and spleen is common; (viii.) a painful cough may indicate enlarged mediastinal glands. In the ANGINOSE VARIETY a membrane is present on the tonsils and surrounding œdema is severe—simulating diphtheria. Vincent's bacilli and spirochætes are often present in the membrane. The FEBRILE FORM is most common in adults. *Symptoms.*—(i.) There is a sudden onset, with sore throat, headache and even a rigor. (ii.) Macular, papular or urticarial rashes appear particularly on the trunk, towards the end of the first week. (iii.) Glandular enlargement is relatively late—even in the third week. (iv.) Fever may be prolonged for three or even four weeks; at first remittent, it later becomes intermittent. (v.) Splenomegaly is rare. In all three clinical forms, the course of the disease may be prolonged. In the glandular variety the glands begin to decrease in 5–7 days without suppuration, but may still be palpable months afterwards: the fever often takes two to three weeks to settle and leaves considerable exhaustion. The Wassermann reaction may be completely or incompletely positive. Shortly after the commencement, the blood shows a leucocytosis between 6,000 and 20,000 per cu.mm.: the differential count reveals a large number of mature and immature mononuclear cells, which may constitute 60–75 per cent. of the total: sometimes cells of the lymphocytic variety predominate.

Diagnosis.—Owing to the difference in prognosis the diagnosis from *leukæmia* is very important. In glandular fever the onset is usually sudden, sweating is marked, the cervical glands are usually first involved, and purpura is very rare. In *acute leukæmia* there is often previous malaise, the glands in different areas enlarge simultaneously, anæmia and purpura are common, and the patient progressively deteriorates. An agglutination test (*Paul-Bunnell test*) shows the presence of heterophile agglutinins for sheep cells in the serum: it is positive in many cases of glandular fever towards the end of the first week, in a dilution of 1 in 64 (§ 924).

The *prognosis* is excellent. *Complications.*—A relapse, hæmorrhagic nephritis, or jaundice may occur.

Treatment is symptomatic and convalescence should be reasonably prolonged. The severe anginose form may respond very rapidly to sulpharsphenamine or neoarsphenamine, giving 0·30 G. to an adult on two successive days, even when Vincent's organisms have not been demonstrated: a transient acute laryngeal œdema has been reported following intravenous medication. Sulphonamides should not be used.

The remaining fevers in this group are PLAGUE, UNDULANT FEVER, YELLOW FEVER, *which are met with abroad;* CEREBRO-SPINAL FEVER, *which until recent years has for a long time been rare in this country; and* RELAPSING FEVER, *met with in epidemic form only in times of famine. In* HAY FEVER, DYSENTERY, *and* CHOLERA, *there is some disturbance of the temperature.* WEIL'S DISEASE is described in § 334.

§ 500. VIII. **Plague** (Bubonic Plague, Typhus Bubonicus, Oriental Plague, the Black Death) may be defined as a highly infectious and fatal fever, characterised by inflammatory glandular and periglandular swellings, hæmorrhages beneath the skin and from the mucous membranes. The last great epidemic in London was in 1666. Its chief epidemic centres in the present day are Northern India, China, Mongolia, and Uganda. Since 1894 there has been a pandemic over most of the civilised world, and our present knowledge of the disease has therefore greatly increased.

Symptoms.—(1) The incubation period is from two to ten days. (2) There is often a prodromal stage, with depression and pains, but usually the onset is sudden, with shivering, and fever rising to 103° or even 107° F. Mental aberration is not uncommon. Prostration is marked, and may be accompanied by vertigo, staggering gait, and lethargy, soon passing into the typhoid state. The spleen and liver may be enlarged. In some cases the speech is halting and staccato, the expression vacant, and the eyes congested; the condition is sometimes mistaken for acute alcoholism. A small vesicle, corresponding to a flea bite, is occasionally observed in the early stages of the disease; and examination of the fluid contents may reveal plague bacilli. (3) On the second or third day a tender swelling of the lymph glands (bubo) appears, the affected group, dependent on the site of the infecting flea bite, being inguinal and femoral in 70 per cent., axillary in 20 per cent. and cervical and submaxillary in

10 per cent. of the patients. The glands rapidly enlarge, pain is intense and suppuration generally supervenes from the seventh to the twelfth day, if the patient survives. (4) Petechiæ and subcutaneous hæmorrhages are not uncommon. A distinctive rash is rare, but when present it resembles typhus. There are six principal *varieties*, which prevail in different epidemics: (i.) The *bubonic* variety is the commonest, glandular swellings occurring in quite 70 per cent. of all the cases. The causal organism is frequently recovered on blood culture. (ii.) The *septicæmic* type is very fatal: the glands enlarge slightly, but they do not suppurate; (iii.) a *fulminant* form, with high fever, little glandular enlargement, vomiting of blood, and death within a few hours; (iv.) a *pneumonic* form, which may be mistaken for bronchitis, influenzal pneumonia, or broncho-pneumonia, attended by intense prostration, no glandular enlargement, and death usually on the third to the fifth day; herpes is absent and the pulse-respiration ratio not so much altered as in true pneumonia; (v.) an *abortive* form, in which there are buboes without much fever, subsiding in fourteen days; and (vi.) an *ambulant* or mild form, with chronic glandular enlargement, great anæmia, and weakness. Intestinal, cerebral and cellulo-cutaneous types are also encountered.

Diagnosis.—Early in an epidemic bubonic plague may have to be distinguished from climatic bubo, soft sore or syphilitic bubo, tularæmia and rat-bite fever. Gland puncture reveals plague bacilli in both smears and culture of the gland juice, and in most of the severe cases of bubonic plague *Pasteurella pestis* can be cultured from the peripheral blood at some stage of the disease. In pneumonic plague the sputum is watery and sanguineous, never viscid and rusty as in pneumonia; the bipolar plague bacilli are present in great numbers in smears of the sputum and this particular form is directly transmitted from individual to individual by droplet infection. Septicæmic plague is diagnosed by positive blood cultures.

Etiology.—Plague is due to the *Pasteurella pestis*. Outbreaks of plague were often preceded by a large mortality among rats and other rodents, and it is now known that the bubonic form of the disease is spread by them. The fleas infesting rats convey the infection to man. The alimentary tract of the flea becomes blocked by a mass of bacilli, the result of growth from infected blood previously imbibed; some of these bacilli are voided during attempts to suck blood and so pass to a fresh victim, being enabled to enter through the puncture made by the flea. Filth and overcrowding predispose to plague. The pneumonic form is directly conveyed from man to man by droplet infection. Age and sex have little influence.

Prognosis.—The case-mortality in the early periods of epidemics is generally 50 per cent. In well-cared-for white patients the mortality varies from 20 to 40 per cent. In the usual course of bubonic plague death occurs before the sixth day; or, if the patient is to recover, convalescence starts between the sixth and tenth day. The pneumonic variety is so fatal that of 43,000 cases in Manchuria only three recovered. Prolonged suppuration of the glands may delay convalescence considerably. The course of the disease is very difficult to forecast. Hæmorrhages usually herald death. The *sequelæ* include boils, pneumonia, dropsy, partial paralysis, and mental disorder.

Treatment.—Careful nursing and fluid diet are essential. Treatment consists of large doses of anti-plague serum intravenously; sulphonamides in full doses have given promising results in bubonic and septicæmic plague, but have so far failed in the pneumonic type. Buboes should be treated with hot fomentations, a kaolin poultice or belladonna and glycerin applications; when suppuration occurs incision should not be delayed. Morphia may be necessary for the pain. Prophylactic treatment consists of the extirpation of rats and the flea vector; dusting floors and rat runs with 5–10 per cent. D.D.T. powder has proved very useful. Prophylactic vaccines are also of value.

§ 501. IX. Undulant Fever. There are two main types: (1) Malta Fever, found particularly in those countries which border on the Mediterranean, in S. Africa, in the southern portions of the U.S.A., and the Punjab, due to *Brucella melitensis*. All ages and both sexes are liable to contract the disease. It is conveyed to man by the milk of infected goats which need not show any signs of ill health. (2) Abortus fever,

contracted from cattle or swine suffering from contagious abortion due to *Brucella abortus* (an organism closely related to *Brucella melitensis*). It is prevalent on the continent of Europe, especially Denmark, in North Africa and the United States. In England many cases are being reported and the disease is by no means uncommon. The disease is conveyed by drinking raw milk, handling the carcases or hides, removing the animal's placenta or slaughtering pigs. Porcine strains of *Brucella* (*B. suis*) are also known.

Symptoms.—The incubation period is fourteen days, though exceptionally it appears to be very much longer; the prodromata include malaise, muscular pains, and dyspepsia. Soon increasing headache, fever, and muscular pains cause the patient to seek advice. The temperature keeps high (102° to 104° F.) for about fourteen days, and may then drop for a few days, only to rise again. After several such undulations the temperature becomes intermittent, with a marked rise at night. The general health of the patient suffers in many ways, the chief symptoms being gastro-intestinal. There are muscular and joint pains, which may be accompanied by considerable swelling, sore throat, sweating, anæmia, enlarged painful spleen, and bronchitis. There are three varieties of the disease. The *malignant* is of acute onset, and runs a rapid course to a fatal termination, preceded by the typhoid state and hyperpyrexia. The *intermittent* variety is of very slow onset, and runs a long course, with sudden elevation of the temperature each evening often with a rigor. The patient does not as a rule make any complaint of specific symptoms until his general health begins to be affected. The *ambulatory* type includes the not infrequent cases in which the *Brucella melitensis* is found in the blood of persons who are in no respect ill.

The *Diagnosis* is arrived at from the clinical signs, by the recovery on culture of the specific organism from the blood or urine (abortus strains grow better with an atmosphere containing CO_2); and by the agglutinin reaction of the blood. An intradermal test, using a killed culture, is frequently positive. In doubtful cases blood should be inoculated into the peritoneal cavity of a guinea pig, as positive cultures are more readily obtained from this source.

Prognosis.—In the common type the mortality is about 3 per cent. Complications are arthritis, neuritis, orchitis, parotitis, mammitis, bronchitis, pneumonia, cardiac failure, and hyperpyrexia, the latter being the usual cause of death. Menorrhagia, abortion and premature labour may result, especially in *B. abortus* infection. The disease may last two years or longer; the average is 3 to 6 months. *Brucella melitensis* infections are usually much more severe than infections caused by *Brucella abortus*.

Treatment.—Prophylaxis consists in avoiding the milk and cheese of infected goats and cows. The milk is rendered safe by boiling. It is important not to handle infected carcases; laboratory workers must be especially careful with Brucella cultures. Careful nursing and a nourishing diet adequate in vitamins is important in so prolonged a disease. Vaccines are of doubtful value; specific anti-serum holds promise, though not yet obtainable commercially. Protein shock in the form of intravenous injection of T.A.B. vaccine, commencing with 50 millions and working up to 250 millions at three-day intervals, and sulphonamide therapy are worth trying. Penicillin is of no value. Where the temperature exceeds 103° F. cold sponging should be instituted. Joint involvement is treated on general lines.

§ 502. X. **Yellow Fever** is an acute infectious disease endemic in a large part of tropical Africa and South America; in severe cases it is accompanied by jaundice, black vomitus and other evidences of hæmorrhage into the mucous membranes or skin.

Symptoms.—The incubation period in man is from 3 to 5 days in mosquito-transmitted infections, and up to 10 days in laboratory workers who have contracted infection from contact with blood containing the virus. Mild, ordinary and fulminating clinical types of the disease are encountered. (*a*) In the *mild* or larval infections there is headache, vomiting and fever of short duration, lasting a few days. Albuminuria is generally demonstrable, but jaundice, if it develops, is mild.

(*b*) In the *ordinary* type three stages are recognised, the *sthenic*, the *remission*, and the *asthenic* stage. (i.) The onset is generally sudden with chilly sensations or a rigor, the temperature rising to 103° or 104° F. on the first day. Frontal headache, backache, pains in the extremities and photophobia are characteristic, the face is flushed, the conjunctivæ injected and the tongue furred with bright red edges. Albuminuria appears about the second day and rapidly increases and the urine soon contains casts; bile salts and pigments are found later. At first the pulse is rapid and bounding, but later it slows and by the third day equals only 60 to 70 per minute despite the elevated temperature. (ii.) About the third or fourth day the temperature drops considerably or falls to normal. (iii.) After the short remission the fever usually returns for 2 or 3 days. In this stage the liver is enlarged and tender, epigastric discomfort is marked, and hiccough and jaundice with hyperbilirubinæmia and a biphasic van den Bergh reaction are common. There is no splenic enlargement. Petechiæ, melæna and black vomit may appear, while oliguria and anuria with nitrogenous retention and acidosis are the rule in fatal cases. Hypotension and bradycardia, due to involvement of the A-V bundle, are characteristic. Death may occur from the 5th to the 12th day. Leucocytes vary from 5,000 to 15,000 per cu.mm. (*c*) *Fulminating* cases develop high fever, purpuric skin rashes, oozing from the gums, early black vomitus and melæna. Jaundice is intense. Hiccough, tremor, delirium and coma due to cholæmia, and uræmia with anuria develop. Death occurs on the 3rd or 4th day.

Etiology.—Yellow fever is due to a filterable virus. Although clinically indistinguishable, three types of yellow fever are recognised, namely, urban, rural and jungle. The first two are transmitted normally by the tiger-banded mosquito, *Aëdes ægypti* (*Stegomyia fasciata*); the third is transmitted by various forest mosquitoes from various animal reservoirs. The blood of man is infective during the first 3 days of fever, but never the excreta. One attack confers immunity and convalescent human serum protects the susceptible monkey, *Macacus rhesus*, when exposed to the virus. The virus may traverse the intact skin in either man or monkey; and in this way many research workers have contracted fatal infections.

Diagnosis.—Important points in diagnosis from other tropical fevers are the severe prostration, early albuminuria, slow pulse, jaundice and the absence of splenic enlargement. In mild cases, intracerebral inoculation into mice of the patient's blood in the early days of the disease produces an encephalitis. Later, and in recovered cases, immune bodies in the patient's blood may be demonstrated by the mouse protection test: mice whose brains have been previously traumatised by injected starch solution are inoculated intraperitoneally with mixtures of virus and suspected serum. If the serum contains no immune bodies, encephalitis results: whereas if immune bodies are present (due to previous infection of the patient), the mice remain well. *Leptospirosis* closely simulates yellow fever, but there is extreme muscular tenderness, neutrophil leucocytosis and a history of a recent immersion accident or an occupational relationship to rats; see § 334. *Malaria* complicated by jaundice, is recognised by the splenomegaly and parasites in the blood, and *blackwater fever* by the hæmoglobinuria. *Infective hepatitis*, *toxic hepatitis* and *acute yellow atrophy* all have a more gradual onset and no stage of remission. In *relapsing fever* with jaundice there is enlargement of the spleen and spirochætes are readily demonstrable in the blood.

Prognosis.—In the average case the mortality is about 20 per cent. Intense and early jaundice, severe nervous disturbances and intractable hiccough, widespread hæmorrhages into the skin and from mucous membranes and anuria are of bad omen.

Treatment.—(*a*) *Prophylactic* treatment includes all measures for the destruction of the mosquito vector, *Aëdes ægypti*, a domestic mosquito which may bite during both day and night. Prophylactic inoculation with chick-embryo cultures of low virulence pantropic virus is protective for four years; the absence of human serum in preparing the vaccine has now removed the risk of homologous serum jaundice

which was previously a serious complication. Rubber gloves should be worn when collecting blood for laboratory purposes, and infected patients should be screened during the first 4 days of fever. (*b*) *Curative* treatment is unsatisfactory. Convalescent serum is of doubtful value once symptoms develop. Careful nursing and abundant fluids during the acute phases of the illness are desirable. Glucose and sodium bicarbonate should be added to all drinks, and 1 to 2 pints of 5 per cent. dextrose may be given intravenously each 24 hours. Calcium lactate gr. 40 daily is useful. Champagne may relieve the vomiting and a mustard plaster over the epigastrium sometimes diminishes hiccough; cold sponging and sedatives are good for the insomnia. Gradual increase of food is allowed after the temperature has been normal several days.

§ 503. XI. **Cerebro-Spinal Fever** (Syn.: Epidemic Cerebro-Spinal Meningitis, Meningococcal Meningitis, Spotted Fever) is due to the meningococcus invading the blood stream from the naso-pharynx, and later reaching the meninges. In some cases two separate stages are evident, with symptoms of septicæmia followed by those of meningitis, but the stages often overlap. *Principal Symptoms:* (i.) In the initial stages there may be nasopharyngeal catarrh: (ii.) fever, accompanied by fleeting joint pains, headache, vomiting and later, skin rashes. The temperature is often irregular at the onset and even subsides to normal for a day or so, before rising again. It is rarely over 102°–104° F. except for a terminal hyperpyrexia. These septicæmic symptoms are accompanied or succeeded by (iii.) symptoms of irritative intracranial inflammation, such as very severe headache, vomiting, photophobia, restlessness, drowsiness and delirium. There is always retraction of the head, and sometimes opisthotonus, owing to the rigidity of the muscles of the back. Hyperæthesia, especially along the spine, neck stiffness, and severe pain in the back, may be so great that all movement is intolerable. Kernig's sign is usually present. Compression symptoms may supervene later. (iv.) A prominent feature is the presence of an eruption, often symmetrical. Herpes simplex is frequent except in infants, and may have unusual localisation. Urticaria and erythema may occur. On the second day or later a purpuric rash sometimes appears, and may cover the body ("spotted fever"); its frequency varies considerably in different epidemics; in some it has been rare. (v.) Polymorphonuclear leucocytosis appears early. Unusual forms are: (i.) The fulminating type is associated with the Waterhouse-Friderichsen Syndrome (§ 244); in this, septicæmia and often hyperpyrexia are associated with acute circulatory collapse and anuria, cyanosis, purpura and often death within 24 hours. With this (ii.) an acute encephalitis may co-exist or the latter may occur alone. The brain involvement gives deep coma and stertorous breathing, sometimes with convulsions: meningitis is not necessarily present. (iii.) Abortive forms occur with moderately severe headache, fever, and neck stiffness; the C.S.F. shows polymorph cells, but meningococci may be very difficult to demonstrate. (iv.) Chronic septicæmic cases show moderate fever, occasional rigors, muscle and joint pains, headache and rose-red spots, sometimes resembling erythema nodosum: a positive blood culture is obtained, but the meninges may or may not be involved later. (iv.) Posterior basic meningitis of infants.

Posterior Basic Meningitis is a subacute form of this disease occurring in infants from three to twelve months old, characterised by (i.) an acute onset with convulsions and gastro-enteritis, or a gradual onset with drowsiness, vomiting and a meningitic cry. (ii.) A few days later there is the gradual onset of the retraction of the head which may amount to opisthotonos with flexor and extensor spasms in the limbs; (iii.) staring of the eyes, with blindness, appearing quite early in the disease, unassociated with changes in the optic nerves, and due to involvement of the occipital cortex; strabismus is common; (iv.) rigidity of the limbs, which may be localised or confined to one extremity; (v.) paroxysms of high fever lasting a day or two at a time. The onset of *Hydrocephalus* is heralded by *vomiting* and *wasting*, with enlargement of the skull in infants, bulging of the fontanelles and opening of the sutures between the bones. A resonant or "cracked pot" note is present on per-

cussion over the anterior horn of the lateral ventricle in infants in whom the fontanelles are closed.

Diagnosis.—In the septicæmic stage a post-nasal swab shows meningococci. In the meningitic stage, tuberculous meningitis may be differentiated by its more insidious onset and absence of eruption. From tuberculous and other forms of meningitis the best method of diagnosis is by lumbar puncture, when the fluid is found to be turbid, and to contain the specific diplococcus either free or in the polymorphonuclear leucocytes. Care should be taken to exclude anterior poliomyelitis with acute onset, in which a stage of cerebral irritation lasting even as long as seven to ten days is not uncommon. When an epidemic is present the diagnosis is simple.

Etiology.—It occurs sporadically and in epidemics, usually in persons under twenty; some epidemics have occurred chiefly among infants, and males more than females. It is most frequent in winter and spring. It is undoubtedly contagious, although much less so than the acute exanthemata. "Carriers" play the chief part in its spread, overcrowding, especially of sleeping quarters, greatly increasing the danger of transmission which occurs as the result of the droplets of secretion being sprayed around during coughing and sneezing. It is due to the *Neisseria meningitidis* (Diplococcus intracellularis meningitidis of Weichselbaum), which is Gram-negative and best grown on tryp-agar or ascitic fluid.

Prognosis.—The prospect of recovery is not good when the disease attacks infants or old people: even with modern chemotherapy the death rate is 20–25 per cent. Amongst the unfavourable signs are the occurrence of hyperpyrexia, purpura, bronchopneumonia, or circulatory collapse or encephalitis (see above): or an unduly prolonged period of illness. The other common complications are acute arthritis, acute sinusitis and optic neuritis. Amongst the sequelæ may be mentioned deafness, iridochoroiditis, panophthalmitis, subacute arthritis, orchitis, chronic hydrocephalus, and transient paralysis of the limbs, aphasia and dementia.

Treatment consists in isolating the patient and nursing him in a darkened room: all attendants must wear masks and gowns. The results have been revolutionised by the use of sulphathiazole and sulphadiazine: sulphamezathine is not quite so effective. For dosage see Table XXVIII; injections of the soluble salts are used till vomiting ceases, and a copious fluid intake insisted on. When speed is essential, intravenous medication four-hourly, or a continuous drip into a vein is resorted to. Penicillin is not so effective as the sulphonamides, but may be given in addition. Fulminant cases with circulatory collapse may respond to adrenal cortical extract or desoxycorticosterone acetate (5 mgm. injected six-hourly), together with 600 c.c. of human plasma and then 600 c.c. 5 per cent. dextrose in half-normal saline. Apart from the initial diagnostic puncture, lumbar puncture is not usually required. Frequent doses of chloral and potassium bromide āā 20 gr., and occasional injections of morphia may be given with advantage. *Prophylaxis.*—Even as small a dose of sulphadiazine as G. 2 has cleared meningococci from the nose of carriers.

§ **504.** XII. **Relapsing Fever** (Synonyms: Famine Fever, Spirillum Fever) embraces a group of infectious fevers due to *Treponema recurrentis* found in the blood, spread either by lice (widespread form) or by ticks (Central African, Peruvian and American forms). The incubation period varies from five to nine days. The primary fever lasts generally from five to seven days, and short febrile relapses are not uncommon.

Louse-borne Relapsing Fever. *Symptoms.*—(1) The fever has a sudden onset, with rigor, headache, backache, and pains in the limbs. The face is flushed, the eyes injected and photophobia is common. Often there is an initial erythematous rash and later roseolar macules or petechiæ. The temperature rapidly rises and after remaining elevated for six or seven days, returns to normal by crisis. The fall is preceded and attended by profuse perspiration or diarrhœa, or both. This is followed by an interval of about a week, during which the patient feels exhausted, and the pulse and temperature are subnormal. At the end of this time a relapse occurs which is similar to the first attack, but shorter, lasting three or four days. In rare cases there is a second and even a third relapse. (2) Abdominal pain and

tenderness, and definite enlargement of the spleen and liver, are present in most cases. Jaundice and epistaxis are not uncommon in severe cases; sometimes there is vomiting of blood. Delirium is very rare, but if present is of the noisy kind, and occurs at the crisis. Convalescence is slow. (3) Treponemata are found in the blood during the pyrexial period. A neutrophil leucocytosis accompanies the fever and a leucopenia the afebrile period.

Tick-borne Relapsing Fever is met with in Central Africa, Persia, America and Spain, and never assumes the epidemic proportions of the lice-borne fevers. It differs from the louse-borne form in the shorter duration of the initial fever, in the greater number of relapses and the paucity of treponemata in the peripheral blood. Epistaxis, hæmaturia and jaundice may occur and the central nervous system may be involved with paresis of the cranial nerves and coma; the C.S.F. may show increased pressure and lymphocytosis. Complications are pneumonia, parotitis and iritis. It is often more resistant to treatment, *e.g.* with organic arsenic, than the louse-borne form.

The *Diagnosis of Relapsing Fever* depends on demonstration of treponemata in the blood. Intraperitoneal injection of patient's blood into young white mice or rats may help diagnosis, as treponemata may appear in the animal's blood in 24–48 hours.

Prognosis.—The case-mortality averages about 5 per cent., but may be very high in the African form. Age has not much influence, but dissipation and debility are unfavourable. One attack does not confer immunity from a second. Death, which occurs generally at the height of the first attack, is usually due to syncope, from hæmorrhage or from myocardial degeneration. When occurring later, it may be due to complications. Untoward symptoms include hæmorrhage, suppression of urine, the typhoid state, cerebral symptoms, or indications of a weak heart. A rapid pulse, a high temperature, and even jaundice, are not necessarily unfavourable.

Treatment.—Arsenical compounds (*e.g.*, neoarsphenamine), gold compounds (*e.g.*, solganol), or penicillin should be injected as early as possible and preferably when the temperature is rising: if given when a natural crisis is imminent grave reactions may occur due to rapid destruction of large numbers of organisms. Digitalis, pituitary extract and strychnine may be required to treat collapse occasioned by the crisis. Paraldehyde is useful for the sleeplessness, and lumbar puncture when nervous manifestations are severe.

§ 505. XIII. Apart from the relapsing fever above described, there are several forms of fever transmitted by ticks, sand-flies, etc. The best known of these are: Tularæmia, Kala-azar, Phlebotomus and Rat-bite Fevers.

Tularæmia (Synonyms: Deer-fly Fever, Pahvant Valley Fever, Ohara's Disease). A rodent disease, due to *Pasteurella tularense*, transmissible to man and prevalent in the United States of America, Russia, Europe and Japan; many accidental infections have occurred among laboratory workers.

Symptoms.—Two principal forms of the disease have been described—glandular and typhoid. The glandular form is characterised by fevers, rigors, generalised pain, headache, the formation of a papule which ulcerates, and enlargement of the regional lymphatic glands. It is the type common in butchers, poultry-men and trappers. In the typhoid type there is a fever of varying degree which lasts a considerable time. There are no localising symptoms; it is the type generally found in laboratory workers. The *diagnosis* is made by agglutination of *P. tularense* by the patient's serum or by culture of the organism from the local lesions or glands.

Etiology.—(1) Bite of horse-fly or wood-tick infected with *P. tularense*. (2) Contamination of hands or conjunctival sac with internal organs or body fluids of rabbits, hares, squirrels, water rats or other animals infected with *P. tularense*.

Prognosis.—Convalescence is slow, but recovery usually occurs without sequelæ. The chief complications are bronchopneumonia, pleural effusion, abscesses in the lungs, liver and spleen, peritonitis and meningitis. The mortality rate is very low.

Treatment.—A serum prepared from a goat or horse inoculated with formaldehyde

suspensions of *P. tularense* has been used with remarkably good results. The dose is 30 c.c. given on two successive days. Streptomycin is also proving effective.

Kala-azar.—A disease found in China, India, Assam and the Sudan, associated with enlargement of the spleen and liver, anæmia and leucopenia, some wasting and irregular fever of long duration. It is caused by *Leishmania donovani*, which are found in monocytes in the peripheral blood and in the reticulo-endothelium of the viscera and bone marrow. An infantile form of the disease occurs throughout the Mediterranean littoral. Transmission is by sand-flies.

Symptoms.—The incubation period varies from one to twelve months and the onset is generally sudden with fever; sometimes it is more insidious. When established there are (1) irregular remittent or intermittent pyrexia, the temperature charts sometimes showing a double daily rise in the afternoon and evening; (2) increased pigmentation of the skin; (3) anæmia of secondary type associated with marked leucopenia (1000–5000 cells per cubic millimetre): there is a relative increase in lymphocytes and monocytes, a decrease in neutrophils with disappearance of the eosinophils; (4) loss of weight, and cachexia; (5) splenomegaly, the spleen being first soft and doughy but not tender, and later enlarging and becoming very hard. Diarrhœa, enlargement of the liver, night sweats, asthenia and low blood-pressure may develop. Cancrum oris associated with agranulocytosis, otitis media, hæmorrhage from mucous membranes, purpura and secondary infections like influenza, pneumonia and tuberculosis may cause death. Hepatic cirrhosis, jaundice and post kala-azar dermal leishmaniasis may follow the disease.

Diagnosis.—Kala-azar has to be distinguished from leukæmia, Banti's disease, schistosomiasis, chronic malaria, undulant fever, relapsing fever and typhoid fever. Diagnosis is made by finding the parasites in juice aspirated from the spleen, liver, bone marrow or lymph gland. The formol-gel test is usually positive after two to five months: the serum added to a drop of commercial formalin becomes opalescent within one to two minutes and coagulates solid like boiled egg white in twenty minutes A positive reaction, associated with leucopenia, is valuable evidence of kala-azar. Sometimes the parasites are demonstrable in blood smears and they may be cultured on rabbit blood agar medium at 22° C.

Treatment.—Antimony compounds are generally curative, although refractory cases are encountered especially in the Mediterranean. Sodium antimony tartrate may be used as described for schistosomal dysentery (see p. 385). Sodium stibogluconate, 0·6 G. in 6 c.c. fluid intravenously daily for 7 days, the course being repeated after a week's rest, gives very good results. Other pentavalent antimonial compounds are also used. Ascites and nephritis are indications for care in the use of antimony, and if pneumonia or jaundice supervene the injections may have to be suspended until these complications are cured. Children tolerate a relatively larger dose than adults. In antimony-resistant cases, propamidine or pentamidine (0·1 to 0·3 G. daily for 7 to 14 days) may be used although toxic effects, such as immediate collapse controllable by adrenalin, may occur. Stilbamidine is now little used because of its immediate, general and delayed neural toxic effects which occur especially with old solutions. Cure is indicated by decrease in the size of the spleen, an absence of pyrexia and clinical symptoms extending over a period of six months, a negative formol-gel test, and a permanent disappearance of parasites. Where agranulocytosis with cancrum oris supervenes, injections of pentnucleotide should be given without delay.

Phlebotomus Fever (Synonyms: Papataci Fever, Three Days' Fever) is a fever affecting new-comers in the summer months in Herzegovina, Dalmatia, Malta, Crete, Mesopotamia, Egypt, India, and other parts of the tropics and subtropics.

Symptoms.—After an incubation period of two to seven days the patient has a rigor, followed by severe headache, fever, and severe pain in the eyeballs and brow, back, and calves of the legs. The eyes are congested, the face flushed, the tongue foul. The fever lasts from one to five days, most often seventy-two hours. Vomiting, bradycardia and leucopenia with relative lymphocytosis may occur. The disease is never fatal. One attack confers immunity.

Etiology.—The disease is due to a filterable virus transmitted to man by the bite of a sand-fly (*Phlebotomus* species). White races are specially affected and the virus is present in the peripheral blood during the first two days and can be transmitted by direct inoculation. The *diagnosis* lies between influenza, malaria and dengue, the latter showing secondary rises of temperature and a rash not observed in sand-fly fever.

Treatment.—The disease is best prevented by the destruction of sand-flies which bite at night, and are so small that they can pass through the meshes of an ordinary mosquito net. Repellents, such as dimethylphthalate, are useful. Medical treatment consists of aspirin, phenacetin and caffein citrate or even opium for the pain; cold sponging is beneficial when the fever is high.

Rat-bite Fever (Synonym: Sodoku) has long been described in Japan as occurring after the bites of rats and cats. Cases are also met in Europe and America. There are two varieties: (1) The first is due to *Spirillum minus*, and the *symptoms* are: (i.) There is a history of a rat-bite which is followed by local pain, swelling and a purple-red discoloration; (ii.) this develops into a chancre-like ulcer 1–3 weeks after the bite, with lymphangitis and lymphadenitis; (iii.) there is fever even to 105° F., which recurs at intervals of about six days. It may last a day or a week and assume an intermittent type; (iv.) the fever is accompanied in most cases by a large macular or papular rash; (v.) the blood shows a moderate leucocytosis, but blood cultures are negative: the Kahn reaction may be positive but the Wassermann reaction is negative. (2) The second is caused by *Actinomyces muris* (*Streptobacillus moniliformis*). *Symptoms:* (i.) After the rat-bite the wound heals quickly: but (ii.) within 2–5 days there is high fever, severe arthritis, and sometimes painful nodules in the muscles: (iii.) there is often secondary anæmia and polymorph leucocytosis.

Treatment.—The disease caused by *Spirillum minus* reacts to salvarsan and to penicillin (given for 7–10 days): that due to *Actinomyces* only to penicillin.

§ **506.** XIV. **Psittacosis** is a disease of parrots due to a filterable virus. The infection is contracted by inhalation of excreta from infected birds, including the green Amazonian parrot, grey parrots and budgerigars.

Symptoms.—The incubation period varies from seven to twelve days and the onset is acute or gradual, usually acute. Headache is marked, the patient becomes dull and apathetic and a typhoid-like condition may develop; occasionally epistaxis occurs. The spleen is not generally palpable; small rose spots may appear, somewhat resembling those of typhoid fever. Pulmonary symptoms are frequent and may be present from the onset, or develop some days later. There is not much expectoration as a rule, but cough is troublesome. The pulse respiration ratio is low. Physical signs vary, but are not infrequently those of massive consolidation with woody dulness on percussion. The disease may terminate in recovery after two or three weeks. The death rate is from 16–35 per cent. Recrudescence during convalescence is sometimes observed.

Diagnosis.—The diagnosis is made from a history of contact with a sick parrot by the patient affected with an obscure fever resembling typhoid or pneumonia. Elementary bodies may be demonstrated in impression smears from the liver and spleen of mice which have been injected intraperitoneally with infected sputum. Agglutination and complement fixation tests are helpful in diagnosis.

Treatment.—Prophylaxis consists in forbidding the importation of infected birds and in strict quarantine. Sick parrots should be immediately destroyed and cages treated with antiseptics. *Treatment* is symptomatic.

§ **507.** XV. **Bornholm Disease.** This disease, also known as "epidemic pleurodynia," "epidemic myalgia" or "devil's grip," is manifested by severe pain in the chest or abdomen with rise of temperature to 102° or 104° F.: the affected muscles are locally tender. The symptoms usually disappear in about twenty-four hours, but recur in nearly a quarter of the cases. The *complications* are pneumonia, pericarditis and orchitis. The disease is very rarely fatal. *Treatment* is purely symptomatic.

§ 508. XVI. **Heat-stroke** and **Allied Maladies.**—In the tropics or where atmospheric temperature and humidity become unduly high, physiological breakdown may occur as (1) heat-stroke (heat hyperpyrexia, sun-stroke, heat traumatism, heat apoplexy, thermal fever, etc.); (2) heat exhaustion; or (3) heat cramp. Stokers and miners outside the tropics and subtropics may be affected.

Symptoms.—(1) The onset of **heat-stroke** is often sudden, with fever, fits and coma, or there may be premonitory symptoms such as restlessness, giddiness, dyspnœa or gastro-intestinal symptoms. Sweating decreases or stops, and coma with rapid pulse and stertorous breathing or Cheyne-Stokes' respiration follow. Fibrillary muscular twitchings develop, the skin feels burning hot and dry as parchment, the face and conjunctivæ are congested and cyanosis appears. The urine contains albumin, indican and perhaps ketone bodies. Violent convulsions with incontinence of urine and fæces ensue. The knee-jerks are absent. The rectal temperature may be 108° to 112° F., and unless appropriate treatment be rapidly instituted the patient dies with a weakening pulse and respiratory failure. Gastro-intestinal features may be so severe that cholera is suspected. (2) **Heat exhaustion** comes on suddenly with weakness, giddiness and faintness. The temperature is 102° to 103° F., the pulse rapid and cardiac failure may supervene. Constipation is common. Unless properly treated heat-stroke may supervene. (3) **Heat cramp** is due to loss of chloride through excessive sweating, and affects stokers and engineers doing hard muscular work in hot atmospheres. The spasms are most painful; implicate the abdominal muscles and those of the extremities, and may last twenty-four hours or longer.

Diagnosis.—Absence of axillary sweating and diminution in urinary volume and chloride are important warning signals. *Cerebral malaria* with coma may be mistaken for heat-stroke, and vice versa. Splenomegaly and the presence of parasites in the blood films should prevent confusion, though in any case of doubt 10 grains of quinine dihydrochloride in 10 c.c. of distilled water should be injected slowly intravenously. *Cerebral hæmorrhage* into the pons is associated with coma and hyperpyrexia, but the pupils are pin-point in size and lumbar puncture may reveal blood-stained cerebro-spinal fluid. The coma of *uræmia, diabetes, alcoholism* and *drugs* is not accompanied by high fever.

Etiology.—All ages and both sexes may suffer. Strenuous work in conventional European clothing under tropical conditions, insufficient intake of water and salt, diseases of the skin affecting the sweat glands, direct exposure to the heat of a tropical sun, a shade temperature exceeding 110° F., lack of air movement and a high humidity, are the factors leading to heat exhaustion and heat hyperpyrexia. Debilitated and intemperate people and patients suffering from malaria and other fevers are especially susceptible. Failure of the mechanism governing heat production and heat loss, circulatory failure secondary to dilatation of peripheral vessels, dehydration from fluid loss, and chloride depletion resulting in cramps, are the means by which a thermal breakdown occurs.

Prognosis.—The case mortality is about 25 per cent. for heat hyperpyrexia. The prognosis largely depends on the rapidity with which treatment is instituted. In the choleraic type and in comatose patients with temperatures over 109° F. the outlook is grave. Even after the temperature has been reduced, debilitated patients may die from cardiac failure and collapse.

Treatment.—In heat exhaustion the patient is put to bed, if possible in a cool room. Citrates, sodium bicarbonate, sodium chloride and glucose are administered with drinks, and, if vomiting occurs, 1 to 1½ pints of normal saline may be injected intravenously. In heat hyperpyrexia hydrotherapy is essential. The patient is placed on a rush or wire mattress under a fan and sprayed with cold water. Ice may also be applied to the head and nape of the neck. As soon as the rectal temperature has reached 102° F. hydrotherapy is stopped. Venesection of 1 pint of blood is performed if cyanosis or convulsions be present. Iced saline enemata and intravenous injections of saline are also helpful, while collapse is treated with nikethamide, strychnine,

pituitary extract and digitalis. Heat cramp responds to hypertonic saline injections intravenously, and the daily consumption of salt should be markedly increased.

HAY FEVER (Hay Asthma), especially the constitutional variety, DYSENTERY, and CHOLERA, give rise to a certain amount of pyrexia of a continued type.

HAY FEVER (§ 179) is recognised by the violent attacks of sneezing.

DYSENTERY (§ 308).—Acute dysenteries may be attended at the onset by some degree of pyrexia, but much the most important symptom is diarrhœa.

In CHOLERA (§ 309) the abdominal cramps, collapse, and diarrhœa are the leading symptoms. During the collapse stage the temperature may be as high as 105° F. in the rectum, although in the axilla and mouth it is subnormal. In the reaction stage, if the patient lives, there is usually a degree or so of pyrexia lasting from a week to a fortnight.

Finally, there are several diseases which in their typical forms belong to Group III or, belonging to Group I, are seen perhaps before or after the eruption comes out, which may present pyrexia of a continued type. It is well in all cases of difficulty or doubt to remember this, and to pass in review the members of all three groups.

GROUP III. INTERMITTENT PYREXIA

§ **509.** In this group of diseases the pyrexia is of an INTERMITTENT (or remittent) type—*i.e.*, the temperature drops at regular or irregular intervals to normal (or nearly to normal). This group is distinguished from Group I by the complete absence of eruption. It is distinguished from Group II mainly by the wide variations of the temperature.

Common.		*Rare.*	
I. Malaria	§ 510	Amœbiasis	§§ 308, 336
II. Latent tuberculosis ..	§ 512	Malignant endocarditis ..	§ 50
III. Visceral syphilis	§ 514	Lymphadenoma	§ 572
IV. Acute septicæmia	§ 515	Pernicious anæmia	§ 539
V. Subacute septic conditions	§ 516	Leukæmia	§ 543
VI. Typhoid and paratyphoid fever (some cases) and occasionally influenza ..	§ 493	Opium habit	§ 900
		Trypanosomiasis	§ 518
		Trichiniasis	§ 593

The clinical investigation of these diseases is often attended by considerable difficulty. MALARIA, which may be regarded as the type of this group, is essentially a *paroxysmal pyrexia*, each paroxysm having three stages (cold, hot, and sweating), and each paroxysm being typically *separated by one or more days' interval of apyrexia*, except in certain subtertian fevers. TUBERCULOSIS and SYPHILIS have a daily rise and fall, and are good examples of *regular diurnally* intermitting pyrexia. ACUTE SEPTICÆMIA, on the other hand, is noted for the *irregular* character and wide range of its temperature and the severity of the rigors. CHRONIC SEPTIC CONDITIONS occupy a position midway between these two types—regular and irregular intermitting pyrexia. In a given case of intermitting pyrexia which has arisen in a tropical or subtropical climate, malaria, undulant fever, amœbiasis or tropical liver abscess are probable, but in England the commonest cause is probably latent tubercle. Tubercle as a cause of this type of fever is nearly as common in the tropics as elsewhere. The SERUM REACTIONS aid us to some extent in the diagnosis of this group.

Turning to the rarer diseases, which must always be kept in mind, MALIGNANT ENDOCARDITIS is chiefly remarkable for the *long course* it may run. In LYMPHADENOMA we usually find the enlarged *glands*; and in PERNICIOUS ANÆMIA the skin is very sallow, and the blood picture is characteristic.

It follows therefore that if we have a patient's temperature chart before us, and it shows definite intermissions or remissions, the disease will belong to one of three sub-groups:

A. REGULAR INTERMITTENT PYREXIA, with one or two days' INTERVAL, which contains only one disease—Malaria .. .. .. § 510

B. REGULAR INTERMITTENT PYREXIA occurring DAILY, such as Tuberculosis, and Visceral Syphilis .. .. §§ 512 *et seq.*

C. IRREGULAR INTERMITTENT PYREXIA, such as Septicæmia, and other pyogenic processes .. .. §§ 515 *et seq.*

§ 510. Malaria (Synonyms: Ague, Intermittent Fever, Remittent Fever, Jungle Fever). Malaria is a non-contagious disease caused by at least four different parasites which infect the red blood corpuscles of man and give rise to periodic paroxysms of fever, enlargement of the spleen and anæmia: transmission is by anopheline mosquitoes.

Symptoms.—The incubation period varies from ten to twenty days as a rule, but may be delayed for months. At onset the initial fever may be continuous or remittent in type. Some time elapses before the typical periodic fever, commencing frequently about mid-day with headache and aches and pains in the limbs and joints, develops. The ague paroxysm has three characteristic phases. First, the *cold* stage, lasting $\frac{1}{4}$ to 2 hours, in which the patient, who lies curled up in bed covered with blankets, feels and looks cold, and shivers or has a rigor despite the fact that the internal temperature is rising; the skin may be livid and the nails blue. This is followed by a *hot* stage in which blankets are discarded. The face is flushed, the skin dry and hot, and nausea, a high temperature (103° to 106°) and perhaps vomiting and delirium may ensue; this generally lasts four to five hours. Then begins the *sweating* stage, which lasts one to two hours and is accompanied by a critical fall in temperature and profuse perspiration which soaks the bedclothes. An apyrexial interval follows, its duration being determined by the species of infecting parasite. In *malignant tertian* the cold, hot and sweating stages are less pronounced and the temperature is rarely so high, but the fever generally lasts at least twelve hours and may continue for days. Examination of the patient during the fever generally reveals a tender and palpable enlargement of the spleen, parasites are to be found in the blood and secondary anæmia is frequent. Herpes is commonly seen on the lips.

VARIETIES OF MALARIA.—There are three common species of malarial parasites, the so-called benign tertian (*Plasmodium vivax*), the quartan (*Plasmodium malariæ*) and the malignant tertian (*Plasmodium falciparum*). A fourth species, *Plasmodium ovale*, is found in some districts: its effects are similar to those of *P. vivax*. There are several types of periodicity (Fig. 119): (1) TERTIAN fever with febrile attacks on alternate days (*P. vivax* or *P. ovale* infection): (2) QUARTAN fever, with attacks every fourth day, and a two-day apyrexial interval (*P. malariæ*): (3) an IRREGULAR or CONTINUOUS fever with a tendency to tertian periodicity

(*P. falciparum*): (4) DAILY OR OTHER PHASIC FEVERS are due to double infection by one or more species. Uncomplicated cases of the benign forms of malaria (*i.e.*, *P. vivax*, *P. malariæ* and *P. ovale*) are rarely fatal.

Malignant Tertian malaria (*P. falciparum*) carries a worse prognosis and is much more difficult to diagnose: the infected corpuscles adhere to one another and to the walls of the capillaries producing local tissue anoxia, and the symptoms vary according to the organs chiefly involved. (i.) *Cerebral malaria* causes delirium, stupor and coma, and may give rise to an epileptiform attack, various pareses and hemiplegia. Meningitis may be simulated. (ii.) "*Pernicious malaria*" is a term applied to the

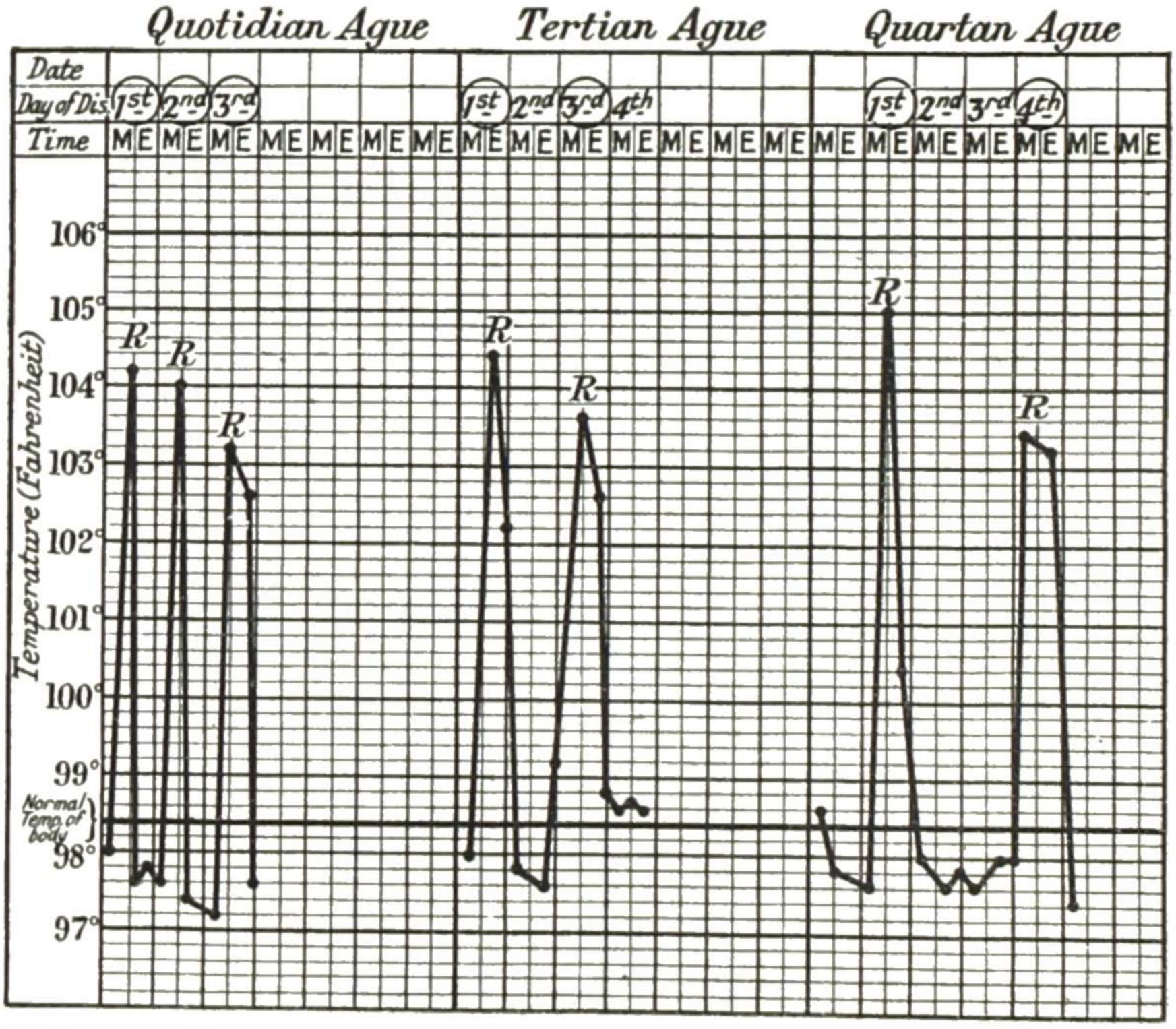

FIG. 119.—TYPES OF MALARIA.—Quotidian (daily) due to two cycles of vivax parasites; Tertian (every other day); and Quartan (every third day). "R" indicates the rigor which ushers in the cold stage.

severe and even grave manifestations of *P. falciparum* infections, which may end fatally unless promptly treated. (iii.) *Hyperpyrexia* causes an internal temperature of 107°–111° F., but the skin may be cold. (iv.) *Abdominal malaria*, by affecting the blood supply to the alimentary tract, may produce epigastric pain, vomiting even of blood-stained material, purging, and even the passage of blood and mucus (choleraic malaria). (v.) "*Bilious*" *remittent fever* may show merely hæmolytic jaundice associated with hyperbilirubinæmia, or toxic jaundice with a biphasic van den Bergh reaction and bile salts and bile pigments in the urine. Bilious vomiting, dark fæces and urobilinuria occur in both varieties, and in some cases very severe hæmolytic anæmia may ensue.

Diagnosis.—The spleen is always enlarged in malaria, though occasionally, especially at the onset or when a patient has been taking quinine,

it may not be palpable at the costal margin. In chronic cases in hyperendemic areas great enlargement ensues and the spleen often extends below the umbilicus or even into the pelvis. Not infrequently the liver is enlarged and tender. Malaria, especially during the primary fever, may be mistaken for other tropical febrile diseases such as typhoid, paratyphoid, relapsing fever and kala-azar : later, periodic fever commencing about midday, splenomegaly, anæmia and the response to specific remedies suggest the diagnosis. In all cases of tropical fever, every effort should be made to demonstrate parasites in the blood (Fig. 128) by taking blood films before treatment is commenced. After full doses of quinine dihydrochloride or of mepacrine B.P. (atebrin), the fever should fall within 96 hours ; if it remains up, or rises, provided the drug is being absorbed, the disease is almost certainly not malaria. In the apyrexial periods, urobilinuria, leucopenia and a monocytosis of 12 to 15 per cent. are suggestive of malaria, while hyperbilirubinæmia is not infrequent. Where secondary anæmia is present, polychromasia, anisocytosis and poikilocytosis are frequent findings.

Etiology.—Malaria has a widespread geographical distribution. In the tropics malignant tertian preponderates, giving rise to fatal epidemics ; in colder climates benign tertian manifesting a definite seasonal prevalence is met with. In Europe malaria does not occur above the 3000-feet level. All races and both sexes are susceptible and children surviving in hyperendemic areas gradually acquire a relative immunity or tolerance ; there is a progressive decrease in the parasitic and spleen rate as age advances.

Life Cycle of Malarial Parasites (see § 532).—(1) Sporozoites are inoculated with the saliva of infected anopheline mosquitoes during the act of biting. (2) On analogy with avian malaria, it is now believed that soon after inoculation into human beings, the parasites first enter cells of the reticulo-endothelial system and the cubical cells of the liver, where they undergo a non-pigmented cycle of asexual development (the exo-erythrocytic cycle). From this source, the red cells later become infected and relapses occur. During this initial cycle, the organisms are relatively insusceptible to anti-malarial drugs, which are so effective in clearing the asexual forms from the blood. In *P. falciparum* infections the exo-erythrocytic stage is short lived, numbering two or three cycles occupying a total of 6–7 days : consequently continuous treatment for 3–4 weeks not only controls the acute attack but, by persistent action in the blood, completely eliminates infection as the reservoir becomes exhausted. In *P. vivax* infections, the exo-erythrocytic cycles persist for several months in indefinite number : consequently no short course of treatment can be guaranteed to eliminate it completely. (3) After the parasites enter the red cells they become vacuolated, develop pigment and enlarge into amœboid-like schizonts. The pigment collects centrally, the chromatin divides and becomes distributed peripherally with its surrounding protoplasm, forming spores (merozoites) ; these ultimately rupture the corpuscle, escape and re-enter other corpuscles, so continuing the asexual or schizogonous cycle in man. (It is possible that the reticulo-endothelial system may be re-invaded by these blood forms.) (4) From time to time sexual forms (gametocytes) appear in the peripheral blood and when these are sucked up by a suitable anopheline mosquito fertilisation ensues in the stomach of the mosquito. The stomach wall is penetrated, and after a series of local developmental changes the mature oöcyst ruptures and sporozoites are liberated into the body cavity and reach the salivary gland and saliva.

Under satisfactory temperature conditions the mosquito phase of the life cycle takes about ten days.

Prognosis.—In the tropics malaria is a major cause of death, and cases of malignant tertian with pernicious manifestations frequently succumb rapidly if untreated. The benign infections are not so often fatal in the absence of complications. The chronic, repeatedly infected malaria case is liable to develop cachexia, pigmented skin, anæmia and "ague-cake" spleen and may die of intercurrent diseases like sepsis, pleurisy, pneumonia and dysentery, or in the presence of certain food deficiencies develop a hæmolytic nutritional macrocytic anæmia which is often fatal, especially in pregnancy. Blackwater fever may supervene in chronic infections with *P. falciparum*. Rupture of the spleen may follow slight trauma. Nephritis with œdema is not infrequent in quartan malaria. Other complications include neuralgia, iritis, corneal ulceration and retinal hæmorrhages, amnesia, while certain psychoses may follow cerebral malaria. Abortion often occurs. After a patient has left an endemic area, relapses can occur up to two years with malignant tertian fever; up to three years, and exceptionally considerably longer, with benign tertian; and up to seven years with quartan fever.

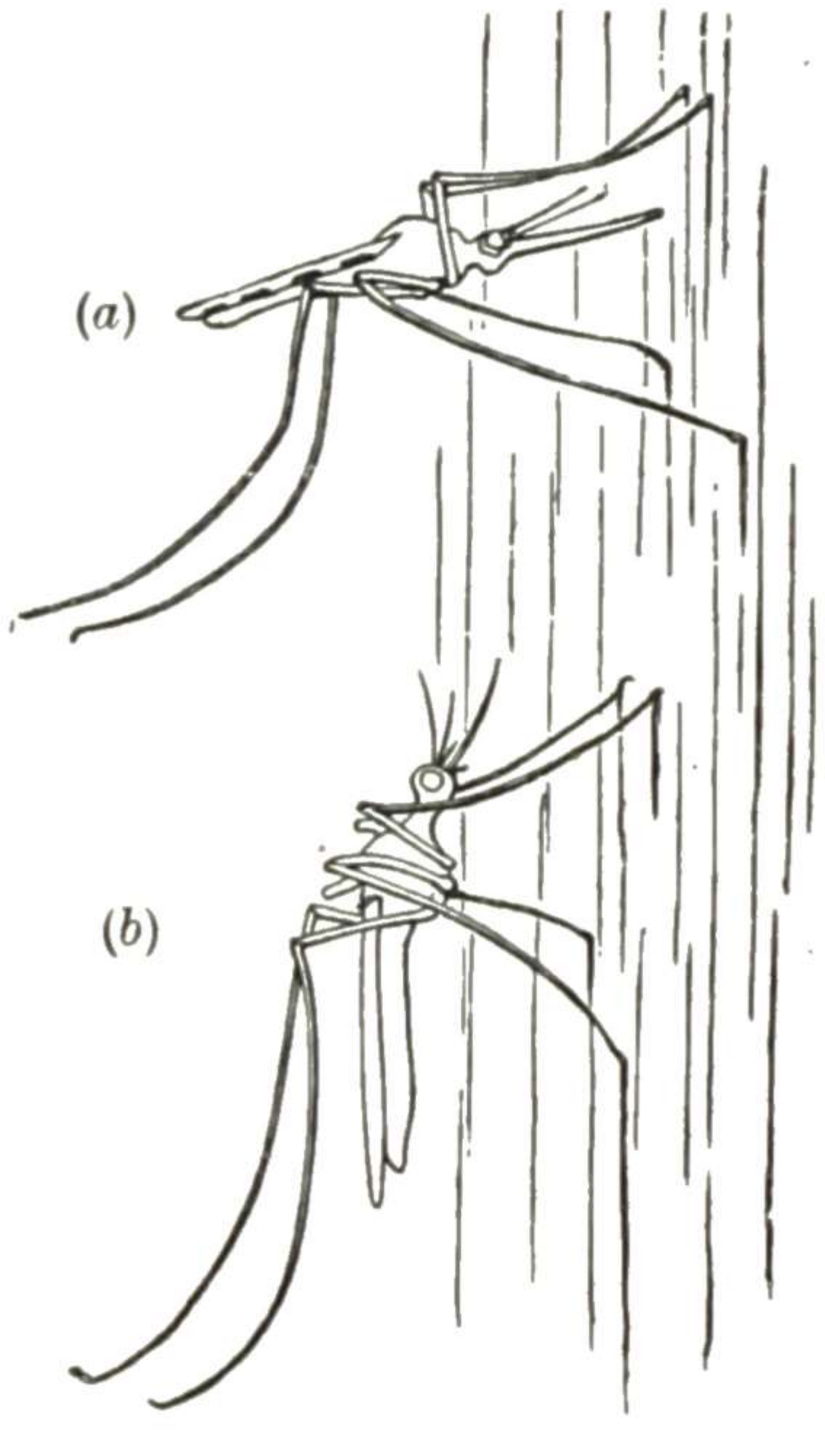

FIG. 120.—MOSQUITOES settling on a wall. There are two chief types of mosquitoes—Anopheline and Culicine—easily differentiated by their attitudes when resting upon a wall. Anopheles (*a*) is the more dangerous one, and is recognised by its spotted wings and its tilted attitude; Culex (*b*) rests parallel to the surface. Anopheline larvæ lie flat on the surface of puddles, whereas Culicine larvæ lie more perpendicularly, and if disturbed rush to the bottom of the pool. Anopheline larvæ are found in puddles which contain algæ and which are too large to be dried up in a week (time needed for the mature insect to be hatched). They are not found in pools which contain minnows, nor in shallow rain pools that are easily dried up. In certain districts they may be found even in rapid streams. 5 per cent. D D.T. in kerosene oil (about ℿ 60 to a pool of 1 square yard) kills all larvæ in six hours.

Prophylaxis.—In order to get rid of the larvæ of the mosquito, marshy tracts and swamps must be drained, cisterns and wells screened, and 5 per cent. D.D.T: in kerosene applied to stagnant or sluggishly flowing water. Bungalow gardens need special attention and, where possible, houses should be made mosquito-proof. Protection against *mosquitoes* is provided by mosquito nets at night, suitable clothing and mosquito boots by day: and the application of repellents, such as dimethylphthalate to exposed parts. *Individual protection* can be ensured by a dose on alternate days of paludrine 0·10 G. In malignant tertian (*P. falciparum*) malaria, this acts as a true causal prophylactic, and kills the parasite in the pre-erythrocytic stage: in benign tertian (*P. vivax*) malaria it is only a

partial causal prophylactic but completely suppresses clinical manifestations. Paludrine probably acts in the same way with *P. malariæ* and *P. ovale* infections. Instead of paludrine, mepacrine 0·10 G. daily can be used: chloroquine as a prophylactic is on trial.

Treatment.—The most efficient anti-malarial drug is the new compound *paludrine* which is remarkable also in the rarity of its toxic effects. Malignant tertian (*P. falciparum*) infections are usually eradicated by 0·10 G. t.i.d. orally for ten days. Benign tertian (*P. vivax*) infections, owing to their long exo-erythrocytic stage, often relapse after a short course of the drug; consequently 0·10 G. t.i.d. is given until the acute attack is controlled: this normally takes only a few days, but after this a maintenance dose of 0·10 G. weekly should be given for six months. Parasites still entering the blood from the exo-erythrocytic reservoir during this period are destroyed by the drug so that clinical manifestations of malaria do not appear, and after six months it is hoped that the reservoir of infection will have become exhausted. The effect of the drug on quartan and ovale infections has not yet been fully assessed. *Mepacrine* B.P. (atebrin) 0·10 G. t.i.d. for five days followed by 0·10 G. daily for three weeks will also eradicate malignant tertian (*P. falciparum*) infections, but stains the skin yellow and sometimes gives rise to gastro-intestinal or other disturbances. *Quinine* gr. 10 t.i.d. is also effective in controlling acute attacks of malaria, but none of the drugs will prevent benign tertian (*P. vivax*) from relapsing. *Pamaquin* B.P. (plasmoquine) 0·01 G. t.i.d., or the much less toxic *pentaquine* 0·02 G. t.i.d., act on the sexual forms of the parasites: in addition they lessen the incidence of relapse but must be combined with a short course of quinine, mepacrine or paludrine. Unfortunately pamaquin is somewhat toxic, and produces gastric symptoms and blueness of the skin (methæmoglobinæmia): at present it would seem satisfactory to rely on a weekly maintenance dose of paludrine to prevent clinical relapses.

Paludrine, mepacrine and quinine control acute attacks of malaria by a schizonticidal effect on the asexual parasites in the blood. Consequently their action is dependent on adequate absorption. In cases of great urgency, such as in "pernicious" or cerebral attacks of malignant tertian (*P. falciparum*) malaria, or where some factor such as persistent vomiting, collapse or coma, interferes with administration by mouth, then intravenous or intramuscular therapy is indicated. A suitable form of paludrine has been prepared for intravenous use. Alternatively mepacrine methanesulphonate B.P. (0·3 G. intramuscularly) may be injected: possibly the most rapid response is obtained with intravenous quinine dihydrochloride (gr. 10), the solution being given very slowly. In grave infections prompt treatment is essential as otherwise irreversible changes may occur in vital organs: one or two parenteral injections usually suffice to control the serious symptoms after which oral therapy can be instituted. In comatose cases removal of cerebro-spinal fluid by lumbar puncture may assist recovery. Intravenous dextrose solution may also be of value in dehydrated and unconscious patients.

§ 511. "**Blackwater Fever**" (Synonym: Hæmoglobinuric Fever), so named from the colour of the urine, is an acute illness developing in patients infected with latent or demonstrable malignant tertian malaria: clinically, it is characterised by the rapid destruction of red blood corpuscles, resulting in hæmoglobinæmia, hæmoglobinuria, fever, vomiting, jaundice and anæmia.

Symptoms.—The onset cannot be foretold. It generally comes on suddenly with chill, fever and loin pain, followed by epigastric discomfort, bilious vomiting and the passage of red urine which in severe cases soon becomes porter-coloured, due to the presence of the blood pigments, oxyhæmoglobin and methæmoglobin. Hæmolytic jaundice follows a few hours after onset and anæmia rapidly develops; 50 per cent. of the corpuscles may be destroyed overnight. Low blood-pressure, pallor, restlessness and cold extremities are characteristic of the early stage. Hiccough and Cheyne-Stokes' breathing often develop in severe cases. The spleen and liver are enlarged and tender and the urine shows albumen, blood pigments, urobilin and a characteristic brown granular sediment containing granular casts; red corpuscles are scanty or absent. Blood chemistry shows a hyperbilirubinæmia and increased blood urea; the plasma contains oxyhæmoglobin and a pigment, methæmalbumin, which had previously been regarded as methæmoglobin. In severe cases anuria and acidosis due to renal failure may supervene. Malarial parasites are sometimes found before and during the first few hours of an attack, but generally soon disappear. The fever generally declines in three to four days, the vomiting lessens and the urine clears; a post-hæmoglobinuric fever sometimes persists. Different clinical types include (1) Transient mild hæmoglobinuria. (2) Fulminating cases, often dying in forty-eight hours. (3) Anuric cases in which oliguria and anuria culminate in death some seven to ten days later with uræmia. (4) Intermittent hæmoglobinuria lasting eight days or longer. (5) Hyperpyrexia followed by death.

Mechanism of Hæmolysis and Anuria. The hæmolytic agent acts intravascularly on the corpuscles, liberating oxyhæmoglobin, and possibly originates from the reticulo-endothelium hypertrophied as a result of chronic malaria. The liberated blood pigment is dealt with by the liver and kidneys. Hyperbilirubinæmia, hæmolytic jaundice and pleocholia with bilious vomiting and dark brown stools result, and absorption of the excess of stercobilin produces urobilinuria. Some of the circulating hæmoglobin is secreted by the kidney as oxyhæmoglobin, and if the urine be acid is converted into methæmoglobin and acid hæmatin which, along with other debris, may block the tubules, but it is now considered that intra-renal vascular changes producing anoxæmia of the kidney are chiefly responsible for the failure of renal function and anuria.

Etiology.—It occurs in various hyperendemic areas of malignant tertian malaria in Africa, India, America and the Balkan peninsula, and generally affects the European, who has been taking quinine irregularly, after from one to five years' residence. The exact cause of the hæmolysis is not known, but it generally follows the administration of quinine or pamaquin. With efficient prophylaxis of malignant tertian (*P. falciparum*) malaria, as by the use of paludrine, blackwater fever should become exceedingly rare.

Diagnosis.—The disease must be distinguished from relapsing fever, leptospirosis and yellow fever by the spectroscopic demonstration of oxyhæmoglobin and methæmoglobin in the urine. The history of residence in malarial countries and of malarial infection is important.

Prognosis.—The case mortality is about 25 per cent. and death results from sudden heart failure, anæmia or anuria. One attack predisposes to another; even if the patient returns to Europe attacks may recur unless the malarial infection be eradicated.

Treatment.—Blackwater fever is best prevented by the eradication of malignant tertian malaria. The patient must be carefully nursed in a recumbent position. Large amounts of fluid containing glucose should be consumed and sodium bicarbonate and citrate given, since the tubules are less likely to be blocked if the urine be kept

dilute and alkaline. The diet must be restricted at first, and proteins only gradually introduced, in view of the renal damage. Intravenous injections of 1 to 2 pints of 5 per cent. dextrose assist the heart's action and help to combat toxæmia and suppression; the latter is treated by hot fomentations, cupping the loins, caffeine citrate and hot colonic lavage (120° F.). Blood transfusion is a life-saving measure in severe anæmia, and should be repeated whenever the red cell count falls below 1,500,000 per cu. mm. Cheyne-Stokes' breathing also suggests the necessity for transfusion. When parasites persist, paludrine or mepacrine should be administered. Iron and liver therapy may be instituted during convalescence.

§ 512. Latent Tuberculosis.—Tuberculosis is often said to be latent in the absence of the obvious signs or local manifestations. In all cases of unexplained pyrexia in this country, one of the possible causes to be suspected is tuberculosis in some part of the body. Although in some circumstances the extension of a tuberculous lesion in the lung may be entirely symptomless, and unattended by any appreciable rise of temperature, it is a good clinical axiom that active tuberculosis in any part of the body is usually associated with a daily intermitting pyrexia; and the degree of fever is a fair indication of the degree of activity of the process. Fig. 121 is a chart recorded from a case with active tuberculosis: the temperature drops each morning to (about) normal, and rises each evening one, two, or more degrees, occasionally *vice versa* (§ 513). The patient may seek advice on account of weakness, dyspepsia, loss of weight and other vague symptoms. Such a condition may go on for weeks without any local manifestations, as in the cases referred to under Tuberculous Meningitis (§ 727). The lungs, kidneys, peritoneum, and various other organs may be affected. (1) The commonest locality in adult life is the *lungs*. In this case X-ray evidence of disease often precedes physical signs: when these appear they may resemble bronchitis or simple pulmonary congestion (§§ 117, 131). (2) Apart from the lungs, the *meninges*, *peritoneum*, and other *serous membranes* are perhaps the commonest positions in childhood in which tuberculosis may be present without definite signs. (3) In the *kidney*, tuberculous pyelitis may be readily overlooked, and in suspicious cases the urine should be carefully examined for pus and tubercle bacilli (§ 412). (4) Tuberculosis may also be latent in other situations, such as the ear, spine, intestines, and other viscera; and, finally, the tuberculous process may be generalised, and give rise to *Acute Miliary Tuberculosis*.

§ 513. Acute Miliary Tuberculosis may be of the meningeal type, usually known as tuberculous meningitis (§ 727); of the pulmonary type (§ 117); or of the typhoid type, with which we are now concerned. It is characterised by intermitting pyrexia, prostration, and a tendency to the typhoid state—due to a generalised infection of the body by the tubercle bacilli.

Symptoms.—(1) The onset is insidious and for some time there are no localising symptoms or signs. The patient is often a child or young adult who complains of lethargy, which is found to be associated with an evening rise of temperature. The inverse type—*i.e.*, a lower temperature in the evening than in the morning—is said to be more common in this than in any other form of tuberculosis. (2) The lassitude

increases, the daily rise of temperature becomes more marked (Fig. 121), and with this increase of toxæmia there is headache, loss of appetite, often a dry tongue and insomnia. In the course of a few weeks the typhoid state develops, with wandering of the mind, a muttering delirium (especially at night) and progressive cachexia. (3) By now, localising signs have often shown themselves in one or more organs, with an especial tendency to signs of tuberculous meningitis. In others, there are signs of generalised bronchitis, with numerous fine râles scattered over the lungs: sometimes the involvement of the peritoneum is shown by general tumidity, with occasionally a palpable spleen. (4) Investigation of the cerebro-spinal fluid may be valuable, and X-ray examination of the lungs may reveal the typical "snow-storm" appearance of the lung fields.

Diagnosis.—(1) Cases of acute miliary tuberculosis in the early stage are sometimes admitted to hospital as bronchitis, in the later stages as typhoid fever. The

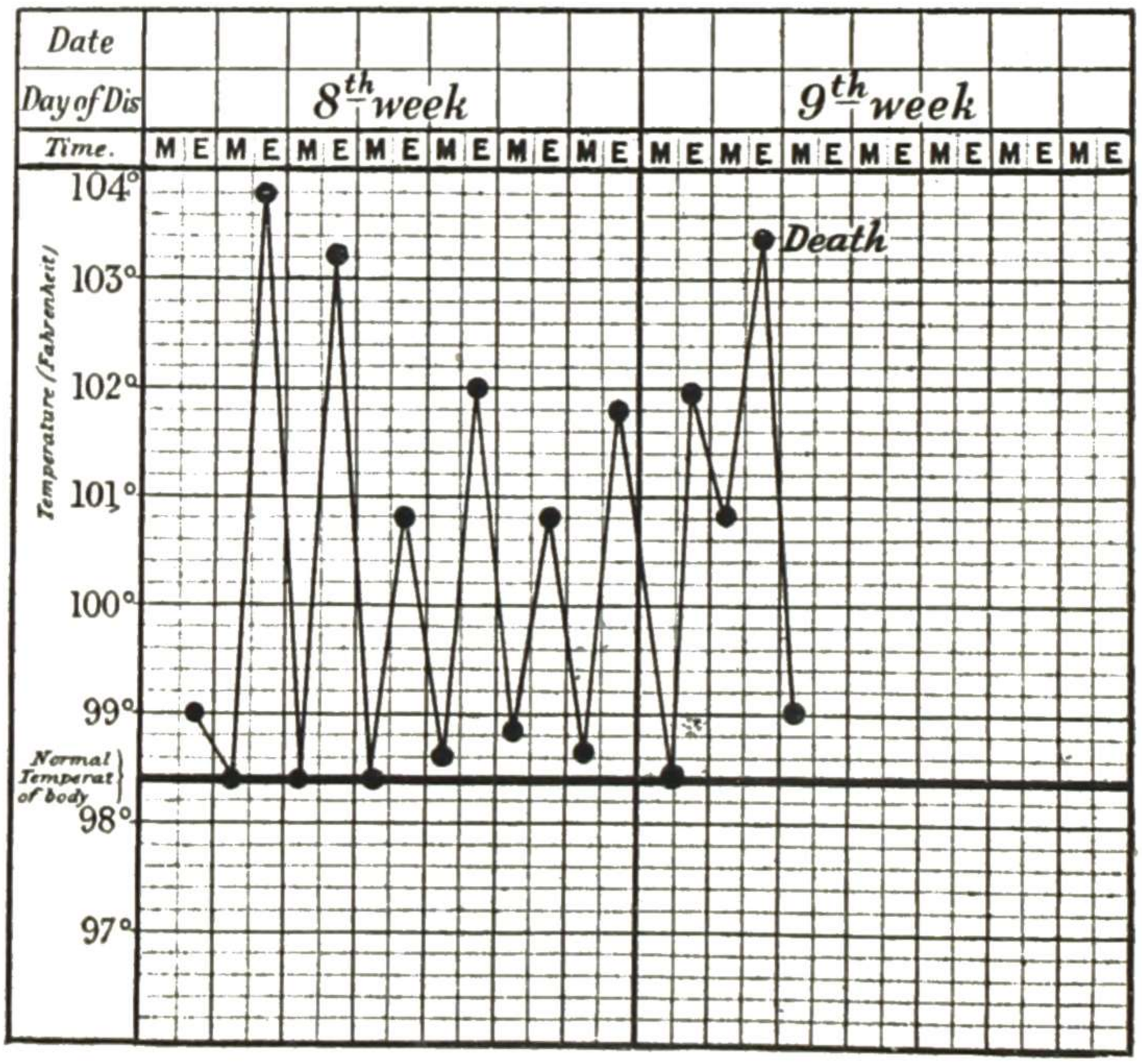

FIG. 121.—ACUTE MILIARY TUBERCULOSIS.—Geo. W——, æt. forty-nine. Seven weeks' history of vague illness before admission, during which time there was profuse hæmoptysis on one occasion. The signs in the chest were very indefinite during life. After death the lungs were sparsely studded with miliary tuberculosis. The liver and peritoneum were also dotted with tiny tubercles hardly visible to the naked eye.

possibility of miliary tuberculosis should be remembered in all cases of "*bronchitis*" attended by an intermitting pyrexia, especially in young adults. The presence of tubercle bacilli in the sputum is unusual; the sputum is usually small in amount, and indeed cough and sputum may be absent. (2) The course of the disease may closely resemble *typhoid fever*: the slowed pulse, rose-red spots and a palpable spleen favour typhoid. The Ehrlich-Diazo reaction occurs in both typhoid and acute tuberculosis, but not the Widal reaction. Choroidal tubercles are sometimes visible on ophthalmoscopic examination, and settle the diagnosis.

Etiology.—The disease is due to a general dissemination via the blood stream (bacteræmia) of tubercle bacilli throughout the body. The usual cause is rupture into a vein of a subacute or chronic focus (often a caseating gland), in a person with a low resistance.

Prognosis.—The disease is almost uniformly fatal in the course of four to eight or more weeks (see § 117). Death occurs by coma, sometimes by pulmonary or other complications. The height and range of the temperature is a fair measure of the virulence and activity of the morbid process.

Treatment.—In such widespread mischief treatment has in the past been uniformly unavailing: now streptomycin is on trial and successes with this have been recorded. As regards prevention, it should always be remembered that convalescence from pulmonary tuberculosis should be very thoroughly re-established before treatment is stopped.

§ 514. Visceral Syphilis.—There are two different stages of syphilis in which intermitting pyrexia may occur. (*a*) At the first development of the primary roseolous eruption there may be some fever. This is generally overlooked, but at other times it may be accompanied by thirst, loss of appetite, and shivering. It always occurs within sixty-five days of the date of the infection, and is only present if no early treatment be given. (*b*) In the later secondary and tertiary stages of the disease intermitting pyrexia may occur in connection with syphilitic

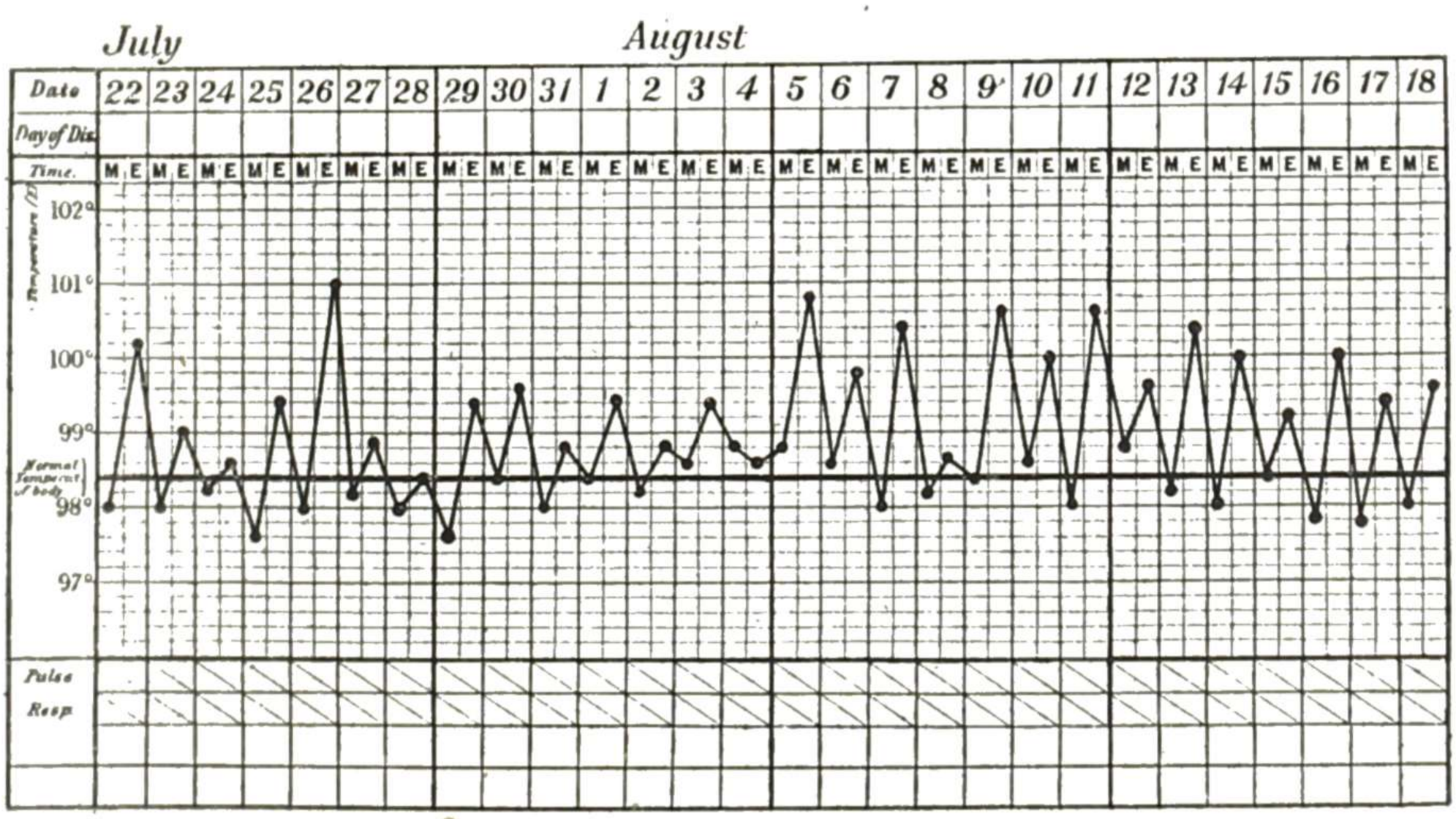

FIG. 122.—VISCERAL SYPHILIS.—Annie L——, æt. sixty-six. The temperature subsided under iodide in large doses, but she ultimately died of exhaustion and hypostatic pneumonia. P.M. —Gummata of liver and bones, hypertrophic cirrhosis, widespread fibrosis of organs.

periostitis, or gummata of the internal organs. Syphilitic lesions of this kind should be considered in cases of prolonged intermitting pyrexia, especially when attended by anæmia. The morning temperature is normal, but in the evening it goes up one, two, or more degrees (Fig. 122). There may also be rigors, nocturnal sweating, and paroxysms of pain in the joints; these symptoms speedily subside when iodide is given. In obscure cases careful investigation should be made of the eyes, liver, ribs, clavicles, and other bones; the Wassermann reaction should be tested, and iodide of potassium tried. In rare instances the fever may be continued and simulate typhoid.

§ 515. Acute Pyæmia, or **Septicæmia,**[1] **is a disease characterised by a wide range of temperature, accompanied by rigors and sweating, due to the direct infection of the blood by a micro-organism, usually through some breach of surface in skin or mucous membrane.**

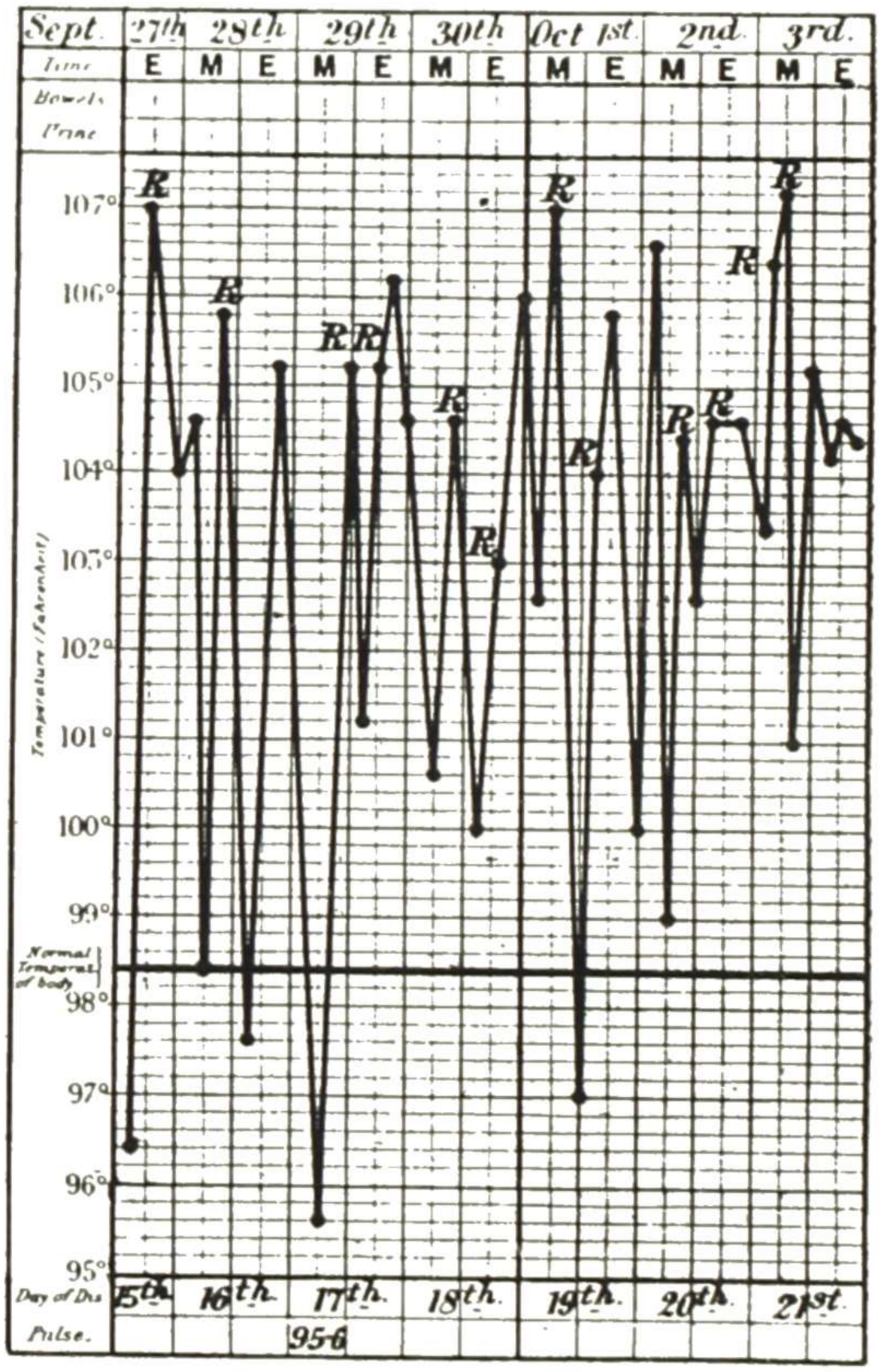

FIG. 123.—ACUTE PYÆMIA (typical of an irregularly intermitting pyrexia).—Catherine W—— æt. six, admitted to hospital. She was taken ill somewhat suddenly fourteen days previously with shivering and vomiting. On admission she was in a condition of prostration. There were no physical signs excepting a systolic bruit over the whole cardiac area, and slight enlargement of the spleen. Three days later, there was rusty sputum with streaks of blood: dulness and crepitations over the right back. She was delirious from time to time, and died six days later. At the autopsy pus was found in the mastoid cells and sinus thrombosis secondary to long-standing middle ear disease (of which a history was now obtained), infarcts in the kidney, and pyo-pneumothorax secondary to rupture of one of the gangrenous-looking abscesses of the lung.

The *Symptoms* are (1) pyrexia, which runs a very characteristic course, and is distinguished from all other diseases not of septic origin by the *wide* and *very irregular* range of the temperature (Fig. 123). The remissions may occur several times a day, and have not the diurnal regularity which marks the two preceding classes of disease (§§ 512 and 514). There may be as much as 6° or 7° difference between the temperature in the

[1] In *Bacteræmia*, living organisms are present in the blood stream but do not produce clinical symptoms and signs. *Septicæmia* is a clinical rather than a pathological conception. A bacteræmia is present, and in addition the patient exhibits signs and symptoms of infection of the blood stream. *Pyæmia* is a condition of metastatic abscess formation due to the presence of infected thrombi in the blood stream.

course of a few hours: when it rises suddenly the temperature is often accompanied by a rigor, followed by very profuse perspiration and a rapid fall. The pulse is rapid and compressible. (2) Toxic Symptoms include prostration, headache, anorexia, nausea, a dry furred tongue, often constipation, and aches and pains in the muscles: the skin is sallow, and anæmia may develop. The mind is clear at first, and remains so for a considerable time, but towards the end there is a tendency to the typhoid state. (3) Later on in the disease emboli may occur in different parts of the body: in the lungs they give rise to a generalised congestion and patches of pneumonic consolidation or abscess (as in the case given in Fig. 123): the spleen may become palpable: and deposits of pus may occur in or around the joints or in other parts of the body. The serous cavities may contain pus, constituting empyema or pyo-pericarditis. The leucocytosis and other changes in the blood may aid diagnosis; a positive blood culture clinches the diagnosis, and should always be performed when a *local* cause for pyrexia cannot be found.

Portal Pyæmia is a condition where the primary focus is in the alimentary tract, the veins of which drain into the portal vein. Appendicitis is the commonest cause and the abscesses are usually confined to the liver. A high leucocytosis with a negative blood culture aids the diagnosis of portal pyæmia.

Acute Osteomyelitis (Acute Periostitis) is a pyæmic process which may set in very suddenly, usually after an injury to one of the superficial bones, generally the tibia. In children there may be no history of injury. The diagnosis is easy when the tissues round the diseased bone are swollen, but during the first day or two pain is often complained of near a joint, and may lead one to diagnose rheumatic fever.

The *Diagnosis* of septicæmia is easy when there is an external wound or abrasion, and should never be difficult when there is the wide variation of the temperature, coupled with the rigors and the sweats. The chart of a typical acute case is like nothing else. When due to some internal cause, it may resemble malignant endocarditis, typhoid fever, coli bacilluria, pneumonia, malaria, remittent fever and acute rheumatism. But when carefully recorded temperatures of several days are available, and a thorough examination of the organs is made, the diagnosis should not be difficult. *Streptococcal* septicæmia is marked by high fever, rapid pulse (over 120), joint pains, skin rashes, rapidly developing anæmia, hæmaturia and often diarrhœa. *Staphylococcal* septicæmia is often associated with a previous history of boils or carbuncles, an initial slow pulse and a tendency to form abscesses in the renal cortex, bones and joints. With *pneumococcal* infections there is no primary focus, a hot dry skin, herpes labialis and a considerable rise in the respiration rate even in the absence of lung signs.

Etiology.—The principal cause is the introduction of a virulent organism either through the *skin* or through a *mucous membrane.* In addition there is often a particular susceptibility of the patient. (1) A mere prick or scratch of the skin may permit the entrance of micro-organisms: cases have been caused by doctors and nurses becoming infected by an accidental prick or cut during a surgical operation or dressing an infected

wound. In hospital practice there may be a spread into open wounds of virulent organisms (especially hæmolytic streptococci) from the nose or throat of a carrier, from soiled fingers and instruments, and even with dust particles. Similarly organisms can pass through mucous membranes, even without a visible abrasion : in this manner a variety of bacteria and viruses can enter the blood stream through the tonsils, nasopharynx, mastoid cells, bronchial mucosa, and the intestinal biliary and urinary passages. Special attention should be directed to the uterus : *recent abortion, perhaps criminally induced, should always be borne in mind when a young woman is admitted with septicæmia.* After recent parturition, the surface of the uterus resembles an open wound, and offers a large surface for the passage of organisms directly into the venous sinuses, by introduction of an infected glove or instrument : here again the original source may be a droplet infection from the nose or throat of a doctor or midwife. The disease is then called PUERPERAL FEVER, or Puerperal septicæmia : when the infection is derived from a previous case of puerperal septicæmia it is especially virulent due to the phenomenon of *passage.* (2) A lowered resistance is due to hygienic causes—overcrowding, lack of fresh air and sunlight, and to poverty : or to special *predisposing causes*—diabetes mellitus, alcoholism, hyperthyroidism, chronic nephritis, agranulocytosis, and ill health due to bad teeth or infected tonsils.

The *Prognosis* has been remarkably altered by modern chemotherapy. Whereas cases of intense septic infection from a wound or from parturition used to run a rapid and fatal course in ten to twelve days, nowadays the majority respond to a sulpha-drug, penicillin or streptomycin when given early and in adequate doses. There still remains a small proportion of cases in which the disease is so fulminant that treatment has no time to be effective ; or the responsible organism may be resistant to all chemotherapeutic agents at present available. Not all cases are of this extreme virulence, and there are a number in which small quantities of septic matter are constantly leaking into the general circulation from some *internal* source over many weeks or months, especially when there is an untreated or undrained primary focus (as in the patient referred to in Fig. 123). There is, in fact, no hard-and-fast line to be drawn between the *acute* septicæmia now under consideration and the *subacute* and *chronic* septicæmia due to pent-up pus or ulceration described below (§ 516). Acute pyæmia is most serious and, if untreated, often fatal. Death may occur either by the intensity of the infection, asthenia, or complications. The *untoward symptoms* are a very high temperature, frequent rigors, or cerebral symptoms. The most frequent *complications* are (1) bronchopneumonia, which invariably occurs in severe cases ; (2) pericarditis, peritonitis or pleurisy, which usually becomes purulent ; and (3) suppurative inflammation of the spleen, liver, brain and other organs, consequent on the infected emboli ; (4) malignant endocarditis. Among the sequelæ in certain less acute cases which recover may be mentioned a destructive form of arthritis.

Treatment.—The indications are (1) to find the cause and to identify the invading organism; (2) whenever possible to administer chemotherapeutic drugs which will lead to the destruction of the causal bacteria; (3) to relieve the symptoms and support the strength of the patient. (1) The *source of the infection* must first be identified. Subsequently drainage of the infected material will be instituted: this may necessitate surgical drainage, *e.g.*, of an abscess cavity, osteomyelitis, etc. (2) *Chemotherapy* indicates the use of drugs which exert a bactericidal or bacteriostatic effect on the invading organism, but without serious detriment to the patient. Salvarsan was the first of these substances discovered by Ehrlich. Modern chemotherapy has led to the use of sulphanilamide and its derivatives, the *sulphonamides* or "sulpha-compounds". These drugs act by inhibiting the multiplication of susceptible organisms (bacteriostasis), thus allowing the defensive mechanisms of the body to destroy them. Sulphanilamide and sulphapyridine have now been mainly replaced by sulphathiazole, sulphadiazine, etc. The drugs most in use are shown in Tables XXVIII and XXIX. They are administered by mouth, after crushing the half-gramme tablets, or intravenously as the sodium salts and well diluted: for surface wounds sulphanilamide powder can be locally applied. It is usual to give a large initial dose and to maintain an adequate blood concentration by four-hourly doses subsequently. During their administration plenty of fluid and an alkaline mixture must be prescribed, as otherwise the drugs or their acetyl derivatives may crystallise out and produce blockage of the renal tubules. Other toxic effects include nausea, mental depression, skin rashes, and drug fever: it is advisable to discontinue administration after a week, unless the blood is watched for leucopenia and agranulocytosis. In certain cases it is helpful to determine the sensitivity of the organism to the particular sulphonamide beforehand, to ensure an adequate therapeutic effect. *Penicillin* is an antibiotic and chemotherapeutic substance: originally derived from the mould *P. notatum* and now mainly from *P. chrysogenum*, it has revolutionised medical treatment. Penicillin acts chiefly as a bacteriostatic and bactericidal agent on a wide variety of susceptible organisms (Table XXIX) and the penicillin sensitivity of organisms can be determined beforehand in the laboratory. It is usually administered by three-hourly subcutaneous or intramuscular injection, its dose being measured in Oxford Standard units (Table XXX). In its more purified forms, it is almost free of undesirable side-effects and even considerable over-dosage produces no toxic effects on the patient: drug fever and urticaria are more common with the less-purified products. It can also be used locally by injection into abscesses, empyemata, and into the cerebro-spinal canal, as well as locally into wounds, as pastilles in the mouth, and by inhalation as an ærosol. *Streptomycin* is derived from the soil organism *Actinomyces griseus*, and differs from penicillin in being effective against such gram-negative organisms as those of the coli-typhoid group, and against the tubercle bacillus (Table XXIX). As it is less rapidly

Table XXVIII.—Average Doses of some of the Principal Sulphonamide Preparations as at Present Recommended.

Disease	*Drugs Recommended with Initial and Subsequent Doses in Grammes*	*Remarks*
Pneumococcal Pneumonia.	*Sulphadiazine, Sulphamezathine, Sulphamerazine* or *Sulphathiazole.*	Especially useful against types 1, 7 and 10: less useful against types 2, 3 and 5 (Whitby). Blood concentration should be 5–10 mgm. per cent.
Adult	2 : 2 : then 1 four-hourly for 36 hours	
Child 1– 3 months.	¼ : Then ⅛ four-hourly for 36 hours	
6–24 „ .	½ : Then ¼ four-hourly for 36 hours	
3 years . .	¾ : Then ⅜ four-hourly for 36 hours	
5 „ . .	1 : Then ½ four-hourly for 36 hours	
Hæmolytic Streptococcal Infection (including Puerperal Fever).	*Sulphadiazine, Sulphamezathine, Sulphamerazine, Sulphathiazole* or *Sulphanilamide.*	
Severe	1st 24 hours, 1 : 1 : 1 : 1 : two-hourly; then 1 : 1 : 1 : 1 : six-hourly.	Doses decreased as temperature falls, but continued at about 2½–3 G. daily for at least 5–6 days after temperature is normal (Colebrook).
	2nd 24 hours, 1 four-hourly.	
	If vomiting: Sodium Salts of drugs 2 G., then 1 G. four-hourly intramusc., or well diluted with N-saline intravenously.	
Moderate and mild	1st 24 hours, ¾–1 four-hourly, reducing as temperature drops to 1 t.d.s. for several days after temperature is normal.	
Meningococcal Meningitis.	*Sulphadiazine, Sulphamezathine, Sulphamerazine* or *Sulphathiazole.*	Blood concentration should be 5–10 mgm. per cent. within 12 hours of starting treatment.
Child 0– 2 years .	1 : Then ½ four-hourly.	
2– 5 „ . .	1½ : Then ¾ four-hourly	
5–10 „ . .	1½–2 : Then ¾–1 four-hourly	
10–15 „ . .	2–2½ : Then 1 four-hourly for 3 days. Then gradually reducing doses for further 6 days.	Can use 20 c.c. saturated solution (0·5 per cent.) Sulphanilamide in N. saline intrathecally, for initial dose.
Adult 15–40 years .	2 : 2 Then 1 four-hourly for 3 days : then 1 eight-hourly for 6 days.	Can combine with penicillin therapy.
Over 40 „ . .	Slightly smaller doses.	
	If vomiting, give sodium salt intramusc. or well diluted with N-saline intravenously, 1 G. four-hourly, till vomiting ceases, then continue with oral doses.	
Gonorrhœa.	*Sulphathiazole* or *Sulphadiazine.*	Penicillin therapy is more effective.
Acute or chronic .	1 four-hourly for 5 days.	
Staphylococcal pyæmia.	*Sulphathiazole.*	Combine with penicillin therapy and blood transfusion.
	4 four-hourly for 24 hours : then 3 four-hourly.	
B. Coli in urine.	*Sulphamezathine* or *Sulphacetamide.*	Combine with alkali.
	1 six-hourly for 5 days.	
B. Proteus and Strept. fæcalis in urine.	*Sulphathiazole.*	Combine with alkali if urine is not already alkaline.
	1 six-hourly for 5 days.	
B. Dysenteriæ (Flexner or Shiga).	*Sulphaguanidine, Sulphasuccidine* or *Phthalylsulphathiazole.*	Not effective against Sonne dysentery.
	6 : 3 four-hourly : later 3 t.i.d.	
Lymphogranuloma Inguinale.	*Sulphathiazole* or *Sulphadiazine.*	Combine with Fouadin.
	½ four-hourly for 5 days: after interval of 3–5 days, give two further courses of ½ six-hourly for 5 days.	

TABLE XXIX.—THE EFFECT OF SULPHONAMIDES, PENICILLIN, STREPTOMYCIN, AUREOMYCIN AND CHLOROMYCETIN ON ORGANISMS.

		Remarks.
Sulphanilamide	*Effective against :* B. coli, Cl. welchii, Lymph. inguinale, Strep. hæmolyticus. *Less effective against :* Br. abortus, Prot. vulgaris, N. gonorrhœa, N. meningitidis, Pneumococci.	
Sulphathiazole	*Effective against :* B. anthracis, B. coli, Proteus vulgaris, N. meningitidis, Pneumococci, Staph. aureus, Strep. hæmolyticus. *Less effective against :* N. gonorrhœa, Strep. fæcalis.	Readily excreted. Well tolerated by most. Liable to produce anuria and hæmaturia.
Sulphadiazine and derivs., viz., Sulphamerazine and Sulphamezathine (Syn. Sulphamethazine)	*Effective against :* B. anthracis, B. coli, B. dysenteria (Flexner and Shiga), B. friedlander, Cl. welchii, Lymph. inguinale, N. meningitidis, Pneumococci, Staph. aureus, Strep. hæmolyticus. *Less effective against :* N. gonorrhœa, Proteus vulgaris.	Very well tolerated, and slowly excreted. Toxic effects on liver and kidneys (especially sulphadiazine).
Sulphaguanidine, Sulphasuccidine (Syn. Succinyl-sulphathiazole), and Phthalyl-sulphathiazole	*Effective against :* B. dysenteria (Flexner and Shiga).	Largely insoluble in gut.
Sulphapyridine	Rarely prescribed on account of toxic side-effects.	
Penicillin	*Effective against :* B. anthracis, Cl. œdematiens, Cl. welchii, Coryn. diphtheriæ, Leptosp. icterohæmorrhagica, M. catarrhalis, N. gonorrhœa, N. meningitidis, Pneumococci, Spirillum minus, Staph. aureus, Strep. hæmolyticus, Trep. pallidum, Trep. pertenue (yaws), Vincent's organisms. *Less effective against :* Actinomyces, B. proteus and Strep. fæcalis (in urine), Strep. viridans.	
Streptomycin	*Effective against :* A. ærogenes, B. coli, B. dysenteriæ, B. friedlander, B. proteus and B. pyocyaneus, Bruc. tularense, H. influenzæ, Salmonella, Streptococci, Staphylococci. *Less effective against :* B. typhosus, M. tuberculosis.	
Aureomycin	*Effective against :* B. coli, Pneumococci, Staphylococci, Streptococci, Strep. fæcalis, Rickettsia organisms, virus of Lymphogranuloma Inguinale and of Primary Atypical Pneumonia. *Less effective against :* Brucella infections.	Administered orally : passes freely into C.S.F.
Chloromycetin	*Effective against :* B. coli, B. proteus, Ps. pyocyanea, Rickettsia organisms, virus of Primary Atypical Pneumonia. *Less effective against :* Brucella infections, B. typhosus and B. paratyphosus.	Administered orally.

TABLE XXX.—COMMON USES AND AVERAGE DOSES OF PENICILLIN—AFTER FLEMING. (Doses in Oxford Units by deep subcutaneous injections unless otherwise stated.)

Actinomycosis. 60,000 3-hourly for 21 days. Also local injections into abscesses of 1,000–6,000 8-hourly via capillary tubes.
Anthrax. 15,000 3-hourly for 5–6 days.
Arthritis, pyogenic. 20,000 3-hourly: plus 30,000–50,000 in 3 c.c. into joint on alternate days.
Bacterial Endocarditis. 120,000 3-hourly for 42 days.
Boils. 15,000–20,000 3-hourly for 5–6 days, with local cream (B.P.) to prevent spreading.
Bronchiectasis. 100,000 in 3 c.c. b.d. with special inhaler.
Bronchitis, acute. 50,000–100,000 in 3 c.c. b.d. or t.i.d. with special inhaler: or as for pneumonia.
Children. 1,500–2,000 per lb. body weight per day, by 4-hourly injection (neonatals 6 hourly).
Cystitis and pyelitis. 15,000 3-hourly gives high urine concentration and often effective against Strep. fæcalis and B. proteus.
Diphtheria and carriers. 20,000–30,000 3-hourly.
Empyema, acute. 120,000 in 10 c.c. into cavity daily, or 240,000 in 10 c.c. into cavity each 2 days: gives adequate blood concentration also.
If for local effect only, 20,000–40,000 in 20–40 c.c. into cavity daily.
Gonorrhœa, acute. 30,000 3-hourly for 5 doses or 100,000 and repeat once in 8 hours.
Ludwig's Angina. 40,000 3-hourly for 3 days.
Meningitis, acute. 30,000 3-hourly for 5–7 days. Also 10,000 each 24 hours intrathecally. Also sulphonamides.
Ophthalmia. Drops of 2,500 per c.c. plus ointment 400–800 per G.
Osteomyelitis, acute. 60,000 3-hourly for 12–21 days.
Peritonitis, acute. 30,000 3-hourly—diffuses freely from blood.
Pneumonia. 15,000–30,000 3-hourly for 5–7 days.
Rat-bite fever. 20,000–30,000 3-hourly for 7–10 days.
Sinusitis, early. 1,000 per c.c. with ½ per cent. ephedrine in N. saline as spray.
Late: wash out with 1,000 per c.c.
Syphilis, early. 40,000 3-hourly for 60 doses, with bismuth and arsenicals.
Late: 6–10 doses bismuth each 4 days with Pot. iod.; then as for early disease; repeat penicillin after 3 weeks.
Vincent's Angina. 15,000–20,000 3-hourly with penicillin lozenges.
Weil's disease. 40,000 3-hourly for 4 days.

excreted than penicillin, it is injected each 6–8 hours: its present state of impurity makes reactions common, and organisms rather rapidly develop resistance to its use. *Chloromycetin* (chloramphenicol) was originally obtained from *Streptomyces venezuelæ*, and is now prepared synthetically: its chief value is against all forms of typhus, the enteric fevers and virus pneumonia. *Aureomycin*, obtained from the mould *Streptomyces aureofaciens*, is effective against a wide range of organisms, including a number of viruses. These last two antibiotics are usually given orally. (3) The patient's general resistance is encouraged by a free supply of fresh air, at least 5 pints of fluid daily, with sugar as the principal food, restful sleep and especially in anæmic cases by blood transfusion.

§ **516. Subacute and Chronic Septic Conditions** (*e.g.*, **Abscess, Ulceration etc.**) also give rise to intermitting pyrexia. The various clinical conditions met under this heading are due to the absorption of some septic or toxic material into the circulation. The possible sources of the sepsis are numerous, and may be grouped into two divisions—(*a*) ABSCESS

and (*b*) SIMPLE INFLAMMATION often with ULCERATION (internal or external). Clinically, the former is more acute than the latter, and indeed, the former might be called subacute, the latter chronic, septicæmia.

(*a*) ABSCESS (PENT-UP PUS).—Pus never forms in any part of the body—*e.g.*, in the pleura (empyema), in the liver (hepatic abscess), or elsewhere—without an intermitting or remitting pyrexia: this may be accompanied by "chills," "shivers" or "rigors." Before the clinical thermometer was invented, these shiverings (sometimes followed by sweatings) were the chief symptoms by which the formation of pus was identified. It must however be remembered that chemotherapy, and especially the use of the sulpha-drugs, may allow pus to develop—sometimes in considerable amounts—while the patient remains apyrexial: it is thus easy to mask the presence of a dangerous infection in a hidden area, *e.g.*, in the mastoid air-cells, or in a subphrenic abscess. In the presence

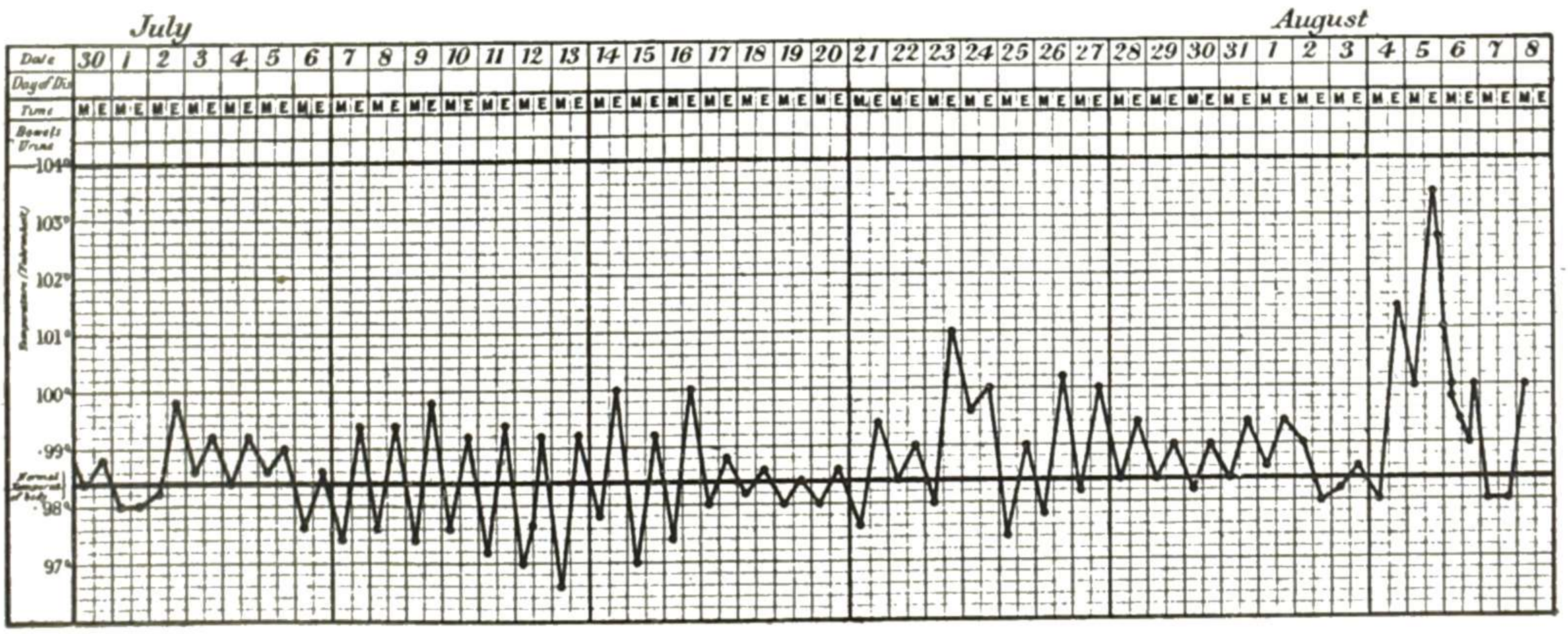

FIG. 124.—CHRONIC PYÆMIA.—Frank T——, æt. thirty-one, had had an attack of gonorrhœal rheumatism two years before, from which he had recovered. The present illness had come on quite gradually a month or so before admission. Stiffness and pain in the joints being the chief symptoms, and the urethra being *absolutely normal*, it was regarded as a case of chronic rheumatism, though none of the usual remedies had any effect. The joints became progressively worse, and though he complained of abdominal pain from time to time attention was not directed to that cavity. He died some two months later suddenly from perforation of the appendix. A review of the case pointed to a chronic septic process having its origin in the appendix, and especially affecting joints which had been previously diseased.

of an abscess, there are marked constitutional effects such as lassitude, debility, pallor (though with a hectic flush on the cheeks), and loss of weight. The blood should always be examined, and the presence of leucocytosis with an increase in the polymorphonuclear cells will afford strong confirmation that pus is present.

Etiology.—Abscess or pent-up pus in any position may produce these symptoms, and careful search should be made for abscess of the liver, gall bladder, pelvic cellulitis or abscess, appendicitis (Figs. 123, 124), caries of the spine, mastoiditis, sinusitis, a dental apical abscess, intracranial abscess, empyema, pyonephrosis, subphrenic and perinephric abscess, etc. Pain is the chief localising symptom, but it may be absent, especially in children. On giving free exit to the pus the pyrexia should rapidly subside.

(*b*) SIMPLE INFLAMMATION, with or without ULCERATION of an INTERNAL

or EXTERNAL surface, is always attended by some degree of intermitting pyrexia, running a more chronic course than the foregoing. This fever also differs from the last in the usual absence of definite rigors. Sometimes the shivering may not amount to more than "chills down the spine"—perhaps thought to be malaria—and sweating which is hardly noticed. The morning temperature is normal, or almost normal, and it is raised one or two degrees some time during the day. Anæmia and failing health are always present, and some degree of leucocytosis is usual. This kind of fever, due to prolonged suppuration and attended by chronic wasting, was formerly known as *Hectic Fever* (Greek, *ἑκτικός* "habitual"). When due to a discharging sinus—for instance, connected with caries, or necrosis of a bone, or a bed-sore—the cause is obvious. But the condition may also be set up by inflammation or ulceration of any of the mucous membranes or internal passages—*e.g.*, ulcerative colitis, appendicitis (Fig. 124). It is called *Urinary Fever* when it arises from chronic infection of some part of the urinary passages—*e.g.*, with a stone impacted in the ureter, or a urethral stricture, or chronic pyelitis. This cause may be suspected if there be a history of renal colic. Similarly, *Acute Cholangitis* (infection of the biliary passages) may be suspected if there be a history of biliary colic. When the infection, due to gall-stones, is situated in the *gall-bladder*, colic and jaundice may be absent, and the patient complains only of the "chills."

§ 517. The **rarer causes of Intermitting Pyrexia** are fully described elsewhere.

Amœbiasis of the liver (§ 336) or amœbic hepatitis may for months show few signs other than bouts of irregular fever interspersed with periods of apyrexia, and no symptoms other than those of dyspepsia, flatulence, constipation or irregularity of the bowels. Occasionally there is a history of right shoulder pain. There may have been no dysentery, and examination of the stools and of fæcal material collected on sigmoidoscopy may fail to reveal cysts or vegetative forms of *Entamœba histolytica*. The liver signs may be indefinite, but generally the organ is demonstrably enlarged and tenderness is elicited below the costal margin on deep inspiration. When there are associated physical signs such as evidence of consolidation or fluid at the base of the right lung, or when X-ray reveals upward bulging or "splinting" of the diaphragm, an abscess of the liver is almost certainly present. There is a mild polymorphonuclear neutrophil leucocytosis, but even when the condition of hepatitis has gone on to abscess formation a neutrophilia not exceeding 80 per cent. and a total count not exceeding 15,000 per cu.mm. are common findings. Amœbiasis should be suspected in obscure cases of fever when the patient has lived in the tropics. Within 48–72 hours, the temperature responds to emetine. Such patients show marked improvement in health when the parasites are eradicated. It is among the amœbic carriers that many cases of hepatitis and liver abscess are found, as infection often persists unsuspected for long periods.

INFLUENZA, TYPHOID, and PARATYPHOID fever, especially when modified by previous inoculation, and other diseases described in Groups I and II may be attended by pyrexia of an intermitting type.

KALA-AZAR has usually intermittent fever after the first period, during which there is fever of a remittent type (§ 505).

TYPHOID FEVER during the first two weeks of its course is attended by typically continued pyrexia, but in the concluding stage of the disease the temperature gradually drops each morning to normal, and the case may be seen for the first time in this stage. Under certain other circumstances also the temperature may be intermitting —viz.: (i.) In rare instances it may commence with symptoms of ague (see *Varieties*, p. 601); (ii.) in very mild cases; (iii.) after lasting a few days, the fever sometimes aborts and takes on an intermitting type.

Various LOCAL INFLAMMATORY DISEASES, other than the septic conditions previously mentioned, may at times be attended by intermittent pyrexia. In cirrhosis of the liver, for instance, a prolonged fever with daily oscillations is occasionally observed.

MALIGNANT ENDOCARDITIS (Multiple Systemic Embolism) (§ 50) is always attended by pyrexia of an irregularly intermitting type, sometimes with sweatings and rigors, very much resembling the chart of septicæmia, though the temperature is usually a little more diurnally regular, and rigors are not usually so frequent (compare charts, Figs. 122 and 124). The diagnosis of these two diseases is sometimes very difficult. Malignant Endocarditis is favoured by (i.) a loud cardiac murmur detected quite

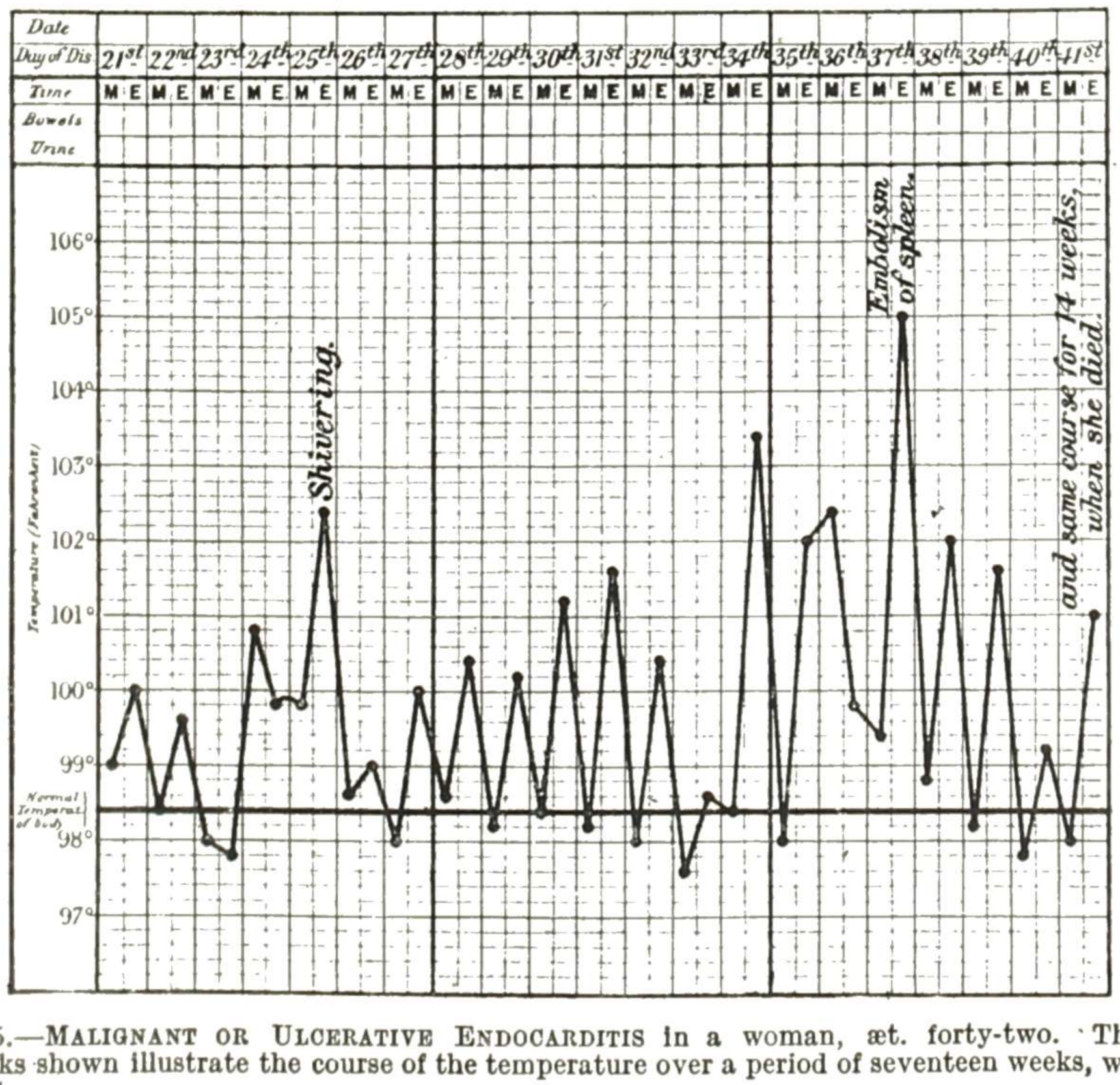

FIG. 125.—MALIGNANT OR ULCERATIVE ENDOCARDITIS in a woman, æt. forty-two. The three weeks shown illustrate the course of the temperature over a period of seventeen weeks, when she died.

early in the case; (ii.) a history of acute rheumatism; (iii.) the secondary emboli in this disease are more frequently found in the systemic arteries, such as those of the spleen, liver, and kidneys, and they do not result in abscesses. In PYÆMIA the emboli occur primarily in the arteries of the lungs, and from the very beginning they suppurate and form abscesses, which constitute centres of secondary infection elsewhere.

HODGKIN'S DISEASE is recognised by the enlargement of the lymphatic glands and pyrexia of a remitting or intermitting type. Sometimes a periodic temperature occurs with glandular enlargement confined to the mediastinal or retroperitoneal glands (Pel-Ebstein Syndrome).

In PERNICIOUS ANÆMIA the temperature is sometimes subnormal, but it is more frequently attended by exacerbations of fever of an intermitting type. The disease is also identified by the intense sallowness of the skin and the condition of the blood.

In ACUTE LYMPHATIC LEUKÆMIA the temperature is high and irregular, somewhat resembling that of septicæmia. It can be diagnosed by the examination of the blood, when there is found to be an increase in lymphocytes (§ 543).

The OPIUM OR MORPHIA HABIT (§ 900) is attended from time to time by attacks of intermittent pyrexia, during the reaction stage, in which there are cold, hot, and sweating stages. Cases are recorded where no cause could be found, but the attack ceased on giving opium.

MALIGNANT DISEASE, especially when involving the liver, is often accompanied by intermittent fever.

§ 518. African Trypanosomiasis (Syn.: Sleeping Sickness), a disease confined to tropical Africa, is characterised by enlargement of the glands, fleeting intermittent erythematous rashes, irregular pyrexia, excessive sleepiness and mental degeneration.

Symptoms.—The incubation period following the bite of infected tsetse flies varies from one to three weeks. Two stages are recognised: (1) In the *first* trypanosomes are demonstrable in the blood and lymphatic gland juice. Irregular, remittent or intermittent fever with periods of apyrexia may last for some months. The pulse is rapid, the respirations accelerated. Patches of circinate erythema appear, mainly on the trunk, and localised puffiness may implicate the feet, legs and face. Polyadenitis with painless enlargement of the posterior cervical glands is common; sometimes the epitrochlear, supraclavicular and axillary or femoral glands may be the group affected. The spleen is generally palpable at this stage and deep hyperæsthesia, especially over bones like the tibia, is characteristic; there is often a definite latent period after pressure before pain appears. This stage is well marked in Europeans, but may not be so evident in natives. Many months may elapse before the second stage, due to trypanosomes invading the central nervous system, occurs. (2) Here the cerebro-spinal fluid contains an excess of lymphocytes and globulin: trypanosomes are sometimes difficult to find. The patient first develops lack of concentration, headache, insomnia, loss of weight and slight tremor of the tongue associated with polyadenitis. Later, the countenance becomes apathetic and morose, emotional instability and laziness increase, and the patient drops off to sleep even when eating. The gait is shuffling, the speech mumbled and slow, and fibrillary tremors develop in the lips and hands. Ataxia is marked and the reflexes increased. Finally, owing to muscular weakness, the patient takes to bed; bed-sores and flexure contractures develop and coma or convulsions terminate the picture.

Etiology.—The trypanosome is introduced into the body by the bite of a tsetse fly. There are two varieties of trypanosomiasis: (i.) a chronic form, lasting months to years, due to *Trypanosoma gambiense* and occurring more in the western half of tropical Africa. This is transmitted by *Glossina palpalis* and allied species; these tsetse flies require shade and proximity to water. (ii.) An acute form, lasting weeks or months, due to *T. rhodesiense*, occurs especially in Rhodesia, Tanganyika and Nyasaland. It is carried by *G. morsitans* and related species which breed in more open orchard bush.

Diagnosis.—This can only be made with certainty by finding the parasite by gland puncture, in the blood or in the cerebro-spinal fluid. White rats should be inoculated with blood in doubtful cases.

Prognosis.—With treatment many patients infected with *T. gambiense* and, in the early stages, with *T. rhodesiense* recover, but in the later stages of rhodesiense infections the outlook is grave.

Treatment.—Early infections of either type respond to suramin (G. 1 weekly)

intravenously for 5 to 10 doses : albuminuria and nephritis may follow its administration. The drug, a cyclical urea compound, does not penetrate to the central nervous system and consequently is ineffective in advanced infections. It is therefore usually combined with tryparsamide G. 2–4 weekly intravenously for 10 to 12 doses. This drug, a pentavalent arsenical preparation, enters the nervous system and must always be used in late cases. Unfortunately *T. rhodesiense* tends to be resistant to arsenical drugs and consequently neither drug influences the late stages of this infection. Tryparsamide may produce optic atrophy. Trypanosomes readily become resistant to arsenic; and various diamidine compounds, such as stilbamidine, pentamidine or propamidine (G. 0·1 to 0·3 intravenously daily for 7 to 14 doses) may be tried. These drugs may produce toxic effects and they often fail to clear parasites from the central nervous system. Propamidine is said to produce abortion in pregnant women. *Preventive measures* include travelling at night to avoid tsetse bites, the wearing of veils, the destruction of breeding-places and the trapping of flies. A single injection of suramin, or of pentamidine, is said to protect against infection for several months.

Chaga's disease in S. America is also due to a trypanosome. **Trichinosis** (§ 593) is usually accompanied by intermittent fever. **Rat-bite** fever may show a temperature of an intermittent type (§ 505).

THE GENERAL TREATMENT OF MICROBIC DISORDERS

Remedial treatment has, for the most part, been given under each disease, but there are some important matters relating to all infections in common which must now be referred to—viz., **Immunisation, Serum Therapeutics, Chemotherapy, Notification** and **Isolation, Disinfection, Diet,** and the treatment of **Pyrexia** and **Hyperpyrexia.** In the first three of these we find ourselves on the threshold of discoveries which are revolutionising the methods of prevention and treatment of infective disorders.

§ 519. Immunity means the ability of the body to defend itself against injury by pathogenic micro-organisms or by their toxic products. Immunity is, as a rule, only relative, and its effectiveness depends upon the balance between the virulence of the invading organism and the resistance of the body.

The virulence of bacteria, in general, depends upon their invasive power and their ability to withstand and overcome the defensive forces of the host, and also upon the production of toxic substances. The latter, in addition to having a damaging effect on the tissues of the host, may also paralyse the protective mechanism by inhibiting the production of phagocytes or by destroying circulating leucocytes. The toxic products of bacteria comprise :

1. *Exotoxins* are soluble substances elaborated by the living organisms and set free in the body fluids or in culture media. They can be obtained from the filtrate of cultures in fluid media after the bacteria have been removed by a Seitz or porcelain filter. Exotoxins are relatively unstable and the majority are destroyed by exposure to sunlight or by boiling for a few minutes. They rapidly deteriorate on storage and may be converted into less toxic substances known as *toxoids* by the action of certain chemicals. Inoculation of a suitable animal with an exotoxin stimulates the production of its particular *antitoxin*; toxoid is equally efficient for

this purpose and is preferable since it is much less poisonous. The organisms of diphtheria, tetanus, botulism and gas gangrene develop powerful exotoxins which in the case of the first three possess a great affinity for nervous tissue. Some strains of streptococci and staphylococci are also capable of producing exotoxins from which it has been possible to separate various components—*e.g.*, a fibrinolysin, a coagulase, an erythrogenic factor, and a spreading factor (hyaluronidase).

2. *Endotoxins* are intracellular toxins which are retained within the bodies of the bacteria until they die and disintegrate. In contrast to exotoxins they are not present in filtrates and are relatively stable, showing resistance to heat and deteriorating but slowly on storage. They cannot be converted into toxoids. Their injection into animals stimulates the production of antibacterial sera which have little or no antitoxic neutralising action. Meningococci, cholera and typhoid bacilli are examples of organisms which form an endotoxin.

3. *Lysins* are enzyme-like substances which digest tissue cells. A lysin may be designated according to the organism which forms it—*e.g.*, staphylolysin, or the cells it destroys—*e.g.*, hæmolysin.

4. *Aggressins* are toxic bodies produced by many pathogenic bacteria, especially when growing in the tissues. They are said to interfere with phagocytosis. Various bacterial products may, however, possess this property and the existence of a specialised substance of this type is uncertain.

5. *Ptomaines* are not substances secreted by bacteria but are toxic bodies resulting from the bacterial decomposition of proteins. They are closely allied to the vegetable alkaloids and are not destroyed by heat. The chief examples are cadaverin and putrescin.

Immunity may be either natural or acquired. NATURAL IMMUNITY is shown by the high resistance of some races to certain infectious diseases, and by the insusceptibility of certain animals to some human infections. Thus hens are resistant to tetanus toxin. But even in this case the immunity is only relative; given a sufficient dose of tetanus toxin, even a hen will succumb. So also sheep, which live an open-air life, are as a rule immune to the tubercle bacillus; but when they are kept penned in, in insanitary conditions, they may become infected. On the other hand, a natural immunity may often (though not always) be enhanced by suitable treatment.

ACQUIRED IMMUNITY is the resistance developed to an organism or its toxin as a result of natural disease or artificial treatment. It is common knowledge that some diseases rarely attack the same person twice, *e.g.*, typhoid, scarlet fever and small-pox. Here again the immunity is relative and not absolute; second and even third attacks have been described. Artificially acquired immunity is the crux of this subject, and is the line of research along which immense progress has been made, and even more is promised. Inoculation of small-pox is probably the earliest example. The serum from a small pustule in a mild case was rubbed into the skin,

and a mild attack of small-pox ensued. Later, Jenner, observing the immunity to small-pox of those already infected with cow-pox, succeeded in immunising people against small-pox by artificial vaccination with cow-pox (§ 480). Whether cow-pox is an allied disease, or a modified form of smallpox, is still a subject for argument, but quite immaterial from the point of view of immunity. After this discovery little progress was made till Pasteur began his work on hydrophobia and anthrax—the starting-point of our knowledge of this now vast subject.

Artificial immunity is divided into two classes, Active and Passive. In *Active immunity* the resistance is developed by the body as a result of the injection of the toxin, or organism or virus. Vaccination is therefore an example of active immunity. In other conditions it is developed by injecting graduated doses of the poison, beginning with weak and working up to strong doses. The modification of the strength is variously obtained: dead bacteria may be used, or old or overheated toxins, or the bacteria may be grown on unsuitable media, such as one containing disinfectants, or at an unsuitable temperature, or in the absence of oxygen or in excess of it. Minute doses only may be used or the appropriate anti-serum added. Later, larger doses or more toxic strains are employed, and finally it may be necessary to give large doses of living virulent bacteria, or fully potent toxin.

In *Passive Immunity* the serum from an animal which has been actively immunised against the poison in question is injected into the subject, thus effecting an almost immediate increase in the patient's resistance to it.

While the observed facts of immunity are clear and definite, the theoretical explanations of the problems are far less satisfactory. It is most important to remember that the theories are only explanations, and are valueless if they cease to provide a satisfactory basis for further research and speculation. As regards the neutralisation of toxin by antitoxin, three theories at present hold the field; not one is completely satisfactory. Ehrlich's theory is based on the presumption that toxin and antitoxin unite as do strong acid and strong base. However, the discovery of the fact that with age a toxin loses its toxicity, but will still unite with the same quantity of antitoxin, necessitated the introduction of a "toxone," a substance allied to a toxin; from this point there have been continual modifications of the original theory to meet newly discovered facts. The explanations are nearly as complicated as the facts they set out to explain—an obvious disadvantage. Nevertheless, this theory has been the starting-point of the greatest amount of work on the subject. Madsen and Arrhenius have suggested that the combination of toxin and antitoxin is comparable to "mass action" in chemistry, on the analogy of the combination of a weak acid and base; the theory has proved helpful, but does not cover all the possibilities. Lastly, Bordet, forsaking chemistry in its narrower sense, has suggested that the union is of the nature of adsorption, the physical electrical interaction of substances in the colloidal state, and this theory, which makes the least hard and fast rules, seems to be the most fully observed.

To account for the almost unlimited production of antitoxin which may follow the injection of comparatively small doses of toxin Ehrlich offers the following suggestions: Toxin and body cell consist (from the chemical point of view) of a number of complicated organic substances or "side chains," loosely attached to a central nucleus. A toxin can only exert its poisonous properties when one of its own side chains unites with the appropriate side chain of the cell. This union is permanent,

and so puts an end to the vital activities not only of the single side chain but also of the whole cell ; when this process takes place extensively, death results. In the case of a non-fatal dose of toxin, the cells ultimately recover ; as they recover they regenerate the side chain neutralised by the toxin. The number of side chains regenerated not only replaces those destroyed, but provides an excess ; as the cells do not need them they are shed into the general circulation and form the antitoxin. As a result of repeated injections the body not only produces a great quantity of antitoxin, but develops the power of developing even more, and that without the stimulus of a further injection of toxin. An immunised animal may be bled repeatedly, till the total volume of blood lost is in excess of its total blood volume and yet the quantity of antitoxin in the new formed blood (*i.e.*, its antitoxin titre) will equal if not exceed that of the blood before the depletion.

The modern view of immunity is a compromise of the theories of Ehrlich, Madsen and Arrhenius, and Bordet, and it is now considered that both chemical and physical reactions involving molecular structure and colloidal phenomena are concerned in the process of antibody production and in the union of an antibody and the antigen which stimulates its formation. Chemical research has demonstrated that antibodies are serum globulins ("immune globulins") possessing specific chemical groupings that permit them to unite with their corresponding antigens.

The practical application of our knowledge of immunity in the treatment of disease must now be briefly considered.

§ 520. Immune Therapy.—This may be undertaken for prophylaxis or treatment. 1. Examples of *prophylaxis* in *passive immunity* are the use of diphtheria antitoxin, of tetanus antitoxin, and of convalescent measles serum for temporary protection of individuals exposed to these infections. *Prophylactic active immunity* may be produced by the use of vaccines as for typhoid and paratyphoid fevers, cholera, plague, staphylococcal and catarrhal infections ; by a mixture of toxoid and antitoxin or by toxoid alone against diphtheria ; by toxin against scarlet fever ; and by the use of a related virus for smallpox or a modified one for hydrophobia.

2. *Therapeutic immunisation* carried out in the presence of the disease depends mainly on the administration of the appropriate antitoxic or antibactericidal serum. Such sera have proved of value in diphtheria, tetanus, botulism, meningococcal and pneumococcal infections.

It must be emphasised here that the success which has attended *chemotherapy* with penicillin, the sulphonamides and allied products has caused this treatment to displace the use of antisera in many infections (streptococcal, pneumococcal and meningococcal).

Vaccine Therapy is based on the principle of producing in the patient a condition of active artificial immunity, and various methods are employed, all leading to this end. The most usual is the injection of suspensions of the dead bodies of the infecting micro-organisms. Almroth Wright and Douglas, while studying the properties of phagocytosis by the leucocytes, originally described by Metchnikoff, found that the proportion of organisms ingested by the polymorphonuclear leucocytes was increased in tests where the blood of persons who had received injections of the organism in question was employed. Further investigation showed that this property of phagocytic increase was situated in the serum, for it did not occur in tests with washed leucocytes. On the other hand, it was found in tests with washed leucocytes from a normal person under treatment with the serum of an inoculated individual. The substance which was the cause of this phenomenon they called *opsonin*. The actual immunity, however, depends on many substances of which opsonin may be taken as a type: agglutinins, precipitins, bacteriolysins and bactericidal bodies.

In its essential constitution every vaccine is a suspension in some fluid of the various organisms employed, but the infinite variety of methods used in making this suspension render it impossible to describe every type. From the infecting focus a culture is made, and from this culture the various types of organism are picked off and examined. Pure cultures of each pathogenic type are prepared, then washed off in weak phenol-saline and a homogeneous suspension made. This is then standardised either macroscopically, by comparing its opacity against that of a standard suspension; or microscopically, by comparing, in a stained film made from equal quantities of the suspension and of blood, the number of organisms and of red blood corpuscles. *Sensitised vaccines:* before standardisation the suspension of organisms is treated with the serum of an animal, or a person immunised against the organism in question. *Detoxicated vaccines* are made by dissolving or otherwise destroying the cell wall of the organism. The doses of most vaccines are calculated in millions of organisms per cubic centimetre, and may be put up in separate ampoules, or kept in bulk in rubber-capped bottles. A word of warning is needed. A vaccine consists of a suspension of protein in a very weak antiseptic, and is therefore a fair culture medium. Great care is necessary not to infect it before or during use. When supplied in ampoules it is unsafe to attempt to seal off a partly used ampoule for use next time.

Vaccines are usually administered subcutaneously over the deltoid, and the usual antiseptic precautions observed. When there is a marked local reaction in the arm, other sites such as the buttock, thigh or abdominal wall are preferable. It is usual to give vaccines in progressively increasing doses, with an interval of a week between the smaller doses, and 10–14 days between the larger ones. The beneficial results depend on the relationship between dose and interval, for the immunisation has to be developed by the patient. Vaccine therapy falls into undeserved disrepute when progressively increasing doses are given without reference to the reaction of the patient. It is a safe rule to increase at each successive injection unless there is a reaction. A *local* reaction consists of swelling, redness or soreness at the site of injection. A *general* reaction varies from slight fatigue and sleepiness to fever and malaise lasting for days, even weeks if the dose has been too large. A *focal* reaction is a lighting up of the infective focus. When the patient feels better after a dose, increase at first by half and later double the preceding dose. In delicate or allergic persons the initial dose should be very small. Never give a dose near a menstrual period, nor until a general reaction has passed off. The "negative phase" or phase of lowered resistance described by Wright and reputed to last from a few hours to a day or two after administration of a vaccine, is not now thought to be as significant as originally considered.

Prophylactic oral vaccination is extensively used on the Continent, especially against typhoid, dysentery and cholera, on the hypothesis that it is advantageous to render the local tissue (in this case, the intestinal mucosa) immune. Although agglutinins appear in the blood as a result of administration of a vaccine by this route they are of lower strength compared with subcutaneous or intramuscular inoculation.

§ 521. Serum Therapy.—In certain diseases, or when it is desired to develop immunity in the shortest possible time, it is possible to confer passive immunity on the patient by injecting an antitoxic or antibacterial serum. Those diseases in which the symptoms are chiefly due to exotoxins—*e.g.*, diphtheria, tetanus, gas gangrene, botulism, require treatment with a serum rich in antitoxins. When the symptoms are chiefly due to endotoxins, give a serum rich in antibacterial substances, although with the exception of Sclavo's serum for anthrax this type of serum is not usually so effective. Antitoxic and antibacterial sera are derived from animals immunised respectively to the particular toxin or organism in question: occasionally an antibacterial serum (or antiviral serum in the case of a virus infection) is obtained from a convalescent patient. In some cases the doses are calculated in arbitrary standard units; in others, in terms of volume. The bulk of serum employed may be considerable.

Serum may be given by four routes: (1) Intravenous. This is the method of

choice when immediate immunisation is required, for the antitoxin is thus instantly available. It is also the best way when doses have to be large, or frequently repeated, as in dysentery or pneumonia, or when its use has been unduly delayed. On the other hand, the immunity is less lasting, and there are certain dangers which will be mentioned later. (2) Intramuscular. The gluteus maximus and the vastus externus are the most convenient muscles. This method is less rapid in its effects, the maximum concentration of antitoxin not being present till twenty-four hours after the injection. It is much safer, and requires less elaborate technique. (3) The subcutaneous method is the slowest and the easiest. The maximum concentration is not reached till seventy-two hours after injection. The injection may be made in the buttocks, abdominal wall or thighs. This route may be of great value as a reserve in support of the intravenous, the antitoxin being maintained in the circulation by slow absorption. (4) Intrathecal. In the treatment of tetanus this route may be of value. A lumbar puncture is performed and cerebro-spinal fluid is drawn off in excess of the quantity of serum which is afterwards injected. A Record or all-glass syringe (autoclaved or dry-sterilised) are essential.

Hypersensitivity to serum is due to the proteins of the serum and not to the antitoxins. It may manifest itself in two chief ways:

(1) *Immediate reaction.* This develops within a few minutes to half an hour of the injection and is particularly prone to occur in asthmatic and other allergic individuals, especially with intravenous injections. *Symptoms* vary from mild urticaria to those of acute anaphylactic shock with respiratory embarrassment and cyanosis ending in sudden death. Rarer symptoms are vomiting, abdominal pain and diarrhœa. To eliminate or minimise the degree of this immediate reaction it is important to determine before any therapeutic foreign serum is administered whether or not the individual is sensitive to such serum—especially when there is a history of previous serum administration or if the person has had asthma or any form of protein hypersensitiveness. Hypersensitivity is tested for by the intracutaneous inoculation of 0·1 c.c. of the serum. If the person is sensitive an urticarial wheal develops at the site of inoculation within half an hour. Then preliminary desensitisation must be carried out before giving the major part of the dose. This is done by beginning with a small subcutaneous dose of 0·1 c.c. diluted with saline solution and doubling the amount every half an hour until 1·5 c.c. have been given. If no reactions have occurred it is then usually safe to give the balance of the dose. *Treatment* of anaphylactic shock is by the injection of 1 c.c. of adrenalin B.P. intramuscularly. The action of the adrenalin is transitory and anaphylactic symptoms may recur after the immediate effects have worn off: in severe reactions it is necessary to repeat the dose. Artificial respiration may be performed and oxygen administered. If adrenalin be not available, atropin or pituitary extract may be given.

(2) *Delayed reaction or serum sickness* usually comes on from the 7th–12th day after an injection of foreign serum and may also occur in persons who have had an immediate reaction. There is usually an erythematous rash or urticaria starting first at the site of inoculation and later becoming generalised. Fever, joint pains, general glandular enlargement and malaise are common. These symptoms occur in about 10 per cent. of the cases when less than 10 c.c. are given and in about 90 per cent. when more than 50 c.c. are used. They are less frequent when concentrated sera are injected. A subsequent injection of the same protein causes the same symptoms, usually within twenty-four hours. *Treatment* is by the subcutaneous injection of adrenalin, and repeating this when necessary. Auto-hæmotherapy often helps (and see § 656).

ALLERGY is defined as a natural inherited condition of hypersensitiveness (cp. § 609). Serum sickness is one manifestation of allergy; it probably explains a number of other conditions. Of these the best known, and the most common, is Hay Fever, the result of hypersensitiveness to the pollen of Timothy and other grasses. Under this heading also comes the hypersensitiveness shown by certain people towards various foods, such as strawberries, eggs, shell-fish and the flour of various grains; to the dandruff of

some animals, as the horse and the cat; to dust, especially house dust, and to certain plants and flowers. Various symptoms are produced; food-stuffs as a rule cause urticarial rashes; animals and flowers, asthma. Complete sets of common proteins are available for testing by intradermal injection or scarifying the skin and applying the substance to be tested to the scratch. In from 10–20 minutes a reaction appears which varies in its intensity with the sensitiveness of the patient. A sensitive patient may react to many substances at the same or at different times. Treatment consists in preventing exposure of the patient to the protein to which sensitivity is proved, or, if this is impossible, in desensitization by a course of inoculations, commencing with minute doses of the substance responsible. Benadryl or antistin administered by mouth are of proved value in the prevention and treatment of allergic states by their antihistamine action.

Special Methods for each Disease.

Diphtheria.—An antitoxic serum has been on the market since 1895. When given early enough and in large enough doses, antitoxin has been found to be of the greatest value for patients suffering from the disease (see further details in § 494).

Treatment.—The remedy should be used as early as possible in the disease. In the mildest cases a single injection of 4000–8000 units should be given; in moderate cases two injections of from 16,000–48,000 units may be required; in severe cases 64,000–100,000 units, repeated on two or more days in succession. The smaller doses for mild cases can be given intramuscularly: the larger doses for cases of moderate and severe type must always be given intravenously: with modern refined sera, anaphylactic reactions are unusual. The earlier the antitoxin is given, the more favourable the prognosis. In suspicious cases, where there is delay before obtaining a bacteriological report, inject the antitoxin without waiting for the report. Children tolerate antitoxin well, and should receive the same doses as adults. *Effects.*—In the course of twenty-four hours there should be an improvement in the patient's symptoms: the membrane ceases to extend, or perhaps begins to loosen, the swelling abates, and the rhinorrhœa is diminished. Danger: serum sickness.

Prophylaxis.—By means of the Schick test we can find out who is susceptible to diphtheria and who immune. Technique: By means of a very fine needle, 1/50 of a M.L.D.[1] of diphtheria toxin in 0·2 c.cm. of fluid is injected into the skin of the flexor aspect of one forearm, while into the skin of the other forearm, as a control, is injected a similar quantity of heated (inactivated) toxin. The results of the reaction come under four heads: 1. *Negative:* complete absence of any reaction in either arm indicates that the patient is immune to diphtheria. 2. *Positive:* complete absence of reaction in the control arm. The test arm shows after 24–36 hours a red circumscribed flush which reaches its maximum on the fourth day, when it may be 1 to 2 cm. in diameter. After this it fades till by the seventh day a brown desquamating stain is left, which may remain for some weeks. Interpretation: the patient is susceptible to diphtheria. 3. *Negative and Pseudo:* by the end of twenty-four hours a diffuse red flush which is equal in both arms has developed. By the fourth day this will have faded to a brownish stain, equal in both arms. Interpretation: the patient is immune. The reaction is the non-specific result of a foreign protein. 4. *Positive and Pseudo:* at twenty-four hours the reaction is as in 3, a diffuse red flush equal on both arms, but by the fourth day the flush on the control arm has faded, while that on the test arm has developed to the circumscribed red area seen in 2, which in its turn fades by the seventh day. Interpretation: the patient is susceptible. If possible the patient should be seen daily till the seventh day; if only a single visit is possible, it should be on the fourth day.

The Schick test allows us to separate the immune from the non-immune. It now remains to immunise the non-immune. Two methods are available: 1. In cases, particularly children, who have been exposed to diphtheria and who have not been

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[1] M.L.D. is the minimum lethal dose of toxin for a guinea-pig weighing 240–260 G.

previously actively immunised it is wise to confer a *passive immunity* by injecting 500–1,000 units of diphtheria antitoxin subcutaneously. This will afford protection for three or four weeks, but it may not be successful if the child is already incubating the disease. Antitoxin prevents the toxic results of infection but cannot eliminate risk of the latter. 2. *Active immunisation* is best carried out by Toxoid-Antitoxin "Floccules" (T.A.F.) or by Alum-Precipitated-Toxoid (A.P.T.). T.A.F. is a suspension of the precipitate of floccules formed when diphtheria toxoid and antitoxin are mixed in appropriate "neutralising" amounts. This preparation possesses very high immunising power with low liability to cause reactions. It is especially suitable for adults. Three doses each of 1 c.c. are given subcutaneously or intramuscularly at intervals of two to four weeks. A.P.T. is a suspension of the washed precipitate produced by adding a small amount of alum to diphtheria toxoid. The precipitate is relatively insoluble and the toxoid is gradually liberated at the site of inoculation. A.P.T. will induce a high immunity even with a single subcutaneous injection of 0·5 c.c. It is preferable, however, to give two injections of 0·3 c.c. and 0·5 c.c. at an interval of four weeks: this is the method of choice in children under eight years. Above this age and in adults it tends to produce a local reaction, and the use of T.A.F. is advised. Active immunisation in children is best carried out between the ages of six months to one year and a Schick test performed eight to twelve weeks after the last injection to confirm a satisfactory result. The immunity should be reinforced by a further single 0·5 c.c. dose of A.P.T. on first going to school, and by 1 c.c. of T.A.F. at the age of fourteen.

TETANUS.—*Passive immunisation* with tetanus antitoxin has proved very effective as a prophylactic measure: 3,000 units should be given subcutaneously or intramuscularly immediately after any deep injury which may be contaminated by soil or dirt, especially if there is laceration of tissue. As the immunity from a single dose lasts only about ten days a second dose should be administered after this period if the wound has not healed. It is wise to repeat the injection before any subsequent operation is performed on the infected area as this may cause acute tetanus. In actively immunised subjects a single prophylactic dose of antitoxin is sufficient.

Active immunisation.—Tetanus toxoid (the toxin rendered atoxic by formalin) is used to produce a high immunity in those persons who may be exposed to tetanus. In certain tropical regions where umbilical tetanus of infants is common the disease has been prevented by active immunisation of mothers during pregnancy. Dosage consists of two injections of 1 c.c. subcutaneously at six to eight weeks' interval. Reactions after injection are insignificant and the active immunity long lasting.

For *treatment* after symptoms have developed a dose of 100,000 to 200,000 units of antitoxin should be given intravenously as early as possible. Intrathecal injections of antitoxin are no longer used. Tetanus bacilli are susceptible to penicillin and in any case of established infection in which surgical excision of the wound is not possible, systemic treatment with this antibiotic in doses of 40,000 units subcutaneously three-hourly for three to four days should be employed to supplement the administration of full doses of antitoxin (and see § 784).

HÆMOLYTIC STREPTOCOCCAL Infections.—Scarlet fever is primarily a toxæmia caused by the toxin of a hæmolytic streptococcus present in the throat. The *Dick test* for susceptibility to scarlet fever is analogous to the Schick reaction for diphtheria, and is carried out with diluted scarlet fever toxin (*e.g.*, 1 in 1,000): 0·2 c.c. is injected intradermally into the skin of one forearm, and into the other is similarly injected as a control a like amount of toxin previously boiled in a water-bath for one hour to render it innocuous. The test is read at the end of twelve and twenty-four hours, being maximum at the latter time. A single reading is best made at twenty-four hours; it should not be delayed beyond this. In a positive reaction a bright red erythematous patch from 2 to 7 cm. in diameter appears in six to twelve hours at the site of injection of the toxin, remains for about twenty-four hours and then fades. There should be no reaction in the control arm. A negative reaction is indicated by a complete absence of erythema in either arm. Pseudo-reactions occur as in the case

of the Schick test and are interpreted as described under the latter. *Active immunisation* with scarlet fever toxin is produced by giving five weekly injections subcutaneously of 500, 2,000, 5,000, 25,000 and 50,000 skin test doses : this usually renders a previously positive Dick reaction either negative or only faintly positive. *Treatment.*—For the usual mild type of scarlet fever seen in Britain in which the symptoms are due to toxæmia, and septic complications dependent on invasion of the bloodstream or tissues by hæmolytic streptococci are absent, the principal treatment should be by concentrated scarlet fever antitoxin. This is obtained by immunising a horse with subcutaneous injections of the sterile filtrate from broth cultures of the causative streptococcus. The dose recommended for an adult is an initial one of 20–50 c.c. (approx. 3,000–12,000 units) intravenously, followed by smaller daily intramuscular injections. Penicillin or sulphonamide therapy is reserved for the treatment of septic complications and for septic scarlet fever. These substances are effective in controlling the septic symptoms in most types of hæmolytic streptococcal infections. The dose is assessed on body weight, but in the case of the sulphonamides children require at least a 50 per cent. larger dose than do adults. For the doses recommended, see Tables XXVIII and XXX.

Streptococcus Viridans Infections.—The importance of this organism in acute rheumatic fever, subacute bacterial endocarditis and in chronic rheumatism and rheumatoid arthritis is well established. In *treatment* of the latter two affections active immunisation with a vaccine of the organism does occasionally give good results. An autogenous vaccine derived from a known septic focus is the most promising. No antitoxin is available. This variety of streptococcus is susceptible to long-continued doses of penicillin but almost completely insensitive to sulphonamides. For the treatment of subacute bacterial endocarditis, when it has been proved to be the causative organism, massive systemic doses of penicillin over a long period—*e.g.*, 1 million units daily for six weeks—are necessary (§ 50). The type of lesion produced by the streptococcus viridans tends to shield it from effective concentrations of penicillin.

Staphylococcus Aureus Infections.—In the *prophylaxis* of chronic or recurrent localised staphylococcus aureus infections a course of a stock, or preferably autogenous vaccine, administered in a quiescent interval may prove beneficial by inducing an active immunity. The promise of staphylococcal toxoid for such purpose has not been fulfilled. The great majority of strains of staphylococci are very susceptible to penicillin and relatively resistant to sulphonamides. Severe staphylococcal infections provide one of the strongest indications for treatment with penicillin. Acute osteomyelitis, cavernous sinus thrombosis, severe carbuncle, meningitis, septicæmia, endocarditis and pneumonia due to staphylococcus aureus from whatever focus indicate immediate penicillin systemic administration. Sulphonamides should be tried in these conditions only if penicillin is not available. Sycosis barbæ and carbuncle are both benefited by local penicillin application.

Anti-Catarrhal Vaccine.—Composed of suitable doses of all those organisms which may infect the nose, throat and lungs. These are the Streptococcus hæmolyticus and Streptococcus viridans, the Pneumococcus, the Pneumobacillus, the Influenza bacillus, Micrococcus catarrhalis, and various strains of Diphtheroid bacilli. It is usual to give this vaccine in three increasing doses, at weekly or ten-day intervals. Inoculations should be made at the beginning of September and repeated again in January. The protection bestowed lasts six to twelve months. Smaller doses than those usually recommended should be given to delicate or allergic persons and those subject to "colds"; otherwise a "cold" is precipitated.

Typhoid and Paratyphoid Infection.—*Prophylactic* inoculation with typhoid and paratyphoid organisms is very effective and confers immunity for at least two years. The customary T.A.B. vaccine consists of a suspension of typhoid, paratyphoid A and B bacilli killed by heat and preserved with phenol : two injections of 500 and 1,000 millions respectively are given with a ten-day interval. Demonstration by Felix of the importance of the Vi antigen in immunisation with typhoid and paratyphoid bacilli, and its ready destruction by heat, has led to the use of an alcohol-

killed vaccine in which this antigen is preserved. This alcohol-killed vaccine (Lister Institute), which is tending to displace the heat-killed variety, consists of a suspension of 1,000 million typhoid and 500 million each of paratyphoid A, B and C bacilli per cubic centimetre in 25 per cent. alcohol as a preservative. The dosage for adult males is two subcutaneous injections of 0·25 c.c. and 0·5 c.c. (for adult females 0·2 c.c. and 0·4 c.c.) at three to four weeks' interval. Somewhat smaller doses are advised for subjects who are below average in physical vigour or development. Both general and local reactions are less marked than with the heat-killed phenolised vaccine.

Treatment of typhoid or paratyphoid fever (or the carrier state) by a combination of penicillin and sulphathiazole and by streptomycin has been claimed to give good results, but these await confirmation: chloromycetin is more promising.

Tuberculosis.—Tuberculin has been used both in diagnosis and treatment. It consists of the broken up protoplasm of the bacillus plus its products in artificial culture medium. It was originally prepared from a six-weeks-old culture in glycerol broth, evaporated to one-tenth of its volume, sterilised by heat and filtered (Koch's "Old Tuberculin"). Koch's "New Tuberculin" is derived by grinding the bacilli (obtained from a growth on solid medium) in 50 per cent. glycerol. The *diagnostic application* depends on the fact that the tissues of a person infected with tuberculosis may exhibit hypersensitiveness (allergy) to tuberculin. In man, the *Mantoux test* is commonly employed: it consists in the intradermal injection of 0·2 c.c. of a 1 in 10,000 dilution followed a few days later by a 1 in 1,000 dilution of Old Tuberculin by means of a syringe with a fine needle. Uninoculated concentrated culture fluid may be used as a control. In a positive reaction an area of erythema and swelling appears at the site of inoculation within a few hours and attains a maximum in twenty-four to forty-eight hours. In a child, up to the age of five years, a markedly positive reaction at 1 in 10,000 is strongly suggestive of active tuberculosis. Negative results in adults, particularly if dilutions of 1 in 1,000 and 1 in 100 also give no reaction, exclude active tuberculosis. Tuberculin P.P.D.—purified protein derivative (Parke, Davis & Co.)—is claimed to be free of extraneous protein derived from the culture medium and to give greater accuracy and sensitivity than the ordinary Old Tuberculin. A specially prepared strip of gauze impregnated with tuberculin ("a tuberculin patch") may be applied to the skin, and avoids a needleprick in children. *Prophylaxis.*—B.C.G. (Bacille Calmette—Guérin) vaccine has been extensively administered in Europe to infants and to Mantoux-negative adults. Since the quality of the vaccine has been improved, it is claimed that it has very materially reduced the incidence of subsequent tuberculosis. *In treatment* tuberculin must be used cautiously, beginning with a very small dose and gradually increasing, care being taken to avoid a constitutional reaction. In pulmonary cases this form of treatment is undesirable. The most successful cases of tuberculin therapy are those of genito-urinary tuberculosis, Bacillary Emulsion (B.E.) being usually employed. The initial dose should not be more than 1/100,000 of a milligram and subsequent doses must be increased very gradually.

Streptomycin (§ 515) is known to act on tubercle bacilli, but its efficacy in the various clinical types of tuberculosis is not yet fully assessed. In early cases of tuberculous meningitis, some success has been achieved with combined intramuscular and intrathecal injections. The systemic dose for adults is 2 G. and for infants 0·02 G. per lb. body weight daily: the intrathecal dose by lumbar puncture for adults is 0·1 G. and for infants 0·05–0·075 G. daily.

Hydrophobia.—The Pasteur treatment of hydrophobia with living virus has obtained a world-wide repute. Rabbits are passaged with street virus until fixed virus is obtained; then the spinal cords are removed and dried, the drying process attenuating the virus. At first the injections are made from emulsions of weak cords, *i.e.*, those dried for fifteen days; later, cords which have been dried only ten days are used: by this means the dosage is graduated. The carbolised vaccine of Semple, in which the virus is killed, is replacing the original Pasteur method.

Indications.—The earlier the treatment the better the results. This is especially the case in face bites, which are often fatal; the virus travels by the nerves, and the

nearer the bite to the brain the shorter the incubation period. The dog should not be killed but kept muzzled and chained up, and if the animal survives ten days it is certainly not infected with rabies ; if it dies, the head should be packed in ice and sent to a Pasteur institute for examination for inclusion (Negri) bodies in the cytoplasm of the brain cells. In cases of doubt start vaccine treatment at once. Immediate treatment consists in encouraging bleeding and carbolising each individual tooth bite. Never sew up the wounds until after three days ; this applies especially to face bites.

PLAGUE.—Haffkine prophylactic vaccine, which consists of a broth emulsion of plague bacilli, is an effective prophylactic for twelve months or so. The dosage is large (5 c.c.) and rather severe local and general reactions may follow. When practicable, it is preferable to give a smaller dosage, on two or three occasions, at weekly intervals. Serum treatment for plague has been tried with doubtful benefit.

CHOLERA.—A cholera bacillus vaccine has proved a valuable prophylactic in epidemics of this disease. Protection lasts for four months or so, and is of less value than T.A.B. in typhoid and paratyphoid. It is most satisfactorily employed during an epidemic, when all persons in the infected area may be immunised, which immunity will last till the emergency has passed. Two inoculations, one of 4,000 millions and the other of 8,000 millions with an interval of a week is the usual procedure. Specific treatment with serum has been disappointing but preliminary reports of chemotherapy with a new sulphonamide compound (" 6257 ")—a condensation product of sulphathiazole and formaldehyde—which can be given orally, are encouraging.

SNAKE POISON.—Calmette introduced an antitoxic serum called antivenene, prepared by inoculating animals with cobra venom, and advocated its general use in snake-bite cases. It is, however, now known that antivenene in most instances is species-specific ; to be effective the antivenene must have been prepared from the same species that has bitten the patient. Polyvalent antivenenes are now available in many different countries for the prevailing poisonous snakes, including those of India (cobra and Russell's viper), Africa and South America. A monovalent antivenene is available for the Australian tiger snake (*Notechis scutatus*). The only poisonous snake in Britain is the adder, the minimum lethal dose of whose venom for an adult is probably 50 mgms. As the actual amount injected by this snake is between 5 and 10 mgms. the results are seldom grave except in small children or invalids. The antivenene most satisfactory for such cases is that prepared by the Pasteur Institute, Algiers, against the venom of the horned viper of Africa (*Cerastes Cornutus*). Supplies are available in this country through the Ministry of Health. Antivenene is given intramuscularly or intravenously in a severe case in doses up to 40 c.c. and saves life if administered up to two-thirds of the death time—*i.e.*, if the patient has received a sufficient dose of venom to kill in nine hours, serum therapy is effective if given within six hours. No case, however, is too ill to receive antivenene, and even paralysed patients with involvement of the respiratory muscles may make remarkable recoveries within half an hour of the injection. Sometimes paresis returns ; if so, serum should be re-administered without delay. Immediate ligature delays the death time, but in patients bitten by really poisonous snakes local treatment is rarely effective as a lethal dose of poison is so rapidly absorbed. Once this has happened specific antivenene is the only possible remedy. Benadryl 50 mgms. t.i.d. by mouth may combat local swelling and pain.

PNEUMONIA.—*Prophylactic* use of a vaccine composed of the prevalent types of pneumococci has proved useful in areas such as the Rand in South Africa where pneumonia reaches epidemic dimensions amongst the native workers. The protection afforded is type specific. *Treatment :* Chemotherapy with parenteral penicillin or with effective sulphonamides (Tables XXVIII, XXX), is the essential treatment for pneumococcal pneumonia. Penicillin is almost non-toxic compared with the sulphonamides, but needs to be given by frequent subcutaneous injection. It is probably preferable for elderly patients and when there is reason to believe the pneumococci are sulphonamide-resistant. As routine treatment, however, for moderately severe or mild

infections the sulphonamides are very satisfactory. The use of anti-pneumococcal serum has regressed following the success of chemotherapy but, combined with the latter, it is still of value if given early in bacteriæmic or severely toxic cases, in elderly subjects, and rarely in those patients who do not tolerate either penicillin or sulphonamide therapy. Commercial antipneumococcic sera are mainly antibacterial in action; they have little antitoxic value. Type-specific sera prepared from rabbits can be obtained (Lederle) for Types 1, 2 and 3 pneumococci and also for the vast majority of the distinct 29 serological types—the so-called "higher types"—previously classified as the heterogeneous Group 4. Treatment with serum necessitates accurate preliminary typing of the infecting pneumococcus and the use of its homologous serum. Sixty thousand units (10–25 c.c. according to type) intravenously is recommended as a minimal initial therapeutic dose. Subsequent dosage depends on clinical progress and evidence of blood infection.

Infections of the RESPIRATORY TRACT, such as chronic pharyngitis, certain types of bronchitis, bronchiectasis, asthma, and secondary infections of tuberculous cavities, react to autogenous vaccines. The infecting organisms may be streptococci, pneumococci, pneumobacilli, influenza bacilli, etc. In the throat and nose, if the predominating organisms be penicillin sensitive, a penicillin spray may prove efficacious. Infection by Vincent's organisms is amenable to penicillin.

ANTHRAX.—The serum of artificially immunised animals—*e.g.*, Sclavo's serum—is used in the treatment of anthrax and has almost entirely replaced surgical measures. It should be given promptly and in large doses—50 c.c. intravenously, and 50 c.c. intramuscularly. N.A.B. (0·6 G. intravenously) is also valuable as an adjuvant to serum and is even preferred to the latter by some authorities. The anthrax bacillus is susceptible to penicillin and encouraging results have been reported with this drug in the cutaneous form of the disease (Table XXX).

GAS GANGRENE.—In a dirt-contaminated wound with gross injury to muscle, prompt and efficient excision of the wound constitutes the most important prophylactic measure. *Passive immunity* is obtained with intramuscular polyvalent gas gangrene antitoxin, the recommended dose being *B. welchii* 9,000 units, *Vibrion septique* 5,000 units and *B. œdematiens* 9,000 units. For *treatment* the dose, given intravenously, should be at least three times the prophylactic doses and it should be repeated as long as symptoms of toxæmia persist. Since the above three chief organisms of gas gangrene are all equally sensitive to penicillin, the latter is indicated both in prophylaxis and treatment. Local application alone is not sufficient for an established infection and systemic treatment for three days is recommended. Penicillin should not replace but only supplement the other methods of treatment (excision of dead muscle and the administration of full doses of antitoxin).

MENINGOCOCCAL MENINGITIS.—Chemotherapy has entirely superseded serum treatment. Both sulphonamides and penicillin are highly effective. Of the former the compounds suitable for use are sulphathiazole, sulphadiazine, or sulphanilamide by mouth in the recommended dosage (Table XXVIII and § 503). In all severe cases, including those coming under treatment late in the acute stage, the first dose or doses of sulphonamide should be by intravenous injection. Intrathecal injections of sulphonamides are contraindicated. Penicillin, if employed, however, should be given intrathecally whenever possible, preferably combined with a short course of subcutaneous injections especially in bacteriæmic cases.

BACILLARY DYSENTERY.—*Prophylactic* vaccines have not proved satisfactory on account of their liability to cause severe reactions. Besredka's oral vaccine has had some success. *Treatment.*—Bacilli of the dysentery group are resistant to penicillin, but Shiga and particularly Flexner infections respond well to sulphaguanidine—a drug of the sulphonamide group which is not readily absorbed from the bowel. For Sonne infections succinyl-sulphathiazole appears to be more effective than sulphaguanidine. Streptomycin is also effective (Tables XXVIII, XXIX). In toxic cases, chemotherapy may be supplemented with 50–100 c.c. of antitoxic serum intramuscularly or intravenously. Shiga serum is the most potent, but the Flexner type is

also satisfactory: a polyvalent variety combining the two is available. No effective serum against the Sonne strain has been produced, but this form is generally mild.

§ 522. Notification and Isolation.—Two duties are laid upon the medical practitioner in cases of the commoner infectious maladies: (1) NOTIFICATION of the case to the medical officer of health of the district in which the case arises. The notifiable complaints in most districts are Anthrax: Cholera: Diphtheria (including Membranous croup): Dysentery, amœbic or bacillary: Acute encephalitis, infective or post-infectious: Enteric fevers (typhoid and paratyphoid): Erysipelas: Farcy: Food poisoning (Foods and Drugs Act, 1938): Malaria: Measles: Meningococcal infection: Ophthalmia neonatorum: Plague: Pneumonia, acute primary and acute influenzal: Acute poliomyelitis, paralytic or non-paralytic: Puerperal pyrexia: Relapsing fever: Scarlet fever: Smallpox: Tuberculosis (all forms): Typhus fever: Whooping-cough. Any infectious disease may at any time be added to the list at the option of the Sanitary Authority. A medical man is bound, under a penalty of forty shillings, to notify any of the maladies named "immediately on becoming aware" of its existence. (2) IMMEDIATE REMOVAL of the patient to a fever hospital is compulsory for the more dangerous infectious diseases; otherwise the parents or guardians must make *proper* and *adequate* arrangements for the isolation of the case at home. In some places the removal is superintended by the medical officer of health.

Unless Home Isolation can be prompt and thorough, it is better to remove the patient to a properly organised Fever Hospital. For ISOLATION at HOME, carpets, curtains, and superfluous furniture should have been previously removed. Books and articles in use must be such as can be afterwards burned. The nurse in charge of an infectious case should wear a washable dress when on duty, and should hold no communication with others, nor should she go out of doors without having first changed her wearing apparel, and, if possible, taken a bath. An airy, quiet room *at the top of the house*, having cubic space of about 12 × 12 × 10 feet, is desirable. The air in this space requires to be changed three or four times in every hour. The bedstead should be so placed as to be accessible on both sides. The temperature, read on a thermometer suspended near the bed, and away from draughts, should be 60° F.

VENTILATION must be ample in fever cases, because of the danger of mixed infections. Many of these cases are due to droplet infection from one patient to another, and that is why mixed infections are more apt to arise when there is not free ventilation and sufficient cubic space. This partly explains the higher death-rate from infectious diseases when overcrowding occurred in former days. The direction of the wind should be constantly noted, and to avoid draught, the windows or ventilators opened on the side of the room away from the wind. A "sash-board" is an excellent contrivance for avoiding draught. It should be about 6 to 8 inches broad, and fit across the bottom of the window, so that the lower sash can be raised without a visible opening, and then ventilation takes place behind the sash-board, and also *in the middle* of the window, the air in both cases being directed upwards. The chief principle in ventilation is that the current of air always takes place from a colder to a hotter medium—usually, therefore, from outside to the inside of a room. The chimney, when the fire is alight, is the only reliable *exit*. Make the window your *inlet* in preference to the door.

§ 523. Disinfection and Prevention.—Before discussing the means employed for disinfection, it is necessary to consider how infection is conveyed. There are three principal ways: through the *air*, by *water* or other ingesta, and by *direct contact* or inoculation.

(*a*) As regards the *air-borne* group, their infectivity varies, also the distance to which the contagion in an active state may be carried. For instance, erysipelas and typhus probably do not spread beyond a few feet, but small-pox and scarlet fever may spread a considerable distance. A frequent mode of spread of bacteria and viruses from the mouth and throat of an infected person is by *droplet infection*. Minute drops of saliva, or nasal discharge, with adhering organisms, are dispersed for some distance into the surrounding air during talking, coughing or sneezing. These organisms usually enter *via* the respiratory tract (nose, throat, tonsils or lungs);

occasionally milk or other foods are contaminated and may be the source of the infection. Streptococci, tubercle and other bacilli can remain virulent in dust for several weeks.

(*b*) Fevers conveyed by *water*, *milk* or *other ingesta* are typhoid, paratyphoid, cholera, dysentery, undulant and abortus fever, and rarely scarlet fever and diphtheria. Two facts form the basis of the propagation and prevention of these diseases :—(1) All matters coming from the patient's bowel and stomach are infective, in typhoid the urine also ; (2) to produce the disease the organism must be introduced by the mouth into the alimentary canal.

(*c*) In the third group the infection is introduced into the blood or tissues of the body by means of a *wound* or a *scratch*, or by the *bite of an insect*. Our profession pays a penalty every year to this group of disorders—a pathologist receives a scratch during post-mortem work, or a surgeon pricks his finger during an operation on a septic appendix. Some of these disorders were formerly considered to depend upon climatic influence, *e.g.*, malaria, which is now known to be introduced into the body by the bite of a mosquito. Tetanus enters through a wound or scratch contaminated with soil ; plague is conveyed by rat fleas ; typhus by lice. Others in this group are the fevers due to tick bites, glanders, anthrax and hydrophobia.

The procedure for disinfection differs somewhat according to which of the above three groups the fever belongs. There is now an increasing tendency to concentrate chiefly upon current disinfection during the illness. Formerly much stress was laid on fumigation and spraying the patient's room after the illness. With careful current disinfection it is unnecessary to have terminal disinfection after measles, scarlet fever and diphtheria.

Current disinfection, *i.e.*, that carried out during the illness in the sickroom. All unnecessary furniture and furnishings such as curtains and carpets should be removed. Hæmolytic streptococci can be conveyed by books, but as a general rule infection (except with small-pox and typhoid fever) is rarely conveyed by bedding and other inanimate objects. Before being washed, the *bed-linen*, blankets and clothes must be soaked in a 5 per cent. solution of phenol for 12 hours. Food and drinking *utensils* should be boiled for 5 minutes ; they must also be protected from flies. *Thermometers* are kept in 5 per cent. phenol. The nurse should disinfect her hands in 1 in 1,000 perchloride of mercury or in dettol. *Sputum* and nasal discharge should be collected in gauze or paper handkerchiefs and burned. Allow no *dust* to accumulate.

With fevers conveyed by water and other ingesta, in addition to the above precautions, it is essential that the excreta are covered and mixed with 5 per cent. phenol, or an equal bulk of 20 per cent. chlorinated lime in water, and allowed to stand for two hours before being emptied down the drain pipe or buried in earth. *Prophylaxis.*—All drinking water should be boiled if there is the slightest suspicion of its being contaminated by leakage, soakage (however small) from cesspools, drains, or the reckless casting of slops, and by flies. Food utensils must be disinfected carefully by boiling, and flies must be prevented from access to food and to excreta. All handlers of food or every individual where large groups of men are crowded together, as in armies, should be examined and treated if found to be "carriers," *i.e.*, apparently healthy persons in whose excreta the cysts of the amœba of dysentery or typhoid, paratyphoid or cholera germs abound.

List of *common disinfectants* for use in the sick room : Extreme heat (200° F. or more, and preferably moist) ; fumes of burning sulphur (SO_2) ; chlorinated lime, 1 to 5 per cent. ; phenol, 5 per cent. ; dettol ; formalin, 2 to 10 per cent. ; lysol, 1 per cent. (or liq. cres. sap. fort., 1½ oz. to 1 gallon water) ; corrosive sublimate, gr. 10 to 1 gallon.

Terminal Disinfection.—Burn as many articles of clothing as possible ; boil others. Mattresses and blankets, books and all clothing which cannot be boiled, should be sent to be disinfected by steam. Boots and shoes can be washed over with lysol. Furniture should be moved from walls, and drawers, cupboards, etc., disinfected with a liquid spray. Wallpapers in some cases are stripped and the walls treated with

hot lime. Doors and windows are closed, crevices are stopped, and the whole room is kept closed for six hours after being thoroughly sprayed with formalin by means of a hand-worked pump. Formalin 8 oz., glycerin 8 oz., water 1 gallon, is the disinfectant most often employed. Then the windows are opened and all is washed down with hot water and soap, and the room is well aired.

Disinfection and the PREVENTION OF DISEASES caused by scratches, bites, etc., differ in each individual case. Thus septicæmia and tetanus almost ceased in surgical cases with the introduction of cleanliness and asepsis. Various tropical fevers are conveyed to man by the bites of mosquitoes, flies, fleas, and bugs. The prophylaxis of these conditions includes measures directed to the extermination of the insect responsible and avoidance of places in which they are known to be present. Insecticides and repellents such as D.D.T. and dimethylphthalate play a large part in preventing disease. Where plague is endemic rats must be destroyed; where bugs infected with disease are found it may be necessary to burn the huts, etc., in which eggs are likely to have been deposited. With many of these insect pests knowledge of their life-history is the necessary preliminary to effective steps for their destruction.

§ 524. The **Treatment of pyrexia and hyperpyrexia** comprises six indications:

(1) *Heat production can be diminished and heat loss increased* to some extent by means of *drugs*, known as antipyretics, such as antipyrine and phenacetin. The first of these is most efficacious, but it requires care, on account of its depressing effect on the heart, and the reaction which follows some hours later. Cryogenin gr. 10 to 15 is the least depressing antipyretic. Quinine in full doses (say 5 grains every three or four hours) may be given until the temperature comes down or physiological symptoms are produced (singing in the ears, deafness, headache, etc.). Salicylates, especially in rheumatic affections, and aconite are also useful. Among the diaphoretics are liquor ammoniæ acetatis, potassium nitrate, spiritus ætheris nitrosi, and camphor: also lemon drinks, dilute acids, and salines.

The Graduated Bath.—Place the patient in a bath one-third full of water at 90° or 95° F. Every five minutes reduce the temperature 5° until 60° F. is reached. If the fever be not then reduced to 100° F. or lower, continue for further quarter of an hour. The pulse must be closely watched, and stimulants given if necessary.

The Wet Pack.—Take off the night-shirt and superfluous bedclothes, and place the patient on a blanket. Moderately wring a sheet out of ice-cold water and lay it along his side. Gently roll him over on to it, and completely envelop him in it, head and all, except the face, so that it is next to his skin, without creases or air, between the legs and beneath the arms. Cover these latter with wet towels. Then put two cradles over the patient, and blankets over all. Leave him thus packed for twenty to forty minutes, until his temperature, taken in the mouth, is reduced to the required extent.

Tepid Sponging.—Lay the patient in a blanket and sponge him gradually all over with tepid water (about 75°). Do half the body at a time, the other half being covered up. Continue the process for twenty to forty minutes, until the fever is reduced.

(2) *The application of ice* in large ice-bags for the head, chest, and abdomen has been used when other means are not available, but the weight of the bags and their localised application are objections to their use.

(3) *Diminish the work done by the internal organs* by diet (§ 297. XVIII), and by promoting the action of the skin and bowels, in order to relieve the kidneys.

(4) In all fevers it is necessary *to watch the heart* and blood pressure carefully, and, if necessary, administer suitable stimulants, such as nikethamide B.P. (coramine) or leptazol. The pulse should be examined several times a day in all fever cases.

(5) *Symptomatic treatment* has been dealt with in the preceding pages.

(6) *Watch for and treat complications* as they arise. The chief of these are (i.) cardiovascular (*vide supra*), and (ii.) delirium and insomnia. If the delirium be of the *raving* kind, chloral and bromides should be given in full doses; if of the *muttering* or typhoid variety, stimulants. Insomnia may be relieved by the same treatment. (iii.) Pulmonary complications, (iv.) suppression or retention of urine, and (v.) collapse, are all dealt with elsewhere.