The malarial fevers of Baltimore : An analysis of 616 cases of malarial fever, with special reference to the relations existing between different types of haematozoa and different types of fever / by William Sydney Thayer and John Hewetson.

ERRATA.

On p. 28, line 1, *for* "degenerate" *read* "sterile."

" " 165, " 25, " " " "

" " 172, " 8, " " " "

THE MALARIAL FEVERS OF BALTIMORE.

AN ANALYSIS OF 616 CASES OF MALARIAL FEVER, WITH SPECIAL REFERENCE TO THE RELATIONS EXISTING BETWEEN DIFFERENT TYPES OF HAEMATOZOA AND DIFFERENT TYPES OF FEVER.

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DIVISIONS OF THE SUBJECT.

I.—PRELIMINARY REMARKS.

During the five years between June 14th, 1889, and August 1st, 1894, 616 cases of malarial fever were treated in the wards and in the medical out-patient department of the Johns Hopkins Hospital. In a considerable number of cases occurring in the out-patient department, hasty or insufficient examinations of the blood failed to show the specific micro-organisms, while in other instances examination of the blood was omitted on account of lack of time. Most of these cases are classified in the hospital records as "malarial fever?"; they have not been included in our analysis. Excepting two or three instances where the patients entered the hospital during convalescence, the specific micro-organism was found in every case of malarial fever treated in the wards.

The writers of this article have observed practically all the cases here classified after October, 1890. In a number of those observed before this time careful notes or drawings were made, which enabled us to draw definite conclusions with regard to the type of the organism. In other cases, however, the entries upon the records were so vague that, while the charts might justify a more or less decided opinion as to the nature of the infection, we have not included them among those cases where the type was definitely differentiated.

As a result of our observations, we believe that we have been able to recognize certain distinct types of parasites which appear to be related in turn to certain almost equally characteristic types of fever. It is the principal object of this paper to determine by a careful analysis of all of our cases in how far our impressions may be justified, and to compare our results with those of the numerous recent observers in this and in other countries.

We have prefaced our analysis by an historical summary of the more important literature concerning the malarial parasite.

At the end of the article will be found a table of references arranged, as far as possible, in chronological order. This we believe to be a fairly complete list of the publications concerning malarial fever which have appeared since the recognition of its parasitic origin.

A great mass of literature from sources where the relation of the haematozoa to the disease is as yet unrecognized has been of necessity passed by.

The table also contains references to the works which have recently appeared on the haematozoa of birds, as well as to the more important articles on haematozoa in other animals.

II.—LITERATURE.

Development of our Knowledge concerning the Malarial Organism: Its Main Morphological and Biological Characteristics.

Since the discovery by Lewis,[8] in 1879, of living parasites in the blood of rats, the pathogenic importance of haematozoa, both in man and in other warm-blooded animals, has claimed yearly more and more attention; and doubtless the most important discovery which has been made in this field is that of Laveran, who in 1880, was able to announce that he had found, in the blood of individuals suffering with malarial fever, living parasites which were, in his opinion, the probable cause of the disease.

The infectious origin of malarial fever has, as is well known, been suspected for many years; it is, however, quite beyond the scope of this article to enter into a discussion of the numerous and interesting theories which have existed in the past.

The presence of pigment in the blood was first noted by Meckel [1] in 1847. In an autopsy on the body of an insane woman who had suffered from malarial fever, he not only observed the presence of pigment in the blood, but pointed out in addition that the pigment was contained for the most part in round, ovoid or spindle-shaped protoplasmic masses which were doubtless the malarial parasites. He did not, however, recognize any connection between the pigment and the malarial process.

As long ago as 1848 Virchow [2] described and pictured, in the blood of an individual dead of malarial fever, pigmented bodies, many of which were probably phagocytes, while others, from the description and from the accurate drawings, were unquestionably examples of what were not to be recognized for thirty-two years as the patho-

genic parasite. Hischl,[3] in 1850, recognized the connection between the presence of pigment and intermittent fever. Planer,[4] in 1854, noted the pigment in the circulating blood, and suggested its origin there as well as in the spleen. He believed that the pigment circulating in the blood arose during the fever, and that it was the cause of many of the symptoms.

The association of melanaemia and pigmented leucocytes with malarial fever, and the diagnostic importance of this condition was thus recognized in many quarters when Laveran in 1880 discovered the fact that the pigment was primarily contained in the body of a living parasite. Laveran,[14, 15, &c.] a French military surgeon, was at this time stationed at Constantine in Algeria. He had set for himself the task of studying carefully the malarial fevers. In November 1880, while examining the blood of a patient with malarial fever, he noted several of these pigmented bodies which possessed long, actively moving filaments which oscillated about among the surrounding corpuscles in so active a manner as to convince him that he was looking upon a living parasite. On the 24th of December, 1880,[15] in a report to the Société des Hôpitaux, Laveran presented the results of his studies in 44 cases of malarial fever, in 26 of which he had found elements which he believed to be parasitic. He described three forms of the organism :

(1). Crescentic or ovoid bodies, 8 to 9 μ in length by 3 μ in diameter; these were quite transparent and colorless, except for a collection of rounded pigment granules near the centre, or more rarely, collected toward one end of the body. Oftentimes the granules were arranged in the shape of a crown or wreath. At times the extremities of the crescentic bodies were connected by a pale, curved line. Change of shape, if there was any, was very slow and slight.

(2). Bodies which in repose were spherical, transparent, about 6 μ in diameter, containing a ring of rounded pigment granules of about equal size. In activity, however, these bodies were surrounded by from three to four fine filaments in active, worm-like motion. The length of these was three to four times that of a red corpuscle, possibly longer, while their ends were slightly swollen and clubbed. They arose at times all from one side of the body, while at others they took their origin from different parts of the periphery. The central body was at this time in extremely active motion, the pig-

ment granules dancing about and changing their position, while the movements of the central body as a whole were like those of an amoeba. At times one of the filaments might be seen to separate from the body and move about free among the corpuscles.

(3). Bodies which were generally spherical, 8 to 10 μ in diameter or sometimes more, slightly granular and non-motile, without peripheral filaments. The pigment granules were generally arranged without regularity, and varied in number. The bodies might be seen to become gradually irregular in shape, while the pigment was usually non-motile. He believed that these were simply cadaveric forms of the former parasite. Furthermore he found generally in his preparations small, rounded, refractive, motile bodies and granulations of pigment of a fiery red or of a clear blue color.

These organisms he found only in malarial fever. They disappeared on treatment with quinine. He concludes that "there exist in the blood of patients with malarial fever, parasitic elements which have heretofore been confounded with melaniferous leucocytes; the presence of these parasites in the blood is probably the principal cause of the manifestations of paludism." Concerning the nature of these bodies Laveran raised the question as to whether they were amoebae or whether possibly bodies 1 and 2 were produced by an agglomeration in a species of cyst formed, perhaps, at the expense of normal elements of the blood, of parasites which, in their full development, were represented by the motile filaments which might, at times, become detached and lead an independent life. To this latter view he inclined.

This preliminary report, which was received with general scepticism, was followed by a number of other notes, in which Laveran defended his former statements, while in 1881 a small monograph [25] appeared, setting forth his observations at greater length. In this monograph the name "Oscillaria malariae" was suggested as a proper one for his newly-discovered parasite. In the same year, before the Academy of Sciences, [23] Laveran added still another form of the parasite to those already described:

These bodies were spherical, transparent elements, containing motile or non-motile pigment granules; they were, however, much smaller than the other forms which had been described, the diameter varying from one-sixth that of a red blood corpuscle upwards to nearly

an equal size. The smallest had but one or two fine pigment granules, while again they might be nearly the size of a leucocyte, and contain numerous actively motile granulations. "These bodies, sometimes isolated, sometimes together, as many as four, sometimes free in the blood, sometimes attached (accolés) to the red corpuscles or leucocytes, seem to represent simply one of the phases of development of the parasitic bodies above described." He still adhered to the view that these pigmented bodies were cysts containing the motile filaments, which in the free stage represented the organism at its stage of most perfect development. He also stated his belief that "it is because it kills these parasites that quinine causes the disappearance of the manifestations of paludism."

The first observer to confirm these observations was Richard,[26] who pursued his studies in 1882 at Phillippeville, in Algeria. He describes carefully the development of the body, stating that in the beginning it is represented by a small, perfectly clear spot in the otherwise normal corpuscle ("toute petite tache claire"). This, growing, develops pigment, while the corpuscle containing the organism becomes decolorized, and finally is reduced to a mere shell, the body developing within it like a weevil in a lentil. At times the organism may escape from this shell which may be seen as a pale rim upon one side. He describes vividly the motile filaments, the crescents, and the melaniferous leucocytes, enlarging thus the observations of Laveran by describing a little more definitely the earliest stages of the body (non-pigmented forms), and differing from him in considering the bodies intra-corpuscular instead of being attached merely to the body of the red corpuscle. Later,[33] however, Richard abandoned the idea of the intra-corpuscular condition of the parasites, accepting Laveran's theory that they were attached to the surface of the corpuscles. He believes with Laveran that the motile filaments represent the organism at its most perfect stage of development. He agrees also with Laveran in the statement that the organisms are present in greater numbers on the days of the paroxysms. They develop rapidly, their number increasing till the beginning of the paroxysm; "they produce the fever, the fever kills the parasite, and falls in its turn." During apyrexia the parasites grow again, until finally another paroxysm is produced. The continuous fevers, where quinine fails to act, Richard believes to be non-malarial.

At the time of these discoveries by Laveran and Richard, the eyes of the world were directed much more toward the work which was then being carried on in Italy by Klebs, Tomassi Crudeli, and other observers,[9, 12, 13, 17, 21, 27, 28, 32, &c.] who believed that they had isolated a bacillus which had a direct etiological relation to malarial fever, and the work of the French observers was received with great scepticism, nowhere more so than in Italy. There, Marchiafava and Celli,[34, 35, 36] who, among others, were believers in the bacterial origin of malarial fever, studied, by means of dried and stained specimens, the changes which occurred in the red blood discs in paludism. In many of the red corpuscles they found small round bodies resembling micrococci, which took up methylene blue, as well as slightly larger ring-shaped forms; further they found larger areas containing dark pigment granules, until finally whole corpuscles were sometimes taken up by large, palely staining pigmented bodies. They suspected that the small spots first mentioned might in some instances be parasitic (micrococci) in nature, while the larger pigmented areas they believed to be degenerative changes in the red discs, changes which had been brought about possibly by the presence of parasites. The plates show that most of these stained bodies were unquestionably malarial parasites.* They noted that the pigment was formed in the circulating blood at the expense of the red blood corpuscles. Later,[36] in a more extensive article, they followed carefully the development of pigment, and described again these so-called degenerative changes in the corpuscles. They referred to the changes which occur in the red corpuscles when exposed in tubes to high temperatures, 42° to 48° C. (the development of motile filaments), and stated without further discussion that these represented the filaments observed by Laveran and Richard. The crescents, they said, were due simply to decolorization of the periphery of the corpuscle while the rest retained its color. It was not until 1885 that Marchiafava and Celli[41, 45] recognized the fact that they had been dealing with a parasite and not alone with degenerative changes. They had then seen the flagellate bodies of Laveran in four cases out of forty-two; they had also seen bodies similar to these with an extremely active, wave-like movement of the peri-

* A number of the smaller dots, those resembling micrococci, were probably similar to those areas found in all anaemias, and described by Ehrlich as degenerative changes.

phery. They described also bodies where the pigment had collected in the middle, the substance of the parasite showing evidences of differentiation into a number of smaller bodies, while in others the pigment was surrounded by a collection of distinct segments into which the organism had divided. They laid particular stress upon the smaller forms of the parasite, and stated that it was then certain that they did not belong to the class of schizomycetes. They inoculated healthy individuals in five cases with the blood of malarial patients with fairly good results, in as much as in all instances, after several inoculations, symptoms of malarial fever with the presence of parasites in the blood were produced in the individuals upon whom the inoculation was practised. Later [45] in the same year they described with great care and accuracy the characteristics of the small hyaline forms. These they described as showing an outer, thicker, more refractive zone, and an inner, less refractive part, which appears sometimes finely granular. The organisms are actively amoeboid, the pseudopodia extending from the outer zone. This outer zone alone is colored by staining reagents, the central part being so thin that the red corpuscle shines through; at times it has the appearance of a clear or slightly colored nucleus. In some instances no pigmented forms whatever were seen, though in several of these cases pigmented leucocytes were found. Among these cases were some of the most severe and pernicious forms. They believed that these parasites were contained within the red corpuscles in opposition to the views of Laveran and Richard, who, it will be remembered, considered them attached to the surface. They described more extensively the segmenting bodies, and suggested that these might represent a process of reproduction, as they had noticed, in one instance, their occurrence during the paroxysm simultaneously with the appearance of new hyaline bodies in other corpuscles. In this early communication they described, in the organs of certain pernicious cases, the appearance of these segmenting forms in small parasites which were quite free from pigment. They claimed for themselves the honor of having first described the small non-pigmented forms, which they considered the most important elements, asserting that the bodies described by Laveran and Richard were vacuoles or other changes in the red corpuscles. They proposed for these small bodies the term "Plasmodia." Thus it will be seen that Marchiafava and Celli have the

honor of having first called attention to the extreme amoeboid activity of these small forms, and also that they were the first to describe and suggest the importance of the segmenting bodies. It can, however, hardly be doubted that Richard's description of the hyaline forms was based upon observations of these same bodies, and not upon vacuoles as Marchiafava and Celli assume, and, while the honor of first describing and of hinting at what has later been shown to be the true significance of the segmenting forms, belongs unquestionably to them, there is, at the same time, no doubt that these bodies had been observed by Laveran some years before. Laveran [60] has indeed published a very clear and accurate plate of a segmenting form occurring during the paroxysm in a case of quartan fever; the sketch was made in 1881. Marchiafava and Celli further vigorously assailed Laveran's ideas concerning the nature of the organisms, denying that they are cystic in character, and denying also the double contour which Laveran and Richard describe in the crescents and ovoid bodies.

Following these articles of Marchiafava and Celli, the literature of malarial fever shows an almost continuous series of articles confirmatory of the discoveries of Laveran. No observers, indeed, of importance who have had opportunities for proper study of malarial blood, have failed to confirm his observations. Among the first of these observers were Councilman and Abbott,[40] who in 1885, in the study of the organs from two cases of comatose pernicious malaria, described pigment-containing bodies in and outside of the red corpuscles, particularly in the capillaries of the brain, and also in the liver and spleen, as well as numerous pigmented phagocytes. They had not been able to find these bodies in the fresh blood, but they remarked their similarity to the parasites described by Laveran. They had not been able to find the bacilli of Tomassi Crudeli.

In 1885, then, our knowledge of the malarial parasite, based upon the observations of Laveran, Richard, Marchiafava and Celli, Councilman and Abbott, may be summed up as follows. There had been observed small, hyaline, amoeboid, intra-cellular parasites, which grew gradually, developing within themselves fine, actively motile pigment granules; these bodies eventually generally filled up the entire corpuscle, decolorizing and perhaps destroying it. Having reached this full-grown stage, the organisms were in some instances seen to show

a concentration of the pigment in the centre of the body with the development of a radial striation and the formation of segments, while in other instances, they appeared to give rise to the motile filaments first described by Laveran. Sometimes the small, intra-cellular bodies appeared to develop into ovoid or crescentic forms with the pigment granules in the middle. The crescents had apparently the power to change again into the ovoid, and then into a round shape, from which, commonly, the flagellate bodies of Laveran were seen to develop. The significance of these different forms was a much disputed point, Laveran believing the most perfect forms of the organism to be the free flagella which develop in the interior of small cysts which were represented by the earlier forms, while Marchiafava and Celli were inclined to believe the parasite to be more like an amoeba, denying entirely its cystic nature. Concerning the significance of the segmenting bodies, Laveran was, at first, apparently inclined to believe that these were rather degenerative forms, while Marchiafava and Celli suggested, distinctly, their reproductive nature. The observations of Laveran showed that the crescentic forms were found more particularly in the patients who had been suffering from chronic and severe malarial fever or relapses.

In the year 1885 a new era in the study of the malarial organisms was introduced with the publication of the researches of Golgi,[49] of Pavia. And from this time, as Barbacci [239] has pointed out in his admirable review of the subject, we must recognize two main schools, with essentially different views concerning the nature of the malarial parasite.

The first party is represented by Laveran and his followers who believe that the malarial parasite is a single polymorphous organism; that there is no constant relation between the different forms in which it appears and the various types of fever.

The second party, at the head of which stands Golgi, believes that, corresponding to and associated with the main types of malarial fever, one may distinguish different types of the malarial parasite, or, possibly, different parasites.

The views of the first party may be summed up in part in Laveran's [277] own words: "This parasite is to be seen in a considerable variety of forms, which one can, however, resolve into the four following types: (1) spherical bodies; (2) flagella; (3) crescentic bodies; (4) segmenting bodies or rosette forms."

(1). He describes the different stages of development of these bodies from the small amoeboid hyaline forms onward. The movements of the pigment granules he believes to be communicated by undulations of the protoplasm. The bodies themselves are sometimes free, sometimes attached to the red blood corpuscles; sometimes several may be attached at one time to a single corpuscle. The development of the parasite occurs at the expense of the red blood corpuscle which becomes decolorized and sometimes disappears altogether. Sometimes one large body may be seen to break up into a number of smaller ones. At times also small sarcodic buds may be seen to form at the periphery of a larger body. These he apparently considers to be reproductive processes. He describes also the gradual deformation and death of some of the large pigmented forms.

(2). The flagella, he asserts, may be seen immediately after the specimen has been prepared, especially if the weather be warm, though ordinarily it is easier to find them in from fifteen to twenty minutes after the beginning of the examination.

At the further extremity of the flagellum one may often see a pyriform swelling, and similar ovoid enlargements may, at times, be made out at different points in the course of the filament. At times a small particle of pigment may be seen to pass into the flagellum as if through a central canal.

After the breaking off of the flagella, which doubtless pursue a separate existence, the body of the parasite is left deformed and motionless—a cadaver.

(3). After describing the crescents as before, he notes that the fine line, which often connects the two horns, represents, doubtless, the remains of the red blood corpuscle at the expense of which the crescent has developed.

(4). The segmenting bodies he describes and pictures as has been noted before. The plates illustrating the segmenting bodies, it is interesting to note, were from drawings made in 1881, which had not been published at that time.

Concerning the development of the parasite he says: "The small hyaline bodies not yet pigmented, which form the little clear spots on the red corpuscles, represent, probably embryonic forms of the parasite; little by little these bodies increase in size till finally their volume equals or even exceeds by a little that of the red corpuscles;

at the same time the number of pigment granules increases; these elements, which possess the power of amoeboid movement, live in a free state in the serum of the blood, or adhere to the red corpuscles at the expense of which they derive their nourishment and their pigment; the flagella develop in the interior of the spherical bodies and at a given moment become free."

The crescents [280] he believes to be encysted forms which develop from the spherical bodies. These forms show a much greater resistance to quinine than the spherical bodies; they may be seen to change into round, ovoid and flagellate forms.

He writes as follows in his last work: [277] "I do not believe that there exists a constant relation between the forms under which the haematozoa appear in the blood and the clinical manifestations of paludism; one can only say that certain forms of the parasite are more often seen in certain cases, the crescents, for example, in relapses and in malarial cachexia, as I have demonstrated long ago" . . . "The differences which one makes out in the evolution of the haematozoa of paludism are not sufficient to authorize one in admitting the existence of several distinct varieties of parasites."

The views of the other school must be entered into at greater length; they date, as has been said, from the researches of Golgi in 1885.

With the appearance of the articles of Golgi on the organism of quartan fever begins, as we have already said, a new era in the history of the haematozoa of malaria.

In the study of twenty-two cases of quartan fever Golgi [49] followed with singular care and accuracy the development and life history of the parasite, determining for the first time the close relations which exist between the development of the organism and the clinical symptoms. Marchiafava and Celli had already mentioned that they had found segmenting bodies during the paroxysm, but Golgi was the first to point out that each paroxysm is always associated with the segmentation of a group of malarial organisms, in other words, that the beginning of every malarial paroxysm corresponds to the ripening of a generation of parasites. He further determined that, generally speaking, the severity of the attack is dependent upon the number of parasites present in the blood.

The parasite of quartan fever, upon the study of which these conclusions were based, requires seventy-two hours for its complete develop-

ment. In their earliest stage the parasites are represented by small, amoeboid, hyaline, intra-corpuscular bodies. Early in the first day of apyrexia one finds, in the red corpuscles, unpigmented forms which are from about one-sixth to one-fifth the diameter of the corpuscle itself; these move slowly, changing their outline. The blood corpuscles in which they lie are of normal size and appearance. These bodies grow gradually larger without changing their general appearance, and develop rather coarse, dark brown pigment granules. Sometimes they may be seen free in the plasma, but this occurs rarely. The movement of the granules, as well as the amoeboid movement of the organism, whether it be intra- or extra-cellular, is always rather slow. Early in the day of the paroxysm the process of reproduction begins, the organisms having by this time so far increased in size as to entirely fill the red corpuscle, of which there is often only a slight peripheral rim remaining. Often, indeed, there is apparently no trace of the corpuscle left, so that one sees free bodies of a colorless substance with irregularly distributed pigment. Gradually the pigment becomes concentrated toward the middle of the body, until finally it forms a sharply defined clump in the centre. At this time one begins to see the appearance of a slight radial striation in the hyaline substance of the organism, the striae becoming more distinct until finally the central pigment clump is surrounded by eight to ten round or pear-shaped bodies, each with a small refractive central point, as regularly arranged as the leaves of a marguerite, the so-called rosette or marguerite forms of Golgi. Soon these bodies become more distinctly separated from one another and from the central mass, until the central pigment clump may be seen to be surrounded by four, to six, to eight, to twelve ovoid or round, clear, hyaline bodies, each with a small refractive central point. This segmentation begins eight to ten hours before the paroxysm, and continues during its first hours, while at the same time fresh hyaline bodies begin to appear in the red corpuscles. The resemblance between these segments and the fresh hyaline bodies is striking, although the actual entry of the newly formed segment into the corpuscle has never been observed. Based upon these observations Golgi founded the following laws: Each febrile paroxysm is closely connected with the cycle of development of a generation of parasites: the beginning of each paroxysm corre-

sponds to the maturity of a generation of parasites: the severity of the paroxysm is, in general, proportional to the number of the parasites which are found in the blood. Some cases of quotidian fever which Golgi observed were due to infection with three groups or generations of quartan organisms, the groups maturing on successive days, causing thus a daily paroxysm, while in other instances, where chills were observed on two successive days with an intermission on the third, he was able to trace infection with two groups of parasites.

This description of the cycle of existence of the quartan organism was confirmed a few months later by Osler[55] in Philadelphia, and has since then been accepted by practically all who have had opportunity to study quartan fever.

Antolisei,[126] in a systematic study of the parasite of quartan fever, added little to Golgi's observations. He laid more stress upon the beginning of segmentation before the actual onset of the fever. While Golgi believed the paroxysm to be due to the invasion of the red corpuscles by the new generation of parasites, Antolisei held that the chill depended rather upon the act of segmentation than upon the actual invasion of the corpuscles. For, by administering quinine in sufficient quantity shortly before an expected paroxysm, the invasion of the red corpuscles by a fresh generation of parasites may be completely prevented, while it is quite impossible to prevent the impending segmentation or the paroxysm. He believed the segmenting parasite to be surrounded by a membrane consisting of the more resistant outer layer of the red corpuscle in which it has developed; this membrane is broken through with the setting free of the segments.

These observations concerning the quartan organism were followed in 1886[50] and 1889[94] by further careful studies of the parasite of tertian fever. This parasite begins its cycle, as does that of quartan fever, as a small, hyaline, unpigmented body; this increases in size and develops pigment during forty-eight hours, at the end of which time it reaches its complete development; it then undergoes segmentation just before and in association with the paroxysm, at which time the appearance of a new generation of organisms in the red corpuscles is to be observed. Golgi noted, however, distinct differences between the tertian and the quartan organisms. In the first place, the amoeboid movements of the young tertian parasite are much more active; the granules are smaller and of a somewhat different color (a lighter,

more reddish brown); the outlines of the body in general, which are quite clear and sharply defined in the quartan parasite, are, in the tertian, very indistinct. The dancing of the granules is also much more active in the tertian organism. With the growth of the quartan parasite the red corpuscle remains about its normal size, or, indeed, tends to shrink about the body, while the decolorization does not occur until later on, so that the organism may have reached almost its complete development without any particular change in the color of the red disc. In tertian infections, however, the corpuscle begins to be decolorized early in the development of the parasite, and instead of tending to shrink about the body, it becomes considerably expanded and swollen, so that at the time of complete development of the parasite it may be very much larger than its normal neighbor. The full grown tertian organism is then somewhat larger than the quartan parasite.

In segmentation also there are material differences between the organism of tertian and that of quartan fever. Golgi describes two distinct varieties:

(1). The pigment gathers in the centre of the body, while a certain differentiation may be made out between the peripheral clear protoplasm and the central part with the pigment; indications of a radial striation begin to appear in the peripheral clear protoplasm, which eventually becomes divided into from fifteen to twenty small hyaline segments. The differences between this mode of segmentation and that of the parasite of quartan fever are, according to Golgi:

(*a*). The greater number of segments, from fifteen to twenty.

(*b*). The difference in the size of the individual segments which are smaller in the tertian parasite.

(*c*). The absence of the central refractive spot in the tertian parasite.

(*d*). The fact that the pigment which gathers in the centre appears here to be contained in a protoplasmic body.

These pigmented bodies Golgi believes to be for the most part, taken up by phagocytic leucocytes, though he does not feel sure that some of them may not remain in function and produce other bodies.

(2). This variety of segmentation differs from the first in that after the pigment has collected into a small clump, the whole mass of the protoplasm becomes divided into small round bodies, which do not

have the regular daisy-like arrangement of the segments in the first variety, but form simply an irregular clump of small spheres about a central free pigment mass.

Golgi suggests a third variety of segmentation, which is probably rather a degenerative process. Here, in the free pigmented body, which has entirely destroyed the red corpuscle, the pigment collects in a point nearer the periphery, leaving a part of the corpuscle entirely clear and transparent. Within this clear area one and sometimes two small spheres develop, which resemble the true spores.

With the tertian as with the quartan organisms, Golgi observed that quotidian fever depended on infection with more than one group of the parasite; he had observed no organism whose cycle of existence lasted but twenty-four hours. This description of Golgi's of the cycle of the parasite of tertian fever has been in the main confirmed by later observers, though it has met with criticism in some respects and with certain additions.

Antolisei,[129] in 1890, in a careful study of the parasite of tertian fever, agrees with Golgi in the main points. He has, however, met with Golgi's second form of segmentation only, while he asserts that the third variety of segmentation is a degenerative process. He describes this process of vacuolization at length. When the pigmented body has wholly destroyed the red corpuscle, and is free in the blood current, one sees, at a certain time, the development, toward the periphery of the body, of a spherical area, into which the pigment granules which are in very active motion, never enter. Within this area one may see a white, sharply outlined sphere, about which there is very often a vacuole which has a semi-circular appearance because the sphere does not lie in the middle but presses to one side. Later there develop elsewhere in the protoplasm of the organism numerous smaller spherules of varying sizes. Between these lie the pigment granules which become motionless, while in the remaining protoplasm the activity of the movements seems to increase. Gradually more spherules appear, of varying size, often becoming steadily smaller, so that finally the whole body is represented by a collection of minute spherules with sharp outlines, between which lies motionless pigment; about them is an outer shell, which possibly represents the outer more resistant layer of the red blood corpuscle. In the meantime there generally arises a sort of hernia

through the outer more resistant layer, which may take various forms; inside of this new spherules develop. This process of vacuolization Antolisei considers to be degenerative in nature, as does he also that of flagellation, which is seen to occur in large bodies exactly similar to those which undergo vacuolization. Furthermore, Antolisei believes that true segmenting bodies are rarely met with in the circulating blood. He asserts that these are not larger than a red blood corpuscle, whereas those forms which one often considers to be full grown tertian parasites are frequently considerably larger. He believes that the majority of these large forms which appear in the circulating blood are over-grown organisms which are no longer capable of reproduction; they undergo only degenerative processes, vacuolization, fragmentation, and flagellation. Those pigmented forms which are capable of producing true healthy spores remain in the internal organs and are not to be found in the peripheral circulation; they never grow as large as these large free forms.

Bastianelli and Bignami [152] have further studied tertian fever, comparing the blood taken from the finger with that from the spleen; they find that while during apyrexia there is no great difference between the character of the blood from these different parts of the circulation, at the beginning of the paroxysm a marked difference is noticeable. At this time the full grown segmenting bodies with their pigment clumps and new spores are rapidly accumulated in the spleen. These forms reach the spleen, they believe, just as do any foreign bodies which enter the blood current. This does not take place while the parasite is endo-globular, or so long as the red blood corpuscles are not gravely altered in their essential characteristics. They suggest that if this same distribution is not observed in quartan fever, it is probably because the red blood corpuscles are less deeply altered by the quartan parasite than they are by the tertian. They believe, as does Antolisei, that Golgi's possible third form of segmentation is a degenerative process. They found these bodies much more frequently in the blood of the spleen than in the blood of the finger, particularly toward the beginning of the febrile paroxysm. They also note that in the irregular quotidian fevers and in anticipating tertians, they find, always in the spleen, and sometimes in the finger, small segmenting forms with five to ten small spores which are collected about possibly but a single pigment granule,

and contained in red blood corpuscles which are not so swollen as is usually the case in tertian fever; sometimes these forms may be free. They suggest, therefore, that in these cases the cycle of development of the parasite may be accomplished in a shorter time than under normal conditions. The large, free, pigmented bodies which may be observed to become fragmented, vacuolated, or to show flagella, they believe to be degenerate forms. They suggest that spontaneous recovery may be associated with the frequency of these forms in the blood. The accuracy in the main of these descriptions of the tertian and quartan parasites has been confirmed in almost all malarial districts; by Grassi and Feletti [205] in Sicily, by Canalis,[104] Patella, [141] Marchiafava and Celli,[144] Terni and Giardina [145] in Italy, by Mannaberg [291] in Austria, by Kamen [242, 243] in Germany, by Sacharow,[153] Titow,[177] Romanowsky,[210] and Korolko,[226] in Russia, by Remouchamps [321] in Holland, and by Dock,[240] one of the authors,[327] and Koplik [305] in the United States.

The student of the literature can, however, hardly fail to notice the difference between these large pigmented bodies of tertian and quartan fever, and the small hyaline bodies—the "plasmodia"—to which Marchiafava and Celli ascribed so much importance, forms which have a likeness only to the very earliest stages in the cycle of existence of the parasites just described. It will also be noticed that the crescentic bodies which played so important a part in Laveran's first descriptions of the parasite, do not occur in the cycle of development of the organism of either tertian or quartan fever. And later observations have tended strongly to show that these organisms are associated with a different type of fever, a form of fever which is seen only in the more malarious districts, which is rare in Pavia where Golgi studied, but common in Rome and Algiers where Marchiafava and Celli, and Laveran made their observations.

Golgi,[49] in his first note on the quartan organism, mentions that in one case with irregular fever he found crescents and ovoid bodies in the blood, and he suggests that these forms may have a special cycle of existence differing from that of the organisms already described.

One of the first observers to call attention sharply to the fact that the more irregular and continuous fevers were associated with a clearly different type of organism was Councilman.[57] In 1887 he speaks as follows: "The character of these bodies" (the malarial parasite) "varies

in different forms of the disease. Although they seem in rare cases to run into one another, still, in general, we can say that where the plasmodia inside the red corpuscles are seen, the patient has intermittent fever, and where the crescentic and elongated masses are found he has either some form of remittent fever or malarial cachexia." At the conclusion of this paper he states that from the examination of the blood we are "not only enabled to diagnosticate the disease as such, but in most cases the particular form."

In 1889 Marchiafava and Celli[100] and Pietro Canalis[104] published almost simultaneously more elaborate descriptions of the type of organisms associated with the "aestivo-autumnal" fevers observed in Rome. The preliminary note by Marchiafava and Celli appeared before that of Canalis, the article of Canalis before that of Marchiafava and Celli.

Canalis gives a careful description of the organisms associated with this type of fever. He refers to the organism as the "semi-lunar variety." He traces the life-history and cycle of development with considerable care, dividing it into two phases: (1) a rapid cycle, and (2) a slower cycle associated with the development of crescentic bodies. He finds that Golgi's rule applies here just as in the more regular intermittent fevers; that each paroxysm corresponds to the maturation of a generation of parasites.

(1). The rapid cycle is difficult to follow in that the blood usually contains several generations of parasites in different stages of development, which are associated with attacks following one another at varying intervals. He believes, however, that the cycle is generally of not less than two days' duration, though he has seen it as short as twenty-four hours. In the first three or four hours of the attack, one finds small hyaline amoeboid intracorpuscular bodies of about one-sixth the diameter of a red blood corpuscle. These bodies show a clear annular peripheral ectoplasm and a more shaded central endoplasm, which, from its shape and situation, resembles a nucleus. Sometimes, instead of one darker central point, one may see two or even four. When the body is in repose the ectoplasm is sometimes quite refractive. Often the blood corpuscles which contain them are shrunken and misshapen. Sometimes one sees free bodies in the plasma. The parasites gradually grow, and the amoeboid movements become more active, while in the peripheral, ring-like, often somewhat refractive zone, one notices

fine granules of a dark red or black pigment. The appearance of pigment begins sooner or later, depending probably upon the length of the cycle of development. Gradually the parasite increases in size while the pigment granules accumulate. At the end of the cycle there are usually but very few minute granules of pigment, rarely more than six or seven. These stages of development occupy the greater part of the cycle, while the later stages are more rapid in their course, and examples are much more rarely seen in the peripheral blood, the process taking place probably in the internal organs. The parasite increases in size and loses its amoeboid movement while the pigment granules collect in a group or in a small block at the centre of the parasite; sometimes they may be placed eccentrically. The organism has a more hyaline appearance, and the distinction between the ectoplasm and endoplasm is no more to be made out. The blood corpuscle in which the parasite lies loses its color which it had retained fairly well before. An indication of radial striation now appears in the protoplasm of the parasite which eventually breaks into from six to ten round or slightly ovoid segments which surround a group of pigment granules or a very small block. These segmenting forms are considerably smaller than those of tertian or quartan fever. By this time the substance of the red blood corpuscle may have wholly disappeared, or the wholly decolorized body may form a pale ring about the parasite or at one side of it. A striking difference between these forms and those of tertian and quartan fever is the small quantity of pigment in the last stages of development. Canalis, however, has never observed segmenting forms without pigment. The segmenting bodies are but rarely seen in the peripheral circulation, though, at the time of segmentation, one may often see the small pigment blocks which have been derived from them, either free or in phagocytes.

(2). The second cycle, that associated with the development of the crescentic bodies, occurs, sometimes, in association with the more rapid cycle, but, at other times, only after this more rapid course of development has been checked by the administration of quinine. He has never observed crescents at the beginning of the process; in one instance only, did they occur before the fifteenth day. He traces the gradual development of the crescents inside of the red corpuscles from the small amoeboid forms; these assume a long elliptical shape, with the pigment collected in the middle, and gradually take on a crescentic

form, decolorize the corpuscle, and finally become free in the blood, showing a double outline which appears to be the evidence of a surrounding membrane. These crescents in turn change into long elliptical, ovoid, and finally into round forms, though the ovoid forms would appear to arise in some instances directly within the corpuscles, without having passed through the crescentic stage. While, in the ovoid and crescentic forms, the pigment is motionless in a clump or in a ring at the centre of the body, in the round forms it is often in active movement, and commonly arranged in the shape of a ring. The ovoid and round bodies show sometimes a double outline, sometimes not. Sometimes the crescents may change into round bodies before the red corpuscle is entirely destroyed. When the crescents have reached this stage sporulation may occur. These bodies, usually round or ovoid, have sometimes a double outline, and contain eight or ten small spherules. The pigment is sometimes in a solid clump in the middle, though more commonly arranged in the shape of a ring in the middle or at one pole. Sometimes the pigment is free, sometimes retained in a mass of hyaline protoplasm which may be extruded from the body. The fresh segments are round or slightly ovoid with an opaque central area and a clearer outer layer which suggests a double outline. The association of these bodies with the paroxysm and with the appearance of fresh hyaline forms in the red corpuscles, convinces him that this is a true sporulation.

The process of sporulation must be, according to Canalis, sharply distinguished from certain degenerative processes which one sometimes sees. "In this degenerative process" he says, "one meets with bodies which have lost their yellowish or ashy color and have become clearer, sometimes refractive, with a double contour much more marked than that of the ordinary parasite, while their substance is transformed into a mass of round or irregular bodies of various sizes, and with a single contour. If one continues the microscopical examination of one of these parasites during the course of several minutes, he may sometimes see that two or three of these spherules become united into a single body, forming, thus, irregular masses, which, continuing the process of fusion, give, finally, to the parasite an homogeneous aspect without traces of spherules.

"The pigment is sometimes arranged as a central crown, sometimes scattered irregularly at an extremity or at one side of the body. The

points which distinguish this process from that of sporulation are: the refractiveness of the degenerating body; the inequality in size of the spherules; the absence in these spherules of a more opaque central area; their fusion into irregular bodies and finally into an amorphous mass." These forms may also be seen in complete apyrexia, without being followed by a paroxysm or by the appearance of fresh hyaline bodies.

The flagellate bodies are often observed here, though they cannot be proven to be a constant phase. They arise, always, from the round forms which do not show a double contour. They appear, generally, several hours before the beginning of the attack, sometimes during apyrexia at a distance from the attack. "They represent, assuredly, one of the last stages in the development of the parasite, for I have never seen them appear in the blood before the formation of the round bodies." The length of this cycle varies in different cases. The period from the beginning of the amoeboid stage to the appearance of the crescents lasts, probably, not less than three or four days; after the appearance of the crescents the round bodies may appear upon the following day, or later. Associated with this type of organism occur the more irregular and continued fevers, the pernicious fevers, as well as many cases of malarial cachexia and fever with long intervals.

Marchiafava and Celli[100] state that where Golgi was dealing with fevers which pursue a regular cyclical course, are never pernicious, and yield, often without, and always with quinine, these cases of "aestivo-autumnal" Roman fever show, usually, an acyclical course; the attacks occur generally daily, following one another at intervals of twenty-four or thirty-six hours; the paroxysms themselves are often of long duration, so that one may be engrafted upon another without the temperature ever reaching the normal point. The chill is often lacking, the patient complaining only of symptoms of continued fever. These cases often show a pernicious character; they rarely heal spontaneously, show frequent relapses, and are associated often with grave anaemia. Some of the most pernicious cases may show no rise in temperature. The examination of the blood at the acme of the fever, and, also, at the beginning of apyrexia, shows the small, round or actively motile bodies—their "plasmodia." A few hours before the attack begins, however, there occurs a change;

there may be seen: (1) Small round bodies with a little mass of haemoglobin or pigment granules in the centre—ring-like forms; (2) small, more or less amoeboid bodies, with one or two extremely minute pigment granules; (3) larger, round, immovable parasites of a more glistening white color, with a round pigment block in the middle or at the periphery. The haemoglobin of the red corpuscle is, in some instances, concentrated about the parasite in the middle of the corpuscle, while the periphery is decolorized. Many of the corpuscles containing plasmodia are also shrunken, somewhat crenated, and of a color resembling old brass (globuli rossi ottonati). In quartan and tertian fever segmenting forms are commonly seen in the circulating blood; in this type of fever they are extremely rare. They are common, however, in the internal organs, particularly in the spleen and, in pernicious cases, often in the cerebral capillaries. Segmentation occurs while the parasite is yet in the red corpuscle which rapidly disintegrates. Pigmentation begins shortly before the paroxysm, and the discovery of pigment in the organisms is a sure sign that the paroxysm is near. The cycle of development appears to last about twenty-four hours or even less. With the paroxysms, and a few hours afterwards, appears the new group of young, fresh, hyaline bodies. They describe the crescents, admitting what they previously had denied, that these appear to have a double contour. They have seen intermediate forms between their plasmodia and the crescentic bodies. They find, as did Councilman, more crescents in the spleen than in the peripheral blood, and agree with Laveran that they are more common after continued attacks. They have, however, seen pernicious cases without crescents. They have never seen evidences of segmentation in the crescents; those bodies which are described by others they believe to be degenerative forms, asserting that what Canalis has considered to be fresh segments, are only vacuoles. In some instances the parasite may run its entire course to segmentation without the development of pigment. They conclude that, in the malarial fevers of the summer and fall in Rome, there occur, generally, daily or frequently repeated paroxysms with a tendency to become pernicious. With this type of fever is associated the presence of a small amoeboid parasite in the red-blood corpuscles. This organism shows a short cycle unaccompanied by the development of pigment, and a longer cycle, where a

few pigment granules are to be seen. This parasite differs from the larger tertian and quartan organisms, which are found only in particular regions, and cause the milder forms of fever. Different malarial parasites are, then, related to the different times of the year, to different malarial regions, and, finally, to the mild and severe forms of the disease.

These observations have been confirmed in their main features by a large number of observers. Among the first were Gualdi and Antolisei,[111] who proved the existence of this separate type of organism by inoculation experiments.

Antolisei and Angelini[119, 131] refer to this variety of the parasite as the "haematozoon falciforme." They believe that it may run through its cycle of existence quickly, reaching the stage of sporulation, in some instances, before the appearance of pigment, as described by Marchiafava and Celli. In other instances it pursues a longer course, developing into the ovoid and crescentic bodies. They confirm Canalis' observations concerning the sporulative and degenerative forms observed in the crescents. The process of gemmation, however, they do not consider reproductive, likening the small, hyaline buds to the "corpuscles d'exudation" of Hayem. Golgi[94, 118] notes that some fevers with long intervals are associated with these organisms, and believes that they are particularly related to the crescentic forms which pursue a slow development, the paroxysms thus occurring far apart.

Patella,[141] Terni and Giardina,[145] Bastianelli and Bignami,[168, 170] Sanfelice[190] in Italy, Grassi and Feletti[122, 205, 221, 339] in Sicily, Mannaberg,[291] von Jacksch[128] in Austria, Plehn[262] and Kamen[243] in Germany, Sacharow,[153] Korolko,[226] and Titow[177] in Russia, Dock,[207] one of the writers of this article,[327] and Koplik[305] in America have confirmed, in the main, these observations, in so far as they recognize a distinct type of organism associated with the aestivo-autumnal fevers, an organism which differs from those observed in the regular tertian and quartan ague. Considerable difference of opinion exists, however, between these observers as to the significance of certain forms, particularly the crescentic bodies. Bignami,[179] Bastianelli,[168, 170] and Marchiafava and Celli,[222, &c.] in their later works, assert, in contradistinction to the views above expressed, that the crescentic and ovoid pigmented

bodies are deviate and degenerate forms; that their presence in the blood has no influence on the condition of the patient. They deny the possibility of sporulation in these forms, but state that they can follow out processes of vacuolization, fragmentation (gemmation) and flagellation, all of which they believe to be degenerative processes. Certain authors have gone beyond this simple division, and have sub-divided the class of "aestivo-autumnal" organisms. Marchiafava and Bignami [218, 245] believe that they can separate two distinct varieties of the aestivo-autumnal parasite. Each is represented in the beginning by a small, hyaline, amoeboid, or ring-shaped body, but the cycle of development, in the one instance, lasts about twenty-four hours, and in the other about forty-eight hours. In other words they recognize a true *quotidian* and a "*malignant tertian*" type of organism. The *quotidian* fever they say may be quite regular, the attacks being definitely intermittent and similar in most ways to those of the double tertian or triple quartan fever, lasting from six to eight, or rarely twelve hours. Usually, however, the attacks do not come at regular intervals, showing often a tendency toward anticipation or retardation, and varying in severity and duration; often a more or less continuous fever may result. The parasite of this quotidian fever passes a good part of its existence as a small, amoeboid, hyaline body. It may then pass on directly to segmentation with but little increase in size, though, generally, it develops a few fine pigment granules in its protoplasm before this occurs. In either case the segmentation occurs within the red blood corpuscle before this is definitely destroyed. Sporulation occurs almost entirely in the internal organs; the appearance of segmenting bodies in the circulating blood is rare. In the spleen, however, they may be found in great numbers. The corpuscles containing the parasites are often shrunken and of a brassy color; the retraction of the haemoglobin about the parasite, as described by Marchiafava and Celli, may be present. After a certain length of time crescentic and ovoid forms usually appear.

The *tertian* type of organism is associated with a fever which, according to Marchiafava and Bignami, has a characteristic type, differing materially from the mild or spring tertian. The individual paroxysm lasts usually more than twenty-four hours, often from thirty to forty hours. There is a marked tendency toward aggrava-

tion, anticipation, and conjunction of the attacks which frequently follow one another in such a manner as to produce a continued fever. They believe, however, that they are able to distinguish certain characteristic points about the febrile curve; a rapid invasion, a status febrilis, with more or less marked oscillations, a slight pseudo-crisis, a pre-critical rise in temperature during which the maximum point of fever is often reached, and finally the crisis. The paroxysms are so long and the periods of apyrexia so short that the patient often believes that he is suffering from a continuous fever, while, from various modifications of the temperature curve, this may actually be the case. Generally the curve becomes more or less complex; this may be brought about by various influences.

(1). *By modifications of the curve in the individual paroxysm;*

(2). *By modifications in the succession of the paroxysms.*

(1). *The important modifications of the curve* are the following:

(*a*). The lack of a sharp initial elevation so that the curve rises in a progressive and continuous manner;

(*b*). the exaggeration of the pseudo-crisis so that the attack tends to lose its individuality;

(*c*). the prolongation of the paroxysm, which is usually associated with an exaggeration of the thermic oscillations during the fastigium;

(*d*). the lack of a sharp pre-critical elevation.

(2). *The modifications in the succession of the paroxysms* may be:

(*a*). The anticipation of the paroxysms, which can occur in the mild as well as in the severe forms;

(*b*). the retardation, which can occur also in the grave infections;

(*c*). the prolongation of the paroxysms, by which apyrexia is made incomplete;

(*d*). the presence of slight oscillations in the temperature during the period which ought to be one of apyrexia; the reduplication of the attacks.

Further irregularities in temperature may be caused by combined infections or by the use of quinine or other remedies.

The parasite which is the cause of this type of fever pursues its cycle of development, according to their idea, in direct relation to the clinical course of the case, just as do the other varieties of the malarial parasite. Its development is very similar to that of the quotidian parasite. It produces, however, a larger quantity of pigment, and, at the

time of its full growth, may be one-half the size of the red corpuscle. The reproductive processes take place in this form as well as with the parasite of quotidian fever, chiefly in the internal organs, and, at the beginning of the attack, it may be almost impossible for several hours to find any malarial parasites in the blood. One sees here, as with the quotidian parasite, the collection of pigment in a clump in the central part of the body which breaks up into segments while it is yet contained within the red corpuscle, which is almost invariably gravely altered—shrunken, crenated, brassy-colored or destroyed. The chief differences between these two varieties of the parasite, Marchiafava and Bignami state to be the following:

(1). *The length of the cycle of development*, which, in the quotidian parasite, lasts about twenty-four hours, and often occurs without the development of pigment, while in the tertian it lasts forty-eight hours, and is always associated with pigmentation.

(2). *The size of the amoeba;* in the same relative stage of development, the amoeba of tertian fever is generally larger and of a more transparent appearance.

(3). *The movements*, which, in the tertian parasite, are retained for a longer time by the larger pigmented forms than in the quotidian parasite; they are also more active in the tertian organism.

(4). *The length of the amoeboid unpigmented stage*, which, in the tertian body, may last more than twenty-four hours.

(5). *The time elapsing after the beginning of the new paroxysm, before the appearance of the new generation of parasites*, which, in the tertian fever amounts to several hours, considerably longer than with the quotidian type.

The differences between the malignant tertian parasite and that of the ordinary mild tertian fever are marked.

(1). It differs in its *size*, which is considerably smaller than that of the organism of mild tertian fever.

(2). In the *appearance of the young forms*, which, in the malignant tertian fever, are ring-shaped, a characteristic not observed in the mild tertian fevers.

(3). In the *character of the pigment*, which, in the organism of mild tertian, is always active, which is not the case in this form; the *quantity* of pigment in the malignant tertian organism is also much less than in the spring tertian body.

(4). The *manner of segmentation;* the segmenting bodies in mild tertian parasites are larger and contain a greater number of spores than those of the malignant tertian organism; they are also found very frequently in the blood of the finger in the one instance, and very rarely in the other.

(5). *The changes occurring in the infected red blood corpuscles;* in the spring tertian these become increased in size and decolorized, while in aestivo-autumnal fever they commonly assume a deeper brassy color and become shrunken and crenated.

(6). Finally, with the amoeba of the aestivo-autumnal tertian is associated the *appearance of crescents* which never occur in the other form.

A still more elaborate classification of the malarial parasite is that of Grassi and Feletti.[221, 339] These observers separate the parasite into five distinct varieties:

(1). The "Haemamoeba praecox," giving rise to quotidian fever with a tendency to anticipation.

(2). The "Haemamoeba immaculata," which is similar to this, excepting that it runs its course sometimes more rapidly without the development of pigment.

(3). The "Haemamoeba vivax," giving rise to tertian fever.

(4). The "Haemamoeba malariae," giving rise to quartan fever.

(5). The "Laverania malariae," giving rise to the irregular fevers.

They insist that the Haemamoeba praecox, which corresponds to the aestivo-autumnal parasite of Marchiafava and Celli, is an entirely separate organism from the crescentic and ovoid forms, to which they give the name of "Laverania malariae." They agree with Canalis, Golgi, Antolisei and Angelini in believing that segmentation may occur in these forms. They have made extensive studies, in the blood of birds, of the haematozoa which so closely resemble the parasites of malarial fever, and they believe that the parasites of the bird and those of the human being are entirely similar, though inoculations from one to the other have proven unsuccessful.

Sacharow,[212] in Tiflis, describes a "parasite of irregular fever" which corresponds to the aestivo-autumnal type of organism, the only difference being in the greater frequency with which segmenting bodies are to be found in the peripheral circulation. He believes, as do Grassi and Feletti, that the crescentic bodies form a separate

type of the parasite; they are associated with irregular fevers. He adopts the following types:[276]

(1). Haemamoeba praecox (Grassi).
(2). Laverania (Grassi).
(3). Haemamoeba febris tertianae (Golgi).
(4). Haemamoeba febris quartanae (Golgi).

Mannaberg[291] has pursued quite elaborate studies of the malarial parasites, and has reached results which are not uninteresting. He divides the parasites into two groups:

(1). *Malarial parasites with sporulation and without syzygia:*
(*a*). The quartan parasite.
(*b*). The tertian parasite.
(2). *Malarial parasites with sporulation and syzygia:*
(*a*). The pigmented quotidian parasite.
(*b*). The unpigmented quotidian parasite.
(*c*). The malignant tertian parasite.

It will thus be seen that he accepts the division of Grassi and Feletti into the pigmented and unpigmented quotidian parasite (the Haemamoeba praecox and the Haemamoeba immaculata). The descriptions which he gives of these bodies are exactly similar to those given by Marchiafava, Celli and Bignami. The great difference, it will be seen, between Mannaberg's classification and that of the Italian observers, is due to his interpretation of the crescentic bodies. These bodies, he asserts, arise from a conjunction of two smaller, intra-corpuscular forms. This conjunction is followed by the development of a membrane about the body; more pigment is formed, and finally the full grown ovoid or crescentic body results. By his staining methods he believes that he obtains definite proof that the crescents represent two individuals. He has seen the division of a crescentic body into its original two constituents. Beyond this transverse segmentation, as he calls it, he has never seen any other evidence of segmentation of the crescents. He denies, however, the assertion of Bignami, Bastianelli and Marchiafava that these are degenerate forms.

Dock[240] has been able to satisfactorily distinguish the tertian, quartan and aestivo-autumnal organisms without any sub-division of the latter variety.

Titow[177] confirmed in the main Golgi's divisions of the parasite, which Korolko[226] has also been able to do.

One of the authors [327] of this note has also been able to confirm the divisions into the tertian, quartan, and aestivo-autumnal varieties.

Finally Golgi [309] has studied the aestivo-autumnal fevers at Rome, arriving at results somewhat different from those of most other observers.

He asserts that "the doctrine of the nosogenic process of the malarial fevers is not yet entirely known." Marchiafava's and Bignami's ideas concerning the regular cycles of twenty-four and forty-eight hours are rather an hypothesis than a fact based upon actual observation. His own observations have led him to believe that:

(1). The parasites which circulate in the peripheral vessels in aestivo-autumnal fever are nothing more than an index, "non necessarie," though almost constant, of the infection; they have of themselves little to do with the pathogenesis of the febrile process; they represent the first phases of a cycle of development which is much longer than has been believed—of as yet undetermined duration.

(2). The entire process of development occurs, not in the peripheral blood circulation, but in the internal organs; here these parasites go through their diverse stages of development.

(3). The doctrine of the quotidian and tertian varieties is not borne out by his researches; "it is not justifiable to accept this classification."

He confirms Baccelli's [263] observations that, in the first few days of the disease, comparatively few organisms may be found in the circulating blood; they may indeed be absent. Those forms which one does find represent only the earliest phases of development. He distinguishes three phases:

(1). The small amoebae without pigment or with but a few granules —the forms seen in the circulating blood.

(2). The small amoebae with central clumps or blocks of pigment, which are thought to be pre-segmenting forms, and forms of more advanced development which may have grown to a size as large as the red blood corpuscle which may have been wholly destroyed. This phase is doubtless longer than the first.

(3). A phase represented by the parasites with marked endoglobular development or even free forms. These present different appearances depending on their ultimate development and particularly on the forms of sporulation which are various.

There are three main varieties of segmenting forms:

(*a*). Regular forms like those of the tertian and quartan organisms; these may vary greatly in size, some being larger than the red blood corpuscles, with as many as forty or fifty segments.

(*b*). Forms of endogenous segmentation, where a layer of substance looking like a membrane remains about the periphery, while within there are eight, to ten, to twelve small spherules with sharp contour, arranged irregularly about a pigment block.

(*c*). Forms with a more advanced development. These may vary from one-third the size of a red blood corpuscle to a size even larger than the corpuscle itself. They always contain a pigment mass. They have an irregular, mulberry-like contour and can change their form; they arrive at reproduction in various manners.

Segmenting bodies are best found from three, to four, to five, to six hours before the paroxysm, but, as the organisms appear to be arranged in foci in the spleen—here a group in one stage of development, here in another—the puncture of the spleen gives uncertain results.

Certain facts suggest that these organisms may continue to develop and even segment within the bodies of large macrophages in the spleen. This, however, and many other points, need further investigation.

He divides the malarial fevers into two groups:

(1). Fevers, the pathogenesis of which is connected with parasites which have their principal habitat in the circulating blood where, by preference, they accomplish the phases of their cycle of existence.

(2). Fevers, the pathogenesis of which is connected with parasites which have their chief seat in the internal organs, particularly the bone marrow and the spleen, where, by preference, they accomplish their cycle of existence in conditions of relative stability.

(1). The fevers of the first group are, unquestionably, associated with different species or varieties of the parasite:

(*a*). *The quartan parasite.*

(*b*). *The tertian parasite.*

(2). "To the second group belong the fevers which appear clinically under multiform types, very often irregular, of which for the present it is impossible to make a grouping based upon an ascertained biology or cycle of development of the parasite. . . . We are dealing, in these cases, with generations of parasites which, occurring in the

parenchyma of organs, in different stages of development, give origin, at periods of a certain regularity, or, in a more or less continuous succession, to colonies of young forms which, in large or small numbers, or in insignificant quantity, may escape into the blood current, permitting one to discover by microscopical examination of the blood the presence of the small endo-globular amoebae." He refers to the crescents as "forms the biology of which has not yet been well determined."

Culture and Inoculation Experiments.

Thus we see that all authors who have had sufficient material at their service, agree in the statement that malarial fever is always associated with the presence of these parasites in the blood. It is, however, unfortunately true, that this discovery fills but one of the classical stipulations of Koch, which go to prove the dependence of a disease upon a specific micro-organism.

Attempts, by many observers, to cultivate the parasite, by the most varied methods, have proven uniformly unsuccessful. Coronado,[273, 297] alone, asserts that he has been able to cultivate the organisms in water from a source from which he believes many individuals had been infected. Sterilization of the water makes cultivation impossible. By introducing malarial blood into tubes containing some of this water with about one-third the volume of mud from the bottom, he obtains, in twenty-four hours, cultures in which, he believes, he can trace the entire development of the malarial parasite. He observes the development of flagella from the pigmented parasites; these become free, and, eventually, break into from eight to fifteen small segments which begin again the cycle of existence developing pigment (!) and arriving, finally, again at the stage of flagellation.

These remarkable experiments have been repeated by Sacharow [324] without success.

If, however, culture experiments have failed, some observers have, at least, succeeded in preserving the organism for a certain length of time, outside the human body. This was first accomplished by Sacharow,[163] who was able to keep the parasites (aestivo-autumnal (?)) alive as long as a week in leeches which were kept on ice. Rosenbach,[214] applying leeches to a case of tertian fever, was able to

demonstrate apparently living organisms after forty-eight hours. He believed that the parasites showed signs of growth and, possibly, of multiplication. Sacharow [324] has repeated these experiments, in order to test the effect of cold on the parasites, with interesting results. He placed the leeches on ice, examining them at varying periods. With the aestivo-autumnal parasite he still found forms with actively amoeboid movements and normal staining reactions after seven days, while an inoculation experiment made on the fourth day was successful. In a case of double tertian fever he found, after forty-eight hours, only the small amoeboid initial stages of the parasite, the older forms being apparently less resistant to the cold.

All experiments, then, directed toward the cultivation of the parasite, with the exception of the as yet unconfirmed work of Coronado, have failed. Experiments, however, with inoculations made, if not from pure cultures, at least from patients whose blood has been carefully examined before and after the inoculation, have given results which tend, strongly, not only to show that these parasites are the specific cause of malarial fever, but also to uphold the view first introduced by Golgi, that certain definite varieties of parasites are associated with certain definite varieties of fever. Gerhardt [38] was the first to show that malarial fever could be transmitted by inoculation of one patient with the blood of another. His results, however, were obtained before the parasite itself had been discovered. In two instances, inoculations were made from patients with quotidian paroxysms. In the first, quotidian paroxysms appeared in sixteen days; in the second, irregular paroxysms gradually becoming quotidian appeared on the sixth day. The inoculation consisted in the injection of a Pravaz syringe full of blood.

In 1884, Mariotti and Ciarrochi,[39] and Marchiafava and Celli,[41] inoculated five patients with malarial blood, obtaining positive results in three cases. Unfortunately though, as, in all these instances, several inoculations were made, it is impossible to state the exact period of incubation. It is interesting, however, to note, that, in case I, chills developed eleven days after the first intra-venous inoculation, a subcutaneous inoculation having been entirely negative before; in the second case, twelve days after the first inoculation; and in the third, thirteen days after the first inoculation. Though these facts were not interpreted in exactly this manner by the authors, it is in every way

probable, in view of what we have later learned, that this represented the true incubation period.

The next experiments were reported by Gualdi and Antolisei [102] from Baccelli's clinic at Rome. Two patients were inoculated intravenously with 3 ccm. of blood from a patient suffering with quartan fever, at a time when the blood showed the earlier stages of segmentation. In the first case an irregular fever appeared in ten days after the inoculation, the blood showing the organisms characteristic of aestivo-autumnal malarial fever. In the second case the inoculation was followed, in twelve days, by a mild irregular fever, the blood showing, as in the former case, aestivo-autumnal organisms, but, also a few quartan forms. These two cases have served and still serve as the strongest argument used by the opponents of the idea that definite types of organisms are associated with definite types of fever. For here are two cases of aestivo-autumnal fever with its characteristic organism, resulting from inoculation with the blood of an apparently pure case of quartan fever. It was, however, discovered, on more careful investigation, [110] that the patient from whom these inoculations were made, was not suffering from his first attack, but had previously suffered from irregular fever, and, later on, had had a relapse, the blood showing the characteristic organisms. In view of the results which have been obtained since then, one is certainly justified in accepting the opinion of the experimenters themselves, as expressed later, that this case was not one of pure quartan infection, and that the aestivo-autumnal organisms being more resistant had developed to the exclusion of the quartan parasites which were present at the same time.

Later, Antolisei and Angelini [103] inoculated two patients with the blood from a case of tertian fever. In each instance, in eleven days, within a few hours of one another, the two inoculated patients showed a rise of temperature, and, in each instance, characteristic tertian organisms were found. In the first instance, however, the fever was of an anticipating character, and later on became quotidian, while in the second case, the fever was at first somewhat irregular, but later showed a tertian character. The irregularity of the fever in the second case they ascribed to the presence of more than one group of organisms.

Gualdi and Antolisei [110] next report a typical case of quartan fever, in which the characteristic quartan paroxysms, with the usual

organisms appeared twelve days after the inoculation. The same authors[111] later made an inoculation from the blood of a patient who had had malarial fever of an irregular type, with small hyaline bodies and crescents in the blood; the hyaline bodies had, however, disappeared under quinine, and after two days' careful examination of the blood by Marchiafava and Celli, nothing but crescentic organisms were found. Irregular fever began on the ninth day, ring-shaped and hyaline organisms were seen on the tenth day, and eight days later, after the administration of quinine, crescentic bodies were for the first time seen; 2 ccm. of blood were used in the inoculation.

Di Mattei[202] injected, intra-venously, blood from a case of irregular fever where he found at first only crescents, into a patient who had suffered from quartan fever which had disappeared spontaneously. A few days after inoculation hyaline bodies without pigment were found. Sixteen days after inoculation irregular fever appeared, and nine days later, crescentic bodies were found in the blood. He then injected blood from a case of quartan fever into a patient whose blood showed crescents. In fifteen days the symptoms of quartan fever appeared, the blood showing typical quartan organisms, while the crescents diminished in number, and finally disappeared.

Calandruccio[205] inoculated himself with blood from a case of quartan malaria, which, at times, had shown regular quartan paroxysms, and, again, evidences of a triple quartan infection. He injected about 1 cc. of blood, with a sterilized Pravaz syringe, into the subcutaneous tissue of his left arm. Eighteen days later he developed a malarial fever, the blood showing organisms similar to those injected, the fever pursuing the same course. He had never had malaria previously, and had never lived in a malarious district. The case from which the blood came was also one of artificial infection. In two other cases Calandruccio obtained positive results from the inoculation with blood containing only crescentic bodies. The time of incubation, was, however, not noted.

Bein[228] made four experiments with tertian parasites. In the first instance, one of tertian fever, a quotidian ague with characteristic tertian organisms appeared on the twelfth day. In the second experiment, a case of quotidian fever with tertian parasites gave rise, in twelve days, to a similar fever with similar organisms. In the third instance a double tertian infection gave rise, in nine days, to a single tertian.

Blood from the same case, injected into a fourth patient gave rise, in nine days, to tertian paroxysms disappearing spontaneously and recurring, after six days, as quotidian fever. In this, as in all the other cases, characteristic tertian organisms were present. The blood, in these instances, was taken in leeches which were then placed in warm water, and opened with sterilized scissors in a sterilized dish; the blood was taken up in a Pravaz syringe and injected intra-venously in one instance, and in the other cases, into the subcutaneous tissue of the forearm.

Baccelli [263] made intra-venous inoculations from a case of double tertian fever and from a case of quartan fever, reproducing, in each instance, the same type of fever and of organism. The period of incubation in the case of tertian fever was six days, in the quartan eleven days.

Sacharow [324] performed an interesting experiment upon himself. He obtained blood in leeches from a case of pernicious, comatose malaria with large numbers of hyaline, ring-shaped and amoeboid, non-pigmented bodies. From one of these leeches, which had been kept on ice for four days, 1 ccm. of the blood was injected, subcutaneously, into the arm. Twelve days later chills and fever appeared, two paroxysms occurring on successive days. On the second day characteristic ring-shaped hyaline bodies were found in the blood. On this date quinine was administered and the organisms and fever disappeared.

The results of these inoculation experiments are certainly striking. In only two instances has the type of organism which was believed to have been introduced, failed to reappear in the blood of the infected individual. These were the first two cases of Gualdi and Antolisei; the probable cause of this variance has already been explained. In all other instances the same type of organisms has appeared, and, with the exception of the instances where infection from a case of apparently single tertian fever produced a double tertian infection, and the converse, the types of fever have been exactly what might have been expected. The average duration of incubation, estimated from these eighteen cases, would appear to be from 11 to 12 days. In individual cases there was a variance of from 6 to 18 days. The experiments of Di Mattei, showing the disappearance of one set of organisms upon the introduction into an already infected individual

of blood from a patient suffering from a different variety of infection, are very interesting. They show the possibility of producing, experimentally, the presence of two varieties of organism at the same time, but they show also, how, in each of the cases, the symptoms were produced by one variety only, the growth and development of one set of organisms being associated with the disappearance or diminution of the other. Bacteriologically occurrences similar to this are, of course, not uncommon. It will be interesting to note, further on, that in the 11 cases of combined infection which we have observed, one variety of organism has always been in great predominance, while the symptoms have appeared to be due to this set alone. We have never seen a combined infection with irregular fever which appeared to be due to the flourishing of two varieties of organisms at the same time.

Dochman,[11] in 1880, reported some interesting results from inoculations with the contents of herpetic vesicles in cases of malarial fever. In three cases typical intermittent fever resulted; the fever was quartan in one instance, tertian in another, and quotidian in the third. In all instances, however, the fever began, either on the same day, or on the day following the inoculation; no examinations of the blood were made. These experiments have never been confirmed, while careful examinations have failed to reveal the presence of organisms in the herpetic vesicles or in sweat.

Methods of Examination of the Blood.

The most satisfactory method, in many ways, of studying the malarial parasite, is in the fresh blood which contains the organisms while yet living. The preparation of such specimens is extremely simple. A minute drop of blood is taken upon a cover glass and allowed to fall upon a clean slide; no pressure is exerted upon the glass, and the specimen is immediately examined. Some observers surround the edge of the glass with vaseline or paraffine in order to prevent evaporation. Some make use of Hayem's special slide, in which a small area in the middle is surrounded by a slight circular depression. A more accurate description of the methods of examining fresh blood will be given later, when we speak of our own proceedings.

One method of examining fresh blood we will speak of here as interesting, and, possibly, of value. We cannot, however, speak from experience. Plehn [176] asserts that he has obtained the best results in the following manner: All examinations of the blood are made at body temperature, the microscope, as a whole, being placed within a specially constructed case made by Lautenschläger of Berlin. He makes use of an ordinary slide, in the middle of which an area about the width of a common cover glass is surrounded with a layer of shellac, thus forming a modified hollowed slide. A carefully-cleaned cover glass is then covered by a drop of fluid paraffine, while another drop is allowed to fall in the middle of the concavity of the slide. The well-cleaned finger-tip, from which he takes the blood, is then painted with pure vaseline in order to prevent the entrance into the blood of foreign substances which might injure its composition. Through this vaseline he makes his puncture collecting the blood, immediately, upon the fresh paraffine drop on the cover glass. This is then laid upon the slide so that the blood spreads out between the two layers of paraffine which protects it from outside influences. In this manner he has seen the blood well preserved for two or three days. The difficulties of this method, it is easy to see, would prevent its daily use in ordinary examinations for diagnostic purposes.

Many different methods have been proposed for the staining of the parasite and for the preparation of permanent specimens. The parasite is well colored by all basic aniline dyes, in fact, by most nuclear stains; it is not colored by the acid aniline dyes. It would be a waste of space to enter into a careful description of all the methods which have been advised. We will take up here but a few of the more important.

The most satisfactory color, upon the whole, for the staining of the parasite is generally acknowledged to be methylene blue, and most observers have obtained the best results by a combination of methylene blue and eosin, the eosin staining the red corpuscles, the methylene blue the parasites.

For making permanent specimens, the blood is collected upon cover glasses and fixed, either by heat or by subjection to the influence of absolute alcohol or alcohol and ether combined in equal quantities.

Chenzinsky [75] recommends the following method: A concentrated watery methylene blue solution, diluted one-half with water, is mixed

with an equal volume of a ½ per cent. solution of eosin in 60 per cent. alcohol. The dried and fixed cover glass specimens are allowed to remain four or five minutes in the staining fluid, and then washed in water, mounted in balsam, and examined.

Celli and Guarnieri[93] recommend an ingenious method which gives, apparently, good results. They endeavored to stain the parasites while yet alive, their mixture consisting of a solution of methylene blue in fluid from a serous transudation. They collected ascitic serum in sterilized test tubes under aseptic methods. The tubes were filled about two-thirds full of serum to which a sufficient quantity of methylene blue was added. This, for a short time, floats upon the surface, and then sinks slowly to the bottom, coloring the fluid a deep blue. After filtering into another test tube, the solution will remain for a long time without changing. Neither microscopical examination nor cultures reveal, after several days, the presence of micro-organisms. To color the blood in the fresh state the finger of the patient is cleansed and punctured with a needle, while, with a glass rod, a drop of the staining fluid is placed upon the drop of blood which appears. From this mixture a drop is placed upon a cover glass and allowed to spread out upon the slide, a little pressure being exerted in order to spread out the red corpuscles and prevent the formation of rolls. The staining requires a little time, the best results being obtained by leaving the preparations from one to three hours in a moist chamber. These specimens are, of course, not entirely permanent.

Feletti[171] advises the following method: A small drop of an alcoholic solution of methylene blue—one part to five—is placed upon a slide and allowed to dry by passing the glass over a flame. One drop of blood is collected upon a cover glass and placed upon the stained area; the cover glass is surrounded by paraffine. The methylene blue is redissolved in the blood serum and stains the parasites satisfactorily.

Plehn[176] advises the following method. The solution which he uses is constituted as follows:

Concentrated aqueous solution of methylene blue	60.
One-half per cent. eosin solution in 75 per cent. alcohol	20.
Distilled water	40.
20 per cent. NaOH	gtt xii.

The cover glass specimens are allowed to remain in absolute alcohol for from three to five minutes, are then placed in this solution for from five to six minutes, washed in water, and mounted.

The results obtained by this method are excellent, and specimens may be obtained as permanent as is possible by the use of eosin and methylene blue.

Mannaberg [291] advises the following method: The dried specimens are allowed to remain for half an hour in a mixture of absolute alcohol and ether of equal quantities, dried upon filter paper, stained in a concentrated watery solution of methylene blue for half an hour, washed with water, dried on filter paper, and colored for about half an hour in a 2 per cent. solution of eosin in 60 per cent. alcohol, washed in water, dried, and mounted in balsam.

Romanowsky [210] advises the following method: He keeps two solutions on hand; a saturated aqueous solution of methylene blue, and a one per cent. watery solution of eosin. The older the methylene blue solution the better the results. The specimen is heated not less than thirty minutes at a temperature of from 105° to 110° C.; the staining mixture is then made just before it is to be used. To one part of the filtered methylene blue solution about two parts of the eosin solution are added. This is carefully stirred with a glass rod, but not filtered, and poured into a watch glass. The cover glasses are allowed to float upon the top of this fluid, the specimens being covered by another inverted glass, and the whole by an inverted cylinder which is moistened upon the inside. In from one-half to three hours—best in two or three hours—good specimens are obtained.

Romanowsky believes that he obtains thus three colors; the red corpuscles are stained red by the eosin, the malarial parasite of a Prussian blue color by the methylene blue, and the nuclear chromatin of a violet color—a neutral stain.

Malachowsky [211] advises the following method: The dried specimens are fixed by being placed in absolute alcohol for several minutes, and then allowed to remain twenty-four hours in Sahli's borax methylene blue solution:

Concentrated aqueous solution of methylene blue	24.
5 per cent. solution of borax	16.
Water	40.

Filter after twenty-four hours.

Sacharow,[212] in studying the small hyaline bodies of aestivo-autumnal fever, advises the use of gentian violet on account of the intense color which the parasites take.

Sforza[288] has used the method of Canon and Pielicke with good results. The dried specimen is fixed by being placed for from five to ten minutes in absolute alcohol. It is then allowed to remain for from six to twenty hours in the following solution at 37° C., washed in water, and mounted. The solution is as below:

Concentrated aqueous solution of methylene blue	40.
¼ per cent. solution of eosin in 75 per cent. alcohol	20.
Distilled water	40.

Laveran[229] advises the following simple method: The dried specimen is fixed in a mixture of alcohol and ether, equal parts, stained for thirty seconds in a concentrated aqueous solution of eosin, washed in distilled water and dried. It is then stained for about thirty seconds in a concentrated aqueous solution of methylene blue, washed again, dried and mounted, either dry or in Canada balsam.

Good results may be obtained by the use of haematoxylin, Mannaberg,[291] in particular, advising this method. His method he describes as follows: "The dried specimen is allowed to float at first for about five minutes upon distilled water, dried between filter paper, and washed in a very dilute solution of acetic acid (acetic acid gtt. j; distilled water 20 ccm.) until complete disappearance of the haemoglobin. The entirely colorless preparation is then floated for two hours upon the fixing solution:

Concentrated aqueous solution of picric acid	30.
Distilled water	30.
Glacial acetic acid	1.

From this it is placed in absolute alcohol for about two hours. This is followed by staining for twelve to twenty-four hours in alum haematoxylin; then by differentiation by means of 0.25 per cent. HCl alcohol (alcohol 75 per cent.) and ammonia alcohol (3 drops of ammonia to 10 ccm. 75 per cent. alcohol), washing in 8 per cent. alcohol, mounting in Canada balsam. The washing of the preparation with water and acetic acid causes the removal of all albuminous substances which would otherwise give rise to annoying precipitates

with the subsequent treatment with picric acid. The preparations made by this method show the parasites as well as the leucocytes of a blue color. The red blood corpuscles remain perfectly colorless. In satisfactory preparations the finer structure of the parasite stands out very beautifully."

Mannaberg uses a solution of haematoxylin (10 grammes of haematoxylin to 100 of absolute alcohol) which is as old as possible. Before use, one part of this is mixed with two parts of a $\frac{1}{2}$ per cent. ammonia alum solution.

The fixing of specimens with osmic acid and a large number of other methods which have been advised will not be entered into here. References may be found in the table of literature at the end of the article.

The Finer Structure of the Malarial Parasite.

Celli and Guarnieri [93] were the first to make a careful study of the intimate structure of the malarial parasite. In the fresh state definite signs of a nucleus are not to be made out. In their specimens colored with methylene blue dissolved in ascitic fluid, they were able to distinguish a deeply colored ectoplasm and a more palely stained endoplasm. The bodies which appear to be ring-shaped, are not really rings, the part within the ring being represented by the endoplasm which is but faintly colored and allows the corpuscle to show through. In the youngest bodies they noticed a deeply staining spot at a point on the border between the endo- and ectoplasm. In the endoplasm, in some specimens, they were able to make out a palely stained body or sometimes one or more sharply stained points or a net-work, which they believed to be the nucleus. They describe the double contour of the crescents and note that these bodies stain more deeply toward the extremities, while the middle is pale; often there is a spot under the pigment in the middle of the crescent which takes a deeper color.

Grassi and Feletti,[122] in their studies of the quartan parasite, go further, stating that the parasites possess a large, clear, bladder-like nucleus, corresponding apparently to the entire endoplasm described by Celli and Guarnieri. This is usually eccentric, with a delicate, often invisible nuclear membrane. The nuclear juice they believe

to be "halbfest;" while the nuclear net-work consists of a more or less eccentric nucleolus-like mass of varying form, sometimes round, sometimes almost triangular or quadrangular, from which three or four very delicate fibres which are almost invisible in the smaller forms, stretch out toward the membrane. The plasma is generally hyaline, but often shows a fine granulation which stains readily with methylene blue; it also shows the granules of melanin. There are sometimes one or more non-contractile vacuoles. As the body grows the nucleolus grows larger and almost fills the nucleus; it often has a rod-like shape. This divides into two parts, and each daughter section again dividing, there results, finally, an amoeba with numerous nucleolus-like granules. Eventually nuclear juice collects, and a thin, delicate membrane forms about each nucleus. Later on the plasma divides in a manner not yet entirely cleared up, the pigment remaining behind, leaving the fresh segments, which they believe to be gymnospores, probably simply young amoebae.

The crescents have a similar nucleus in the middle, about which the pigment is usually collected. The crescent is surrounded by a membrane which, they believe, arises from the blood corpuscle in which it has developed, as does the delicate membrane surrounding the segmenting bodies. The plasma (ectoplasm) alone is concerned in the formation of flagellate bodies, the nucleus taking no part; this fact, they believe, is sufficient to prove that these forms are not regenerative in nature.

Celli and Sanfelice [190] likewise describe the pale, non-staining nucleus.

Romanowsky [188, 210] studied the tertian parasite on dried cover glass specimens stained, by a particular method, with eosin and methylene blue. He separates, always, two distinct parts of the organism; one of irregular shape of a Prussian blue color; and one entirely uncolored of an ovoid or round form lying within the blue colored rim. In this central area, always close to the periphery, he found a small body of a dark carmine-violet color. Because these minute bodies were present in every parasite, and because they showed a coloring similar to that of the nuclei of the leucocytes, and because, also, they showed at times signs of a fibrillary metamorphosis, he believed that these represented the chromatic part of the nucleus while the rest of the clear central area was the clear nuclear fluid. He believes that at

the time of segmentation he can distinguish karyokinetic figures in the chromatic substance of the nuclei.

Sacharow,[212, 324] studying the aestivo-autumnal organism, notes also the pale central area—nucleus—with the deeply staining granule —nucleolus. He states that as the organism approaches segmentation, with the collection of the granules into a central mass, the nucleus disappears.

Mannaberg[203, 291] states that the nucleus is represented in the unstained specimen by a refractive body which takes up the greater part of the spore; that the small, more refractive point within it represents the nucleolus; the clear space which one occasionally sees in the large free forms represents the bladder-like nucleus which Grassi and Feletti described in stained specimens. The nucleus is represented as a relatively large, more or less round, bladder-like affair which lies, generally, excentrically. It is colorless or only very slightly colored, and shows at a point on the periphery a deeply staining body about which one sometimes sees a more palely stained zone. This body, which contains the greater part of the chromatin substance, is the nucleolus, while the clear substance represents the nuclear juice. As the parasite grows one can distinguish an outer layer of protoplasm taking a deeper stain and showing the granules of melanin, and an inner clearer layer free from granules, lying about the nucleus. The nucleus is usually excentric. The nucleolus grows with the organism, but before segmentation it disappears, passing out apparently into the substance of the parasite. The nucleus at this stage has a diffuse pale blue color, and is only to be distinguished from the parts outside by its lack of pigment; at this time one may speak of a "plasma part" and a "nuclear part" of the parasite. With segmentation we begin to see, in the nuclear part, the appearance of new nucleoli which finally form the centres of new spores. He cannot confirm Romanowsky's views concerning the karyokinetic division. He divides the life of the parasite into a vegetative and a reproductive stage. The reproductive stage begins with the disappearance of the nucleolus.

More recently Bastianelli and Bignami[331] have studied minutely the structure of the aestivo-autumnal parasites. They fixed their specimens with alcohol, and stained with eosin and haematoxylin. According to them the young parasite consists of two substances;

an outer colored and an inner uncolored cytoplasm. In the former one sees one or more granules of chromatin though no real nuclear structure is to be recognized. The ectoplasm is in functional activity during the entire life of the parasite. During the further development of the body these three portions remain quite clear and distinct, while granules of melanin begin to appear in the cytoplasm. As the increase in size progresses the small granules or masses of chromatin substance disappear, entering probably into solution in the cytoplasm. The cytoplasm increases in quantity and shows a slightly granular or homogeneous appearance. At this time the endoplasm develops a slight staining propensity. The pigment then begins to leave the chromophilic zone and tends to collect toward the middle or at one side of the parasite; thus arise the small bodies with central pigment, bodies one-fourth to one-fifth the size of a red blood corpuscle. These bodies consist of an apparently homogeneous substance more deeply colored in its outer part than in the middle, but without sharp boundaries between the two substances. In this stage the phase of reproduction may suddenly take place, but often the bodies keep on growing, the chromophilic substance ever increasing in quantity; the largest individual forms however are always smaller than a red blood corpuscle. The largest forms which one sees free in the plasma and, especially, in the spleen show changes which lead the authors to believe that they are degenerative, and incapable of reproduction. The reproduction begins with the formation of very small, deeply colored points of thickening of the chromatin substance; these increase steadily in size, becoming, finally, round or slightly ovoid in shape. Later on each one of these chromatin bodies becomes surrounded by a fine border of chromophilic protoplasm. A small amount of faintly stained protoplasm remains apparently unused. These spores differ from the young parasites in (1) that they have a regular, constant form; (2) that they possess no apparent achromatic cytoplasm (with occasional exceptions); (3) that they are immovable. The authors conclude that one cannot recognize in this variety of parasites, any body which has the various constituents of a true nucleus. The granular bodies of chromatin which form a part of the cytoplasm and become dissolved in it when the body is ready for reproduction, bodies which form the most important part of the young spore, represent that part of the parasite which performs the

function of the nucleus. The phase of a resting nucleus is wanting in this organism, probably because of its rapid cycle of development. The crescents, they say, stain faintly and usually take a diffuse color; often they have no chromatin granules. They have no membrane, and show, usually, no differentiation of the protoplasm. These facts convince the authors all the more that these are sterile forms of the parasite. It will be seen in this description that the chromophilic granule or granules are said to exist in the ecto-plasm of the parasite, while most of the above mentioned authors have assumed that it lies upon the border of the endoplasm.

No one has been able to distinguish with certainty a membrane about the malarial parasite. Antolisei [126] has described a double outline about the spores, while, as has been stated, numerous observers interpret the more refractive outline of the crescentic and ovoid bodies as representing a distinct membrane. Antolisei and Angelini [119] believe that this contains haemoglobin.

In summary, then, the substance of the parasite has, by careful study, been shown to consist of a more deeply staining outer part, which contains the pigment granules, and an inner part which is pale and non-staining, excepting for a small, more deeply colorable body which is usually situated close at one side on the border line between this area and the more deeply staining outer layer. This colorless area is generally interpreted as a bladder-like nucleus, the dot at one side representing the chromatin substance or the nucleolus. Bastianelli and Bignami can distinguish no body in the aestivo-autumnal organisms which has all the characteristics of a nucleus. While Grassi and Feletti, Mannaberg, Bastianelli and Bignami have been unable to distinguish characteristic karyokinetic changes at the time of division, Romanowsky believes that he has done so.

Manner of Reproduction.

Most observers agree that reproduction may take place by sporulation, and even Laveran is inclined to-day to accept the process first described by Marchiafava and Celli [45] as one of the modes of reproduction. Some observers, Laveran,[229] Mannaberg, [291] Dock, [151] and Manson, [347] believe that the flagellate body may represent another method of reproduction. The fragmentation of the large, extra-

cellular bodies, and the budding of certain crescentic and ovoid forms, which were thought, at first, to represent reproductive processes, are now believed by most observers to be rather degenerative than regenerative processes.

The spores resemble very closely the young individuals, differing from these chiefly in their lack of motility and in their regular form. Plehn [176] believes that they possess one or more flagella and asserts that he has seen them move about actively among the blood corpuscles.

Antolisei [126] describes a double contour.

Classification of the Parasite.

Much has been written concerning the classification of the malarial organism and its position among the protozoa; it will be, however, scarcely worth while in a paper of this nature to enter too closely into the literature upon this point.

Laveran,[25] without definitely suggesting the biological position of the parasite, proposed the name "Oscillaria malariae" for the organism, believing that the flagellate bodies represented the more important stage. But later on,[60] wishing to hold himself aloof from any too early conclusions as to the nature of the parasite, he accepted the term "Haematozoon" used by Osler.[55] In his last publication he has accepted the classification of Metchnikoff.[59]

Osler,[55] in 1887, believed that until further studies had been made it should be classified as belonging to the genus "Haematomonas," species "Haematomonas malariae."

Metchnikoff,[59] in 1887, places the parasite in the class of Sporozoa, to which class it has been, generally, since then referred. Metchnikoff believes that the organism should be considered among the Coccidia, and proposes the name "Haematophyllum malariae." This classification has been accepted by Laveran.

Danilewsky also inclines toward this view in so far as he ranks the parasite among the Sporozoa. He proposes, however, a new group, "Haemosporidia," in which he would place these organisms as well as the similer parasites observed in birds. With this view Celli and Sanfelice [190] and Mannaberg [291] agree.

Celli and Sanfelice[190] with Kruse [164] distinguish in this subdivision, three genera:

(1). *Haemogregarina* (Danilewsky) (Frogs and Reptiles).
(2). *Haemoproteus* (Kruse) (Birds).
(3). *Plasmodium* (Marchiafava and Celli) (Man).

Kruse [251] later separates the Sporozoa into four orders:

Gregarinida.
Sarcosporidia.
Myxosporidia.
Microsporidia.

The Gregarinida he divides into the following subdivisions:

(1). *Polycystideae.*
(2). *Monocystideae.*
(3). *Coccididae.*
(4). *Haemogregarinidae.*

The Haemogregarinidae are separated into four genera:

Haemogregarina (Tortoise-Lizard).
Drepanidium (Frog).
Haemoproteus (Birds).
Plasmodium (Man).

A few authors have objected to the inclusion of these parasites among the Sporozoa. Among others, Antolisei [139] considers them to belong to the Gymnomyxa (Ray Lankester) or more exactly to the Proteomyxa, while Grassi and Feletti [122] include them among the Sarcodinia, more especially the Rhizopodia, in the division of Amoebae.

Similar Haematozoa in other Animals.

It is scarcely worth while in this article to enter into the subject of the haematozoa of certain other cold and warm-blooded animals which so closely resemble the malarial organism. Following the earlier work of Lewis,[8] Gaule,[10, 20] Osler,* and others, extensive studies, more particularly of the blood of birds from malarial regions, have been made by Danilewsky,[44, 52, 53, &c.] Chalachnikoff,[79] Kruse,[164, 251] Celli and Sanfelice,[190] Grassi and Feletti,[205, 221] Laveran,[227, 229] Labbé [298, 310, 318] and Sacharow.[300] It has been clearly shown that birds may suffer from a malarial infection very similar to that in man.

* Canadian Naturalist, Vol. X, No. 7.

Danilewsky [232] divides the parasites of birds into:

(*a*). The Haemocytosporon malariae, which is the cause of acute malaria; this may be seen to grow, to develop pigment, and to divide into spores just as does the malarial parasite in man.

(*b*). The parasites of chronic infection, which are represented by the Polimitus and the Laverania malariae.

He is not yet certain as to whether the parasites are the same in man and in birds, but he finds a close resemblance between the organisms of acute malarial fever in man and the Cytosporon in birds, and a similar resemblance between his Polimitus and Laverania in birds, and the flagellate and crescentic bodies in man.

Celli and Sanfelice [190] find three forms of the parasite in birds:

(*a*). A parasite with slow development which corresponds to the quartan organism in man.

(*b*). One with a more rapid development corresponding to the tertian organism in man.

(*c*). A third with the most rapid development, corresponding to the quotidian * in man. They believe, however, that the identity of the parasites of man and birds is not, as yet, established.

Grassi and Feletti [205, 221] go farther and believe that the malarial parasites of birds are the same as those seen in man; they identify in birds all the forms which they have distinguished in man. They have, however, been unable to successfully transfer organisms from man to birds or from birds to man. Inoculations from bird to bird have proven unsuccessful, excepting in a very few instances, and then only when birds of the same species were used.

Laveran [227, 229] has also made careful studies of the organisms in the blood of birds. While he recognizes the great similarity in many instances between the parasites of birds and those of the human being, he is not yet convinced that they represent the same organism.

Labbé [298, 345] divides the parasites of birds into:

(*a*). The Proteosoma Grassii; this corresponds to the Amoeba of Grassi and Feletti. Labbé describes, however, but one species.

* At this time the Roman authors had not subdivided the aestivo-autumnal parasite into a quotidian and a tertian variety, but considered that the parasite had a cycle of development lasting about twenty-four hours.

(*b*). The Halteridium Danilewskyi (Grassi and Feletti); this corresponds to the Laverania of the Sicilian authors. Danilewsky,[185] Sacharow,[300] and Labbé,[345] all describe haematozoa which develop in the leucocytes of birds, "Leucocytozoa."

Form in which the Parasite exists outside of the Body. Manner of Infection.

Notwithstanding all the studies which have recently been made concerning the malarial parasite, we have, as yet, no knowledge as to the form in which it exists outside of the body, nor have we gained any positive information concerning the manner in which it enters the system.

The contagium of malaria has been supposed to enter the system in various ways; the most important points of entry which have been suggested are:

(1). The respiratory tract.

(2). The digestive tract.

(3). The skin (insect bites, etc).

(1). That infection may take place through the respiratory tract there can be little doubt, though it must be said that we have as yet no positive proof of its occurrence.

Celli and Sanfelice[190] assert that they have succeeded in transfering a malarial infection from one bird to another by intra-pulmonary inoculations. Their results, however, have been disputed by Grassi and Feletti,[221] who have been quite unable to accomplish the same thing.

Grassi and Feletti,[205] have however, found certain small amoebae in very large numbers in malarial regions. One of these, the Amoeba guttula, is readily encysted and easily carried about by the wind. This amoeba they found in the nostrils of young doves which they had placed in cages which were hung for two nights in a malarial region about two metres above the ground. In nine days these birds showed Laverania in their blood. This suggestive observation has never been repeated. More recently, Labbé[345] asserts that he has succeeded in transferring the infection by intratracheal injections of blood.

(2). Many observers still believe that the parasite is introduced chiefly through the digestive tract. Among these is Coronado.[273, 297] We have, however, no positive evidence in favor of this idea, and much against it. Celli [46] allowed six individuals to drink large quantities of water from the Pontine marshes without ill effects, while Marino [172] had similar results from like experiments.

Zeri,[132] in Baccelli's clinic, experimented in thirty cases with inhalations, drinking and enemata of water from malarious districts without a single positive result. Grassi and Feletti [205] allowed healthy individuals to drink dew collected from malarious regions without ill effects. The same observers caused healthy men to drink blood from malarial patients, and fed birds of prey on infected birds, but in no instance did they obtain positive results.

Labbé's[345] experiments with frogs and birds were also unsuccessful.

(3). Inoculation experiments have given positive proof that infection may take place through the skin, which renders more plausible the old idea that insect bites may serve to convey the contagion.

Particularly interesting in this connection are the remarkable researches of Theobald Smith,* who has shown that the haemocytozoon of Texas fever in cattle (Pyrosoma bigeminum) is conveyed from animal to animal by means of the cattle tick (Boöphilus bovis).

Experimentally, then, it has been shown that while infection through the alimentary tract is improbable, subcutaneous infection is possible, as is also intra-pulmonary infection, if we can accept Celli's and Sanfelice's and Labbé's observations on birds.

There is much room for further experimentation in this field.

Relation of the Parasites to some of the Main Symptoms of Malarial Fever.

(1). *The Intermittent Fever.*

Laveran,[23] in 1881, suggested that the parasites which during apyrexia remain largely in the internal organs, enter finally into the general circulation, and by an irritating influence on the nervous

* "Investigations into the Nature, Causation and Prevention of Texas or Southern Cattle Fever," Theobald Smith and F. L. Kilbourne. U. S. Department of Agriculture, Bureau of Animal Industry, Bulletin No. 1, Washington, 1892.

centres bring about the febrile paroxysm. The afebrile period, which is often so constant and regular, may represent the time which the nervous system requires to recover from the exhaustion following the paroxysm. Richard [33] believes that the rapid multiplication of the parasites produces the fever which represents the reaction of the organism against the invaders; "they" (the parasites) "excite the fever, the fever destroys them and falls in its turn;" with apyrexia the parasites multiply again.

With the more exact knowledge which we have gained concerning the cycle of development of the parasites, the coincidence of the paroxysms with the segmentation of groups of organisms has been made out.

Golgi [49] first attributed the paroxysm to the invasion of the red blood corpuscles by a new group of parasites, and asserted that the severity of the paroxysm depended on the number of fresh organisms which attacked the red corpuscles.

Antolisei [126] later called attention to the fact that it was not upon the number of new organisms which invaded the red blood corpuscles, but rather upon the number of segmenting bodies, that the paroxysms depended. Quinine given before a paroxysm may entirely prevent the development of a new group of parasites, but it cannot prevent the segmentation or the chill.

Baccelli [263] speaks of the importance of chemical poisons in producing the symptoms of malarial fever. He says that the symptoms of malarial fever depend upon, (*a*) a morphological haemodyscrasia; (*b*) a chemical haemodyscrasia. The former depends upon the progressive destruction of the red blood corpuscles by the parasites which live at their expense. The latter manifests itself in a much more intense and rapid manner, and depends upon the entrance into the circulation of as yet undetermined chemical poisons which are set free at the time of sporulation, poisons due either to the act of sporulation or to substances set free from disintegrated red blood corpuscles. These poisons are injurious to the nervous system and specially to the vasomotor ganglia; it is to their liberation that the febrile paroxysms are due. During the paroxysm many spores are destroyed, but a certain number remain to begin again their cycle of existence.

Golgi [274] in 1892, accepts this conception of the toxic origin of the fever. Plehn [262] asserts, also, that the febrile manifestations are due

to the circulation of toxic substances in the blood, and makes the interesting suggestion that in some instances the febrile paroxysms occurring in individuals immediately after exposure to severe malarious influences, may be dependent upon the absorption of a quantity of these toxic substances produced by the parasite, sufficient to cause a single paroxysm. He relates two cases where individuals showing a paroxysm of this nature, developed, nine to twelve days later, characteristic malarial fever with organisms in the blood.

Mannaberg [291] likewise adheres to Bacelli's theory, which is probably accepted to-day by most observers. Strongly in favor of the idea of the toxic origin of the febrile manifestations of malaria are the observations of Brousse * and of Roque and Lemoine,[174] who have demonstrated an increased toxicity of the urine following malarial paroxysms, and of Queirolo,[108] who has shown that the same increased toxicity is observed in the sweat obtained during the paroxysm.

Even more striking evidence in favor of this view is the occurrence of the disseminated areas of necrosis in the liver described by Guarnieri,[66] Bignami,[179] and noted by Barker in another part of this fasciculus. These changes which are so characteristic of various severe infectious processes may be produced, as first shown by Welch † and Flexner, as well by soluble toxines as by actual infection.

It must be said, however, that Laveran [277] in his last work does not speak with any degree of certainty on these points. He states that toxic products may have an influence on the febrile manifestations, but that at present this is a mere hypothesis. He says "the degree of irritability of the nervous system which varies with individuals and with the date of the infection, seems to play an important role in the determination of the form and type of the fever. If the case be one of a robust individual who has the fever for the first time, the nervous system reacts vigorously against a pathogenic agent to which it is not accustomed, and one observes a continuous or at least a quotidian fever. If the patient be anaemic, reduced in strength by repeated attacks of fever, the nervous system having become less impressionable, the result is a fever with long intervals."

* Soc. de Méd. et de Chir. pratiques de Montpellier. 14 Mai, 1890. Quoted by Laveran.[229]

† The Johns Hopkins Hospital Bulletin, No. 20, March, 1892.

(2). *The Anaemia.*

Red Corpuscles.—All observers agree that the anaemia is due primarily to the actual destruction of the corpuscles by the parasites; this may be excessive. Kelsch [6] has seen as small a number of red blood corpuscles as 500,000 to the c. m. m.

A reduction in corpuscles follows each paroxysm; these reductions are more marked after the early paroxysms than in those occurring later. When a certain degree of anaemia has been reached, the losses per paroxysm are much less. When the number of corpuscles is reduced to 2,000,000, or 1,000,000, there is little tendency toward a further fall; sometimes there may be slight rises in the curve between the paroxysms—often, however, the number of corpuscles remains stationary for weeks. In pernicious cases the number of corpuscles may fall between paroxysms.

Kalindero,[92] from 400 blood counts made in fifteen cases, concludes that the number of red corpuscles is greatly diminished in malarial fever. This diminution is greater the longer the disease lasts, and the more intense the manifestations.

During the paroxysm the number of red corpuscles as well as of the white tends to increase. These changes are particularly noticeable during the first paroxysms. When, on the other hand, the anaemia is profound, the number of corpuscles tends to fall to a nearly constant number which does not appear to be modified by the paroxysm. If the paroxysms are suppressed before they have lasted long, and before the spleen is much hypertrophied, the number of red and colorless corpuscles returns to the normal.

If the fever has lasted long and the spleen is much hypertrophied, while the general condition of the patient is bad, the diminution tends to become permanent. There is no intimate relation between the enlargement of the spleen and the diminution in the number of the corpuscles.

Dionisi [173] made a careful study of the variations in the number of the red blood corpuscles during malarial fever with the following results:

(1). In aestivo-autumnal fever, the reduction in the number of red blood corpuscles bears a direct relation to the number of organisms.

Where the parasites are numerous there is a constant reduction of from 200,000 to 1,000,000 with each febrile paroxysm; where the parasites are scanty the reduction is less.

(2). When crescentic bodies are present in addition to the other forms, they seem to exert no influence on the blood changes.

(3). When, after a paroxysm, the number of corpuscles has suffered a sudden and very marked diminution, the succeeding paroxysms may be followed by but a slight reduction only or even by an increase.

(4). In relapses the reduction per paroxysm is less than in a primary infection.

(5). In infections determined by the amoeboid forms (acute aestivo-autumnal infection) there is, during apyrexia, no complete return of the red corpuscles to their normal number. Some attempts at restitution may be seen during the first several days of apyrexia, while after this, during perhaps eight to fifteen days, there may be a steady reduction of from 1– to 500,000 red blood corpuscles without the appearance of any parasites in the blood.

(6). Only after marked and continuous reductions following each paroxysm does there occur in the afebrile period a relative restitution of the red blood corpuscles; this may be slow or rapid.

(7). If the increase in the corpuscles has begun, the presence of crescents has no deleterious effect.

(8). In tertian and quartan fevers the same changes are observed, excepting that in the afebrile period there is a rapid and almost complete restitution of the red blood corpuscles.

(9). The colorless corpuscles follow the same course as the red, both in apyrexia and fever. In later periods, however, when the red corpuscles have increased, there may still be a marked diminution in the colorless elements.

Bastianelli [246] noted the association of the anaemia of cachetics with actual changes in the marrow produced by the infection.

Bignami and Dionisi [332] distinguish four types of post-malarial anaemia:

(1). Anaemiae in which the examination of the blood shows alterations similar to those observed in secondary anaemiae, from which they differ only in that the leucocytes are diminished in number. The greater part of these cases go on to recovery; a few, without any further change in the haematological condition, pursue a fatal course.

(2). Anaemiae in which the examination of the blood shows alterations similar to those seen in pernicious anaemia—presence of gigantoblasts. These cases end fatally.

(3) Anaemiae which are progressive, as a result of the lack of compensation by the marrow for losses brought about by the infection. At autopsy the marrow of the long bones is found to be wholly yellow, while the marrow of the flat bones is also poor in nucleated red corpuscles.

(4). Chronic anaemiae of the cachectic, which differ from the above mentioned types by clinical and anatomical characters in that the special symptoms of malarial cachexia prevail, while one observes post-mortem, a sort of sclerosis of the bone marrow. The marrow of the long bones is red and of an increased consistency; the giant cells are very numerous and many are necrotic; the nucleated red blood corpuscles are very rare, and the colorless polymorphonuclear * corpuscles are present in small numbers.

Colorless Corpuscles.—Kelsch [7] noted that the leucocytes were diminished during the paroxysm more than the red blood corpuscles, an absolute diminution sometimes to one-half or one-third the normal number. From this they may show a slight increase just at the beginning of the paroxysm. Usually the number of leucocytes returns to normal much more slowly than that of the red corpuscles.

The minimum of the leucocytes corresponds to the maximum of the splenic enlargement. In cachexiae with chronic splenic tumor he found, generally, a diminution in the number of leucocytes, though in some pernicious cases there was a leucocytosis.

Hayem † noted the absence of increase in the colorless corpuscles.

Kalindero [92] noted a marked diminution in the number of the leucocytes, especially in the more acute cases. During the paroxysm there is a tendency toward an increase in the number.

Dionisi,[173] as has been stated, noted that the colorless corpuscles show the same variations in number as do the red, excepting that in some long continued anaemiae the white corpuscles remain subnormal in number for a longer time.

* This term first used by Cabot (Boston Med. and Surg. Journal, March 20, 1894), a translation of the German term "Polymorphkernige" appears to me the best which we have in English.

† Le Sang, Paris, 8°, 1889.

Pée* remarked the absence of any leucocytosis in intermittent fever.

Bastianelli [246] noted also a diminution in the number of leucocytes during the attacks; this he thought might depend on the active phagocytosis with subsequent necrosis. He noted colorless elements in karyokinesis in the spleen and sometimes in the circulating blood—a regenerative process, he believed, to compensate for the active destruction which had occurred. He made a series of differential blood counts in specimens stained according to Ehrlich's methods, showing that in these cases with a diminished number of leucocytes the relative proportion of the small mononuclear elements remained normal, while that of the large mononuclear leucocytes was much increased, and the polymorphonuclear neutrophiles appreciably diminished; eosinophilic cells were generally scanty in number.

The striking similarity of these counts to the condition seen in typhoid fever will be noted.

Billings,[338] in this clinic, made a series of observations confirming, in the main, these results. He notes that the leucocytes, which are generally sub-normal in number, show a slight increase at the beginning of the febrile paroxysm. Following this increase there is a rapid diminution continuing throughout the paroxysm. The smallest number of leucocytes is seen at the end of the paroxysm when the temperature is sub-normal. From this time the number shows a gradual slight increase, which, as has been said, is slightly accentuated just at the beginning of the paroxysm. The changes in the relative proportion of the different varieties of leucocytes he found to be just as noted by Bastianelli. In four cases of post-malarial anaemia, Billings found quite a marked leucocytosis.

Haemoglobin.—Rossoni [106] studied the variations in the percentage of haemoglobin in association with blood counts, and arrives at the following conclusions:

(1). No acute infection results in as active a deglobulization as does malarial fever.

(2). In all cases of malarial fever there is an immediate diminution in the number of corpuscles and the amount of haemoglobin. This loss generally bears a direct relation to the duration of the infection. In pernicious cases, however, a diminution of as much as two-thirds of the total amount may take place in from one to three days.

* Diss., Berlin, 1890.

(3). The gravity of pernicious cases does not always bear a direct relation to the extent of the loss in haemoglobin.

(4). The destruction of haemoglobin and corpuscles bears, generally, a direct relation to the number of parasites in the blood. Occasionally, however, cases with high fever and marked losses in haemoglobin and corpuscles, may show but few parasites in the circulating blood. A long-continued diminution of haemoglobin is often associated with the presence of crescents.

(5). The loss in haemoglobin and corpuscles is rarely evident during the paroxysm, but begins with apyrexia and may continue for several days afterwards.

(6). Recovery from malarial anaemia is slower than from the other acute anaemiae.

(7). Usually the haemoglobin and corpuscles are equally diminished, but sometimes the haemoglobin is reduced disproportionately.

(8). The rapid diminution in haemoglobin is sometimes a valuable point in differential diagnosis between malarial fever and enteric fever or pneumonia.

(9). The restitution of the haemoglobin in malarial anaemia is often incomplete, and individuals living in malarious districts have often a slightly smaller percentage of haemoglobin than those living elsewhere.

(3). *Other Symptoms.*

The pathogenesis of a number of the other important symptoms of malarial fever has been much elucidated by the knowledge we have gained concerning the parasites.

The *coma* in some pernicious cases has been shown by many observers to be associated with enormous collections of malarial parasites and pigment in the cerebral capillaries. The parasites may be free and are often in the process of segmentation; they may be contained in red corpuscles; they may form actual thromboses. The endothelial cells of the capillaries are often swollen and degenerated, while in many places perivascular punctate haemorrhages may be seen. These so-called "pigment thromboses" were first noted as long ago as 1854, by Planer[4] who attributed to them the comatose symptoms.

In one case of pernicious fever with symptoms of *bulbar paralysis* Marchiafava [167] demonstrated the special localization of similar changes in the region of the bulbar nuclei.

While these local conditions may be reasonably supposed to account for many of the cerebral symptoms in pernicious fever, it must be acknowledged that we cannot deny a possible toxic cause for some. It is also interesting to note the hypothesis of Guarnieri,[66] who, finding enormous accumulations of large macrophages blocking many intra-lobular capillaries in the liver, and extensive areas of necrosis, called attention to the similarity between the cerebral symptoms in these cases and those produced artificially in animals by ligature of the portal vein.

In cases with *choleriform symptoms*, enormous accumulations of the parasites have been noted in the gastro-intestinal mucosa, producing marked secondary changes. Marchiafava [330] has recently devoted a paper to this point.

Melaniferous Leucocytes—Phagocytosis—Spontaneous Recovery.

The presence of melaniferous leucocytes in the blood of patients suffering with malarial fever has, as has already been said, been known for years. Laveran,[29, 60] in his earlier articles, noted their appearance, especially during and just after paroxysms. Marchiafava and Celli [61] early noted that they might contain the red blood corpuscle as well as the pigment and parasite. Golgi,[49] in his first article on the quartan organism, noted that phagocytosis was most marked during the paroxysm, from its height on to the period of apyrexia, the leucocytes taking up the pigment left free by the sporulating forms.

Metchnikoff [59] lays much stress on phagocytosis as an active protective process. The malarial organisms are engulfed and destroyed particularly by the macrophages of the spleen and liver, and to a lesser extent, by the ordinary leucocytes.

Guarnieri [66] asserts that the process has one of its most important seats in the capillaries of the liver, the slow current and the relatively large size of the vessels affording a particularly good opportunity for the engulfing of the parasites by the macrophages. The endothelial cells of the capillaries have also a phagocytic action.

Golgi,[78] in 1888, devotes a special study to the phagocytosis in the tertian and quartan fevers. In these fevers phagocytosis takes place periodically as a regular function of the leucocytes. This process occurs in connection with certain distinct phases in the cycle of existence of the parasite, and at a regular period in each paroxysm. In fresh blood one first notices phagocytosis with the beginning of the paroxysm; the process becomes more marked several hours later, and ends several hours after the paroxysm, lasting altogether from eight to twelve hours. At the beginning of the attack, the leucocytes contain either the whole segmenting forms, fragmenting bodies, or the free pigment blocks left after segmentation. The simple pigment-bearing forms are the commonest. Toward the end of the paroxysm the forms containing the whole parasite are rare, probably because the engulfed bodies have been digested leaving only the fine granules. Punctures of the spleen show that a much more active phagocytosis is carried on there than in the circulating blood. Golgi believes that all this supports Metchnikoff's theories of phagocytosis; he inclines to believe that it is largely through the action of the phagocytes that any given attack of malarial fever is prevented from becoming pernicious, though he acknowledges that it remains to be definitely proven that the parasites which are taken up are at the height of their functional activity, and not forms which are already of somewhat diminished vitality.

Bignami [179] in 1890 in his studies of the pathological anatomy of pernicious fever, describes the extensive phagocytosis which takes place in the spleen, liver, and bone marrow, and notes also the fact that the phagocytes may contain not only whole parasites but the red corpuscles, usually degenerated, in which the organism may lie. He is inclined to ascribe considerable importance to phagocytosis as a protective process. He notes, however, degenerative changes in some large macrophages—loss of the staining power of the nucleus, fragmentation of the nucleus—and suggests the possibility that in these instances spores which have been taken up may preserve their vitality and later, after the death of their host, escape and become the cause of a relapse.

While these observers rather incline to regard the phagocytosis in the sense of Metchnikoff, as an active warfare against the parasites, other observers take a rather more sceptical view.

Osler,[91] in 1889, believes that we have, as yet, insufficient evidence to prove an aggressive warfare of the part of the leucocytes against the malarial parasites.

Bastianelli,[246] in 1892, published an elaborate study of the leucocytes in malarial infection. He confirms Golgi's observations concerning the phagocytosis in tertian and quartan fevers, and devotes himself especially to the aestivo-autumnal fevers. Here, as in the regularly intermittent fevers, there are indications of a periodicity in the phagocytosis, but this periodicity is by no means as well marked. The pigmented leucocytes are more numerous at the time of sporulation, beginning to appear with the paroxysm, and increasing to a maximum at the precritical elevation (malignant tertian fever), during the crisis, or in the first hours of apyrexia. At the beginning of the attack, owing to the small number of parasites in the circulating blood, the pigmented leucocytes may be the chief evidence of the malarial nature of the process. These phagocytes may not, however, disappear during apyrexia, owing, in part, to the great frequency of the shrunken and brassy colored red corpuscles which are readily taken up. Again, owing to the irregularity and multiplicity of the paroxysms, phagocytes dating from a former access are often present at the beginning of a second.

Sometimes the number of phagocytes is enormous. In the milder cases one sees only a few ordinary leucocytes with pigment granules, and a few macrophages containing blood corpuscles as well as parasites. These latter forms are much more frequent in severe infections; they may show various degenerative changes in their protoplasm. Large endothelial cells containing pigment and parasites may also be seen. These often show degenerative changes. The following, in order of frequency, are the bodies which are more commonly found included in phagocytes: (*a*) pigment; (*b*) sporulating forms and spores; (*c*) red corpuscles, normal or decolorized, containing sporulating forms or bodies with central pigment clumps; (*d*) red corpuscles, decolorized or brassy colored and shrunken, containing parasites; (*e*) free bodies with central pigment clumps; (*f*) more rarely red corpuscles of normal appearance containing parasites in the amoeboid stage, or free amoeboid bodies; (*g*) crescentic bodies. Sometimes one may see entire phagocytes engulfed by macrophages. The phagocytes themselves often become necrotic, showing vacuolic and fatty degen-

eration of their protoplasm, and fragmentation or loss of affinity for coloring matters in the nucleus. "The phagocytic action of the leucocytes occurs at all moments in the life of the parasite in this class of fevers, as well in the pyrogenic as in the non-pyrogenic * cycle: it occurs whenever parasites or pigment become free, or when the red corpuscles are profoundly altered (necrosis with brassy color, decolorization). Therefore one cannot say absolutely that the phenomena of phagocytosis are associated with a definite phase of the cycle of evolution of the parasite."

With this the observations of Marchiafava and Bignami [245] agree. Bastianelli disputes Golgi's assumption that the phagocytosis is the chief element which prevents the ordinary tertian and quartan infections from becoming malignant. In cases of spontaneous cure there is no particular increase in the phagocytosis—rather the opposite.

In the severe cases, on the other hand, there is no evidence of a lack of activity on the part of the phagocytes; indeed, the process here is much more active; it is not upon the absence of phagocytosis that the severity of a paroxysm depends, but rather upon the amount of toxic material which is set free in the circulation. It is not evidence of increased phagocytosis which one observes in the cases of spontaneous recovery, but rather an increased number of fragmenting and degenerating parasites—parasites the vitality of which has been injured by some other cause (Celli, Bastianelli and Bignami, Antolisei). Furthermore, Bastianelli notes the rhythmic course which untreated malarial infections often pursue; a gradual increase in the severity of the paroxysms; a period of oscillation; a spontaneous recovery; a relapse after one or two weeks, which pursues the same course, and so forth. It is difficult to see why, if phagocytosis alone be the cause of these spontaneous cures or rather arrests, they should always occur after a certain number of paroxysms and not at the beginning of the infection. It would seem more probable that after a certain time some other factor comes into play which diminishes the vitality of the parasites and makes them an easy prey for the phagocytes. The important element in spontaneous recovery is the oscillation in the virulence of the parasite and not the phagocytosis. The parasite may die in the blood current without the intervention of

* Crescentic and ovoid forms (?) (W. S. T.).

the phagocyte. "If, however, the phagocyte is not the preponderant factor in determining the course of the infection, it maintains always a most important position in malarial processes; its constant action is exercised in eliminating a large number of pathogenic elements and in facilitating the return of the organism to its normal functions by freeing it from all extraneous injurious substances." With Bignami, he agrees in suspecting the possibility that some spores may remain living in the macrophages of the spleen, liver, and bone marrow, whence they may later escape, causing a relapse.

Mannaberg [291] asserts that the febrile paroxysm, either from the high temperature or from the circulating pyrogenic substance, exerts an injurious action on both the half- and full-grown parasites. He concludes: "The spontaneous cure of malaria depends upon three factors, namely: the activity of the macrophages of the spleen and the bone marrow (to a lesser extent of the endothelial cells of the cerebral vessels); on the circumstance that numerous parasites remain sterile; finally, on the destructive action of the febrile paroxysm which is manifested by the fragmentation of numerous half- and full-grown parasites."

Action of Quinine.

The specific action of quinine in malarial fever cannot be discussed here. Its direct action on the parasite has, however, been studied of late with interesting results.

As long ago as 1867, Binz * concluded that the efficacy of quinine in paludism depended upon its action as a protoplasmic poison on some lower organism which he assumed to be the cause of the process.

Laveran, [23] in 1881, asserted that "it is because it destroys the parasite that quinine causes the disappearance of the manifestations of paludism," a statement which has received abundant confirmation since. He showed that by allowing a 1–10,000 solution of quinine to run under the cover glass, the movements of the parasite were immediately arrested.

Marchiafava and Celli [45] showed that the same results could be obtained by using an 0.5 or 0.75 per cent. salt (NaCl) solution, and also with distilled water or Pacini's solution, while Grassi and

* Centralblatt für die Med. Wiss., 1867, p. 308.

Feletti [221] showed that after shaking malarial blood with distilled water for an hour, inoculation experiments remained negative.

Binz,[323] however, asserts that these latter experiments are no evidence that quinine does not act in this manner, as both salt and distilled water are protoplasmic poisons.

Rosin [311] alone, on testing the action of 1–5000 solutions of quinine on the tertian parasite, found active movements of the pigment granules forty-eight hours afterwards.

Further proof as to the manner of the action of quinine on the parasites has been obtained by a study of the organisms found in the circulating blood after its administration.

Golgi [274] studied the action of quinine on the tertian and quartan organisms. The quartan parasite in its endoglobular stage shows a coarser granulation with a metallic reflex, while the protoplasm shows a certain cloudiness; at times one may see abortive segmenting forms which are smaller than the normal, with a lack of regularity and fewer segments; the pigment, also, may not collect as sharply in a clump in the middle of the parasite. In the tertian parasite the changes are more marked, owing to the greater normal activity of the organism. The body is round and immovable, and shows a sharper outline than usual, while the pigment has a peculiar metallic reflex and tends to collect in clumps. Full grown tertian forms may show the large transparent swollen condition with very active movements of the pigment. Sometimes the pigment collects toward the periphery and a hyaline space is left in the middle.

Mannaberg [291] asserts that three hours after the administration of 0.5 of quinine the amoeboid forms of the tertian parasite show a marked diminution in their activity. In several hours more the number has greatly diminished, while many of those present are fragmented ("zerrissen"), so that they form several separate spherules in the red corpuscle. The full grown forms show a cessation of the movements of the pigment, the body showing a somewhat refractive homogeneous appearance. The large hydropic forms with active pigment may also be seen. Both of these forms, according to Golgi and Mannaberg, may be seen normally during the paroxysm; they are probably degenerate forms. The segmenting forms are sometimes imperfect.

Baccelli [263] noted that in aestivo-autumnal fever there was at first after quinine, an increase in the activity of the small amoeboid forms which shortly—often in twenty-four hours—disappeared without showing any outward signs of degeneration.

Marchiafava and Bignami [245] also studying the aestivo-autumnal fevers, note that the administration of quinine is followed by an increase in the number of shrunken, brassy colored corpuscles; they believe that the included parasites are incapable of further development.

More direct proof of the destructive action of quinine on the malarial parasite is offered by the researches with stained specimens by Romanowsky [201, 210] and Mannaberg.[203, 291] Both of these observers note the loss of staining properties in the chromatin substance of the nucleus. They note also that in the sporulating forms, after quinine has been given, the greater part of the segments show no nucleolus. These changes in the nucleus they believe to be evidence of a necrotic process; the spores without nucleolus Mannaberg terms "still-born." Romanowsky studied the tertian parasite; Mannaberg both tertian and quartan.

All observers agree that the crescentic bodies are affected slowly, if at all, by quinine.

Golgi [274] asserts that in tertian and quartan fever quinine acts most markedly on the young free spores, less upon the more advanced forms where the red corpuscle is in greater part destroyed, and least upon the young endoglobular forms.

If quinine be given several hours before a paroxysm it will not prevent segmentation, but it destroys the new group of organisms—the fresh segments. Segmentation taking place and toxic substances escaping, the chill occurs, being at most a little modified and retarded; further development of this group of organisms is, however, cut off.

This, then, is, according to Golgi, the best time to administer the drug, though continued doses may be needed to wholly eradicate the infection. By giving single doses in this manner a double tertian infection, or a double or triple quartan may be changed at will into a single tertian in the one instance, or into a single or double quartan in the other (vide page 113).

Marchiafava and Bignami,[245] studying the aestivo-autumnal parasite, conclude that "the maximum and most rapid action of the remedy is exercised on that phase of the extraglobular life of the para-

site which follows the completed segmentation." They note, as does Golgi, that the segmentation cannot be prevented if quinine be given when the parasite has reached the preparatory stages. "Quinine acts on the amoeba of malaria," they say, "during those phases of its life in which it absorbs nourishment and develops; when the nutritive activity comes to an end, the transformation of haemoglobin into black pigment being accomplished, and the phase of reproduction begins, then quinine becomes inefficacious against this process." They agree with Golgi that to best combat the development of the infection, quinine should be in solution in the blood at the time of the setting free of the spores: *i. e.*, it should be given several hours before the paroxysm.

III.—GENERAL ANALYSIS OF 616 CASES OF MALARIAL FEVER.

During the period between June 14th, 1889, and January 1st, 1894, 616 cases of malarial fever were observed in the wards and at the out-patient department of the Johns Hopkins Hospital. Of these, 333 were treated in the wards of the hospital, while 283 were treated at the out-patient department. Relapses of cases occurring in the hospital, treated later in the out-patient department, have not been counted in the list. Two of the 333 cases treated in the hospital were relapses of cases already on the list, and have therefore been left out in some of the tables.*

Age.

Of 614 cases in which the ages were obtained, there were:

Between	1	and	10	years	of	age	.....	18
"	10	"	20	"	"	"	.....	146
"	20	"	30	"	"	"	.....	204
"	30	"	40	"	"	"	.....	130
"	40	"	50	"	"	"	.....	65
"	50	"	60	"	"	"	.....	36
"	60	"	70	"	"	"	.....	11
"	70	"	80	"	"	"	.....	3
"	80	"	90	"	"	"	.....	1
Total							.....	614

*Relapses of cases treated in the out-patient department are not counted as new cases.

Below is a table with the ages of 614 patients selected at random from the admissions to the hospital and the out-patient department—331 from the hospital, and 283 from the dispensary.

Between 1 and 10 years of age	14
" 10 " 20 " " "	92
" 20 " 30 " " "	207
" 30 " 40 " " "	114
" 40 " 50 " " "	84
" 50 " 60 " " "	59
" 60 " 70 " " "	33
" 70 " 80 " " "	11
" 80 " 90 " " "	0
Total	614*

A comparison of these two tables shows clearly the greater frequency of malarial fever among children and young adults. This is probably due not so much to a greater susceptibility as to the fact that the young adult is more exposed to malarial influences—remaining out of doors in malarial districts at night, etc.

Sex.

Of these 614 patients there were—males, 493; females, 121. A table of 614 admissions to the hospital and out-patient department for the same time shows males 396; females 218. The differences in the number of women depends, probably, largely on the fact that the men are so much more likely to be employed in malarious districts: boating on the bay; farming; fishing; while the women, remaining in the house, are spared.

Race.

Of these patients there were: white, 585; colored, 29, or 4.7 per cent. In the hospital and dispensary, taking the cases at random, there were: white, 539; colored, 75, or 12.2 per cent. These figures would tend to uphold the generally accepted view that the negro is relatively insusceptible to malarial infection.

* As there is no children's ward in the hospital, while the cases treated in the children's room at the out-patient department did not come under our observation, the statistics as regards children under ten years of age are of no value.

Relation of the Cases to the time of Year.

The following table shows the relation of the occurrence of these cases to the various months of the year.

Jan.	Feb.	Mar.	Apr.	May.	June.	July.	Aug.	Sept.	Oct.	Nov.	Dec.	Total.
12	8	18	28	35	33	74	67	129	137	45	28	614

From this table it appears that while in the winter months, December, January, February, and March, malarial fever is at a minimum, with the month of April the number of cases begins to increase, as a general thing, showing a gradual steady rise until the climax which occurs in the months of September and October. In November and December, a well-marked fall begins. This table, while it gives a good general idea of the distribution of the malarial infection throughout the year, is, however, a trifle misleading if taken too strictly. The cases during the latter half of the year 1889 were few, as the hospital was new and the clinics had not yet developed, while the cases from January to August of 1894 represent a much larger clinic. The proportion of cases occurring in the first seven months is thus over-represented, while the second half-year suffers, the under-representation of the cases in August being especially marked. The following table, dealing with the cases during the four years from January 1st, 1890, to January 1st, 1894, gives a more accurate representation of the variation of malarial fever with the seasons:

Jan.	Feb.	Mar.	Apr.	May.	June.	July.	Aug.	Sept.	Oct.	Nov.	Dec.	Total.
9	8	8	17	21	18	38	66	122	120	38	25	490

It may thus be seen that more than five-sixths of the cases of malaria observed by us occur in the second half-year; nearly one-half occur in the months of September and October.

It has seemed to us, however, a matter of interest to make another table, which appears below, showing the time at which the patient observed the first symptoms of the affection; this shows several interesting variations from the other tables:

Jan.	Feb.	Mar.	Apr.	May.	June.	July.	Aug.	Sep.	Oct.	Nov.	Dec.	Not Stated.	Total.
8	2	21	21	44	23	83	103	156	69	16	8	60	614

We see thus that the smallest number of cases occurred in the months of December, January, and February, only two cases beginning during the month of February. From this time on there is a fairly steady increase until the month of May which shows the spring maximum. In July again an increase begins, reaching the climax in September, when 156, or more than one-fourth of all the cases, appear to have shown their first symptoms; 103 cases originated apparently in August, while only 69 appear to have originated in October; in 60 cases the date of onset could not be obtained. Thus, nearly one-half of all the cases originated in the months of August and September, and whereas 137 cases were first admitted to treatment in October, only 68 dated their symptoms from that time.

Of these 616 cases, there were:

Primary attacks	396
Relapses or new infections	166
Uncertain	52
Relapses of cases already classified	2

General Summary of some of the more important Symptoms and Complications.

The following tables deal with some of the more important symptoms noted in these 616 cases taken *en masse* without regard to type.

Chills.—There were:

Chills in	479 cases.
Chilly sensations in	41 "
Vague symptoms of headache, anorexia, muscular pains, etc., in	90 "
No history in	6 "

Vomiting.—Vomiting was noted in 84 cases, though it is probable that it occurred in many more.

Epistaxis occurred in 19 instances.

Condition of the Bowels:

Diarrhœa occurred in	80 cases.
Constipation occurred in	161 "
Alternate diarrhœa and constipation	5 "
The bowels were regular in	157 "
No note was made in	213 "

Urine.—The analysis of the urine in the 335 cases occurring in the hospital shows the following results:

The urine was normal in	151	instances.
Albumin was noted in	133	"
Casts of the renal tubules were found in	31	"
The diazo reaction was present in	18	"
Acute haemorrhagic nephritis was present in	3	"
Severe subacute diffuse nephritis was present in	1	"
No note was made in	51	"

In not a single instance of malarial fever observed in the hospital or in the out-patient department, was haematuria present, with the exception of the three cases of acute nephritis, where the blood was present merely in the shape of altered red corpuscles, giving a smoky color to the urine.

Condition of the Blood.—In 94 cases pallor was noted; in 21 cases there was grave anaemia.

Cutaneous manifestations.—In 61 cases, *herpes labialis* was noted; in 3, a *petechial* eruption; in 3 instances an eruption suggesting the *rose spots* of typhoid fever was found; in one case, general *erythema;* in one, a rash resembling *measles;* in one, *eczema;* in one, a *varioliform eruption; urticaria* was present during the paroxysm in 3 cases; *herpes zoster* was present in one case.

Respiratory Organs.—In 16 cases, *bronchitis* was noted, while in a number of others a slight cough, without physical signs, was present.

Complications.—Among the chief complications, the following may be mentioned:

Chronic valvular disease of the heart	5
Arterio-sclerosis	1
Pregnancy	2
Secondary syphilis	3
Congenital syphilis	1
Incontinence of urine	1
Epilepsy	2
Pleurisy	2
Pneumonia	2
Asthma	1
Cancer of the uterus	1
Cancer of the jaw	1
Subacute rheumatism	1
Tonsillitis	1

Amoebic dysentery	1
Entero colitis	2
Typhoid fever	1
Chronic nephritis	1
Acute nephritis	2
Anasarca	1
Keratitis	1
Furunculosis	1
Parotitis	1
Adenitis	1
Acute mania	1
Alcoholism	1

Cases of Pneumonia associated with Malarial Fever.—Two cases of malarial fever in the hospital were complicated by pneumonia.

Case 9424.—C. J., aged 30, a laborer, native of the United States, admitted March 16th, 1894, complaining of loss of appetite and cough. Family and personal history bear no relation to his present trouble, excepting for the fact that he had malarial fever a year ago; chills at uncertain intervals. He has been living recently in a very malarious district. The mistress of the house in which he lives and her three children are all suffering from chills and fever at present. For several weeks, has not been feeling well; appetite poor; has been languid and easily tired; gave up work three weeks ago.

Two days ago the patient began to complain of a very severe headache, nausea and vomiting, and thinks that he has had fever since this time; no chills; diarrhoea, three or four movements daily; slight cough for several weeks.

Hasty examination of the *blood* on admission showed no malarial organisms. *Urine* normal, yellow, cloudy, acid, 1020, trace of albumen, distinct diazo reaction, no sugar nor bile; microscopically, leucocytes and epithelial cells; one doubtful granular cast.

The temperature on admission was 102°, reached 105.2° at 10 p. m., and was 101.8° at 8 a. m. the next morning.

17–3–94. Patient was in bed; well nourished; tongue coated; pulse, twenty-five to the quarter, regular in force and rhythm; heart and lungs negative; abdomen negative, excepting for an increased area of splenic dulness.

At 10.30 a. m. the blood showed half- and full-grown malarial organisms of the tertian type with fine, dancing, brownish pigment; one intracellular hyaline body; one early segmenting form. Temperature steadily elevated.

At 4 p. m. no malarial organisms seen in two slides. Leucocytes, 10.000.

18–3–94. "Last night the patient complained of pain in the right axilla—a "stitch"; respiration at the right base appeared somewhat enfeebled, and the resonance was slightly impaired. Though the malarial organisms were few in number, the patient was ordered quinine, gr. x (0.65), at nine and twelve, and gr. v (0.32), every four hours afterwards. Patient passed a restless night, the temperature this morning being 102.3°. Pulse is rapid, over 130, rather soft." Well marked evidences of consolidation were found at the right base.

Leucocytes at 10 a. m., 14,500; at 4 p. m., 17,000. From this time on, the patient went through a very serious attack of pneumonia, the temperature falling by lysis. The quinine was continued only three days, gr. lxxxv (5.32) in all. The temperature reached the normal on the 26th of March. No malarial organisms were seen after the 17th.

On the afternoon of the 9th of April, the patient complained of having a headache, and the temperature was found to be 103.6°. It fell at midnight to 99.2°. On the 10th, the temperature rose between 12 and 4 p. m. to 103.8°, falling gradually to 99.2° at 8 a. m. on the following morning. Examination of the blood on the 10th showed tertian parasites. Quinine, gr. v (0.325), three times a day, was ordered; the patient made an uninterrupted recovery.

This case is of interest in that it is the only one which has occurred, since the opening of the hospital, where malarial organisms were found in the blood during the actual existence of a pneumonia. It is in every way probable that the patient had had for a week or two a tertian infection which had not yet reached a sufficient intensity to produce actual chills; that during this time the pneumonia also developed. During the convalescence, twenty days after the omission of quinine, a relapse of the tertian fever occurred. So far as could be made out, the presence of the malarial infection caused no essential modification of the chart of the pneumonia.

Case 9963.—W. B., aged seven, admitted on May 24th with single tertian malarial fever, though indications of a second group of organisms were present. As the chart shows, the patient had an abortive paroxysm on the 26th, the temperature remaining normal afterwards until the 30th. Quinine was given on the 26th, and no malarial organisms were seen afterwards.

On the 30th the patient had a chill at 4 a. m., associated with some vomiting. The blood showed a slight leucocytosis. The temperature remained continuously elevated until the 3rd of June. Nothing could be made out on physical examination until the 2nd of June, when evidences of consolidation at the right apex appeared. Crisis on the evening of the 3rd. Quinine was discontinued on the 1st of June. On the 18th of June the patient had a chill, temperature rising at 1.30 p. m. to 103.8°, blood showing one group of organisms. Quinine was begun on the 19th. A few fragmented, extra-cellular bodies were seen on the 20th, when the patient was discharged with a prescription for quinine, the temperature having remained normal.

In this case it will be seen that the pneumonia developed during the malarial infection which was never quite eradicated, a relapse occurring twenty-three days after the last organisms had been seen. In neither of these instances did the pneumonia show anything remarkable in its course, nor is it likely that the malaria exerted any

influence upon the pneumococcus infection, excepting in so far as it may have prepared the soil.

Case of Typhoid Fever combined with Malarial Fever.—In one instance malarial fever was associated with typhoid fever.

The patient, J. D., aged 20, Irish, was admitted on the 16th of October, 1891, complaining of chills, fever, headache, cough, and occasional bleeding from the nose.

The temperature on admission, was 100°; it fell on the morning of the 17th to 96°.

The *blood* on the 17th showed fairly numerous, non-pigmented, intracellular, hyaline bodies. Physical examination was negative. On the 17th, as the chart will show, the patient had a chill, the temperature remaining elevated for nearly twelve hours. During the next several days, there were slight oscillations in the temperature, which remained nearly normal. Quinine, 0 26 three times a day, was ordered on the 17th. The last malarial organism seen in the blood was an ovoid body, with coarse pigment granules, which was seen on the 23d. The temperature began to rise on the 22d, reaching 104.8° at 4 p. m. on the 23d, the patient passing through a long, severe attack of typhoid fever. Quinine was omitted on the 26th.

The patient made a good recovery, leaving the hospital on the 19th of January. No malarial organisms nor symptoms of malarial fever were noted.

In this instance, the typhoid fever unquestionably developed during the course of a malarial infection, organisms still being present in the blood at the beginning of the rise of temperature. The case demonstrates the possibility of the co-existence of the two affections.

IV.—THE VARIETIES OF THE HAEMATOZOA OBSERVED IN THE MALARIAL FEVERS OF BALTIMORE.

Methods of Examination of the Blood.

Almost all the examinations of the blood upon which this article is based, were made with fresh specimens. In a number of instances we have used different staining methods, but the examination of the fresh blood, when carefully carried out, has always seemed to us simpler and more satisfactory. The steps toward the preparation of the specimen are simple, but certain precautions must be rigidly adhered to. The cover glasses and the slides must be carefully washed in alcohol, or alcohol and ether, in order to remove all fatty substances. They should always be washed immediately before use. The blood may be taken from any part of the patient's body, though

in our practice we prefer the lobe of the ear, inasmuch as it is less sensitive and more easily approached than the finger tip, while a smaller puncture will draw more blood. This method is also more satisfactory than the puncture of the finger in that the patient cannot so readily observe the proceeding, a point of considerable importance in nervous patients and children. The ear is at first thoroughly cleaned; the lobe is then punctured with a small knife or lancet. The first several drops of blood are wiped away. The freshly cleaned cover glass is then taken in a pair of forceps and allowed to touch the tip of a minute drop of blood; it is then placed immediately upon the perfectly clean slide. It is well, if a third person be present, to allow the slide to be vigorously rubbed with a clean linen cloth just before the application of the glass. The spreading out of the drop of blood will thus be considerably facilitated. If the slide and the cover are perfectly clean, the blood will immediately spread out between them, and unless the drop of blood has been too large, the corpuscles may be seen lying side by side, entirely unaltered in their main characteristics. The drop of blood which is taken should be very small, unless the patient is very anaemic, and care should also be exercised that the tip of the drop only should touch the cover. If the cover be placed rudely against the drop, and pressed, perhaps, also against the ear, the blood may so far spread out that the process of drying may have begun before the glass is laid upon the slide. If this be the case, the immediate spreading out of the blood between the slide and the cover does not occur. No pressure whatever should be exerted upon the cover which should not be pushed or allowed to slide. We have not, in our examinations, used the prepared slides of Hayem, nor have we endeavored to preserve our specimens for a longer time by the application of vaseline or paraffine about the cover glass. The specimens will remain in good condition for a considerable length of time, an hour or more, long enough to be thoroughly examined. For the examination of fresh blood, a good oil-emersion lens is almost necessary. It should not be forgotten, however, that in the absence of such optical assistance, we may yet study the organisms with some satisfaction, for Laveran made his discovery and the majority of his researches with ordinary dry lenses of moderate power. As has been said, however, for satisfactory work a $\frac{1}{12}$ oil-immersion lens, with a 4 eye-piece, is advisable, and, indeed,

if the lens be good, eye-pieces as high as 8, or even more, give satisfaction.

For the preparation of permanent and stained specimens, we have had best results with eosin and methylene blue. In the preparation of these specimens we rather prefer fixing by means of absolute alcohol, or absolute alcohol and ether, to the methods of heating. A specimen hardened for half an hour in absolute alcohol and ether, may be stained with a concentrated aqueous solution of methylene blue for from half a minute to a minute with excellent results.

A good contrast stain may be obtained by the following method: The specimens are placed for thirty minutes in absolute alcohol and ether, dried, and stained for from thirty seconds to five minutes in a $\frac{1}{2}$ per cent. solution of eosin in 60 per cent. alcohol, washed in water, dried, and placed for from thirty seconds to a minute in a concentrated aqueous solution of methylene blue, washed, dried between filter paper, and mounted in Canada balsam. The methylene blue stain may not be very intense, but at times beautiful pictures may be obtained.

The most satisfactory results which we have obtained have been with a modification of Romanowsky's method. Romanowsky's [210] (vide p. 43) directions are carried out strictly, excepting that the specimens, instead of being fixed by heat, are placed for from ten to twenty minutes in absolute alcohol. By this method beautiful specimens may sometimes be obtained inside of half an hour, while in other instances it may be necessary to stain longer.

The Parasite of Tertian Fever.

The earliest forms of the tertian parasite begin to appear in the blood during the latter part of the paroxysm or just after it. They are small colorless bodies (Plate I, 1, 2, 3, 4) which fill but a small part of the corpuscle. They have appeared to us to lie within the corpuscle, and not upon it, as Laveran believes. We have never seen hyaline bodies which were engaged in the process of entering the corpuscles or which appeared to be attached to them previously to the probable entry, as Mannaberg believes he has observed. When in the resting stage they are round and apparently disc-shaped, this form being very possibly due to the shape of the corpuscle in which they lie.

When one examines the fresh blood, they appear as pale bodies which, while they seem to have no color of their own, do not show the complete lack of color and the sharp outline which is characteristic of certain vacuoles commonly observed in some of the red corpuscles in fresh preparations, particularly in the blood of anaemic patients. On examining carefully one of these bodies, one gains the impression that he is looking through a thin layer of haemoglobin containing substance with which the body is covered; that is, it would appear to lie in rather than upon the corpuscle. In this stage the organism is usually actively amoeboid. It suddenly changes its shape, often assuming rapidly the shape of a cross or of a star with four or more arms, becoming then often even more irregular, and finally, perhaps, returning again to its original disc-like shape. In the fresh specimen there is, at this stage, no indication whatever of a nucleus, unless, perhaps, the centre of the body, where the nucleus probably lies, has a more transparent and paler appearance than the outer part, which seems a trifle thicker and more refractive. Sometimes the small body may assume the shape of a ring, owing generally to the meeting and fusing of the pseudopodia (Plate I, 5). In the middle of this ring lies apparently a bit of the corpuscular substance. As time passes on, this small body increases in size and begins to develop reddish brown pigment granules (Plate I, 5, 6, 7). These granules are at first very minute. They are irregular in size and shape, appearing sometimes as small, irregular fragments, sometimes as minute rods. They are generally in very active motion, a motion much more marked than the ordinary Brownian movements. This activity would appear to be communicated by lively undulations of the protoplasm in which the pigment granules are contained. At this stage in the development of the organism, one commonly sees, on looking at a specimen of fresh blood, what, at the first glance, would appear to be collections of minute granules scattered throughout different parts of certain corpuscles, and the first impression is usually that the corpuscle contains several distinct haematozoa. Almost invariably, however, upon careful search, it may be noted that these little groups of pigment granules are contained in the bulbous extremities of the pseudopodia of a single extremely amoeboid organism. The pigment tends to collect at the extremities of the pseudopodia, while the index of refraction of the protoplasm of the organism differs so little from that of the surrounding corpuscle, that it is some-

times almost impossible to distinguish the outlines of the body. With the growth of the organism and the development of pigment, the red corpuscle which harbors the body becomes paler and usually expands, showing a diameter appreciably larger than that of its unaffected neighbors. As the organism increases in size, and pigment accumulates, its amoeboid properties become less marked while the pigment, which may still be extremely active, tends to seek a peripheral arrangement (Plate I, 7, 8). Before the end of forty-eight hours the organism has usually completely filled the red corpuscle, the pigment granules are greatly increased in number, and about the full grown body which is now about the size of the normal red corpuscle, may be traced only the pale shell-like outline of the expanded red disc (Plate I, 9). Sometimes all indications of the red corpuscle disappear. When this stage is reached, indications of segmentation begin to be seen (Plate I, 10–14). The pigment, which has formerly been so very active, becomes almost motionless, and tends to collect in the centre of the body, in the form either of a single block of pigment or a close collection of granules. The substance of the organism about this central clump assumes a finely granular, more refractive, appearance. Shortly after this, one may notice distinct indications of a radial shading or striation which begins to appear in the peripheral part of the protoplasm and becomes steadily more marked until, finally, the central pigment clump is surrounded by from twelve to twenty or even more separate segments arranged in a characteristically rosette-like form. Each of these segments shows, usually, a central spot, which is more refractive, having been sometimes mistaken for pigment. It often looks like a central depression, and probably represents the nucleus. A little later than this we may see the central pigment clump surrounded by a mass of entirely separate round, hyaline bodies (Plate I, 14), which are in every way similar to those already described as the first stages in the development of the organism. At this time, also, one begins to notice the appearance of similar small hyaline bodies in some of the red corpuscles. We have thus a very suggestive chain of evidence in favor of the view that this is a reproductive process; that these hyaline segments resulting from the division of the organism are identical with the fresh hyaline forms that appear in the red cells. Commonly, however, segmentation does not occur with quite such regular figures. The smelting, so to speak, of the granules into a

solid block may not occur, and the segmentation may take place before the granules have all collected in the centre. Again, instead of the regular radial arrangement of the segments, we see the organism break up throughout its substance into a number of round, hyaline bodies, with central refractive points (Plate I, 13), while later on we find the central pigment mass surrounded by a group of separate hyaline bodies. We have never seen figures corresponding exactly to Golgi's first form of segmentation, where he shows the pigment left in a central protoplasmic body, while a peripheral layer of protoplasm alone segments. We have not been able to make out a distinct double outline in the case of the spores, as Antolisei asserts that he has done. Not infrequently, at the time when we observe full-grown organisms in the blood, as well as during the days when only half-grown forms are to be seen, occasional pigmented bodies may be found outside the red corpuscles free in the plasma. Some of these represent entirely full-grown bodies which have destroyed the surrounding corpuscle (Plate I, 18), while in other instances the half-grown forms may actually leave their host (Plate I, 21). This process may be occasionally observed under the microscope. The corpuscle containing the parasite suddenly collapses like a bladder, its color becoming immediately diffused into the surrounding plasma, while the parasite at the same moment bursts out of the corpuscle into the serum. Almost immediately after its escape from its host, the free parasite becomes irregular in outline, or fragmented. The pale decolorized expanded shell of the corpuscle may sometimes be distinguished for a short time after the escape of the parasite. This bursting of the half-grown form from the corpuscle has been well described, also, by Bastianelli and Bignami. The budding or breaking up of the extra-cellular forms into several small bodies, is very commonly observed (Plate I, 19–20). The large extra-cellular forms are often several times the size of the normal red corpuscle. They have generally a pale, transparent, swollen look. The outlines are indistinct, while the pigment is commonly extremely active. After observing these bodies for a time, certain changes are often seen to take place.

(1). The pigment remains for a considerable time extremely active, while the outlines of the body become very indistinct and somewhat irregular, and the whole parasite becomes more and more expanded

until it reaches almost the size of the ordinary polymorphonuclear leucocyte. Gradually the motion of the pigment becomes less active, the outlines more irregular, till finally there remains only a misshapen mass of protoplasm containing fine brown motionless granules, a picture very similar to that drawn by Laveran in his description of the swollen, cadaveric forms.

(2). The large extra-cellular forms very often become fragmented. A small prominence will be noted upon one side of the body, which rapidly becomes shut off from its mother form, forming a separate circular pigmented body. In this manner, one large form may give rise to four or five smaller bodies. The motion of the pigment may be quite active, but very commonly after a short time it becomes less marked, the outline of the bodies becoming indistinct, until they remain as pale shadows in the field. Not infrequently one sees several of these small bodies, the results of fragmentation, connected together by thread-like processes in which pigment granules may be seen (Plate I, 21). This process of budding and fragmentation we believe to be degenerative in nature.

(3). Not uncommonly, one of these large, swollen, extra-cellular bodies may be seen to develop a pale vacuole-like area usually of a disc-shape, in which sometimes one or two bodies resembling segments may be seen. About this area, a number of small irregular vacuoles develop, while the pigment between them is often very active. As time goes on, and the vacuoles increase in number, the pigment generally becomes motionless, lying as small brown or black specks between the vacuoles (Plate I, 23, 24). Often one of these bodies, filled with vacuoles, may assume a most irregular shape. These elements we believe, with Antolisei, to be degenerative, and not, as Golgi suggested, regenerative forms; for, notwithstanding the fact that the round bodies seen in the large clear area are not dissimilar to the segments seen in the other forms of segmentation, as one observes them in the fresh specimen, the vacuolization of the rest of the substance, the irregularity of the shape, and, more important than all, the fact that these bodies do not stain in a characteristic manner, leads us to believe that they are degenerative.

(4). Another change often noted in these large, extra-cellular organisms, is the development of the so-called flagellate forms. Here the pigment assumes at first a particularly active motion. It dances

with surprising rapidity, while now and then at the periphery of the organism we may note marked wave-like protrusions and undulations. Suddenly the granules assume a more central position, still being extremely active, while at the same moment one or more thread-like processes, several times the length of the organism, break out from different parts of the periphery (Plate I, 22). These flagella show often a slight swelling at their extremity, and occasionally other olive-shaped swellings at one or more points in their course. Sometimes granules of pigment may be seen in the flagella. Often the body from which the filaments come gives off buds, or fragments into several smaller pigmented bodies, all of which are moved about with great activity by the mobile flagella. The length of time during which these motions may exist varies; sometimes they may be observed for as long as half an hour. Sometimes the flagella may break off from the main body; but with the breaking off of the flagellum, its power of individual motion does not cease, and free flagella are not infrequently seen, making their way about among the red corpuscles. They have in this stage quite the appearance of spirilla, such as occur in relapsing fever.

Phagocytosis, as pointed out by Golgi, occurs, generally speaking, at stated intervals in tertian fever; that is, at the time of the paroxysms. Wherever segmenting bodies are seen, we may observe pigmented leucocytes, and the pigment in these leucocytes is generally in the form of large blocks, similar to those left after the segmentation of the parasite. But this free pigment is not the only constituent of the malarial parasite which is taken up. Commonly, the small, extra-cellular bodies, which result from the breaking up of the large, full-grown, swollen, extra-cellular organisms, are also taken up, a process which may be observed under the microscope. Again, the same fate may befall the half-grown bodies which break out from the corpuscles, so that at times pigmented leucocytes may be seen at a considerable distance from the paroxysm. The very best opportunity which we possess for studying phagocytosis under the microscope is offered us, however, in the presence of the flagellate bodies. Wherever flagellate bodies develop, we may almost invariably observe the active process of phagocytosis. The appearance of flagella seems to be, in most instances, the signal for an attack upon the parasite by the surrounding leucocytes. Not all the varieties of leucocytes appear to take part

in this warfare. While pigment granules are very commonly found in mononuclear elements in the circulating blood, we have never seen a mononuclear leucocyte attack a flagellate body under the microscope. The "multinuclear" neutrophiles appear to monopolize this function in the fresh specimen, and at times we have seen a single flagellate body attacked by as many as three leucocytes at once. We have never seen a lymphocyte or small mononuclear form containing pigment, nor have we ever seen any indication of phagocytosis among the eosinophilic leucocytes.

We believe, then, that we can trace in the blood the life-history of the tertian organism, beginning with the hyaline body directly after segmentation, and ending, after nearly forty-eight hours, with the full-grown form which has destroyed the red corpuscle, while the process of reproduction is represented by the segmenting forms of Golgi. The segmenting bodies, as has been noted by Antolisei [129] and Bastianelli and Bignami,[152] are disproportionately scanty in comparison to the number of adult forms seen some hours before the paroxysm, a fact which is doubtless explained, as pointed out by these observers, by their greater frequency in the spleen. The segmenting bodies are usually at first surrounded by the pale rim of a decolorized red corpuscle. This is often so pale that it is overlooked; it shows more distinctly in colored specimens. In the more advanced forms this rim may be no longer distinguishable. The segmenting bodies which are observed in the peripheral circulation are usually about the size of a red blood corpuscle, sometimes larger, sometimes smaller. Occasionally we have found smaller segmenting bodies contained in red blood corpuscles which show relatively little decolorization (Plate I, 16, 17). We have not been able to definitely associate these forms with anticipating fevers, as Bastianelli and Bignami [152] have done to their satisfaction. The large extra-cellular forms, with pale protoplasm and dancing granules, are probably, in some instances, degenerative forms, but we do not feel that there is as yet sufficient proof to warrant the assumption that this is true in all instances. We have seen segmenting bodies develop from some quite large forms. There are, also, some reasons which would suggest that the flagellate forms are, as so many persons believe, degenerative in nature, but we do not feel at present quite ready to accept that view.

We find that the fever keeps pace with the development of the organism, the paroxysm being invariably associated with the segmentation of the full-grown bodies and the appearance of the fresh group of young individuals. The presence of segmenting forms is always, in our experience, an indication that the paroxysm is impending or has already begun. Not infrequently these forms may be seen several hours before the onset of the paroxysm, but never have we seen segmenting bodies in tertian fever without their being definitely connected with a paroxysm.

Double Tertian Infection. Multiple Infections.

Such, then, is the course of development of the tertian parasite as we observe it in studies of the fresh blood. More commonly, however, we have a somewhat more complicated picture: namely, the presence of two instead of one group of parasites. Thus, for example, if we examine the blood during the paroxysm, we find not only full-grown segmenting forms, and perhaps fresh hyaline bodies, but also another set of organisms which show the development characteristic of about twenty-four hours' growth; in other words, there is a double infection, two sets of organisms, becoming mature on successive days, and, as one might be justified in expecting, the clinical picture in these cases is one of quotidian fever. It is probable that in some instances there may be still further complications by infection with more than two groups, or by infections with organisms which are not so sharply distinguished into separate generations as in the great majority of instances.

The Parasite of Quartan Fever.

This parasite, in its earliest stages of development, is scarcely distinguishable from the organism of tertian fever. The youngest forms are small hyaline, amoeboid bodies, filling but a small part of the red corpuscle. The very earliest forms are quite indistinguishable from the tertian parasite, but as they begin to grow, certain differences are readily made out. In the first place, they show a much sharper outline than the tertian parasite, while the protoplasm has a somewhat more refractive character, and the amoeboid movements are slower

and much less extensive (Plate I, 26). The first forms, as in tertian fever, appear with the paroxysm, and shortly afterwards begin to develop pigment granules (Plate I, 27). These granules, however, differ a little in appearance from those in the tertian parasite. They are generally a little larger and also a little darker in color. While the pale, yellowish-brown granules of the tertian parasite are always in very active motion, these larger darker granules lie almost motionless, arranged generally about the periphery of the somewhat refractive, colorless parasite. In these young pigmented forms, there is still a certain amoeboid movement, but it is slow and lazy as compared to the rapid changes of outline which are seen in the tertian parasite. As the parasite grows and the pigment increases in quantity, the red corpuscle does not become decolorized and expanded, as does the corpuscle containing the tertian parasite. On the other hand, the infected corpuscles are usually a trifle smaller than their unaffected neighbors, while the color is, if anything, a little darker than the normal. They are also more refractive and sometimes there is a distinctly greenish, brassy appearance (Plate I, 28–34). At the end of from 64–72 hours, the parasites have reached their full development. They are then round or ovoid bodies, somewhat smaller than the normal red corpuscle; about them may be seen a very thin layer of still colored, refractive, haemoglobin-containing substance. In this stage, the amoeboid movements of the bodies are entirely lost, while the pigment, which tends to be peripherally arranged, is coarser and darker than in the tertian parasite, the individual granules differing also more markedly in size; these pigment granules are almost motionless. The index of refraction of the protoplasm is quite high, and the picture is quite different from that presented by the tertian parasite, so much so that the organisms may be readily distinguished by the skilled observer on the first examination. At this time some of these bodies may seem to have entirely destroyed the corpuscle, remaining apparently free in the serum (Plate I, 35). On staining, however, most bodies show evidence of a slight layer of corpuscular substance about them, and it is a question of doubt in our minds as to whether any true segmenting bodies are not, in the beginning, contained in the shell of the red corpuscle. Six to eight to ten hours before the febrile paroxysm begins, some of these full-grown bodies begin to show certain striking changes (Plate I, 36–39); the pigment granules which, though

scattered throughout the body, have tended toward a peripheral arrangement, begin to collect at the centre. The process of the accumulation of the pigment in the centre of the quartan organism gives pictures which one does not see in the case of the tertian parasite, namely: the arrangement of the pigment in a star-shaped form, as though it tended to arrive at the centre of the body through certain definite currents which flow inward from the periphery. Finally, the pigment is collected in a central clump or solid block, while the protoplasm of the organism becomes somewhat more refractive and of a slightly granular appearance. A radial shading begins to be evident, similar to that observed in the tertian parasite, and finally the protoplasm divides into from six to eight to ten to twelve small pear-shaped leaflets, each containing a central more refractive point. The regularity of the arrangement of these leaflets is decidedly more marked than in the case of the tertian parasite, most exquisitely symmetrical marguerite forms being at times observed. Later on, these pear-shaped leaflets separate from the central mass and are seen as small, round or ovoid bodies surrounding the central pigment clump. Simultaneously with this we may note the appearance of fresh hyaline forms in certain of the red blood corpuscles. Some of the full-grown parasites do not segment on reaching their complete development, but undergo certain changes similar to those observed in full-grown tertian organisms:

(1). The pigment granules, which have previously been extremely lazy in their movements, may take on a considerable activity, while the body may expand, equalling or even slightly exceeding the size of a normal red corpuscle (Plate I, 40). These bodies are very transparent, and closely resemble the analogous forms of the tertian parasite. Eventually, the movements of the pigment become less marked, the outlines of the body become irregular and indistinct, and a motionless cadaveric form remains.

(2). Forms similar to those just described may undergo a further change, namely: fragmentation into a number of small bodies, which eventually become indistinct and deformed, just as in the case of the tertian parasite.

(3). Vacuolization of these forms we have also observed (Plate I, 42).

(4). These bodies may develop flagella just as in the case of the tertian parasite (Plate I, 41). The granules become suddenly very

active, collecting at a given moment more toward the centre of the body, while long, thin, flagella burst from the contour, making active, serpentine movements among the surrounding corpuscles. These forms differ from those of the tertian parasite in their smaller size and in the greater coarseness of their granules. The movements of the flagella are not, so far as we can make out, essentially slower than those in the tertian organism. As the parasites are smaller, and the granules darker and larger, the complete bodies resemble much more closely the forms about to be described in the aestivo-autumnal parasite, than those developing from the tertian organism. Flagellate bodies were observed in two of our five instances of quartan fever.

Phagocytosis is observed in quartan infection with the same extreme regularity as in tertian fever. It begins with the paroxysm and lasts during it and for several hours afterwards. The forms taken up, as in the case of tertian fever, are the central pigment clumps, the small, fragmented, extra-cellular forms, the flagellate bodies, and not infrequently the segmenting bodies. In a number of instances we have been able to follow, under the microscope, the engulfing of an entire segmenting body by a "multinuclear" leucocyte. In other words, the extra-cellular forms alone are usually taken up by the phagocyte.

Double and Triple Quartan Infections.

As, in tertian infection, two or more groups of parasites, showing different stages of development, may be present in the blood, so in quartan infection, this is a very common occurrence. Sometimes we may see two groups of quartan organisms which reach maturity on successive days. As the febrile paroxysm is always associated with the segmentation of a group of parasites, we see, in these instances, paroxysms on two successive days, with one day of intermission,—*double quartan fever*. Again, with considerable frequency, we may see three groups of organisms, which, reaching maturity on successive days, cause daily paroxysms—*triple quartan infection*. Three of our five cases of quartan fever were triple infections. It is probable, as has been noted in the summary of the literature, that infection with multiple groups of parasites may take place, causing irregular febrile manifestations, though this we have not, in our limited number of

cases, been able to observe. We have, then, distinguished a parasite which differs from the tertian organism in several distinct manners:

(1). *The length of the cycle of development*, which lasts forty-eight hours in the one case, and seventy-two in the other.

(2). *The appearance of the organism itself;* pale and indistinct in the tertian; sharply outlined and somewhat refractive in the quartan; actively amoeboid in the former; slightly amoeboid in the earlier, and motionless in the later stages in the latter.

(3). *Character of the pigment;* often a reddish-brown in the one; coarser, more irregular in size, and darker in the other; actively motile in the former; lazy and almost motionless in the latter.

(4). *The volume;* reaching the full size of the red blood corpuscle in the tertian; never reaching so large a size in the quartan; the large, full-grown, free (degenerative?) forms being sometimes twice as large as the red blood corpuscle in the former; rarely larger than the red corpuscle in the latter.

(5). *The segmenting forms;* usually as large as the red corpuscle in the one; not as large in the other; the segments numbering usually from fifteen to twenty in the former; from six to twelve in the latter; the whole organism breaking not infrequently into irregularly arranged segments in the former; typical rosette forms almost always in the latter.

(6). *Behavior of the infected corpuscle:* The corpuscle becomes expanded and decolorized in the tertian infection; shrunken and often brassy-colored in the quartan.

It is not just, as some of the critics have done, to assert that the chief difference between the quartan and tertian parasites consists in the number of their segments. There are differences which the skilled observer can detect in every stage of development, unless it be in the very earliest forms,—those immediately following segmentation.

In tertian infection, while many full-grown and nearly full-grown forms are to be found some hours before segmentation, at the time of segmentation the bodies observed in the peripheral circulation are distinctly less frequent; the explanation is, probably, that segmentation takes place for the most part in the internal organs. This is, however, not true of the quartan parasite. Here all stages are seen with equal frequency in the peripheral circulation, and segmenting bodies may be found where very few organisms are present. In

tertian fever, for instance, it is extremely rare to see segmenting bodies in cases where they are not associated with a definite febrile paroxysm. In quartan fever, on the other hand, one may follow the entire life-history of a single group of parasites for weeks, where the number of organisms is so slight as to produce little or no visible febrile reaction.

The Parasite of Æstivo-autumnal Fever.

The third type of organism which we have been able to distinguish, is identical with that which has been described by Sacharow as the organism of Febris irregularis, the Haematozoon falciforme of Antolisei and Angelini, the aestivo-autumnal parasite of Marchiafava and Celli. This type of organism shows quite marked differences from the forms above described. The youngest forms of the parasite are quite similar to those observed in tertian and quartan fevers; they are small hyaline bodies. There are, however, certain differences which may be striking. The hyaline forms are usually smaller than those of the tertian parasite, while they are generally more highly refractive. They often have a decidedly ring-like appearance (Plate II, 1, 2), which is probably in most instances only apparent. These ring-shaped bodies are very small—the smallest seen. The outer layer of the parasite shows quite a sharp glistening refraction, while the central part is shaded, appearing as though it were thinned, the coloring of the corpuscle showing through. While observing one of these very small, refractive, ring-like forms, we not uncommonly see it become suddenly expanded, more homogeneous, and paler (Plate II, 3–6). The outer rim no longer seems more refractive and thicker than the centre, and the ring-shaped appearance is lost. A wavy undulation of the border is commonly to be seen, while, very frequently, most active amoeboid movements develop, similar in every way to those of the tertian parasite. Sometimes, in this stage, we may see two pseudo-podia join one another, enclosing a central piece of corpuscle, thus causing a true ring. While in the organisms of tertian and quartan fever we have been able to follow out and to trace the length of the cycle of development with perfect clearness, we have not been able to do this with the same accuracy in the case of the aestivo-autumnal organisms. This difficulty is due, in part, to

the fact that the earlier stages of development only are found in the peripheral circulation, the later stages in the cycle occurring in the spleen, marrow, and other internal organs, and, in part, to the fact that in most cases, when they come under observation, several groups of organisms are present at the same time. We are inclined to believe from our observations that the length of the cycle is subject to great variations, amounting, in some instances, to twenty-four hours or less, and in others to forty-eight hours, or even more. The small hyaline forms above described, appear, usually, during and shortly after the paroxysm. In a variable length of time after this, pigment granules begin to make their appearance. These are not, however, numerous and active as in tertian infection, or coarse as in the quartan. Often, only one or two most minute dark granules appear in the periphery of the homogeneous, disc-shaped organism (Plate II, 7–12); sometimes, in the more ring-shaped refractive variety, they may be situated at the inner edge of the more refractive border, close to the central pale area, though more commonly they are observed, as in the more expanded forms, just at the periphery. The pigment granules show but little movement. Before the appearance of the pigment, the organism increases somewhat in size; rarely, however, does its diameter exceed a third that of the red corpuscle itself. The corpuscles in which these bodies lie, show no indication of decolorization. Not infrequently, however, they are shrunken, often crenated or spiculated, and of a deeper brassy color ("globuli rossi ottonati"), an alteration indicating, probably, degenerative changes in the corpuscle (Plate II, 7, 16). In some cases we may see corpuscles containing small, refractive, ring-like bodies, with or without pigment, where the haemoglobin seems to have left the outer part of the disc and collected about the parasite, leaving the outer part decolorized though still showing the outline of the original corpuscle (Plate II, 13). The haemoglobin here shows generally the brassy green color. Later on we may see in the larger forms of the organism a small collection of non-motile or slightly motile pigment granules about the centre of the body (Plate II, 13, 16–19). This is seen only in the larger forms, forms which may have a diameter more than one-third the size of that of the red corpuscle. The pigment, however, in these instances is never as profuse as in the tertian form. With these bodies, which occur only before and during the paroxysms, certain still more characteristic forms may be

seen in the circulating blood, forms which we have never seen excepting in association with the paroxysm. Here, in similar bodies, those which are, perhaps, a trifle more than one-third the size of the cell in which they are contained, a few pigment granules may be seen to have gathered together near the centre, and to have become smelted, as it were, into a solid clump, while the surrounding body has a peculiarly homogeneous, refractive appearance (Plate II, 14, 15, 20). These forms, as we have said, have only been noted just before or during the paroxysms. They are always associated with pigment-containing leucocytes, while the pigment in these leucocytes is usually in the form of similar blocks. Occasionally these bodies may reach nearly the size of a normal red corpuscle. From the fact that these forms are observed only during the paroxysms, from the fact that we have never seen these solid blocks of pigment in tertian or quartan fever, excepting in segmenting forms, from the fact that they are always associated with leucocytes containing similar blocks of pigment, we might easily conclude, even had it not been proven by the examination of the splenic blood, that these are early or pre-segmenting forms. We have never seen actual segmenting forms in the circulating blood, as described by Sacharow,[212] possibly because we have not had so large a number of severe cases to deal with. During the early part of the paroxysm, indeed, and for several hours before, very few organisms are to be found in the peripheral circulation. In several instances at this stage we have been unable to find any, while some hours later the organisms were present in large numbers. We have not carried out a systematic study of the splenic blood, though in several instances we have found, on puncture, segmenting forms similar to those described by Marchiafava, Celli, and Bignami. Examination of the splenic blood at the beginning of the paroxysm reveals always a large number of intracorpuscular parasites with central pigment blocks, as well as a certain number of similar organisms, which are free.

The advanced segmenting forms, which we have seen, have showed no traces of the surrounding blood corpuscle (Plate II, 21–24). Both in the number of segments and in the manner of division, the segmenting aestivo-autumnal parasite resembles closely the similar stage of the tertian organism. It is, however, much smaller, as is shown in the plate.

As has been said above, we have not been able to sharply define the length of time required for this cycle of development. We believe, however, that it varies considerably from twenty-four hours, or even less, to forty-eight hours, or somewhat more. In a majority of instances, where the fever has lasted more than one week, other characteristic bodies may be noted in the blood. Here, at first, one may notice more of the larger rounded bodies with central pigment granules. Commonly, these assume an elongated or ovoid shape. Occasionally, forms may be seen nearly as large, or larger, than the corpuscle. These show a peculiarly refractive appearance, the pigment granules become more numerous, coarser, and show a tendency to a ring-like arrangement in the centre. The bodies lie usually at one side of the red corpuscle, the remains of the cell forming a bib-like attachment, as it were, upon the other side (Plate II, 26–33). Often the red cell becomes much decolorized; sometimes it shows a crenated outline. Finally, we see still larger forms, which are usually ovoid or crescentic in form, the remains of the red corpuscle forming a convex bib, connecting the two horns of the crescent, or attached to one side of the ovoid form. Sometimes the crescentic or ovoid bodies may lie in the middle of the cell (Plate II, 25); more often, the remains of the cell are attached to them as a bib. Some of the apparent separate ovoid bodies are, probably, simply crescentic forms which are viewed through the microscope from the convex side of the crescent. This may at times be clearly shown by the revolving of one of these bodies on the slide. These forms are highly refractive, so much so that the outer border has been described as a double outline, and interpreted as a capsule. Whether this apparent double outline represents an actual capsule, or only a thickening of the outer parts of the body, we do not feel quite certain. We have never been able to observe that this so-called double outline showed a coloring with haemoglobin, as described by Antolisei and Angelini.[119] The pigment granules are coarse, often in the form of rods collected about the centre in a clump, or not infrequently in a ring. Finally, we see large crescentic or ovoid bodies, averaging eight to nine micromillimetres in length; the red corpuscle in which they have developed is represented by but a small, faintly-colored attachment upon one side of the ovoid, or at the concavity of the crescent, while, in some instances, all trace of the corpuscle may be absent. At times one may observe actual changes from

the ovoid bodies into the crescentic forms, or the converse, beside the occasional picture of the revolving crescent before referred to. Often, in association with these crescentic and ovoid bodies, we may also see a number of somewhat smaller round bodies (Plate II, 34, 35, 38); indeed, at times, we may trace the change from a crescent or an ovoid form into one of these round elements. The round bodies do not as often show a "double outline," nor are they, as a rule, quite as refractive. In the crescents and the ovoid and round bodies, we see, occasionally, changes which show a certain analogy, as Antolisei and Angelini [119] have pointed out, to processes occurring in the large full-grown tertian forms:

(1). Sometimes, for example, one of these bodies may show one or more small protrusions from the surface, which may, indeed, be cut off from the rest of the body as small, clear, hyaline droplets (Plate II, 30, 36). This is the gemmation which, by some of the earlier observers, was supposed to be a reproductive process.

(2). Again, we may see the development of a large number of small vacuoles of different sizes; the parasites at the same time lose their sharp refraction, becoming pale and more indistinct (Plate II, 37); this process is clearly degenerative in nature.

(3). Lastly, whenever these round bodies occur, flagellate forms may be seen to develop (Plate II, 38–40). These flagellate bodies are distinctly smaller than those of the tertian parasite, being much more similar to the quartan forms. The pigment collects frequently in the shape of a ring in the centre of the organism, and assumes the same active movements that one sees in tertian fever, while the periphery of the body shows the same violent undulations which suggest so strongly that some body within the parasite is trying to escape; and just as in the tertian parasite, one or more active flagella eventually break forth. The same breaking off of the flagella, the same budding and fragmentation of the body, the same phenomena of phagocytosis, are noted here as in tertian infection.

The small hyaline and slightly pigmented forms disappear quite rapidly after the administration of quinine, though they are considerably more resistant than the similar forms of the tertian or quartan parasite. The crescentic and ovoid bodies, however, may remain for a very long period, notwithstanding large and continued doses of quinine. In cases where quinine is given during the first week of the disease,

the organisms disappear in the majority of cases without the occurrence of crescentic bodies, a fact which would tend to show that the formation of the ovoid and crescentic forms does not occur before the end of the first week. In the cases where we have found crescentic and ovoid bodies alone in the blood, fever has rarely been noted, the febrile paroxysm always being associated with, or followed by the presence of small hyaline and amoeboid bodies.

In our studies, then, which have been mainly conducted with fresh blood, we find a type of organism quite separate from that of ordinary tertian or quartan fever. The cycle of existence of this parasite begins with a small hyaline body which, when it has reached its full development, is rarely half the size of the red corpuscle. During its growth, marked changes (crenation, brassy color, retraction of haemoglobin) are often caused in the red corpuscles. The advanced segmenting forms are rarely seen in the blood current, though pre-segmenting bodies (bodies with central pigment) are not infrequently observed. The process of segmentation, and probably the greater part of development, goes on in the internal organs. We have been unable to trace a constant length of the cycle of development, and we have been unable further to separate two or more types of the parasite depending either upon the length of the cycle of development or upon any other morphological or biological differences. We believe that the length of the cycle varies greatly in different cases, lasting usually from twenty-four hours or even a little less, to forty-eight hours or more. After the infection is five days or a week old, certain of the organisms, instead of segmenting, pursue a further growth, developing into the hyaline, refractive, ovoid and crescentic bodies which show a particular resistance to quinine, having been considered by many to be encysted forms. Do these crescentic bodies represent forms with a longer cycle, giving rise to fevers with long intervals between the paroxysms, as Canalis,[104] Golgi,[118] Antolisei,[131] and others believe? We do not feel justified in making positive statements concerning this point. We have never observed segmentation of the crescentic, ovoid or round bodies, though the frequency of relapses in cases where they are found suggests the possibility of its occurrence. We have, on the other hand, seen processes of vacuolization and of gemmation, which we believe to be degenerative in nature.

We have met with nothing in our observations suggesting that the crescents are conjugate forms, as is believed by Mannaberg.[291]

Phagocytosis we have observed here, as in tertian and quartan fevers, particularly at the time of the paroxysm, though pigmented leucocytes are found occasionally at all stages of the cycle. The presence of the large mononuclear macrophages, described so well by Bastianelli,[246] we have found very rarely in the peripheral circulation. While mononuclear elements with pigment are not uncommon, we have never seen the act of phagocytosis performed under the microscope by a mononuclear leucocyte, while we have many times seen the engulfing of flagellate bodies by the polymorphonuclear neutrophiles.

V.—GENERAL ANALYSIS OF 544 CASES IN WHICH THE TYPE OF ORGANISM WAS CLEARLY DISTINGUISHED.

Of these 616 cases, in 542, not including the two relapses, the type of parasite was definitely differentiated. The following table shows the number of cases of each type observed in the hospital and out-patient department:

		Hosp.	Disp.	Total.
Infection with the tertian parasite.	Single tertian infection.....	57	93	150
	Double " "	116	72	188
Infection with the quartan parasite.	Single quartan infection.....	2	0	2
	Double " "	0	0	0
	Triple " "	3	0	3
Infection with the aestivo-autumnal parasite.....		104	84	188
Combined infection with aestivo-autumnal and tertian parasites....		9	2	11
		291	251	542

It is interesting to note the greater frequency with which single tertian infection was seen in the dispensary than in the hospital—93 cases occurring in the dispensary from a total of 251, and 57 in the hospital out of a total of 291. This is doubtless due largely to the fact that the cases of mild malarial infection are unwilling to enter the hospital, while the double tertian cases and the aestivo-autumnal infections, which are more severe, are more ready to enter the wards.

The tables below show the relation of the different types of malaria to the time of year:

		Jan.	Feb.	Mar.	Apr.	May.	June	July.	Aug.	Sept.	Oct.	Nov.	Dec.	Tot'l.
Tertian.	Single....	5	1	7	16	20	14	27	14	17	19	7	3	150
	Double...	2	5	8	9	12	13	23	27	30	43	10	6	188
	Total.....	7	6	15	25	32	27	50	41	47	62	17	9	338
Quartan.	Single....	0	0	0	0	0	0	0	0	0	0	1	1	2
	Double...	0	0	0	0	0	0	0	0	0	0	0	0	0
	Triple....	0	0	0	1	0	0	2	0	0	0	0	0	3
	Total.....	0	0	0	1	0	0	2	0	0	0	1	1	5
Aestivo-autum...		1	0	1	0	1	2	17	18	65	55	18	10	188
Combined Aestivo-aut. and Tertian.		0	1	1	0	0	1	2	0	0	5	0	1	11
Total.....		8	7	17	26	33	30	71	59	112	122	36	21	542

Thus in the first half-year there were:

Tertian infection.	Single	63
	Double	49
		112
Quartan infection.	Single	1
	Double	0
	Triple	0
		1
Aestivo-autumnal infection		5
Combined infections		3
Total		121

While in the second half-year there were:

Tertian infection.	Single	87
	Double	139
		226

Quartan infection.	Single	1
	Double	0
	Triple	3
		4
Aestivo-autumnal infection		183
Combined infections		8
Total		421

These tables show in an interesting manner how the severity of the type of infection increases as the summer and fall approaches; thus, in the first half-year we have more single than double tertian infections, while in the second half-year, when malarial fever assumes a more severe type, we have nearly twice as many cases of double tertian as of single tertian infection. The increase in severity of the malarial fevers becomes more evident when we observe the course of the aestivo-autumnal cases. While in the first half-year only 5 cases were noted, a little less than one twenty-fourth of the total number of cases observed, in the second half-year we see 183 cases, or nearly an half of all the cases which occurred.

Thus, it may be seen that with the earliest cases of malarial fever in the year, the mildest types of infection are met with,* the single tertian type predominating. As the season advances, and the months approach which are richest in malaria, the single tertian cases become less frequent and the double tertian infections more common, while at the height of the malarial season a majority of the cases are of the aestivo-autumnal, the most severe type in this climate. Marchiafava and Celli[144] have, in some of their writings, been inclined to believe that a patient suffering from one malarial infection may show the organisms and the fever characteristic of aestivo-autumnal malaria during the fall, and later, in the spring, without a new infection, simply as a relapse, show the regular types of fever, tertian or quartan, with their characteristic organisms. In a number of our cases, patients who had

*This is an old observation, dating back to Hippocrates and Sydenham. In fact, not only were the spring tertians known to be mild, but they were even thought to be beneficial. Thus a contemporary of Sydenham, Richard Morton, whose chapters on malaria (Pyretologie Opera Medica, 1696) are unequalled at that date, says (p. 51): "Quod *Febris Intermittens verna sit Remedium Regium;* h. e., saluteferum & certerorum morborum prophylacticum, &c."

suffered, for instance, with aestivo-autumnal malaria during the fall, have, in the following spring, had a characteristic tertian or double tertian infection, or the converse. In none of our cases, however, has it appeared to us that these were true relapses, all of them giving histories, and having been subjected to circumstances which would wholly justify the assumption that a second infection had occurred. Against this view, also, speaks the course of the infection in cases of aestivo-autumnal fever, which, having arisen in tropical climates, come to Baltimore in the spring months. This was the case in two of the five instances of aestivo-autumnal fever admitted in the first half-year. One of these cases originated in Jamaica, the other in Cuba. In neither instance did the organisms or the progress of the case differ in any way from the ordinary aestivo-autumnal infections, though they occurred at a time of year when the milder tertian infections formed the vast majority of all cases observed. Particularly striking is the history of one of the three cases of combined aestivo-autumnal and tertian infections. This man arrived in February with a fever which he had contracted in Cuba. His symptoms at the time of his arrival appeared due rather to the tertian organisms, which were preponderant, than to the aestivo-autumnal. Under quinine the fever disappeared, and the organisms were no more seen in the peripheral circulation. Seven or eight weeks later, in April, he had a relapse while still in the hospital where he had undergone an operation for the radical cure of hernia; but in this relapse only aestivo-autumnal forms—small hyaline amoeboid bodies, ovoid and crescentic forms—were seen. The less resistant tertian parasites had yielded to quinine, while the aestivo-autumnal forms persisted. Surely no better opportunity could have been offered for the change in the type of the parasite were this really possible.

While, in our experience, we have seen nothing which would justify us in positively denying the possibility of the change of an organism from one type into another according to the influences to which it is subjected, we have seen nothing whatever to suggest that this does occur, and we are decidedly inclined to believe that the tertian, quartan, and aestivo-autumnal parasites are permanently different varieties of closely allied sporozoa.

Relation of the Different Types of Infection to Race.

We have seen that the colored, as compared with the white race, presents a marked relative insusceptibility to malarial infection. Should we then expect to see, in the colored race, only the more severe types of malarial fever, or should we rather expect to find that infection once taking place in relatively unfavorable ground, the disease would pursue a milder course? Among the 27 cases of malarial infection in the colored race, where the type was clearly differentiated, there were:

Single tertian infections	9
Double tertian infections	7
Aestivo-autumnal infections	9
Combined infections	2

That is, 59.2 per cent. of the cases occurring in colored patients were tertian infections, and 33.3 per cent. aestivo-autumnal; while among the white patients, 62.5 per cent. were tertian, and 34.7 per cent. aestivo-autumnal infections. There would then appear to be no essential difference between the susceptibility of the white and the colored patient to the various types of malarial fever.

On further analysis of these cases, one point is, however, rather striking. While, among the white patients, only 43.7 per cent. of the tertian infections were single,—56.3 per cent. being double—in the colored we find 56.2 per cent. of single tertian infections, and 43.8 per cent. of double. The explanation which would naturally suggest itself is that the negro, having a certain relative immunity from malarial infection, is more resistant against the organism when the infection has once taken place; the process is thus much more likely to remain a single infection than to increase in intensity and develop, as it does so frequently in the white race, into a double infection.

VI.—ANALYSIS OF THE TYPES OF FEVER ASSOCIATED WITH THE DIFFERENT TYPES OF ORGANISMS.

In considering the 544 * cases in which the types of fever were definitely made out, we shall take up separately those cases occurring in the hospital and those cases occurring in the dispensary, noting finally what conclusions may be drawn from the combination of the cases from both sources. The studies of the ward cases were much more satisfactory. In certain ways, however, the addition of the dispensary cases makes the note more complete.

Tertian Infections.

There were 339 cases in which typical tertian organisms were observed. Of these, there were:

Single infections	151
Double infections	188

(1). *Single Tertian Infections.*

Of the 151 single tertian infections, 58 occurred in the hospital and 93 in the dispensary.

Cases of Single Tertian Infection Observed in the Hospital.—Of the 58 cases showing typical tertian organisms, one was a relapse of a case previously treated.

Of these 58 cases, 52 showed, either outside or within the hospital, typical tertian *paroxysms*. Of the remaining 6 cases, one gave a history of having taken a few doses of quinine whenever a paroxysm appeared, with the resulting occurrence of a chill about every ten or eleven days. Treatment was begun in this case immediately, so that it could not be studied further.

One case complained of chills at intervals of about seven or eight days.

One case gave a history of having had tertian and quotidian chills, which became irregular after the spasmodic use of quinine. There was but one paroxysm in the hospital.

* This includes the two relapses above referred to.

One case had a single chill the day before entrance, the fever disappearing spontaneously after admission.

One case gave a vague history of occasional chills, headache and vomiting for two weeks, but showed no further fever or symptoms after the paroxysm during which he was admitted, excepting a slight rise in temperature on the fourth day.

One case, where there had been daily paroxysms before entrance, showed no symptoms after the chill during which he entered. This case was probably one of double tertian infection which was dying out; it was classified among the tertian cases because but one set of organisms was seen on entrance.

Of the 52 cases showing typical tertian paroxysms, five had had quotidian attacks sometime before entrance.

Of these 58 cases of tertian infection, 11 showed a *spontaneous disappearance* of the fever after admission. In 3 of the 47 remaining cases, the fever disappeared after one or more paroxysms without the administration of quinine.

The *average duration* of the paroxysms from the beginning to the end of the rise in temperature (above 99°) was between eleven and twelve hours (11.8).

Out of 24 cases with multiple paroxysms, ten showed, perhaps, a slight tendency toward anticipation, three toward retardation; eleven showed paroxysms occurring at the same hour.

Of these 58 cases of tertian fever, 55 cases had had, in or outside of the hospital, "*shaking*" *chills*. The other 3 had chilly sensations.

Organisms.—In all of these cases typical tertian organisms were found. In 15 of the cases segmenting bodies were noted during the paroxysm. In 5 cases flagellate bodies were noted, in three instances during the paroxysm, in the fourth a few hours before the paroxysm, and in the fifth case during apyrexia, eleven hours before the paroxysm.

Cases in the Out-patient Department.—There were 93 cases in the out-patient department in which typical tertian organisms were found. Of these, 75 gave a history of having had tertian *paroxysms*. Of the 18 who gave no history of tertian paroxysms, 3 showed their first chill on the day of consultation or upon the day before; in 3 the history was not noted; in 2 the first chill had been followed by quinine, the symptoms afterward being indefinite; in 2 there were vague general symptoms—headache, pains in the back and limbs, and other

symptoms characteristic of any acute infectious process; in one case the only complaint was of haemoptysis; in the remaining 7 cases chills and chilly sensations occurred, but the patients were unable to give definite statements as to the type.

In these 93 cases, there were noted:

Chills in	79
Chilly sensations in	8
"Paroxysms" in	2
Haemoptysis in	1
Vague febrile symptoms in	1
No note in	2

In the 75 cases giving a history of having had sharply-defined tertian paroxysms, four had had, at one time or another, quotidian paroxysms.

Organisms.—In five of these cases segmenting bodies were seen during the paroxysm; in one a flagellate body was also noted.

Summary of the Cases of Tertian Fever in the Hospital and Dispensary combined.—Thus in the hospital and dispensary together there were 151 cases showing single tertian infection; one of these was a relapse. Of these 151 cases, 127 had tertian paroxysms. Of the 127 which had had tertian paroxysms, 9 had had at some time quotidian paroxysms.

In the 151 cases, there were noted:

Chills in	134
Chilly sensations in	11
"Paroxysms" in	2
Vague febrile symptoms in	1
Haemoptysis in	1
No note in	2
	151

The *average duration* of the paroxysms was between eleven and twelve hours (11.8).

Organisms.—Segmenting bodies were noted in 20 cases, always at the time of the paroxysm; flagellate bodies were noted in 6 cases,—in four instances during the paroxysm, in one shortly before it, in one eleven hours before it.

Cases.

Case 4934 is an illustration of typical tertian fever with regular paroxysms.

Man, aged 24, English, a laborer; admitted March 25th, 1892, complaining of headache and fever.

Family and personal history negative; has been living in a very malarious district. He has had chills and fever off and on for six months; gives no clear history as to type; says that he would go to bed for several days at the beginning of his attack; would then get up, and in about two weeks would have another attack. His last paroxysm occurred the day before entry. Physical examination negative, barring a large, palpable spleen, the border reaching nearly to the median line. The *blood* on the day of entry showed a large number of half-grown tertian organisms. The chart shows three typical tertian paroxysms, with a remarkable regularity as to the degree of fever, and the time of onset.

The following case (10089) is an interesting example of the so-called fever with long intervals, which, as has been shown, may depend upon the presence of any of the three main varieties of parasites.

The patient, a man aged 30, German, was admitted to the hospital on June 14th, 1894, complaining of headache and chilly sensations. Four years ago he had two chills a week apart, which were immediately stopped on the beginning of treatment. Four weeks before entry he had a shaking chill, followed by fever and sweating. A week later he had a second attack, and a week after that a third; yesterday a fourth.

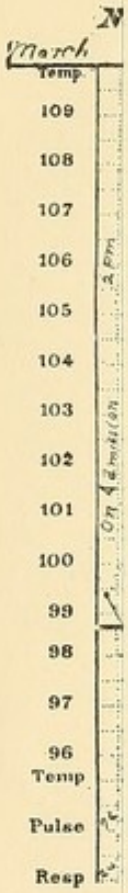
Examination of the *blood* yesterday in the dispensary, while the patient was in the sweating stage, showed two or three large, extra-cellular pigmented organisms, characteristically tertian in type, with the pigment in active motion. On entrance to the hospital, the examination showed a well-nourished man, complexion sallow, herpes about nose and lips, spleen readily palpable. Sonorous and sibilant râles heard occasionally on inspiration. Examinations of the blood in the hospital were negative. The temperature remained normal until the 18th, with the exception of a rise to 99.4° on the 16th.

On the 18th, at 11.30 a. m, the patient had a chill, exactly eight days after the last. The *blood* during the chill at 11.30 a. m. showed one hyaline, intra-cellular parasite in active motion; two large, extra-cellular, full-grown bodies, with actively moving pigment.

19–6–94. The *blood* showed a small number of half-grown intra-cellular pigmented parasites of the tertian type.

The patient insisted upon leaving the hospital, and was discharged with a prescription for quinine.

This is clearly an instance of tertian infection, where, with each paroxysm, the greater part of the new group of parasites was destroyed, the patient passing, as it were, through a fresh incubation period of seven or eight days between each attack.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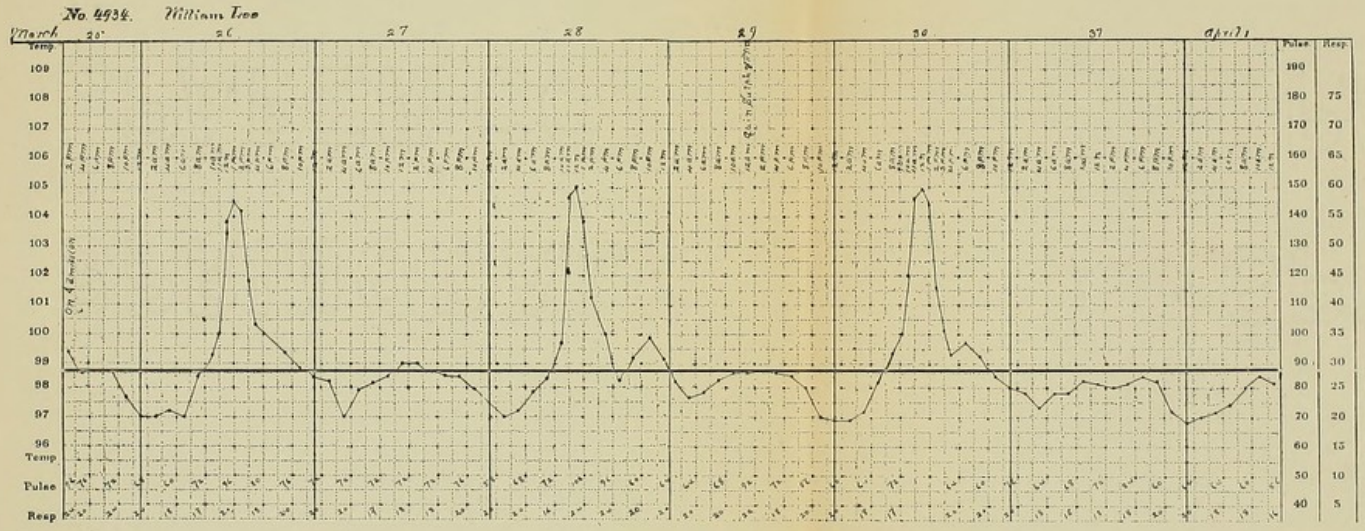
No. 4934. William Tree
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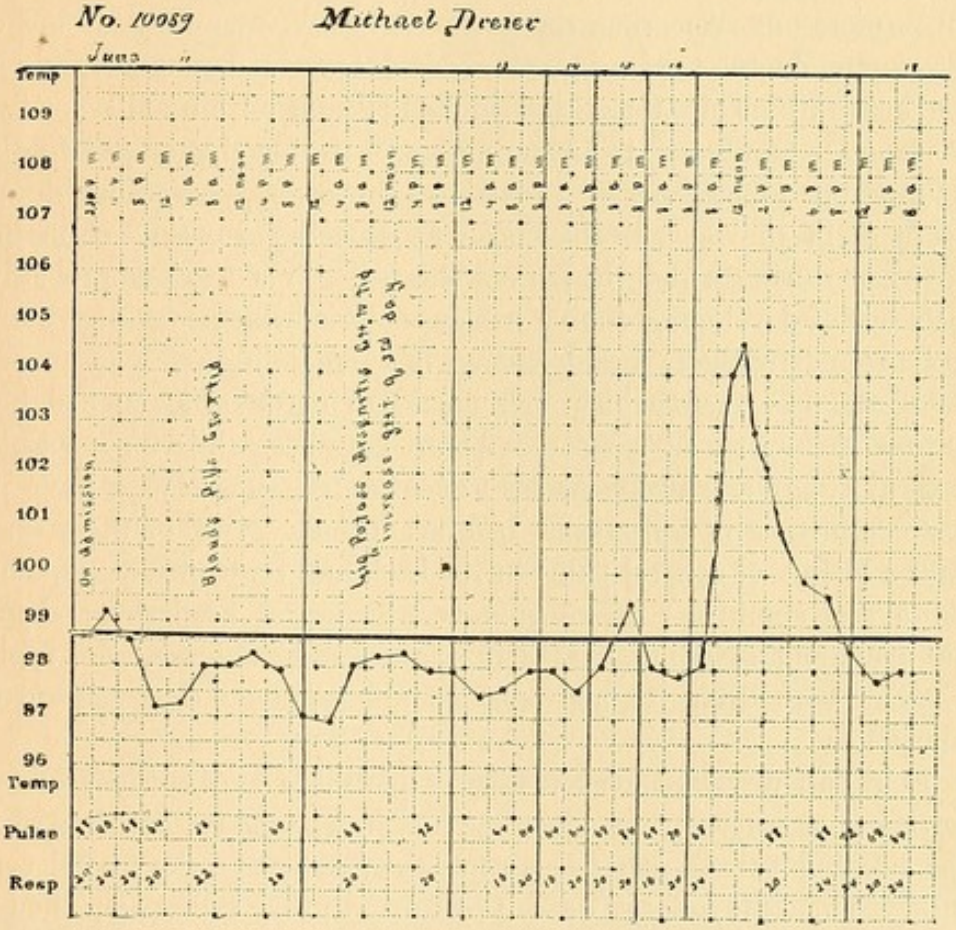
On Admission
Discharged

The examination of the blood on the day of discharge makes it probable that in this attack there would have been a paroxysm on the following day, a considerable number of half-grown bodies having been found.



(2). *Double Tertian Infections.*

There were 188 cases of double tertian infection. Of these, 116 occurred in the hospital, and 72 in the out-patient department.

Cases of Double Tertian Fever occurring in the Hospital.—116 cases in the hospital showed typical double tertian infection. Of these, 114 showed characteristic quotidian *paroxysms*, either in the house or outside. The two which did not have quotidian paroxysms, had tertian fever. The first of these cases was a man 28 years of age, who gave a vague history of headache, thirst, and general debility for

five days. This patient showed a slight paroxysm on the day of admission. On the following day the temperature varied between 97.1° and 100.7°. On the third day there was another slight paroxysm, the fever disappearing spontaneously after this. The blood showed on entrance two distinct sets of parasites, one group being much more numerous than the other. The case was probably one of developing double tertian infection, which recovered spontaneously in the hospital. The other case had had regular tertian chills for two weeks. On admission, the examination of the blood showed two distinct groups of organisms. There was, however, spontaneous disappearance of the fever in the house, no distinct paroxysms occurring after that during which the patient entered. This case was probably, also, one of developing double tertian malaria, which was interrupted in its course by the favorable change of surroundings.

Of the 114 cases which had quotidian paroxysms, 20 had had tertian paroxysms at some time before entrance, while 9 gave a history of irregular paroxysms before entrance. Two cases gave no distinct history of paroxysms before entrance. One of these cases gave a history of general pains in the back and limbs, weakness, diarrhoea, and vomiting; the other gave a history of headache, abdominal pain, and diarrhoea. One of these was a foreigner, who spoke English with difficulty, and was not able to give a clear account of himself.

Four patients, who gave a history of quotidian fever outside, showed tertian fever after entrance into the hospital. One patient showed in the hospital two tertian paroxysms, the first severe, the second very mild. After this quinine was given, and recovery followed. Though the paroxysms in the hospital were tertian in character, two sets of organisms were found on entrance, and the case was, doubtless, either a double tertian infection which was dying out, or, what is not improbable, the patient's history of daily chills was incorrect, as he spoke but little English, and we were dealing rather with a beginning double tertian infection. The second case was one of a dying-out infection, only a few half-grown organisms being found on the day of entrance. No paroxysm was observed on the following day, and but a feeble one on the third.

One case had an abortive paroxysm on the day of entry and tertian attacks later, the second group of organisms disappearing.

One case was changed to a tertian infection experimentally (see page 113).

Of these 116 cases, three showed marked irregularity in the paroxysms. One case showed daily abortive paroxysms, with a tendency toward continuity. The irregular temperature followed several doses of quinine. One case was complicated with an abscess of the thigh, which probably accounted for the slight irregularity. One case was that of a child ten months of age, whose chart showed considerable irregularity in the temperature. The examination of the blood in this case showed organisms in nearly all stages of development, and it is probable that the irregularity of the temperature may be accounted for by the lack of the ordinary arrangement in groups.

Two cases showed a more or less steady elevation of temperature with daily exacerbations. The first showed rather irregular daily paroxysms, the temperature remaining elevated on one occasion for thirty-six hours. This was one of the earlier cases, and as the notes concerning the organisms are not as satisfactory as could have been wished, one cannot state whether in this case the presence of organisms in different stages of development may have had any relation to the irregularity of the symptoms.

The second case showed at first a more or less continuous temperature, with daily exacerbations; it was mistaken for a case of typhoid fever. After five days' treatment with cold baths, the temperature became quite regularly intermittent. The case is of enough interest to cite more particularly.

W. Y., aged 29, German, was admitted to the hospital on the 8th of August, 1892, complaining of loss of appetite, general malaise, and fever. His family and personal history bore no relation to his complaint at that time, which began four days before admission with loss of appetite and fever. He had had no chills, no abdominal pain, no nose bleed. He complained of shortness of breath, some cough, occasional nausea, no vomiting. There was constipation at first; later diarrhoea. The examination of the blood, which, unfortunately, was very superficial, showed no malarial organisms.

Physical examination. The patient was a large, well-nourished man; thorax and abdomen were negative on examination, except for a palpable spleen. The *urine* showed a trace of albumen; no casts seen; diazo reaction absent. Between the 8th and 10th of August the temperature ranged between 99° and 104.5°, being continually elevated. The case was believed to be one of typhoid fever, and cold baths were ordered. After the 10th of August, the patient had an irregularly intermittent temperature, ranging between 97.6° and 105.8°. He was given, in all, ten tub baths. On the 14th, by which time, as the chart will show, the temperature had become more

regular in character, the examination of the *blood* showed typical full- and half-grown, intra-cellular bodies, a number of hyaline, amoeboid, intra-cellular bodies, and one segmenting body. The examination was made during the paroxysm. Quinine, five grains every four hours, was begun at 4 p. m. on the 15th, after which date there were no further paroxysms.

The case is of considerable interest on account of the rarity of irregular and remittent fevers in association with tertian infections. The probability is, that we were dealing here with an infection with several groups of the parasite in different stages of development, though it may be that the regular course of the fever was somewhat interrupted by the treatment with cold baths. It is of interest, that at the time when the organisms were discovered, two groups only were found. At this time, however, it will be noted that the temperature, which had previously been irregular, had assumed a more regular course. On the whole, the consideration of the case, and the inspection of the chart, would suggest that the probable course of events had been as follows; primarily, severe infection with multiple groups of the tertian organism, modification of the infection by rest in bed, and the treatment with cold baths, until finally, at the time when a thorough examination of the blood was first made, only the two stronger groups of organisms remained. It will be noted, by consulting the chart, that the paroxysms on the 10th, 12th, and 14th occurred in the morning; while those on the 11th, 13th, and 15th occurred in the afternoon.

In 3 cases there was no fever in the hospital.

In 13 cases with fever on entrance, there was a *spontaneous disappearance* of the fever in the hospital.

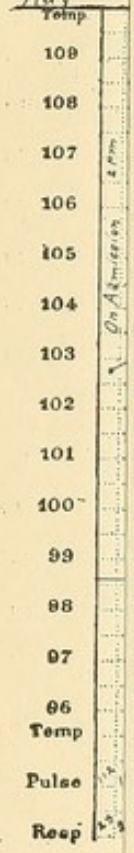
In two of these cases apparent spontaneous recovery was followed later by a relapse, the fever recurring in the first in six, in the latter in three days.

In the 116 cases, there were noted:

Chills in	107
Chilly sensations in	4
Vague general symptoms in	5
	116

One of the instances in which no chill was noted was a child ten months of age.

Aug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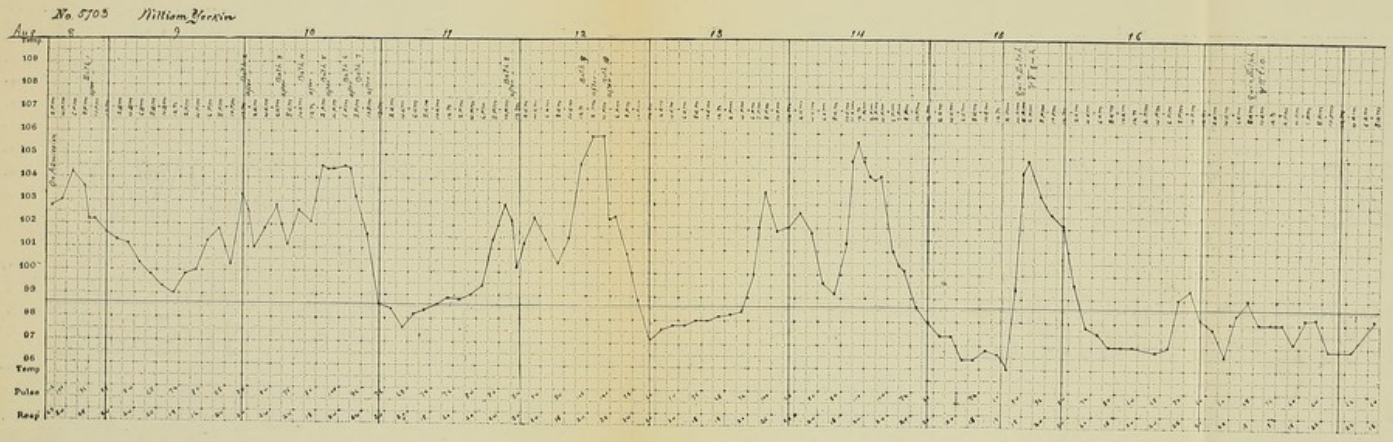
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The *average duration of the paroxysms* was about eleven hours (10.7).

Organisms.—In all these instances characteristic tertian organisms were seen, arranged distinctly in two groups. In 10 cases flagellate bodies were noted; in 7 instances during the paroxysm; in 2 just before the paroxysm; in 1 between paroxysms when the temperature was normal. In none of these instances had the patients had quinine.

Segmenting bodies were noticed in 42 cases, always during the paroxysm.

Cases of Double Tertian Infection in the Dispensary.—There were 72 cases of double tertian infection treated at the dispensary. Of these, 58 gave a history of having had quotidian *paroxysms*; 8 gave a history of tertian paroxysms, all showing, however, a double set of organisms; 3 cases gave a history of having had tertian paroxysms becoming irregular after quinine; 2 gave a vague uncertain history of quotidian fever; one case had had but one chill, the day before entry.

Of the 58 cases having had characteristic quotidian paroxysms, 14 had had tertian paroxysms at one time or another. Of the cases giving vague uncertain histories, one complained simply of anorexia and vague general pains. The other was a Slav, who was unable to make himself understood, further than that he complained of chills.

In the 72 cases, there was a history of:

Chills in	65	instances.
Chilly sensations in	3	"
Fever only in	1	"
Headache in	1	"
"Paroxysms" in	1	"
No note in	1	"
	72	"

In 5 of the 72 cases, segmenting organisms were noted; in 2, flagellate bodies were seen, in each instance at the time of the paroxysm.

Summary of the Cases of Double Tertian Fever in the Hospital and Dispensary.—There were 188 cases of double tertian infection seen in both hospital and dispensary. Of these, 172 gave a history of having had quotidian *paroxysms*. Thirty-six had had, at one time or another, tertian paroxysms. There were:

Chills in	172	cases.
Chilly sensations in	7	"
No chills in	7	"
"Paroxysms" in	1	"
No note in	1	"
	188	"

Organisms.—Segmenting bodies were noted in 47 instances, always during the paroxysm. Flagellate bodies were noted in 12 instances, in all during or just before the paroxysm, with one exception, where the temperature was normal, between paroxysms.

Cases.

A good example of the double tertian infection is the following:

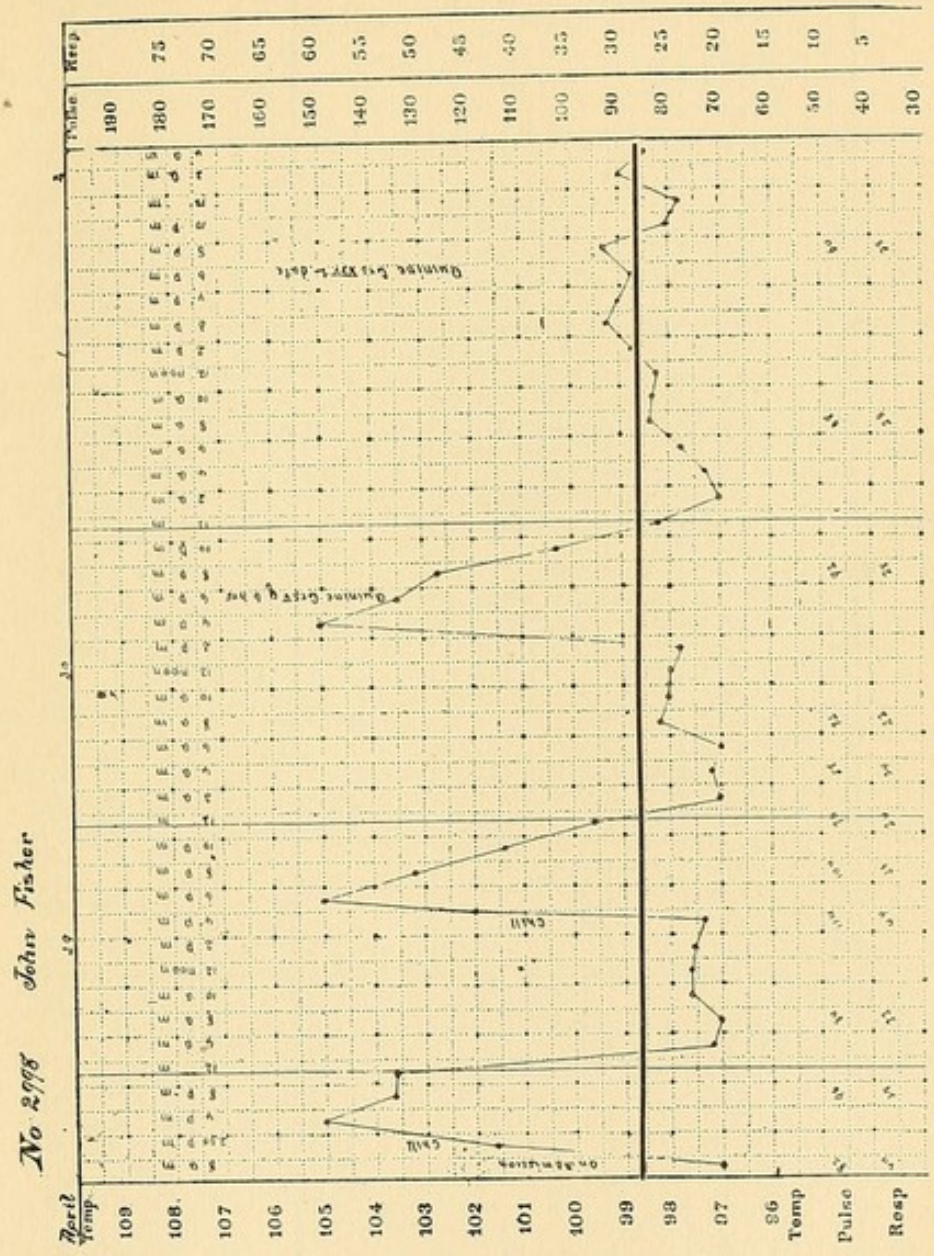
Case 2998.—J. F., aged 37, German, admitted July 28th, 1891. Has had frequent attacks of malarial fever during the last seven years in Texas; has been in Baltimore seven weeks. About a week ago he began to have chills in the afternoon, which have occurred daily. Temperature on admission 97°. *Physical examination* negative, excepting for the palpable spleen. The *blood* showed typical intra-cellular tertian organisms, full and half grown, and extra-cellular fragmenting forms. The chart shows three characteristic paroxysms.

It is interesting to note that the paroxysms on the 28th and 30th began at about 2 p. m., while that on the 29th occurred between 4 and 5 p. m. This point is one of considerable interest, as it serves, sometimes, to demonstrate very clearly the fact that the daily chills depend upon two different sets of organisms. Sometimes it is possible to observe, through a considerable length of time, the regular difference between the time of onset of chills following one another on alternate days, those on the first and third day occurring at one time, while those on the second and fourth occur at another.

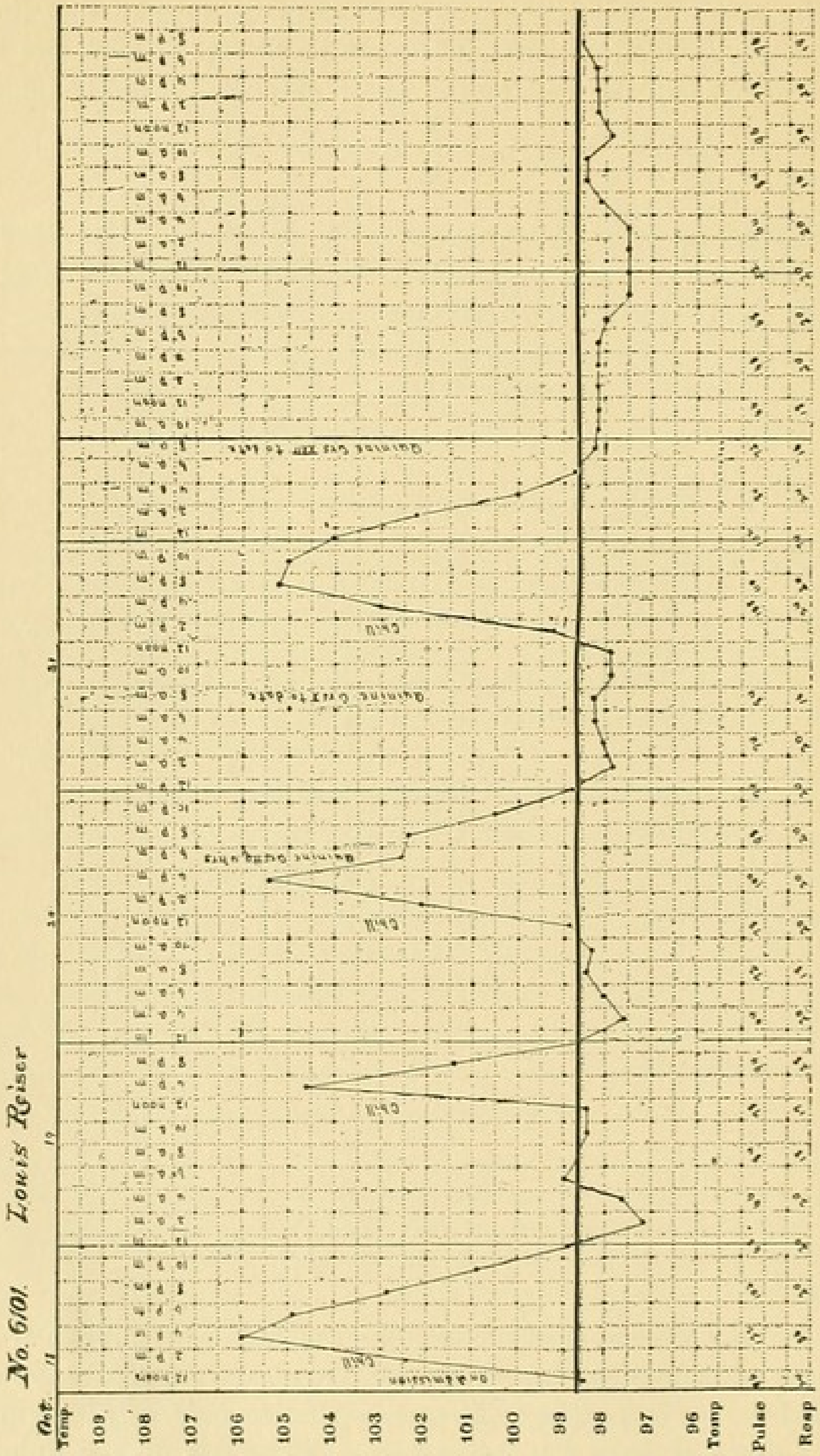
Case 6101.—L. R., single, aged 16, native of the United States, admitted October 18th, 1892. The present is his first attack of malarial fever. It began six days ago with creeping chills. Yesterday he had a severe shaking chill. The spleen was readily palpable. The *blood* showed two sets of tertian organisms. The chart in this case shows a regular quotidian intermittent fever, with paroxysms occurring at almost exactly the same hour daily.

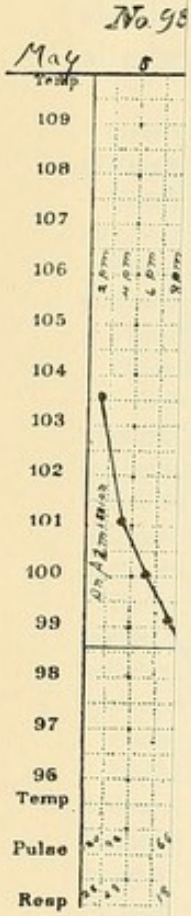
The fact that these cases depend on the action of two groups of tertian parasites is demonstrated not only by the examination of the organisms, and by the fact that one may trace in the temperature curve

the similarity of the chills on alternate days one with another (hour of onset, severity, duration); it is often possible to demonstrate this point with great clearness by the use of quinine. Golgi has shown



that the parasites are most successfully combated with quinine at the time of segmentation, before the new group of young parasites has entered the red corpuscles. After segmentation, only very large doses of quinine will destroy the organisms. Thus, one dose of quinine,


No. 6/01.
Louis Reiser
Oct.
Temp.
109
108
107
106
105
104
103
102
101
100
99
98
97
96
Temp
Pulse
Resp
Chill


No. 98
May 6
Temp
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108
107
106
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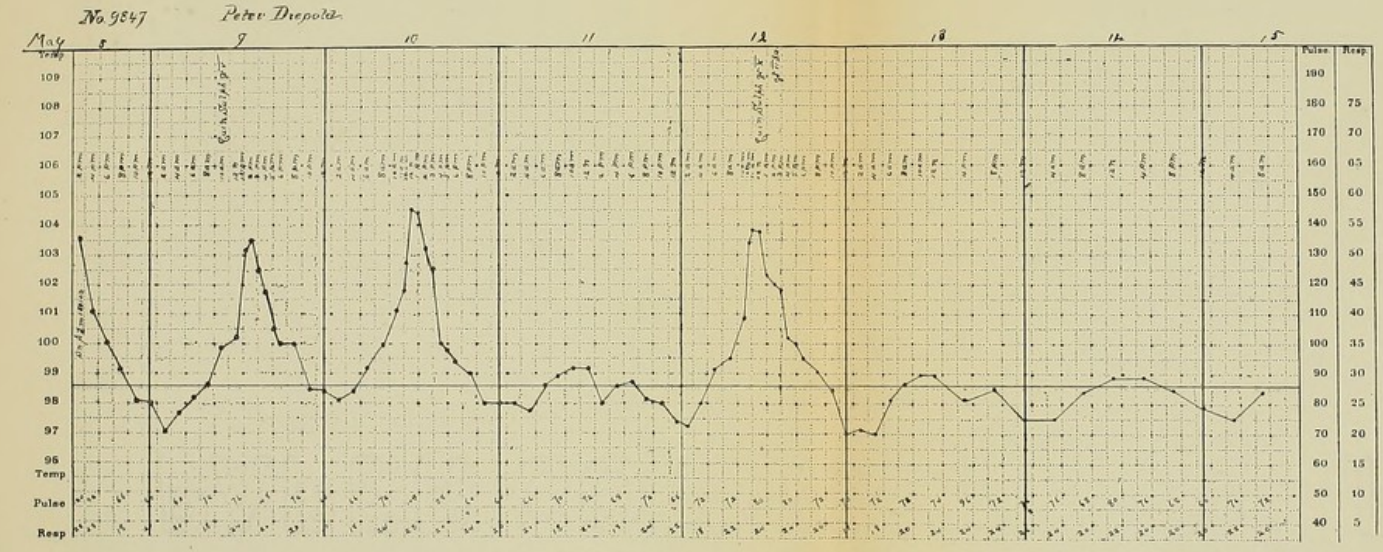
97
96
Temp
Pulse
Resp


No. 9847
Peter Diepola
May
8
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10
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12
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14
15
Pulse
Resp.
109
108
107
106
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104
103
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101
100
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97
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Temp
Pulse
Resp
190
180
170
160
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5

given just before or early in the paroxysm, will, at times, almost destroy an entire group of organisms which has reached its perfect development and has begun to segment, while a half-grown set of parasites will continue in its course of development. In this way, then, we should be able to change a quotidian into a tertian malarial fever by the administration of quinine in a single moderate dose before or early in the paroxysm. This is the fact, as may be shown very clearly by the following case. This case was modified experimentally before the ward class.

CASE 9047.—P. D., male, aged 36, German, laborer, admitted May 8th, 1894, complaining of cough, fever, thoracic pains and weakness.

Family and personal history bear no relation to his present trouble, excepting that two years ago he had an attack of chills and fever of unknown type.

Present illness began a week before entry. Chills on the third, on the fifth, sixth and seventh, and also at noon on the day of entry.

Physical examination was negative, excepting for the palpable spleen.

Urine normal. Temperature 103.6° on entry.

8–5–94. *Blood* at 4.15 p. m. showed a number of nearly full-grown typical tertian organisms, a few amoeboid, intra-cellular, hyaline forms, two fragmented extra-cellular bodies, pigmented leucocytes.

9–5–94. A chill being expected, five grains of quinine were given at 11.15 a. m.; chill at 12. The blood at 9 a. m. showed a few large, full-grown, extra-cellular bodies and a number of half-grown forms.

10–5–94. Chill again about eleven o'clock. *Blood* at twelve showed a number of typical segmenting parasites, a few large, full grown forms, several amoeboid, intracellular, hyaline bodies, one large, fragmenting, extra cellular body, pigmented leucocytes, *no half-grown forms.*

11–5–94. No paroxysm.

12–5–94. Paroxysm about ten o'clock. *Blood* at eleven showed a few segmenting bodies, several full-grown and large fragmenting, extra-cellular forms, no half-grown forms. Quinine gr. X (0.65) at the height of the paroxysm; gr. II (0.13) three times a day afterwards. The organisms disappeared almost immediately afterwards; no further fever.

Surely no better proof than this case could be asked to demonstrate the dependence of these quotidian paroxysms upon a double tertian infection.

The same point is sometimes brought strongly to one's notice in the case of an individual who enters the hospital with one strong and one weaker set of organisms. Placing the patient in bed and upon a good diet is often sufficient to bring about the spontaneous disappearance of one group, so that the quotidian paroxysms are succeeded by tertian fever.

Case 4889.—C. M., single, aged 34, Pole, admitted March 16th, 1892. Second attack, possibly a relapse of an attack for which he was treated by methylene blue in the hospital. Daily chills for five days.

Patient had paroxysm in the dispensary. The *blood* showed characteristic segmenting bodies of the tertian type, with fifteen or more segments; large, transparent forms, with actively-moving pigment granules; a *very large number of fragmenting, extra-cellular, pigmented forms;* a few half-grown, intra-cellular forms; *no fresh hyaline bodies.*

At 4 p. m., a number of half and nearly full-grown intra-cellular, pigmented forms, fragmenting extra-cellular bodies, *no hyaline bodies.*

17–3–92. Paroxysm at noon.

Blood at 3.45 p. m.; occasional large, full-grown, tertian bodies, a certain number of extra-cellular, fragmented organisms, small, actively amoeboid, hyaline forms, only an occasional half-grown organism.

18–3–92. Temperature normal. An occasional fully-developed, intra-cellular parasite, numerous extra-cellular, fragmenting bodies, no hyaline bodies, a number of half-grown forms.

Paroxysms on the 19th, 21st, 23rd, the *blood* showing characteristic single tertian infection. At 8 p. m. on the 22nd, and 8 a. m. on the 23rd, eight grains of quinine were given, having no influence whatever upon the paroxysm of the 23rd. After this, quinine was given regularly without further fever, the organisms rapidly disappearing.

This case shows, in an interesting manner, the association of large numbers of extra-cellular, fragmenting bodies with the spontaneous disappearance of one group of organisms. It also demonstrates clearly the inefficacy of moderate doses of quinine in preventing a paroxysm, if given when the organisms have already entered into the red corpuscles; the paroxysm on the 23rd, it will be seen, occurred just as if nothing had been done.

Quartan Infections.

There were five cases of quartan infection, all occurring in the hospital. Of these there were:

(1).	Single quartan infection	2
(2).	Double " "	0
(3).	Triple " "	3
		5

(1). *Single Quartan Infections.*—Of the two cases of single quartan infection, both showed characteristic quartan paroxysms. The paroxysms lasted between 10 and 11 hours (10.6). In both instances there were *chills.*

March

Temp

109

108

107

106

105

104

103

102

101

100

99

98

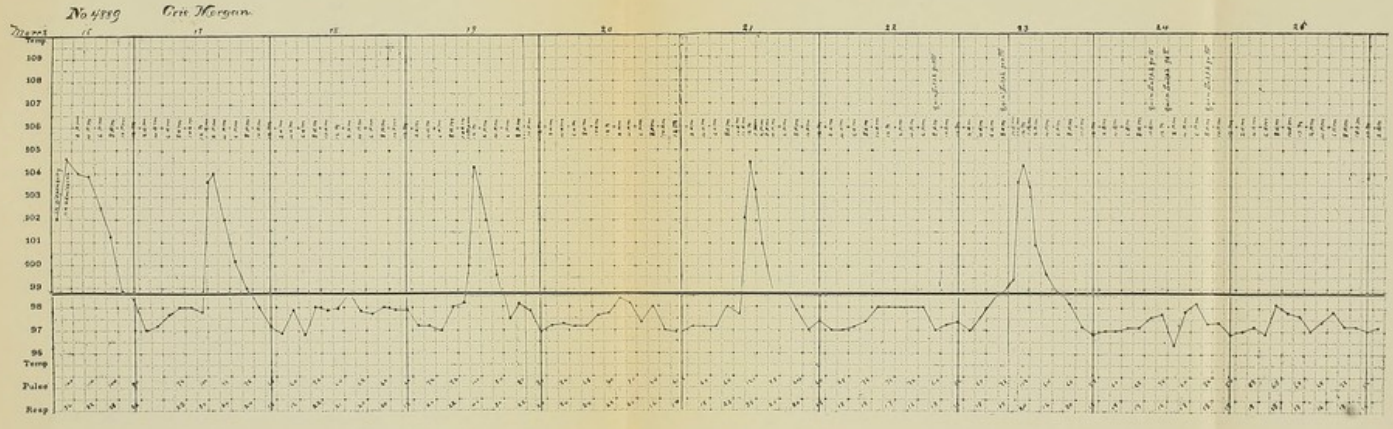
97

96

Temp

Pulse

Resp


No 4589
Orie Morgan
March
15
17
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Temp
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Pulse
Resp

Organisms.—The organisms in both instances were of the characteristic quartan type described by Golgi. Segmenting bodies were noted in one case; in the other, the examination of the blood was imperfectly made. Flagellate bodies were not seen.

(2). *Double Quartan Infections.*—There were no cases of double quartan infection noted.

(3). *Triple Quartan Infections.*—There were three cases of triple quartan infection admitted to the hospital. Of these, the types of fever were as follows:

Abortive quotidian elevations of temperature	1
Slight quartan paroxysms	1
One paroxysm on day of entry, afterwards normal	1
	3

Chills occurred in all these instances.

The *duration of the paroxysms* averaged about ten hours.

Organisms.—All of the cases showed three groups of characteristic quartan organisms. Segmenting organisms were seen in all cases during the several hours preceding the paroxysms; in several instances they were found as much as eight hours before the paroxysms.

In a number of instances where there were but few parasites, segmenting bodies were seen on days when no paroxysm occurred.

In two cases, flagellate bodies were seen.

Cases of Quartan Fever Occurring in the Hospital.

CASE 1.—L. G., male, sixteen years of age, admitted to hospital November 29th, 1890.

Family history good. Has always been in good health, excepting for an attack of tertian ague in July, 1889. For two weeks he had chills every other day; then a period of rest would follow, lasting two or three weeks. This lasted until October, 1889. After Christmas he had chills off and on until July, 1890. The day before entry he had a chill lasting about half an hour, followed by fever and sweating. Throughout the last year he has taken quinine in broken doses, omitting treatment usually as soon as the chills disappeared. The examination of the *blood* showed "a few intra-cellular organisms, no crescents or flagellate bodies."

The physical examination was negative, excepting for a greatly enlarged spleen. The urine was dark yellow, clear, acid, 1028, no albumen, no casts, no diazo reaction.

At 8 p. m. on the 29th the temperature was 100.5°.

30–11–90. Temperature practically normal throughout the day.

1–12–90. Paroxysm in the afternoon, temperature reaching 104.2° at 4 p. m.

2–12–90. Temperature normal.

3–12–90. Temperature normal.

4–12–90. Chill in the afternoon.

A chill occurred also on the afternoon of the 7th, and on the 10th, the temperature being perfectly normal between.

On the 11th, treatment with one grain of quinine, three times a day, was begun, the temperature remaining quite normal thereafter until the 29th of December, when the patient was discharged, the examination of the blood being negative. The organisms throughout showed rather coarse pigment. On the day of the chill, segmenting bodies were always observed; these bodies were very numerous during the morning hours, from three to six hours before the chill. They were most beautifully symmetrical rosettes, showing, in all instances where the leaflets were counted, from six to eight segments.

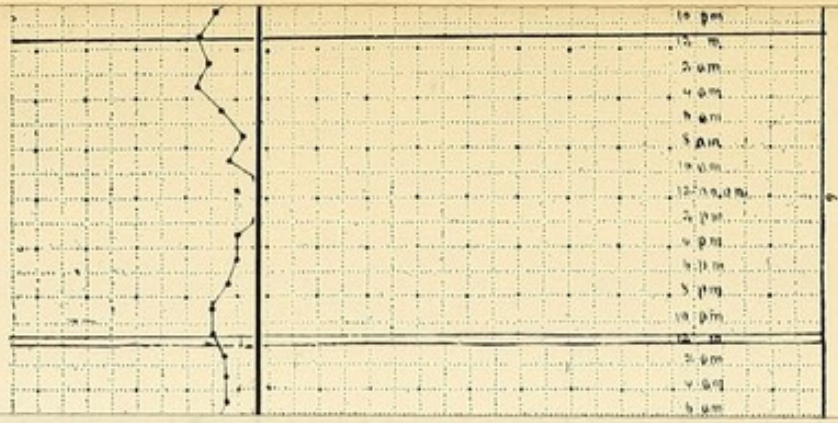
Case 2 (4368).—Male, aged 52, German. The family history was negative; personal history good. Present illness began on the 8th of December, when he had a severe chill, lasting for about an hour, followed by fever and sweating; none on the two following days. The physical examination was negative, excepting for the palpable spleen; the urine was normal. The *blood* showed fairly numerous rounded and ovoid, coarsely pigmented, intra-cellular bodies, which did not quite fill the corpuscle. The markedly greater refraction and the sharper outline of the body, as compared to the ordinary tertian forms, were noted. The amoeboid movements were very slight, and the pigment was almost motionless; in some bodies no motion could be made out. The pigment granules appeared coarser than those in the ordinary tertian form of the parasite, and of a slightly different color. As the chart shows, the patient had two paroxysms, four days apart. The examination of the blood was, however, not carefully made at the time of the paroxysms, and segmenting bodies were not noted. The fully-developed organisms, however, were not as large as those in ordinary tertian fever. On the 15th of December methylene blue, 0.1 four times a day, was ordered. No organisms were seen after the 18th. There were no further attacks of fever. The patient died of an attack of influenza, with extensive broncho-pneumonia, on the 9th of January.

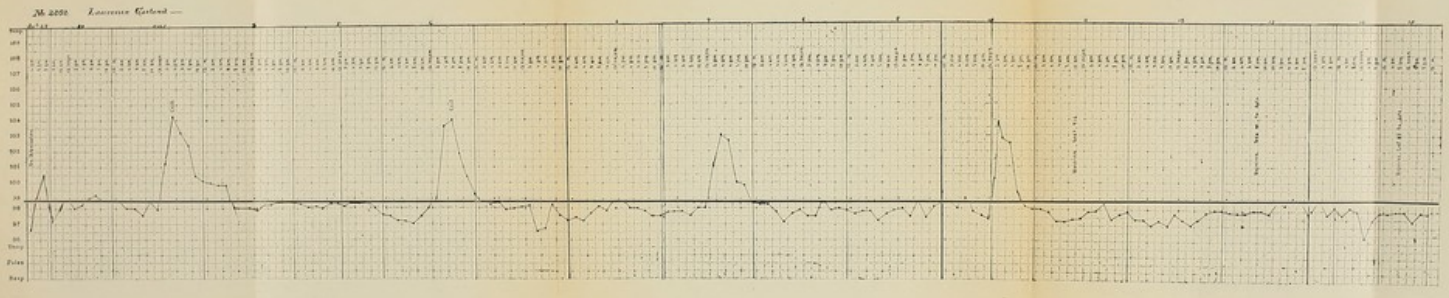
Case 3 (9773).—J. S., single, aged 10, Pole, admitted April 30th, 1894. She speaks but little English, and the history is not satisfactory. Chills and fever last fall; also two months ago. For two or three weeks chills at uncertain intervals.

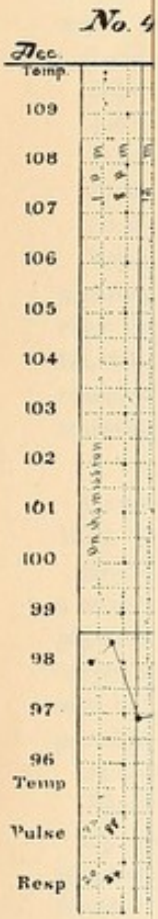
On entry, 8 p. m., the *blood* showed one half-grown intra-cellular body, with a small amount of very dark pigment which was rather larger than that seen in tertian parasites, and very slightly motile, while the body was round and scarcely at all amoeboid; several fragmented, extra-cellular parasites.

1–5–94. Physical examination negative, excepting for the palpable spleen.

Blood, 9 a. m. A few organisms seen this morning, nearly filling up the body of the corpuscles. These corpuscles are not expanded, as one ordinarily sees in tertian infection; on the other hand, they appear to be rather smaller than the others about them, as if contracted about the body. The pigment is rather dark and coarse. The movements of the pigment granules are slow, while the surrounding protoplasm is quite refractive. One form, which was slightly elliptical in shape, a little smaller than an ordinary red corpuscle, with almost non-motile, black pigment, showed a






No. 4
Dec.
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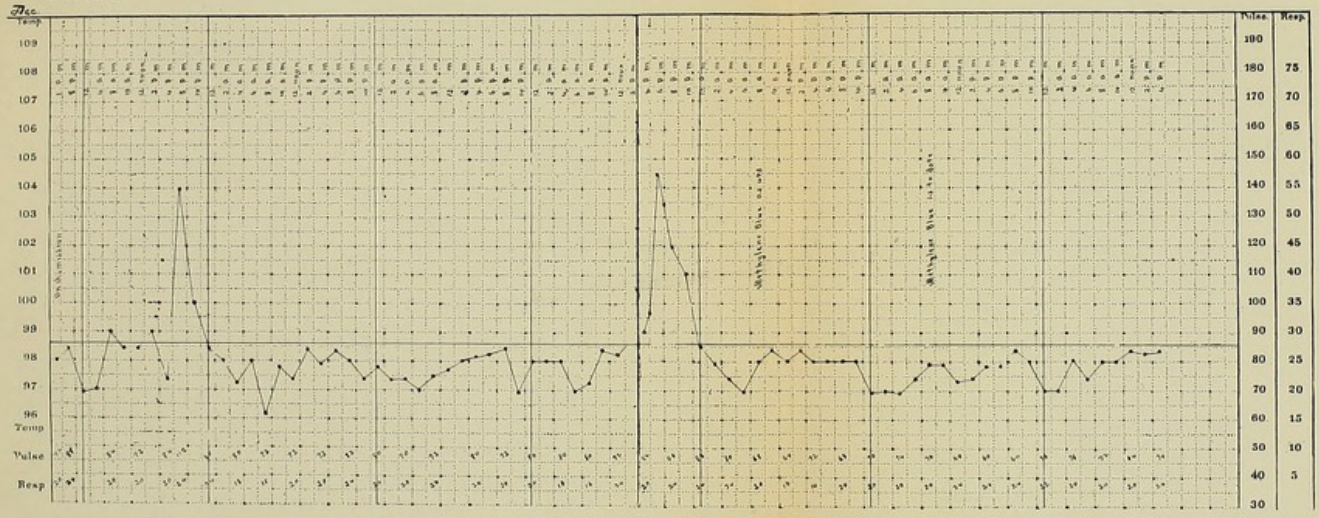
Pulse
Resp

No. 4368



suggestion of a double contour; it was very similar to the ovoid aestivo-autumnal forms in appearance, except for the irregular arrangement and the quantity of pigment. A number of fragmenting and vacuolating, extra-cellular forms, and several bodies nearly, but not quite filling up the red corpuscle, with almost non-motile pigment and quite refractive protoplasm, were seen; also other smaller bodies, about one third the size of a corpuscle, quite refractive, with very slow amoeboid movements and slightly motile pigment granules. Several early segmenting forms were found.

At 2 p. m. a number of characteristic segmenting bodies, with from six to ten segments, were seen. Paroxysm in the afternoon. During and just after the paroxysm, small, amoeboid, intra-cellular forms were seen.

2–5–94. Temperature, at 8 p. m., 100.1°.

3–5–94. Temperature normal.

4–5–94. Temperature 100.5° at 8 p. m.

7–5–94. Temperature 99.8° at 8 p. m.

10–5–94. Temperature 99.8° at twelve, midnight.

13–5–94. Temperature 101.5° at 8 p. m.

Examination of the *blood* revealed a characteristic triple quartan infection, segmenting bodies being observed during the first four days, notwithstanding the slight rises in temperature. The strongest group of organisms reached maturity on the 1st, 4th, 7th, 10th, and 13th, causing slight abortive paroxysms. The patient was removed from the hospital by her parents on the 13th, when she was given a prescription for quinine.

Case 4 (10429).—A. K., single, aged 12, Pole, entered the hospital on July 19th, 1894. Does not speak English; history imperfect.

20–7–94. Examination of the *blood*, at 12 m., showed typical quartan organisms, a number of early segmenting forms, other small bodies just beginning to develop pigment, other more advanced bodies nearly filling up the shrunken, brassy-colored corpuscle, a few extra-cellular, fragmenting bodies; one small pigmented form was seen to burst from the corpuscle which became immediately decolorized; the escaped parasite became immediately deformed. Temperature, at 6 p. m., 99.6°.

21–7–94. Temperature subnormal during the night; 100.6° at 8 p. m.

Blood, 2 p. m., showed a few segmenting bodies.

9 p. m.; a number of characteristic quartan organisms, nearly filling the shrunken corpuscle, with almost immobile pigment; a few hyaline, amoeboid, non-pigmented forms.

22–7–94. Temperature subnormal during the night; 99.2° at 8 p. m.

Blood, 3 p. m. A few intra-cellular, hyaline bodies, one or two larger pigmented bodies, several nearly full-grown pigmented bodies, large and fragmented extra-cellular bodies with active pigment granules, pigmented leucocytes.

23–7–94. Temperature subnormal during the night; 99° at 10 a. m., 2 p. m. and 8 p. m.

Examination of the *blood* unfortunately not noted.

24–7–94. Temperature subnormal during the night; 103.8° at 6 p. m., to-day.

Blood at noon showed segmenting bodies.

8 p. m.; a few intra-cellular, apparently half-grown and some nearly full-grown bodies, several swollen, extra-cellular forms with active pigment, one flagellate body.

25–7–94. Quinine, two grains (0.13) every four hours. Temperature normal on the 26th. Slight paroxysm on the 27th and 28th. Normal on the 29th and 30th, when the patient was discharged with quinine. The organisms were present in the blood until the day of discharge. On that date none were to be seen.

The case was one of typical triple quartan infection, the organisms showing characteristics entirely different from those of the tertian parasite. It is interesting to note how, with the abortive paroxysms, the whole life history of the parasite could be traced in the circulating blood. The inefficacy of the quinine in stopping the paroxysms on the 27th and 28th is what might have been expected, the administration of the drug having been begun when the parasites had already entered the corpuscles.

Case 5 (10431).—19–7–94. A. K., single, aged 15, Pole, complains of chills and fever; no further history obtainable. Is a sister of the last patient.

Physical examination negative, excepting for the palpable spleen.

Temperature 102.2° at 8 p. m.; no marked paroxysms after this, though slight rises in temperature were noted on the 25th and 28th. Quinine begun on the 25th.

Examination of the blood showed a dying out triple quartan infection. Flagellate bodies noted on the evening of the 23rd. Segmenting bodies were observed on the day of entry and on several other occasions, notwithstanding the slight abortive rises of temperature.

It is interesting to note that, in these dying out quartan infections, we observed, as has Antolisei, extra-cellular forms with active pigment granules, fragmenting forms, and flagellate bodies, just as we have noted in tertian fever. The large, extra-cellular forms, however, are materially smaller than those of the tertian variety; they are not as frequent; they are not as transparent; the pigment is larger and coarser. There was no question in any of these cases of a combined infection, not an organism having been observed which was not quite distinctively of the quartan type.

A sixth case may probably be added to those above mentioned:

A girl, aged 15, a German, was admitted to the hospital on the 26th of January, 1892. The family history was negative. She had never had previous illnesses, excepting two years before, when she had malarial fever of unknown type. The illness of which she then complained began in August with chills which occurred, she said, about twice a week. At times she did not have regular chills, but "felt badly." This continued until October, when regular chills began, which were stopped by quinine. After two weeks the chills recurred, and for the past two weeks patient had had a chill every fourth night, the chill, associated with severe headache, lasting

an hour. This was followed by fever and sweating. Bowels regular. The physical examination was negative, excepting for the palpable spleen. The patient showed no paroxysms in the hospital. She had had quinine outside before entrance. The blood showed a very few organisms similar to those observed in the other quartan cases, but, owing to the imperfect entry made concerning them, we have not felt justified in including this case among those where the type was definitely made out. We have little doubt, however, that this also represented a case of quartan malaria.

Æstivo-autumnal Infections.

There were in all 189 cases of aestivo-autumnal fever observed in the hospital and dispensary. Of these, 105 cases were treated in the hospital, and 84 in the dispensary.

Cases of Aestivo-autumnal Infection Observed in the Hospital.

In the 105 cases of aestivo-autumnal infection observed in the hospital, one of which was the relapse from a case previously treated, the types of fever may be divided as follows:

Quotidian intermittent paroxysms	38*
Daily paroxysms, with a tendency to become continuous	16†
Continuous fever, with quotidian exacerbations	13
Tertian intermittent paroxysms	6
Continuous fever, with no sharp paroxysms	9
Normal or subnormal temperature	8
Moderate irregular fever	8
Indefinite	7‡
	105

Thirteen of these cases which did not show tertian fever in the house gave a history of having had tertian paroxysms before entrance.

Thus, of the 105 cases, only 38 showed sharp quotidian intermittent paroxysms, though 67, or not quite two-thirds, showed a distinct

* In several instances the patient was admitted during the paroxysm, and showed only one or more slight daily rises of temperature on the following days, with a normal temperature afterwards; so clear a history was, however, given of sharp paroxysms before entering the hospital that the cases were placed in this list.

† Under this heading are classed those cases which showed several distinct paroxysms, where, on one or more instances, the temperature failed to reach the normal point before the beginning of the following paroxysm, "subintrant fever."

‡ Cases showing but one paroxysm in the house, with a vague, indefinite history.

tendency toward quotidian exacerbations. Six showed tertian paroxysms, while 20 gave a history of having had tertian paroxysms at some time. On the other hand, 38, or more than one-third of all the cases, showed a more or less continuous fever.

Of these 105 cases, 68 either showed, in the hospital, or gave a clear history of having had, before entrance, distinct *chills*, and 7 chilly sensations; 30 complained only of headache, pains in the back and limbs, etc., the symptoms ordinarily accompanying an acute infection.

The *duration of the paroxysms* in these cases differed considerably from those in the tertian and quartan infections, averaging between twenty and twenty-one hours, while in the tertian and quartan fever it averaged from ten to twelve hours. In many instances the paroxysm lasted considerably longer—in one case, for instance, for thirty-eight hours, while in a number of instances long paroxysms which would probably have brought up the average duration considerably, could they have been reckoned among those on which this calculation is based, were followed by a second paroxysm before the fall to normal occurred ("subintrant" cases), so that the length of each paroxysm could not be estimated. It will also be noted that, while in 97.2 per cent. of the cases of tertian and quartan infection in the hospital, chills or chilly sensations were present, in only 71.4 per cent. of the cases of aestivo-autumnal fever were these symptoms noted.

While in some cases with quotidian paroxysms the periods of subnormal temperature during the attacks were similar to those observed in double tertian fever, there were many instances where the overlapping of paroxysms caused a continuous fever, thus showing a chart quite different from that observed in the common double tertian intermittent. In some cases a continuous elevation of temperature, most suggestive of typhoid fever, was noted. In 5 cases where there was fever on admission, the temperature disappeared spontaneously.

Organisms.—These 105 cases all showed the presence of the organisms characteristic of aestivo-autumnal infection. In all the cases in which fever was present during the stay in the hospital, the small, hyaline, ring-shaped and often actively amoeboid bodies described in an earlier section were noted. In several of the cases where no fever was present, only the crescentic and ovoid bodies were found.

In 35 cases, only these small, hyaline bodies, with or without a few minute granules of pigment, were seen. Of these, 27 were primary attacks, 8 were repeated attacks or relapses.

In 70 cases ovoid and crescentic bodies were found. Of these cases, 46 were primary attacks, 24 were repeated attacks or relapses. In 5 cases nothing was found in the blood on admission, while later ovoid and crescentic forms were seen.

In 29 cases hyaline bodies alone were present on admission, ovoid and crescentic forms appearing later. Of these 29 cases in which hyaline bodies alone were found on admission, with the development of the crescents later, the crescentic forms appeared before the beginning of treatment in 11 instances, while in 18 cases the treatment had been begun previously. In these 18 cases, the treatment was begun in the first week in only 4 instances.

Of the 70 cases in which crescentic and ovoid bodies were seen, in only two instances were these bodies noted before the eighth day of the disease. The first case was that of a man who had had previous attacks, and had been living in Jamaica, having left for Baltimore two weeks before entering the hospital. He dated his symptoms, however, but two days back. It is highly probable that in this case the disease had lasted longer than the patient fancied, the crescents being the remnants of a previous attack, from which complete recovery had never occurred. The second case was a patient who had recently arrived from Cuba. He dated his quotidian chills, fever and delirium but five days back. It is somewhat striking that both of these patients had been living in the tropics, and that one had had already several previous attacks. In 28 of these 70 cases the crescents were noted before the fourteenth day. In all the remaining cases the patients had been ill at least two weeks.

In 5 cases the patients had taken quinine from five to nine days before the appearance of crescents.

Hyaline amoeboid bodies were found alone on entrance in 64 instances. In 29 of these instances crescents appeared later; while in 35, hyaline bodies alone were seen throughout.

Of the 35 cases in which hyaline bodies alone were seen, in one case the disappearance of the organisms before the beginning of quinine is noted. Case 8268 entered on the fifth day; no organisms were seen after the sixth; quinine given on the 14th day. It should

be said, however, with regard to this case, that the discovery of hyaline forms is so delicate a matter that it is not impossible that a more careful, continued search would have shown these bodies.

Out of the 35 cases where hyaline bodies alone were seen, 19, or about one-half, lasted over two weeks before the disappearance of the organisms; 16 lasted over twenty days. In two of these 16 cases there is considerable probability that the real attack may have been of much shorter duration than would appear from the history. With the exception of these two cases, the longest period during which symptoms existed, with the presence of hyaline bodies alone in the blood, occurred in case 6289, where the duration of the case was from eight to nine weeks, and in case 8105 which lasted six weeks. Of the 19 cases, where hyaline bodies existed alone for more than two weeks after the onset, 15 were first attacks.

Of the 35 cases, in 17, treatment was begun in the first week; in 3 in the second. In 2, the duration of the case was not known, while in 13, with the exception of two cases in the tenth week, treatment was begun all the way from the third to the ninth week; in 2 instances, as noted above, the cases had existed from nine months to a year.

Out of 64 cases, where hyaline bodies alone were present on admission, in 21, treatment was begun in the first week, crescents appearing in only 4, or 19 per cent.; in 8, in the second week, crescents appearing in 5, or 62.5 per cent.; in 35, where the treatment was begun after the second week, the crescents appeared in 20 instances, or 57.1 per cent.

In these 105 cases, flagellate bodies were noted in 18. In 6 of these cases quinine had been previously administered; in one case there was some question as to whether the patient had, or had not had quinine. In 10 instances these bodies appeared before quinine was given. The earliest period at which they were noted was on the eighth day. They were, in all instances, associated with the presence of crescentic, ovoid, and round bodies. In 9 of the 18 cases the temperature was normal at the time when the flagellate bodies were found; in 4, they were found during the paroxysm; in 3, during the mild continuous fever; in one instance they were found after death in the spleen. In one case in which the organisms were found during the paroxysm, early in the course, they were found

again five days later, when the temperature was normal, after the administration of quinine. In another case they were found, first, ten days after the administration of quinine, and nine days after the temperature was normal; they remained present here till the thirteenth day.

Cases of Aestivo-autumnal Infection observed in the Out-patient Department.—There were 84 cases of aestivo-autumnal fever observed in the dispensary. There were:

Quotidian paroxysms in	35
Tertian paroxysms in	7
"Paroxysms" in	5
Irregular paroxysms in	8
Vague general complaints in	29*
	84

Of the 29 cases complaining of vague general symptoms, one complained of tertian paroxysms, but stated that he believed his fever had been continuous. Of the cases showing quotidian paroxysms, nine had, at one time or another, had tertian attacks.

In only 59 cases were *chills* or chilly sensations noted.

Organisms.—Among the 84 cases, crescentic and ovoid forms were found in 35 instances; of these, 25 were first attacks; 5 were repeated attacks or relapses; 5 were uncertain, probably relapses.

Hyaline bodies alone were noted in 49 instances; of these, 35 were first attacks; 13 were repeated attacks or relapses; 1 was uncertain.

Of the 84 cases, 21 were seen during the first week, and of these only 3 (14.2 per cent.) showed crescents. In two of these cases they were noted on the seventh, and in one on what the patient believed to have been only the fourth day of his disease. 15 cases were seen in the second week, and in only 3 of these (20 per cent.) were crescents found. 46 cases were seen after the second week, and in 27 (58.6 per cent.) of these, crescents were seen. Out of 33 cases admitted or seen later than the third week, crescents were found in 20 (60.6 per cent.). Of 2 cases, where the duration of the disease was doubtful, crescents were seen in one.

Of the 13 instances in which hyaline bodies alone were found after the third week, in 3 the patients had had quinine before, with

* Headache, pain in the back and limbs, and the symptoms generally associated with acute infections.

a temporary relief of the symptoms. In 4 of the instances where crescents were found, quinine had been administered before their appearance.

Flagellate bodies were noted in two instances, on both occasions after the administration of quinine and during normal temperature.

Cases of Aestivo-autumnal Infection in the Hospital and Out-patient Department.—There were 189 cases which showed the organisms characteristic of aestivo-autumnal fever. One was a relapse of an attack previously included in the classification. If we combine the observations of the temperature in those cases which were in the hospital with the most reasonable deductions that may be drawn from the statements of the out-patients concerning their attacks, we obtain the following result:

Quotidian intermittent fever	73	cases.
Tertian fever	13	"
Continued fever, generally associated with daily paroxysms.	66	"
Moderate irregular fever	21	"
Normal or subnormal temperature	8	"
Indefinite	8	"
	189	

Organisms.—In 117 cases there were *chills;* in 17 chilly sensations; in 55 vague general symptoms only.

In the 189 cases of aestivo-autumnal fever seen in the hospital and out-patient department,

Hyaline bodies alone were found in 84. Of these there were:

Primary attacks	62
Relapses or repeated attacks	21
Uncertain	1
	84

Crescentic bodies were found in 105. Of these there were:

Primary attacks	71
Relapses or repeated attacks	29
Uncertain	5
	105

The following table shows, graphically, the time at which crescents generally developed in the hospital, and, so far as could be made out, in the dispensary cases.

1st week: Admitted to Hospital.....	36;	crescents	2	
" " Dispensary.....	21;	crescents	3	
	57		5	8.8 per cent.*
2d week: Cases admitted to the Hospital, or present without having previously shown crescents.....	35;	crescents	27	
Cases consulting at Dispensary.....	15;	crescents	4	
	50		31	62 per cent.
After the second week: Cases admitted to the Hospital, or still remaining, without having shown crescents...	48;	crescents	35	
Cases in Dispensary.....	46;	crescents	26	
	94		61	64.8 per cent.
Cases of doubtful duration: House.....	8;	crescents	5	
Dispensary.	2;	crescents	2	
	10		7	70 per cent.
Relapses, House.....	1;	crescents	1	100 per cent.

Actual advanced segmenting bodies were never seen in the circulating blood, though forms with a central pigment block were noted in a number of instances.

Flagellate bodies were seen in 20 cases.

In 8 cases quinine had been previously administered.

In 1 case they were found both before and after the administration of quinine.

In 11 cases the temperature was normal at the time when the flagellate bodies were noted.

In 4 cases the bodies were found during paroxysms.

In 3 cases the bodies were found during mild continuous fever.

In 1 case the bodies were found first during a paroxysm, and again, five days later, when the temperature was normal, following quinine.

In 1 case they were found in the spleen after death.

* This rather high percentage is explained by the fact that of the two cases showing crescents in the hospital during the first week, one, as has been stated, had had numerous previous attacks, so that it is uncertain as to whether the case may not have been a relapse, while the other came from a most malarious district (Cuba) and had probably had his disease longer than he stated—five days. Of the three cases in the out-patient department, the crescentic bodies were noted on the 7th day in two, while in the other the patient asserted that it was but the 4th day of the disease.

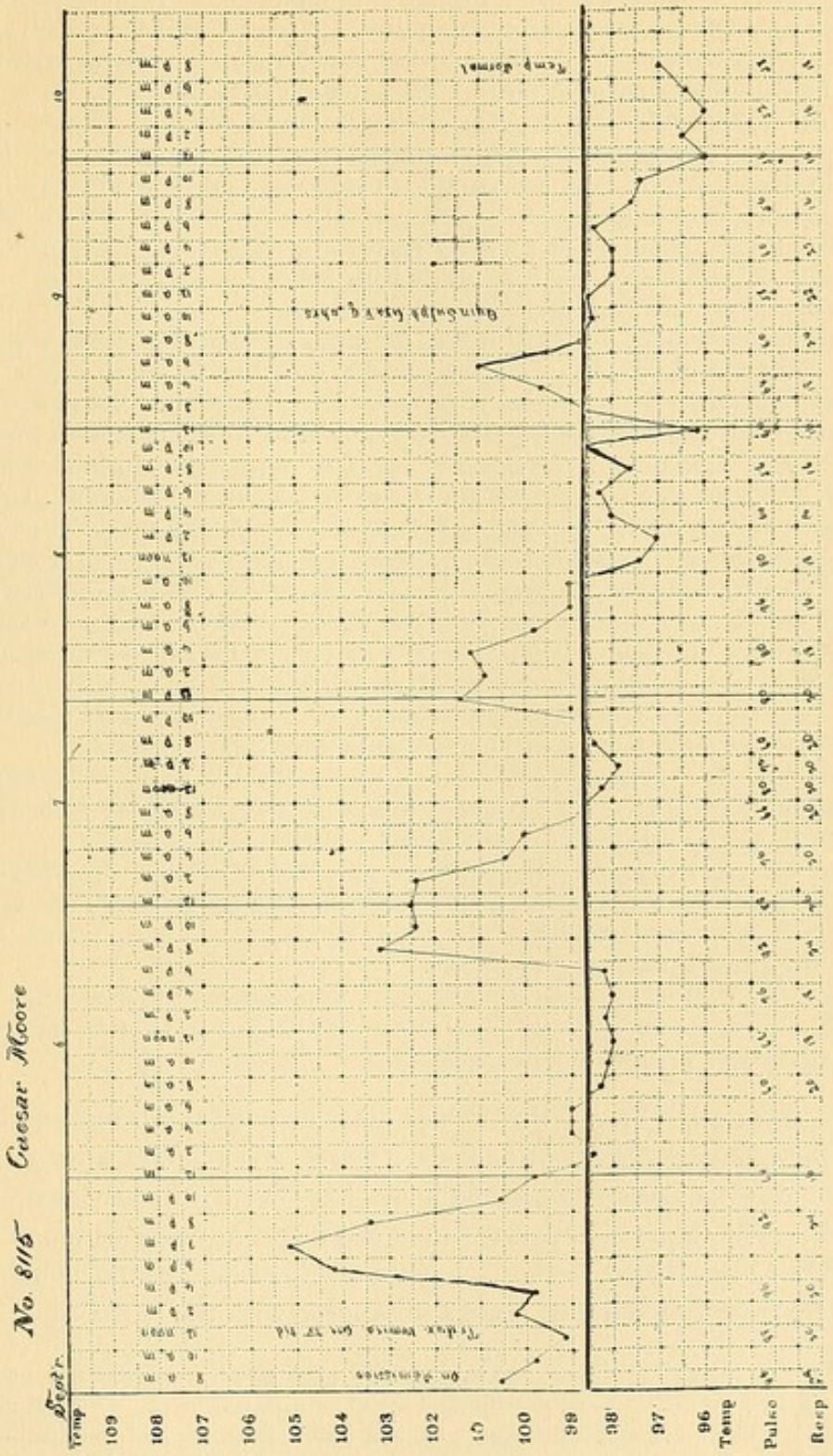
Cases.

The following cases will serve to illustrate some of the different varieties of fever which were found associated with aestivo-autumnal organisms. The first case shows a chart very similar to that of ordinary double tertian or triple quartan fever.

Case 8115.—Patient, a man aged 24, colored, entered the hospital at 8 a. m., September 5, 1893. He had had previous attacks of malarial fever, the last attack a year ago; had been ill seven days with headache, general depression, anorexia; no chills, no vomiting, no marked sweating, no nose bleed; has taken no medicine. On the day before entrance, the sixth day after the beginning of the symptoms, the *blood* showed fairly numerous intra-cellular, non-pigmented, hyaline, malarial organisms, small, many of them ring-shaped with sharp outlines. The temperature on entrance was 100.5°. Physical examination was practically negative, excepting for herpes at the corner of the mouth, and a palpable spleen. The urine showed a faint trace of albumen; no casts. The course of the temperature is shown in the chart. The paroxysms were fairly sharp in onset, and associated with chilly sensations, though there were no actual shaking chills. For the first four days only small, hyaline, ring-shaped and amoeboid bodies were seen, which showed, between the paroxysms, one or two very fine pigment granules. Just before and during the early part of the paroxysms the organisms were very scanty in the peripheral circulation, a note having been made on the afternoon of the sixth that no organisms were to be seen at all. The forms seen shortly after the paroxysms were always free from pigment. No segmenting bodies were seen at any time. On the ninth, for the first time, one pigmented crescent was seen, and after this the crescentic and ovoid bodies became very numerous. On the tenth, flagellate bodies were seen for the first time, and while, after the beginning of quinine on the ninth, the small, hyaline forms disappeared with great rapidity, and the temperature returned to normal, the ovoid, crescentic and flagellate bodies were found continually, in considerable numbers, up to the date of discharge, the 14th.

In this case, it will be seen that the paroxysms were very similar to those observed in the ordinary spring tertian fever. There was a tendency towards spontaneous recovery, and the administration of quinine was followed by the immediate disappearance of the fever. The examination of the blood suggested that this was a case of true quotidian malaria, only one set of organisms, apparently, being present.

Case 7767.—G. E., single, white, aged 29, ship carpenter, admitted to the hospital July 22nd, 1893. Was in the hospital last year, during the latter part of August, with double tertian fever. He has been well since September, 1893. Three days ago he started to work in the morning, when he was seized with an intense frontal headache, anorexia, fever and sweating; the next day he had a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"dumb chill" To-day, has had a shaking chill lasting forty-five minutes, accompanied by vomiting; complains of constipation. The patient entered at 7.30 p. m. with a temperature of 104.6°. The physical examination was negative, excepting for the considerably enlarged spleen. The urine showed a trace of albumen; no casts were found. The entry on the morning of the 23rd is as follows: "Last night, at 8 p. m., the *blood* contained a very considerable number of the smallest variety of hyaline bodies, some of them homogeneous in appearance, others more or less ring-shaped, some of them amoeboid; no other organisms found. There was no leucocytosis; indeed, rather a small number appeared to be present." The following morning the bodies were less numerous, a trifle larger, and some contained a few fine pigment granules lying at the periphery of the body.

July 23rd, 3.30 p. m., the *blood* showed relatively few organisms. Those which were found were for the most part small, hyaline discs, some of which showed one or two extremely minute particles of pigment at the periphery. 4.15 p. m., temperature about 103°; the *blood* from the spleen showed a number of pigment clumps, which appeared to be free. Many others contained in large mononuclear, colorless cells. There was a considerable number of apparently free organisms a little larger, or about the size of the bodies with central pigment clumps, which were filled with very active, brown pigment granules. They resembled the extra-cellular pigmented forms seen in the spring tertians, excepting for the greater abundance and activity of the pigment. A number of apparently free bodies were seen; some others within red corpuscles, in which there was a small central pigment clump, the surrounding protoplasm being somewhat granular in appearance, with a slightly "scalloped" outline. These were probably early segmenting forms. 11 p. m.; more of the smaller, hyaline bodies present, but still forms with occasional pigment granules.

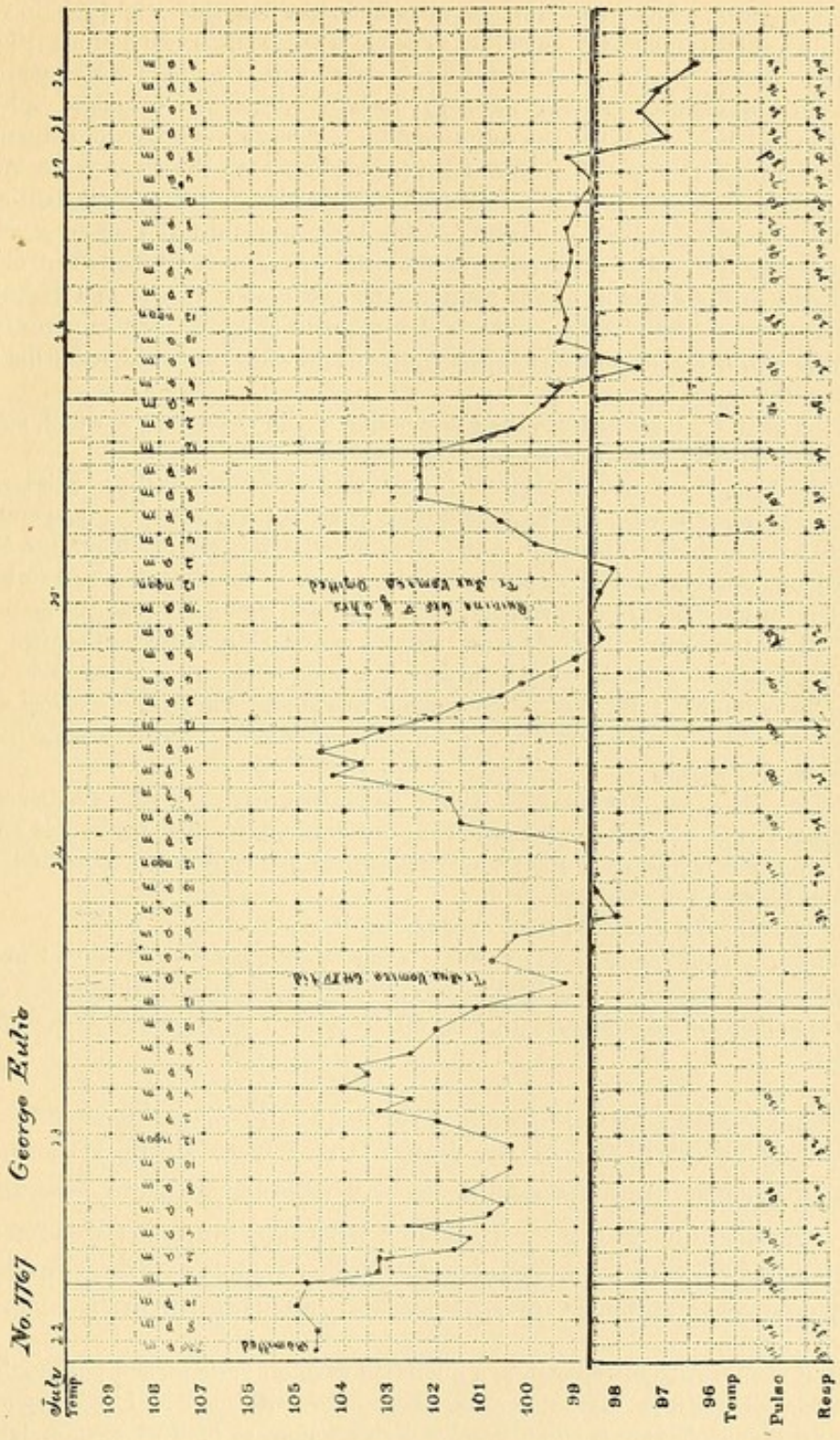
July 24th; in the morning, a majority of the organisms had one or two fine pigment granules. At 11 p. m., at the beginning of the decline of the fever, the blood showed only a few organisms; none were seen which contained pigment.

25–7–93. 10.30 a. m. Hyaline forms are rather larger, and about one-third contain a few fine pigment granules in the periphery. Several similar bodies, extra-cellular, hyaline, rather refractive, with a few granules grouped in the centre. Quinine, five grains (0.325) every four hours.

27–7–93. 10.15 a. m. The blood showed a few organisms, one or two ring-like forms, a few larger amoeboid; no pigmented forms were seen. The temperature, as the chart shows, was normal after the 25th.

In this case, it is seen that two paroxysms overlapped one another, the fever having been continuous for thirty-seven hours after entry. The paroxysms occurring in the house were wholly unassociated with chills. The impression that one obtained from the examination of the blood was that there was but one main group of organisms, though all pigmented forms did not, always, disappear with the paroxysms.

Case 8024.—E. B., female, single, aged 13, admittted to the hospital on the 24th of August, 1893. This was the first attack of malarial fever. It began about ten days before entry with abdominal pain and diarrhoea which has continued until


No. 1767 George Kuhn
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the day of entry. She complains now of pain in the left side, slight cough, considerable headache, anorexia, no chills. The child was well-formed and nourished; lips and mucous membranes of good color; tongue coated; pulse dicrotic; marked typhoidal appearance. Thorax negative; hepatic border just palpable; splenic border to be felt 5½ cm. below the costal margin. Abdomen negative on palpation, not distended, no rose spots. Examination (rather hasty) of the *blood* on the afternoon of the 23d, and at 8.30 p. m., showed no malarial organisms, no pigment-containing leucocytes; a distinct increase in the large mononuclear leucocytes,—five out of twenty-five. The appearance of the child was characteristically typhoidal, and sponge baths were ordered, and continued for twenty four hours. The irregular, continued course of the temperature is shown by the chart, no distinct paroxysms occurring while the patient was in the hospital; no chills at any time during the course of the fever.

On the 26th, for the first time, the examination of the blood showed small, amoeboid, and ring-shaped hyaline bodies.

On the 27th, the fourteenth day of the disease, beside the hyaline bodies, crescentic forms were noted. The hyaline bodies, at 10.20 a. m., when the temperature was 101.8°, contained no pigment. At 7.30 p. m., the temperature 103.8°, the *blood* showed numerous hyaline bodies a trifle larger than in the morning, some with a few pigment granules at the periphery, one larger body with a few pigment granules collected in the centre. At 8.30 p. m., several more bodies with small central collections of pigment granules were to be seen. A number of the organisms were contained in crumpled, refractive, brassy-colored corpuscles; the hyaline bodies were mostly of medium size, a number with a few pigment granules; one free ovoid body; pigmented leucocytes.

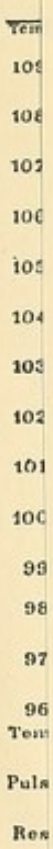
28–8–93. 11 a. m. Temperature 100.4°. Organisms perhaps a trifle smaller than last night; very few forms with pigment; one ovoid, refractive, pigmented body. At 3 p. m., the temperature 100.2°, very few organisms; only a few amoeboid and non-pigmented forms were seen.

℞. Quinine, gr. v (0.325) every four hours.

29–8–93. Temperature nearly normal; a few hyaline bodies, and several ovoids and crescents were seen. The hyaline bodies disappeared rapidly, though the crescents remained for some time, none, however, being seen on discharge, 19th of September.

This is a fairly good example of continued fever. There were no sharp paroxysms in the house, though there were slight rises daily. It would seem quite impossible to say whether we were dealing in this case with one group of organisms with overlapping paroxysms,* or with an infection with organisms in different stages of development, where, perhaps, different groups were segmenting through consider-

* If so, should it be interpreted as a quotidian case, or, perhaps, as a tertian, showing two long paroxysms, beginning respectively on the 24th and 25th? The examination of the blood, in view of the few stages of development which we see circulating, is insufficient to clear up this point.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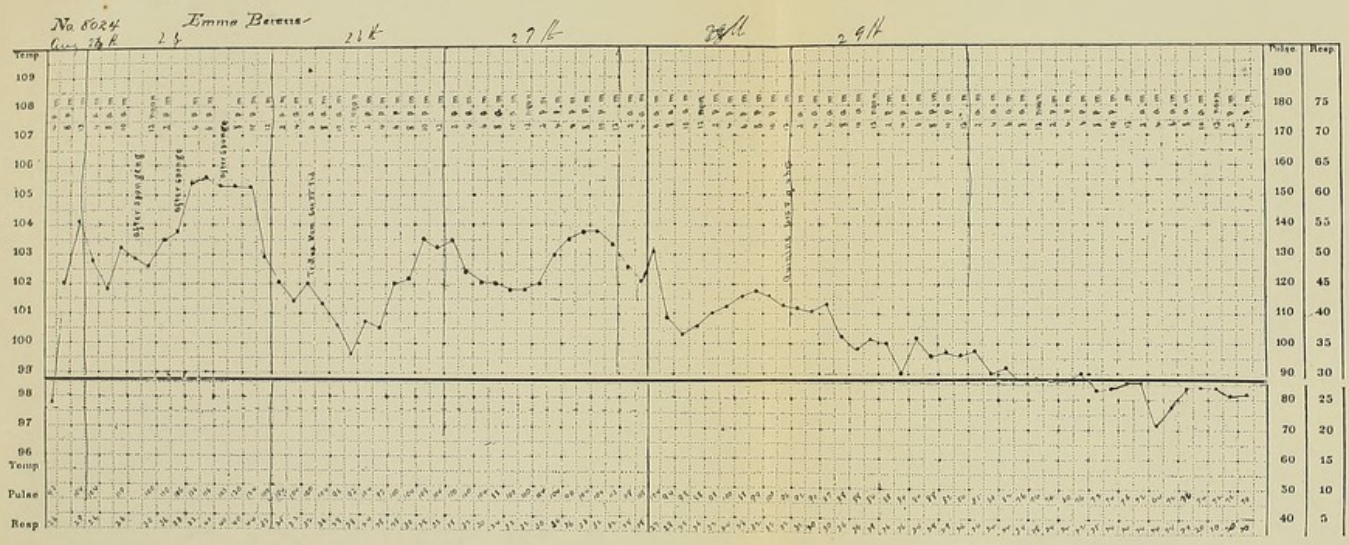
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able periods of time. The first crescents were seen here on about the fourteenth day.

CASE 10480.—F. P., female, aged 28, German, admitted 25–7–94, complaining of headache and pain in the back and limbs.

Family history negative. Personal history bears no relation to her present trouble.

The present illness, her first attack, began two weeks before entry with severe headache, a feeling of giddiness, aching pains in the back and limbs, anorexia, occasional vomiting; bowels regular.

On July 20th, had chilly sensations, lasting for about half an hour to an hour, followed by fever and profuse sweating; no nose bleed.

25–7–94. Temperature on entry 98°; 100.7° at 8 p. m.; 101.8° at 10 p. m.

Blood at 8 p. m.: Numerous actively amoeboid hyaline bodies, some containing one or two minute pigment granules, also numerous ring- and disc-shaped bodies.

Urine; dark amber, hazy, acid, 1013, faint trace of albumen, no sugar; diazo reaction present. Microscopically; epithelial cells and leucocytes; no casts found.

26–7–94. Temperature remains elevated. "Patient is in bed, on her back; tongue clean; pupils equal, respond to light and accommodation; lips and mucous membranes of good color; no herpes; pulse full, regular in force and rhythm, rather soft, 96, no thickening of the vessels. Thorax; well formed, costal angle wide, expansion good; fronts, axillae and back clear on percussion and auscultation.

Heart. Position, area of dulness, and sounds normal. Border of the liver not palpable; right kidney just palpable; splenic dulness obliterated by abdominal tympany; border is not felt.

Abdomen, not distended, generally tympanitic, negative on palpation. No rose spots, no glandular enlargements.

Blood, 2 p. m. Large numbers of hyaline bodies, many actively amoeboid, some ring-shaped, a few showing pigment granules.

8 p. m. A few hyaline and ring-shaped bodies.

27–7–94. Temperature remains elevated, no sharp paroxysms.

Blood, 9.30 a. m. Numerous, rather large, hyaline bodies, about a quarter the diameter of a red corpuscle.

2 p. m. A number of smaller bodies, some actively amoeboid, some showing occasional pigment granules. 8 p. m.; a few actively amoeboid hyaline bodies.

28–7–94. Patient is dull and drowsy; temperature remains elevated. The blood at 9 a. m. showed a few hyaline forms. At 3 p. m., negative; at 8 p. m., negative.

℞. Quinine, gr. v (0.325) every four hours.

29–7–94. Temperature has remained continuously elevated since entrance, the course much resembling typhoid fever. Patient has the same dull look, the same dry coated tongue.

Blood, 10 a. m. One amoeboid, hyaline body, several pigmented leucocytes.

3 p. m. Two crescentic, pigmented bodies, several pigmented leucocytes.

8 p. m. One hyaline body with a few pigmented granules, one crescent.

30–7–94. The temperature has remained elevated and uninfluenced by quinine; spleen not palpable; no rose spots.

Blood, 8.45 a. m. Several ring-like bodies; a few hyaline, amoeboid forms, one containing pigment; one large, ovoid, pigmented body.

2 p. m. Negative.

8 p. m. Several crescentic bodies.

31–7–94. Temperature has been steadily falling since the 29th; no great change in the condition. This afternoon the left parotid gland is very tender, and somewhat swollen; temperature at 8 p. m., 101.6°.

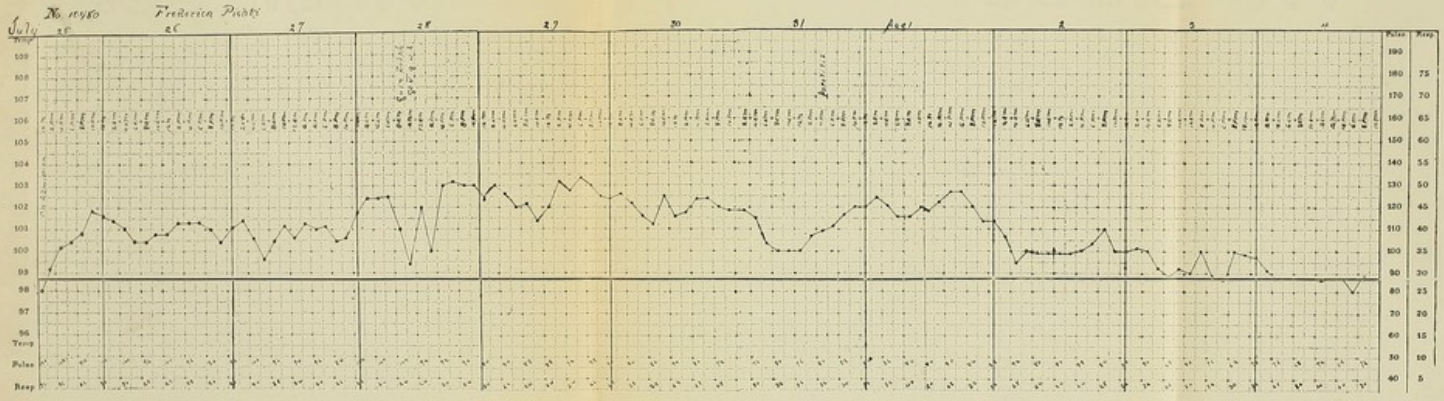
Blood at 9 a. m., negative; at 2 p. m., negative.

1–8–94. Temperature in the morning was 101.6°; at night, 102.6°. Whole left parotid gland greatly swollen, red and tender.

Blood. No organisms seen, excepting an occasional crescent. Leucocytes, 5000 to the cu. m. m. From this time on, no hyaline organisms were noted in the blood. The parotid swelling gradually disappeared, the temperature reaching normal on the 4th of August. The patient insisted on leaving the hospital on August 8th, when she felt perfectly well.

This case is of remarkable interest, in that it simulated typhoid fever so closely. The temperature showed a continuous elevation without intermissions; the tongue was dry and coated; the patient was, at first, in a drowsy typhoidal condition. The urine showed throughout a diazo reaction. There were no chills and no sweating while she was in the hospital. The presence of the amoeboid bodies in the blood alone revealed the true nature of the case. Moderate doses of quinine, begun on the 28th, showed, on the 30th and 31st, a slight influence upon the fever. No hyaline forms of the parasite were observed in the blood after the 31st. The appearance, however, of the parotitis on the evening of the 31st caused an elevation of temperature, which would lead one to believe, on superficial examination, that the process had not reacted to quinine.

This is one of those cases which shows the importance of the examination of the blood in all doubtful cases of fever. It is also of interest in that it was quite impossible to distinguish any separate groups of the parasites in the blood. No examples of the later stages of development were ever found. It is probable that here the spleen and internal organs contained multiple groups of organisms in all stages of development, while continuous segmentation and liberation of toxic substances was occurring throughout the course of the fever. The question may arise whether it is not possible that the case was one of typhoid fever combined with malarial fever. We see no reason to believe that this was the case. On entrance to the hospital, the patient's temperature was normal. She had had chills on at least one instance before entry. We are not justified in taking the patient's statements as indicative that the temperature before entry had been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continuously elevated. It is not at all unlikely that it had been, at first, somewhat intermittent. As soon as the fall in temperature began, the patient was given a full diet, which was perfectly well borne. She was, also, able to be out of bed and about within two days after the time the temperature reached normal, without showing the debility which one would expect following typhoid fever. There were never, at any time, any abdominal symptoms.

The following case is an interesting example of that class of cases in which the existence of malaria is often unsuspected, owing to the absence of any acute febrile symptoms.

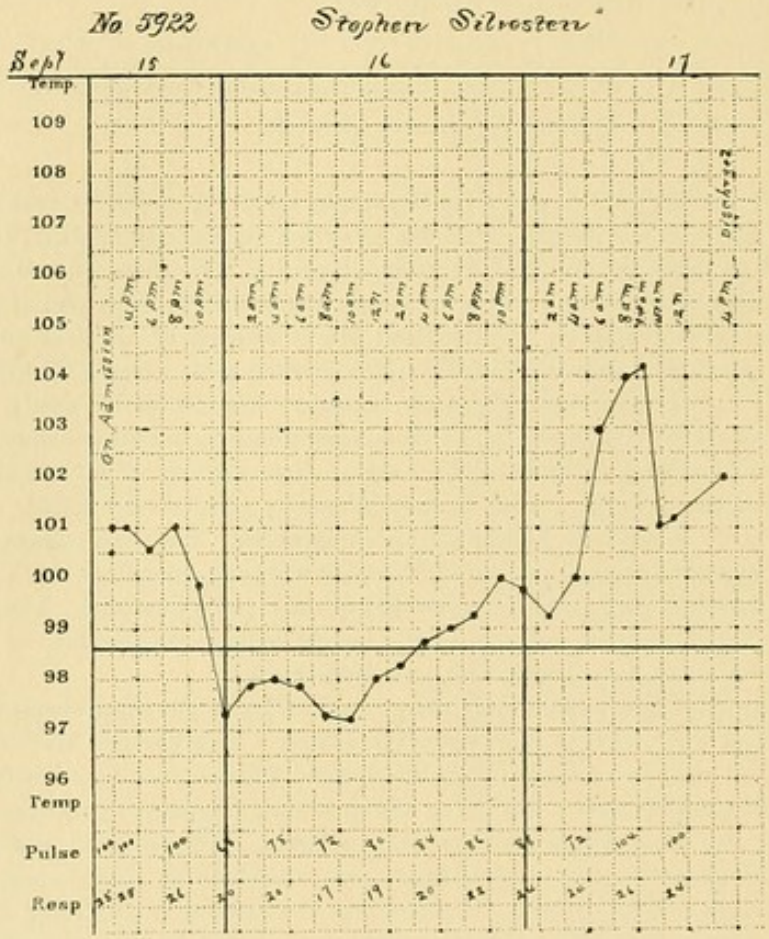
CASE 7677.—The patient was a female, single, aged 23; mentally rather feeble; has never had malaria before. She was admitted on the 8th of July, 1893, complaining of an illness of six days' duration, of pain in the abdomen and vomiting; severe headache and general muscular pains; slight cough, anorexia; the vomitus was at times blood-stained; constipation; slight oedema of the feet and ankles. Physical examination showed a fairly well-nourished girl; tongue slightly coated; color good; thorax negative; abdomen negative; splenic border easily palpable. Patient was very nervous, and marked vaso-motor disturbances were seen on the skin. She was given, at first, a light, later a general diet; tincture of nux vomica. The urine was negative, barring a faint trace of albumen; no casts were found. An hasty examination of the *blood* showed no malarial organisms. The temperature, on entry, was 100°, but was never again above 99.5°, and, during the eight days that the patient was in the hospital, was, for the greater part of the time, sub-normal. The girl complained, however, bitterly and continually, of headache. On the 16th of July the patient, owing to a misunderstanding, was discharged.

She returned five days later, July 21st, complaining of the same symptoms. She was very dull and heavy; tongue thickly coated. Temperature 99.2° on entry; rose to 101.3° at twelve midnight, but was normal afterwards. Examination of the *blood*, on the 22nd, showed a few ovoid and crescentic pigmented parasites. On the 23rd there was a moderate number of pigmented crescentic and ovoid bodies, with an occasional hyaline, intra-cellular form, amoeboid or ring-shaped. On the 25th, the temperature still being normal, and the patient complaining bitterly of headache, she was given five grains of quinine every four hours. For several days after this the temperature was sub-normal. On the 27th no hyaline forms were to be seen, though numerous ovoids and crescents were present. On the 18th of August no malarial organisms were to be seen.

The following cases, 6 in number, are the only ones of surely tertian fever which we observed, though there are many in which this had existed, if we are to believe the statements of the patients.

CASE 5922.—S. S., single, aged 26, Pole, was admitted on the 15th of September, 1892. Patient could speak no English; he was a laborer, in a very malarious dis-

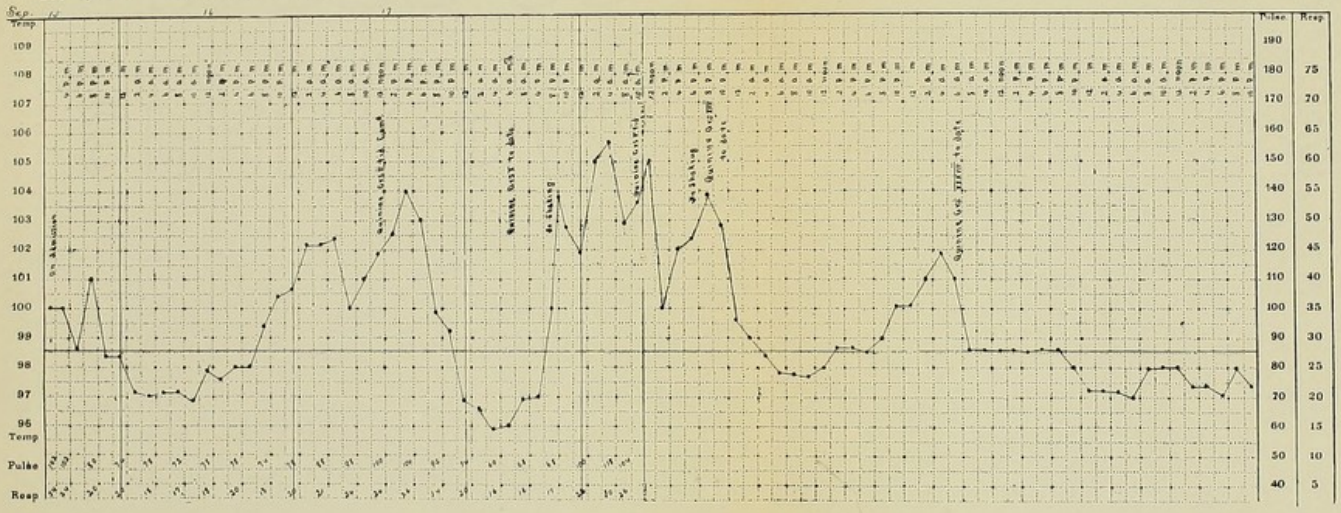
trict. So far as could be made out, there had been no previous attack. Present illness began, two days before entry, with a shaking chill, accompanied by headache, fever and sweating. He had no chill yesterday, though he feels badly to-day. The patient was admitted with a temperature of 101°. By midnight it was sub-normal, and there was no fever till the evening of the 16th, when it began to rise gradually until, at 9.45 a. m. on the 17th, it had reached 104.2°. There was a fall after this time to 101.2° at noon. At 4 p. m., the temperature being 102°, the patient was



discharged for insubordination. The *blood* on the 16th and 17th showed a few small, intra-cellular, hyaline bodies.

Case 5923.—C. R., single, aged 25, Pole, admitted to the hospital on the 15th of September, 1892. He was a companion of the last patient, working with him in the same place. He has always been a healthy man; no serious illnesses previously. Present illness began two days before entry, when patient complained of chilly sensations, headache, fever and sweating. His symptoms came on at almost exactly the same time as those of his companion who lives in the same house and works at the same place. On entry the physical examination was negative, excepting for the palpable spleen. The urine contained a trace of albumen; no casts seen. As may

No 5923. Caspar Rebstein

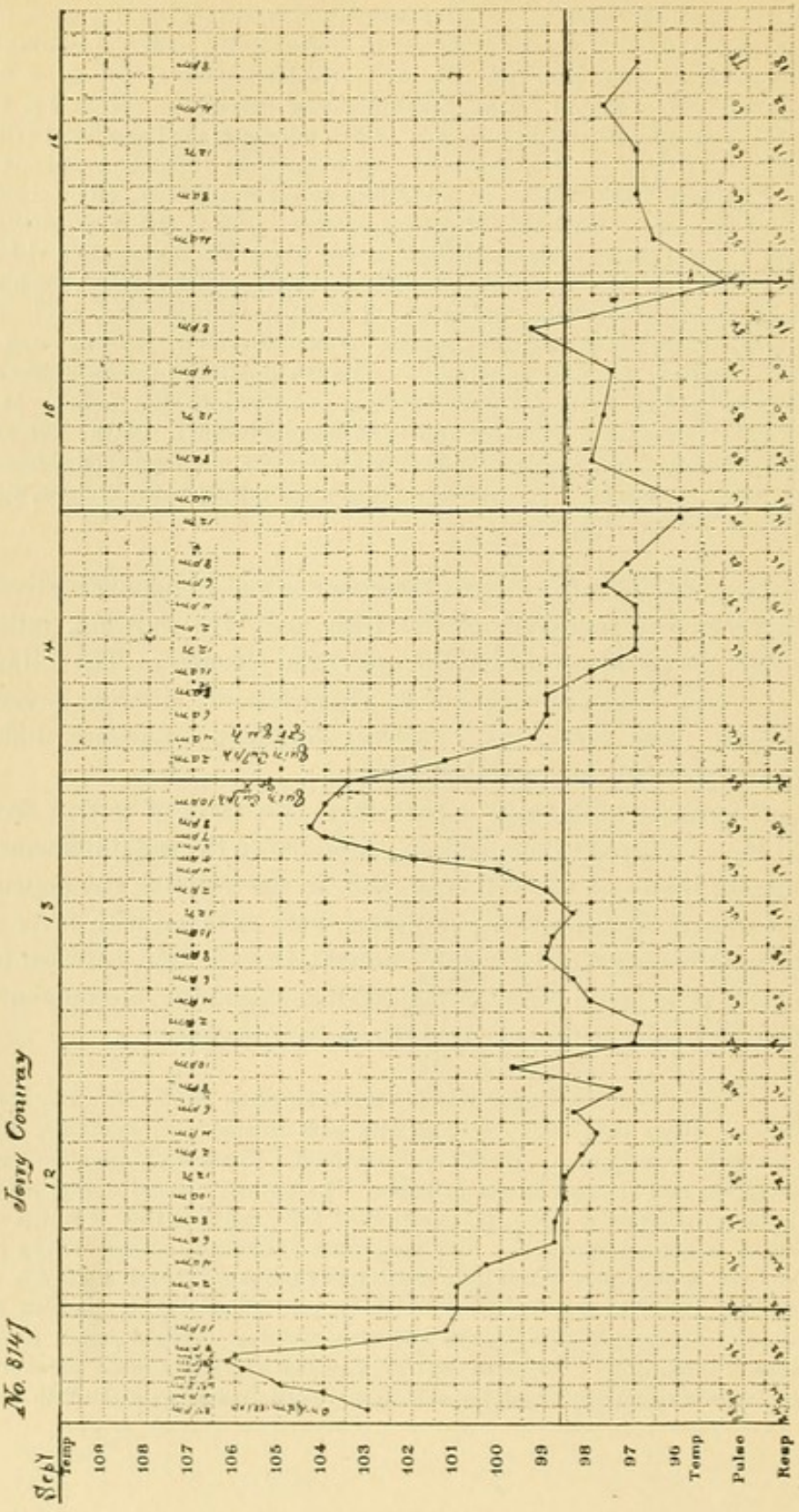


be seen by consulting the chart, the temperature, which was 101° at 8 p. m. on the 15th, was normal by 10 p. m., and remained so nearly all day, until the evening of the 16th, when it began again gradually to rise, reaching 102.4° at 6 a. m. on the 17th. It fell then to 100° at 8 a. m., rising gradually after this to 104° at 4 p. m., and reaching normal only between ten and twelve midnight, the paroxysm having lasted over thirty-eight hours. During the morning of the 18th, the temperature was normal, rising to 105.7° at 4 a. m., and falling to 102.8° at 8 a. m., with a second rise to 105° at noon on the 19th. There was another break in the fever between noon and 2 p. m., the temperature falling, in two hours, five degrees, and rising, gradually again, with chilly sensations, but without a shaking chill, to 103.8°, reaching normal by 2 a. m. on the 20th. Quinine, gr. ij (0.13) three times a day, was begun on the 17th. There was but a slight paroxysm on the 20th and the early morning of the 21st; a normal temperature afterwards. The examination of the *blood* showed, on the morning of the 16th, a very few small, intra-cellular, hyaline forms. At 8 a. m. on the 17th the same organisms were to be seen, still scanty. On the 18th and 19th the same forms were noted; at 8.30 a. m. on the 19th one form showed one or two fine pigment granules. The organisms disappeared rapidly under quinine, none being seen on the 21st and 23rd.

This case corresponds, well, to Marchiafava and Bignami's aestival-tertian fever, the paroxysm of the 16th and 17th showing, rather strikingly, the pseudo-crisis and the precritical elevation. The following paroxysm, however, was not so characteristic, showing several oscillations. The organisms, however, showed no apparent differences from those in the quotidian cases.

It is of considerable interest that these two cases of tertian fever should have occurred in companions, subjected to the same influences. The attacks began on the same day, and, in the hospital, the patients showed almost simultaneous paroxysms, both entering with fever on the 15th, the temperature reaching normal, in each case, between ten and twelve p. m., with a rise in temperature beginning, almost simultaneously, on the evening of the 16th in each instance.

Case 8147.—J. C., colored, aged 39, laborer, admitted on September 11th, 1893; first attack. Illness began five days ago with pain in the back, headache, some abdominal pain, constipation; no chill, no nose bleed. Physical examination negative, excepting that the spleen was palpable. The patient entered during a paroxysm, the temperature at 2.45 p. m. having been 103°, reaching 106° at 6.30 p. m., and falling to normal by 6 a. m. The temperature remained normal during the 12th and the greater part of the 13th, starting to rise again between 3 and 4 p. m., and reaching 104.3° at 8 p. m., from which time it fell gradually, reaching the normal point at about 6 a. m. on the following morning. Quinine, gr. x (0.65), was given at the height of the paroxysm; gr. v (0.325) every four hours afterwards, the temperature remaining normal or sub-normal until discharge on the 20th. On


No. 8147
Jerry Conway
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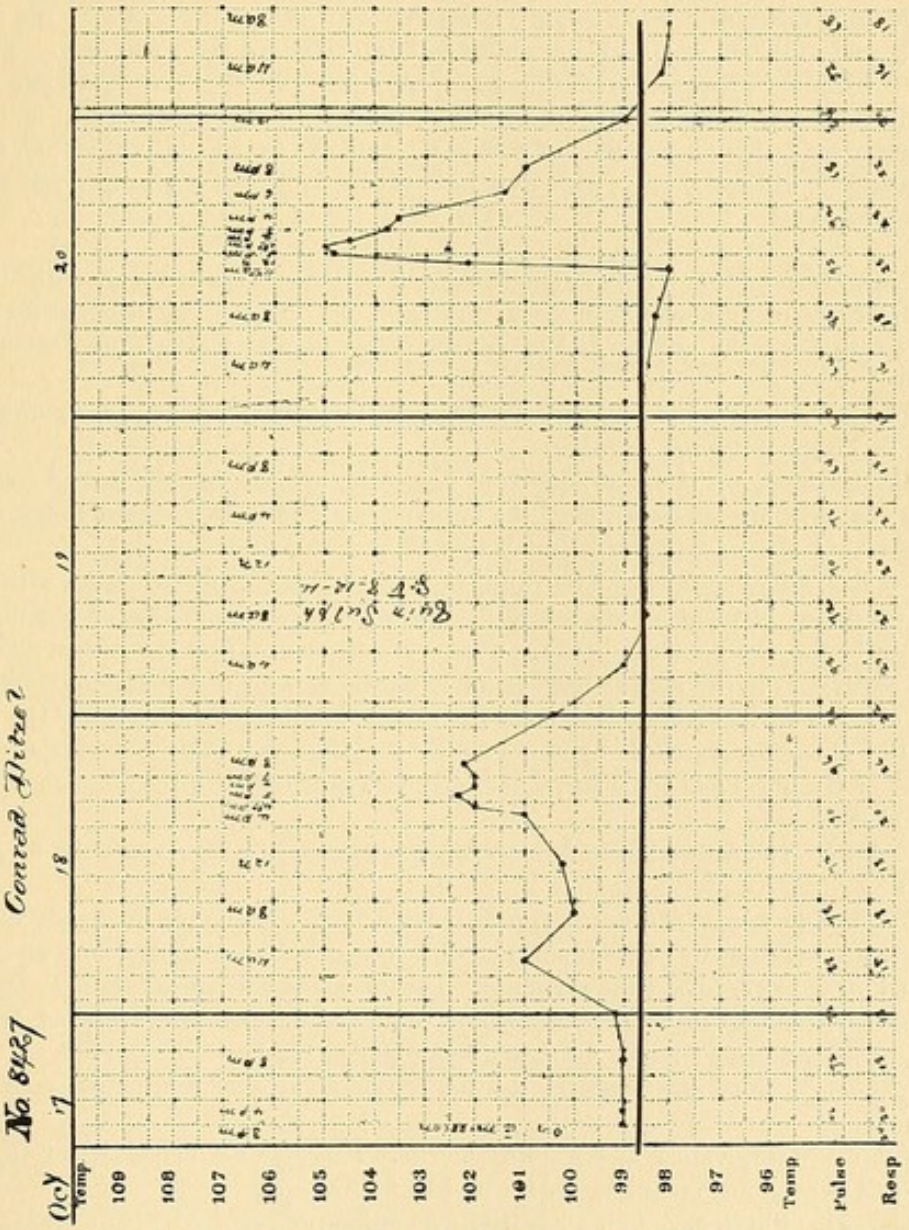
admission the *blood* showed a few small, hyaline malarial organisms. On the following day similar amoeboid, ring-like bodies were seen, but no pigmented forms were made out. During the 13th a few forms with occasional pigment granules were seen. On the 15th no malarial organisms were to be made out, and none were seen afterwards.

This would appear to be an undoubted example of a retarding tertian infection, though the temperature does not show the oscillations described by Marchiafava and Bignami as characteristic.



Case 8427.—C. D., aged 54, stevedore; first attack; admitted October 17th, 1893. About a month ago had a shaking chill, followed by headache and fever, which continued through several days. Has had headache and fever most of the time

since, with periodical sharp paroxysms, associated with shaking chills. On admission, the temperature was 99°. On the following day, shortly after midnight, there was a gradual rise in temperature, reaching 102.4° at 5 p. m., and reaching normal at about 4 a. m. on the 19th. Quinine, gr. v (0.325) every four hours, was ordered on the 19th, when the temperature was normal. On the morning of the 20th, between eleven and twelve o'clock, there was a sharp chill, the temperature reaching 105° at 1.30 p. m., and falling to 99° at about midnight. The patient left, early on the morning of the 21st, against advice. The *blood* on entry showed actively amoeboid, intra-cellular, hyaline bodies, several ovoid forms, one of which was filled with vacuoles of different sizes, apparently a degenerative form. At 8.30 p. m., two crescents and only one small hyaline, intra-cellular, ring-like form was seen. These small hyaline bodies, and crescentic forms, were seen throughout the patient's stay in the hospital; no segmenting forms, and no flagellate bodies were seen. It is interesting to note, that on the 20th, at 8.30 a. m., only one hyaline form was seen, after long search, while at 3 p. m., none were to be seen. Ovoid and crescentic forms were, however, noted.

Case 10465.—U. S. G., male, single, aged 25, laborer, admitted July 24th, 1894, complaining of headache, pain across the back, and chills. Has been ill for four days with headache and general pains; no chills; no nose bleed; some abdominal pain.

On entry, the temperature was 103.4°; rose to 105° at 4 p. m.; was normal at 6 a. m. on the following morning.

Blood, 2.30 p. m. A large number of amoeboid, hyaline, non-pigmented bodies; also smaller, more refractive, ring-like forms; two bodies with pigment collected in a central block; no actual segmenting forms.

8 p. m. Numerous amoeboid, hyaline organisms, ring-like forms, bodies with one or two grains of pigment, pigmented leucocytes. The course of the temperature is shown by the chart on the opposite page. It will be seen that the patient showed two paroxysms in the house; one beginning on the evening of the 25th, and one on the evening of the 27th, each showing the initial rise, the pseudo-crisis, and the pre-critical elevation described by Marchiafava and Bignami. The following are the notes of the blood and the urine, which may be compared with the temperature on the chart.

25–7–94. The urine showed a faint trace of albumen; no diazo reaction; no casts seen.

Blood, 8.45 a. m. Parasites appear a trifle larger than they were last night. There are not so many of the small ring-like forms, while a majority show an occasional pigment granule at the periphery. The amoeboid movements are less marked than they were last night. Several bodies contained in shrunken, crumpled, brassy corpuscles were seen; leucocytes containing pigment blocks.

2.30 p. m. Numerous ring-like hyaline bodies, many amoeboid forms, some pigmented.

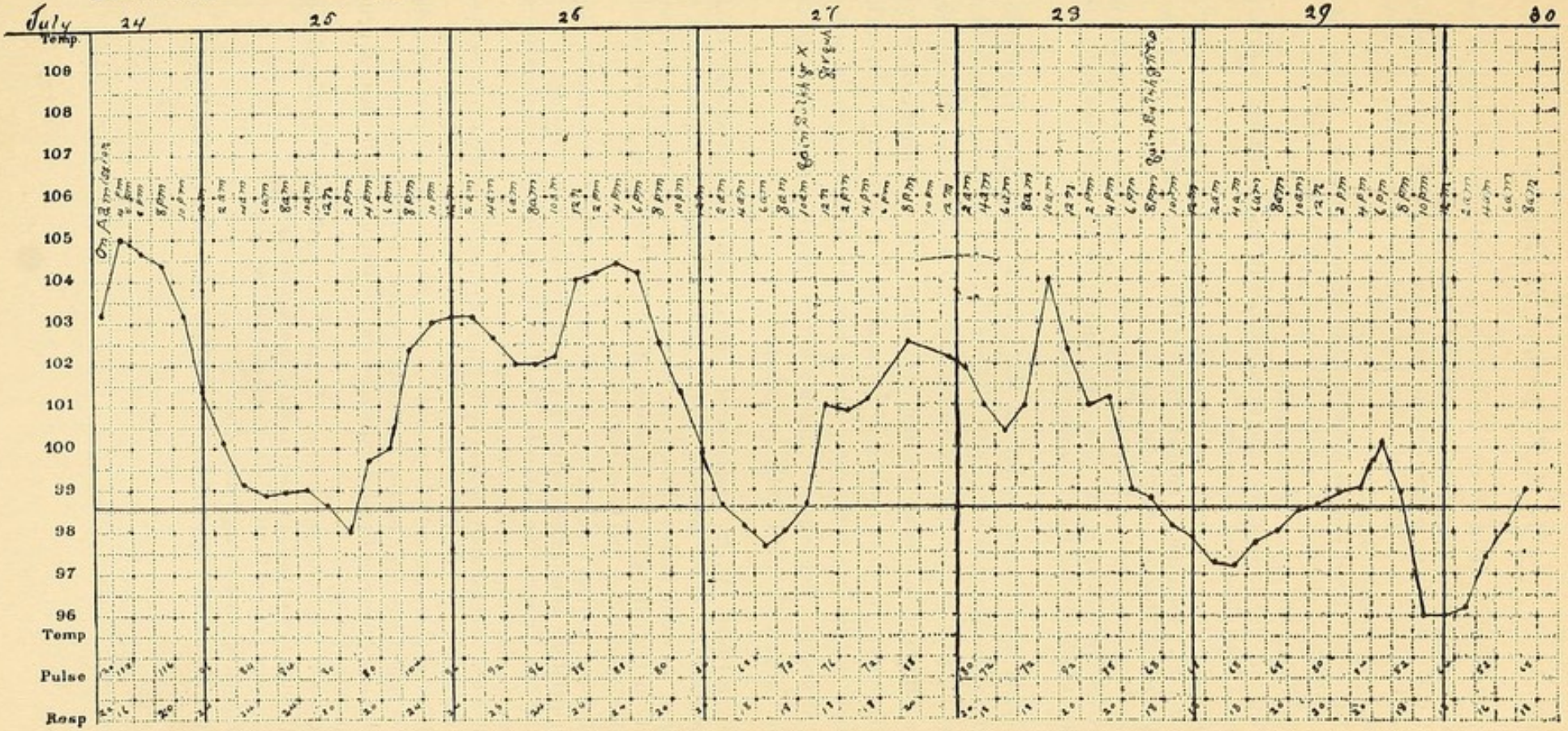
8 p. m. Temperature is beginning to rise. Examination of the blood showed nothing beyond one non-pigmented, ring-like form.

26–7–94. Blood, 9.30 a.m. Negative; no organisms seen.

2 p. m. A few ring-like bodies.

8 p. m. Numerous ring-like, amoeboid, hyaline bodies.

No. 10465 U. S Grant



27–7–94. The blood shows a few actively amoeboid, hyaline bodies; a few ring-like forms; a few bodies showing occasional pigment granules.

2 p. m. Numerous larger ring-like forms, one showing two quite active pigment granules; one larger body with a clump of pigment in the middle; two leucocytes containing pigment blocks.

7.45 p. m. Blood showed a few hyaline, amoeboid, bodies. At noon, quinine, gr. x (0.65), were given, to be followed by gr. v (0.325) every four hours.

28–7–94. 8.30 a. m. Blood negative.

2 p. m. One crescent and one ovoid body, with coarse pigment granules in the middle; two pigmented leucocytes.

8 p. m. Crescentic bodies and numerous pigmented leucocytes.

29–7–94. Temperature normal. Blood at 10.15 a. m., negative. At 3 p. m., ovoid and crescentic bodies. At 8 p. m., the same.

30–7–94. Crescents still visible. There was a slight abortive rise in temperature on the evening of the 29th; temperature was normal on the 30th, when the patient insisted upon leaving the hospital.

This case shows, as far as the clinical chart goes, the closest approach to Marchiafava's and Bignami's aestival-tertian fever that we have seen. While the examination of the blood revealed, apparently, but one set of parasites, the few stages of development, however, which were visible, makes it impossible for us to say with certainty whether this was the case. There was, so far as we could discover, no difference between the morphological characters of these parasites and those associated with quotidian fever.

Case 10534.—M. R., female, single, colored, aged 29; first attack. Duration? Entered the hospital July 31st, 1894, in an hysterical attack; opisthotonos, grinding of the teeth, tossing about, complaining of general soreness and pain, particularly in the left breast. Temperature, 100.1°; 101° at 8 p. m.; nearly normal the following morning; the blood not examined.

1–8–94. Patient is better, complaining only of headache; examination negative. Temperature, as noted on chart, beginning to rise during the evening.

2–8–94. Temperature elevated. Blood at 10 p. m. showed a considerable number of small, ring-shaped and amoeboid hyaline bodies.

3–8–94. Temperature normal during the morning, beginning to rise in the afternoon.

Blood, 3 p. m., showed a large number of hyaline bodies, many showing distinct spots of pigment, some smaller ring-shaped forms; pigmented leucocytes.

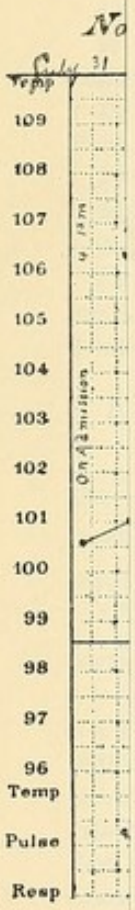
8 p. m. Numerous ring-like bodies, several hyaline forms with pigment granules; pigmented leucocytes.

4–8–94. Temperature elevated. Blood at 9 a. m. showed a few ring-like bodies with one or two hyaline forms; some pigmented leucocytes.

2 p. m. Several hyaline bodies; pigmented leucocytes.

7.30 p. m. A few ring-like bodies.

5–8–94. Quinine, gr. v (0.325), every four hours. Temperature normal.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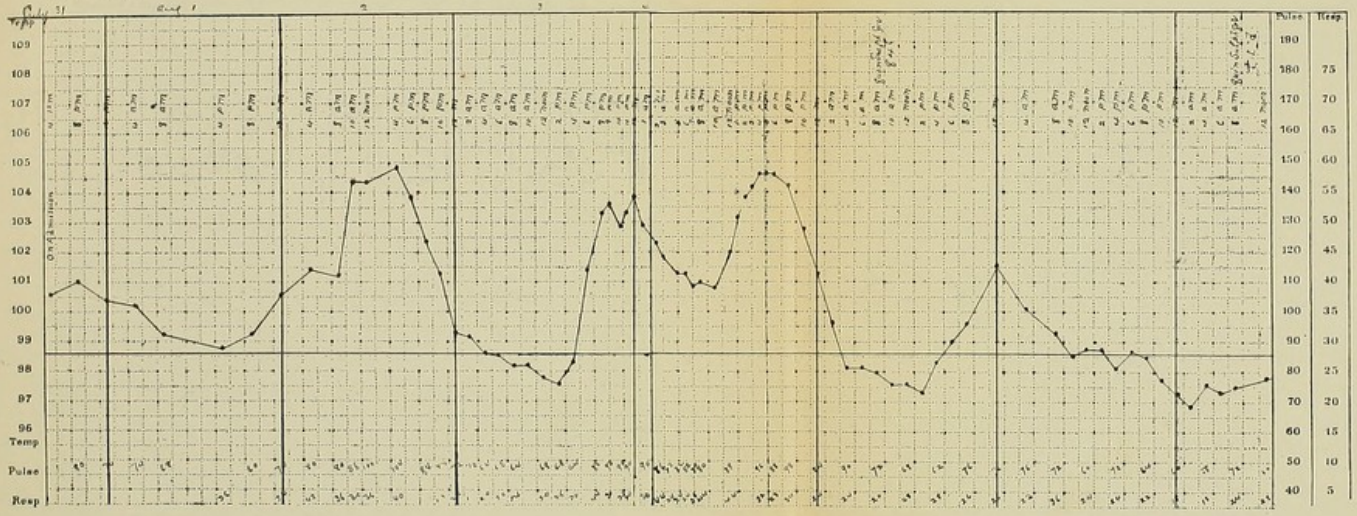
No. 10534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9 a. m. A few ring-like bodies; one or two amoeboid forms.

3 p. m. A few ring-like bodies with one pigment granule; pigmented leucocytes.

7.20 p. m. A few ring-like bodies. Temperature beginning to rise.

6–8–94. Temperature normal. Blood negative at 9 a. m. and 2 p. m.

7, 8, 9, 10, 11–8–94. Temperature normal and blood negative.

14–8–94. Temperature normal. No blood examinations for several days. To-day, ovoid and crescentic forms are seen.

15–8–94. Ovoid, crescentic, round and flagellate bodies; pigmented leucocytes.

16–8–94. Crescents and ovoids; no flagellate bodies to-day at 2 and 8 p. m.

17–8–94. Crescents, ovoids, and flagellates; pigmented leucocytes, the pigment being in fine granules.

18–8–94. Blood examined at 9.30 a. m., 2 and 8 p. m.; only crescents and ovoids were seen.

19–8–94. Crescents, ovoids and flagellates.

20–8–94. Crescents and ovoids.

21–8–94. Crescents and ovoids.

From this time on the blood was negative. The chart here shows two anticipating tertian paroxysms; one of them shows the pseudo-crisis and pre-critical elevation described by Marchiafava and Bignami.

Examination of the blood, in this case, is particularly interesting, in that it shows the development of flagellate bodies ten days after the beginning of quinine, nine days after the temperature had been normal. These were found as late as the fourteenth day of normal temperature.

The following case is included as a possible instance of aestival-tertian fever, though the temperature was, for some time, continuous.

Case 7753.—J. W., married, aged 38, laborer, admitted 21st July, 1893. He says that he had intermittent fever at fifteen; has been, otherwise, always well. His present illness began four days before entry with a shaking chill in the morning, followed by fever and sweating. This was repeated two days ago, and to-day, July 21st, the patient entered the hospital with a temperature of 102.6°. The physical examination was negative; the spleen was not palpable. The urine showed a slight trace of albumen; no casts were found; a faint diazo reaction was present. The blood, on entry, showed only a few very small, ring-shaped, hyaline bodies. The chart shows the course of the fever.

On the 22nd, at 3.45 p. m., the blood showed but a few small, hyaline, ring-shaped bodies.

On the morning of the 23rd, at 9.45 a. m., the blood contained a very considerable number of hyaline organisms, some very small and often ring-shaped, others a trifle larger and amoeboid; no pigmented forms were seen. At 3.45 p. m. numerous hyaline bodies, slightly larger, but no pigmented forms. At 11 p. m. about the same appearance.

On the evening of the 24th the blood showed a similar appearance; still no pigmented forms.

On the 25th, at 10.30 a. m., the organisms were much more numerous than the night before, mostly a little larger than last night, and a few contained one or two very fine pigment granules.

On the 26th very few organisms; no pigmented forms. Quinine, gr. v (0.325), every four hours.

On the 27th, at 10.15 a. m., no pigmented forms seen. The organisms are less numerous.

28–7–93. Temperature normal; patient leaves at his own request.

In this case, a history of tertian paroxysms before entry was given, though the examination of the blood did not allow us to follow out the cycle of development of the organism. The temperature, however, is a good example of the more or less continuous variety of fever which is sometimes seen with this form of malaria. We have not included the case among those with tertian paroxysms, though we are inclined to think that Marchiafava and Bignami would place it under that heading. Does the continuous fever from the 22nd to the 24th and from the 24th to the 26th represent one or two paroxysms? The examination of the blood, not as complete as might have been wished, does not wholly clear up the matter.

The following case, though it is included, in our classification, among the combined infections, would, perhaps, be better mentioned among the aestival-tertian cases.

Case 10529, male, single, aged 29, admitted July 31st, 1894, complaining of chills and fever; first attack. He has been feeling poorly for a month, having had chills and fever, he believes, at irregular intervals; general soreness, vomiting, variable appetite.

On entrance, temperature was 103.8°, reached 104.3° at 8 p. m., and was normal by early the following morning. The appended chart will show the course of the fever.

Blood, 6 p. m., showed a few amoeboid, non-pigmented, hyaline bodies.

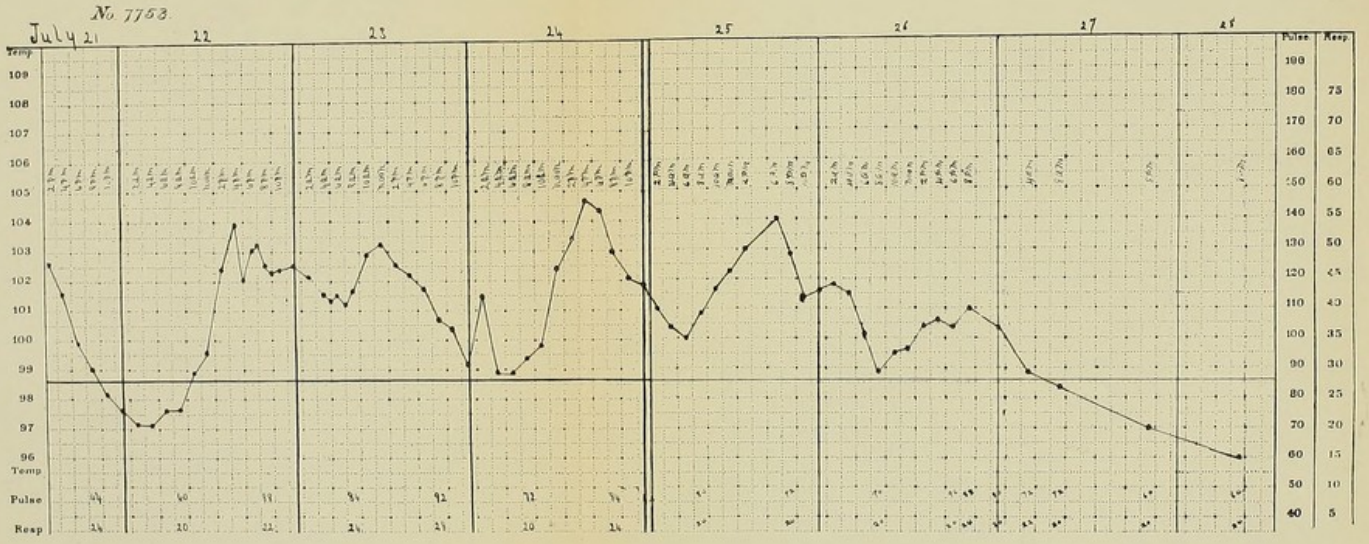
1–8–94. Physical examination showed a coated tongue, herpes on lips; spleen not palpable.

Blood. One amoeboid, hyaline body, with two spots of pigment, at 8.30 a. m.; at 9 a. m., the same; at 2 p. m., a few rather large ring-like bodies, more hyaline forms, several having distinct blocks of pigment.

8 p. m. Hyaline bodies a little larger, some ring-shaped, one nearly full-grown parasite, apparently of the tertian variety, the red corpuscle being expanded and decolorized, pigment granules in the body being brown, fine, and in active motion.

2–8–94. Blood, 9 a. m. Negative.

2 p. m. Numerous small ring-shaped bodies, few hyaline forms, several with distinct pigment granules, two larger bodies nearly filling the blood corpuscle, with a clump of pigment in the middle. Corpuscles were not expanded, but were rather pale.


No. 7753.
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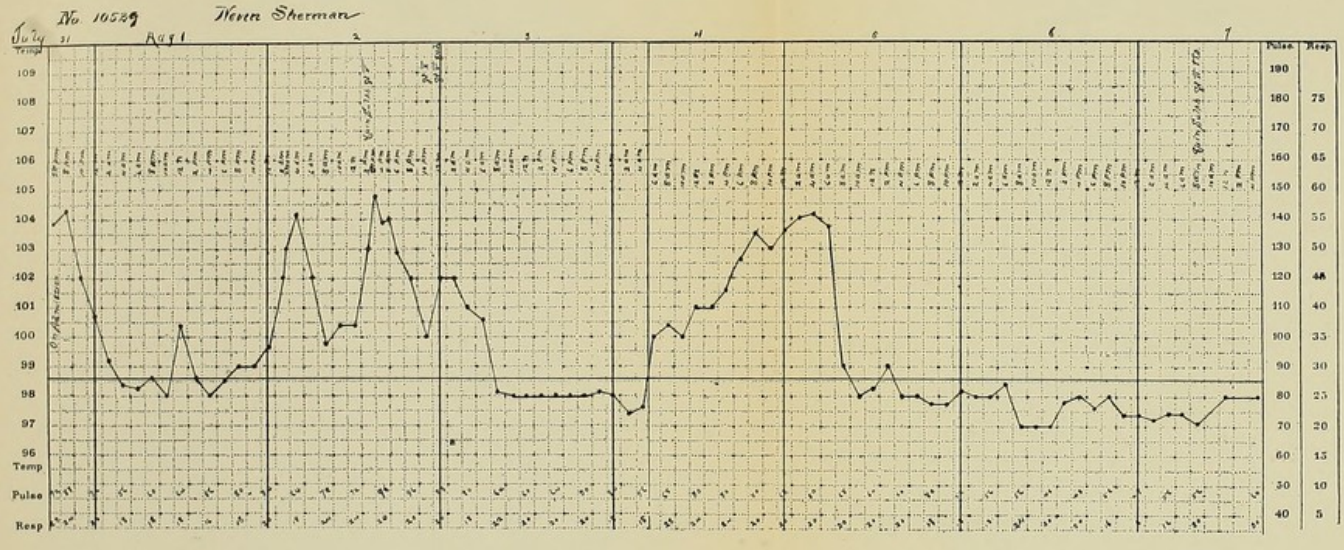
No. 10589
Nevia Sherman
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8 p. m. Numerous small ring-shaped bodies, a considerable number of hyaline forms. The patient had two distinct chills, one at 2 a. m. and one at 2 p. m.

At 3 p. m. the patient was given quinine, gr. v (0.325), which was vomited. At 10 p. m., gr. x (0.65), afterwards gr. v (0.325), every four hours. During the afternoon, a most profuse urticarial eruption appeared over the whole body. About 7 p. m. patient suddenly sat up in bed; his eyes became fixed and staring, he fell back again muttering to himself, apparently quite unconscious; profuse sweating; face livid; pulse uncountable at the wrist; no biting of the tongue; no involuntary micturition or defecation; no rigidity of the limbs. In fifteen minutes the attack had passed off.

3–8–94. Temperature normal. Blood, 8.30 a. m., showed a fair number of amoeboid, hyaline bodies in unaltered corpuscles, some ring-like forms, occasional bodies with one or two minute pigment granules; pigmented leucocytes, the pigment being for the most part in fine granules.

3 p. m. A few ring-like hyaline bodies, several forms having minute pigment granules; pigmented leucocytes similar to those in the morning.

8 p. m. A few ring-like forms, two bodies having minute pigment granules.

4–8–94. The temperature rose early this morning with chill, another chill occurring at 4 p. m.

Blood, 9 a. m. A number of small hyaline bodies, one with a pigment granule, a few ring-like forms, one large, full-grown, swollen, extra-cellular tertian parasite, with pigment in active motion.

2.45 p. m. One body filling about two-thirds of the red corpuscle, containing a central clump of pigment in active motion; several pigmented leucocytes.

5–8–94. Temperature normal. Examination of the blood at 9 a. m., 3 and 7.20 p. m., showed a few ring-like bodies and pigmented leucocytes.

The blood of the 6th and 7th of August showed no organisms.

8–8–94. One pigmented leucocyte with scattered granules.

8–9–94. No organisms seen; patient discharged.

This case is interesting from several standpoints. As with all the other cases of combined infection which have been noted, while organisms of both tertian and aestivo-autumnal types were present, one of these types—in this case the aestivo-autumnal—was preponderant, causing all the symptoms. It is an interesting question as to how we should regard the chart. Was the elevated temperature between the early morning of the 2nd and the morning of the 3rd a single paroxysm, and the case one with intervals of about fifty-two hours, or are we to assume that we were dealing with multiple groups of parasites? We do not feel that the examination of the blood justifies a conclusion. It is an interesting point, that on the 2nd there were two chills, one at 2 a. m., and another at 2 p. m.; while on the 4th there were also two chills, one at 6 a. m., and one at 4 p. m. The marked irregularity of the temperature between the 2nd and 3rd

is striking. It may, also, be noted that there was a slight rise of temperature at noon on the 1st. The presence of occasional pre-segmenting forms during the paroxysms is of interest. The curious nervous manifestations, during the paroxysm on the second, may have been dependent upon some interference with the intra-cerebral circulation on the part of the parasites.

Cases of Pernicious Malarial Fever.

Only three cases of pernicious fever have been admitted to the hospital since its opening. Of these, two resulted fatally, and one recovered. The first two cases we will quote from Dr. Osler's note in the Johns Hopkins Hospital Bulletin, December, 1891.

Case 131.—Lewis K., admitted July 18, 1889, complaining of pains in the head and of coldness and numbness of the feet and hands. He has enjoyed fairly good health, and, for his age, is a vigorous, healthy-looking man. On the 9th, while picking berries in a field in Anne Arundel county, he had a heat stroke; was unconscious for two hours, and had to be carried home. He was up the next day and was able to work; has not felt well since, and has had headache and occasional feelings of sensation of cold.

On the 18th the following note was made: Healthy-looking, much sun-burnt, pulse full, vessel-walls soft, no oedema of feet. The lungs are clear in front and behind; respiration is a little prolonged. The apex beat of heart is neither visible nor palpable; the sounds are weak, the second is scarcely audible at base. The area of liver dullness is reduced; the spleen not enlarged. The urine is light yellow in color, specific gravity 1010; no albumen or casts.

I saw the patient only during the first four days of his stay at the hospital, and thought that he was suffering from the effects of a sun-stroke. He was given a tonic mixture. The patient's temperature was normal, but on the 20th and 21st the morning record was 97.6° and 97.8°.

On the 25th, at 11.30, he had a chill, and the temperature rose to 105° and remained high all afternoon. At 7.30 p. m. it was again 105°, and he had a graduated bath.

Throughout the 26th the temperature fell, but did not get below 101°; the pulse was rapid and feeble.

On the 27th the temperature at 8 a. m. was 100.5°; rose in the afternoon to 103°, and in the evening was 100.3°; pulse 104, extremely irregular and intermittent. There were feeble râles, with a high-pitched percussion note in right infra-scapular region. Towards evening the patient sweated profusely, and the breathing was of the Cheyne-Stokes type.

On the 28th the temperature fell rapidly, sinking from 103° at 4 p. m. of the 27th to 97.3° at 8 a. m. of the 28th, and to 95.5° at 10 a. m. The pulse is extremely feeble and irregular. He vomited twice; no expectoration. There was marked

feebleness of breathing at the right base. Throughout the afternoon of the 28th the temperature rose, and at 8 p. m. was 100°.

29th. Cheyne-Stokes respiration persists; has had slight diarrhoea. He speaks with difficulty, but appears to be conscious.

Throughout the 30th and August 1st he gradually sank, and died on the morning of the 2d.

I did not see this patient from the date of his chill until the morning of the 2d, just before his death. The case was regarded as one of low anomalous pneumonia. The day after the chill it is stated in the note that the blood was examined with negative results; but there is no initial to indicate by whom the examination was made.

The following note of the microscopic examination was appended to the post-mortem report by Dr. Welch: "Blood from the finger shows in small numbers malarial organisms, namely, spots of the shape and size of the red blood corpuscles with pigmented plasmodia, free round pigmented corpuscles, varying in size from blood plates to twice that size, and pigmented crescents, the pigments in a ring in the middle. I found in one specimen of splenic pulp two actively free flagella. In the capillaries of the brain are a few pigmented corpuscles."

Case 1769.—J. B., aged 34, admitted September 10th, 1890. I saw him in the dispensary at 1.30 p. m. He was very weak and tremulous, with eyes congested and cheeks flushed, and with a dazed, stupid appearance. The tongue was swollen, heavily furred and indented. He looked like a man who had been drinking, and I told his brother that it would be impossible for us to admit him to the wards in his present state. He assured me, however, that he had not been drinking to excess, and on ascertaining that there was not the slightest trace of alcoholic odor in the breath, I signed the order for his admission.

The following history was obtained. Family and personal history good. The patient is a sailor by occupation, and has enjoyed excellent health; he left Boston for Savannah five weeks ago; spent a week in the latter place, and as the weather was oppressive he, with several of his shipmates, was in the habit of sleeping upon the grass all night. He remained well on the voyage to Baltimore, where he landed August 31st. He was about the house all week, not feeling quite himself, but the present illness dates from Sunday the 7th, when, without any chill or fever, he began to have vomiting. He felt extremely weak and prostrated, so that he could not get up on Monday morning. Throughout Monday and Tuesday the vomiting continued at intervals, and he was completely prostrated. He had no chills, but on Monday and Tuesday he took some quinine pills. In the dispensary, after failing to detect any alcoholic odor in his breath, and on learning that he had recently come from the South, the blood was at once examined; large numbers of Laveran's organisms were found, which rendered the diagnosis clear. His temperature on admission in the ward was 101°; pulse 104, small; tension not increased; radials not stiff. The abdomen was soft; nowhere tender. The edge of spleen was just palpable on deep inspiration; upper border of dulness at the ninth rib.

Apex beat of heart in 5th interspace within nipple line; sounds clear; examination of the lungs negative.

Blood. Small intra-corpuscular forms in extraordinary abundance, often 6 or 8, to be seen in the field of the $\frac{1}{12}$ im. The majority of them are not pigmented, and undergo very rapid changes in outline. The pigmented forms have the granules

more concentrated than is usual in this stage of the evolution of the parasites. An unusual number of the leucocytes presented pigment granules.

11th. Very bad night; much vomiting; temperature sank to 98.6° at 10 a. m., and to 98.2° by 8 a. m. At the morning visit the patient looked depressed; tongue heavily furred; pulse 80, small and thready; respirations 20. Has no headache, and complains chiefly of profound weakness. At noon the temperature began to rise, and at 4 p. m. reached 102.2°, and for six or eight hours remained about 102°, gradually falling through the early morning hours, and at 8 a. m. reaching 98.5°. The blood condition remains practically the same.

12th. 10 a. m. Patient passed a better night. The vomiting has stopped, but the tongue is still furred; no increase in splenic dulness. The bowels have been freely opened. He still looks depressed and dull, and complains of a feeling of great prostration.

13th. Temperature has been about 98° for the past twenty-four hours, pulse 72, small. The vomiting has not been so distressing, and he has taken the milk and brandy better than on any day since admission. The blood examination shows a marked diminution in the number of corpuscles containing the plasmodia, doubtless under the influence of the quinine.

14th. Temperature has been sub-normal, not rising above 97.5° all day. The vomiting has returned, and for the first time it contained blood, not in large amount, but sufficient to color the fluid. His mind is perfectly clear, and his sole complaint is of the extreme depression.

15th. 10 a. m. Patient's condition is worse since 8 p. m. last evening. The temperature has been below 97°, and at 12 midnight sank to 96°; pulse 64, respirations 20. Tongue still swollen, heavily furred and indented. Note on the blood to-day is: "Plasmodia very much diminished in number; leucocytes still show much pigmentation." The urine is amber colored, specific gravity 1010, acid and contained a slight amount of albumen. At 9 p. m. I made the following note: patient is in a very peculiar condition; is drowsy, dull, roused with difficulty, and does not answer clearly. He has behaved oddly all day, and has been very restless. There has been very little vomiting; temperature has been sub-normal, and is now 96.5°. For the first time the tongue is distinctly dry.

16th. Through the night the patient was very restless, and had much hiccough; was not delirious, but acted queerly. The temperature sank through the night, and at 2 a. m. was 96°; at 4 a. m. the thermometer could not be made to register more than 95°, and remained at this point until 10 a. m. The vomited matter last night contained flakes of blood enough to tinge the whole fluid. He had retention of urine, and this morning 1500 cc. were withdrawn, which showed a narrow ring of albumen and contained hyaline and granular tube-casts. The nurse says that he does not understand questions, but he seemed to recognize me, and gave fairly rational answers, but complained of great oppression in the abdomen. The pulse is 72, and, considering his condition, the volume and tension were remarkably good. At 6 p. m. I made the following note: temperature has risen through the day, and is now 97.2°. The tongue is dry, pulse 96, regular and of very fair volume. He is extremely restless, and his face has a dusky hue; the respirations are at times gasping, 24 to the minute. He answers questions, but talks and rambles in an incoherent way. To-day very few red blood corpuscles containing plasmodia have been found; the leucocytes

are still much pigmented. Patient became much more restless, threw himself about on the bed, then became unconscious, and died at 8 o'clock. The treatment consisted of half drachm doses of quinine every six hours, which was given hypodermically when the vomiting became excessive.

The drawings made from the blood in this case showed most characteristic aestivo-autumnal parasites.

A further comment upon the anatomical lesions in these cases will be found, in another part of this fasciculus, in the article by Dr. Barker.

The first of these cases is a very interesting example of death with a sub-normal temperature, occurring after the number of malarial parasites had been materially reduced by quinine.

CASE 10419.—F. O., single, aged 40, commercial traveller, admitted to the hospital July 19th, 1894. The patient, on entrance, could give no history, but from friends, and, later on, from himself, the following notes were obtained:

Since the 11th of June the patient has been travelling for the greater part of the ime in very malarious districts further south, having been "on the road" all the way from Maryland to Florida. For three weeks before entrance patient had not felt well, having, he believes, had fever off and on, but never chills nor sweating. His appetite was poor; he had considerable headache and, at times, nausea. He took to bed on the 16th, and became dull and stupid, recognizing no one after the morning of the 18th; no diarrhoea; troubled much with hiccough for six days before admission.

Immediately after admission the patient was seen and the following note was made: "Large, well-formed man, rather corpulent; is lying on his back in bed; respirations quiet, ten to the quarter; pulse regular and full, twenty-seven to the quarter, rather soft. The patient is quite comatose; the eyes are closed, the mouth open. A clonic spasm of the lower facial muscles on the left side is frequently noted, the mouth being drawn a trifle to the left. Pupils are equal, of moderate size, react readily to light on raising the lids. There is a well-marked sub-icteroid tint to the skin and to the conjunctivae, and the urine, which has been passed involuntarily, stains the bed clothing a markedly yellow color.

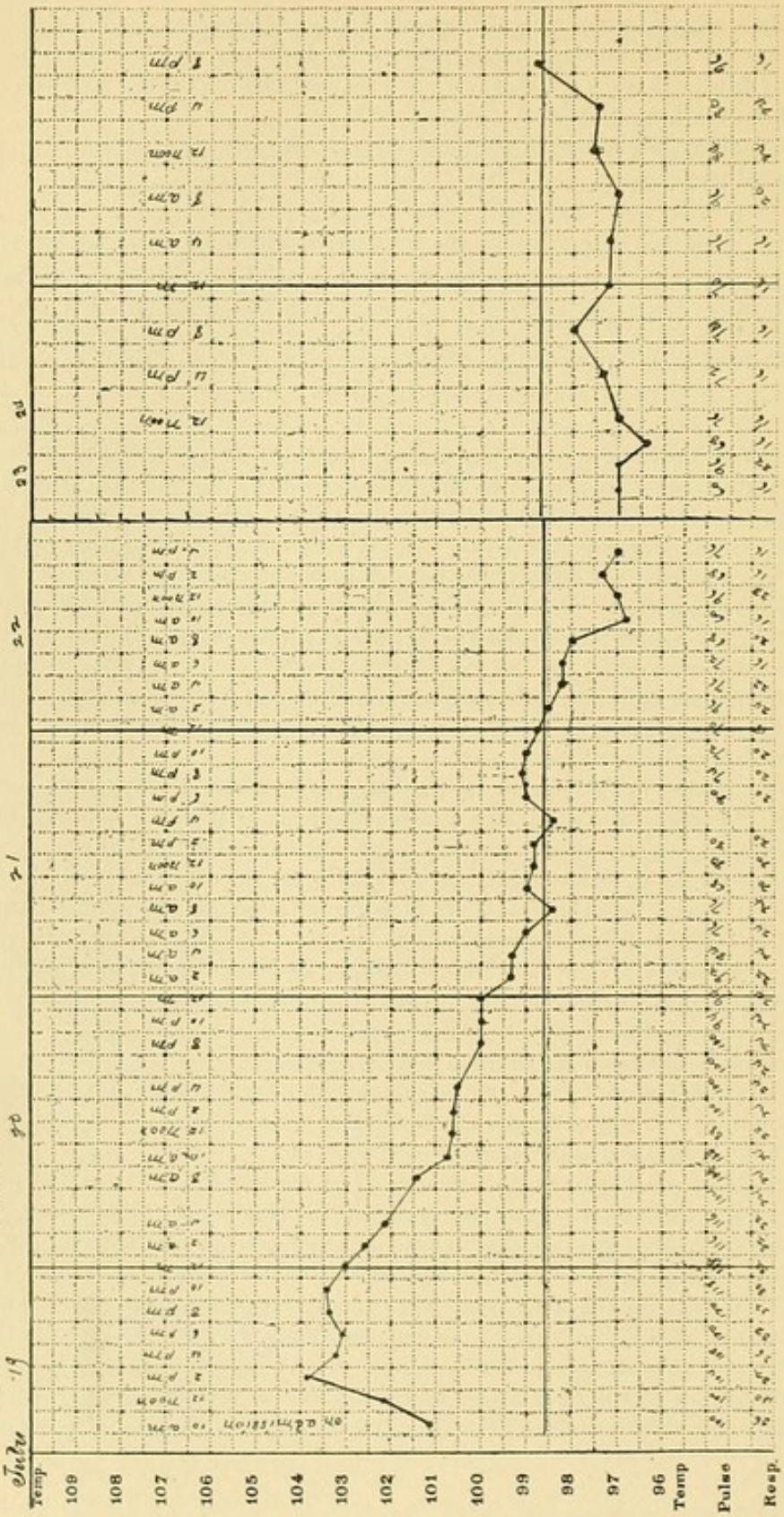
Thorax; negative on auscultation and percussion.

Heart; point of maximum impulse in the fifth space a little inside the mammillary line; relative dulness at the fourth rib; does not pass left sternal margin; sounds clear, of normal relative intensity.

Hepatic flatness begins at the fifth space, and reaches about to the costal margin; the border is not palpable, possibly because of the lack of deep respirations.

Splenic flatness begins at the eighth space and reaches anteriorly to the costal margin. The border is not distinctly palpable. The extremities are relaxed; there is no increase of the reflexes. While the patient does not answer questions, and pays no attention to sharp requests to put out the tongue, he occasionally moves an extremity, and when one grasps his hand, he makes a slight effort to close his fingers."

Examination of the *blood* at the bedside showed a considerable number of the smallest ring-shaped, intra-cellular, hyaline bodies, situated, for the most part, in


No. 19
Ward M. F. O
Temp
109
108
107
106
105
104
103
102
101
100
99
98
97
96
Temp
Pulse
Resp.

crumpled, brassy-colored corpuscles. In one of these the haemoglobin was noted to have retracted from the outline of the corpuscle about the ring-shaped organism. No apparent leucocytosis; no pigmented parasites nor pigmented leucocytes. Muriate of quinine and urea, gr. xx (1.3), was immediately given hypodermically. Surprised by the hypodermic injection, the patient started for a moment, opened his eyes, and turned over in bed. Afterwards he had a slight attack of hiccough, lasting not more than a minute. The *urine*, on admission, was of a mahogany brown color, bile-stained, clear, acid, 1021, faint trace of albumen, no diazo reaction, no sugar, microscopically, negative. Temperature rose to 103.8° at 2 p. m.

Blood. 11 a. m. A considerable number of small ring-shaped and amoeboid hyaline bodies. Almost the majority of these were contained in crumpled, brassy-colored corpuscles. In many the haemoglobin was retracted about the organisms.

At 12 m.; the same appearance, excepting that in one parasite a few minute pigment granules were seen.

At 2.15 p. m.; organisms much more scanty, almost all ring-shaped, in crumpled corpuscles.

From 3 to 5 p. m., various examinations showed similar appearances.

At 8.30 p. m.; organisms very scanty, mostly ring-shaped and amoeboid hyaline bodies. One was seen about one-quarter the diameter of a red corpuscle, with several pigment granules in the middle. It was lying in a crumpled, brassy colored, corpuscle with retracted protoplasm. During the afternoon the patient became more restless and a little brighter, tossing about much in the bed. He opened his eyes when spoken to, and occasionally answered a question, but was confused and wandering. Muriate of quinine and urea, ten grains, (0.65), hypodermically, at 5 p. m. and 11 p. m.

20–7–94. Temperature 101.4° at 8 a. m. This morning, is tossing about in bed and restless, occasionally mumbling to himself. He answers sharp questions in a confused manner. Patient was fed yesterday entirely by enemata; to-day takes liquids. ℞. Sulphate of quinine, gr. v (0.32), every four hours. Temperature, by evening, had fallen to 100°.

The blood, in the morning, showed a number of intra-cellular hyaline forms, amoeboid and ring-like; no pigmented forms; no crescents. Late in the afternoon, but a few hyaline bodies were seen in two specimens.

21–7–94. The following note was made: "The temperature, which on entry was 101.2°, rose, on the afternoon of the 19th, to 103.4°, since when it has steadily fallen, until 8 a. m. to-day, when it is 98.3°. Throughout the day yesterday the patient became gradually clearer mentally, and to-day is quite rational. Ever since the afternoon of the 19th the patient has had obstinate hiccough for the greater part of the time. The slight jaundice still persists; pulse and respiration are slow and quiet. The spleen is readily palpable on inspiration. He is taking quinine, gr. v (0.325), every four hours. The blood shows only an occasional intra-cellular hyaline body."

22–7–94. Temperature normal. The speech, which has been a little thick before this, is quite clear. The blood showed but one hyaline body after long search. The urine is normal in color, free from bile, no albumen.

23–7–94. No hiccough since yesterday. From this time onward recovery was steady; no further organisms were found in the blood.

30–7–94. Leaves to-day, well.

This case is one of considerable interest in as much as it is the only example of comatose pernicious fever which we have had in the hospital. A particularly interesting point is the fact that, notwithstanding the severity of the symptoms, but few organisms, and those almost entirely the very small hyaline forms, were found in the peripheral circulation. The hiccough and the spasm of the lower facial muscles on the left side, as well, also, as the slight thickness in enunciation, are interesting points.

It will be noted that all these cases showed the aestivo-autumnal organisms, and, while severe symptoms may occur during the paroxysms in cases of tertian fever (delirium, etc.), true pernicious fever we have only observed in aestivo-autumnal infection, an observation which agrees entirely with those of the Italian and Russian authors who have dealt particularly with such cases.

The analysis of the types of fever in these cases certainly justifies us in distinguishing, sharply, the fevers associated with the aestivo-autumnal organisms, from those seen in the ordinary tertian or quartan infections. While, as has been previously noted, certain cases show charts not unlike those of tertian or quartan infections, the majority show distinctly longer paroxysms, lasting, on an average, at least nineteen or twenty hours, and frequently overlapping one another, causing continuous fever. The proportion of continuous and irregular fevers is much greater than in tertian infections. The individual paroxysms differ further from those in tertian or quartan fever, in that, in many, the rise of temperature is more gradual, frequently occurring without the sharp initial rigor.* Acknowledging, then, these differences between the regularly intermittent and the aestivo-autumnal fevers, can we distinguish any ground type or types among the latter? We have learned to recognize, in the regularly intermittent fevers (tertian and quartan infections), that the febrile symptoms bear a distinct, direct relation to the life history of the specific parasite; that the paroxysm is always associated with the arrival of a group of organisms at maturity and with their segmentation. The observations of numerous students, particularly in Italy, make it probable that this paroxysm is due to toxic substances set free

* The term initial rigor, however, it should be remembered, is not always correct, as neither in tertian nor in aestivo-autumnal fever, can the chill be regarded with certainty as the initial step in the paroxysm.

by the parasites at the time of their segmentation. Do these rules, which apply so accurately to the regularly intermittent, tertian and quartan fevers, hold also for the aestivo-autumnal infections. If they do, how are we to account for the great variation in the febrile manifestations?

The cycle of development of the tertian and quartan organisms is easily followed out by the examination of the blood taken from peripheral vessels. We find the organism, in all stages of its development, in blood from the capillaries of the finger or the ear, and it has been shown, in a most interesting manner, that, just as in certain tertian and quartan fevers the paroxysms anticipate one another slightly, or show a tendency toward retardation, so the parasites, particularly of tertian fever, may, in certain instances, show a tendency to earlier segmentation, bodies being found in the process of sporulation which have not yet reached the ordinary full development, showing a smaller number of segments than is usually seen. In other words, it has been shown that while, regularly, the cycle of development of the tertian organism lasts approximately forty-eight hours, we may, not infrequently, see a parasite which matures every forty-six hours, or indeed, in some instances, every forty-four hours, or perhaps, in forty hours, while in others the cycle may take a somewhat longer time than the ordinary two days. And in all these instances the febrile manifestations follow the same course as the parasite, anticipating or retarding as the case may be.

Now are we to explain the irregularity of the aestivo-autumnal fevers by assuming a variability in the length of time required for the development of the parasite, recognizing, also, the frequency of infections with multiple groups of organisms? Must we assume that one of the chief characteristics of these infections is the extreme variability in the length of the cycle of development of the parasites, a variability dependent, perhaps, upon the malignity of the organism or upon the resistance of the individual affected; in other words, that this type of fever is essentially irregular? Or must we assume that there are two or more ground types of aestivo-autumnal fever dependent upon two or more varieties of the parasite?

From the observations which we have made, we feel that it is probable that there are aestivo-autumnal infections with but one group of organisms, which show daily paroxysms. Likewise, it appears to be

true that there are other fevers which, with one group of organisms, show paroxysms occurring at intervals of forty-eight hours or even more. It may also be stated that in most of the cases with longer intervals the paroxysms have been rather unusually long, while, in some instances, paroxysms strongly resembling those described by Marchiafava and Bignami as dependent upon their aestival-tertian organisms, have been seen. In some of these, however, as in Case 7753, it is most difficult to say whether we are really dealing, in each instance, with a single or with multiple paroxysms, while, owing to the few stages of development of the parasite which are found in the peripheral circulation, and to the small number of parasites which we see altogether in some cases, we do not receive the same assistance from examination of the blood that is given to us in the tertian and quartan fevers. Moreover, in these cases with quotidian and tertian chills, we do not see the same regularity in the hour of development of the paroxysms that we note in tertian and quartan infections; the variations are so great that it is not at all clear that we can draw a distinction between the two forms. Do we not rather see every intermediate stage between the two? We have certainly been unable to make any sharp distinction between the cases with tertian paroxysms, and other cases where the paroxysms occurred, instead of, perhaps, at intervals of forty-eight hours, rather at intervals of between twenty-four and forty-eight hours, suggesting, thus, a connecting link between the two forms of fever. Had we been able to distinguish, in these cases, any marked differences between the organisms observed in each, such as exists between the organisms of tertian and quartan fever, we might have been led to suspect that there were, in reality, two distinct types of infection. But this is not the case. As a matter of fact, the organisms, in our few cases with tertian paroxysms, have had all the characteristics of those observed in the other forms of aestivo-autumnal infection. We have not, unfortunately, been able to study carefully the later stages of development of the segmenting bodies, but the differences pointed out by Marchiafava and Bignami in the development of the organisms and in their segmentation, appear to us too slight to justify the division that they have made. These differences appear to us to be scarcely greater than those between the ordinary tertian parasite and the tertian parasite which assumes a slightly more hasty development, and undergoes precocious segmentation. The differences

consist almost entirely in the size of the adult forms, in the quantity of pigment which is present, and in the number of segments found, the organism which has taken longer to develop growing slightly larger, showing slightly more pigment, and a greater number of segments.

In conclusion, then, we have been able to distinguish, in infections with the aestivo-autumnal parasite, fevers with paroxysms occurring at intervals of about twenty-four hours, as well as others with intervals of about forty-eight hours, more or less. But we find, also, intermediate forms which constitute a connecting link between these two varieties of fever. The fevers with longer intervals show, generally, longer paroxysms. There is a large class of cases showing a more or less continuous fever where it is impossible to distinguish any ground type. We have been unable to distinguish any morphological or biological differences between the parasites associated with these various types of fever. In most cases, owing to the fact that but the earliest stages of development of the parasites are to be found in the peripheral circulation, and, sometimes, owing to the very small number of parasites which is to be found altogether, we are quite unable to distinguish whether we are dealing with one or with more groups of parasites. In a few cases, however, with characteristically intermittent fever, the examination of the blood, taken in connection with the course of the fever, has suggested to us that we were dealing with single groups of parasites whose cycle of development lasted from twenty-four hours or less, to forty-eight hours or a little more. The fever in these instances, as in the case of the tertian and quartan intermittents, we believe to be due to some toxic substance set free at the time of sporulation; it is essentially intermittent, and it is undoubtedly the fact that this intermittency is more evident in those cases which are observed at the beginning of their course. Though our studies of the parasite have been made almost entirely in the circulating blood, and do not justify a positive conclusion, we are, however, inclined to believe that the irregularity in the febrile manifestations is due chiefly; to the tendency on the part of the parasite to irregularities in the length of its cycle of development; to the fact that the period of time required for the sporulation of one group of organisms is materially greater than in the regular infections, owing to the fact that the arrangement of the parasites in definite sharp groups, sporulating

nearly at the same time, is much less distinct than in the tertian and quartan intermittents; to the fact that, frequently, organisms in all stages of development are present at one time, segmentation occurring almost continuously.

We do not believe, then, that we can, as yet, separate the aestivo-autumnal fevers into two or more distinct types.

With regard to the relations of the crescentic and ovoid bodies to the febrile manifestations, we shall speak later on. We are not, as yet, inclined to accept the view of Bignami, Marchiafava, et al., that they are degenerative forms, though we have never been able to trace their sporulation.

Much, however, remains to be done in the study and analysis of these fevers; a systematic study of the splenic as well as the peripheral blood should be carried out.

Combined Infections.

The cases of combined aestivo-autumnal and tertian infection observed were eleven in number. Of these nine were seen in the hospital, and two in the dispensary.

Case 1.—The first case was that of a man, single, aged 17, admitted to the hospital October 27th. Family history good; no previous illnesses. This is the first attack of malarial fever. Illness began fourteen days ago with chill, followed by fever and sweating. This has been repeated every day, chills occurring at about ten in the morning. The physical examination was negative, excepting for the palpable spleen; urine, negative. The *blood* showed numerous large, amoeboid, pigmented, intra-cellular organisms, characteristic of tertian fever, and the case was considered one of double tertian infection. The chart showed characteristic quotidian paroxysms with periods of subnormal temperature. The patient was treated with methylene blue, 0.1 five times a day, beginning on October 29th. After November 3rd the temperature was nearly normal, rising, however, slightly above 99° every day. The tertian organisms disappeared rapidly from the blood, but on November 3rd, five days after entrance, nineteen days after the beginning of the paroxysms, the patient showed crescentic and ovoid bodies characteristic of aestivo-autumnal malaria. On November 7th a few actively motile, small, hyaline bodies were also to be seen. Four days later the patient was discharged, the blood showing at this time no organisms. Eleven days later the patient returned to the dispensary, complaining of headache, loss of appetite, and thirst. The blood showed again crescentic and hyaline bodies, no tertian organisms. The patient was given quinine and was lost sight of.

Case 2 (4847).—A little girl, aged 7, admitted to the hospital on the 10th of March, 1892. For five or six months before entrance the child had suffered from quotidian paroxysms. She had had treatment, off and on, ever since then, the chills being at times tertian, and again irregular, according to the history. At other times she complained only of continued fever, headache, and sweating. On entering the hospital, tertian organisms were found in the *blood*, one strong group, and one group less developed. The temperature chart showed typical paroxysms on the 12th and 14th of March, the temperature being slightly elevated on the days between, but showing no sharp paroxysms. On the 14th, beside the typical tertian organisms, one crescent was seen. Quinine was given eight days after entrance, the paroxysms having disappeared on the sixth. The tertian organisms disappeared quite rapidly, but crescents were found in the blood for some time afterwards, while small, hyaline, actively amoeboid bodies, in association with the crescents, were noted for some time after the tertian forms had ceased to appear. The last date on which organisms were seen was on the 22nd of March, three days after the beginning of quinine. On this date a small, ring-like hyaline body was noted.

This case is interesting in that it showed a spontaneous disappearance of the tertian infection after rest in bed and tonic treatment, while the small organisms characteristic of aestivo-autumnal fever, being more resistant, continued present in the blood, only to disappear after the beginning of quinine.

Case 3 (5387).—A colored man, aged 32, admitted to the hospital June 15th, 1892. He had had his first attack of malarial fever during the fall before, no chills having occurred since January. Six days before entrance he had a shaking chill, lasting two hours, followed by fever, headache, and sweating; another, two days after this, and a third, two days later, the last occurring the day before entrance. The patient was a well formed man. Physical examination; negative, excepting for the palpable spleen. On the day of entrance the patient had a typical tertian paroxysm, lasting twelve hours, the temperature remaining below 99.8°, after this, without the administration of quinine. The *blood* showed, in the hospital, at the time of the chill, typical tertian organisms. Numerous segmenting bodies were seen, all showing from twelve to twenty segments. One of these bodies was of unusually small size, not having entirely filled the corpuscle. One typical crescentic body was seen. The tertian organisms disappeared entirely during rest in bed, and, after the 13th, only ovoid and crescentic forms were found. The patient was discharged on the 15th with a prescription for two grains (0.13) of quinine three times a day.

In this instance the symptoms appeared to be entirely due to the tertian organisms. It was probably a case of fresh tertian infection engrafted upon an old, attenuated aestivo-autumnal infection dating from the previous fall.

Case 4 (6090).—Male, aged 20, Pole, first attack of malaria, admitted to the hospital October 9th, 1892. He dates his illness back five weeks before entrance, having

had, at first, daily paroxysms, which had continued, off and on, up to the time of entry. The patient was anaemic, but otherwise the physical examination was negative, barring the palpable spleen. He showed a well-marked paroxysm on the day of entrance, and a slight rise on the following day. Quinine was given immediately, and the temperature was normal afterwards. The blood showed, at first, typical tertian organisms. On the second day after entrance crescents were found. On the 15th no organisms were to be seen. He remained in the hospital, taking quinine, until the fifteenth day of the next month, and was discharged well.

This case occurred at the season of the year when aestivo-autumnal malaria is particularly common; the patient had had paroxysms off and on for a number of weeks before entrance. It was doubtless a case of double infection.

Case 5 (6748).—A man, aged 23, admitted February 9th, 1893. He had arrived, a month before entrance, from Cuba, where he had had various malarial attacks. He showed, on entrance, a typical double tertian infection. The paroxysms disappeared immediately after the administration of quinine on the 11th, and no organisms were seen on the 15th. Nearly a month later, while in the surgical ward, where the patient had been operated upon for hernia, typical crescentic bodies were found in the blood. On April 4th, the patient returned, complaining of headache, anorexia and slight fever. The blood showed a typical aestivo-autumnal infection; hyaline bodies, ovoid and crescentic forms.

Doubtless the crescents, here, were the remnants of an old aestivo-autumnal infection. The tertian infection yielded readily to quinine, while the more resistant aestivo-autumnal parasites remained, causing a relapse.

Case 6 (8302).—A young man, aged 30, admitted to the hospital October 2d, 1893; first attack. Two weeks ago, after working on the Shell road for about a week, he complained of headache and general lassitude, slight chill and vomiting. Since then he has had nearly daily chills, with headache, fever and sweating. In the hospital the patient had a paroxysm on entry and one on each of the following days, lasting respectively 19 and 10 hours. The blood showed great numbers of aestivo-autumnal organisms, small, hyaline, amoeboid bodies, some showing occasional minute pigment granules, and also a certain number of tertian forms. Ten days later crescents were seen. Quinine was begun on entry, the tertian organisms disappearing rapidly, and the temperature remaining normal after two days.

In this case, also, there were clearly two distinct sets of organisms; the paroxysms here were apparently due to the aestivo-autumnal rather than to the tertian infection.

CASE 7 (8317).—Female, married, aged 27, admitted to the hospital October 4th, 1893; first attack. Present illness began about a month before entry with a shaking chill, followed by fever and sweating, which was relieved by quinine. For four days the legs have been swollen. The patient was in the seventh month of pregnancy. The temperature was never above 99.5°; the spleen was readily palpable. There was well-marked aortic insufficiency. The *blood* contained numerous ring-shaped and amoeboid hyaline bodies, and crescents; one tertian organism was also seen. Quinine was given on the day of entrance, and, after three days, no organisms were seen. The patient had been living in a very malarious district, and had undoubtedly suffered from a combined infection.

CASE 8 (8454).—Man, aged 23, admitted October 25th, 1893; first attack. He had been living in an extremely malarious district. His complaint, on entrance, was of general weakness and chilly sensations, with constant fever for two weeks, headache, and pain in the back. The *blood* showed hyaline bodies, crescentic and ovoid forms, and a few half-grown intra-cellular organisms of the tertian type. On the following day flagellate bodies were seen. The temperature was irregular, showing slight daily rises for several days. Quinine was given on the 21st, five grains every four hours, and, after this day, no tertian organisms were seen; only crescents and ovoid bodies were noted. The temperature was subnormal after the 23rd.

Case 9 (10529) has been mentioned under the cases of aestivo-autumnal fever. See page 142.

Cases of mixed Infection with Tertian and Aestivo-autumnal Organisms Observed in the Dispensary.

There were two cases of mixed infection observed in the dispensary.

CASE 7546.—A colored woman, aged 17, admitted to the dispensary on December 2nd, 1890. She complained of having had quotidian chills during August and September. Quinine was followed by relief, but, after a month, the paroxysms returned, and have recurred, she says, nearly every morning for the last six weeks. The *blood* showed a considerable number of typical tertian, intra-cellular organisms. Quinine, two grains three times a day, was given. Five days later the patient returned, stating that she had had no chills, but complained of feeling "terrible funny" at about the time when she ordinarily had the chill. The blood showed crescents and pigmented leucocytes.

This patient, who lived in an excessively malarious district, had probably been subjected to repeated malarial infection. Small doses of quinine readily overcame the tertian infection, while the aestivo-autumnal bodies resisted for a much longer time.

CASE 10351.—A man, aged 53, admitted to dispensary July 7th, 1891. He dated his symptoms back for four or five days, complaining of headache, vomiting, general lassitude, and occasional chills, fever, and sweating. The temperature at the time of admission was 102°. The *blood* showed typical aestivo-autumnal, hyaline bodies. Three months later the patient returned, giving a history of a return of his symptoms several weeks back, with daily chills for three or four days. Typical tertian organisms were found in the blood. Four days later, after the administration of quinine, five grains, three times a day, the patient said that he felt perfectly well. The blood showed no tertian parasites, but one ovoid aestivo-autumnal body.

It is probable that this case was one of fresh tertian infection on top of an old aestivo-autumnal fever.

In all these cases, then, it will be noted that, while two varieties of organisms were made out, the fever and the clinical symptoms appeared, in each instance, to be due to one particular set, that which was most strongly represented. In no case have we seen complicated temperature charts as a result. In cases 2, 3, 4, and 5, it would seem that there was probably a fresh tertian infection engrafted upon an old aestivo-autumnal fever; while in cases 6, 7, 8, and 9, the aestivo-autumnal organisms appeared to be the important group. It is interesting, in connection with this, to remember the experiments of Di Mattei, who found that on injecting blood from a case of quartan fever into one of aestivo-autumnal, the organisms injected increased in number, giving rise to clinical symptoms, while those already present showed a tendency toward diminution and disappearance. The converse was noted when aestivo-autumnal organisms were injected into a quartan case. In neither of his cases did a complicated fever chart result.

Most of these patients had been in very malarious districts, and had probably been again and again subjected to infections, and it is not unlikely that the predominating organism in each instance represented the fresher infection. Some may be inclined to use these cases as an argument in favor of the complete unity of the malarial organisms; as an argument that the tertian parasite may give rise to crescentic and ovoid forms. It is interesting, however, that, in most of these cases, not only the crescents were found after the disappearance of the tertian organisms, but also the other forms of the aestivo-autumnal parasite, forms which are notoriously more resistant to quinine than the tertian parasites. We have never seen any transitional

stages between tertian parasites and crescentic or ovoid bodies, while every stage can be readily followed out in the aestivo-autumnal group. We have never seen any transitional stages between tertian, quartan, or the aestivo-autumnal organisms, nor have we met with observations which would give sufficient ground for the assumption that this could occur.

General Conclusions with Regard to Types of Fever.

In conclusion, then, we believe that we can distinguish three distinct types of malarial fever:

(1). *Tertian fever.* } Regularly intermittent fevers.
(2). *Quartan fever.* }
(3). *Aestivo-autumnal or irregular fever.*

(1). *Tertian Fever.*

The tertian type of fever depends upon the presence, in the blood, of a parasite which passes through its cycle of existence in about forty-eight hours. The segmentation of this organism is always associated with a febrile paroxysm; these paroxysms occur, with considerable regularity, at intervals of forty-eight hours, though, in many cases, there is slight anticipation or retardation. The duration of the paroxysm is ordinarily from ten to twelve hours. The onset of the fever is generally sudden, associated, in the great majority of cases, with a distinct shaking chill or marked chilly sensations. The febrile period lasts for a variable length of time, while the fall of temperature is accompanied, generally, by profuse sweating. Frequently, owing to the presence of two sets of organisms, there are quotidian paroxysms. More rarely, probably owing to the presence of more than one group of organisms, or to the fact that the organisms are not arranged sharply in groups, a more irregular, somewhat continuous fever may be seen; in these cases rest in bed and general treatment will often reproduce a true intermittent type of fever. During the period between the paroxysms the temperature is generally sub-normal. The single tertian infections, representing the mildest forms of the disease, occur, more commonly, in the earlier months of the spring and summer; the double tertian infections, which are more severe, form the

majority of the cases later on. Spontaneous improvement is very common, though it is not generally permanent; more commonly, in the course of ten to fourteen days, a relapse occurs.

(2). *Quartan Fever.*

More rarely in this climate, we see fevers dependent upon the presence, in the blood, of a parasite which passes through its cycle of existence in seventy-two hours. As in tertian fever, the paroxysms are definitely associated with the segmentation of groups of the parasite. The paroxysms resemble, strongly, those observed in tertian infections, both in the manner of their onset and in their duration. Not infrequently, double or triple quartan infections may be observed, with resulting variations in the febrile manifestations. As in tertian fever, the symptoms yield rapidly to quinine, the organisms disappearing quickly from the blood.

(3). *Aestivo-autumnal Fever.*

Thirdly, we see a type of fever, occurring in the late summer and fall, dependent upon the presence in the blood of the aestivo-autumnal organism of Marchiafava and Celli. The cycle of existence of this parasite has not been followed out in an entirely satisfactory manner. We are inclined to believe that its duration may vary under different circumstances (malignity of the special parasite, different conditions in the infected individual, etc.) between twenty-four hours or slightly less, and forty-eight hours or more. This type of fever, in its pure form, is intermittent, while the paroxysms may be very similar to those of tertian or quartan fever. Commonly, however, the paroxysms show material differences; their length averages over twenty hours; the onset occurs often, without chills or chilly sensations; the rise in temperature is frequently gradual and slow, instead of sudden; the fall, likewise, occurs, often, by lysis instead of by crisis. The tendency toward anticipation and retardation of the paroxysms is much greater than in tertian or quartan fever, while, frequently, from the lengthening of one paroxysm, or the anticipation, perhaps, of another, the chart may show a more or less continuous fever. Sometimes there occurs a continued fever without sharp paroxysms. We believe that

these phenomena on the part of the temperature are due to irregularities in the duration of the cycle of existence of the parasite, to the presence of multiple groups of the organism, and, often, to the fact that segmentation is going on almost continuously in the internal organs. It is in these fevers that haematuria and haemoglobinuria are seen. These infections include, also, the pernicious fevers as well as the so-called "remittent" fevers, though we believe that the great majority of cases of "remittent fever" referred to as such in this country, are not malarial in nature.

These fevers are much more resistant to quinine than the tertian and quartan infections, though, when given in sufficient doses, the specific action is always manifest, unless the case be one of pernicious fever resulting fatally before the drug has had time to act.

VII.—CONCERNING THE NATURE AND SIGNIFICANCE OF THE CRESCENTIC BODIES OF LAVERAN.

The general results of our observations of the organisms in the aestivo-autumnal fevers have been stated in our description of the parasite, in an earlier part of this paper, and, in this section, we wish more particularly, to discuss the significance of the so-called crescents, which, though they are never found at the beginning of the process, appear, in most of the cases of aestivo-autumnal fever, after a certain length of time. It will be remembered that Laveran,[15] in his original articles, believed that these crescents represented a species of cyst containing the developing parasites, which, at their full growth, were represented by motile filaments, the flagella which might frequently be seen to break forth from the round bodies into which the crescents changed. With these views Richard [26, 33] and Danilewsky [194] agree.

Richard [26] suggested that the crescentic bodies represented corpuscles containing malarial organisms which, before they had reached full development, had been caught in capillaries through which they passed with difficulty, and moulded into this shape during their passage.

Marchiafava and Celli, as late as 1884,[36] denied that these were parasites, but later on, when they had recognized the organism, their

descriptions were similar to those of Laveran, excepting that (1885)[45] they denied that they were able to see a double contour. They did not agree with Laveran's conception of the nature of these bodies, denying that they were cystic in character.

Celli and Guarnieri,[93] however, describe the double contour, and note that often, on staining with methylene blue, a round body which is more deeply colored, may be seen near the middle, surrounded by the pigment, while the area about this is pale; the poles of the crescents show a marked affinity for the coloring matter. They note, also, for the first time that these crescentic and ovoid forms may show small round bodies—buds, as it were—about the periphery, one or more in number. The development of these minute round bodies, they suggest, may represent a method of reproduction. They also note the vacuolic degeneration of these crescentic forms, a process which had been previously described by Laveran.

Canalis,[104] in 1889, described the aestivo-autumnal organisms in an elaborate article which has already been referred to. He believes that there are two distinct cycles of development, the first lasting for a short time—about twenty-four hours—the parasite developing but a very small quantity, or, indeed, no pigment, and then segmenting in the ordinary manner; the second cycle lasting considerably longer—a variable length of time—and ending in the development of these crescentic and ovoid bodies. He also describes the double contour, suggesting a membrane, and notes that this is best seen in preparations several hours old, or fixed by osmic acid. He asserts that he has seen unquestionable evidences of sporulation in these crescentic and ovoid forms. He has seen round forms with or without double contour, containing eight or ten round or slightly ovoid bodies, each with a more obscure central part, while the periphery has the appearance of a double outline. Sometimes the pigment mass is in the middle, more frequently arranged in the shape of a crown at the centre or at one of the poles; at times the pigment appears to be retained in a small corpuscle; it may be seen to be extruded, contained in a protoplasmic mass; sometimes one sees groups of small bodies regularly arranged about a central pigment clump. He has never seen the whole process of segmentation, but he believes that these bodies are sporulating forms, both on account of their appearance and on account of their relation to the paroxysm. He also mentions the

possibility that gemmation, as described by Celli and Guarnieri, may likewise occur as a reproductive process. After sporulation we have, again, small, hyaline, amoeboid bodies. The cycle of development varies in length, lasting generally three or four days, at least, before the appearance of crescents. He notes the constant appearance of young hyaline bodies after the paroxysms, slight though they may be. Canalis insists that this sporulation must be sharply distinguished from the processes of degeneration which one may often observe. "The evidence of this degeneration consists in the presence of bodies which have lost their yellow or ashy color, and have become more clear, sometimes refractive, having a double contour much more distinct than that of the ordinary parasites, and a substance transformed into a mass of round or irregular bodies, generally of different size, and with a single contour. If one prolongs the microscopical examination of one of these parasites, he may observe, sometimes, in the course of several minutes, the fusion of two or three of these bodies into a single globule, forming, finally, irregular masses which eventually unite, giving to the parasite an homogeneous aspect without any further trace of the small bodies. The pigment is sometimes arranged in a central crown, sometimes irregularly placed at one extremity or at one side of the body. The characteristics which distinguish this process from that of sporulation are; the refraction of the degenerating body; the inequality in the size of the spherules; the absence, in these, of a more obscure central part; their fusion into irregular masses, and finally into one amorphous mass." These forms may also be found during complete apyrexia without any following rise of temperature, or any subsequent appearance of amoeboid forms; they represent a cadaveric state.

Marchiafava and Celli,[100] in their article on the aestivo-autumnal fevers, note the double outline of the crescents, and assert that it represents a distinct membrane, though they say that, at times, it may not be very evident. They have seen pernicious forms of fever without the development of crescents. They have never seen sporulating crescents, and do not definitely commit themselves as to the nature of these parasites. They insist, however, that the crescents filled with small round bodies are simply forms undergoing vacuolic degeneration, and that sporulating forms, as described by Canalis, do not exist.

The theory of Canalis concerning segmentation of the crescentic forms is accepted by Golgi,[118] though he states distinctly that he has never seen the actual process of segmentation. He believes, however, that in patients whose blood contains these bodies, paroxysms occur at long intervals—intervals of ten, twelve, fifteen days—which are doubtless associated with the development of new forms from the crescents. He regards their presence in the blood, as does Canalis, as a constant menace of further paroxysms.

Antolisei and Angelini,[119, 131] in the clinic of Baccelli in Rome, state that they, also, have observed the segmentation of the crescents, asserting that the spores of the segmenting bodies have a distinct double outline, in contra-distinction to the simple outline of the degenerate vacuolating forms which represent the death of the parasite. Vacuolization occurs as well in the crescentic, as in the ovoid, fusiform, and round bodies. The sporulation, they say, they observed before Canalis, though Canalis anticipated them in his article. The bodies show eight or ten segments with double contour, similar to those of the parasite of quartan fever. There is no doubt, they say, as to the nature of the process. They describe the crescents in a somewhat different manner from the previous observers, believing that they possess an outer layer of varying thickness, which is colored with haemoglobin; this, they think, represents a membrane similar to that observed about the red blood corpuscle. The outer border of the double outline is the only smooth sharp line; the inner part shades gradually into the substance of the crescent. This membrane does not stain with methylene blue. The crescents, they believe, are very resistant forms which do not disappear readily with quinine, the parasite pursuing a sort of latent life and reviving again later, going on to sporulation.

Korolko [275] believes that the double outline represents a membrane derived from the red corpuscle; he states that it may be stained with eosin.

The view that sporulation occurs in the crescentic bodies is also held by Grassi and Feletti.[221, 339] They believe that the crescents, however, are a totally different variety of parasite from the small hyaline forms which appear so frequently with them; they describe them as a distinct species of organism under the name of Laverania, a division which is accepted by Sacharoff.[212, 276] They believe that the

crescents are surrounded by a membrane which, like the membrane surrounding segmenting bodies, arises from the substance of the red blood corpuscle. The segmentation, they say, is similar to that in the Haemamoebae, but the resting stage is much longer, from eight to ten days, while the appearance of segmenting forms in the peripheral blood is abnormal. They doubt, seriously, whether the forms observed by Canalis, in the peripheral circulation, were true segmenting bodies. They believe that they have seen crescents with two nuclei. Later on, Antolisei [139] asserts that the crescents are not really encysted, but that there is a cutinizing or thickening of the peripheral layers of protoplasm, the same process which they believe to exist in the spores, giving them the double outline.

Thus it may be seen that, while, between Canalis, Golgi, Antolisei and Angelini, Grassi and Feletti, and Sacharoff there are some differences of opinion as to the development of these crescentic organisms, all believe that they may undergo a reproductive process—segmentation. The persistence of these bodies under quinine has been noted, and various of these observers have suggested that it is to the resistance of these encysted or, at least, protected forms of the organism that the long continuance of this type of malaria and the liability to relapses is due.

Bignami,[179] however, in May, 1889, in his work on the pathological anatomy of the pernicious fevers, suggests that this form of parasite is not a living body performing its normal functions, but merely a deviate and degenerate form which does not go on to reproduction. Bastianelli and Bignami [170] discuss this question at length. They conclude that the crescents belong to the same type of organisms as do the smaller hyaline bodies, not forming, as Grassi and Feletti and Sacharoff believe, a separate group of parasites. If quinine be given early, at the beginning of an attack of fever, the organisms may disappear before the appearance of crescents, while, if quinine be begun later on, the crescents, which appear ordinarily at about the end of the first week, may be present in the blood for a considerable length of time. In these crescents one frequently sees evidences of vacuolization, which is a degenerative and not a regenerative process.

Flagellate bodies, which they believe to be also degenerative forms, develop, often, from the round bodies. They call attention to the fact that, at the time of segmentation in, for instance, the tertian parasite,

not all the organisms fulfil this process, but, as is well known, a considerable number of large swollen forms, which are usually extra-cellular, occur. When one observes these bodies, they may be traced through various changes; sometimes they undergo vacuolization; sometimes they break up into a number of smaller, extra-cellular forms, in which the pigment is usually seen after a while to become motionless, while the outlines of the body become indistinct and often irregular; sometimes they develop into flagellate bodies. These changes, they believe, are sufficiently proven to be degenerative. They note the remarkable analogy between these processes occurring in the crescentic, ovoid and round bodies in aestivo-autumnal fever and those which are seen in the large swollen tertian parasites. Here, as in the large tertian forms, one not infrequently sees vacuolization, deformation, and also gemmation or budding which they consider analogous to the fragmentation of the tertian parasite. In these forms, alone, do we see the development of flagellate bodies.

When crescents exist alone in the blood they have no influence upon the temperature or the general condition of the patient. Convalescence may have begun and may continue, after the administration of quinine has been omitted, while these bodies are yet present in the blood. The attacks occurring at long intervals, they believe to be true relapses, in no way connected with the slow maturation of the crescents. They note, with apparent reason, that these relapses are commonly separated by the time ordinarily required for the incubation of the disease; they believe that they are due to spores which have remained living in the internal organs. These views, first set forth by Bignami and Bastianelli, have been accepted and elaborated by Marchiafava and Celli,[220, 222, 245] both of whom insist that the presence of crescents, alone, in the blood has no influence upon the health of the patient. Dionisi,[173] also, in studying the blood corpuscles, notes that the presence of the crescents appears to have no influence in producing anaemia.

Mannaberg[249, 291] takes an entirely new view of the origin and significance of the crescentic bodies. He calls attention to the fact that many observers have noticed the not infrequent presence of several small hyaline bodies inside of one blood corpuscle. He insists that, in many instances, the two parasites thus included move toward one another and finally become joined together. It is a process of

conjunction, of copulation. After joining together in this manner, a membrane is developed about them. The nuclei of the two small corpuscles which enter thus into copulation are close to one another, forming in this manner a pale, unstained area in the centre of the parasite, while the outer, more deeply staining part of the ecto-plasm constitutes the more deeply staining poles of the crescent. Not infrequently one may see the two small nucleoli present in the middle of the body, though these are very often hidden from view by the pigment, becoming evident only after treating the specimens in such a manner as to dissolve the pigment. Mannaberg mentions four reasons which he believes form a convincing argument in favor of his views: (1) The fact that the crescent possesses a membrane; (2) the structure of the parasite as revealed by staining; (3) the formation and arrangement of the pigment; (4) the segmentation.

(1). This is, according to Mannaberg, the one variety of the malarial parasite which possesses a membrane, a fact which proves the biological difference between these bodies and the other forms. With the other protozoa, the formation of syzygia is, also, always followed by encystment.

(2). With regard to the structure of the crescent, Mannaberg insists that when one carefully examines the body, two distinct component parts may always be made out. Celli and Guarnieri first noted that only the poles, and sometimes one or two granules toward the middle of the crescent, take on a deep color with staining fluids. Mannaberg states that "the young crescents—that is, those in which the pigment is scattered in fine granules along the whole of the body—take, on staining, a general pale color, while the poles and the zones about the border are of a slightly deeper hue. In fully developed crescents, which one recognizes by the concentration of the pigment in one or two clumps, sometimes in the middle, sometimes more toward a pole, one sees, almost without exception, the evidences of duality, in that, beside the colored poles and the border, a transverse part also, over which the pigment lies, which divides the crescent into two symmetrical halves, takes on a deep stain. It is, moreover, to be noticed that the inner parts of both constituent bodies remain almost colorless, while beneath the pigment, in the transverse bridge before mentioned, there appear two deeply-stained points. These points one rarely sees in ordinary preparations, because they are generally hidden

by the pigment; but, if one dissolves this by allowing the specimen to remain several hours in weak ammonia, they may be seen in many fully-developed forms, though they may stain more faintly as a result of this treatment. Such a ripe crescent, freed from pigment, appears very like the early stages of conjunction. The slight differences between the two pictures consist in the fact that, in the crescent, the plasma mass at the point of conjunction between the two individuals (the transverse bridge) has become more marked, while the nucleoli have diminished in size and in staining propensity."

(3). With regard to the origin and arrangement of the pigment in the crescentic bodies, Mannaberg is of the opinion that "by the conjunction of the two copulating parasites, an appreciably increased vital activity develops in both of them, which manifests itself in the rapid development of pigment and the coincident decolorization of the red blood corpuscle. While the amoeboid forms are very slightly, or, indeed, not at all pigmented, there is always more or less pigment in crescents. This pigment appears in separate distinct granules and rodlets, just as in parasites of the tertian and quartan type. In fresh specimens these separate pigment granules within the crescent show slight vibratory movements. Owing to currents in the plasma they change their place slightly, and form, as a result, ever-changing groupings. In the already concentrated pigment one never sees any motion. As in the parasites of the regularly intermittent types of fever, the pigment, in the ripe crescents, becomes concentrated, but often this occurs in a manner which speaks for the duality of the crescent. Granules move from the two limbs toward the middle in such a manner that, at a certain point of time, they take an aster-like form. If the concentration proceeds yet further, we then see two clumps of pigment corresponding to the two limbs, which very frequently remain separated from one another, or finally run together into a single mass. This aster-like arrangement of the pigment is so very common that one cannot doubt that, in the two halves of the crescent, there are independent currents which cause this grouping; from this process also, then, the dual nature of the crescent makes itself evident. In those crescents in which the concentration of the pigment occurs, not in the middle of the body, but at one or the other pole, one may assume that they have arisen from the conjunction of two forms dissimilar in size."

(4). The transverse segmentation of the crescents, which has also been noted by Grassi and Feletti, Mannaberg has been able to confirm. Segmentation occurs, frequently, through the middle of the body, and, before the total separation of the two halves, these bodies may hang together like a pair of sausages. With either half, a part of the pigment remains. These segmenting bodies possess a deeply-staining granular contents. He believes that the segmentation and the deeply-staining granules which are often present in great numbers, suggest a reproductive process, yet this is not definitely proven. He believes that from the transverse segmentation of the bodies, only one conclusion can be drawn, namely, that the crescents are dual in nature. The size of the crescents, their somewhat delayed appearance in the blood, their resistance against quinine, the difference in their internal structure, are, he believes, to be explained by this view.

The process, he believes to be a pseudo-conjugation. He has not been able to determine the fate of the segmenting bodies. He does not believe in the hypothesis of Bastianelli and Bignami, that the crescentic bodies are degenerate forms. Against this argument he brings forward the fact that they are so rarely seen included in phagocytes.

Van der Scheer [356] and Laveran [350] have been unable to confirm Mannaberg's observations. The former is sceptical as to the existence of a membrane about the crescentic bodies, inclining, rather, toward the view that the double outline is due to changes occurring in the parasite after the preparation of the microscopical specimen.

Manson [347] believes that the crescent "is intended to carry on the life of the species outside the human body."

Coronado [146] holds a view different from all of the above-mentioned authors; he asserts that the crescents are empty cysts left after the escape of the flagella.

Sforza,[313] recently, in staining the parasites by Canon's method,* notes that the crescents, instead of taking up the methylene blue, show a pale rose color resembling the hue which is shown by degenerating

* Harden in alcohol abs., 5–10 minutes.

Stain in;

Methylene blue (conc. aq. sol.)	40.
Eosin (0.25/70 per cent. alcohol 100)	20.
Aq. dest	40.

for twenty-four hours. Wash in distilled water and mount.

red blood corpuscles. He concludes that, in the crescentic bodies we are dealing with a degenerative form of the parasite "which, during its cycle of development, invades but in part the red blood corpuscle, and that the greater part of the crescentic body is nothing more nor less than the degenerate red corpuscle."

Laveran, in November, 1892,[280] and again in 1894,[350] reiterates his views concerning the crescents. He denies vigorously that they can be empty cysts, stating that he has, many times, watched the bodies after the disappearance of the flagella without ever seeing them take a crescentic form. On the other hand, he has frequently observed the transformation of crescents into round bodies, and, in turn, into flagellate forms. He says, also, that he has frequently seen febrile symptoms in patients whose blood contained crescents alone.

He has never been able to see anything which would lead him to believe that Mannaberg's theories are true. He suggests an interesting explanation of the development of crescents. The malarial parasite, he says, "is found in the blood in two principal forms; (1) amoeboid bodies in different stages of development, free in the serum, or attached to red corpuscles; (2) encysted bodies in the red corpuscles,* presenting first a spherical form, then a crescentic form. We have seen, above, that the encystment of the parasitic elements in the red corpuscles explains, very well, this singular crescentic form. The existence of a cystic membrane appears indubitable. These modifications of the haematozoa of paludism are more easily understood when one considers that this parasite lives in a medium the composition of which is variable; the blood of a patient who is profoundly anaemic and cachectic is very different, from the point of view of the number and the resistance of the red corpuscles, of the composition of the serum, and of the activity of the leucocytes, from the blood of an individual who, having recently arrived in a malarious district, is attacked by fever for the first time. I have shown, in my preceding communication, that crescents are seen, almost always, in individuals who are cachectic or who are, at least, markedly anaemic. It seems to me easy to comprehend that in such cases the haematozoon may develop differently than in those patients where the blood has not yet undergone profound alterations. Its presence in the form of amoeboid

* Laveran acknowledges that the crescents may develop *in* the red corpuscle.

bodies, in the blood of these latter patients, excites a lively reaction, and the parasites, which become the prey of the leucocytes, or which are destroyed by the quinine, have not the time to become encysted. On the other hand, with the cachectic individual, the parasites develop without encountering the same obstacles. The impoverished blood is more easily overcome and the parasites become encysted." He believes that those cases where the crescents are found during what the patients believe to be the first few days of the illness, are really instances of old latent infection. The resistance of these forms against quinine, Laveran believes to be due to their encysted condition, the encysted parasites remaining a long time latent. He sums up his views concerning the crescents as follows: "The parasite of paludism develops first in the blood in the form of amoeboid bodies which live in the free state in the blood, or which adhere to the red corpuscles; generally the development of these parasitic elements in the blood provokes a lively reaction and one is obliged to interfere early and to give quinine. In these conditions the haematozoon does not arrive at its phase of encystment. On the contrary in cachectic individuals the economy, accustomed to the presence of the parasites, reacts but little, and the haematozoon can go through all its phases, penetrate the red blood corpuscles, and become encysted, all the more, because, as the patient has not had violent attacks, one delays considerably the administration of quinine."

To sum up, then, the various views held to-day with regard to the nature of the crescentic bodies: Many observers believe that the double outline of the crescent is due to the presence of a membrane. Antolisei suggests that this is rather a condensation of the external part of the body, and not a true membrane. Laveran believes that the crescents represent an encysted form of the parasite; that they are active, indeed unusually virulent parasites, resisting, more than the others, the action of quinine; that while their mode of reproduction is not known, their presence in the blood is always the menace of a relapse; that frequently, without the presence of other forms, they may cause active febrile symptoms. Canalis, Antolisei, Angelini, and Golgi believe that these represent a more resistant form of the aestivo-autumnal organism, a form which has a cycle of development longer than that of the smaller variety, from which, however, they are directly derived. They believe that sporulation occurs in a manner similar

to that in the case of the quartan parasite; that, in the blood containing this form of organism alone, the paroxysms occur at long intervals, ten, twelve, fourteen days, or even longer. Grassi and Feletti and Sacharoff believe that the crescent represents a separate and distinct type of the parasite, which they call Laverania. The former assert, also, that they have observed segmenting forms. Bignami, Bastianelli, Marchiafava and Celli believe that they are deviate and degenerate forms of the parasite. Mannaberg believes that they are encysted forms following a pseudo-conjugation of two individuals; that they can again segment into two bodies similar to the original. He does not believe that they are degenerate forms, though he has been unable to follow out their further development. Manson believes that the crescents are forms "intended to carry on the life of the species outside the human body." Coronado believes that the crescentic bodies are empty cysts from which flagella have escaped. All agree that the crescents do not appear at the beginning of the infection. Bastianelli, Bignami, Antolisei and Angelini, who have more carefully followed out their development, have shown clearly that they appear, generally, in the spleen from the fifth to the eighth day; in the blood from the seventh day on.

Our own observations with regard to the nature of the crescents have been, for the most part, already stated in the preliminary section concerning the organisms. We have noted, as well as the other observers, that, in the fresh specimen, the crescent has a somewhat refractive protoplasm, while the border shows a greater refraction, similar to that which, as Antolisei states, one observes about the border of the red corpuscle. Whether this has the significance of an actual membrane, or whether it is simply the indication of a slight cuticular thickening of the outer part of the body, we do not feel clear, though we incline rather to the latter view. We have never noted that this more refractive border or double outline showed the color of haemoglobin, though, during a considerable part of its existence, the body is probably surrounded by some corpuscular substance. In stained specimens we have never seen any tendency on the part of this outer border to take up eosin or acid coloring matters, as is the wont of bodies containing haemoglobin. We have observed, also, the fact that the poles of the crescents stain more deeply than the central part, in which there exists a clear area, and, at times, we have also made out

darker staining spots beneath the pigment. We have not, however, carried out studies of stained specimens with regard to the finer structure of the parasite, with sufficient system to speak positively concerning Mannaberg's observations. We can only say, from what we have seen, that the idea that the crescent is formed as a result of conjugation, appears to us to lack confirmation. From a considerable experience in the study of fresh specimens, we can say that, while the presence of two parasites in one corpuscle is occasionally seen, it is a rather rare occurrence; that while we have seen two parasites lying side by side, as is shown in Plate II, No. 19, this has been extremely rare. On the other hand, we have been able, again and again, to trace what we believe to be every step in the formation of crescents from the bodies with pigment gathered in the centre, such as one occasionally sees at the time of the paroxysm, and we feel that there can be little doubt that the crescent develops from these bodies. With regard to the time of their appearance, the tables, which have been already given, show, in an interesting manner, how thoroughly our results agree with those of Bastianelli, Bignami, Antolisei and Angelini; these forms are not seen during the first days, but appear generally during the second or third week. Taking, for instance, the cases which were observed in the hospital, as those in which the observations were most reliable, the following table shows:

Cases observed in the first week.....	35;	crescents 2;	* 5.7 per cent.
Cases observed during the second week, where crescents had not been previously observed.....	35;	crescents 27;	77.1 per cent.
Cases observed after second week, where crescents had not been previously observed.....	48;	crescents 35;	72.9 per cent.
Cases of doubtful duration.....	8;	crescents 5;	62.5 per cent.
Relapse of a case where crescents had been previously seen.....	1;	crescents 1;	100 per cent.

It will thus be seen that, in these instances, the percentage of cases showing crescents in the second week is even a trifle higher than in

* In both of these cases the patient had had previous attacks of malaria, and, while they stated that their symptoms had lasted only two days, it is not at all improbable that the process was a relapse from a previous attack.

the later weeks, showing, quite clearly, the time at which these bodies first appear. They are, indeed, found with nearly equal frequency from the beginning to the end of this week.

Another point that is clearly shown by our tables is the fact that, in those cases where the treatment with quinine is begun during the first week, the organisms may often disappear without being followed by the appearance of crescentic forms; thus it may be remembered that in twenty cases where hyaline bodies alone were present on admission, and treatment was begun in the first week, crescents appeared in only four—20 per cent.; in six cases, where treatment was begun in the second week, crescents appeared in three—50 per cent.; in thirty-one cases, where treatment was begun after the second week, crescents appeared in seventeen instances—54 per cent. This, again, is good evidence that crescentic bodies are not formed during the early part of the first week.

The question concerning the significance of the crescents is a much more difficult matter to decide. As we have stated, we do not believe that they are conjugate forms, as asserted by Mannaberg. They do not appear to us, from what observations we have been able to make, to represent cysts, as we cannot persuade ourselves that there is any direct evidence of their possession of a membrane. What, then, is their relation to the other organisms of this group, and what influence do they exert upon the fever? With regard to their influence upon the fever, we can only state that in 3 of the 8 afebrile cases, crescents alone were found; that while in many cases, during an afebrile period, we have been unable to find other forms in the blood than crescents, we have always, when the patients have shown febrile relapses, seen small hyaline bodies associated with them. Are we, then, to consider this a proof, as do Golgi and his followers, of the segmentation of these crescents? Are we to consider the small, fresh, hyaline bodies as the offspring of these; and are we to ascribe the febrile paroxysm to reproductive processes going on in these crescentic organisms? Or are we to believe with Bignami, Bastianelli, and others, that these resistant bodies—for resistant they surely are—are deviate and degenerate forms of the parasite?

Segmentation of the crescents we have never observed. We have, however, occasionally seen the much discussed vacuolization, as shown

in the plate. This vacuolization, in the instances in which we have observed it, has been, clearly and unmistakably, a degenerative rather than a regenerative process. We have also observed the development of the small peripheral bodies, the gemmation, which has been so frequently described, a crescentic or ovoid body occasionally showing, on one side, a smaller, round, clear protrusion of the protoplasm, which may be sometimes drawn in or again cut off, so as to lie separately beside the body; this process is particularly common in the flagellate forms. We have not supposed that this was a regenerative process. And lastly, we have seen the crescents, as well as the ovoid forms, change into the round bodies, which often develop flagella. The round forms show a distinctly less sharp index of refraction, while the so-called double outline is less noticeable. We have seen, then, in the crescents, what we believe to be evidences of degeneration (vacuolization, gemmation), and we have seen, further, the change into the ovoid and round forms which we have learned to recognize as the precursors of flagellation, concerning the nature of which we shall next speak. We have never seen the transverse segmentation of Mannaberg, nor, indeed, have we ever seen any indications of segmentation, as is described by Canalis, et al. We have seen the crescents present in both the febrile and afebrile periods. When seen alone, they are rarely or never associated with fever; with the fever we always see the advent of small, hyaline, amoeboid forms. The small hyaline forms disappear quickly after the administration of quinine, while the crescentic forms remain much longer—often for weeks, sometimes for months. From practical observation, then, we can say that the crescents represent a very resistant form of the organism; that their presence in the blood alone is often unassociated with fever; that in many instances where they have previously been seen without fever, relapses have occurred, but always in association with the presence of small, hyaline and amoeboid forms; that in connection with these attacks of fever, we have never seen reproductive forms, while we have occasionally seen what we believe to be degenerating bodies; that it is clearly demonstrated that the crescents may change into the round bodies from which flagellation is frequently observed. We feel that our observations do not justify a definite conclusion with regard to the significance of these bodies.

VIII.—THE FLAGELLATE BODIES.

Concerning the significance and nature of the flagellate bodies there has been a continual dispute since the first note by Laveran.[15] Their extreme activity, the remarkable manner in which they agitate the surrounding corpuscles, the power of individual motion which the separate filaments possess, led Laveran to assume that they represented the highest stage of development of the malarial parasite. He described them in his first article somewhat as follows: In repose they are represented by a spherical body about six micro-millimetres in diameter, containing a ring of rounded pigment granules of equal size. In motion they are surrounded by, usually, three to four fine filaments in active, serpentine motion. The length of these filaments is three or four times that of the red corpuscle, possibly longer; the ends are slightly swollen. They may arise from one or from various points on the periphery of the body. The central mass, at the same time, may be in active motion, while the granules change position. The movements of the central body are like those of an amoeba. He saw filaments break loose from the body, and found them moving about free in the blood. This original description by Laveran was, at first, quite generally discredited, notwithstanding the fact that Richard, shortly afterwards, confirmed his observations. Marchiafava and Celli,[34, 35, 36] not having seen the bodies, insisted, at first, that they were not parasites but simply degenerative changes in the red corpuscles, similar to those produced by subjecting blood to a high temperature. In 1885,[41] however, when they had found flagellate bodies in four cases out of 42, they recognized their parasitic nature. Later in the same year,[45] they expressed the opinion that the flagellate forms represented a further stage of development which the parasite rarely reached. In 1886,[55] Osler described them clearly, and, in 1888, Councilman [81] noted the fact that they were much more frequent in the blood of the spleen than in the circulating blood. Excellent drawings of flagellate bodies may be found in Vandyke Carter's [70] article in 1888. Since then most observers who have been able to study the blood in malarial fever have noted these forms. They have been seen in all types of malaria, though they appear to be less common

in quartan fever than they are in tertian or in aestivo-autumnal infections.

Canalis,[104] in 1889, studied the flagellate bodies with care, and notes that, in aestivo-autumnal fever, they are developed only from the full grown round forms, which, in turn, come from the crescents and ovoid bodies. He believes that they are seen, usually, several hours before the febrile paroxysm, though they may occur in apyrexia. They are more commonly found in the internal organs than in the circulating blood. They are smaller than the flagellate forms occurring in tertian and quartan fever, which, particularly in the former, may be double the size of the red blood corpuscles. They show a scant collection of granules in the centre, with a fairly clear peripheral zone, from which the filaments burst forth. After a certain length of time the movements of the pigment cease, while the granules collect in a small, dense, irregular mass; the movements of the flagella become slower and finally cease. The distinction between the more clear peripheral zone and the pigmented central area of the parasite, begins to disappear, while the entire substance of the body becomes more refractive. This is probably a cadaveric state of the flagellate body. Canalis does not commit himself as to the significance of these forms.

Golgi [118] believes that the flagellate bodies are a passing phase in the development of crescents, and rather suggests that they are degenerate forms.

Antolisei [129] believes that flagellation is a degenerative process similar to fragmentation and vacuolization. In studying the tertian parasite, Antolisei noted that the flagellate bodies develop only from the large, swollen, fully-grown forms of the organism, which either fragment, become vacuolated, or develop flagella—never segmenting. The flagella, he believes, are sarcodic prolongations of the protoplasm. He [139] states that he has seen the flagellate bodies themselves become vacuolated.

Grassi and Feletti [221] call attention to the fact that they never have observed flagellate bodies until the blood has remained twenty minutes or more on the slide. They do not believe that they are reproductive forms, but, rather, that they represent involutive or degenerative changes. They note that the nucleus does not take part in the process, neither dividing nor entering into the flagella. They mention what Councilman [81] and Marchiafava and Celli [41, 45] have also noted,

that certain of these ovoid, crescentic, or round forms may show an extremely rapid undulation of the outline without the presence of flagella. They liken the process of flagellation to the development of filaments from degenerating red corpuscles.

Sacharoff,[212] in his studies on the "parasite of irregular fever" (the aestivo-autumnal parasite), is inclined to believe that the flagellate bodies develop only outside of the organism; they represent changes provoked by exposure of the blood to a low temperature. He notes, as do Grassi and Feletti, that they are not observed until about a quarter of an hour after the preparation of the blood is made. Their appearance begins, nearly simultaneously, at different points in the preparation. He has succeeded in staining the flagella by the following method: He collects a series of drops of blood on cover glasses, some of which are placed immediately in a moist chamber, while one is placed upon a slide, with vaseline at the borders of the glass, and is submitted to microscopical examination. He is able to follow the transformation of the crescents into ovoid and round bodies, the arrangement of the pigment in the shape of a crown, and, shortly afterwards, the appearance of movable filaments. After waiting a short time to allow the number to increase, he removes the cover-glasses from the moist chamber, spreads out the blood, dries, fixes, and colors with gentian violet. The filaments are intensely stained of the same color as the protoplasm of the parasite, which takes so deep a stain that the pigment granules are no longer distinct. He has published photographs[276] of these forms.

Terni and Giardina[145] observed flagellate bodies in twenty-five out of sixty-two cases of aestivo-autumnal fever; they were noted, generally, just before febrile attacks. They were always accompanied by the round bodies, from which they had doubtless developed.

Bastianelli and Bignami,[152] in their studies of the tertian and quartan infections, agree with Antolisei in believing that the flagellate bodies, as well as the large, swollen, extra-cellular forms from which they develop, are degenerative in nature. They find them most numerous toward the beginning of the paroxysm. They compare the changes in the crescents (fragmentation, gemmation, vacuolization, and flagellation), as does Antolisei, to the changes occurring in the large swollen forms of the tertian parasite, believing them all to

be degenerative changes. This standpoint has since been taken by Marchiafava and Bignami.[245]

Recently [300, 301, 324] interesting studies of the flagellate bodies have been made by Sacharoff. He notes that after a short exposure to lower temperature than that of the body, the crescents rapidly change into round forms, and then into flagellate bodies. In coloring flagellate bodies after the manner of Romanowsky, and studying their structure, Sacharoff has convinced himself that "the process of formation of the flagellate bodies consists in a perversion of the karyokinetic nuclear division, in a breaking up of the nucleus into the chromatin filaments, and in the escape of these from the parasite; these filaments, which are in lively motion, represent the flagella." This, he believes, is, undoubtedly, a degenerative process, the rapidity with which it occurs showing that the crescent cannot be long exposed to cold without dying. The same process, he states, may occur in the full-grown tertian parasites and in the parasites of chronic malaria in birds, which divide in the same way—by karyokinesis.

Opposed to these views, that the flagellate forms are degenerative in nature, are a number of observers, the more important of whom are Laveran,[229] Danilewsky,[194] Dock,[151] Mannaberg,[291] Coronado [273] and Manson.[347] Laveran [229] believes that these bodies are cysts containing the fully developed flagella, which represent the parasites at their most perfect stage of development. He denies that the flagellate forms have any relation to the similar appearances produced by the action of heat upon the red corpuscles. "The differences," he says, "which exist between the flagella of paludism and the sarcodic prolongations of the normal red corpuscle, submitted to the action of heat, are numerous: firstly, the flagella of the haematozoa of paludism are seen at the ordinary temperature of the Laboratory. I have seen them frequently at a temperature not above 15° C. The sarcodic prolongations of the red corpuscle do not develop until one heats the blood to 56° or 57°. Secondly, the haematozoa have never been observed excepting in patients suffering with malaria. In the blood of these patients they are always associated with other parasitic elements, spherical pigmented bodies, from which they appear to arise. Flagella never arise from the red corpuscles, as do, always, the sarcodic prolongations which one can bring about by heating the blood strongly. Thirdly, the flagella of paludism

differ from the sarcodic prolongations by their form and their dimensions, which are much more regular, and in the vivacity and the variety of their movements. None of the observers who have, themselves, seen the flagella go through their various motions, rolling and unrolling upon themselves, causing the most varied movements among the surrounding red corpuscles, which they sometimes seem to seek to pierce, would venture to assert that one could confound these movements with those of the sarcodic prolongations produced by heat. The flagella move, sometimes, so rapidly that they cause changes in the position of the spherical body to which they are attached. When they are free, they preserve the same vivacity, the same variety of movement." (Page 87.)

Danilewsky [194] holds similar views concerning these bodies.

Dock [151] suggests that the flagellate bodies "represent resting states of the organism, capable of existing independently, perhaps even of reproducing themselves, but also able, under favorable circumstances, of reproducing the typical growth of the parasite."

Mannaberg [291] takes an interesting view not dissimilar to that of Dock. He writes as follows: "In my opinion, these forms, as has been already said, are by no means to be regarded as phenomena of death ('agonieproducte'). It could hardly be explained why only a relatively small number of the parasites present show these changes when all the bodies in the preparation die in a short time. Moreover, one ought to see, here and there, flagella in the circulating blood, in which, as I shall later show, there occurs, at the time of the paroxysm, a great mortality among the parasites, dying forms being present in numbers. The same would be expected after the giving of quinine; but none of these things actually occur. Finally the remarkable activity of the movements is a convincing argument against the idea that the process is a phenomenon of the agony. My idea is, that we have, in the flagella, organs which permit the parasites to enter into a saprophytic existence. I suspect that the flagellate bodies enter upon the first steps of a cycle of existence outside of the human body, and that, as a result of the unfitting culture medium, the death of the young spores occurs." He notices, also, that they do not develop until the blood has been outside of the body for some little time.

Manson [147] believes that . . . "the flagellated organism which proceeds from the crescentic body is the first stage in the life of the

malarial organism outside the human body, and the living moving flagella, into which it breaks up, the second stage. The central sphere to which the flagella are at first attached, and from which they are derived, must be looked on as residual."

Lastly, Coronado,[273] as has been stated above, in his cultivation experiments, believes that he has seen the longitudinal segmentation of free flagella into young individuals, a fact which, if true, would demonstrate that the free flagellum was a fully-developed, perfect individual.

Which of these several views are we to take? This is a very difficult matter to decide. We have observed flagellate bodies in all varieties of malarial fever. In the tertian and double tertian fevers the flagellate bodies were always noted a little before or during the paroxysm. In tertian infection, out of 174 cases observed in the hospital, flagellate bodies were noted 15 times. In quartan infection, flagellate bodies were noted in 2 out of 5 cases. In 105 cases of aestivo-autumnal fever observed in the hospital, flagellate bodies were noted 18 times. In the cases of tertian fever the flagellate bodies were noted, always, during or shortly before the paroxysm. In one instance, only, was a body seen eleven hours before the chill, and once when the temperature was normal between paroxysms. In the eighteen cases of aestivo-autumnal fever, in four cases they were seen during the paroxysm; in nine cases the temperature was normal; in three the fever was continuous; in one case the organisms were found in the spleen after death. In quartan fever the parasite was observed once several hours before a paroxysm, and once in association with degenerative forms during an abortive paroxysm. In quartan fever the flagella developed from full-grown, extra-cellular forms. In tertian fever the flagellate bodies developed, always, from the large, full-grown, extra-cellular forms, forms which are often considerably larger than the red corpuscle. In aestivo-autumnal fever the bodies developed, invariably, from the round, pigmented bodies which, in turn, could be traced to the crescents. We have never seen the appearance of flagella in bodies still contained in the red blood corpuscles.

In tertian and quartan fever, then, the process of flagellation was observed, invariably, at the time when full-grown organisms were found in the blood, at the time when segmenting organisms were to

be seen—reproductive forms—but also at the time when degenerative processes—vacuolization, fragmentation—were most common. In one instance a flagellate body was seen during apyrexia, at a time when only occasional large swollen forms were seen, beyond the half developed forms within the red corpuscles, from which we have never seen flagellate bodies develop. The tertian flagellate bodies were materially larger than the quartan forms which resembled much more, the flagellate bodies in aestivo-autumnal infection. We have seen nothing which would lead us to believe that the development of flagellate bodies in aestivo-autumnal fever had any connection whatever with the paroxysm. On the other hand, in the majority of cases these forms were noted after the paroxysms had ceased, when the temperature was entirely normal. In 6* of the 18 cases of aestivo-autumnal fever quinine had been previously administered, and in seven of these instances flagellate bodies were observed for days after the fever had entirely disappeared. These statistics give us little particularly definite, then, with regard to the nature of the bodies. Their appearance, their activity, the regularity of outline, the shape of the flagella are very much against their being compared to the sarcodic prolongations of degenerating red corpuscles, which are certainly very dissimilar in appearance. Their occurrence in tertian and quartan fevers, generally in association with segmenting forms at the time of the paroxysm, might lead us to lean toward the opinion of Dock and Mannaberg, that they represent a reproductive process differing from that which usually takes place. On the other hand, the arguments of Bignami, Bastianelli, Marchiafava, Celli and others, who call attention to the fact that, in tertian fever, the flagella develop, regularly, from the large, swollen forms which otherwise end, apparently, only in vacuolization and fragmentation, and draw so interesting an analogy between these forms and the crescentic, ovoid, and round bodies, from which the flagella develop in aestivo-autumnal infections, have, also, much to say in their favor.

The most suggestive point in our analyses is, it appears to us, that concerning the time at which the flagellate bodies in aestivo-autumnal infections appear. In an half of the cases the paroxysms

* In both of the two additional instances in the dispensary where flagellate bodie were noted, quinine had been previously administered.

had ceased; in 8 out of 20 instances quinine had been previously given; that is, for days and, sometimes, for weeks after the activity of the infection had certainly been overcome, we were able to see flagellate bodies in association, sometimes, with other unquestioned degenerative changes. There is another point which has been, singularly enough, very little, if, indeed, at all, noted in the literature. Whatever our opinion may be concerning the primary influence of phagocytosis on the cure of malarial or other infections, it is an undoubted fact that any lifeless or dying foreign material in the blood current is attacked with particular activity by the phagocytes. The young intra-cellular parasites in the midst of relatively normal red corpuscles are almost never engulfed. What forms, or what constituents of the malarial parasites are most commonly attacked?

(1). Most commonly, we see the engulfing of the free pigment clumps which are left after segmentation—the lifeless pigment.

(2). Again we see the small, extra-cellular bodies, the result of fragmentation from large tertian or from quartan forms, or those half-grown forms which have burst from the corpuscle and become deformed and immovable in the field.

(3). Next in frequency, perhaps, do we see the engulfing of segmenting forms.

(4). Again, we may, in aestivo-autumnal infection, see small forms, contained in crumpled, brassy colored (necrotic) corpuscles, taken up together with the corpuscle.

All of these forms, with the exception of the segmenting parasites, are generally considered to be degenerative in nature. It is, however, to be remembered that it is at the segmenting stage that the parasite is most vulnerable, as proven by the experimental administration of quinine, while it is an accepted fact that many of the segmenting forms are, normally, destroyed in the blood serum at the time of each paroxysm.

(5). But the one form of malarial organism which one may clinically observe to be invariably, or almost invariably, attacked, is the flagellate body. Where a flagellate body is seen to develop in the field, the writers have, again and again, seen one, two, or even three leucocytes crawl into the field of the microscope and attempt to engulf the parasite, and, in many cases, the attempt is not unsuccessful. Often, to be sure, the flagella escape and the central body alone is engulfed,

but in many instances the whole parasite is taken up. It is true that this argument might be used by others as indicating a special virulence on the part of the flagellate body, which would call forth an immediate attack from the protectors of the economy, but it would be interesting to find that the forms most commonly attacked were, in the one instance, the undoubted degenerative forms, and in the other the most perfectly developed full grown bodies.

Another argument in favor of the degenerative nature of these forms of the parasite is the fact of the rarity of their appearance immediately after the formation of the specimen. In our observations they appeared, always a few minutes, usually five, to ten, to fifteen, after the preparation of the specimen. We have never found them in the first few minutes of observation.

The nature, then, of the flagellate bodies does not appear to be entirely understood. There are rather strong arguments which speak in favor of the view that they are degenerative stages of the parasite, and others which speak against it. No observations have, however, been made, with the exception of the as yet unconfirmed work of Coronado, which suggest a possible function, or which tend to clear up their relation to the cycle of existence of the parasite.

While our observations concerning the time at which these bodies appear, their association with undoubted degenerative forms, their persistence after the disappearance of fever and after the administration of quinine, the manner in which they are engulfed by the phagocytes, are all, it seems to us, suggestive evidence that these bodies are degenerative in nature ; on the other hand, the extreme regularity in the shape of the flagella, their extraordinary activity, their power of individual motion, cause us to hesitate seriously in accepting this view.

We believe that the nature of the flagellate bodies is not yet clearly understood, and must be decided by future research.

IX.—THE ACTION OF QUININE ON THE MALARIAL PARASITE.

We have not made a systematic study of the action of quinine upon the fever or upon the parasites, and in this article we will only touch upon the subject. Suffice it to say that our observations have all tended to support the views first advanced by Golgi, that the time at which the malarial organism is best attacked is just at the period of segmentation.

In dealing with the tertian organism, we have found that a moderate dose of quinine, given just before the paroxysm, so that the drug may be in solution in the blood at the time of the segmentation of the organisms, is always followed by an almost complete obliteration of the group of parasites then undergoing segmentation. An excellent illustration of the effect of quinine has been shown in Case 9047, page 113. Ordinarily, quinine, gr. v–x (0.325–0.65), given at any time during the paroxysm, will be sufficient to prevent the appearance of the next chill, though not generally to completely obliterate the group of parasites. When the parasite is in the endo-globular stage (between paroxysms) quinine has relatively little effect, though in many mild tertian cases it will succeed, even in this stage, in preventing an approaching chill, if given ten to twelve hours before a paroxysm.

In quartan infections the same rules appear to hold true. In most of the tertian infections, as they occur in Baltimore, very small doses of quinine are sufficient, if the patient be kept in bed, to eradicate the fever. Thus, in most cases of tertian and double tertian fever, several days' rest in bed and two weeks' treatment with as little as gr. ii (0.13), three times a day, is followed, generally, by a permanent recovery. The organisms usually disappear from the blood within the first four days.

In the aestivo-autumnal infections, our observations concerning the time at which quinine is most efficacious are too few to justify us in expressing any opinion. We have seen no cases where, as in tertian or quartan fever, a single large dose of quinine, given at the proper time, has appeared to almost destroy the infection—at least to cause the disappearance of the fever for a considerable length of time. Here

the doses of quinine must be materially larger. In most instances we place the patient simply upon quinine, gr. v (0.325), every four hours, keeping him in bed for three or four days; in the hospital for from one to two weeks. Under these circumstances permanent recovery is usual, after two or three weeks' treatment. In the same manner the cases in the dispensary, so far as we could follow them, recovered under similar doses continued through a proper length of time—two or three weeks. In severe and pernicious cases much larger doses of quinine may be necessary. In our cases we have used, generally, the muriate of quinine and urea which we have given, hypodermically, in doses as high as gr. xx (1.3). We have had no experience with the intravenous administration of the drug, as advised by Baccelli. It will not be worth while to discuss, in this paper, the value of other remedies against malaria. The only drug which deserves any serious consideration, beyond quinine and the other cinchona derivatives, is methylene blue, the value of which has been shown, by many observers, to be very slight. We see no reason to depart from the conclusions reached by one of the writers several years ago—that, while methylene blue has a certain definite action upon the malarial parasite, it is materially less efficacious than quinine, failing to accomplish its purpose where quinine acts satisfactorily; that it has no advantages over quinine which would warrant its further use.

X.—GENERAL CONCLUSIONS.

Malarial fever is rare in Baltimore during the winter months, but becomes more frequent as the season advances, reaching a maximum in the month of September, the majority of all the cases occurring in August, September, and October.

Any differences between the susceptibility of individuals of different ages, and of the two sexes, depend, apparently, only upon the varying chances of exposure to infection.

The relative susceptibility of the negro is, by nearly two-thirds, less than that of the white population.

We have distinguished three varieties of the malarial parasite:

1. *The tertian parasite.*
2. *The quartan parasite.*
3. *The aestivo-autumnal parasite.*

(1). The *tertian parasite* requires about forty-eight hours to accomplish its complete development, and is associated with relatively regular tertian paroxysms, lasting, on an average, between ten and twelve hours, associated, almost always, with the three classical stages—chill, fever, and sweating. Frequently, infection with two groups of tertian organisms gives rise to quotidian paroxysms; rarely, infection by multiple groups of organisms gives rise to more irregular, sub-continuous fevers.

(2). The *quartan parasite* is an organism requiring about seventy-two hours for its complete development. It is rare, in this climate, and is associated with a fever showing regular quartan paroxysms, similar, in nature, to those associated with the tertian organism. Infection by two groups of the parasite causes a double quartan fever (paroxysms on two days, intermission on the third). Infection, with three groups of the parasite, is associated with daily paroxysms.

(3). The *aestivo-autumnal parasite* passes through a cycle of development, the exact length of which has not, as yet, been determined; it probably varies greatly from twenty-four hours or under, to forty-eight hours or more. But few stages of development of the parasite are found, ordinarily, in the peripheral circulation, the main seat of infection being, apparently, in the spleen, bone-marrow, and other internal organs. Infection with this organism is associated with fevers varying, greatly, in their manifestations. There may be quotidian or tertian intermittent fever, or, more commonly, more or less continuous fever with irregular remissions. The individual paroxysms last, on an average, about twenty hours. The irregularities in temperature depend, probably, upon variations in the length of the cycle of development of the parasite, or upon infection with multiple groups of organisms.

We have not been able to separate two distinct varieties of the aestivo-autumnal parasite, though we feel that more investigation is needed upon the subject.

The cases of malaria in the spring and early summer are of the milder, more regularly intermittent varieties (tertian and quartan fever), the severe aestivo-autumnal infections beginning to appear only in the later summer, and reaching their maximum in September.

The colored race, while showing a relative insusceptibility to malarial infection, is equally susceptible to the various forms. The

infections which occur are, however, more apt to take a simpler, milder course—the single tertian cases, for instance, outnumbering the cases of double tertian fever.

The majority of all the cases of malarial infection in this climate depend upon the tertian parasite; these tertian infections form the vast majority of all the cases in the first half year, but occur throughout the malarial season. The majority of infections during the height of the malarial season depend, however, upon the aestivo-autumnal parasite.

The earliest cases of tertian infection are more commonly single in nature, while as the season advances double tertian infections become more common.

Nothing, in our experience, has led us to believe that these varieties of the parasite are interchangeable. They are, we believe, distinct varieties, though closely allied to one another biologically. Combined infections, with parasites of different varieties, may occur, but they are rare—forming less than 2 per cent. of all the cases which we have observed.

The crescentic bodies, associated with the aestivo-autumnal parasite, develop from the small hyaline forms. We have seen nothing to support the views of Mannaberg that they are the result of conjugation. We have never seen sporulating forms which we believe to have developed from crescents. We are not, as yet, inclined to accept the view that these are degenerate forms; we believe that their true nature is still undetermined.

The nature of the flagellate bodies which may develop in all types of malarial fever, is not yet determined.

The specific action of quinine upon these three varieties of the parasite is undoubted. It exerts its influence most strongly when the parasite is undergoing the process of segmentation, before the entrance of the fresh segments into new red corpuscles. It is best administered, then, just before the beginning of a paroxysm, if we wish to obtain the greatest effect with a single dose. The action is much more rapid and certain in the tertian and quartan fevers than in the aestivo-autumnal infections.

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APPENDIX.

After the greater part of this article had already gone to the press, there appeared two communications, which are of too much importance to pass over in silence. The first of these, by Di Mattei of Catania,[359] treats of the experimental malarial infections in man and animals. He publishes several new inoculation experiments in man. In his first experiment he inoculated four individuals, hypodermically, with blood from a case of quartan fever. In the first two instances, where 2 cc. were injected under the skin of the forearm, a typical quartan ague, with the characteristic parasites, appeared after an incubation period of 17 days in the first instance, and 11 in the second case. In two cases where, respectively, 1. and 0.5 cc. were injected, the result was negative. In the second experiment, a healthy individual was inoculated with blood from a case of aestivo-autumnal fever. Hyaline bodies and crescents were found in the blood at the time of inoculation. The patient suffered from epistaxis, and the blood flowing from the nose was collected in a vessel containing sterilized water at 37°. 4 cc. of a mixture containing equal quantities of blood and water were injected hypodermically. On the 15th day after the inoculation an irregular fever began, the blood showing hyaline aestivo-autumnal parasites. Eight days later crescentic bodies were found.

The author then reviews the literature of experimental malarial infection and concludes: "That the malarial parasites may be divided into several species, though in certain stages these resemble one another from a morphological point of view; that each species has for itself a special biological cycle; and that one variety never merges or changes into another. That between the several varieties of the malarial parasites and the types of fever, there exists an undeniable (unverwischbares) relation of dependence, for the former" (the parasites) "are to

be recognized as the cause, the latter" (the fever) "as the effect; that, thus, one type of fever does not change into another because it is caused by a distinct variety of parasite. That in those forms of malarial fever where no ground type is to be made out, we have often to do with, so to speak, impure cases, with individuals whose system is invaded by different varieties of malarial parasites at the same time."

The author then speaks of the results of an elaborate series of studies on the experimental infection of birds with the haematozoa which so closely resemble the malarial parasites in man.

Careful estimations of the temperature in infected birds appear to show that there is no change from the normal.

Quinine, bichloride of mercury, arsenic, have no effect on the course of the infection.

In 83 attempts to transfer the infection by inoculation, intra-venous, hypodermic, intra-abdominal, intra-pulmonary, the results were all negative.

He examined the blood of doves from malarious and non-malarious districts, and studied healthy birds kept in various localities, at varying altitudes, and during the different seasons of the year, and concludes that, while infection with the haematozoa is rather commoner in summer than in winter, and in birds kept close to the ground rather than in those whose cages are hung in lofty positions, yet there appears to be no difference between the frequency of infection in malarious and non-malarious districts.

The close association of healthy with infected birds does not appear to be followed by infection; nothing in his observations suggested the possibility of hereditary infection.

In 16 cases, inoculation of birds with the blood of malarial men gave negative results.

In 4 instances the hypodermic injection of the blood of infected birds into healthy men was without effect. In one instance 1 cc. of the blood of an infected bird was injected into one of the veins of the forearm of a healthy man, but without any particular effect.

The author then compares, in the following table, the differences between malarial infections in man and infections with the similar haematozoa in the dove:

In the malarious individual.	*In the infected dove.*
Elevation of temperature occurring as paroxysms of fever.	No elevation of temperature.
Paroxysms occurring in relation to the cycle of the parasite.	No relation between the cycle of the parasite and the temperature.
Quinine and arsenic are efficacious.	Quinine and arsenic have no action.
Local conditions are a considerable and important factor in the infection.	Local conditions have no influence.
The oft-confirmed hereditary infection.	Hereditary infection does not occur.
Artificial inoculation of an healthy individual with malarial blood always produces the infection.	Artificial infection by means of the blood from infected to healthy doves does not occur.

From these facts he concludes that the two processes are not identical; that the parasites occurring in birds, though similar morphologically, differ materially from the malarial haematozoa of man. He believes, therefore, that these haematozoa of birds should not be called "malarial."

In the second paper, Bastianelli and Bignami [358] present the results of some valuable studies upon malarial infection.

In the first part of their paper they treat of the finer structure of the parasites of the aestivo-autumnal fevers. A review of this part of their work may be found in an earlier part of this article (vid. p. 47).

Particularly interesting are their views concerning the crescentic bodies. They trace the gradual development of these forms from the small hyaline bodies; they deny the existence of a membrane.

The central chromatin spot or spots, on which Mannaberg lays so much stress, are often lacking; "usually there is a lack, then, of the structure which, in these parasites, represents the nucleus."

"In (p. 180) the body with central pigment, after the solution (fusione) of the central body" (chromatin granule), "the chromatin substance increases in a more or less marked manner, and from these forms segmentation occurs. On the other hand, in the bodies not destined to sporulate (semilunar phase of the parasites) the dispersion of the chromatic granule of the protoplasm takes place as in the others, but, with the ulterior development, the nuclear substance does not increase. This is not an hypothesis. We have, in fact, seen that the young form of the semilunar phase has more

chromatin than the adult form, indeed the adult forms are the paler the more voluminous they are.

"But we already know that with all malarial parasites the chromatic substance increases with the increase in volume, especially just before division. In the forms of the semilunar phase the contrary occurs. So, then, by this fact also, as well as for the reasons to which we have given utterance elsewhere, we may arrive at the conception that the crescents are sterile forms of the aestivo-autumnal parasites."

Mannaberg's idea that the crescents are conjugate forms, they believe to be without foundation.

With regard to the biological significance of these bodies, they assert that in several unicellular parasites belonging, especially, to the coccidia, the existence of two cycles of development has been demonstrated. One cycle is accomplished during the ordinary life of the parasite. But after the parasite has lived, as such, through a series of generations, there begins a second cycle of existence, which is represented by forms which cannot terminate their development unless in the external air or in the tissues of another animal. If these forms of the second cycle do not escape from the body of the animal in which they are formed, they remain sterile and, after a certain time, degenerate and die. So many facts of this nature have been recently discovered that it appears not improbable that this may be a general law for this class of endo-cellular parasites.

It appears probable to the authors that these parasites, which develop in a closed cavity and cannot reach the external air, have a phase of life which represents a rudiment of this second cycle.

Being deprived of the possibslity of completing the cycle, they have lost, also, the power to reach the complete development that belongs to the other forms of this second cycle in other closely related organisms. "The semilunar phase of the malarial parasites represents an abortive phase, sterile, of that cycle of development which, in closely related parasites, is completed only in the external air (ambiente). The analogy is also found in the fact that the forms of this abortive phase make their appearance only after a greater or less number of generations which have passed through only the ordinary cycle of the parasite."

They then pass on to consider certain points in connection with phagocytosis. Golgi[309] has recently advanced the hypothesis that

the entire cycle of development of the parasite may be passed through while it is yet contained within a phagocyte. Bastianelli and Bignami assert that, with the exception, occasionally, of spores, all included parasites are rapidly destroyed unless they be contained in red blood corpuscles. If this progressive growth of the included bodies occurs, they believe that one should find all stages of development, with equal frequency, within the phagocyte. But this is not the case. While the included parasites may be in every stage of development, certain forms are found with much greater frequency than others. The youngest forms are, for instance, rarely seen, while the older are more common; facts which, they believe, are strong evidence against Golgi's idea.

The second part of their paper is devoted to a consideration of certain lethal infections with but few parasites.

They assert that if one takes into consideration the number of parasites in the whole system, not only in the peripheral blood, there exists, always, in pernicious fever, a considerable number of organisms. They have never observed a case of pernicious fever where the diagnosis was not to be made by the examination of the peripheral blood. They take up those acutely fatal cases with marked cerebral symptoms which, at autopsy, show evidences of but a slight or, indeed, of an old cured malarial infection, in association with cerebral hyperaemia, pulmonary hypostaxis and haemorrhages, the other organs showing no grave degenerations. These cases, which occur almost invariably, at the hottest season of the year, often in individuals who work in the fields, they believe to be very possibly instances of isolation and not due, as some have supposed, to an unusual toxicity of the parasites.

Another section of the paper treats of the period of incubation of the experimental malarial fevers, and of the nature and origin of the recrudescences and relapses.

They report four new cases of experimental infection with the aestivo-autumnal parasites.

In the first case the injection (how made?) consisted of 2 cc. of blood; irregular fever with the typical parasites appeared two days later.

In the second case, where the parasites were few, 5 cc. were inoculated with exactly the same result.

In the third case, $\frac{3}{4}$ cc. of blood produced fever in five days; the inoculated blood contained but few organisms.

In the fourth case, where $\frac{2}{10}$ cc. of blood, containing a fair number of parasites, were inoculated, the incubation period lasted four days.

From a table of all observations which they have collected, they conclude that the time of incubation in the several varieties of fevers varies as follows:

	Maximum. (days)	Minimum. (days)	Mean. (days)
Quartan fever	15	11	13
Tertian fever	12	6	10
Aestivo-autumnal fever	5	2	3

The cases of Antolisei and Angelini,[111] Sacharoff,[324] and Di Mattei,[358] where the incubation period for aestivo-autumnal fever was materially longer, are not included in this list. The periods of incubation in these cases were respectively 9, 12, and 15 days. In the first of these cases, however, the parasites were only scanty in the inoculated blood (only crescents were seen); in the second, they had been four days in the body of a leech on ice; in the third, the blood was mixed with sterilized water.

The authors conclude that "the period of incubation with one variety of parasites varies inversely with the quantity of material inoculated."

The period of incubation represents "the time necessary for the inoculated parasites to reach, by multiplying, the quantity necessary to determine the fever." . . . .

"The mean and minimum periods of incubation, under similar conditions, vary in the various groups of fevers: it is least in the aestival fevers, longer in the tertian, and still longer in the quartan." . . . .

"The period of incubation in experimental malarial infection is not a constant quantity, but varies in the same group of fevers and in different groups of fevers. In the same group of fevers it depends chiefly on the quantity of the inoculated material. In different groups of fevers it varies with the rapidity of the cycle of development of the parasite and with the special capacity for reproduction of the parasitic variety."

The ordinary recurrences and relapses, the authors ascribe, as they have before, to the fact that certain spores which have escaped destruc-

tion, continuing their development, begin again to multiply, increasing until the parasites have reached a number sufficient to produce fever. The length of time separating the relapse from the last attack depends on the number of organisms which have escaped destruction.

Those relapses which do occasionally occur at intervals of weeks or even months from the primary attack, the authors can explain only by the hypothesis advanced first by Bignami, that certain spores which have been included by phagocytes remain a long time living. These bodies, they assert, certainly retain their form and staining properties for some time, even if they do fail to show any sign of a membrane; if they be not spores, in the proper sense of the word, yet they have some properties which seem to indicate that they possess a greater resistance. The writers state, however, that nothing appears to them "a priori contrary to the hypothesis that, of these so-called spores of malaria, some, born like all the rest without membrane, may finally acquire one." These bodies, then, might lose their staining properties and, being so small and perhaps scanty, they might escape notice. To their ultimate development, then, the relapses might be ascribed. In some sporozoa, for example, the *Benedina octopiana*, similar processes occur; the spores are born without membranes, which they afterwards acquire, losing at the same time their staining properties.

Lastly, the writers report an interesting case of grave malarial infection presenting the syndroma of Dubini—the so-called "Electric Chorea."

The most interesting points, it appears to us, in this paper, are the views advanced concerning the crescentic bodies.

Most authors have interpreted Bignami's original assertion,[179] that the crescentic bodies were "forms of a deviate and interrupted evolution (forme di evoluzione deviata e interrotta)," as an indication that he considered them degenerative in nature. The present theory, it is interesting to note, is similar to that recently advanced, independently, by Manson, who believes that the crescents are forms "intended to carry on the life of the species outside the human body."

DESCRIPTION OF THE PLATES.

The drawings* were made with the assistance of the camera lucida from specimens of fresh blood. A Winkel microscope, objective, 1/14 (oil immersion), ocular, 4, was used.

Figures 4, 13, 23, 24, and 42 of Plate I were drawn from fresh blood, without the camera lucida.

PLATE I.

The Parasite of Tertian Fever.

1.—Normal red corpuscle.

2, 3, 4.—Young hyaline forms. In 4, a corpuscle contains three distinct parasites.

5, 21.—Beginning of pigmentation. The parasite was observed to form a true ring by the confluence of two pseudo-podia. During observation the body burst from the corpuscle which became decolorized and disappeared from view. The parasite became, almost immediately, deformed and motionless, as shown in Fig. 21.

6, 7, 8.—Partly developed pigmented forms.

9.—Full grown body.

10–14.—Segmenting bodies.

15.—Form simulating a segmenting body. The significance of these forms, several of which have been observed, is not clear to the writers who have never met with similar bodies in stained specimens so as to be able to study the structure of the individual segments.

16, 17.—Precocious segmentation.

18, 19, 20.—Large swollen and fragmenting extra-cellular bodies.

22.—Flagellate body.

23, 24.—Vacuolization.

The Parasite of Quartan Fever.

25.—Normal red corpuscle.

26.—Young hyaline form.

27–34.—Gradual development of the intra-corpuscular bodies.

35.—Full-grown body. The substance of the red corpuscle is no more visible in the fresh specimen.

36–39.—Segmenting bodies.

40.—Large swollen extra-cellular form.

41.—Flagellate body.

42.—Vacuolization.

*The writers desire, here, to express their gratitude to Mr. Broedel for his admirable work.

PLATE II.

The Parasite of Aestivo-autumnal Fever.

1, 2.—Small refractive ring-like bodies.

3–6.—Larger disc-like and amoeboid forms.

7.—Ring-like body with a few pigment granules in a brassy, shrunken corpuscle.

8, 9, 10, 12.—Similar pigmented bodies.

11.—Amoeboid body with pigment.

13.—Body with a central clump of pigment in a corpuscle, showing a retraction of the haemoglobin-containing substance about the parasite.

14–20.—Larger * bodies with central pigment clumps or blocks.

21–24.—Segmenting bodies from the spleen. Figs. 21–23 represent one body where the entire process of segmentation was observed. The segments, eighteen in number, were accurately counted before separation, as in Fig. 23. The sudden separation of the segments, occurring as though some retaining membrane were ruptured, were observed.

25–33. Crescents and ovoid bodies. Figs. 30 and 31 represent one body which was seen to extrude slowly and, later, to withdraw two rounded protrusions.

34, 35.—Round bodies.

36.—"Gemmation," fragmentation.

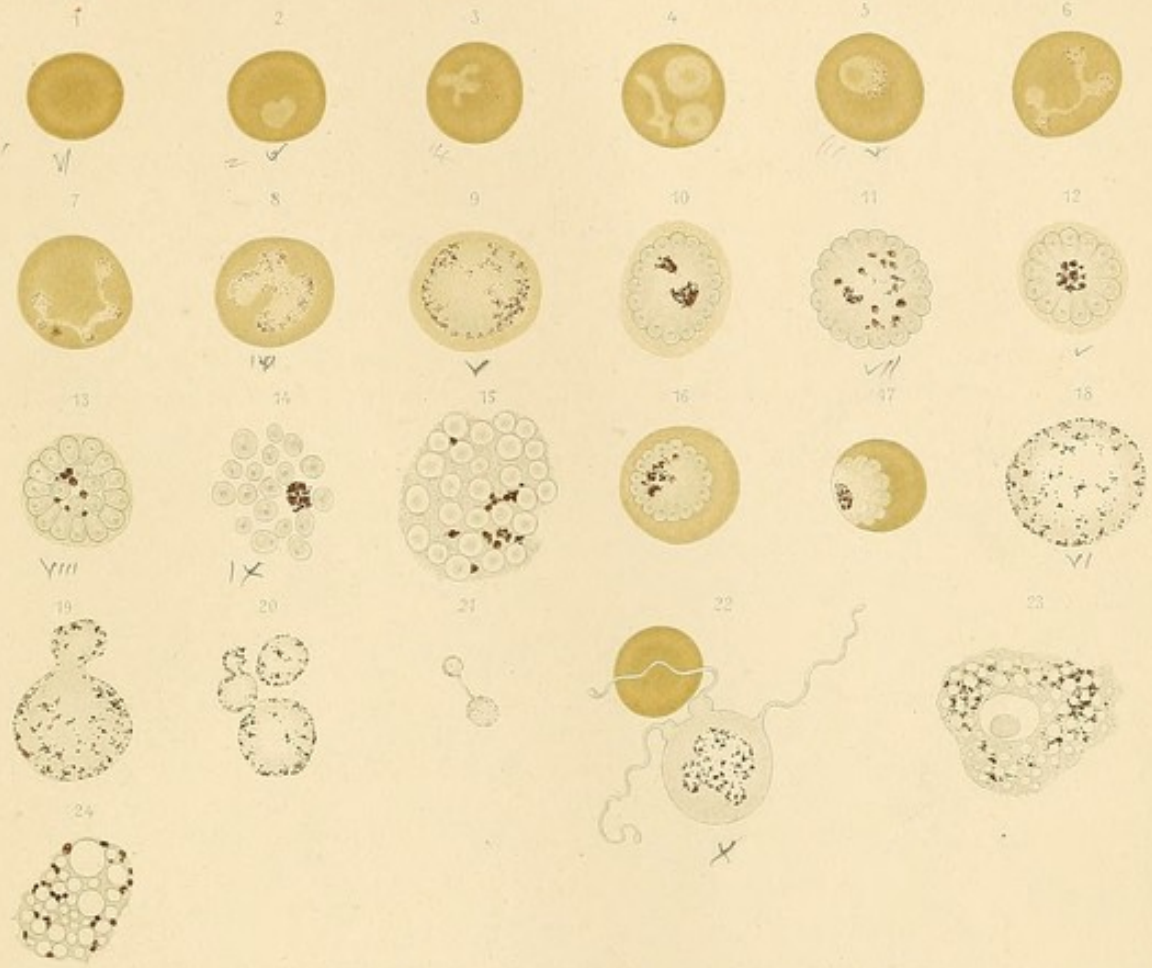
37.—Vacuolization of a crescent.

38–40.—Flagellation. The figures represent one organism. The blood was taken from the ear at 4.15 p. m.; at 4.17 the body was as represented in Fig. 38. At 4.27 the flagella appeared; at 4.33 two of the flagella had already broken away from the mother body.

41–45.—Phagocytosis. Traced by Dr. Oppenheimer with the camera lucida.

* It is unfortunate that the plate does not contain a few examples of larger forms with central pigment blocks. The writers have drawings of several as large as the segmenting body in Fig. 21.

The Parasite of Tertian Fever.



The Parasite of Quartan Fever.

Max Brödel, fec. Lith. Anst. v. E. A. Funke, Leipzig.