock.

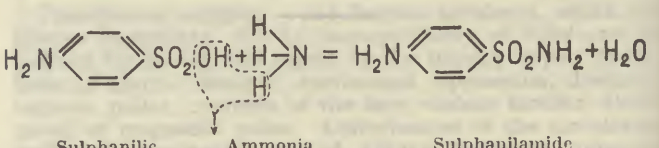


CHAPTER XI

SULPHONAMIDE TREATMENT IN INFECTIOUS DISEASES



Aniline — Sulphuric acid — Sulphanilic acid



Sulphanilic acid — Ammonia — Sulphanilamide

Chemical Data.

The fundamental basis of sulphonamides is a simple derivative of sulphanilic acid : amide of sulphanilic acid. The name of this composition *sulphanilamide* is derived from the substances which compose it—*i.e.*, sulphuric acid (SO_4 H_2) and aniline $NH_2.C_6$ H_5, and has been officially adopted in America by the " Council of Pharmacy and Chemistry ". With regard to the sulphonamides which are obtained by substitution either in the NH_2 group or the SO_2 NH_2 group, American authorities have proposed that aminic nitrogen should be designated as N^4 and that of the sulphonic group as N^1. In the case of substitutions in the N^1 group, the Council of Pharmacy and Chemistry has adopted the following abbreviations : *sulpha-pyridines, sulpha-thiazols, sulpha-guanidines,* etc.

Basic component: Sulphanilamide (Septoplix, Prontalbin, Prontylin, 1162 F, Sulphamidol, Gombardol).

DERIVATIVES OBTAINED BY REPLACEMENT OF THE N^4 *(aminic nitrogen)*: *Prontosil rubrum, soluble Prontosil, Rubiazol, Septazin, Solu-Septazin.*

DERIVATIVES OBTAINED BY REPLACEMENT OF THE N^1 *(sulphonic nitrogen)*:

Sulpha-pyridine: *Eubasinum, Sulfapyridine, Dagenan, 693 M & B, Haptocil, Sulforonin.*

Sulpha-thiazol: *Eleudron, Cibazol, Thiazomide, Ultra-septyl, Lucosil, Globucid.*

Sulpha-guanidine: *Sulfaguanidine.*

Sulpha-pyrimidine: *Sulfadiazin, Diazil, Pyrimal*; also: *Albucid, Irgamid, Uliron, Neo-Uliron, Uliron C.*

COMPOUNDS OF THE DIPHENYLSULPHONIC SERIES: *Rodilon, Tibatin, Promin.*

OTHER COMPOUNDS: *Marfanil, Amonal A.*

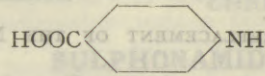
Action of Sulphonamides.

The idea that the anti-bacterial action of sulphonamides was due solely to the stimulation of the body's natural means of defence, the reticulo-endothelial system, etc., has undergone considerable modification in recent times. It remains true, however, that it would be very difficult, in the light of the researches so far conducted, to conceive this anti-bacterial activity against infectious agents as exercised independently of the co-operation of the body's means of defence.

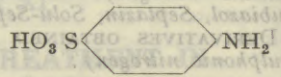
Recent researches (STAMP, GREEN) have brought to light in cultures (*Streptococcus, Brucella abortus*, etc.) a substance possessing the power of inhibiting the bacteriostatic action of sulphonamides.

WOODS has isolated, in cultures of yeast, a substance chemically very much like para-amino-benzoic acid, and it is known that this acid is an important factor in the growth of a whole series of micro-organisms and that it has an inhibitory effect on sulphonamides. KUHN calls it *vitamin H* and regards it as an integral part of the enzymatic system (which governs the metabolism of bacteria).

Its chemical structure closely resembles that of sulphonamides.



Factor of growth.



Inhibitory factor (released by the sulphanilamide molecule).

By the action of sulphonamides, this important factor in the metabolism of bacteria (vitamin H[1]) is replaced to an extent which varies in different microbic species and with their sensitiveness to the action of sulphonamides.

Indications.[1]

Streptococcal infections. All streptococcal infections benefit by treatment with sulphonamides. The best results are obtained with azoic derivatives (Prontozil, Rubiazol), which seem to exercise a more definite action on the streptococcus.

Erysipelas and streptococcal sore throat are treated by administering 2-3 gm. of Prontozil or Rubiazol daily for 2 or 3 days, continuing with decreasing doses for a further 6 or 7 days.

In puerperal sepsis, the specific treatment (serum, vaccine and immuno-transfusion) is combined with sulphonamide treatment with Tibatin, which seems to have given the best results. The prescription is 5-10 gm. of Tibatin daily by intramuscular or intravenous injection. The interval between injections should not exceed 8 hours; the first injection should be of at least 2 gm.

In cases of streptococcal meningitis, it is recommended that, with intravenous injection of Tibatin (5-10 gm. daily and also, if need be, 0.5 gm. daily by intraspinal injection) should be combined treatment with Prontosil or Rubiazol; a dose of 2-3 gm. being administered daily by *the mouth*. The duration of the treatment will depend on the examination of the cerebrospinal fluid, to be carried out daily. The foci of infection whence the meningitis originates must be treated surgically.

[1] Cf. The Medical Use of Sulphonamides, *Med. Res. Council War Memo.* No. 10, 2nd ed. H.M.S.O. London. 1945.

In *malignant endocarditis*, encouraging results have been obtained with prolonged sulphonamide treatment. Sulpha-thiazols (Eleudron, Cibazol), owing to their reduced toxicity, afford the possibility of prolonged treatment without accidents. The treatment is begun with a daily dose of 8 gm. of Eleudron or Cibazol and is continued with a dose of 6 gm. daily for several months. The chances of success are increased if the treatment is begun early.

Staphylococcal infections. Sulpha-thiazols (Eleudron, Cibazol) have a satisfactory action on staphylococcal infections. The dosage depends on the severity of the infection and the site of the lesions. On the average, it is recommended that 5 gm. of Eleudron or Cibazol be given the 1st day, 4 gm. the 2nd, 3 the 3rd and 2 the 4th day. The tablets will be administered at 1 to 2 hours intervals. In serious cases (an acute malignant staphylococcal infection of the face), up to 18 gm. daily for 15-20 days are prescribed (see Penicillin, p. 288).

Meningococcal infections. Sulpha-pyridines are especially recommended (Eubasinum, Sulphapyridine, Dagenan), which appear to be the most active, and also sulpha-thiazols (Eleudron, Cibazol), which, being less toxic, make a more prolonged treatment possible.

In *epidemic cerebrospinal meningitis*, a daily dose of 8-12 gm. for 2 to 4 days of one of the compounds above mentioned will be prescribed ; treatment will be exclusively *per os*. The treatment will be begun with a dose of 2 gms. and subsequently 1 gm. will be given every 4 hours (also during the night). Treatment will be continued with decreasing doses for a further 3-5 days, the cerebrospinal fluid being examined daily.

Pneumococcal infections. In *pneumonia*, sulphonamides have a marked effect on the temperature curve ; defervescence takes place speedily in the form of a crisis. The general condition rapidly improves and the signs of intoxication soon disappear. The most active sulphonamides are : the sulpha-thiazols (Eleudron, Cibazol) and the sulpha-pyridines (Eubasinum, Sulphapyridine, Dagenan). The prescription is 8-10 gm. daily for 3 to 4 days, with a com-

mencing dose of 2 gm. followed by 1 gm. every 4 hours (also during the night). The treatment will be continued with decreasing doses for 2 or 3 days after the total disappearance of clinical symptoms.

In *pneumococcal meningitis*, the doses may be increased to 15 gm. per day, to be administered exclusively by the mouth, in combination with specific serum and vaccine treatment.

Gonococcal infections. Shock treatment with sulphathiazols (Eleudron, Cibazol). The prescription is 5 gm. in a day—1 gm. every hour—for 2 days. If necessary, the treatment will be repeated after an interval of at least 1 week. Amino-benzo-sulphones may also be used (Uliron, Neo-Uliron, Albacid).

Plague. Encouraging results have been obtained with Prontosil, Dagenan, 1162 F and 693 M & B; 6-8 gm. daily in bubonic plague continued for ten days after defervescence. Intramuscular injections of Solu-Dagenan (2-3 ampoules daily).

Simple chancre. There are cases which are beneficially affected by shock treatment with Eleudron, Eubasinum, Albucid, Sulphapyridine or Uliron.

Brucellosis. The sulpha-thiazols (Eleudron, Cibazol), and the sulphapyridines (Eubasinum, Sulphapyridine) have been tried with success. To begin with, the dose is 5 gm. per day; the treatment is continued with decreasing doses for a week. After an interval of one week, the treatment should be repeated.

Bacillary dysentery. Excellent results, particularly with the sulpha-thiazols (Eleudron, Cibazol). The prescription is 5-7 gm. daily for 3-6 days. Sulphaguanidine has also proved very successful.

B. coli infections. In some cases good results have been obtained with sulpha-thiazols and even better with sulphaguanidines.

Dysentery-like enteritis. Is definitely benefited; cure follows in a few hours. Sulpha-thiazols (Eleudron, Cibazol), 4-5 gm. daily for 3-5 days.

Gas gangrene. Simultaneously with the anti-gangrene-serum treatment, Marfanil-Prontalbin powder is applied to the surgically treated wound and Marfanil is prescribed to be taken by mouth : 6-8 gm. daily, beginning with a dose of 2 gm. and continuing with 1 gm. at intervals of 4-6 hours (also during the night).

Cholera. Treatment with sulpha-thiazols and sulpha-guanidine might be tried.

Epidemic encephalitis. Sulphonamide treatment has been tried, sometimes with success.

Poradenitis. In addition to specific and antimony treatment, sulphonamide treatment may be prescribed : one of the sulpha-thiazols (Eleudron or Cibazol) to be taken *per os* and Marfanil to be applied locally.

Accidents.

Accidents are caused by too large doses or by too prolonged treatment and by neglect of contra-indications. Intolerance take the form of gastric disorders, headache giddiness, asthenia and general or local rashes. Serious accidents are characterised by cyanosis, sulphemoglobinæmia, anæmia, agranulocytosis and even death. Anuria due to crystallisation of the drug in the ureters has been observed, especially in children.

General Indications.

Sulphonamides should always be given after meals and with a large quantity of fluid.

Contra-indications.

Hepatic or renal insufficiency and cachexia.

Incompatibilities.

Foods rich in sulphur (eggs, etc.), drugs with a sulphur base (sodium sulphate, magnesium sulphate, etc.) and antipyretics (pyramidon, antipyrine, etc.).

Tobacco, alcohol. Fatigue and undue exposure to the sun are to be avoided.

Sulphonamide treatment supplements but does not replace classic medical (specific and non-specific) or surgical treatment.

ANTI-BIOTIC PRODUCTS[1] of Microbic Origin (Fungi, Bacteria).

The range of methods of treatment of microbic infections has been extended by a series of products obtained from cultures of different fungi and from certain bacteria. Their action is characterised by a very active bacteriostatic power in respect of a considerable number of microbic species.

Penicillin.

In 1929, FLEMING observed that colonies of *Penicillium notatum* contaminating a culture of staphylococci prevented this germ from developing. The filtrates of the fungus contain a substance, since known as *Penicillin*, which has a great power of inhibiting the development of certain germs, is non-poisonous to animals and has no effect on the normal functions of leucocytes.

Subsequent researches by British and American workers established the methods for the preparation and purification of penicillin, and defined its bacteriostatic properties and therapeutic effects.

The present preparation necessitates complicated processes which render its mass production somewhat difficult. A modified *Czapeck-Dox* culture medium, buffered by phosphate mixtures to maintain a pH (between 6 and 7) favourable to the stability of the solution, promotes a good development and an increased yield of active principles. After culture for 10 days in this medium, the activity of

[1] League of Red Cross Societies: "*Hygiene, Biology, Medicine*" *(Notes and Abstracts)* 1944, No. 2, Note No. 91.
HALLAUER, C., WETTSTEIN, A., RIEBEN, G., *Schw. med. Wschr.* 1944, 74, 611-629.

the filtrate equals 6-10 international units [1] per cc. (an arbitrary unit [1] adopted by the author in his experiments). The extraction and concentration of penicillin, according to the method of ABRAHAM & CHAIN, makes it possible to obtain a solution of sodium salts of penicillin containing 200-1000 internat. units per cc. From this solution is obtained the sodium salt containing 20 to 50 units per mgm.; this salt is used for parenteral treatment, while the calcium salt is generally used for local applications.

Penicillin is a very unstable substance: it does not resist boiling, or the action of certain bacterial enzymes, of acids or alkalis, of hydrogen peroxide, or even contact with the ions of heavy metals such as copper or lead.

The bacteriostatic action of penicillin is very intense with regard to certain species of microbes; the very weak dilutions indicated below completely inhibit their growth:

N. gonorrhoeae	1 : 2,000,000
N. meningitidis	1 : 1,000,000
St. aureus	1 : 1,000,000
B. anthracis	1 : 1,000,000
Act. bovis (hominis)	1 : 1,000,000
Cl. tetani	1 : 1,000,000
Cl. welchii	1 : 1,500,000
Cl. septicum	1 : 300,000
Cl. oedematiens	1 : 300,000
St. viridans	1 : 625,000
Pneumococcus	1 : 250,000
C. diphtheriae (mitis)	1 : 125,000
C. diphtheriae (gravis)	1 : 32,000

The absorption of penicillin is very rapid when administered by subcutaneous or intramuscular injection. It is speedily eliminated in the urine, bile and saliva, but not in tears or the pancreatic juice. So far there is no chemical method of ascertaining the presence of penicillin in the blood and this can only be demonstrated by its bacterio-

[1] The International Conference held in London in October 1944, under the auspices of the Health Organisation of the L.o.N., which standardised penicillin adopted a unit which is practically identical to the provisional one chosen by FLOREY and known as the Oxford unit.

static action. According to FLEMING, the destruction of germs attacked by penicillin is always effected with the aid of the body's cells, immunity reactions playing an important part.

Penicillin cannot be administered by the mouth, as it is destroyed by the hydrochloric acid of the gastric juices, or by the rectum, as it would be destroyed by the bacterial enzymes. The parenteral administration of penicillin necessitates large quantities of the substance, as much as nearly 2 million units. Local application is much more economical and constitutes the best method for the treatment of infected wounds, sinusitis, mastoiditis, osteomyelitis, infected burns, certain infections of the eyes, etc.

The results of the clinical tests recorded in the report of the " Committee on Chemo-Therapeutics and other Agents " relate to 500 cases of septic diseases, 22 groups of investigators having co-operated in these studies.

Staphylococcal septicæmia : Among 91 cases treated, there were 54 cures or remarkable improvements. In most of the cases, large doses were used (500,000 to 1,000,000 units) ; the best results were observed when the treatment was continued for at least ten days to a fortnight ; at the outset 10,000 units, every 2 or 3 hours, by intravenous or intramuscular injection.

Staphylococcal infections without bacteriæmia : 137 cases treated ; 109 complete cures.

Sulphonamide-resisting streptococcal infections : 33 cases treated with generally favourable results.

Pneumonia : 76 cases treated with favourable results, (average total dose 100,000 units in 3 days).

Pneumococcal meningitis : 21 cases treated, 7 cures.

Subacute endocarditis : 17 cases treated, results unfavourable except for 3 temporary improvements.

Sulphonamide-resisting gonorrhœa : 129 cases treated, all cured in 48 hours, except 4 cases in which there were relapses (average dose 100,000-160,000 units in 48 hours).

Generally speaking, the dosage does not yet seem to have been fixed with any degree of precision ; further investigations are necessary.

War wounds : The local application of penicillin was studied in North Africa by FLOREY & CAIRNS with a group of ten surgeons. The treatment was carried out either with a solution in distilled water containing 250 penicillin-calcium units per cc., or with a powder in which this salt was mixed with a sulphonamide in the proportion of 500, 2,000 or 5,000 penicillin units to 1 gm. of sulphanilamide. The results obtained with this treatment appear to have been excellent. They are better still if, from the beginning, the wound is sprinkled with the mixture of penicillin and sulphonamide. In complicated fractures, intravenous and intramuscular injections were used with good results. According to MCINTOSH & SELBIE, in *Cl. welchii* and *Cl. oedematiens* infections, penicillin is more effective, while in *Cl. septicum* infections, sulpha-thiazol gives the best results, whence the advisability of combining the two therapeutics.

Notatin and *penatin*, which are extracts of filtrates of certain strains of *Penicillium notatum*, are, it seems, inactive in the body.

PYOCYANIN.

In chloroform extracts of cultures of *Pseudomonas pyocyanea*, SCHÖNTHAL has succeeded in identifying three substances: *pyocyanin*, *alpha-oxyphenazin* and another *colourless* substance. The first two have bactericidal properties for many species of germs ; the third possesses them in respect of the cholera vibrio.

TYROTHRICIN.

DUBOS & HOTCHKISS have extracted from cultures of *B. brevis* a substance soluble in alcohol, insoluble in water, which they call *Tyrothricin*. By the action of acetone and ether, this substance is separated into soluble *Gramicidin*, which is active against gram-positive species (particularly the cocci) and insoluble *Tyrocidin*, which is active against gram-positive species and also against certain gram-negative species. Their use is limited to local treatment, which, it seems, gives encouraging results. Their toxicity for animals restricts their use.

PATULIN.

Pure *Patulin*, which has been isolated by RAISTRICK from cultures of *Penicillium patulum*, has a bacteriostatic action upon gram-positive germs and on certain gram-negative species. More toxic than penicillin, it is less active than the latter on gram-positive germs, but much more active on gram-negative germs. Local applications of patulin seem to have more effect than any other substance on the common cold.

Part III

THE COLLECTION OF PATHOLOGICAL SPECIMENS FOR BACTERIOLOGICAL, SEROLOGICAL, ETC., DIAGNOSIS, THE CAPTURE OF VECTOR INSECTS, ETC.

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CHAPTER XII

THE COLLECTION OF PATHOLOGICAL SPECIMENS FOR BACTERIOLOGICAL, SEROLOGICAL, ETC., DIAGNOSIS, THE CAPTURE OF VECTOR INSECTS, ETC.

General observations. Blood. Sputum. Fæcal matter. Purulent exudates. Urine. Pathological specimens collected at post-mortem examination. Capture of vector insects (germs or virus). Special methods for collection and despatch of pathological specimens to the laboratory.

GENERAL OBSERVATIONS

The accuracy of a laboratory diagnosis (whether bacteriological or serological) depends to a great extent on the methods employed for the collection of the pathological material to be examined.

1. Each specimen must be contained in a previously sterilised receptacle (by prolonged boiling, if no autoclave or sterilising oven is available).

2. In the course of the collection of the specimen, care must be taken to avoid the introduction of traces of antiseptic substances, which might interfere with the multiplication of the pathogenic germ.

3. One receptacle for each pathological specimen.

4. Each receptacle must be labelled ; the label will give the following information :

(a) Nature of specimen ;
(b) Name and christian name of patient ;
(c) Locality ;
(d) Date of collection ;
(e) Provisional clinical data ;
(f) Examination required.

5. Receptacles will be sent express to the laboratory in order to avoid any alteration in the specimen.

6. They will be packed in boxes or chests, firmly closed so as to prevent their being broken open, and to keep out light and heat (in tropical countries).

7. Each package will bear the address of the laboratory and be marked " Infectious material ".

BLOOD

A. Blood Culture.

In order to identify pathogenic germs in the blood (the agents of typhoid fever, paratyphoid fevers, brucellosis, and other septicæmic infections), a blood sample is taken with a view to the cultivation and subsequent identification of the germ.

As a rule, it is advisable that the blood sample should be taken by the staff of the laboratory which is to perform the examination.

Material required.

1. A 10-cc. syringe with a needle 0.6-0.8 mm. (*ca.* $^1/_{40}$-$^1/_{32}$ inch) in diameter mounted in the syringe, the whole previously sterilised (autoclave, oven, or prolonged boiling for half-an-hour in water with a pinch of borax or CO_3Na_2).

2. Appropriate culture media.

3. A constricting band (rubber tube, elastic band, etc.) to arrest the circulation of the veins above the elbow joint.

4. Alcohol, ether, tincture of iodine, sterilised cotton-wool, required for thoroughly cleansing the anterior surface of the elbow or other part whence the blood is to be taken. Traces of tincture of iodine will be removed with alcohol and ether.

When the puncture has been made, the blood will be placed in culture media with the usual sterilisation of the opening of the tube in the flame of a spirit lamp.

B. Blood Smears.

Examinations required.

Blood picture, leucocytic formula, parasitological examin-

ation (malaria, relapsing fever, trichiniasis, filariasis, trypanosomiasis, etc.).

Preparation of the material.

1. The glass slides will be perfectly clean and free from grease. For this purpose, they will be left for 12-24 hours in a solution of 50 gm. of potassium bichromate, 100 cc. of sulphuric acid and 1,000 cc. of water.

2. Another method consists in boiling slides in a 5% solution of CO_3Na_2 or in soapy water.

The slides are then carefully rinsed in water, distilled water or alcohol and dried with a piece of fine linen.

3. They may also be held in the flame of a well-adjusted Bunsen burner (blue flame).

Collection.

Clean the skin (of the finger or lobe of the ear) with alcohol or ether, puncture with a fine Francke needle or an ordinary needle (previously sterilised).

(a) Blood smear. The first drop of blood is wiped away and a second is collected on the surface of a slide (without touching the skin); the drop is spread in a thin smear by one movement with the polished edge of another slide. The smear is then fanned (for rapid desiccation) to avoid the deformation of the bloodcells (Figure 5 (1-4)).

(b) A *thick drop.* 2 or 3 drops of blood are placed on a slide and spread over a circular surface 1 cm. in diameter, with the needle or the end of another slide; it is dried under a cover (Figure 6 (5-9)).

The smears are then sent to the laboratory in a special box or in a white paper wrapping, on which is written the name of the patient, the locality, etc.

(c) Collection of blood for serological examination or for the ascertainment of the blood group.

For an *agglutination test*, it is necessary to take 2 or 3 cc. of blood (typhoid or paratyphoid fevers, brucellosis, hæmorrhagic jaundice, exanthematic typhus, tularæmia, etc.).

At least 10 cc. of blood is required for serological tests for syphilis (Bordet-Wassermann, Meinicke, Kahn, Citochol, Sachs-Georgi, etc.).

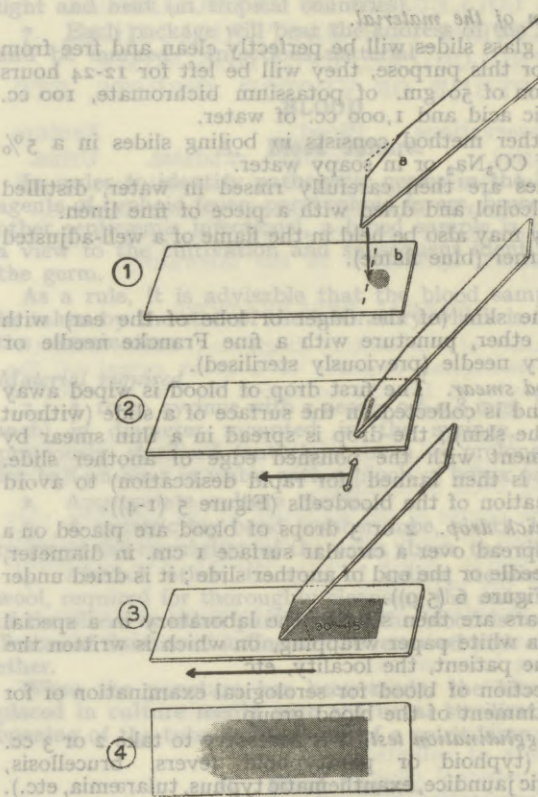

Figure 5. — Making blood smears (1-4).

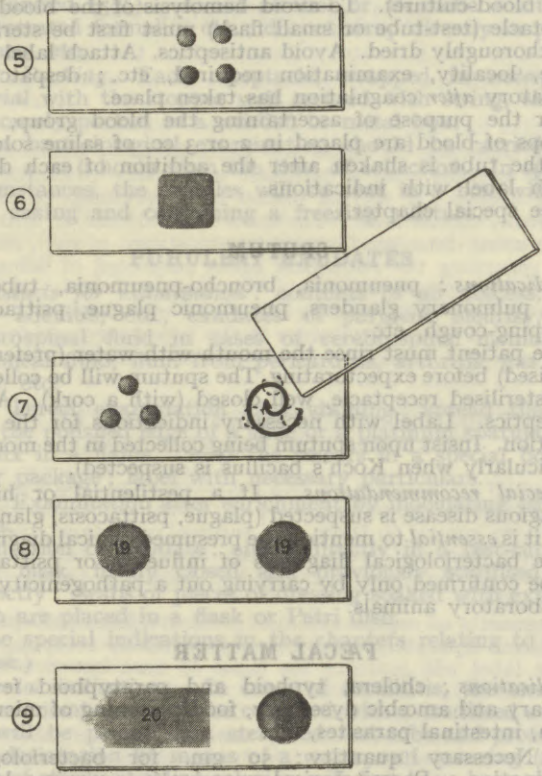

Figure 6. — Making a thick drop film (5-9).

The blood is taken either by pricking a finger (1-2 cc.) or by puncture of a vein (according to the method described for a blood-culture). To avoid hemolysis of the blood, the receptacle (test-tube or small flask) must first be sterilised and thoroughly dried. Avoid antiseptics. Attach label with name, locality, examination required, etc.; despatch to laboratory *after* coagulation has taken place.

For the purpose of ascertaining the blood group, 2 or 3 drops of blood are placed in 2 or 3 cc. of saline solution and the tube is shaken after the addition of each drop; attach label with indications.

(See special chapter.)

SPUTUM

Indications: pneumonia, broncho-pneumonia, tuberculosis, pulmonary glanders, pneumonic plague, psittacosis, whooping-cough, etc.

The patient must rinse the mouth with water (preferably sterilised) before expectorating. The sputum will be collected in a sterilised receptacle, well closed (with a cork). Avoid antiseptics. Label with necessary indications for the examination. Insist upon sputum being collected in the morning (particularly when Koch's bacillus is suspected).

Special recommendations. If a pestilential or highly contagious disease is suspected (plague, psittacosis, glanders, etc.), it is *essential* to mention the presumed clinical diagnosis.

The bacteriological diagnosis of influenza or psittacosis can be confirmed only by carrying out a pathogenicity test on laboratory animals.

FÆCAL MATTER

Indications: cholera, typhoid and paratyphoid fevers, bacillary and amœbic dysentery, food poisoning of microbic origin, intestinal parasites, etc.

(*a*) Necessary quantity: 50 gm. for bacteriological examination. Parasitological examination requires larger quantities and even an entire stool. Avoid admixture with urine. Collect in well-closed, previously sterilised, receptacles; avoid antiseptics.

(b) Intestinal worms sent to the laboratory for identification should be preserved in water—either pure or slightly formalinised (5%). Avoid alcohol or alcoholic solutions, concentrated formalin, etc.; do not wrap directly in paper or linen, etc.

(c) Packing. Each receptacle, wrapped in *waterproof material* with the stopper well secured with string, should be securely packed in a wooden or metal box.

The bacteriological examination should be carried out within 4 to 6 hours from the time of collection. In special circumstances, the samples will be sent in a box with an inner casing and containing a freezing mixture.

PURULENT EXUDATES

Products for examination: contents of an abscess, pus from adenitis, etc., exudates of purulent pleurisy, the cerebrospinal fluid in cases of cerebrospinal meningitis, peritoneal fluid, fluid from pericarditis, arthritis, gas gangrene, etc.

1. Direct examination after staining: spread the pus with the polished edge of a slide or a platinum spatula, dry and fix in a flame. Send the smears in a special box or paper package; label with necessary particulars.

2. Examination after enrichment by inoculating culture media.

Collection of exudate: either directly in a test-tube or small flask, firmly closed and previously sterilised; or indirectly: swabs or pieces of dressing soaked with exudate which are placed in a flask or Petri dish.

(See special indications in the chapters relating to each disease.)

Special indications. In cases of tonsillitis, the exudate or false membranes will be collected with a sterilised swab; this will be placed in a sterilised test-tube and protected from desiccation by means of a waterproof covering (some drops of sterilised saline solution will first have been placed at the bottom of the tube).

Pus collected by puncture of a lymph gland—bubonic plague, poradenitis, epitrochlear adenitis, etc.—will be placed

in a sterilised test-tube, labelled with the necessary data and the supposed clinical diagnosis.

In cases of cerebrospinal meningitis, the cerebrospinal fluid collected by lumbar puncture (8-10 cc.) will be sent express to the laboratory, protected in the same manner (see technique, p. 190).

URINE

The collection of urine for bacteriological examination will be effected with a catheter, with every precaution to ensure asepsis ; it will be placed in a previously sterilised and firmly closed flask. The label will indicate, in addition to the usual data (see General Observations, p. 293), indications regarding the etiological agent suspected of being the cause of the infection.

The sample will be packed in a box with an inner casing containing a freezing mixture if the laboratory which is to undertake the examination is at some distance.

PATHOLOGICAL PRODUCTS COLLECTED AT POST-MORTEM EXAMINATIONS

In order to ensure a correct bacteriological diagnosis, the post-mortem examination must be carried out under aseptic conditions similar to those of a surgical operation : the skin must be sterilised with tincture of iodine and alcohol, instruments and gloves must be sterilised, hands disinfected, etc.

Fragments of organs removed with sterilised forceps will be placed separately in previously sterilised receptacles.

The label will indicate the lapse of time between death and removal of the part.

If possible, it is better that the taking of post-mortem specimens should be done by the staff of the laboratory which is to be entrusted with the bacteriological examinations.

Fragments of organs for pathological examination will be placed in a fixative (preferably a 10 to 15% solution of formalin, Bouin's fluid, etc.).

CAPTURE OF INSECTS, VECTORS OF GERMS OR OF PATHOGENIC VIRUSES

The presence of vector insects in an epidemic zone constitutes another factor facilitating diagnosis and likewise prophylaxis.

Examples : certain breeds of anopheles and the existence of malaria ; sandfly *(Phlebotomus pappatasi)* and the existence of sandfly fever ; body-lice infected with rickettsia and the existence of exanthematic typhus ; rat fleas infected with the plague bacillus and the existence of cases of human plague ; dog ticks and the existence of boutonneuse fever, etc.

Doctors and their aids will in such cases have to undertake the capture of insects and obtain their identification.

Culicidae (anopheles, culex, aëdes, etc.).

Live insects captured will be sent in small cages $8 \times 6 \times 6$ cm. (with a metal frame, wooden top and bottom and sides of meshed gauze—7 mesh to 1 cm. (18 mesh to 1 inch)).

On a label pasted on the top of the cage will be marked the place and date of capture.

The cages will be sent in wooden boxes with 2 or 3 holes in them ; the cages will be covered with a piece of moistened gauze. In some cases, the insects may be sent killed by chloroform vapour or NH_3 and placed between two layers of cotton in small boxes or test-tubes ; a few crystals of naphtaline will also be added. Labelled as usual.

Phlebotomi. Live insects will be sent in very fine gauze cages (gauze used for straining) ; less humidity is necessary than for mosquitoes.

Phlebotomi killed by fumes of ammonia will be sent in alcohol at 80° ; a piece of cottonwool will be inserted to immobilise the insects in transit and thus prevent the breaking off of external organs. A label, in pencil, will be inserted in the tube.

Lice and Fleas. Living insects will be placed in a test-tube together with a strip of paper reaching from the bottom of the tube to halfway up. The tube is plugged

with non-absorbent cottonwool ; a label written in pencil is inserted in the tube. Tubes are packed in strong, firmly closed boxes. Killed insects may also be sent in a bottle containing 80° alcohol, a label also written in pencil will be inserted.

Ticks, Bugs. The methods described above will be used both for live and killed insects.

* * *

SPECIAL METHODS FOR THE COLLECTION AND DESPATCH OF CERTAIN PATHOLOGICAL SPECIMENS

Cholera. The post-mortem must be carried out within a few hours after death.

After the abdominal wall has been cut open, a loop of the small intestine 15 cm. in length (cut between two ligatures at each end) will be removed and placed in a securely closed glass receptacle which has been previously sterilised. The receptacle will be sent with all speed to the laboratory in a box with an inner casing and containing a freezing mixture.

Label : " Infectious material ".

Plague.

(a) *Pathological specimens collected from the patient.*

Pus from lymph glands obtained by puncture with a previously sterilised syringe.

Observation. In the suppurating bubo, the plague bacillus will rarely be found by direct examination. Cultures and the inoculation of guinea-pigs are essential.

Blood. A blood culture will be made in accordance with the directions already given (p. 294).

Pustules on the skin. Smears and cultures will be prepared after puncture with a capillary pipette

Sputum. The examination of sputum is particularly important in cases of pneumonic plague.

Sputum will be collected in accordance with the methods described (p. 298).

(b) *Pathological specimens removed at post-mortem examination.*

In carrying out the post-mortem examination, care will be taken to avoid disseminating infection. The coffin must be watertight.

Smears : of lymph glands, spleen, liver, exudate from the lungs.

Cultures : of heart, spleen, lymph glands, etc.

Fragments of the same organs will be aseptically removed for the purpose of inoculating guinea-pigs with them (pathogenicity test).

Especial care will be taken in packing. Packages will be labelled " Infectious material ".

(c) *Bodies of rats.*

These will be immersed in petroleum and despatched with all speed to the laboratory in well-closed metal boxes labelled " Infectious material ".

CHAPTER XIII

BRIEF DIRECTIONS WITH REGARD TO THE BACTERIOLOGICAL EXAMINATION OF WATER

Water is a factor in the dissemination of epidemics of water-borne diseases such as cholera, typhoid, dysentery, etc.

I. Methods of ascertaining the Purity of Water.

1. *Inspection of the site* whence the water is obtained, and of the construction and upkeep of wells.

2. *Examination of the physical properties of water :* colour, smell, taste, temperature.

3. *Chemical analysis :* ascertainment of the presence, and in what quantities, of organic substances, ammonia, nitrites and nitrates.

4. *Biological analysis :* study of plankton and saprophytic germs.

5. *Bacteriological analysis :*

(a) Total bacterial count.

(b) Detection and enumeration of colon-bacilli (colimetry).

(c) Detection and identification of pathogenic germs : cholera vibrio, typhoid bacillus, paratyphoid bacilli, etc.

(d) Indirect evidence of the presence of pathogenic germs by the finding of the specific bacteriophage (*e.g.*, antityphoid bacteriophage).

II. Collection and Despatch of Samples of Water for Analysis.

Samples of water will be collected in flasks (preferably with emery stoppers) of a capacity of 250 cc., sterilised in

an autoclave or by boiling. Sterilisation by chemical agents must be avoided. The samples will be sent to the laboratory in the shortest possible time. In summer, especially when transport takes several hours, it is necessary to send water samples in boxes containing pieces of ice.

III. **Methods for Purification of Water.**

A. *Disinfection of Wells.*

1. 10 kilograms of lime, slaked in 40 litres of water (25 lbs of lime to 10 (imperial) gallons of water) immediately before use, are poured into the well. After three days the water can be used.

2. Javel water (sodium hypochlorite) : 50 gm. for each cubic meter of water (1 fluid ounce to 130 imperial gallons or 157 american gallons).

B. *Extemporary Purification of Water.*

1. *Physical agents :* boiling.

2. *Chemical agents :*

(a) *Chlorine* in different forms : liquid chlorine, calcium hypochlorite, Javel water (sodium hypochlorite), chloramine, caporit.

The purification of 1 litre of water requires a quantity of 0.2 to 1 mgm. of active chlorine (depending on the amount of organic matter in the water) (*i.e.* : *Ca.* 1/64 to 1/16 gr. per gallon). In practice, to 1 litre of water is added either 1 cc. or a 1% solution of calcium hypochlorite or 2 cc. of a 1% dilution of Javel water.

(b) *Iodine :* 10-15 drops of tincture of iodine to 1 litre of water ; it is left in contact for 30 minutes.

(c) *Silver nitrate or fluoride :* 0.2 gm. to 10 litres of water (about 1.4 gr. per gallon) ; left in contact for 30 minutes.

3. *Filtration* with Seitz filters, specially constructed for military use, constitutes the best method for purification of water in the field.

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GENERAL INDEX

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