NON-MALARIAL, REMITTENT, AND OTHER FEVERS; AND THE THALLOPHYTE BLOOD PARASITE ASSOCIATED WITH THEM.

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(PLATE XIII.)

THE study of the Imperial Chinese Maritime Customs Reports for the last ten years, of the proceedings of various medical societies in the Far East, of missionary medical reports and journals, and such like sources of information, show that there has long been prevalent over a great part of China a protean febrile disease, as to the nature of which there is the greatest diversity of opinion among the medical men who have to deal with it. During the last two or three years it has become much more prevalent in all the Chinese treaty ports, from Hongkong upwards; and in the autumn of 1896 it broke out in Chefoo, for the first time within my experience, which dates back to 1891. Some medical men regard it as a fever peculiar to the Far East, unnamed as yet; others call it typhomalaria. I hope to show that it is really a fever hitherto not differentiated from the mass of little-known fevers which are prevalent in various parts of the Far East; that what has been called dengue at Shanghai, and what is commonly called typhoid fever in most of the treaty ports, though recognised as being of aberrant type, and which has become very much commoner of late, are all varieties of one fever which possesses characteristics differentiating it from all the hitherto recognised fevers; one of these being its causative association with a blood parasite only recently discovered.

In the spring of 1896 I began systematically to examine the blood in every case of fever, and at once came on objects of unknown nature, quite unlike anything described by Laveran, Bignami, Mannaberg, and other writers: thus, the red corpuscles were often studded with double-contoured circles and crescents (Plate XIII. Fig. 1, *a*), of all sizes, some sunk in their substance, others evidently adherent to the surface (*b*); the double contours were remarkably black and brilliant, so that in a pencil sketch they must be put in in ink; the white interiors of these objects did not stain with methylene-blue, unlike the malaria parasites, which I also found sometimes; and

they were never pigmented. Then, highly refracting rods (*c*), which were sometimes seen bending nearly double (*d*) and then straightening out, often jerking the corpuscle some distance, were common; as were also reniform bodies (*e*), in which a double-contoured object could be seen folded up, and which when they are rolled over become circles, with a clear centre (*f*). One very remarkable point was the extraordinary profusion of these objects, even in cases in which the symptoms were very slight (later, I found them equally abundant in quite healthy persons); in one field 70 or 80 per cent. of the corpuscles might be thus affected, or be otherwise abnormal. I then observed that an enormous proportion of what I took to be red corpuscles, injected or normal, were in more or less active movement, with the peculiar hopping motion belonging to the fungus spore, which after a long time I recognised these objects to be.

I studied them for over a year, believing them to be protozoa, before, almost by accident, I hit upon the method by which the parent structures were revealed.

If a few blood films, from anybody who has lived for a few months in North China, be prepared in the usual way, fixed in absolute alcohol, and stained with carbol-fuchsin (Neelsen's stain), *undiluted*, for half an hour to an hour, in one or more of them will generally be found a patch of typical fungus hyphæ laden with spores, as shown in Plate XIII. Fig. 2, which is copied from a photograph of a somewhat unusually clear specimen. Usually the branching hyphæ are much shorter, and the masses of spores much denser, so that their arrangement is less clear. By substitution, this growth may be made to take up other stains, but the one mentioned is the only one, as yet found, which will stain it initially. For over a year I was daily examining blood films treated with all the usual stains, eosin, methylene-blue, methyl-violet, etc. etc., without suspecting the existence in them of this tissue, with which they none the less were, in many cases, full, as I have ascertained, by restaining some of my old specimens. This curious fact of course explains why so widespread a parasitic growth has so long escaped observation.

In febrile cases this fungus growth is much more abundant, and in fatal cases seems to be a main cause of death, its luxuriant growth producing thrombosis. In such cases, hyphæ of all kinds are found in great profusion; some are easily visible in fresh blood preparations, without the use of any stain; they are very translucent, generally colourless, and so are easily overlooked.

Plate XIII. Fig. 3 shows peculiar branching hyphæ, one springing from close to the extremity of its predecessor, which were found in great profusion in the blood of one fatal case, a child, the day before her death. These stain readily with methyl-green, alcoholic magenta, etc. etc.

One of the commonest forms of hyphæ is that shown by *h* in Plate XIII. Fig. 10 springing from a reniform spore; this attains a great length, being often found, in fresh blood preparations, running right across the cover glass, *i.e.* from $\frac{1}{2}$ to $\frac{3}{4}$ in. long; the edges are deeply incised; they are translucent, colourless, and do not take any stain, not even carbol-fuchsin; so that unless searched for they are liable to be overlooked.

Another characteristic of this parasite is the abundant occurrence of plasmodial growths (using *plasmodium* in its original biological sense, namely, a mass formed by the fusion of numerous swarm-spores, supposed to be characteristic of the myxomycetes). If a dozen fresh blood

preparations be made, with aseptic precautions, carefully sealed, and put aside in a not too cold place for a few days, in a large proportion of them one or more growing plasmodia will soon be visible to the naked eye.

On the third day of such a preparation, about one-third of the space under the cover-glass is occupied by a colourless growth with much branched periphery; as it grows, it pushes the formed blood elements before it, crowded together into a dense red mass, against which the white branches of the plasmodium stand out conspicuously. Here and there, in its mass, are islands, as it were, areas of the original space, crowded with blood elements, cut off by the fusion of the branches between which they lie. The growing mass is 10 to 12 μ higher than the rest of the preparation; and in its substance pale yellowish masses of spores may be seen gradually becoming more and more apparent. Sometimes the growing margin is not thus branched, and the mass is apt to be mistaken for an air bubble; if regarded obliquely, however, it may be seen to have a sort of satiny sheen, and to be marked with faint wavy lines, parallel to the free margin. Some plasmodia are vacuolated, full of air, or of some gas; and if the containing capsule be ruptured, air bubbles may be set free from it. Until this is done, however, if a liquid stain be run under the cover-glass, it will spread only between the branches of the plasmodium, making them more distinct than ever. It takes days, sometimes weeks, before the stain gradually diffuses into the substance of the plasmodium. A microscope field may be largely occupied by plasmodial masses, which may be coarsely branched; the spaces between are packed with the blood elements, as indicated in two places. The growth of such can easily be watched, two hours, *e.g.*, making a very perceptible difference. If non-vacuolated they stain readily, with methyl-green, dahlia, etc.; if vacuolated, they will not stain (see above), and are all the more likely to be mistaken for air bubbles.

The SPORES, which swarm in the blood in millions, and are commonly mistaken for red corpuscles, are of three kinds—

1. *Zoogonidia* (see Plate XIII. Fig. 4).—These are more or less actively mobile bodies of very varied shapes. The most common are very much like crenated red corpuscles (*l*), being of about the same size, of a reddish-brown colour, and sometimes almost or quite motionless. They may commonly be distinguished by noting that between the marginal crenations are to be seen short brilliant black lines, which shift about, being now visible on one side, now on three, and so on; they are bits of the labial organ to be described directly. *i* shows another common form, a clump of round bosses, something like a raspberry; flat hexagons or circles (*c*, *e*) are also very common; some of the flat forms attain a large size, up to 16 or 17μ across (*d*); often they are curled up or folded; *g* shows a form in which one curved end stands vertically up at right angles to the rest of the body, which therefore cannot be focused simultaneously; *f* shows a saddle-shaped form, and *h* a small spherical body covered with slender projections, only coarser than cilia. Each has, in the centre of one surface, or at one end, a single orifice, the germ-pore, leading into a cavity of varying size. Round the germ-pore is a very mobile thickened lip (*vide* Plate XIII. Figs. 4 and 5), which, when expanded, is sometimes shaped much like a Hodge's pessary (5, *b*).

It is a very brilliant, highly refracting organ; and during life is commonly in unceasing movement, expanding, contracting, stretching out one end far beyond the body, and so on; when circular, widely expanded, and stretched out away from the body (*a*), it causes an appearance as of one delicate ring floating over the disc-like body, the intervening tissue being very transparent. *d* shows a specimen from an osmic-acid preparation, photographed with dark ground illumination, which shows clearly the relationship of the labial ring to the rim of the body; with ordinary transmitted light it is not so easy to be certain that the appearance is not due to the overlapping red corpuscles casually associated.

2. Another variety of spores is a *simple tubular body*, with an opening at each end. These nearly always float with their long axes vertical; and in permanent stained preparations are generally much contracted (Plate XIII. Fig. 6, *d*), so that their real nature is not readily apparent. By the use of oblique illumination, varied, the central aperture can be seen to be perforating; *e* shows one semi-contracted, with the ends dilated. In fresh preparations a few are occasionally to be found with their long axes horizontal (*a–c*); they have then a very worm-like appearance, heightened by their worm-like, wriggling motion, which soon carries one across and off the field; *a–c* show three successive stages, passed through by one specimen, as fast as could be sketched; an orifice was seen at each end, sometimes widely gaping, sometimes contracted to a pin's point.

3. *Zygospores* are the third variety. These are mostly reddish-brown bodies, reniform in profile (Plate XIII. Fig. 8), circular in other aspects, with a clear central space. The hilum is filled by a delicate membrane, the external border of which continues the curves of the ends; by careful focusing, a double-contoured body can be seen folded up inside. If one be watched for a long time, over two hours in one instance, it can be seen struggling violently and eventually rupturing its capsule, and coming out as a flat leaf-like body, or as an amœbiform, object. At a somewhat earlier stage (Plate XIII. Fig. 7) the zygospores appear as perfectly colourless flat discs, very transparent, and without any obvious structure.

Structure.

The spores are enveloped in a rather thick, structureless, colourless, transparent membrane, a projection of which forms the labial organ; it can be projected at any point, by the body substance, in the form of blunt bosses, or long slender processes, like a snail's horns, which are thrust in all directions with great activity. This membrane is most evident in blood films, fixed in a cold saturated aqueous solution of perchloride of mercury (Plate XIII. Fig. 9), and stained, *e.g.*, with dahlia, which leaves the membrane unstained. Victoria-blue stains the membranes only, and is invaluable in the study of the

swarm spores. In a film stained by Gram's method, the body substance is violet, the investing membrane reddish. Plate XIII. Fig. 9, *a*, shows a group of spores stained with carbol-gentian-violet. By fixing a blood film as soon as spread, before it has had time to dry spontaneously, with cold saturated perchloride of mercury solution, the zygospores may be found in all stages of letting their contents escape as *swarm spores*; the empty capsules are to be seen in myriads. The swarm spores collect in masses, which soon fuse, forming plasmodia.

Germ-organ.—The cavity mentioned as lying below the germ pore contains an organ of most varied structure. The addition of a drop of 1 per cent. osmic acid to a fresh blood preparation will often cause the projection of this organ. Sometimes it is a small or large disc or cup borne on a slender stalk (Plate XIII. Fig 10, *a*, *b*), sometimes a delicate sac, with a faint double contour, plain (*c*), or traversed from base to top by a highly refracting band, made up of a very fine coiled tube, much like an insect's trachea; it may be a single tubule (*e*), or a bunch of much coiled tubules, or a single grass-blade like structure (*f*): or there may be up to as many as seven of the latter, etc. etc. Plate XIII. Fig. 10, *h*, shows a reniform spore, still with its sheath, from one side of which is sprouting a hypha such as has been described; it is unstained, and so shows up white on the stained background. *g* shows a swarm spore from which several hyphæ are beginning to sprout.

Reproduction is of two kinds, asexual and sexual.

1. *Asexual.*—The zoogonidia which are about to sporulate lose their special shape and become smooth spheres, of a clear greenish colour (probably due to contained air); often they may be seen to shed their germ organs; many dark specks, which appear as whitish spherules when not exactly focused, then appear either scattered all through the sphere or collected at one pole. Then one or more strings of sporules, or a number of single sporules, appear on the outside of the sphere, but attached to it by a slender thread; they dance about with the greatest vigour, until they break away, and soon dance out of the field. They vary from 0·5 to 1 μ in diameter; rarely are they as large as 2 μ. The same spheres may give off hollow buds from their periphery; sometimes they produce buds only; these are small spheres 2–3 μ in diameter; they also dance off eventually, less actively than the smaller sporules. The sporules ultimately separate, and adhere to or sink into the substance of the red corpuscles (Plate XIII. Fig. 1, *a*, *b*), appearing as bright specks, or indistinct ones, according to their position; they grow very rapidly. In four hours' time the shape of the future spore, whether flat, spherical, or what other it may be, is already apparent; it is the double-contoured, highly refracting peripheral membrane which causes the appearances described in connection with Plate XIII. Fig. 1; *e.g.* a single edge of a leaf-shaped spore appears as a bright rod. In febrile cases the plasma having become a more or less suitable medium for their development,

this may occur in it; in healthy persons it appears probable that a large proportion of the sporules are destroyed; in patients treated with methylene-blue I have several times found phagocytes crowded with blue-stained sporules, as well as with whole spores.

The germ organ may develop into gonidiophores, like those shown in Plate XIII. Fig. 2; or into hyphæ of the ordinary character, some of which may give origin to swellings, in which gonidia develop; these gonidia are often of a dark brownish colour, almost black.

2. *Sexual process.*—The spores may conjugate in any numbers. It is quite common to find them in pairs, conjoined by their germ-pores, through which the body substances unite. The tubular spores are often found in pairs, joined end to end.

Plate XIII. Fig. 11 shows two groups, of two and four conjugated spores respectively; those portions of the enveloping membranes which, at first, separate the cell contents, speedily disappear; ultimately, even the exterior shows no sign of any separation between the constituent items.

The result of the union of a small number of spores, a zygosphere, is usually a more or less spherical body, it may become granular, a number of spores appearing in its substance, or it may unite with other similar bodies to form a plasmodium, which may continue to grow, or may itself sporulate.

Vacuolation may occur at any stage of the above process;—in the original spores, before their fusion is complete, in the zygospheres, or in the plasmodium. Similarly, sporulation may commence at any stage, sometimes before the original spores have completely fused; it is not rare to find open networks of partially fused spores, through whose widely gaping germ pores the cell substance may be seen broken up into a mass of primary spores.

The bodies which result from the conjugation of several spores, instead of sporulating, or growing into a plasmodium, or uniting with other like bodies to form a large plasmodium, may produce one or many gonidiophores. Sometimes a group of spores may conjugate and at the same time evert their germ-organs, which may unite, forming large hyphæ. This was seen in a preparation made by mixing a drop of fowl's blood (infected with this parasite) with one of a saturated aqueous solution of methyl-green in 1 per cent. acetic acid; the spores became green-stained, but were not killed; all the stain was eventually taken up by the rapidly growing parasites, and the one large flattened hypha, which is formed by the junction of numerous buds from the conjugated spores, is unstained. Dark shaded masses of conjugated spores may readily be seen.

Fructifications.—Gonidiophores have already been mentioned, arising both from single spores and from the product of the conjugation of these (see Plate XIII. Fig. 2); and also dilated hyphæ, bearing gonidia. Another variety is sometimes found In some severe cases

of fever I have found a close network of hyphæ, from parts of which short stems, 10 to 15 μ long, sprang vertically upwards, each bearing a small black sporangium.

I have occasionally found a large, solitary, ascus-like globular body, one about 200 μ in diameter, growing from a large hypha; and other asci-like structures in blood films, each composed of a dense mass of spores surrounded by a sort of thick loose capsule, formed by interlaced closely ramified hyphæ.

Physiology.

These spores are extraordinarily resistant to noxious influences. They will stand a temperature of 100° C. for half an hour on three successive days without injury; not only so, but an old cultivation can best be rejuvenated by boiling it for a few seconds. They grow and develop with little, if at all, diminished luxuriance in a 1 per 1000 solution of quinine, a 1 per 500 solution of carbolic acid; in weak solutions of salicylic acid, salicin, arsenious acid, salicylate of soda, etc. etc. Perchloride of mercury, 1 per 1000, however, kills them instantly; it causes the zoogonidia, whatever their shape, to become small spheres. One per cent. osmic acid may paralyse them for a while, after a short period of greatly increased activity; but they often recover, and may live in it for many weeks, for eighty-one days, in one instance; apparently undergoing their normal evolution. Methylene-blue is the only drug so far found which is quickly toxic to them; a 1 in 400 solution kills them within an hour or two, after causing them to emit millions of sporules; and even a 1 in 10,000 solution, though entirely without any visible effect at the time, will cause all the spores in a preparation of fresh blood to disintegrate and disappear in a much shorter space of time than they would otherwise have done.

Naturally, therefore, it is very easy to cultivate them. I have grown them in various fluid media, bouillon, milk, whey, Pasteur's fluid, and other artificial media; if any such be inoculated with a speck of infected blood, the life-history of the parasite can be studied much more easily than in the blood, the phenomena being less complex at first. After a while a dense crust, formed of interlaced hyphæ, forms on the surface; it is dark brown, sometimes nearly black. From its upper surface project myriads of short aërial hyphæ, each bearing a small black sporangium, much like those described in the blood, only very much larger. If some of these sporangia be shaken up in 1 per cent. of osmic acid, and examined under the microscope, they will be seen to exhibit the same phenomena as the spores in the blood, which they also resemble in structure. Their movements are the same; they project long coils of tubular germ-organs, and swarms of sporules.

The range of this parasite may be inferred from the fact that for nearly two years I have searched in vain for a single specimen of blood, from any warm-blooded animal which is free from it. I have examined several hundred human beings—residents, visitors from all the treaty ports, missionaries from all parts of China, sailors, etc. etc.; also oxen, sheep, pigs, cats, dogs, and fowls. Considering how resistant to heat the spores are, it is hardly surprising that the gravy from a hot roast joint should be found swarming with live spores, nor that a drop of boiled milk should resemble one from a milk cultivation of the parasite; facts which amply account for the amount of human

infection. Under the circumstances it would be surprising to find anybody free from it.

As regards its life-history outside the animal body, the only observation which I have as yet is this. I once had sent to me, for examination, the carbon block from a filter, its outside being plentifully sprinkled with white blotches; these, I found, were due to dense masses of the transparent, colourless, non-staining hyphæ before described.

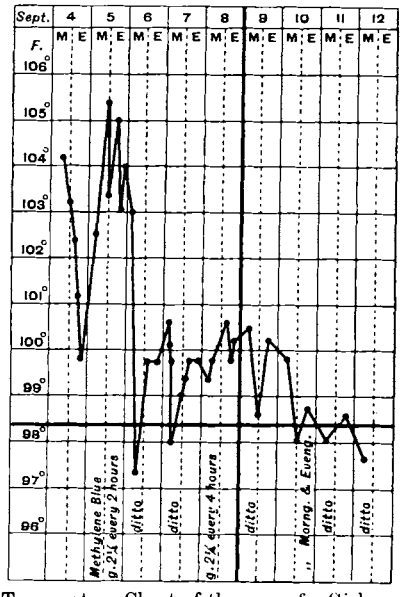
PATHOLOGY.

The febrile disorders which occur in persons infested with this parasite are legion, and extremely varied in character; they range from slight, hardly noticeable attacks, of a few hours' duration, to the utmost degree of severity, lasting many weeks; some are short and sharp, like dengue; others of a mild type, but persisting for many months. But they all agree in certain characteristics which discriminate them from any hitherto recognised fever; and, unlike as are the extremes, yet one variety passes into another by imperceptible gradations, so that no hard and fast lines of distinction can be drawn. In my detailed monograph I have described thirty cases in detail; here, for brevity's sake, I propose to treat them collectively.

They may be classified as—(1) acute and (2) chronic.

1 ACUTE CASES.—These fall into four classes, according to their severity and duration; and one merges imperceptibly into the next.

Class 1 includes cases, mostly children, in which there is a sharp rise of temperature without any obvious cause, and without any accompanying special symptoms; merely those due to the pyrexia, which also may be very slight. The skin is hot, the face flushed; the child may be thirsty; may refuse food; exceptionally, the onset is associated with vomiting. There is never an initial rigor. Sometimes the child will eat as usual, and only a slight languor and the dry hot skin, warn the attendants of the existence of fever; I have seen a 4-year-old child, with a temperature of 105° F., struggling against being put to bed, declaring she was quite well. The period of elevation is short; the rise is often very rapid, the temperature flashing up from normal to 104° F. within half an hour. The drop is usually rapid also, and commonly associated with profuse sweating. Often there is only one such flash of fever, or it may be repeated once or twice; the child suffers no after consequences, and continues in as good health as before.



Temperature Chart of the case of a Girl, aged three years.

Class 2 includes cases in which the fever lasts longer, and so causes more

definite illness; but in its mode of onset, and the absence of other symptoms than those common to pyrexia, resembles Class 1.

The Chart shown is that of an English child, very fretful all night, found next morning, at nine o'clock, to be at 104°·2 F. Aconite mixture was given all day, without effect; then methylene-blue was given (see Chart). The child ate well throughout, and also slept well, except that "she was jerking and twitching all the time," a statement volunteered by the mother.

Adults usually complain of languor, malaise, and of pains in the limbs, usually not severe. Frequently they do not feel ill enough to take to bed. Occasionally the fever is very high, causing much headache; and if there be pains in the limbs, such cases in autumn are sometimes called dengue, even in North China.

Class 3 includes cases in which the fever is of long duration, from two or three weeks to as many months; I have been told of cases lasting over six months. These are, I believe, the cases which are commonly classed as typhoid fever, by exclusion. The only point in which they resemble genuine typhoid fever is their long duration. There are no abdominal symptoms; often the bowels are natural; more generally they are constipated; there are no roseolæ, nor any rash of any kind. Usually there is but little subjective feeling of sickness. The patient eats well, sleeps well, and his sole symptoms may be slight languor and disinclination for any kind of exertion, physical or mental. Generally there is but little loss of flesh, except in cases of very long duration, when a degree of emaciation may result. The fever usually remits at least 2° F. every day. Irregularity of the temperature curve is one of the main characteristics of this fever, several marked fluctuations commonly occurring each twenty-four hours.

In a somewhat more severe case, treated with methylene-blue, the cutting short of the fever was indubitable; there were two relapses, of progressively decreasing severity; each occurring as soon as the daily use of the drug was stopped. Pains in the head and limbs (along the nerve-trunks chiefly) were a prominent symptom in this case.

The *mortality* in these cases is practically nil. I have never heard of an adult dying; a point in which this fever differs markedly from genuine typhoid (see, however, Class 4 and comments).

Obviously, it is desirable to apply the serum test in these cases; unfortunately, I have no means of procuring the necessary pure culture.

Class 4 includes cases of a more severe type, in which the pyrexia is persistently high; and death, with very characteristic symptoms, ultimately results, obviously due to the blood becoming gradually so impoverished that it is unable to support life, and also to the peripheral blood vessels becoming blocked by the parasitic growth. These should perhaps be regarded only as severe cases of Class 3; I have separated them because their symptoms are so extremely characteristic, that the question of diagnosis from typhoid fever could hardly arise.

A very delicate girl had had slight feverish attacks from time to time, in various Chinese treaty ports, but never any very severe one. She was always quickly prostrated by a few days fever.

This patient now had an attack which set in with great severity, the temperature persistently ranging from 103°–105° F., and no medicine seemed to have any effect upon it; on the eighteenth day it rose to 106°·4 F.; on the sixteenth day she appeared moribund, being quite unconscious, passing all excretions into the bed—thready pulse, etc. Cold packing was then begun, and methylene-blue given frequently, from 12 to 24 grs. per diem, with such success that by about the thirtieth day she seemed to be out of danger, and the drug was stopped. The fever speedily returned, with daily increasing violence, and it was several weeks before cold bathing and the persistent use of methylene-blue lessened its severity. After about the tenth week one to two cold packs per diem

sufficed to keep the temperature from rising much above 100° F., but although the child ate and slept well she did not regain strength; the pulse persisted at 140–150, and her pallor increased from day to day. On the eighty-first day she suddenly developed the ordinary symptoms of acute anæmia, and then gradually became comatose; the pulse suddenly dropped from its extreme frequency to 80; the teeth were firmly clenched, evidence of cerebral cortex irritation from peripheral thrombosis, and the patient succumbed.

At the autopsy the intestines were found quite healthy; the abdominal organs were extremely pale and anæmic; from the severed large vessels there escaped only a slightly pinkish water-like fluid. There was still some subcutaneous fat, emaciation being not at all marked. Throughout the second period of her illness the child never complained, and never seemed to feel very ill; her appetite was good, she slept soundly, and was always cheerful and in good spirits. There were no abdominal symptoms; in fact, the only symptoms were high temperature and those due to gradually increasing weakness. Death was due to her inability to supply fresh blood tissue fast enough to compensate for the waste.

It is especially children who are exposed to serious danger from this fever. A child with infested blood may have pretty good health, at the worst having only an occasional short flash of high fever, which passes off speedily without ill effects. But if it have some other illness, which reduces its vital resistance, and makes its blood plasma a more favourable medium for the growth of the always present parasite, this may suddenly start growing with extraordinary luxuriance, and cause death within a few hours—often soon after convalescence from the primary disease appeared to be well established. This is the rationale of many sudden and unexpected deaths in children.

It may well be argued, that since the parasite is universal, it cannot be the cause of any disease, otherwise everybody would be sick. The difference between the blood of a person in good health, and that of one with one of these fevers, both infested, is however very great, though more easy to realise than to put on paper. In febrile blood the spores are far more active and lively; a much larger proportion have their germ organs protruded, or even already in process of development; the masses of fructifying gonidiophores, and of other forms of fructifications are much greater; the zygospheres are far more abundant, etc.

2. CHRONIC CASES.—These include, on the one hand, persons who are merely in a condition of depressed health, so that they are less fit than of yore for their work, or for sustained effort of any kind; and, on the other, cases in which there is fever of a mild persistent type, sometimes so slight as to escape the sufferer's or, in case of children, the relation's notice. If so, it is observed in children that their nutrition is impaired, their growth stops or is delayed, and so forth; in adults, that they are gradually becoming feeble, and finally incapacitated for their ordinary work. If careful temperature records be made, one or two daily rises to 100° F., occasionally to 101° F., will be noticed, usually at about the same time each day.

One of the most convincing proofs of causative relationship be-

tween the parasite and the fevers described, I owe to Staff-Surgeon Barnes, R.N., from whose report on an epidemic of fever aboard H.M.S. *Tamar* at Hongkong, in the autumn of 1897, I take these facts.

At the end of May 1897 the new ship's company for H.M.S. *Undaunted* arrived in Hongkong, after a trying passage through the Red Sea and Indian Ocean, and a halt at Trincomalee during the hottest season; they were berthed aboard H.M.S. *Tamar*, and kept busily employed between her and H.M.S. *Undaunted*, which was being recommissioned. On 6th September the first case of fever occurred, the last on 30th October; in all, about 300 men were attacked out of 450; there were 285 cases on board, and all the men who were sent to hospital on shore with other diseases developed the same fever. The other ships in the harbour were unaffected. None of the Chinese employed on board the *Tamar* and *Undaunted* were affected. Neither age nor occupation was material.

The cases were too numerous for thermometric observations to be taken; but in his own case Dr. Barnes "was surprised at the large and rapid fluctuations," there were four to five distinct rises and falls of 2° to 3° F. during the day. In some of the cases the maxima were at noon, in others near midnight, in the early morning, or from 7 to 8 P.M.

Usually there was constipation, diarrhœa in a very few cases. Very rarely was there any rigor. There were no premonitory symptoms beyond malaise. The most constant symptoms were intense frontal headache, often also lumbar pains, and weakness of the legs. In many cases nothing but weakness and malaise were present. An officer, with a temperature over 100° F., wanted beef-steak, pudding, and salad; doubtless many men contrived to obtain similar articles of diet.

Many cases were admitted with a temperature of 103° to 104° F., but in no instance was there any anxiety for more than two to three hours. By Dr. Barnes' courtesy I was enabled to examine a specimen of blood from one of the latest convalescents (in December 1897). I found it swarming with spores, fructifying hyphæ, etc.

If an experiment on a larger scale had been deliberately planned, it could hardly have been more successful, or more instructive, than this one.

Etiology.

The facts stated, as to the infection of food-animals, and the resistance of the spores to heat, indicate clearly enough the channels of human infection, and also the methods by which this may be prevented in future. As to the disease in cattle I have no observation. In 1895 a virulent cattle plague swept over Shantung, as over other parts of China, and destroyed a large number of beasts. As it was after this that fever cases became common in Chefoo, before remarkably free from fevers of all kinds, there is some slight ground for associating the phenomena. Unfortunately, I have had no chance to examine cattle suffering from this plague; but, if it be due to the parasite under discussion, all the required conditions are fulfilled. Those animals which recovered would still be infected, and their milk and flesh alike would convey the infection to whoever consumed them.

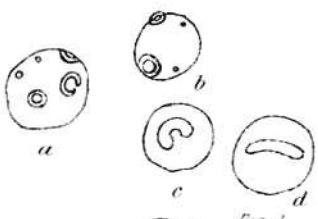


Fig. 1.


Fig. 2.

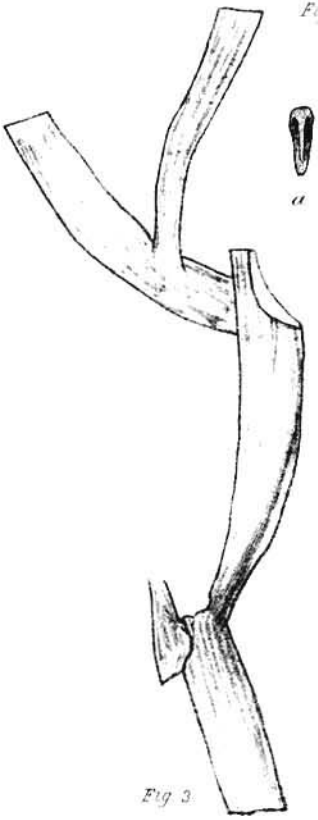


Fig. 3.

Fig. 4.

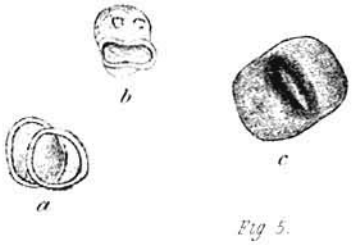


Fig. 5.

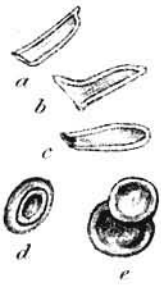


Fig. 6.

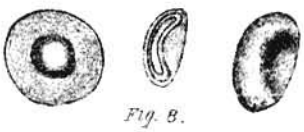


Fig. 8.

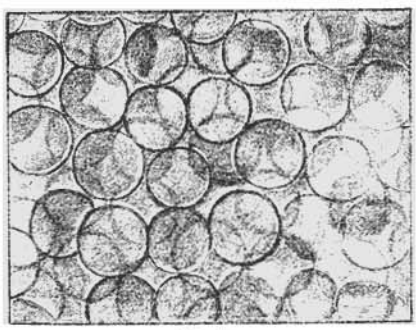


Fig. 7.

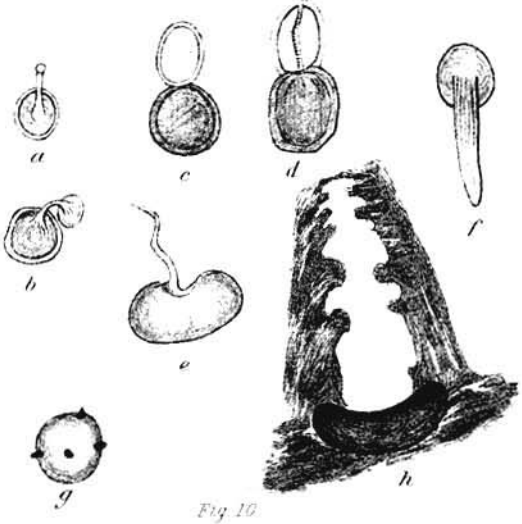


Fig. 10.

Fig. 9.

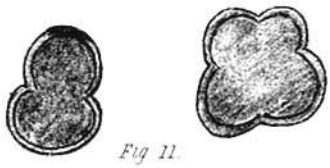


Fig. 11.

TREATMENT.

In a large proportion of cases little is required beyond rest and attention to the general condition. If the fever persists, salol is a very useful drug, as are other kindred drugs unnecessary to enumerate. Quinine is absolutely useless; in severe cases its administration only adds to the distress of the patient. As yet, methylene-blue is the only drug found to have any curative effect, and a study of detailed cases recorded in my longer paper will show that in some cases its efficacy has been very marked. I find that in adults, 1 to 2 grs., repeated every two to six hours, according to the gravity of the case, suffices; in children, $\frac{1}{3}$ gr. to $\frac{1}{2}$ gr. every two to four hours. It may be given in capsules or in compressed tabloids. I have given an average of about 20 grs. a day to a child of 13, without any bad effects. Sometimes it causes painful micturition, with spasm in the bladder. This may be obviated by the simultaneous administration of small doses of tincture of nutmeg.

Constipation should be prevented, for which purpose small doses of calomel, grey powder, or the hepatic stimulants are generally to be recommended.

DESCRIPTION OF PLATE XIII.

Figs. 1–8 are all made from fresh preparations.

FIG. 1.—*a*, *b*, Red blood corpuscle studded with double-contoured circles and crescents; *c*, *d*, red blood corpuscles showing highly refracting rods; *e*, *f*, red blood corpuscles with peculiar reniform bodies in two positions.

FIG. 2.—Patch of typical fungus hyphæ, in the blood, laden with spores. From a photograph.

FIG. 3.—Shows peculiar branching hyphæ.

FIG. 4.—Zoogonidia. *a–i*, *l*, *v*, show various shapes found in the blood.

FIG. 5.—Zoogonidia. *a–e*, show germ-pore and thickened lip.

FIG. 6.—*a–e*, Zoogonidia of simple tubular form with opening at each end, in various positions.

FIG. 7.—Zygospores as perfectly colourless flat discs.

FIG. 8.—Zygospores at somewhat later stage than Fig. 7.

FIG. 9.—Spores treated with perchloride of mercury. *a* is a group stained with carbol-gentian violet, *b* stained with dahlia.

FIG. 10.—*a–f*, Blood preparations treated with 1 per cent. osmic acid to show germ-organ; *g* shows a swarm-spore from which several hyphæ are beginning to sprout; *h* shows a reniform spore still with its sheath, from one side of which a hypha is sprouting.

FIG. 11.—Shows two groups of two and four conjugated spores respectively.