Malaria / by W.H. Welch and W.S. Thayer.

MALARIA.

WELCH AND THAYER.

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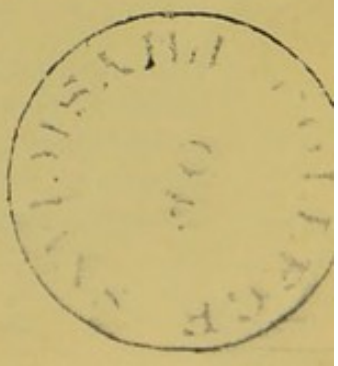


MALARIA.

By WILLIAM H. WELCH, M. D., and WILLIAM S. THAYER, M. D.

DEFINITION, SYNONYMS, HISTORY, AND PARASITOLOGY.

By WILLIAM H. WELCH, M. D.

Definition.

Malaria comprises the diseases caused by the specific protozoan parasite called *Hæmatozoön malariæ*.

The name "malaria," derived from the Italian *mal' aria* and signifying "bad air," was applied originally to the miasm or poison which was supposed to produce the disease. It is now used to designate the disease itself, and is the most convenient term for this purpose.

The most characteristic malarial manifestations are intermittent or remittent fever, certain forms of the disease described as "pernicious," and a chronic cachexia with enlarged spleen and anæmia. The parasite discovered by Laveran is invariably present in malaria and produces from the hæmoglobin of the red blood-corpuscles the brown or black pigment granules which are characteristic of the disease.

Synonyms.

Malarial fever; Intermittent fever; Chills and Fever; Fever and Ague; Paludism or Paludal fever; Swamp or Marsh fever; Miasmatic fever; Periodical fever; Autumnal fever.

Names derived from localities where the disease has prevailed with especial intensity have sometimes been used; as, Walcheren fever, Batavia fever, Hungarian fever, African fever, Panama fever, Chagres fever.

Special names have been applied to certain types or manifestations of malaria; as, remittent fever, bilious remittent fever, hemorrhagic remittent fever, congestive fever, dumb ague, black-water fever, black jaundice.

History.

There are few diseases which can be traced so surely and continuously as malaria in medical writings from ancient times to the present. Various types of malarial fever are described by Hippocrates, Celsus, Galen, and other ancient writers, although it is often impossible to determine the precise characters of many of the fevers described by these authors.

Celsus and Galen divide intermittent fevers into quotidian, tertian, quartan, semi-tertian, and irregular. They recognized intermittent fevers with long intervals. The nature of their semi-tertian fever (hemitritæus) has given rise to much discussion. Certain forms of intermittent fever were believed by Galen to have their seat in the spleen, others in the liver. The influence of marsh effluvia and of seasons of the year in the causation of certain of these fevers was recognized. Various symptoms were discriminated as to their prognostic significance, often with much acuteness of observation. A passage in Celsus clearly alludes to the type of malarial fever now called æstivo-autumnal fever.

The Arabian physician Rhazes described the so-called subintrant malarial fevers. No important advance beyond the knowledge of Celsus and of Galen concerning malarial fevers was made until toward the end of the sixteenth century, when Mercatus in his work on malignant fevers described various forms of pernicious paroxysms in association with intermittent fever, particularly with the tertian type.

The introduction of cinchona bark from Peru into Europe by the Countess del Chinchon and her body-physician, Juan del Vego, in 1640, gave great impetus to the study of malarial fevers, and, indeed, in its revolutionizing influence upon medical doctrines this event marks an epoch in the history of medicine.

In the latter half of the seventeenth and the beginning of the eighteenth century there appeared a voluminous literature regarding malarial fevers. The most notable of the works upon this subject of this period are those of Sydenham, Richard Morton, Torti, Ramazzini, and Lancisi. These works remain to this day the great classics upon malaria. They contain the fundamental clinical and therapeutical facts and many etiological data relating to this disease. Morton and Lancisi demonstrated clearly the relation of malaria to marsh miasm. Sydenham pointed out the differences between vernal and autumnal intermittent fevers. Especially complete and keen in analysis is the nosography of Torti,[1] whose classification of the malarial fevers, particularly of the pernicious and mixed forms, has been followed by most subsequent authors. The diagnostic as well as the therapeutic value of the preparations of Peruvian bark was recognized, and assisted materially in the discrimination of the malarial fevers from the other so-called essential fevers. It is interesting to note the relative accuracy of diagnosis and of description of the group of malarial fevers from the latter half of the seventeenth century onward, in contrast to the confusion which existed regarding the other essential fevers until the discrimination of the latter by the pathological-anatomical studies of the present century.

The military and colonial enterprises of England in the eighteenth century served to extend the knowledge of the geographical distribution of malaria, particularly in tropical climates, the works of Pringle and of Lind containing especially noteworthy observations on this point. But the great mass of the very extensive literature on the epidemiography of malarial diseases which has been so industriously collected and ably analyzed by Hirsch[2] belongs to the present century.

[1] Torti: *Therapeutice specialis ad febres quasdam perniciosas, etc.*, Mutinæ, 1712.

[2] Hirsch: *Handbuch der historisch-geographischen Pathologie*, Stuttgart, 1881.

The significance, as regards malaria, of the active studies in morbid anatomy of the first half of the present century relates to the clear differentiation of typhoid fever from malarial and other fevers rather than to the actual contributions to the pathology of malaria, although these were not lacking. The occurrence of enlarged spleens, so-called fever-cakes or ague-cakes, and even the dark color of the organs in association with malarial fevers, had been occasionally observed by the older writers, notably by Lancisi, but the intimate relation of these alterations to malaria was not established until during the first half of the present century.

Audouard (1808, 1812, 1818) emphasized congestion and enlargement of the spleen as the essential anatomical lesion of malarial fever. Bailly (1825) noted in a series of autopsies on cases of pernicious malarial fever observed in Rome in 1822 the dark color of the cortical gray matter of the brain and the congestion of the cerebral meninges and substance. He laid especial emphasis upon evidences of supposed inflammation of the central nervous system and of the stomach and intestine. These anatomical observations, together with those of Nepple (1828, 1835), and, to a less extent, of Maillot (1835), were interpreted in favor of Broussaisism, which at this period exerted such a pernicious influence upon medical practice.

Valuable contributions to the pathological anatomy of malarial fevers, especially of the remittent type, were made in the United States during the fourth decade of this century by Stewardson in Philadelphia, Swett in New York, and Anderson and Frick in Baltimore. Stewardson demonstrated the bronzed color of the liver in remittent fevers, and regarded this as the characteristic anatomical criterion of the disease. His observations were confirmed and extended by the other writers named. Alonzo Clark in 1855 demonstrated that the bronzed color of these livers is due to the presence of granules of yellow, brown, and black pigment, which he regarded as derived from the coloring matter of red blood-corpuscles. The monumental work of Daniel Drake on *The Principal Diseases of the Interior Valley of North America* (1850, 1854) contains a large amount of valuable information, based upon personal observation and research, as to the distribution and characters of the malarial fevers in the then Western States of this country.

In the light of recent discoveries it is interesting to note the ingenious arguments advanced by John K. Mitchell in his work *On the Cryptogamous Origin of Malarious and Epidemic Fevers*, published in 1849, in favor of the doctrine of contagium animatum. This book deserves to rank with the more frequently quoted work of Henle relating to the same line of argument. At about the same period Bassi and Rasori in Italy also advocated the parasitic theory of malaria.

The discoverer of the malarial pigment is Heinrich Meckel, who found and described the pigment in 1848 in the blood and organs of the dead body of an insane patient. He was, however, ignorant of the relation of this pigment to malaria. The next report concerning the pigment was in 1849 by Virchow, who observed it in the body of a man who had suffered from chronic malaria. There soon followed the observations of Heschl, Planer, A. Clark, Tigri, Frerichs, and others, fully establishing the relation of the pigment to malaria. The source of the

pigment was regarded by Meckel and Virchow as in the spleen, and this doctrine was elaborated by Frerichs. Planer (1854) was the first who saw the pigment in the fresh blood of living patients, and he suggested that the pigment may be formed in the circulating blood—a view which was more fully presented and advocated by Arnstein (1874) and by Kelsch (1875).

There is no doubt that some of the pigmented bodies which are now recognized as parasitic organisms had been seen by earlier observers without knowledge of their true nature. Thus Meckel noted the presence of pigment granules in colorless, hyaline bodies devoid of definite nuclei. He, and more particularly Virchow and Frerichs, observed pigment in fusiform and curved bodies in the blood, which, although interpreted as endothelial cells of splenic origin, in all probability were, at least in part, the crescentic forms of the parasite. Some of the larger pigmented spherical organisms must have been seen and mistaken for pigmented leucocytes.

In November, 1880, Laveran discovered the parasitic nature of these and previously unrecognized forms in the blood of malarial patients, and thereby introduced a new era into our knowledge of the malarial diseases.

The discovery of the malarial parasite has furnished an unfailing means of diagnosis of malarial diseases, has materially advanced our knowledge of their pathology, has led to a better understanding of their clinical phenomena and various types, has furnished important data for prognosis, and has led to improvements in methods of treatment.[1]

Parasitology.

Historical.

In 1879, A. Laveran, a French military surgeon, stationed at the time in the province of Constantine, Algeria, began to study the pathological anatomy of malaria, and at once directed his attention to the much discussed question of the origin of the pigment. He observed in the blood of malarial patients certain pigmented bodies different from the melaniferous leucocytes, but he was uncertain as to their nature until, on November 6, 1880, he discovered that some of these pigmented bodies threw out long flagella endowed with such active lashing movements as to convince him, as they have convinced every one who has since then seen them, that they are living parasites. Laveran published his observations in a note to the Académie de Médecine in Paris, presented November 23, 1880. This was followed by the publication of several notes in 1880 and 1881, and in the latter year appeared a small monograph by Laveran on the parasitic nature of malaria.[2]

[1] The so-called bacillus malariæ described in 1879 by Klebs and Tommasi-Crudeli, which for a short period had a certain vogue, chiefly with Italian writers, never rested upon satisfactory observations which indicated that it bore any relation to malaria, and it deserves no more consideration than the palmella of Salisbury and the other alleged malarial organisms described before Laveran's discovery.

[2] Only occasional references to the voluminous literature on the parasitology of malaria are given in this article. A full table of references to the works treating of malarial fever since the recognition of its parasitic origin up to and partly including the year 1895 will be found in "The Malarial Fevers of Baltimore," by William Sydney Thayer, M. D., and John Hewetson, M. D. (*The Johns Hopkins Hospital Reports*, vol. v., 1895).

In these various early publications Laveran describes (1) pigmented crescentic and ovoid bodies; (2) spherical, transparent bodies, sometimes free, sometimes applied to the surface of red blood-corpuscles, the smallest about one-sixth of the diameter of a red blood-corpuscle and containing only one or two fine pigment granules, these representing an early stage of development of (3) larger, pigmented, spherical bodies averaging 6 μ in diameter, but sometimes larger than a red blood-corpuscle, and containing numerous, often moving, pigment granules; (4) bodies similar to the last mentioned, but beset with actively motile flagella; (5) free motile flagella; and (6) swollen spherical or deformed bodies, 8–10 μ in diameter, containing pigment, and regarded as cadaveric forms of the spherical parasites. Laveran noted amœboid movements of the spherical forms, grouping of the small spherical bodies together, and the occurrence of small, colorless, motile bodies, without specific characters, which he suggested may perhaps represent the first phase of development of the parasitic elements. He regarded all of the forms as different stages of development of the same species of organism, and considered the free flagella, which he believed were formed within the spherical bodies and escaped by rupture of the enveloping membrane, as the most characteristic and perfect stage of development of the parasite.

Laveran communicated his results to his colleague Richard, stationed in Philippeville, Algiers, who in February, 1882, published a communication confirming Laveran's observations and adding certain points of importance. He describes the development of the parasite from small, perfectly transparent bodies contained in otherwise normal red blood-corpuscles. This clear body grows larger, forms pigment out of the hæmoglobin of the enveloping red corpuscle, which thereby becomes gradually decolorized and reduced to a mere colorless shell-like rim, which finally ruptures and sets free the parasite. This now generally accepted view as to the intracorpuscular development of the parasite, which was first announced by Richard, was, however, in the following year abandoned by him in favor of Laveran's view that the parasites develop either free in the plasma or in close attachment to the surface of red corpuscles or in depressed spots on the surface. Richard observed amœboid movements of the parasites, and noted spherical bodies with a central block of black pigment from which delicate lines radiated so as to produce rosette forms.

Laveran continued to publish brief communications in 1882 and 1883, and in 1884 he published a larger work [1] presenting his observations and views in detail. In this work he describes more fully the forms already mentioned, and he notes the occurrence of segmenting forms, which, however, he interpreted as forms of degeneration, not of reproduction.

The observations of Laveran and of Richard were made by microscopical examination of the fresh blood. In 1883 and 1884, Marchiafava and Celli published in a number of articles the results of their studies of stained specimens of dried malarial blood. With the exception of small, spherical stained bodies in the red blood-corpuscles, which they thought might be micrococci, they interpreted the various other stained and usually pigmented bodies found in the red corpuscles of malarial patients as probably degenerative changes. As a matter of

[1] Laveran: *Traité des Fièvres palustres*, Paris, 1884.

fact, the coccus-like dots were probably in part Ehrlich's degenerations, whereas their drawings show that the supposed degenerative forms were in reality the actual parasites, which in many of their phases were accurately depicted, although not recognized as such.

In 1885, Councilman and Abbott in the organs from two cases of pernicious comatose fever found and described small pigmented hyaline bodies in and outside of red corpuscles, most abundantly in capillaries of the brain.

In 1885, Marchiafava and Celli, as the result of the examination of fresh malarial blood, came to a correct interpretation of these bodies and described them fully and accurately. They emphasized especially the amœboid, unpigmented, transparent intracorpuscular bodies, to which they gave the inaccurate name of plasmodia, which has been widely adopted. They described clearly the intracorpuscular development of the parasite, the formation of pigment out of the blood coloring matter, the consequent changes in the blood-corpuscles, and they pointed out the probable reproductive nature of the segmenting bodies, which they described more fully and accurately than had been done by Laveran and Richard.[1]

The publications of Marchiafava and Celli attracted wider attention than had those of Laveran, and from the year 1885 up to the present time there has been a steadily flowing stream of literature upon the various questions connected with the parasitology of malaria.

Immediately following the confirmation of Laveran's discoveries by Italian observers came similar confirmation from Sternberg, Councilman, and Osler (1886–87), and somewhat later by James (1888) and Dock (1890), in this country, and within a few years numerous reports from various parts of Europe, America, Asia, and Africa demonstrated the invariable association of Laveran's parasites with all cases of malarial fever. There are no observers of any prominence who, with sufficient opportunity and training for such examinations, have failed to recognize the parasites in cases of malaria, nor is there now any authoritative voice of dissent from the acceptance of the parasite as the specific cause of this disease.

Since the fundamental researches of Laveran, Richard, and Marchiafava and Celli (1880–85) other observers have greatly extended our knowledge as to many details concerning the structure and life-history of the parasite and its relation to various types, phenomena, and lesions of malaria, although not a few important questions still remain unsettled. The most important of these later discoveries are due to the demonstration by Golgi (1885–86) of a definite relation between the cycle of development of the parasite and the different stages of malarial fever, and to the recognition by Golgi (1885–86) of the two varieties of the parasite belonging respectively to quartan and to tertian fever, and by Marchiafava and Celli and Canalis (1889) of the variety or varieties belonging to æstivo-autumnal fever. These observations have led to

[1] Marchiafava and Celli claim for themselves the discovery of the intracorpuscular amœboid forms with and without pigment, and of the segmenting forms, but, as is apparent from the review of Laveran's and Richard's preceding publications, this claim cannot be admitted. Marchiafava and Celli, however, described and interpreted these phases of the parasite far better than Laveran, and to them belongs the credit of demonstrating the intracorpuscular development of the parasite.

two schools of doctrine—the one, headed by Laveran, holding to the unity of a pleomorphic malarial parasite, the other, headed by Golgi and other Italian writers, upholding the plurality of malarial parasites. The latter doctrine has the larger number of supporters.

Dock (1890–92) was the first to differentiate the three principal varieties of the malarial parasite in the United States, and recently Thayer and Hewetson[1] have published a thorough study of the malarial fevers of Baltimore with careful descriptions of these varieties.

Investigations concerning the intimate structure of the malarial parasites have been made especially by Celli and Guarnieri, Grassi and Feletti, Romanowsky, Sacharoff, Mannaberg, Antolisei, Bastianelli and Bignami, and others.

The results of these later studies concerning the malarial parasites will be considered in various parts of this article. They are fully and systematically presented in the recent monograph of Thayer and Hewetson, already cited.

Nomenclature.

Various names have been suggested for the malarial parasite. Among these may be mentioned Oscillaria malariæ (Laveran), Plasmodium malariæ (Marchiafava and Celli), Hæmatomonas malariæ (Osler), Hæmatophyllum malariæ (Metchnikoff), Hæmamœba malariæ (Grassi and Feletti), Hæmococcidium malariæ (L. Pfeiffer), Hæmosporidium malariæ (Danilewsky), Hæmatozoön or Hæmocytozoön malariæ (Osler and various authors).

Of these names, Plasmodium malariæ has gained wide currency, but it is on zoölogical grounds singularly inappropriate, and there is no reason why it should be perpetuated.

The name Hæmosporidium malariæ has much to recommend it, but it has not been generally adopted. Upon the whole, the name Hæmatozoön malariæ, which expresses nothing as to the zoölogical classification of the parasite, and which has been adopted by many writers, may be provisionally accepted until more precise knowledge is reached concerning the zoölogical position of the parasite. Hæmocytozoön is more precise, but the other term has the advantage of greater brevity.

Zoölogical Position of the Malarial Parasite.

The malarial parasite belongs to the class of Protozoa, under which name are grouped the unicellular organisms with the physiological characters of animals. Bütschli divides the Protozoa into the orders—Sarcodina, Mastigophora, Sporozoa, and Infusoria. Grassi and Feletti classify the malarial parasite among the Sarcodina, subdivision Rhizopoda, and adopt the name Hæmamœba malariæ. Antolisei considers that the parasite belongs to the Gymnomyxa, or, more precisely, the Proteomyxa of Ray Lankester. The great majority of authors classify the malarial parasite among the Sporozoa, which are divided by Balbiani into the groups Gregarinida, Sarcosporidia, Myxosporidia, and Microsporidia. Under the Gregarinidæ are included the Coccidia, with which

[1] *Op. cit.*

some writers group the malarial parasite. Kruse makes under the Gregarinidæ a special family which he designates as Hæmogregarinidæ, and to which he refers the malarial parasite and similar hæmocytozoa in lower animals. Danilewsky suggests forming a new group under the Sporozoa to be called Hæmosporidia, in which he places the malarial and similar hæmatozoa, and Labbé calls the group Gymnosporidia.

As we know nothing of the malarial parasite in the outer world, it is evident that our knowledge of its life-history is incomplete, so that any attempt at a zoölogical classification must be regarded as only provisional. Such information as we possess favors classifying the parasite among the Sporozoa, but it possesses characters which do not enable us to fit it exactly into any of the existing subdivisions of the Sporozoa, so that the suggestions of Kruse and of Danilewsky of establishing a new subdivision of the Sporozoa or of the Gregarinidæ to include the malarial parasite and similar organisms in birds seems to be a good one, and the name Hæmosporidia for this new subdivision appears to be appropriate. According to this classification, the malarial parasite may be called the Hæmosporidium malariæ.

Methods of Investigation.

The methods for demonstrating and studying the malarial parasite will be described under the heading *Diagnosis*. It may here be stated that generally the most useful procedure is the examination of thin layers of fresh blood with an oil-immersion objective. The description of the parasite which is to follow is based mainly upon this method. This procedure may be advantageously combined with the examination of stained specimens. For the study of the finer details of structure this latter method is indispensable.

General Morphology and Biology.

The malarial parasite is a unicellular, protozoan organism which develops within the red blood-corpuscles, and therefore belongs to the group of Hæmocytozoa. As will be described subsequently, organisms closely resembling the malarial parasite have been found in the blood of birds. The numerous attempts to cultivate artificially the malarial parasite have hitherto been unsuccessful, nor has this organism been recognized in the outer world. Our entire knowledge of it is derived from its study in human beings.

Three varieties of the parasite have been differentiated. These varieties are that of quartan fever, that of tertian fever, and that of æstivo-autumnal fever. This last variety it is proposed by the writer to call the Hæmatozoön malariæ falciparum. Before considering the justification of this division and the special characters of each of these varieties it is desirable to describe the more important characters common to all varieties of the malarial parasite.

The cycle of development of the malarial parasite embraces a vegetative and a reproductive phase. Its duration varies from twenty-four to seventy-two hours, according to the variety of parasite.

The vegetative phase begins in the form of small, colorless, amœboid,

hyaline bodies, 1–2 μ in diameter, within the red blood-corpuscles.[1] These amœboid bodies increase in size, and, with the occasional exception of the æstivo-autumnal variety, they develop within them a variable number of dark pigment-granules, situated, as a rule, near the margin of the parasite. The pigment increases in amount and in the coarseness of the granules as the organisms continue to develop. It occurs in the form of irregular grains and of fine rods, which may be in active motion within the parasite.

Having attained a certain stage of development, which differs as regards the size of the organism in the different varieties, the parasite gradually ceases its amœboid movements, assumes a spherical or oval shape, and becomes somewhat sharper in contour. In this condition it may continue for a while to grow. When it has reached its full size it may completely fill the red blood-corpuscle or may occupy only a small part of it, these differences depending mainly upon the variety of parasite. The parasite now may be called the full-grown or adult form.

Coincidently with these stages of development the enveloping red blood-corpuscle may undergo various changes, which are of significance in distinguishing the varieties of parasite from each other. The corpuscle may become swollen and pale, or shrunken, or brassy-green in color, or otherwise deformed, or it may appear unaltered, as will be described in considering the varieties of the parasite.

The subsequent stages in this cycle of development belong to the reproductive phase, which is shorter in duration than the vegetative. The first evidence of this reproductive phase is the collection of the pigment into a mass of granules or a solid block situated usually at or near the centre, but sometimes near the periphery, of the organism. These bodies with clumps of pigment may be designated, in accordance with Thayer and Hewetson's suggestion, as the presegmenting forms (*corpi con blocchetto* of the Italian writers).

Coincidently with or following this gathering of the pigment into a clump, sometimes without a definite collection of the pigment, the process of segmentation begins. In its most typical form segmentation is ushered in by the appearance of delicate lines radiating from the periphery toward the centre. Eventually the substance of the spherical organism is divided into a variable number of round or oval bodies called spores. The enveloping red corpuscle, which now may be

[1] As has already been mentioned, Laveran believes that the forms of the parasite which have, since the publications of Marchiafava and Celli, usually been regarded as within the red corpuscles, are attached or applied (*accolés*) to the outer surface of the corpuscles. Mannaberg (1893) has again raised this question by his statement that many of the amœboid forms, particularly in their younger stages of development, are attached to the corpuscles, often in little niches or indentations on the surface. There is no doubt that the organism may be situated as described by Mannaberg. Marchiafava and Celli, who had previously noted this appearance, interpreted it as indicating the extrusion of the parasite from the red blood-corpuscle. It is, in fact, often very difficult to determine with precision whether the organism is on the surface of or within the corpuscle, but the evidence is that the majority of the younger forms are intracorpuscular. Marchiafava and Bignami (1894) describe in the following words their conception of the manner of penetration of the youngest forms into the corpuscle: "The youngest amœbæ, the offspring of sporulation, by virtue of the viscidity of their protoplasm adhere to the surface of, and by their movements bury themselves in, the contour of the red corpuscle. In this position the parasite attacks the external strata of the corpuscle as a means of nourishment, and after altering these layers is able to penetrate within, and thus becomes entirely endoglobular."

reduced to a narrow pale rim, bursts and the spores are set free, or the corpuscle may have disappeared before the process of segmentation is completed. The pigment remains behind, and is quickly engulfed by phagocytes. Sometimes in the æstivo-autumnal variety segmentation occurs in organisms entirely devoid of pigment. These segmenting bodies are called also sporulating forms.

The free spores speedily invade fresh red blood-corpuscles, where, as the small, colorless, amœboid, hyaline bodies already mentioned, they begin again the cycle of development. The direct transformation of the motionless[1] round spores into the small, hyaline, amœboid bodies has been very rarely observed, but there is no reason to suppose that there exists any stage intervening between these two forms.

In the complete sporulating cycle of development which has been described we can distinguish, therefore, the following forms of the parasite: (1) unpigmented, amœboid, hyaline bodies; (2) pigmented, amœboid, hyaline bodies; (3) full-grown or adult bodies; (4) presegmenting bodies; (5) segmenting or sporulating bodies; and (6) spores. All of these various bodies are depicted in Plates I. and II.

As already mentioned, in the æstivo-autumnal variety this cycle may be completed without the appearance of pigment. These bodies are to be thought of, not as separate and distinct forms, but simply as successive stages of development with all transitions from the youngest to the most advanced. Especially can no sharp distinction be drawn between bodies (1) and (2) and between bodies (3) and (4). The recognition, as a distinct form, of the body designated as presegmenting is of less practical importance for the quartan and tertian varieties than for the æstivo-autumnal.

The name "plasmodium" was applied by Marchiafava and Celli originally to the unpigmented, amœboid forms. It is frequently employed to designate both the pigmented and the unpigmented amœboid bodies, as well as the parasite in all of its forms. These amœboid bodies may be called, in general, hyaline forms or amœbæ.

As will be explained subsequently, it is only the quartan variety which is found in all its forms with equal frequency in the peripheral circulation and in the blood of internal organs; whereas segmenting tertian parasites are more abundant in the spleen and bone marrow than in the peripheral vessels, and the æstivo-autumnal parasite develops mainly in the internal organs, its segmenting forms being extremely rare in the peripheral circulation.

Each of the forms of the parasite which have been described as developing within the red blood corpuscles may also be found free in the plasma. They probably escape by rupture of the enveloping corpuscle, a process which one can often witness when examining the fresh blood microscopically. Extracorpuscular mature forms may possibly segment in the usual way, but there is no evidence that forms in the earlier stages may complete their cycle of development free in the plasma.

The important discovery was made by Golgi that all of one generation of the parasite form a group, the members of which develop

[1] Plehn claims to have observed that the spores are actively motile and flagellated, but this statement is opposed to the observations of all others.

approximately at the same time, and that a definite relation exists between the phases of development of the parasite and the stages of malarial fever. The onset of a paroxysm corresponds to the ripening of one generation of the parasite. A few hours or shortly before the paroxysm segmenting forms appear, and enable the observer to predict the approaching paroxysm. The spores which are set free by the act of sporulation invade the red blood-corpuscles and start a fresh generation, which pursues during the paroxysm and the subsequent apyrexia so regular a development that in typical cases the experienced observer can tell approximately by examination of the blood the stage of the disease—that is, the time which has elapsed since the last paroxysm and the time when the next paroxysm may be expected.

It is not, however, always the case that the parasite develops with the regularity expressed by Golgi's law, and especially in the æstivo-autumnal fevers irregularities are very common. The simultaneous occurrence of two or more generations in different stages of development may render difficult the interpretation of the phases observed, although even here careful observation will enable the observer to draw correct conclusions in tertian and quartan fevers.

It has not been satisfactorily demonstrated that there occurs any other cycle of development of the malarial parasite in human beings than that which has been described, although the possibility of such an occurrence is by no means disproven. Canalis (1889) believes that he has found evidence that a second, slower cycle of development of the æstivo-autumnal parasite occurs, which is represented in certain of its phases by bodies of the crescentic group, to be described subsequently; and this view, with certain modifications, has been accepted by Golgi, Antolisei and Angelini, Grassi and Feletti, and Sacharoff. This doctrine is, however, opposed by many observers, and it does not at present rest upon sufficient evidence.

It seems necessary to suppose, on the basis of clinical evidence, that the malarial parasite may remain for months in a latent condition in the human body, and then begin to develop again, causing a relapse of the fever. As such relapses may occur in forms of malaria in which crescents do not appear, there must be in these cases some resistant organism other than bodies belonging to the group of crescents. We know nothing as to the nature of these resistant bodies. The hypothesis is advanced by Bignami that they may be spores which are enclosed within leucocytes and other cells, and which have become surrounded by a resistant membrane and have lost their usual staining properties.

Besides the forms which have already been described as representing phases of the regular sporulating cycle of development of the malarial parasite, there occur other forms which cannot at present be referred to any cycle of development. These other forms are—(1) crescentic bodies and fusiform, oval, and round bodies belonging to the same group; (2) flagellate bodies and free flagella; and (3) degenerative forms.

The crescentic and flagellate bodies, from their size and remarkable appearance, are the most striking forms of the parasite, and from the beginning have attracted much attention. Their significance, although there are many hypotheses concerning it, is not understood.

(1) The crescents develop only from the æstivo-autumnal parasites,

and will therefore be described in connection with these. They are never formed from quartan and tertian parasites.

(2) *Flagellate bodies*, on the other hand, may form from each variety of the parasite, tertian, quartan, or æstivo-autumnal. The weight of evidence is that they do not exist in the circulating blood, but develop after the blood has been withdrawn from the body, usually within ten to twenty minutes, sometimes earlier. Some observers have found them frequently, others only rarely. They are frequently found if the blood is examined at the right stage of the disease and time is allowed for their development. Councilman showed that they are more commonly found in blood aspirated by a hypodermic needle from the spleen than in the peripheral blood. They develop in tertian and quartan fevers from the mature, full-grown extracorpuscular forms—in tertian especially from swollen forms larger than the red blood-corpuscles. They are therefore found most frequently a short while before and during the paroxysm. In infections with the æstivo-autumnal parasite the flagellate bodies develop from round bodies belonging to the group of crescents, and do not occur in definite relation to the stage of the fever. Rarely intracorpuscular bodies may develop flagella.

The spherical bodies which become transformed into the flagellate bodies are always or nearly always pigmented. Marchiafava and Celli state that they once saw an unpigmented flagellate body. These bodies may be somewhat smaller or larger than the red blood-corpuscles, the size varying to some extent with the different varieties of the parasite, as will be explained later. The process of development of the flagella may be studied under the microscope. The pigment granules, which at first (æstivo-autumnal variety) may have been in repose, usually begin to dance about within the organism, often in a lively way. In the æstivo-autumnal variety they usually gather in the central part, but in the others they may be near the periphery or irregularly distributed. The spherical body may acquire an oscillatory or jerking movement. Projections may be formed and retracted at the periphery, and the whole edge may acquire a vigorous undulating movement. These changes are attributed to the movements of the flagella within the body or in its peripheral layers, and have been graphically compared by Richard to the struggles of an animal to get free. Suddenly the flagella shoot out from the periphery, and with their active lashing movements produce a violent commotion among the red blood-corpuscles and other small particles which may be in their neighborhood (Plate I. Figs. 22 and 41 ; Plate II. Figs. 43, 44).

The flagella are pale and thin, and present often at their extremities and along their course small olive-shaped swellings which may change their position. Here and there a pigment granule is occasionally seen in a flagellum. The flagella vary in size, number, and position. Their length may be three or four times the diameter of a red blood-corpuscle or not more than half that size. One to six may be attached to the spherical body. They may project from one side or from any part of the circumference of the body. Their movements may be somewhat rhythmical ; they may become slow or even cease, and again start up.

Flagella may become detached and move about freely among the red blood-corpuscles. On account of their pallor such free flagella would

usually be overlooked were it not for the commotion which they produce among the red blood-corpuscles. The motion of the flagella may be observed on the slide for half an hour, sometimes longer.

These flagellate bodies are the most startling forms of the malarial organism, and no one who sees them doubts for a moment that he is looking at a living parasite. It is not surprising that they attracted in an especial manner the attention of Laveran, who, as already mentioned, regarded the flagella as the most characteristic and perfect form of development of the parasite. Subsequent studies have not, however, tended to confirm the conception of Laveran as to their significance. As has already been made clear, the flagellated bodies do not belong to the regular sporulating cycle of development of the malarial parasite in the human blood. The most prominent theories as to their significance are the following:

(*a*) They are forms of degeneration or appearances belonging to the death-agony of the parasite. In support of this view it is urged that the flagellate bodies do not belong to any known cycle of development; that they are developed only outside of the human body; that they are developed from mature forms which are known frequently to undergo undoubted degeneration, such as hydropic swelling, vacuolation, and fragmentation, and which may already show beginning evidences of degeneration; that nuclear substance is absent from the flagella; and that similar appearances of extrusion of motile filaments in other unicellular organisms are known to zoölogists and are interpreted as degenerative.

(*b*) Sacharoff, from the study of their structure on stained specimens, believes that the flagella are extruded chromatin filaments derived from perverted karyokinetic nuclear division. He regards the process as degenerative.

(*c*) Dock 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."

(*d*) Mannaberg's opinion is that the flagellate bodies may represent a state belonging to the saprophytic existence upon which the mature forms of the parasite enter soon after the blood is withdrawn from the body. On account of unsuitable conditions of environment they are unable to continue this existence in the blood outside of the body and soon perish. A similar view is advanced by Manson, who suggests that the flagellate bodies represent the first stage, and the detached flagella, in search of their appropriate host, represent the second stage of life of the parasite outside of the body. Manson[1] conjectures that the mosquito is the extracorporeal host of the malarial parasite, and he reports observations of Ross showing the development of flagellate forms in the stomach of mosquitos fed on malarial blood.

There are arguments for and against each of these theories. Reluctant as one may be to consider such striking forms as the flagellate

[1] Manson: "The Goulstonian Lectures on the Life History of the Malaria Germ Outside the Human Body" (*The British Medical Journal*, 1896, March 14, 21, 28). Manson lays much emphasis upon supposed analogies between the malarial germ and the filaria sanguinis. Only future investigations can determine the correctness of Manson's hypothesis.

bodies as phases of degeneration, the existing evidence seems upon the whole to be more in favor of this hypothesis than of any other which has been advanced. Still, if Sacharoff's observation as to the presence of nuclear material in the flagella be correct, the objection of Grassi and Feletti, that the flagella are incapable of reproductive development because the nucleus of the parasite does not divide and enter them, would be overthrown and the hypothesis of Mannaberg and Manson would become more probable. It is evident from the description of these bodies that the use of the word "flagella" to designate the motile filaments is of doubtful propriety, but it is the term commonly employed.

(3) There are various bodies, often seen in the examination of malarial blood, which are undoubtedly *degenerative forms* of the parasite, and others which are probably degenerative, although opinions concerning the latter are divided. The more common signs of degeneration of the parasite are vacuolation, pseudo-gemmation, fragmentation, deformities of shape, particularly swelling, granular condition of the protoplasm, certain alterations in the arrangement and appearance of the pigment, disappearance of nuclear material, defects and irregularities in staining, and changes in the refraction of the organism. These various degenerative changes produce forms too numerous to describe in detail. They have often been misinterpreted and described as special forms of the parasite, some of them, particularly certain vacuolated and budding forms, as special modes of reproduction.

Degenerations may occur in any form of the parasite, but they are particularly common in the extracorpuscular forms. Mannaberg describes the disintegration of young intracorpuscular forms, with disappearance of their nuclei. Fragmentation of forms extruded from the blood-corpuscles can sometimes be watched while examining fresh blood under the microscope (Plate I. Fig. 21). As a rule, only a certain number of the mature forms actually enter into reproductive segmentation, and many of the spores or segments perish. If all segmented and the offspring survived, the number of the parasites after a few paroxysms would become enormous. As a matter of fact, degenerations of full-grown parasites are often observed. An interesting form of such degeneration, found most frequently in the mature forms of the tertian variety, is the appearance of swollen, pigmented, so-called hydropic bodies, often much larger than red blood-corpuscles (Plate I. Figs. 18, 40), and sometimes containing vacuoles (Plate I. Figs. 18, 19, 23, 24, 40, and 42). Round bodies simulating spores are sometimes seen in these vacuoles, but on properly stained specimens they are devoid of the nuclear material of genuine spores. Pseudo-gemmation, or the appearance of sarcodic buds on the surface of the organisms, is doubtless a form of degeneration. Such buds may become separated, in the form of hyaline balls, from the parent organism (Plate I. Figs. 19, 20). These evidences of degeneration may appear also in crescents and bodies belonging to this group (Plate II. Figs. 40, 41) and in flagellate bodies. From the latter small hyaline balls with a flagellum attached may break off and move around actively. Such bodies might be mistaken for flagellated spores.

There is no good evidence that the malarial parasite ever multiplies

by budding[1] or by simple cell-division. The only form of multiplication which has been demonstrated is that of sporulation, also called segmentation, already described, although it cannot be denied that other forms of reproduction may exist.

Various interesting degenerative changes are produced by the influence of quinine. These will be fully described under TREATMENT, *Action of Quinine on Malarial Parasites*, page 146.

As the malarial parasite passes its vegetative life mostly within the red blood-corpuscles, it is evident that it finds its food in this situation. This food may be appropriated both by intussusception and by diffusion. Evidence of intussusception is found in the occasional presence of fragments of the corpuscular substance within the body of the amœboid forms. Doubtless diffusion is the more important mode of nutrition of the parasite.

The question has been raised whether the parasite may develop in other cells of the body than the red blood-corpuscles. Nearly all forms of the parasite have been found enclosed in cells, chiefly leucocytes, splenic or medullary cells, and endothelial cells. As such included parasites often present evidences of degeneration, these appearances have been generally interpreted as referable to phagocytic destruction of the parasites, and such they unquestionably usually are. Golgi and Monti have, however, recently published observations intended to show that the æstivo-autumnal parasite may develop within endothelial and other cells, as will be explained in considering this variety of parasite.

The malarial parasite in the condition in which it exists in the human body is very susceptible to injurious agencies. It is quickly killed by the addition of distilled water and of dilute acids and alkalies. Under ordinary conditions it does not long survive in blood withdrawn from the body. Under certain special circumstances it has been kept apparently alive for two to four days, possibly for a week. Sacharoff observed amœboid movements in æstivo-autumnal hyaline bodies which had been for a week in the intestinal canal of leeches kept on ice, and he obtained a positive result by inoculating himself with malarial blood preserved in this way for four days in leeches. The tertian and quartan parasites were found to be less resistant than the æstivo-autumnal. Ripe bodies may segment in blood outside of the body, but no further development or multiplication of the parasites has been positively observed in the various attempts made to preserve or cultivate them. The parasite does not continue to develop and multiply in the human body after death.

Of course no inferences can be drawn from these observations as to the resistance of the parasite in its natural condition in the outer world. As to what this natural condition is we can only speculate. Grassi and Calandruccio have thought that certain species of amœbæ which they have observed in malarial districts might be the extraparasitic form. The failure of artificial cultivations and certain analogies drawn from the zoölogical characters of the parasite have led to the prevalent theory

[1] Celli and Guarnieri for a time believed that spherical bodies of the crescentic phase may multiply by the formation of buds (gemmation), but they subsequently abandoned this view and adopted the now generally accepted opinion that these budding forms are degenerative. The "buds" are devoid of the structure of genuine spores.

that the malarial parasite passes at least a part of its existence as a parasite in animal or vegetable organisms. Mention has already been made of Manson's hypothesis that the mosquito may be a host for the malarial parasite. That the germ is capable of entering upon some resistant phase of development seems highly probable in view of the evidence that malaria can be contracted from the air. There is no evidence that the malarial parasite is eliminated from the human body in a condition capable of infecting another individual or the locality. The disease, however, can be transmitted by inoculating into healthy individuals, either subcutaneously or intravenously, blood from a malarial patient.

Unity or Plurality of the Malarial Parasite.

As has already been mentioned, there are two schools of doctrine as to the malarial parasite—the one led by Laveran holding that the malarial parasite is a single species with pleomorphic characters, the other believing that there are three or more species, or at least varieties, of malarial parasites. The observations upon which the latter doctrine is based originated with the Italians, and have been supported by investigations in this country and elsewhere.

Golgi in 1885 and 1886 first differentiated the parasite of quartan fever from that of tertian fever, and Marchiafava and Celli and Canalis in 1889 and 1890 differentiated the variety of parasite characteristic of æstivo-autumnal fever.[1] There is much difference of opinion as to the number of æstivo-autumnal parasites. All adherents of the doctrine of plurality agree that there are at least three varieties of malarial parasite —namely, the quartan, the tertian, and the æstivo-autumnal—distinguished from each other by morphological and biological characters to be subsequently described. The discovery by Golgi of the definite cycle of development of the malarial parasite and the recognition of several distinct varieties have done much to bring order out of the earlier chaotic condition when a multitude of parasitic bodies were described without knowledge of their significance or relations to each other. There remain, however, many unsolved problems which it may be expected that further investigations will clear up.

[1] Marchiafava and Celli on the one hand, and Canalis on the other hand, have conducted a polemic as to which of them belongs the credit of first distinguishing the æstivo-autumnal parasite. The differentiation of this parasite was not made all at once, and with the same precision in all details, as in the case of Golgi's sharp separation of the quartan and tertian parasites. Golgi from the beginning of his researches (1885–86) suggested that the crescentic bodies belong to a special cycle of existence different from that of the tertian and quartan organisms, and noted their occurrence in irregular malarial fevers. Councilman in 1887 emphasized the association of crescents with remittent fevers and malarial cachexia. Golgi in February, 1889, definitely expressed the opinion that in addition to the malarial fevers caused by the quartan and the tertian parasites we must recognize another type of fever associated with unpigmented amœboid forms and crescents. On September 13, 1889, appeared a preliminary communication of Marchiafava and Celli, which must be regarded as furnishing the first clear and sharp description of the essential differential characters of the æstivo-autumnal parasite, with especial emphasis on the occurrence of unpigmented organisms. On October 10, 1889, appeared the preliminary communication of Canalis, in which likewise the essential characters of this parasite were described, and a greater emphasis was laid upon its relation to the crescents than had been done by Marchiafava and Celli. The full publication of Canalis anticipated by a short time the complete article of Marchiafava and Celli on the æstivo-autumnal parasite.

In opposition to the doctrine of plurality it is urged by Laveran that all of the so-called varieties of the parasite may be explained simply as phases of a single pleomorphic organism influenced by various conditions of environment, such as locality, season, individual predisposition, and various unknown circumstances. He contends that the characters upon which a division into separate varieties is based are insufficient for such a purpose and inconstant; that one so-called variety under certain conditions may be transformed into another; and that there is no definite, necessary relation between the types of fever, such as quartan, tertian, quotidian, irregular, continued, and the form of parasite present. The variations of the malarial parasite can be explained, he thinks, in large part by the varying rapidity of development. He emphasises the view that malaria with all its diverse manifestations is nevertheless clinically and anatomically one disease, and has always been so regarded. He argues that the experimental production of malaria by inoculation does not support the doctrine of plurality.

In considering the force of these objections it must be admitted that so long as we are unable to cultivate the malarial parasite artificially, and are ignorant of its life-history and the conditions of its existence outside of the human body, the possibility must be admitted that under certain conditions, at present unknown, one variety may be transformed into another. But, on the other hand, the existing evidence—and it is already considerable—goes to show that under the conditions which we can at present control and study each of the three principal varieties of the parasite preserves its identity and is not transformed into another variety; that is to say, there is no evidence that a quartan parasite ever becomes metamorphosed into a tertian, or either of these into an æstivo-autumnal parasite.

The principal arguments in support of this doctrine of plurality may be summarized as follows:

(1) Each well-established variety of parasite presents morphological and biological characters which suffice for its identification.

(2) Each variety of parasite corresponds to definite types of fever. Genuine quartan fever can be produced only by the quartan parasite. As will be explained in the clinical part of this article, other types of fever may be caused by more than one variety of parasite, and much complexity may result from multiple and mixed infections and various irregularities; but all of this does not prevent the recognition of certain fundamental types of fever especially characteristic of each variety of the parasite.

(3) Cases of pure infection with one variety of parasite have been carefully studied for weeks and months without any indication of the transformation of one variety into another (Calandruccio, Grassi and Feletti). Opportunities for such study are exceptional. The appearance of a second variety of parasite in localities where there is opportunity for renewed infection cannot of course be interpreted in favor of the metamorphosis of one variety into another.

(4) In certain localities only one or two of the varieties of the parasite are met with. In a few places only the quartan, or more frequently only the tertian, parasite is observed; in most places where malaria is mild and infrequent only tertian, and occasionally quartan, parasites,

with entire absence of æstivo-autumnal parasites, are found. Instances of this localized distribution of the parasites, which manifestly is a strong argument in favor of the doctrine of plurality, will be subsequently mentioned (page 99).

(5) Strong arguments in favor of the constancy of the varieties of the malarial parasite are furnished by the experimental production of malaria. Gerhardt in 1882 and 1883 (reported in 1884) was the first to produce malaria experimentally by the subcutaneous injection of blood obtained from malarial patients. At this time the malarial organism was not generally recognized. Since these first experiments similar ones have been repeated, usually in the manner of intravenous injections of malarial blood, with positive result in over thirty cases. The experiments before 1889 were made without determination of the exact variety of parasite injected and found in the experimental case. In 1889, Gualdi and Antolisei, without full knowledge of the critical nature of the experiment, injected two patients intravenously with 3 c.cm. of blood from a patient suffering with quartan fever and possessing quartan parasites. In each of the inoculated individuals irregular fever with æstivo-autumnal parasites developed. These two cases are constantly adduced as a main support of the doctrine of mutability of the varieties of the parasite, but unjustly so, for it was subsequently determined that the patient from whom the blood was obtained had previously suffered from irregular fever, and he subsequently developed characteristic æstivo-autumnal organisms, so that the experimenters themselves later expressed the opinion that at the time of the inoculation the patient furnishing the blood had combined quartan and æstivo-autumnal organisms, the latter being overlooked. In view of the uniform results yielded by the numerous subsequent experiments in support of the doctrine of immutability of the varieties of the parasite there can be little doubt that this later opinion of Gualdi and Antolisei is correct. It has been found regularly since these experiments that if blood containing only the tertian or the quartan or the æstivo-autumnal parasite be injected intravenously into a person unaffected with malaria, the variety of parasite injected, and only that variety, appears in the blood of the experimental case. When two varieties of parasite are injected, or when the malarial blood is injected into a patient already affected with a malarial organism other than that injected, then it usually happens that one variety supplants the other, most frequently the one injected supplanting that already existing in the inoculated individual. For such displacement of one organism by another we have numerous examples in bacterial infections.

The bearing of the inoculation experiments upon the determination of the periods of incubation of malaria will be considered in the clinical part of this article (pages 97, 98).

These already numerous inoculation experiments, showing the identity of the parasite in the experimental case with that in the blood used for injection, furnish the strongest existing arguments in favor of the plurality of the malarial parasites.[1]

Whether, accepting this doctrine, we shall designate the different

[1] Di Mattei: "Contributo allo Studio della Infezione Malarica Sperimentale nell' Uomo e negli Animali," *Arch. per le Scienze Mediche*, vol. xix. N. 4, 1895.

types of the malarial organism as separate species or separate varieties is with our present knowledge a matter of secondary importance and of individual judgment. If it be admitted that under no existing circumstances one type is transformed into another, then we are justified in speaking of separate species of malarial parasites. As at present we can study only a small part of the conditions which surround the entire life-history of the parasite, it seems to the writer preferable to designate the different types as varieties rather than species.

Classification.

We have already had occasion repeatedly to mention the division of the malarial parasites into three principal varieties—the quartan, the tertian, and the æstivo-autumnal. No further subdivision of the quartan variety has ever been suggested. Nor has any attempt been made to subdivide the tertian parasite originally described by Golgi; but, as it has since been found that the æstivo-autumnal parasite—or, according to some observers, one form of this parasite—may likewise produce tertian fever, the latter form of the æstivo-autumnal organism is designated by Marchiafava and Bignami as malignant tertian or æstivo-autumnal (summer-autumn) tertian, and the former is called mild or vernal (spring) or genuine tertian or Golgi's tertian parasite. This so-called æstivo-autumnal or malignant tertian is, however, in no sense a subdivision of the tertian parasite originally described by Golgi, which remains a well-differentiated, separate variety. When the name "tertian organism" is used without any epithet, it is always this variety which is meant.

The name "parasite of æstivo-autumnal fever," introduced by Marchiafava and Celli and already adopted by many writers, leaves much to be desired. It is intended to indicate that this form of the parasite is the cause of the malarial fevers prevailing in summer and autumn. This application, however, is correct only for certain localities, chiefly those warmer regions where severe as well as mild types of malaria occur. In localities where the prevailing type of the disease is mild at all seasons the summer and autumn malarial fevers are caused generally or exclusively by tertian or quartan parasites. Even in the warmer situations where the æstivo-autumnal parasite is common, not all of the summer-autumn fevers are caused by this parasite, but often a large proportion are caused by the ordinary tertian parasites. In subtropical and tropical regions the æstivo-autumnal parasites may occur in winter and spring fevers. It is evident that the epithet "æstivo-autumnal," as applied to a special variety of malarial parasite, is sufficiently designative for many localities, as, for example, the southern parts of the United States and Central and Southern Italy, but it is not so for all.

The term "parasite of æstivo-autumnal fever" does not at once suggest the relation of the parasite to a definite type of malarial fever, and is therefore out of harmony with the designations "parasite of quartan fever" and "parasite of tertian fever." But it is characteristic of a large proportion of the fevers caused by æstivo-autumnal organisms that they do not correspond to any definite type, but are notably irregular. Hence these organisms were designated by Golgi and by Sacharoff as the "parasite of irregular malarial fevers." But the objection to this latter name is

that æstivo-autumnal organisms may cause typical quotidian and tertian fevers. Indeed, this is the only form of malarial parasite which, it is believed, may complete its cycle of development in twenty-four hours, and thus when present in only a single group or generation may cause quotidian fever.

As leading characters of the æstivo-autumnal organisms are their small size, their slight formation of pigment, and the ring-like shape of the amœboid forms, they are sometimes spoken of as the small malarial organisms (*forme piccole*), or the unpigmented, colorless, or slightly pigmented organisms, or the ring-like, annular organisms. They are also called the organisms of grave or pernicious malaria, although they may likewise cause mild types of the disease.

As it is to the group of æstivo-autumnal parasites that the crescents exclusively belong, these parasites have been described as the semilunar variety. They may be designated as crescent-producing. Hæmatozoön falciparum is suggested by the writer as a suitable technical name for this variety of parasite.[1]

The three varieties of the malarial parasite may therefore be technically designated—(1) *Hæmatozoön febris quartanæ;* (2) *Hæmatozoön febris tertianæ;* (3) *Hæmatozoön malariæ falciparum.* The name æstivo-autumnal parasite, as the more commonly used and generally understood designation, will, however, continue to be used, as well as the term "Hæmatozoön falciparum," in this article for the last-named variety.

There is no difference of opinion, except among the unicists, that the æstivo-autumnal organisms form a variety or group which is to be differentiated from both the quartan and the tertian organisms even more sharply than the tertian and the quartan are differentiated from each other. But the question as to the unity or the plurality of the æstivo-autumnal organisms is still an open one, and is the most important unsolved problem relating to the divisions of malarial parasites. Its solution is attended with unusual difficulties, but we may reasonably expect that they will be surmounted by future investigations.

In distinction from the quartan and the tertian organisms the æstivo-autumnal are often irregular and atypical in their cycle of development. Some, it is believed, may complete their cycle in twenty-four hours, others in forty-eight or a longer period: their tendency to develop simultaneously in well-defined generations is far less marked than is the case with tertian and quartan organisms, so that several or all phases of development of æstivo-autumnal forms may be observed in the internal organs at the same time. The occurrence of multiple groups of the parasite is common. Forms appear which pass through their amœboid, mature, and segmenting phases without any formation of pigment within the parasite. The development takes place largely in the internal organs. The development of crescents occurs at a variable period after

[1] The name Hæmatozoön falciforme suggested by Antolisei and Angelini is objectionable, as it implies that the shape is always falciform, and is applicable only to the crescentic forms. The adjective "falciparum" (*falx*, "sickle," *parire*, "to bring forth," "to produce"), on the other hand, indicates that the property of forming crescents is a distinctive character of the organism, and it is therefore applicable to the variety of the parasite which possesses exclusively this property.

the onset of the disease, but rarely in less than a week. Corresponding to these variations and irregularities the types of fever with which æstivo-autumnal organisms are associated are various and irregular.

The attempt has been made to deduce certain laws controlling these variations and apparent irregularities, and to subdivide the æstivo-autumnal organisms into certain varieties or subvarieties, but there is little agreement of opinion as to this subdivision.

The following are the principal divisions of the malarial parasite which have been proposed, the essential differences in these various divisions relating, of course, to the different views held concerning the æstivo-autumnal organisms:

I. Marchiafava and Celli (1889) recognized a short cycle of development of the æstivo-autumnal parasite, unaccompanied by development of pigment, and a longer cycle with formation of a few pigment granules. Marchiafava and Bignami (1891) make two varieties of this parasite—viz. the amœba of æstivo-autumnal quotidian, with a twenty-four-hour cycle, and the amœba of æstivo-autumnal tertian, with a forty-eight-hour cycle—*Amœba febris quotidianæ* and *Amœba febris tertianæ æstivo-autumnalis*. The latter variety is the malignant tertian organism of these authors. The main differences between these varieties, according to Marchiafava and Bignami, relate to the length of the cycle of development, but there are claimed to be also minor morphological and biological differences to be mentioned subsequently (page 51).

These authors, therefore, make four different varieties of the malarial parasite. They divide the malarial fevers into two main groups:

1. Mild malarial fevers which prevail in winter and spring. These are—

(*a*) Quartan fever (with its varieties of double and triple quartan). This is caused by the *Amœba febris quartanæ* (Golgi), which completes its life cycle in seventy-two hours.

(*b*) Tertian fever (with double tertian and rarely certain subcontinued fevers). This is caused by the *Amœba febris tertianæ* (Golgi), which completes its life cycle in forty-eight hours.

2. Severe or æstivo-autumnal fevers, including the pernicious and most of the subcontinued fevers. This group comprises—

(*a*) Æstivo-autumnal quotidian fever (to be distinguished from quotidians of tertian and of quartan origin), caused by the *Amœba febris quotidianæ*, which completes its cycle in twenty-four hours. This is the only variety of malarial parasite which can complete its life cycle in so short a period as twenty-four hours.

(*b*) Æstivo-autumnal or malignant tertian fever, caused by the *Amœba febris tertianæ æstivo-autumnalis*, which completes its cycle in forty-eight hours. Most of the pernicious cases belong to this variety, the remainder to the æstivo-autumnal quotidian variety.

II. Canalis (1889) does not subdivide into varieties the æstivo-autumnal parasite, which he calls the "semilunar variety," but he considers that it has two cycles of development: (*a*) a rapid cycle with the usual phases of amœboid, mature, segmenting forms and spores, and (*b*) a slower cycle associated with the development of crescentic bodies, which he considers to be reproductive and to represent one phase in this second cycle. A similar view is held by Antolisei and Angelini.

III. Grassi and Feletti (1890) regard the crescent-producing forms as an entirely separate species, which they call *Laverania malariæ*, and which they distinguish both from the directly spore-forming unpigmented æstivo-autumnal forms, which they call *Hæmamœba immaculata*, and from similar rapidly developing, but pigmented, æstivo-autumnal parasites, without crescents, which they call *Hæmamœba præcox*. Their classification of the malarial parasite is as follows: (*a*) *Hæmamœba malariæ*, identical with the quartan parasite; (*b*) *Hæmamœba vivax*, which is identical with the tertian parasite of Golgi; (*c*) *Hæmamœba præcox*, a form of the æstivo-autumnal parasite, giving rise to quotidian fever; (*d*) *Hæmamœba immaculata*, similar to the preceding, but without development of pigment; (*e*) *Laverania malariæ*, the crescent-producing variety, giving rise to irregular fevers.

Sacharoff formerly regarded the crescents as belonging to a separate species of malarial parasite, and adopted the following classification: (*a*) *Hæmamœba febris quartanæ* (Golgi), (*b*) *Hæmamœba febris tertianæ* (Golgi), (*c*) *Hæmamœba præcox* (Grassi), (*d*) *Laverania* (Grassi). Recently (1896) he holds that all variations of the æstivo-autumnal parasite are modifications of a single variety due, mainly, to the development of the parasite within nucleated red blood-corpuscles.

IV. Mannaberg (1893) accepts Marchiafava and Bignami's division of æstivo-autumnal parasites into quotidian and tertian, and also adopts Grassi and Feletti's division into pigmented and unpigmented quotidian parasites. He does not, however, consider the crescents as belonging to a species or variety distinct from these, but considers them as developing from each of these three divisions of æstivo-autumnal parasites. He has a peculiar view as to the origin of the crescents from conjugation of cells, and regards them, therefore, as forms of syzygia. He divides the malarial parasites into two groups—the *first group*, with sporulation and without syzygia, comprising (*a*) the quartan and (*b*) the tertian parasites of Golgi; the *second group*, with sporulation and with syzygia, comprising (*a*) the pigmented quotidian parasite, (*b*) the unpigmented quotidian parasite, and (*c*) the malignant tertian parasite.

V. Golgi (1893), an admirable and successful investigator of the malarial parasites, does not consider the semilunar forms as belonging to a species or variety distinct from the ordinary sporulating æstivo-autumnal parasite. He attempts no subdivision of the æstivo-autumnal parasite. His conception of the mode of development of this parasite differs in essential points from that of Marchiafava and Bignami and of most other investigators, as will be explained in considering the special characters of the æstivo-autumnal parasite.

The following statement of Golgi's classification of the malarial fevers is quoted from Thayer and Hewetson's work on *The Malarial Fevers of Baltimore*, already cited.[1] Golgi 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

[1] The writer wishes to acknowledge his indebtedness to this excellent monograph for much valuable assistance in the preparation of this article.

which have their chief seats 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—viz. (*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 endoglobular amœbæ." Golgi refers to the crescents as "forms the biology of which has not yet been well determined."

VI. Thayer and Hewetson (1895) were likewise unable to confirm Marchiafava and Bignami's subdivision of the æstivo-autumnal parasite into a quotidian and a tertian variety. They say: "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 [æstivo-autumnal] 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." They do not feel justified in making any positive statement as to the significance or capacity of reproductive development of the crescentic bodies.

The question has been raised whether in tropical regions, where pernicious types of malaria are common, any form of malarial parasite different from those already mentioned occurs. The observations of Van Dyke Carter, Dock, van der Scheer, Plehn, and others show that the same parasites are found in India, Panama, Java, and other tropical countries as elsewhere. The negative reports which have been published are referable doubtless to insufficient training in such examinations on the part of the observers. The fact that a large part of the tropical malarial fevers are caused by æstivo-autumnal organisms which appear in the red blood-corpuscles as small, pale, feebly-staining, delicate, diaphanous, often unpigmented amœboid rings of hyaline protoplasm, difficult to detect in many cases, and sometimes scanty or at times even absent, will account for many of these negative observations.

The singular distribution of the hæmoglobinuric type of pernicious malarial fevers in certain definite localities suggests the possibility that this may be caused by a special type of organism. The sporadic cases of malarial hæmoglobinuria examined in Italy have shown, however,

ordinary æstivo-autumnal organisms. Plehn[1] found in cases of black-water fever occurring on the West Coast of Africa small, annular amœboid forms, staining with great difficulty and never pigmented, in the red blood-corpuscles. "Out of the amœba there develops by thickening of the peripheral zone an oval or egg-shaped body, with well-staining double contour. In course of time this divides into five or six small oval forms, staining at one pole, which, when they are set free, move about with great rapidity in the blood. These probably develop into the amœboid forms." The organism never attained a size larger than one quarter of the red blood-corpuscle. Crescents were occasionally found. Plehn seems to regard this organism as allied to, but not identical with, the æstivo-autumnal parasite described by Italian writers. Although his description presents certain peculiarities of the parasite which he observed in the pernicious malarial hæmoglobinuria and other pernicious fevers of the West Coast of Africa, especially the constant absence of pigment, the extremely small size, the sporulation in the blood, and the apparently motile spores,[2] nevertheless it is not sufficiently complete and satisfactory to justify the inference that the organism differs from forms of the ordinary æstivo-autumnal parasite as previously observed.

From the preceding review of the various investigations and opinions concerning the divisions or varieties of the malarial parasite, especially of the æstivo-autumnal form, we may draw the conclusion that whereas the separation into quartan, tertian, and æstivo-autumnal varieties rests upon a sound basis of fact, the various attempts to further subdivide the æstivo- autumnal group have not as yet been sufficiently successful to justify our acceptance at the present time of any of these subdivisions. There is, however, some reason to believe that this last group, as at present constituted, may comprise varieties which will hereafter be satisfactorily differentiated from each other.

We will now consider the special characters of each of the three varieties of the malarial parasite.

I. The Parasite of Quartan Fever (Hæmatozoön Febris Quartanæ) (Plate I. Figs. 25–42).

In most malarial regions this is the rarest form of the malarial parasite, but there are certain places (none of these have been recognized in this country) where it is the prevailing variety. Being particularly common in the neighborhood of Pavia in Italy, the quartan parasite was the first to be differentiated and described by Golgi (1885–86), to whose masterly description nothing of essential importance has been added by subsequent investigators, with the exception of certain details of intimate structure.

The quartan parasite completes its cycle of development in seventy-two hours and entirely within the circulating blood. The youngest forms of the parasite are small, amœboid, when at rest discoidal, hyaline bodies,

[1] Plehn: "Ueber das Schwarzwasserfieber an der afrikanischen Westküste," *Deutsche med. Wochenschrift*, 1895, Nos. 25, 26, 27.

[2] It may here be mentioned that Plehn considers that the spores of all varieties of the malarial parasite are flagellated—a view which has not been confirmed by other observers.

within the red blood-corpuscles. They are about one-fifth to one-fourth the size of the red blood-corpuscle (Plate I. Fig. 26). The central part of the body may appear paler than the peripheral. These unpigmented, youngest forms are found during and for several hours after the paroxysm; they may begin to appear two hours before the paroxysm. The very earliest forms are not to be distinguished from the youngest tertian parasites, but as they begin to develop they present a sharper outline and somewhat more refractive appearance, and their amœboid movements are more sluggish and restricted than those of the corresponding stages of the tertian organism. These movements become more active on the warm stage of the microscope. The presence of more than one parasite in a red blood-corpuscle is sometimes observed.

Shortly, or within twelve to eighteen hours, after the paroxysm pigment granules appear within these hyaline bodies, which continue to increase slowly in size, and for a while to exhibit lazy amœboid movements (Plate I. Figs. 27, 28, 29). The pigment appears in the form of brownish or black rods and grains, which are coarser and darker than those seen in tertian parasites. The rod form of pigment is less common than in the tertian organism. These pigment granules are arranged generally in the peripheral part of the parasite, and they present only a sluggish movement in comparison with the active motion of the pigment in the tertian parasite. With the gradual increase in size of the hyaline bodies and in the amount of contained pigment the red blood-corpuscles enclosing them may appear unchanged, or often they become a little smaller, more refractive, and deeper in color, which may be somewhat greenish or coppery in tint (Plate I. Figs. 28, 29). There is not that tendency to decolorization and swelling of the infected red blood-corpuscles which is noticed in the case of the tertian parasite, although in the more advanced stages of development there is usually some loss of color in red corpuscles containing quartan organisms.

In the process of development the amœboid movements cease, and the parasite appears as a quiescent, pigmented, spherical, or ovoid body occupying perhaps one-half to two-thirds of the red corpuscle (Plate I. Figs. 30, 31). Such bodies are usually seen within forty-eight hours after the paroxysm. These bodies continue to grow, and when they have reached their full development in sixty to seventy hours after the paroxysm they are somewhat smaller than the normal red blood-corpuscles. These full-grown forms are spherical or ovoid, refractive, hyaline bodies, with nearly or quite motionless dark pigment granules of variable size, but coarser than in the tertian parasite, and with a tendency to peripheral arrangement, but at times irregularly distributed. Around these bodies a thin layer of the colored, refractive substance of the red blood-corpuscle can usually still be seen (Plate I. Figs. 32, 33, 34), or the hæmoglobin may be entirely removed, so that only a delicate, thin, colorless rim or line surrounding the parasite is all that is left of the original red blood-corpuscle. In unstained specimens these latter forms often appear to be free in the plasma (Plate I. Fig. 35), and are sometimes spoken of as free bodies, which may also occur.

In six or eight to ten hours before the febrile paroxysm the first phases of reproduction begin to appear. These are ushered in by the gradual withdrawal of the pigment from the periphery toward the centre

of the body. The pigment in this process is often arranged in definite radial striæ (Plate I. Fig. 36). Such regular stellate arrangements of the pigment as are seen in this stage of the quartan parasite are rarely, if ever, observed in the tertian (Thayer and Hewetson). Finally the pigment is concentrated into a central mass of granules or a solid block of coalesced pigment, less frequently into two or more collections, and the organisms assume a somewhat more refractive and slightly granular appearance.

At the same time or soon afterward radial divisional striæ begin to appear in the periphery (Plate I. Fig. 37), and quickly extend to the central part of the parasite, whereby the substance of the spherical organism becomes divided into six to twelve ovoid or pear-shaped segments arranged with characteristic and exquisite regularity around the central mass of pigment like the petals of a daisy (rosettes of Golgi) (Plate I. Fig. 38). In each of the segments can be seen a small round glistening body which represents the nucleus or nuclear material. The pyriform segments assume rapidly a round or oval shape, and become separated from the central mass and from each other. The delicate enveloping membrane, which may not be recognized on unstained specimens, derived from the red blood-corpuscle ruptures, or it may previously have disappeared, and the small round or oval bodies, each provided with a bright nucleiform dot, are set free in the plasma (Plate I. Fig. 39). These bodies are the so-called spores. Simultaneously with this process of sporulation young amœboid hyaline bodies, formed directly from the spores, make their appearance in the red blood-corpuscles, and the cycle of development is completed and another cycle is begun.

Segmenting or sporulating forms of the parasite may appear six or eight hours before the paroxysm, and are most abundant shortly before and during the onset of the paroxysm. It is of course not to be understood that all of the parasites of one group pass through their developmental phases and mature at exactly the same moment. One parasite of the group may be several hours in advance of another, but this does not interfere with the recognition of distinct groups or generations, each standing in definite relation to a paroxysm, or with the establishment of Golgi's law that the onset of each paroxysm corresponds to the maturation of one group of organisms.

The cycle of development of the quartan parasite is attended with fewer irregularities than that of any other variety of the malarial parasite. Nevertheless, certain irregularities may occur. As pointed out by Antolisei, segmentation may occur exceptionally in pigmented bodies considerably smaller than the usual full-grown forms, containing less pigment and filling only a part of the red blood-corpuscle. Here the segments do not usually exceed four to six or eight. The accumulation of pigment in the segmenting forms may be peripheral, or distributed between the spores, or otherwise irregular.

As the quartan parasite completes its development entirely within the circulating blood, there is no appreciable difference at any stage between the splenic and the peripheral blood as regards the number and variety of the parasitic forms observed. Moreover, segmenting forms of the quartan parasite are often seen in small number in the blood at a

period before the total number of organisms is sufficiently large to produce by their ripening a paroxysm, whereas segmenting tertian parasites are very rarely seen in the peripheral blood without the occurrence of a paroxysm in relation to the segmenting forms.

Not all of the mature forms proceed to sporulation. Some, especially those which may have escaped from the red corpuscles, swell up, become transparent and larger than a red blood-corpuscle, and present irregularly distributed and actively moving pigment granules (Plate I. Fig. 40). These swollen, hydropic forms are probably sterile. It can often be seen in examining these bodies in fresh blood that the pigment becomes quiescent, the outlines of the body become irregular and indistinct, and evidently cadaveric forms result. Or these bodies may break up into a number of fragments which become misshapen and indistinct, or the whole body may become vacuolated, as is represented in Plate I. Fig. 42. Bodies more or less resembling spores, but without the nuclear structure of spores, may appear in these vacuoles.

As may occur with any variety of the malarial parasite, the mature forms of the quartan parasite, instead of sporulating, may develop into flagellate bodies in the manner already described. These bodies are smaller and contain coarser pigment than the flagellate forms of the tertian parasite. (Compare Plate I. Fig. 41 and Plate I. Fig. 22.) Degenerated and flagellate forms are less common in quartan than in tertian infections.

Not only may mature forms degenerate in the ways described, but forms in earlier stages of development may be liberated from the red corpuscles and likewise degenerate.

The phenomena of phagocytosis are observed with regularity during and for some hours after the paroxysm in quartan as well as in other malarial infections. The pigment set free by the process of sporulation is taken up by phagocytes. Extracorpuscular organisms, particularly the various degenerated forms, are engulfed by phagocytes. The assault on the flagellate bodies by leucocytes can be watched with interest on the slide of fresh blood. The leucocytes can also be seen to take up segmenting bodies and spores when the specimen of blood is kept for a while. The details and the significance of these phagocytic phenomena will be considered subsequently (page 65).

The intimate structure of the quartan and other malarial parasites, as revealed by methods of staining, will also be described subsequently.

Two or more groups of quartan parasites are often present in the blood at the same time, causing double and triple quartan infections. On account of the regularity in the development of the quartan parasite, anticipating, retarding, and irregular fevers are less common in quartan than in the other malarial infections. Careful examination of the blood enables the observer to recognize the presence of two or more groups of the parasite by noting the simultaneous occurrence of bodies in noticeably different stages of development; as, for example, during the paroxysm the association of segmenting and young hyaline bodies with half-grown pigmented bodies.

II. The Parasite of Tertian Fever (Hæmatozoön Febris Tertianæ) (Plate I. Figs. 1–24).

This variety of the malarial parasite is common in most malarial regions. Where only mild types of malaria occur it is, as a rule, the prevailing, and sometimes the sole, variety observed. The tertian and the quartan parasites cause most, or in some places all, of the winter and spring intermittents, but they, and especially the tertian parasite, may cause in districts of even severe malaria not a few of the malarial fevers of summer and autumn, although the more severe and irregular of these latter fevers are caused chiefly by the æstivo-autumnal parasite. The tertian parasite may, however, produce severe, as well as mild, types of malaria.

The tertian parasite was differentiated from the quartan and described in its essential characters by Golgi in 1886 and 1889. Other observers, particularly Antolisei (1889–90) and Bastianelli and Bignami (1890), have added to, and in some points corrected, Golgi's first description.

The chief points to be emphasized in this description of the tertian parasite are those which distinguish it from the quartan parasite. Unlike the quartan parasite, certain stages of development of the tertian—namely, those concerned with sporulation—take place by preference in the spleen and the bone marrow, although segmenting forms are seen also in the peripheral blood. The cycle of development is completed in forty-eight hours.

During the paroxysm or shortly after it small, unpigmented, hyaline, amœboid bodies are found within the red blood-corpuscles, of which they are about one-fifth to one-fourth the size (Plate I. Figs. 2 and 3). Usually one hyaline body is found, but not very infrequently two or more are present, in a single blood-corpuscle. The tertian amœbæ, especially in their pigmented stage, change their shape and position within the corpuscles much more actively than the quartan amœbæ, these movements being vigorous at ordinary room temperature. Several branching pseudopodia are sent out, often reaching nearly or quite the periphery of the corpuscle, and are retracted. All sorts of shapes may thus be assumed by the parasite, which with its long branching processes may seem to pervade nearly the whole corpuscle. By the union of two pseudopodia the shape may be that of a ring enclosing a bit of the corpuscular substance (Plate I. Fig. 5). The tertian amœbæ are paler, less sharply outlined, than the quartan (compare the two varieties in Plate I.). In a short time fine reddish-brown or yellowish-brown rods and granules of pigment, varying somewhat in size, appear in the margins of the amœbæ (Plate I. Fig. 5). Pigment granules often collect in the bulbous ends of pseudopodia (Plate I. Figs. 6 and 7), and the intervening parts of the pseudopodia may be so thin and delicate as to be readily overlooked, so that the appearance may be that of several distinct bodies within one red blood-corpuscle. Careful examination will, however, detect the fine connecting processes or the retraction of the apparently separate bodies into the substance of one parasite. Two or more parasites may, however, be present occasionally within one red corpuscle (Plate I. Fig. 4). The pigment is in finer grains and rods, and of a lighter, somewhat different, tint in the tertian, than in the

quartan parasite. (See Plate I.) It is also in much more active movement in the tertian amœbæ. This movement is not altogether like the Brunonian or molecular motion, and is probably due to intrinsic protoplasmic movements or currents.

With the continued growth and increased pigmentation of the amœbæ the infected corpuscles as a rule become distinctly swollen and paler than normal—a change which may be already indicated even with quite small pigmented forms, and which is one of the most distinctive characters of the tertian parasite (Plate I. Figs. 4–9). Occasionally the enveloping corpuscle is not noticeably swollen or altered, and exceptionally it may even shrink and acquire something of the brassy appearance commonly seen with red corpuscles infected with the æstivo-autumnal parasite.

On the day of apyrexia the parasite, now with somewhat sharper contour and more richly pigmented, may attain a size equalling one-half to two-thirds that of the infected blood-corpuscle. The amœboid movements have become more sluggish, but they persist in stages of development corresponding to which forms of the quartan parasite have become quiescent. The pigment continues in active motion.

The fully developed parasite is about the size of a normal red corpuscle, sometimes a little smaller, sometimes somewhat larger, and it is therefore smaller than the swollen corpuscle in which it is contained. It is nearly or quite spherical in shape, and without amœbic movements. The pigment for a while preserves its marginal arrangement or less frequently is irregularly distributed (Plate I. Fig. 9). The expanded red blood-corpuscle enveloping the parasite becomes still paler.

These fully grown forms change into the presegmenting bodies by the collection of the pigment, which has already become quiescent, into a mass of granules or into a solid block situated usually in or near the centre or sometimes near or at the margin. As with the other varieties of the malarial parasite, the pigment with the development of the parasite becomes coarser, and the delicate rod-like forms of pigment become relatively less numerous. These spherical bodies with central pigment clumps are more refractive than is the parasite in preceding stages of development. Stained specimens show that in these presegmenting bodies there appear multiple, deeply staining chromatin granules, which represent nuclear substance, and which are the first indication of the inception of sporulation.

This phase of segmentation presents more variation than is observed in the quartan parasite. Sometimes it begins with the appearance of radial striation extending from the periphery to the centre, and proceeds by a division of the substance of the parasite into twelve to twenty or even more segments arranged in a rosette form around the central clump of pigment. A little later the pigment clump is surrounded by a group of small round bodies, which are the spores. More commonly, without the formation of such regular figures, the protoplasm breaks up into a mass of fourteen to twenty or more spores. Sometimes one sees an outer and an inner ring of spores concentrically arranged around the central mass of pigment. The larger number of segments or spores formed by the tertian as contrasted with the quartan parasite is an important differential characteristic.

The modes of segmentation described (Plate I. Figs. 10–14) correspond in the main to Golgi's second type of segmentation. His first mode of segmentation of the tertian parasite has not been noted by other observers. It is as follows: After the collection of the pigment in the centre the organism is differentiated into a peripheral zone sharply separated from a central body containing the pigment. The peripheral ring becomes radially striated, and then divides into fifteen to twenty small hyaline segments. The central pigmented body does not segment, but remains behind after the separation of the spores. Golgi's third variety of segmentation is now generally recognized as a process of degenerative vacuolation.

Sometimes the segmenting bodies show, instead of one central accumulation of pigment, two or more clumps excentrically placed, or the pigment may be concentrated in the periphery or distributed between the spores or otherwise irregularly arranged.

The spores are set free by rupture of the enveloping membrane derived from the red corpuscle, or this membrane may have disappeared before the segmentation is completed. The individual spores are somewhat smaller than those of the quartan parasite. They usually show a refractive nucleiform dot, which is, as a rule, less distinct than in the quartan spores.

Coincidently with sporulation the young, colorless amœbæ, formed from the spores, make their appearance in the red blood-corpuscles and start on a fresh cycle of development.

The segmenting bodies may make their appearance several hours before the paroxysm. They are most numerous shortly before and during the onset of the paroxysm. They may be scanty in the peripheral blood, for the process of sporulation takes place largely in the internal organs. The red corpuscles containing mature and presegmenting bodies accumulate especially in the spleen and the bone marrow, and there the organisms complete their reproductive development. During most of the period of apyrexia no noticeable difference is observed in the number and kinds of parasites between the peripheral blood and that withdrawn by hypodermic syringe from the spleen. But shortly before and during the paroxysm far more ripe and sporulating forms are found in the splenic than in the peripheral blood.

Precocious segmentation into five to ten spores may occur in bodies, sometimes containing only a grain or two of pigment, which have not attained a size exceeding one-half to two-thirds that of the red blood-corpuscles (Plate I. Figs. 16, 17), the usual size of a segmenting body being about that of a red corpuscle, but sometimes considerably larger. Such immature forms of segmentation are associated by Bastianelli and Bignami with anticipating fevers, but Mannaberg and Thayer and Hewetson, although not inclined to discredit this interpretation, were unable to convince themselves of this relation.

Partly developed and mature tertian parasites are often seen free in the plasma. Swollen, transparent, extracorpuscular forms, which may attain the size of large leucocytes, and which contain scattered dancing pigment granules, are generally considered to be degenerative or incapable of reproductive development (Plate I. Fig. 18). These so-called hydropic forms are considerably larger and paler and more common than

the similar forms of the quartan parasite. These swollen, richly pigmented forms are very common in tertian infections. In general, the various forms of degeneration which have already been described, such as fragmentation, vacuolation, pseudo-gemmation (Plate I. Figs. 19, 20, 21, 23, 24), are more common with the tertian than the quartan parasite. Flagellate bodies are likewise more common. They are, as a rule, larger and contain finer pigment than the quartan flagellates (Plate I. Fig. 22). They develop chiefly from the round, swollen, extracorpuscular forms with scattered pigment, although flagella have been observed to develop from forms still surrounded with a distinct layer of hæmoglobin-containing substance of the red blood-corpuscle. Flagellate bodies are most abundant in blood withdrawn from the spleen shortly before and during the paroxysm. Phagocytosis occurs with the same regularity and with similar phenomena in tertian as in quartan infections.

Infection with two groups of tertian parasites (double tertian), as described for quartan infection, is more common than with a single group, especially in the later period of the malarial season in the spring and in summer and autumn. The resulting type of fever is quotidian. In some cases there seem to be several irregularly distributed generations causing remittent or subcontinued fevers. It is not necessary to attribute the presence of two or more groups of the same variety of parasite to corresponding multiple infections from without. There is evidence that certain members of a group may, in their development, lag behind or advance beyond others of the same group, and in course of time by further multiplication may constitute a separate group capable of causing its own paroxysms of fever. It is remarkable, however, that the second group should be separated in its cycle of development by such definite intervals from the first as we usually observe in quotidian fevers of tertian origin. Genuine mixed infections with malarial parasites, the most frequent combination being that of the tertian and of the æstivo-autumnal parasites, are not very uncommon.

The length of the cycle of development of the tertian parasite may occasionally be noticeably shorter than forty-eight hours, perhaps only forty hours or less, or, on the other hand, it may be longer than the normal period. This may explain the anticipating and the postponing fevers.

III. The Parasite of Æstivo-autumnal Fever (Hæmatozoön Falciparum) (Plate II.).

This was first clearly differentiated from other varieties of the malarial parasite by Marchiafava and Celli (1889), and was subsequently more fully described by the same authors and by Canalis (1889–90). (See footnote, page 32.) The extensive literature concerning the parasitology of malaria during the last six years has been concerned to a large extent with this variety, but we are still far from possessing so full and accurate knowledge regarding the characters and development of the Hæmatozoön falciparum as regarding those of the quartan and tertian parasites. Such knowledge is much to be desired in view of the frequency of the æstivo-autumnal parasite in regions, such as the southern part of the United States, where the more severe types of malaria occur,

and of the almost exclusive association of this parasite with pernicious malarial fevers.

Chief reasons for the difficulty in investigating the entire life history of the Hæmatozoön falciparum are that it develops mainly within the internal organs and often in multiple groups, and that the later reproductive phases of development are met with in the circulating blood only very exceptionally. Under the *Classification* of the malarial parasites we have already presented the more important opinions which have been advanced concerning possible subdivisions of the æstivo-autumnal variety (page 35 *et seq.*).

The youngest forms of this parasite are small hyaline bodies, about one-sixth the diameter of a red blood-corpuscle, which make their appearance in the blood-corpuscles during or shortly after the paroxysm. It is not uncommon to find two or more hyaline bodies in a single corpuscle. These æstivo-autumnal hyaline bodies are in general the smallest forms of the malarial parasite which are observed in the red blood-corpuscle (Plate II. Figs. 1 and 2). The youngest forms may be quiescent, but as they develop they manifest amœboid movements resembling in their activity those of the tertian amœbæ.

The young æstivo-autumnal amœbæ may not be readily distinguishable from the similar forms of the quartan and tertian parasites. Particularly characteristic, however, of the young hyaline forms of the Hæmatozoön falciparum when in repose and in stained specimens is the ring shape. The appearance in fresh specimens is that of a somewhat refractive, clear, hyaline ring, usually thicker on one side, surrounding a small round central, or oftener excentric, shaded part, or sometimes two or three such parts, through which the color of the red corpuscle shows. In stained specimens the ring appears thinner than in fresh specimens, and the central or excentric part is unstained, while a minute deeply stained granule is situated in the outer ring.

The study of the further development of these forms, especially on stained specimens, has demonstrated that these apparently annular bodies are not actual rings, as some have supposed, enclosing a bit of the red corpuscle, but that the clear area which does not stain is a transparent part of the organism, which, as will be subsequently explained, some regard as the nucleus. Actual rings, however, as has already been mentioned, may be formed by the junction of pseudopodia, which thereby enclose some of the corpuscular substance, but such is not the explanation of the typical annular appearance of the æstivo-autumnal hyaline bodies. It is not uncommon to find free hyaline bodies in the blood plasma.

These hyaline bodies may, while under observation, become somewhat expanded and paler and lose their annular appearance, and again resume the ring shape. While the very smallest intracorpuscular hyaline bodies may present no amœboid movements, as they grow larger these movements become active. Hyaline bodies are occasionally observed to change their position within the corpuscle without change in their shape. Manifold shapes are assumed during the amœboid movements (Plate II. Figs. 4–6).

Usually in the course of development a few very fine dark reddish-brown or black pigment granules appear in the outer layer of the

hyaline bodies (Plate II. Figs. 8–12). They may be situated near the periphery or on the inner margin of the ring near the clear part. Sometimes the pigment does not appear until shortly before a paroxysm. The presence of many bodies containing a considerable number of grains of pigment is generally indicative of an impending paroxysm. The pigment granules are at first very minute and few, and may be readily overlooked. The granules of pigment increase in number and size, but it is one of the characteristics of the æstivo-autumnal amœbæ that the formation of pigment is, as a rule, scanty and in fine grains. Often only one or two very fine pigment granules are seen in the periphery or on the inner edge of the refractive border of the hyaline bodies. Usually about six or seven granules of pigment are developed in the hyaline bodies. The pigment generally shows but little motion in contrast with that in the tertian amœbæ.

The æstivo-autumnal amœboid forms do not generally grow larger than one-quarter to one-third the diameter of the red blood-corpuscle, and they may remain smaller. The infected red corpuscles may appear otherwise normal. They do not become swollen and decolorized in this stage, as is the case in the tertian infections. On the other hand, they often become shrunken, creased, or otherwise deformed, and present a deep brassy color (*globuli rossi ottonati* of the Italian writers) (Plate II. Figs. 7, 16). Sometimes the hæmoglobin separates from a part or the whole of the outer part of the stroma of the corpuscle and collects around the enclosed hyaline body (Plate II. Fig. 13). These changes in the red corpuscles, which are particularly characteristic of the æstivo-autumnal variety, although not absolutely limited to it, are to be regarded as degenerative or necrobiotic. Marchiafava and Celli and some others have thought that the parasite within these profoundly altered corpuscles is also dead or incapable of further development. Bastianelli states that sporulation forms are not observed in the brassy corpuscles, but this statement is opposed to observations of Marchiafava and Bignami and others. The view that parasites within profoundly altered corpuscles are incapable of further development is by no means proven, and is opposed to the natural interpretation of many observations.

As the time for the onset of a paroxysm approaches, the hyaline bodies gradually cease their amœboid movements, assume a spherical or ovoid shape, become somewhat more refractive and homogeneous, and present a small collection of quiescent or but slightly moving pigment granules at about the centre or often near the periphery (Plate II. Figs. 13, 16, 17, 18). This pigment usually fuses into a single small, black, round or irregular mass or block (Plate II. Figs. 14, 15, 19–24), or there may be two such blocks.

These round, refractive bodies with pigment blocks or collections of pigment granules (*corpi con blocchetto*) are the presegmenting bodies, and when they are present the onset of a paroxysm, within at most a few hours, may generally be safely predicted. These bodies are much smaller than the corresponding forms of the quartan and tertian parasites. They do not generally exceed one-quarter or one-third of the size of the corpuscle, although they may be considerably larger. They are surrounded with hæmoglobin-containing substance of the corpuscle, which is often of a brassy color.

The next phase of development is that of sporulation, but the segmenting forms are found in the peripheral blood only most exceptionally, save in some pernicious cases, in which they may in rare instances be even abundant. Sacharoff observed in the Transcaucasus sporulating forms in the blood, and on this account, but apparently without sufficient reason, he regards this form as a special variety. For a few hours before and during the early stage of the paroxysm very few parasitic forms of any kind are to be found in the circulating blood, and at this period they may be entirely absent, in marked contrast to quartan infection. During this period the presence of pigmented leucocytes in the blood may aid in the diagnosis. In tertian infections an analogous condition is found, but not in the same degree. The disappearance of the parasites from the blood is believed by most authorities to be due to their deposition in internal organs, especially the spleen and the bone marrow, and is attributed to the profound changes in the red blood-corpuscles containing them, these changes rendering the corpuscles virtually foreign bodies which, like other foreign particles, are caught and retained especially in the spleen and the bone marrow.

Blood withdrawn by puncture of the spleen at this time will, with rare exceptions, show abundant intracorpuscular and free round bodies with central or peripheral pigment, and also segmenting forms. In certain cases segmenting forms are few in the spleen, but abundant in certain other internal organs, as has been shown by post-mortem examinations. These sporulating bodies are smaller than those of the quartan and tertian parasites, and occupy, as a rule, only a relatively small part of the corpuscle, which is always altered in appearance, being shrunken and brassy-colored or more frequently decolorized. They may appear to be free or may be actually free. In pernicious cases they are present in large, often enormous, numbers in the internal organs, especially in the spleen and bone marrow, and in some types of pernicious fever in the capillaries of the brain and in those of the intestinal mucosa. This varied distribution of the parasites in internal organs is in relation with the types of pernicious fever. The stage of sporulation occupies a rather long period and takes place in successive groups. This circumstance is believed to explain the long duration of the paroxysm in æstivo-autumnal fevers. In pernicious cases sporulation seems to be going on continually in the vascular areas of certain internal organs.

In æstivo-autumnal infections the process of sporulation is in general similar to that of the tertian parasite, but it is more irregular and variable and the spores are much smaller (Plate II. Figs. 25–28). The number of spores formed by a segmenting æstivo-autumnal organism is extremely variable. There may be not more than six to ten spores, or even fewer; often there are ten to twenty, and the number may exceed thirty. Some segmenting forms are much larger than others. Golgi has observed exceptionally very large ones containing as many as forty to fifty spores. There are slight differences often to be observed in the finer structure between the æstivo-autumnal spores and those of the quartan and tertian parasites, as will be described when we consider the intimate structure of the malarial parasites.

The young hyaline bodies of the new generation may be found in the blood in the early part of the paroxysm, but often they do not make

their appearance until several hours after the beginning of the paroxysm or during its decline.

Not all of the æstivo-autumnal amœbæ develop pigment. Sporulation may occur in bodies, usually of small size, entirely devoid of pigment. As a rule in these cases both pigmented and unpigmented forms occur, but cases of æstivo-autumnal malaria have been observed, especially in tropical climates, in which only unpigmented bodies could be found at any stage of the fever before the appearance at a later period of crescentic bodies which always contain pigment.

As has already been mentioned (page 38) Grassi and Feletti regard the parasites which do not develop pigment as belonging to a distinct variety (*Hæmamœba immaculata*), but it is difficult to reconcile this view with the frequent association of pigmented and unpigmented forms, the frequent transitions from one to the other as regards the quantity of pigment developed, and the absence of any points of distinction other than the presence or absence of a variable, but generally small, amount of pigment. Still further researches, especially of the grave tropical malarias, may perhaps demonstrate the existence of a distinct unpigmented variety of the parasite.

There is considerable uncertainty as to the length of the cycle of development of the Hæmatozoön falciparum. This uncertainty is due to the manner of development of the parasite, usually in multiple groups, in the internal organs, the most characteristic reproductive phases being absent from the circulating blood. So far as one can judge from the study of these phases in connection with the different types of fever with which they may be associated, the length of the cycle of development may vary from twenty-four hours or less to forty-eight hours or more.

The Hæmatozoön falciparum may be associated with typical quotidian fever or with tertian fever, and in some of these cases the blood shows apparently only one group of organisms. As already mentioned, Marchiafava and Bignami believe that there are two distinct varieties or subvarieties of the æstivo-autumnal parasite, the one a true quotidian organism, with a cycle of twenty-four hours' duration, and the other their so-called malignant or summer-autumn tertian variety, with a cycle of forty-eight hours' duration; and this division has been accepted by some other authors. This distinction is based mainly upon the apparent duration of the cycle of development—in the quotidian about twenty-four hours, and in the malignant tertian forty-eight hours, more or less—but there are claimed to be other differences of a minor character relating to the pigmentation, the size, and the amœboid movements of the organisms.[1] The differential diagnosis is said to be possible only

[1] The following are the biological and morphological differences between the æstivo-autumnal quotidian and malignant tertian parasites, according to Marchiafava and Bignami (*On Summer-Autumn Malarial Fevers*, translation, p. 83, The New Sydenham Society, London, 1894): Duration of cycle of development in the quotidian, about twenty-four hours, in the summer tertian, forty-eight hours, more or less; in the quotidian sporulation on rare occasions is completed before the amœbæ have become pigmented—this is not observed in the summer tertian; the fine granules of pigment in the periphery of the summer tertian are sometimes endowed with oscillatory movements—this is not noticed in the quotidian; in the same relative stage of development the tertian amœba is usually larger than the quotidian, the adult pigmented tertian forms may be one-third of the size of the red blood-corpuscles, and the forms of segmentation may be one-half or two-thirds of it;

with the adult forms. The differential characters claimed to exist between the quotidian and the tertian varieties of the æstivo-autumnal parasite are, for the most part, only such as one would expect with a malarial parasite developing more rapidly in some cases than in others, and they, at least so far as at present formulated, scarcely suffice for a distinction into two well-defined varieties.

Thayer and Hewetson, while confirming Marchiafava and Bignami's recognition of quotidian and tertian fevers caused by the æstivo-autumnal parasite, emphasize the occurrence of intermediate types of fever, and in general the essential irregularity of the fevers caused by this organism. They were unable to distinguish any morphological or biological differences between the parasites associated with these various types of fever. Although unwilling to commit themselves to a positive conclusion, they are "inclined to believe that the irregularity of 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 (this variability being dependent, perhaps, upon the malignity of the organism or upon the resistance of the individual affected); 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."[1]

Golgi also considers that Marchiafava and Bignami's division into quotidian and tertian æstivo-autumnal organisms is based upon insufficient evidence, and that the duration of the cycle of development of the æstivo-autumnal parasite is indeterminate, or at least has not as yet been accurately ascertained. This cycle is probably, he thinks, longer than is supposed by Marchiafava and Bignami. This form of parasite, according to Golgi, is characterized by the fact that it develops entirely in the internal organs, and that the forms, chiefly of the earlier stages of development, which appear in the circulation, although they are found there at certain periods of the disease in practically all cases, are, in a sense, accidentally present in this situation, being washed into the circulation from their foci of development, as nucleated red blood-corpuscles may be conveyed from the bone marrow into the blood current in certain anæmias. Golgi at first thought that the forms present in the circulation degenerate, but he does not now deny that they may lodge in internal organs and there develop into segmenting organisms. Marchiafava and Bignami with much reason vigorously contest Golgi's conception of the "accidental" nature of the presence of æstivo-autumnal organisms in the circulating blood, although they also believe that a large part of the parasites develop wholly in the internal organs, and

in the tertian the amœboid movements are maintained longer, even in the adult pigmented forms, and the motion is more lively than in the quotidian during the pigmented phase; the duration of the non-pigmented amœboid phase in the tertian is relatively long and may exceed twenty-four hours; the young forms of the new generation in the tertian usually appear in the blood several hours after the beginning of the paroxysm, which is much later than in the quotidian.

[1] *Op. cit.*, pp. 151, 153.

that sporulation occurs only most exceptionally in the circulating blood.

The two most important and original points in Golgi's doctrine concerning the æstivo-autumnal parasite are that groups of the parasitic organisms are variously distributed in vascular areas in the internal organs, and there develop more or less independently of each other, "with relative stability," and that a large number of the organisms develop within leucocytes, endothelial cells, and other tissue-cells. All phases of development, according to Golgi, are found within these cells. The spleen and the bone marrow are situations preferred by the parasite, but the capillaries of the liver, of the brain, of the lungs, of the intestinal mucosa, may also contain them enclosed within cells.

A. Monti[1] has recently described these intracellular forms in pernicious malaria, and he confirms the observation of many others that cells containing parasites frequently degenerate and die. He finds apparently intact parasites not infrequently within cells, particularly endothelial cells.

It is contended by Marchiafava, Bignami, and Bastianelli that the intracellular inclusions of the parasite, upon which Golgi bases his doctrine, are simply the well-known phagocytic phenomena, and that such enclosed parasites belong chiefly to the later stages of development (presegmenting and segmenting bodies and spores), and that, instead of developing, they degenerate within the cells. The young amœboid bodies, which, according to Golgi's doctrine, should be frequently found within cells, they found only with comparative infrequency within phagocytes, and then almost always within their corpuscular hosts, which had been swallowed by cells. They admit the possibility of some development of intracorpuscular parasites which have been taken up by phagocytes, but not of free parasites within cells.

As with the other varieties of the malarial parasite, the æstivo-autumnal do not all mature and segment. Extracorpuscular forms are common, and it is more particularly these forms, deprived of the protective covering of the red blood-corpuscles, which degenerate. Adult and presegmenting bodies and bodies of the crescentic phase frequently become swollen and pale or vacuolated or fragmented, or throw off buds, or present other degenerative changes which have been described.

Phagocytism in the æstivo-autumnal, as in all malarial infections, is a phenomenon of much importance, as will be subsequently explained.

The frequency with which two or more groups of parasites in different stages of development are found in æstivo-autumnal infections has already been repeatedly emphasized. Marchiafava and Bignami believe that even in the pernicious fevers there are not generally present more than two groups of the æstivo-autumnal parasite, and that the short cycle of development and the prolonged period of sporulation suffice to explain the simultaneous presence of parasites in notably different stages of development. Combined infections with the æstivo-autumnal parasite and one of the other varieties occasionally occur.

It is important to bear in mind the discrepancy which characterizes æstivo-autumnal malaria between the number of parasites in the blood and the number in the internal organs. In the majority of cases the

[1] A. Monti: *Bollettino della Società medico-chirurgica di Pavia*, 1895.

more severe the infection the greater the number of parasites found in the circulating blood, but there are so many exceptions to this that the number of parasites in the blood cannot be considered a trustworthy index of the number within the body. Pernicious cases have been repeatedly observed where the splenic blood examined during life or the internal organs examined after death contained enormous numbers of æstivo-autumnal parasites, although the blood of the finger showed very few. The organisms may be few even in the spleen when they are abundant in the cerebral capillaries or in some other situation. As will be explained subsequently, the varying symptoms and types of pernicious malaria can be explained in large part by the varying distribution of the parasites in internal organs.

It is evident from the description which has been given of the æstivo-autumnal parasite that this variety is characterized especially by its great activity in multiplication, and it will appear from the consideration of the clinical features of the infections caused by this parasite that other most important characteristics are its virulence, greater than that of other varieties, and its greater resistance to quinine.

There is a group of bodies of crescentic, fusiform, oval, or round shape, presenting certain common and peculiar characters, which develop only from the Hæmatozoön falciparum. The crescents are the most typical of these bodies, which may be designated, therefore, as bodies of the crescentic (or semilunar) phase or group. They merit special consideration.

Bodies of the Crescentic Group.—When a malarial fever caused by the Hæmatozoön falciparum has lasted a week or more bodies of the crescentic or semilunar phase are likely to appear in the blood. They are very rarely found in the blood in the latter part of the first week. If the fever is treated with sufficient doses of quinine during the early part of the first week, crescents do not appear, but the administration of quinine after the fever has lasted much longer than a week does not prevent their appearance. They may persist in the blood two weeks or more after all other forms of the parasite have disappeared. In such cases they are often unassociated with any febrile manifestations or any symptoms which can be definitely referred to their presence. If a relapse of the fever occurs, then the young hyaline bodies already described are always present. The crescents themselves are very resistant to the action of quinine. Councilman in 1887 called attention to the occurrence of crescentic bodies as characteristic of the irregular and remittent forms of malarial fever and malarial cachexia.

There was for a time much doubt as to the origin of the crescents, but Marchiafava and Celli's demonstration in 1886 of their intracorpuscular development has been abundantly confirmed by the later studies of Canalis, Bastianelli and Bignami, and others. The early intracorpuscular stages of development of the bodies of the crescentic group are rarely seen in the circulating blood, except in certain pernicious cases, but they can often be found in the splenic blood. Bastianelli and Bignami have found these early phases so abundantly in the bone marrow that they consider that they develop by preference in this situation.

Certain of the intracorpuscular spherical forms of the Hæmatozoön falciparum with collected pigment granules, instead of continuing their

regular cycle of development into segmenting forms, are transformed into the young bodies of the semilunar phase. This transformation takes place only after a number of febrile paroxysms; that is to say, only after the parasite has repeatedly passed through its regular sporulating cycle of development.

The young bodies of the crescentic group occupy perhaps one-quarter of the red corpuscle. Their shape is round, oval, or fusiform. They present a characteristic homogeneous, refractive appearance, being more refractive than the presegmenting bodies with central blocks of pigment. They contain dark pigment, usually in the shape of fine rods, sometimes collected in a mass, but oftener irregularly distributed. In the fusiform bodies the pigment is often arranged along the longitudinal axis of the spindle. The hæmoglobin is frequently retracted into a denser stratum around the bodies. These bodies increase in size without a correspondingly large increase in the amount of pigment, and, as will be explained later, without a corresponding increase in their chromatic or staining substance—a point which distinguishes the direction of crescentic development from that of the regular sporulating development.

It is some time after these young semilunar bodies have begun to form in the bone marrow and spleen before the adult crescents appear in the circulating blood. These completely developed typical crescents are on the average 8–10 μ long, and in the middle 2–3 μ broad (Plate II. Figs. 31, 32, 33). They do not often exceed in length one and a quarter or one and a half times the diameter of a red corpuscle. They present a characteristic, homogeneous, refractive appearance. An outer double-contoured border can sometimes be seen, especially after treatment with certain reagents, and this is interpreted by Laveran, Mannaberg, and many authors as evidence of a distinct enveloping membrane; but the weight of evidence is opposed to the view that the crescents, any more than any other form of the malarial parasite, possess a membrane other than that which pertains to the enveloping red corpuscle. The outer refractive margin of the crescents, as pointed out by Antolisei and Angelini—who interpret it as a cuticular envelope derived from the red blood-corpuscle—may be slightly colored by hæmoglobin, and it may show evidence of this presence of blood coloring matter by the staining with eosin. On the typical crescent-shaped forms a fine line can often be seen stretching like a bow across the concavity, its attachment at each end being within the extremities of the horns. This line is derived from the red blood-corpuscle within which the crescent has developed, and represents the outer contour of the partly or completely decolorized corpuscle. This contour of the corpuscle can sometimes be detected also on the convexity of the crescent, and parts of the corpuscle still containing hæmoglobin may occasionally be seen on the margin of the crescent, or the whole crescent may be surrounded with hæmoglobin-containing corpuscular substance (Plate II. Fig. 29). Similar evidences of the partly or completely decolorized enveloping blood-corpuscle can frequently be seen on the margin of the round and oval bodies (Plate II. Figs. 34, 35, 36, 38, 39).

Bodies of the crescentic group are always pigmented. The pigment is very dark in color, often black, and mostly in fine rods. In the typical crescents the pigment, which is without movement and in fine rods

and grains, is usually collected in the middle, sometimes in a single clump or in two clumps, often in a coronal shape. Mannaberg emphasizes the frequency with which the pigment is arranged in two adjacent clumps near the centre, presenting a figure-of-8 shape. In the immature crescents the pigment is often scattered, or is arranged longitudinally, as it often is in the fusiform bodies. The amount of pigment varies; it is often considerable. In certain pernicious fevers young crescents with scattered pigment may be abundant in the blood. In the oval and round bodies the pigment is usually concentrated in the centre, often in the form of a circle, but it may be distributed throughout the body. Ovoid, round, and fusiform bodies may be changed into typical crescents, and, on the other hand, crescents may change into fusiform, oval, and round bodies. The appearance of a fusiform or ovoid body may be presented when a crescent is seen from the convex side.

From the round bodies flagellate forms may develop in the manner already described (Plate II. Figs. 42, 43, 44). The æstivo-autumnal flagellate bodies develop only from round bodies of the crescentic group. They are smaller than the tertian flagellates, resembling rather the quartan. The process of transformation of crescentic bodies into oval and round forms, and the development of flagella from the latter, can sometimes be observed in studying the fresh blood microscopically. Councilman once observed a rapid undulatory movement of a body presenting the general appearance of a crescent.

Crescents and the other bodies belonging to the same phase not infrequently become vacuolated or contain or throw off from the margin little hyaline balls (pseudo-gemmation), or disintegrate or present other degenerative changes (Plate II. Figs. 34, 41, 40). Danilewsky has observed crescents of unusually large size, as much as 20–22 μ long and 4–6 μ broad.

The biological significance of the crescents is unknown. These bodies do not belong to the regular sporulating cycle of development of the parasite, and there is no positive proof of their capacity for further development.

Dr. Thayer in a personal communication to the writer reports a valuable experiment made by himself which demonstrates the incapacity of crescents when inoculated into the blood of healthy individuals to develop or to cause any symptoms. The blood was taken from a patient who had had acute æstivo-autumnal fever, which was arrested by administration of quinine. Crescents persisted in the blood. For seven days the blood was examined without finding hyaline bodies or any form of the malarial parasite other than crescents. Seven days after the disappearance of the hyaline bodies a hypodermic syringeful of blood containing crescents in considerable number was withdrawn from the median basilic vein of the patient and immediately injected into the corresponding vein of a healthy man. No elevation of temperature or other symptoms followed the injection, nor did crescents or any parasitic forms make their appearance in the blood, which was examined daily for two weeks and at intervals for over a month. In the inoculation experiments of Gualdi and Antolisei and others in which it is stated that the blood contained only crescents and infection with the Hæmatozoön falciparum followed in the inoculated individual, it is probable that hyaline

bodies were present in the blood used for the inoculation in such small number that they escaped detection.

The following are the principal views which have been advanced regarding the interpretation of the crescents:

1. Laveran regards the crescentic bodies as encysted forms from which the flagella develop. There is no proof that these bodies are encysted.

2. Canalis and Antolisei and Angelini believe that they have found evidences of sporulation in the crescents and the ovoid and round bodies belonging to the crescentic phase. Grassi and Feletti and Sacharoff likewise believe that these bodies may sporulate. Golgi considers them capable of reproductive development in long cycles, and brings them into special relation with relapses and with fevers of long intervals. Most observers have been unable to find genuine sporulation or other evidences of reproduction in these bodies.

3. Grassi and Feletti consider that the crescents belong to a separate species which they call *Laverania*, and of which they represent a regular phase of development. The sporulating hyaline bodies with which the crescents are usually associated constitute, according to these writers, different species. This view is not generally accepted, and is opposed to the observed facts.

4. Mannaberg regards the crescents as encysted syzygies formed by conjugation of two æstivo-autumnal parasites and capable of reproduction by segmentation. His view is unconfirmed by any other observer, and is improbable. It fails to explain the ovoid and round bodies which belong to the same phase of development, and it cannot be reconciled with the appearances noted in the steps of development of the crescents, as has been shown by Bastianelli and Bignami.

5. Councilman suggests that the crescents may be of the nature of spores. Several authors have called attention to a resemblance between these bodies and the falciform spores of coccidia, but there are such essential differences between the two that the apparent resemblance is only of the most superficial character.

6. Bastianelli and Bignami have described the crescents as deviate and sterile forms. This has been interpreted to mean that they regard the crescents as degenerative forms—a view held by Kruse and some others—but in their latest publication[1] they suggest that these bodies are a rudimentary phase of a second developmental cycle which cannot be completed within the human body, but requires for its continuation some new environment in the outer world. They call attention to the occurrence of two cycles of development in several unicellular parasites, especially the coccidia, which, after passing through several generations in their ordinary parasitic life, enter upon forms belonging to a second cycle. The forms of this second cycle remain sterile, degenerate, and die, unless the parasite can escape from its host and find its appropriate new conditions of life. Manson independently also has advanced the hypothesis that the crescents are intended for the continuance of the life of the species in the external world. It has already been mentioned that a similar view has been suggested also regarding the significance

[1] Bastianelli and Bignami: "Studi sulla Infezione Malarica," *Bullettino della R. Accademia Medica di Roma*, Anno XX., 1893–94.

of the flagellate bodies, and that Manson believes that the mosquito may serve as the host for this second cycle of development.

Differential Diagnosis of the Varieties of the Malarial Parasite.

An inexperienced observer may possibly mistake for the unpigmented intracorpuscular hyaline forms of the malarial parasite the vacuoles which occasionally are present within red blood-corpuscles or the clear spots which may result from certain deformities in the shape of the corpuscles. These vacuoles and clear spots may be distinguished in the fresh specimen by their sharp outlines, the absence of amœboid changes of shape, and a difference in refraction often suggestive of an empty space or hole, and which can be described less readily than it can be appreciated by actual observation. The absence of definite staining readily distinguishes these vacuoles from the hyaline bodies of the parasite in stained specimens.

There are occasionally seen in red corpuscles in stained specimens of the blood, especially in anæmic conditions, small stained dots which do not bear much resemblance to forms of the malarial parasite, but which should be known to the observer in order to avoid the possibility of mistake. They are believed by some to be the result of degenerative changes in the corpuscles, and by others to be remnants of nuclear chromatin derived from the originally nucleated condition of the red corpuscle.

Blood-plates can be mistaken only for free spores or very small extracorpuscular hyaline bodies. In general no attention should be paid as regards diagnosis to bodies free in the plasma which resemble blood-plates. In fresh specimens it is practically impossible to diagnose free spores with any certainty. Clumps of blood-plates have been mistaken for sporulating bodies, but they can be readily distinguished from the latter by the absence of pigment.

For the sake of convenience the principal characters which enable us to distinguish each of the three varieties of the malarial parasite, and which have already been described in detail, will here be summarized. For modifications and amplification of these general statements the reader must consult the detailed descriptions already given.

1. Duration of the Cycle of Development.—In the quartan parasite, seventy-two hours; in the tertian, forty-eight hours; in the æstivo-autumnal, irregular, varying from twenty-four hours to forty-eight hours.

2. Amœboid Hyaline Bodies.—In their earliest stages often indistinguishable from each other. Later, those of the quartan parasite, sharply outlined, somewhat refractive, sluggishly amœboid, with development of dark brown or black, relatively coarse pigment granules, which have but little motion. Amœboid movements cease in a relatively early stage of development of the pigmented hyaline body.

Those of the tertian parasite, pale and indistinct, actively amœboid, with development of reddish-brown, actively motile, relatively fine pigment granules, which tend to accumulate in the bulbous swellings at the extremities of the delicate branching pseudopodia. Amœboid move-

ments continue in late stages of development of the pigmented amœbæ.

Those of the æstivo-autumnal parasite, small, somewhat refractive, in repose ring-shaped, actively amœboid, with development of a few very fine dark reddish-brown or black, only slightly motile, pigment granules, or sometimes without pigment throughout all phases of the sporulating cycle of development.

3. Fully Developed Hyaline Bodies.—Those of the quartan parasite are somewhat smaller in size than the normal red blood-corpuscle, and are usually surrounded by a border of the colored refractive substance of the enveloping red blood-corpuscle.

Those of the tertian parasite attain the full size of a normal red blood-corpuscle and lie in swollen decolorized red blood-corpuscles. Swollen, extracorpuscular, transparent bodies with dancing pigment granules are common.

Those of the æstivo-autumnal parasite do not generally exceed one-quarter to one-third the size of the red blood-corpuscle. The enveloping corpuscle is often shrunken and brassy. They contain much less pigment than the quartan and tertian forms, and sometimes none at all.

4. Presegmenting Bodies.—In the process of collection of the pigment into a mass or block in the centre or excentrically the pigment granules often assume a more regular stellate arrangement in the quartan than in the tertian forms. The differential points between the three varieties in this stage relate to the same differences in size, in the amount of pigment, and in the condition of the infected corpuscle as have been mentioned under the preceding heading. The presence in the blood of quartan and tertian presegmenting bodies is associated with that of sporulating forms, whereas with the æstivo-autumnal presegmenting bodies sporulating forms are almost always missed in the circulating blood.

5. Sporulating Bodies.—Those of the quartan parasite in equal proportion in the peripheral and the splenic blood. They are somewhat smaller than the red corpuscles, and present typical rosette forms with a division into six to twelve ovoid or pyriform segments, each segment becoming an oval or round spore containing a bright nucleiform dot.

Those of the tertian parasite are more numerous in the splenic than in the peripheral blood. They are as large as the red blood-corpuscle, and present less regularity in segmentation than the quartan parasite. They segment usually into from fourteen to twenty spores, which are a little smaller and with less distinct nucleiform dot than those of the quartan organism.

Those of the æstivo-autumnal parasite are found only most exceptionally in the circulating blood in ordinary cases. They are abundant in certain internal organs, including, as a rule, the spleen. They do not generally exceed one-third to one-half the size of the red blood-corpuscle. They segment irregularly, the number of spores being sometimes six to ten, sometimes ten to twenty or even more. The spores are smaller than those of the quartan and the tertian parasites. The stage of sporulation is a prolonged one.

6. Behavior of the Infected Corpuscles.—These often become

somewhat shrunken and deeper in color in the quartan infections; swollen and decolorized in the tertian; and shrunken and brassy, sometimes with retraction of hæmoglobin from the outer part of the corpuscle, in the æstivo-autumnal.

7. Crescentic Bodies.—Crescents and bodies of the crescentic phase appear only in infections with the æstivo-autumnal parasite.

8. Pigmented Leucocytes.—Most abundant during and shortly after the paroxysm, they usually disappear during the period of apyrexia in quartan and tertian infections, whereas it is not uncommon to find them in all periods of æstivo-autumnal infections.

The Intimate Structure of the Malarial Parasite.

The first systematic study of the finer structure of the malarial parasite was made by Celli and Guarnieri (1888–89). This was followed by similar investigations by Grassi and Feletti, Romanowsky, Sacharoff, Mannaberg, Antolisei, and Bastianelli and Bignami. The small size and the but slightly differentiated appearance of most forms of the parasite, and the difficulty of obtaining clear differential stainings, obscure the insight into their intimate structure.

Little detail of structure can be made out in unstained specimens. The substance of the parasite presents in general a homogeneous, colorless, hyaline appearance. In the amœboid hyaline bodies of the quartan and tertian parasites, particularly in the larger forms, an area of variable size in the centre, or more frequently excentrically placed, may sometimes be differentiated by its clear, pale appearance from the more refractive outer zone. This area corresponds to the unstained structure interpreted by many observers as the nucleus in stained specimens. Occasionally two or more such clear spaces can be seen. Sometimes in the larger amœboid and the mature forms a finely granular appearance of the protoplasm can be detected. It is particularly characteristic of the æstivo-autumnal parasite that the young intracorpuscular hyaline bodies show, when at rest, a clear space surrounded by a ring of protoplasm, usually thin and delicate on one side and thicker on the other. This clear space appears unstained on stained specimens. The mature forms in which the pigment has collected into one or more clumps appear uniform in structure in fresh specimens, or may perhaps present a slightly granular appearance. Within the spores, especially distinctly in those of the quartan parasite, a bright body can often be distinguished, which represents the nucleus or a nucleiform material.

The methods for staining the parasites will be described under *Diagnosis*, page 139. These methods are useful, not only for the study of the finer structure, but also for the ready detection of the unpigmented young hyaline forms, particularly of the æstivo-autumnal parasites, which may, without very careful observation, escape recognition on fresh specimens, whereas the presence of pigment at once attracts attention in the fresh specimens to the other parasitic forms.

On suitably stained specimens the intracorpuscular young hyaline bodies show a stained outer part, an unstained, usually excentrically placed, internal part, and one or more deeply stained round or elongated particles situated, as a rule, near the border of the stained and

unstained parts. The constant unstained part is not to be confounded with vacuoles which may occasionally be present. There have been various interpretations of the structures thus differentiated. Celli and Guarnieri designated the stained part as ectoplasm and the unstained part as endoplasm. The deeply staining particles they interpreted as the beginning differentiation of a nucleus, which they thought they could recognize in larger forms as a definite, stained or pale body within the endoplasm. Grassi and Feletti do not recognize a division of the protoplasm into ectoplasm and endoplasm, and in this they are followed by most observers. The clear unstained part they interpret as a relatively large, vesicular nucleus, and the deeply staining particles as nucleoli from which may proceed a delicate reticulum of chromatin connecting them with the nuclear membrane which they assume to exist. The rest of the bladder-like nucleus is filled with clear nuclear juice. Although not all of these details in the structure of the nucleus, such as the membrane and the reticulum, have been observed by subsequent investigators, Grassi and Feletti's interpretation of the unstained part as a nucleus and of the deeply staining particle as a nucleolus or a concentration of nuclear chromatin has been adopted by Celli and Sanfelice, Romanowsky, Sacharoff, and Mannaberg, and has been widely accepted.

Bastianelli and Bignami, while not denying that this interpretation is applicable to the quartan and tertian amœbæ, adopt a different view as to the structure of the æstivo-autumnal amœbæ, which they have studied with great care. They differentiate in the latter an outer colored, chromatic cytoplasm in the form of a stained ring, usually thicker on one side, and an inner uncolored, achromatic cytoplasm, which is all of the clear part enclosed by the ring. The deeply staining chromatic particle they find in the chromatic and not in the achromatic cytoplasm. Often there are two particles, each at opposite points in the ring. This particle is the only representative of nuclear material in the parasite, and they interpret it as fulfilling the functions of a nucleus. They consider that the rapidity of development and multiplication of these æstivo-autumnal parasites prevents the formation of a definite nucleus in a resting stage, such as is described for the quartan and tertian forms.

According to Grassi and Feletti and Romanowsky, the nucleus and nucleolus can be found in all stages of the regular cycle of development of the parasite. The nucleus divides directly—or, according to Romanowsky, by karyokinesis—to form multiple nuclei just before sporulation, each nucleus then entering into the structure of a spore.

The evidence, however, is in favor of the view that at a certain stage of development the nucleus and the nucleolus disappear as differentiated structures, the latter to reappear in multiple form shortly before sporulation. Mannaberg was the first to demonstrate this clearly in his studies of the structure of the tertian parasite. He observed that as the amœboid bodies approach their mature form, and then become the pre-segmenting bodies, the deeply staining particle (nucleolus) disappears, and later the clear, previously unstained part (nucleus) stains diffusely, so that there is in this stage no definite differentiation of structure in the parasite, although the outer part, as a rule, stains more deeply than the

central part. He, however, speaks of the outer part, which contains pigment granules, as the "plasma part," and the inner part, into which the pigment does not penetrate, as the "nuclear part." He attributes the deeper and more diffused staining of the parasite in this stage to the solution of nuclear chromatin into the protoplasm. The first evidence of sporulation on stained specimens is furnished by the appearance of numerous small, deeply staining granules of chromatin in the periphery of the protoplasm. These are the forming nucleoli, which increase in size, and around each the general protoplasmic substance, during the process of segmentation, divides, so that each segment or spore is a cell composed of a nucleiform, deeply staining body surrounded by its protoplasmic envelope. In the quartan and tertian spores a clear unstained part later is usually differentiated around the chromatin granule, and the nucleus now resembles that seen in the young amœboid hyaline bodies within the red corpuscle.

Bastianelli and Bignami likewise demonstrated the disappearance of the deeply staining nucleiform body in the forms of the æstivo-autumnal parasite containing collected pigment (presegmenting bodies), and soon afterward the appearance of diffuse staining in the previously achromatic cytoplasm, so that in this stage no sharp differentiation of structure can be made out within the parasite, which is richer in chromatic material than before the disappearance of the nucleiform body. The first sign of sporulation is the formation of multiple nucleiform chromatin granules in the periphery and the development of spores proceeds in the manner already described, save that the æstivo-autumnal spores are composed only of the deeply staining nucleiform body immediately surrounded by cytoplasm. The presence of the small, clear, unstained part, which with the chromatin particle is interpreted as the nucleus, often seen in the tertian and quartan spores, is rarely observed in the æstivo-autumnal spores.

It is evident from this description that the spores of the malarial parasite possess a definite structure, a most important feature being the presence of a deeply staining body which serves the function of a nucleus. The recognition of this structure renders it possible to distinguish from genuine spores the various pseudospores which have been at times erroneously interpreted as phases of reproduction of the parasite, and which belong to the category of degenerative forms. Although Antolisei has described a double contour, which he interprets as a membrane, about the spores, this observation has not been confirmed, and the spores are to be regarded as naked, thus belonging to the class of gymnospores. Some have objected to the designation of these segments as spores, but this nomenclature is in accordance with that employed by zoölogists for similar bodies formed in a like manner in certain other unicellular organisms.

It is evident from the preceding description that investigators are not wholly agreed as to what structure in the malarial parasite shall be called the nucleus, some applying this name to an unstained part containing the deeply staining chromatin particle, others regarding the chromatin granule itself as the only representative of the nucleus. There is, however, general agreement that this deeply staining particle or body is an essential constituent of the nucleus, and that the

presence of a nucleus or of a nucleiform body in the parasite has been demonstrated. This demonstration fulfils the important biological condition that something performing the functions of a nucleus belongs to every cell capable of reproduction, and it has served to remove any lingering doubt which may have been entertained as to the recognition of these bodies as parasitic organisms.

It is interesting to note that during the regular cycle of development there is a continual increase in the amount of staining or chromatic substance from the small hyaline body to the sporulating bodies, and that the cell becomes multinucleated just before segmentation occurs. As the chromatic substance is to be regarded as endowed with especial functional activity, these changes are highly significant.

The mature crescents, as a rule, stain feebly and diffusely, or often only at the poles, and perhaps also along the margin. Near the middle one or two deeply stained granules, often covered up by the pigment, may be present, but they are not constant. Mannaberg finds often a narrow stained band in which are two or more deeply stained granules, stretching across the middle of the crescent. Bastianelli and Bignami find that the young developing bodies of the crescentic phase stain diffusely and less intensely than the bodies with a central block of pigment which develop into segmenting forms. Whereas in the forms of the parasite which develop into sporulating bodies there is a continual increase in the chromatic substance as the bodies continue to develop, in the development of the semilunar bodies there is no correspondingly large increase of staining substance. With rare exceptions these observers found no chromatin granules in these developing crescentic bodies, nor did they ever find in any body of this group those changes of structure, such as the appearance of several chromatin granules, which indicate sporulation.

Laveran, Celli and Guarnieri, and, with especial emphasis, Mannaberg, consider that the crescents are enveloped in a double contoured membrane. A number of other observers have also adopted this view. We do not consider that any definite membrane, which can be regarded as a part of the parasite itself, has been satisfactorily demonstrated around the crescents or around any form of the malarial parasite. A double contour can sometimes, but not regularly, be seen in the periphery of the crescents, but this alone cannot be considered as proof of the existence of a membrane. The manner in which little hyaline pieces (pseudo-gemmation) can sometimes be seen to form at the margin of the crescentic bodies speaks against the presence of an actual membrane.

The Malarial Pigment.

The question as to the origin of the malarial pigment, which was so long discussed without conclusive result before the discovery of the malarial parasite, has been definitely settled by this discovery. The pigment is formed by the parasite out of the hæmoglobin of the blood-corpuscles by what may be regarded as a process of digestion. The pigment occurs in the form of little granules, which may be fine or coarse, and of distinct rods and spicules, which may be as much as 1 μ long. Such rods often present a certain superficial resemblance to

deeply stained bacilli. The pigment may occur in the form of extremely fine dust-like particles not easy to detect. It may be fused into black blocks. The color varies from a yellowish-brown or rusty, reddish-brown to black. Laveran speaks of fire-red and even light-blue pigment, and Rosenbach observed a greenish hue of the pigment. The malarial pigment is somewhat loosely ranked by pathologists among the melanin pigments. The differences in the characters of the pigment belonging to the different varieties of the malarial parasite have already been sufficiently described. The deposition of the pigment in the various organs will be described under the *Pathological Anatomy*.

Since the examinations of malarial pigment by Meckel and by Frerichs it has been known that concentrated sulphuric acid and hydrochloric acid do not alter it, and that it disappears upon the addition of strong alkalies and of chloride of lime. Kiener observed that the pigment is dissolved by ammonium sulphide.

The demonstration of the origin of the malarial pigment from the blood coloring matter at once raised the question whether, like many pigments of hæmatogenous origin, it contains iron demonstrable by our micro-chemical tests. A statement by Perls as long ago as 1867, that pigments in the spleen of intermittent fever respond to the test for iron, has given rise to much confusion. It is not wholly clear that Perls examined the malarial pigment, but, if he did, there can be no doubt that he mistook for the true malarial pigment other pigments which are abundantly present in certain organs of those dead of malaria, and which respond to the chemical tests for iron (hæmosiderin). It has been shown by Neumann, Bignami, Stieda, Dock, and others that the pigment formed directly by the malarial parasite does not contain iron in a combination which will respond to our ordinary micro-chemical tests for this element. This, of course, does not prove that it may not contain iron in some combination, such as that in hæmoglobin, which cannot be demonstrated by our micro-chemical reactions. As has been pointed out by the writers named, the organs of those dead of malaria, particularly the spleen, the liver, and the bone marrow, contain a large amount of hæmosiderin, the presence of which is doubtless to be explained by the extensive destruction of red blood-corpuscles in malaria. There is no evidence that hæmosiderin is formed directly by the malarial parasite. Marchiafava (1889), however, has advanced the hypothesis that the black pigment may be formed not only within the malarial parasites, but also within the leucocytes out of red corpuscles altered by the action of the parasite. He thus explains the intense melanosis of the spleen, liver, and bone marrow in certain æstivo-autumnal pernicious infections where the parasites appear only slightly pigmented. Bignami [1] comes also to the conclusion, from his extensive examinations of melanotic organs in malaria, that the black pigment without micro-chemical iron reaction may have this double origin, being formed either within the malarial parasite without an intermediate hæmosiderin stage or within cells out of hæmosiderin derived from destroyed red corpuscles. The objection to this conclusion of Bignami is that hæmosiderin is found in the liver, spleen, and bone marrow very commonly in anæmias, but that the black pigment, without micro-chemical iron

[1] *Bullettino della Reale Accademia Medica di Roma*, Anno xix. fasc. ii. p 230, 1893.

reaction, which characterizes malarial infections, does not appear under these conditions. It is possible that the malarial parasite may produce some chemical change in the substance of the red blood-corpuscle which permits the transformation of the specifically altered hæmoglobin into black malarial pigment within certain cells of the body. This, however, is a pure hypothesis.

Phagocytism.

The presence of malarial pigment in leucocytes and other cells has long been known. Since the observation of phagocytic phenomena in malaria by Laveran, Marchiafava and Celli, and Metchnikoff, important studies of this subject have been made, especially by Guarnieri, Golgi, Bastianelli, and Marchiafava and Bignami.[1] These investigations have shown that phagocytosis is a common and important phenomenon in malaria, although there is much difference of opinion as to the interpretation of some of the observed facts. Some assign to the phagocytes no higher rôle than that of scavengers charged with the collection and removal of the pigment and débris resulting from the activities of the malarial parasites and from the death and disintegration of the parasites themselves. The amount of slag which is produced in severe cases of malaria in the form of pigment, dead and disintegrating red blood-corpuscles, and degenerated and broken-up parasites is so large that even this office of scavengers becomes an important one. But Metchnikoff, Golgi, and some others believe that the phagocytes devour large numbers of intact, healthy parasites in certain phases of their development, and that in this contest between cell and parasite is to be found the most important agency for the defence of the body. The arguments for and against this latter conception are essentially similar to those which are adduced as to the phagocytic theory in bacterial infections, the main difficulty being to determine to what extent fully active and virulent parasites are taken up and destroyed by phagocytes, and, even admitting the occurrence of this mode of disposal of the parasites, whether or not it is the most essential and the predominant factor in their destruction. That malarial parasites, as well as bacteria, may perish in the blood plasma without incorporation within cells cannot be doubted, as we have direct observations demonstrating this.

The cells which assume the functions of phagocytes in malaria are the leucocytes, the endothelial cells of the walls of the bloodvessels, and large cells, found especially in the spleen, the bone marrow, and the liver, and called by Metchnikoff "macrophages." Of the leucocytes the large mononuclear, the polymorphonuclear, and the transitional forms act as phagocytes. The small lymphocytes and the eosinophils have never been observed to contain pigment or débris in malaria. Of the leucocytes it is the large mononuclear forms which are the most active and important phagocytes within the body in malaria, but, as has been pointed out by Thayer and Hewetson, the polymorphonuclear leu-

[1] Especially valuable are the articles of Golgi, "Il fagocitismo nell' infezione malarica," *Riforma Medica*, 1888, and of Bastianelli, "I leucociti nell' infezione malarica," *Bull. della R. Accademia Medica di Roma*, 1892.

cocytes are the ones which can be observed to be active in the fresh blood during examination under the microscope. It is the latter which pick up the pigment and the extracorpuscular and degenerated parasites, and which attack the flagellated bodies in the fresh blood withdrawn from the body, so that there may be a notable difference between the blood examined immediataly after its withdrawal from the body and that examined at a later period as regards the number of polymorphonuclear leucocytes containing foreign elements. Endothelial cells containing pigment, parasites, or fragments of parasites or of red corpuscles are rarely seen in the circulating blood withdrawn for microscopical examination; but the study of microscopical sections of organs of those dead of malarial infections shows that the endothelial cells lining the capillaries and small bloodvessels, especially those of the spleen, bone marrow, and liver, in certain cases also of the brain, intestine, and other parts, manifest extensive phagocytic activities. So too the macrophages, although they have repeatedly been found in the circulating blood, are met with chiefly in the splenic blood and in the microscopical examination of organs of those dead of malaria. These macrophages, which may attain an enormous size and are frequently destitute of nuclei, and therefore necrotic, are mononuclear cells derived probably in part from mononuclear leucocytes and certain fixed cells of the pulp of the spleen and bone marrow. Their contents may be varied, consisting sometimes within one cell of pigment, intact or degenerated parasites, and red blood-corpuscles and entire smaller phagocytes. Dock has counted as many as twenty parasites within one phagocyte in the spleen. Under *Pathological Anatomy* will be described the appearances of these various phagocytes as seen in sections of the different organs of the body.

The foreign elements which are found within these phagocytes in malaria are—(1) malarial pigment; (2) yellowish or reddish-yellow pigment derived directly from disintegrated red corpuscles (hæmosiderin); (3) red corpuscles, sometimes intact, but usually more or less altered and fragmented; (4) malarial parasites, either free or enclosed within red corpuscles, which are usually altered, such parasites appearing sometimes intact, often degenerated and fragmented; (5) particles which are probably often derived from the disintegration of parasites, but which do not present appearances sufficiently characteristic to enable one to determine their origin. It has already been mentioned that a phagocyte may be enclosed by a macrophage. Leucocytes either with or without pigment may be thus enclosed. As phagocytes and other cells often degenerate and become necrotic and disintegrated in malaria, it is evident that from this source may be derived material for inclusion within living cells.

First in order of frequency are phagocytes containing malarial pigment. In the examination of malarial blood obtained from the peripheral circulation the only form of phagocyte which is to be seen with any frequency in the perfectly fresh specimen is the melaniferous leucocyte. Leucocytes containing clearly recognizable parasites are rarely, if ever, seen in the freshly drawn specimen of peripheral blood. Macrophages containing definite parasitic forms may occasionally be found in this situation. Both mononuclear and polymorphonuclear leucocytes may contain the pigment, but in the perfectly fresh specimen the former

preponderate. The pigment is found most frequently in the form of blocks and coarse granules, corresponding to that set free by the process of sporulation, but sometimes the pigment within the leucocytes is in fine rods and grains, such as belong to the earlier stages of development of the parasite. The inference is a probable one that in the latter case the leucocyte may have enclosed the parasite.

As has already been stated, in the fresh blood removed from the body and examined for a while under the microscope the polymorphonuclear leucocytes can be seen to engulf pigment and certain parasitic forms—viz. extracorpuscular forms, especially degenerated and fragmented forms, segmenting forms and spores, and altered red corpuscles —and especially do they attack the flagellate bodies, as has been demonstrated by Thayer and Hewetson (Plate II. Figs. 45–49). Such enclosed parasitic forms, with the exception of the spores, can be seen rapidly to become indistinct and unrecognizable within the leucocytes.

From the examination of the fresh circulating blood alone one obtains a very inadequate conception of the extent and nature of the phagocytic processes in malaria. A fuller idea of these processes can be derived from the study of blood withdrawn by puncture of the spleen, where phagocytic phenomena are far more active than in the circulating blood; but it is especially in the microscopical examination of the organs of those who have succumbed to a malarial attack that the best opportunity is afforded to learn the extent of phagocytosis in malaria. Here one finds abundantly leucocytes, endothelial cells, and macrophages containing pigment, parasitic forms, and altered red blood-corpuscles.

Parasites in their later stages of development, especially when they are free, are frequently taken up by phagocytes—in their early stages rarely, unless they have become extracorpuscular or the corpuscle containing them is degenerated. Sporulating forms, and somewhat less frequently forms with collected pigment (presegmenting bodies), are the ones most commonly found in a recognizable condition within the phagocytes. It is stated by Bastianelli and Bignami that the bodies with pigment blocks (presegmenting) are found most frequently within macrophages, and sporulating forms within polymorphonuclear leucocytes. Pigmented amœbæ they found rarely, and red blood-corpuscles containing unpigmented amœbæ very rarely, within phagocytes. Bastianelli gives the following as the order of frequency in which the various parasitic elements are found within phagocytes: (1) pigment; (2) sporulating forms and spores; (3) red corpuscles, normal or decolorized, containing sporulating forms or bodies with central pigment blocks; (4) brassy and decolorized red corpuscles containing plasmodia (hyaline bodies in the amœboid stage); (5) free bodies with central pigment clumps; (6) more rarely free amœbæ or red corpuscles of normal appearance containing parasites in the amœboid stage. According to the observations of the writer, free bodies with central pigment clumps occupy a higher place in this scale than that assigned to them by Bastianelli. Crescents enclosed in phagocytes may be found even in the circulating blood. The various bodies within phagocytes often lie in an area surrounded by a clear zone like a vacuole.

Golgi (1887–88) discovered that phagocytosis occurs in quartan and tertian infections with a definite periodicity which stands in relation to

certain phases in the cyclical development of the parasite, and therefore to certain periods of malarial fever. This is readily understood when one considers that it is especially the free pigment and the mature and segmenting parasites and the degenerative forms which are taken up by phagocytes. The pigment is liberated by the process of sporulation which, as has already been explained, occurs shortly before and during the early stages of the paroxysm. Corresponding with this, Golgi found that pigmented leucocytes are present in the circulation during the paroxysm and for a short time afterward, and that they disappear from the circulation during the apyrexia. This periodicity in the appearance of melaniferous leucocytes and of other phagocytes can be observed regularly in quartan and tertian infections. There are frequently indications of it also in æstivo-autumnal infections, but on account of the irregularities in the cyclical development of the Hæmatozoön falciparum, of the prolonged period of sporulation, of the frequent occurrence of multiple groups of parasites, and of the presence at all periods of degenerated red corpuscles, this periodicity in the occurrence of phagocytosis is often obscured or is not manifest at all. Pigmented leucocytes may be found in many cases of æstivo-autumnal infection during all periods of the disease, although they are more numerous during the paroxysm and shortly afterward. In the severe prolonged cases they are generally abundant, and they may persist in the circulation for several days after cure is effected. As long as crescents are present pigmented leucocytes may be found.

Parasites which, to all appearances, are normal are found within phagocytic cells. What is the fate of such enclosed parasites? That many degenerate and die cannot be questioned, for these degenerative alterations can be directly observed in progress under the microscope in examining fresh blood, and in studying malarial blood and tissues one frequently encounters evidences of this fate of the parasites. It is claimed, however, by Marchiafava, Bignami and Bastianelli that enclosed spores, although prevented from further development, may survive for a long time within leucocytes and other cells, and that such latent spores may after an indefinite period be set free and cause by their development a relapse of the fever.

Attention has already been called to Golgi's belief that the æstivo-autumnal parasite may, and to a considerable extent does, develop within the leucocytes and endothelial cells of internal organs, in ordinary cases chiefly of the spleen and bone marrow. He adduces a number of considerations in support of this view, but the objective evidence he and his pupil, A. Monti, find in the detection of the frequent presence of this parasite, apparently intact and in all stages of development, within these cells. In opposition to Golgi, however, it is claimed by Marchiafava, Bignami and Bastianelli that early phases of development of the parasite are rarely seen within the cells, and that, therefore, the much more commonly enclosed late phases cannot have developed within the cells from young parasites. Golgi also brings to his support the observation, made by all who have studied the subject, that many of the cells containing parasites degenerate and die, as is made evident especially by the loss of their nuclei. He interprets this as meaning that in the conflict between cell and parasite the latter often comes off the

victor. Further investigations are needed to determine to what extent Golgi's doctrine as to the intercellular residence and development of the Hæmatozoön falciparum is correct. Certainly the greatly preponderating number of intact æstivo-autumnal parasites observed in examining the organs of those dead of pernicious malaria are found within free red blood-corpuscles in the vessels of internal organs.

The theory of Metchnikoff that the essential factor in the resistance of the body to the malarial parasite resides in the activities of phagocytes is opposed by many considerations. The most important factors in determining the gravity and the course of a malarial infection are the degree and quality of virulence possessed by the parasite, on the one hand, and the resistance of the individual receiving the parasite, on the other hand. There is no evidence that phagocytic functions are in abeyance in severe and pernicious cases of malaria. On the contrary, we find here often enormous numbers of parasitic enclosures within phagocytes. There is no proof that spontaneous recoveries from malaria are associated with an increase of phagocytic activity. Inasmuch as phagocytes regularly attack degenerated and fragmented parasites, and as we know that such degenerations occur frequently within parasites free in the plasma, it is permissible to suppose that many of the parasitic forms found within phagocytes were already impaired in their vitality before they were engulfed by cells. After the administration of quinine, which directly injures the malarial parasite, a distinct increase in the number of phagocytes has been often observed. Certainly quinine does not stimulate the leucocytes to swallow the parasites. Here the increase in the phagocytes must be attributed to the increase in the number of damaged parasites.

There is evidence that the blood-plasma may exert a parasiticidal effect upon the malarial organism, as well as upon other protozoa (Faggioli), when the parasite has escaped from the protective covering of the red blood-corpuscle. The period when the largest number of malarial parasites are destroyed is that of sporulation and of free spores, and it is during this phase of the life-history of the parasite that quinine acts most effectively. We may, at least provisionally, adopt a theory to explain natural resistance to the malarial parasite similar to that which many accept regarding resistance to bacteria—viz. that the parasites are destroyed by parasiticidal substances contained both in the plasma and within leucocytes and other phagocytic cells. The substances injurious to the parasite are in the last analysis furnished to the plasma by the cells, and are in a more concentrated or potent form within the cells than in the fluids. This theory assigns to the phagocytes a higher rôle than that of mere scavengers. They are endowed in especial degree with the power of destroying the parasite, but this power is shared by the plasma.

Pathogenesis.

The discovery of the malarial parasite has placed within our reach the means of solving many problems concerning malaria which we could not formerly even attack with any hope of success. Already we have attained a satisfactory understanding of not a few previously unexplained manifestations of malaria, and other formerly obscure malarial phenom-

ena have been brought at least within the range of our comprehension. Much still remains to be elucidated, but we cannot doubt that further studies will continue to throw fresh light upon what remains obscure.

In the description of the symptoms and lesions of malaria attention will frequently be called to their relations to the parasite, and in this connection only certain salient points, relating more particularly to pathogenic properties of the parasite, require consideration.

The mere presence of the malarial parasite in the body is not sufficient to cause symptoms. The organisms must have multiplied to a certain point before their presence is manifested by recognizable symptoms. The bearing of this fact upon certain malarial phenomena, more particularly upon the varying periods of incubation as determined by experimental inoculations of malarial blood and upon fevers with long intervals, will be considered in the clinical part of this article.

It may be stated as a general rule, which was first formulated by Golgi, that the larger the number of organisms present in the body the more severe are the manifestations of the disease; but the number of the organisms is by no means the only factor which determines the gravity of the disease. The variety of parasite which is concerned in the infection is a factor of fundamental importance. The quartan variety produces the mildest attacks, the tertian is more virulent than the quartan, and the æstivo-autumnal variety is the most virulent of all, and is the one which is almost exclusively associated with the pernicious attacks. These variations in virulence are best explained upon the assumption that the malarial organism produces toxic substances of varying virulence according to the variety of parasite. There is also clinical evidence that one and the same variety may vary in virulence, so that, for example, some æstivo-autumnal parasites are more virulent than others.

In seeking an explanation of the varying clinical characters of malarial infections we have to reckon not only with the number, the varieties, and the virulence of the parasites, but also with several other factors, such as predisposing conditions on the part of the individual infected, the occurrence of multiple groups of the parasite, the distribution of the organisms in internal parts, the circulatory and other anatomical disturbances induced by the parasites.

Periodicity is the most striking clinical characteristic of malarial fevers, and the explanation of this phenomenon has exercised the minds of pyretologists from ancient times. It is true that intermittence is not limited to fevers of malarial origin, but regularity of rhythm in the occurrence of the paroxysms is especially characteristic of malaria. One of the most interesting additions to our knowledge resulting from the discovery of the malarial parasite is the demonstration by Golgi, which has been abundantly confirmed, that this rhythm in the malarial paroxysms corresponds to a rhythm in the development of successive generations of the parasite.

The onset of each paroxysm corresponds to the ripening and sporulation of a generation of parasites and the setting free of a new brood.[1]

[1] The old idea that the periodicity of malarial fevers depends upon the periodical production in the blood of a *materia peccans* is thus confirmed. It is interesting in this connection to note the line of argument presented by Griesinger in his admirable and sug-

Exactly what the connection is between this act of sporulation, with the liberation of a fresh brood of young parasites, and the cause of the febrile paroxysm, is not definitely known. It was at first suggested by Golgi (1887) that the paroxysm is due to the invasion of the red blood-corpuscles by the new group of parasites, but it was shown by Antolisei (1890) that the paroxysm depends rather upon the act of segmentation than upon the invasion of the blood-corpuscles by a new generation of organisms, for quinine, administered before a paroxysm in sufficient quantity, may, by destroying the fresh brood, completely prevent the invasion of the red corpuscles, but it cannot prevent the segmentation and the impending paroxysm. The view is now widely held, and seems plausible, that in the act of sporulation and of liberation of the spores chemical poisons are set free, and that these poisons, by their action on the nervous centres concerned in the production of fever, cause the febrile paroxysms. This toxic theory of malaria has been elaborated especially by Baccelli.

The fact that the malarial parasite resides in, feeds upon, and destroys the red blood-corpuscles furnishes an entirely satisfactory explanation of two of the most characteristic and important manifestations of malaria—the melanæmia and the anæmia. The malarial pigment, for which we formerly had no adequate explanation, is formed as an undigested residue within the body of the parasite by metabolic processes directly out of the hæmoglobin of the infected red blood-corpuscle. Various stages of the formation of the pigment within the parasite can be seen. The liberation of this pigment, its inclusion by phagocytes, its deposition in various internal organs, have all been described, and will be further considered under the *Pathological Anatomy*. The relations of the biological characters of the parasite to malarial anæmias and to hæmoglobinuria will be fully considered in the anatomical and clinical parts of this article (pages 93, 116, 125, and 130).

The ways in which the red blood-corpuscles may be altered by the action of the malarial parasite are various. The extent of these changes varies with the variety and the virulence of the parasite. They are least in quartan infections, greatest in the æstivo-autumnal. The infected blood-corpuscle may appear otherwise normal. It may be swollen or shrunken or variously deformed. It may divide into two or more pieces. It may be partly or completely decolorized, or the hæmoglobin may separate from the stroma and be dissolved in the plasma, or may be concentrated around the parasite. Especial significance in the æstivo-autumnal infections attaches to that alteration in the cor-

gestive article on the malarial diseases (*Virchow's Handb. d. spec. Path. u. Therap.*, Bd. ii. Abth. 2, 2te Auflage, p. 41, Erlangen, 1864): "The cause of the periodicity of the fever cannot, therefore, be referred to the disposition of the nervous system to rhythmical vital actions, as many have formerly done, but it must, at least according to our present although very incomplete knowledge concerning the causes of heat, be attributed to something periodically occurring in the blood, which is connected with the increased production of heat. It has been formerly conceived that a certain substance, a *materia peccans*, appears periodically in the blood and incites the febrile heat and reaction: this material requires for its production and complete development sometimes longer, sometimes shorter, periods, and herein lies the cause of the rhythm of the fever. . . . . As an explanatory hypothesis this conception accomplishes more than the later attempts at explanation. . . . . The continuous morbid process which causes the poisoning incites periodically changes in nutrition or in the blood which arouse the nervous apparatus to abnormal manifestations."

puscle which has been repeatedly referred to as the brassy change, on account of the resemblance in the color of the shrunken corpuscles to brass, sometimes compared also to copper or old gold. Nor are the corpuscles which are actually infected by the parasite the only ones which may be altered. Uninfected corpuscles may also be changed in appearance, and may be destroyed, especially in cases of hæmoglobinuria.

These changes in the red blood-corpuscles, which must be regarded as degenerative and destructive, cannot be brought wholly into parallelism with the development of the malarial pigment. In fact, the most profound lesions and the greatest destruction of the red corpuscles occur in infections with the æstivo-autumnal parasite, which is characterized by the small amount or even the entire absence of pigment. To explain many of these changes we must have recourse again to the theory that toxic substances are produced by the parasite and directly damage the blood-corpuscles.

These alterations in the red blood-corpuscles not only explain the malarial anæmias and the hæmoglobinuria with their concomitant symptoms and lesions, and the accumulation of malarial and other pigments in certain organs, but they are utilized, although less conclusively, to explain certain other malarial phenomena. We know from physiological observations that the physical integrity of the red blood-corpuscles is an important condition in the maintenance of their circulation within the blood current. It is reasonable to suppose that corpuscles as profoundly altered as are many of those infected with the malarial parasite will circulate with difficulty, and will tend to accumulate in certain situations where local conditions of the circulation favor the lodgement of foreign particles which get into the circulation. Many writers, therefore, attribute to these alterations in the physical properties of the infected red corpuscles the accumulation of the parasites within the vessels of certain internal organs, more particularly the spleen, the bone marrow, the liver, and the brain, and they explain the absence of such accumulation in quartan infections by the comparatively slight lesions of the infected corpuscles, and the large accumulation in tertian, and still more in æstivo-autumnal, infections by the more serious damage inflicted upon the infected red corpuscles by the varieties of the parasite causing these latter infections. Doubtless these factors—changes in the infected red corpuscles and local conditions of the circulation—are important in determining the localization of the parasites in certain internal parts, but with our present knowledge we cannot explain the varying distribution of the parasites observed in different cases exclusively by their aid, any more than we can adopt a similar explanation for the localization of the micro-organisms in other infections.

The localization of the parasites in some cases, more particularly in æstivo-autumnal infections, within definite vascular areas of internal organs stands in relation to corresponding symptoms and lesions. The comatose and the choleriform types of pernicious malaria are associated with an accumulation, which may be enormous, of the parasites in the capillaries and small vessels of the brain and of the stomach and intestine respectively. Other special localizations of the parasites will be mentioned in the subsequent part of this article. In these cases cap-

illaries and other small bloodvessels may be partly or completely plugged with parasites, chiefly within red blood-corpuscles. Swollen, degenerated, and desquamated endothelial cells, pigment, macrophages, and other phagocytes contribute to this occlusion of the vessels. Genuine thrombi also occur.

Serious disturbances of the circulation must result from such extensive plugging of the vessels. It is not easy to determine how far these mechanical disturbances of the circulation are responsible for symptoms and lesions with which they are associated. Marchiafava and Bignami and others regard them as the essential cause of the grave nervous symptoms in comatose pernicious fever, and of other symptoms and of lesions. Many years ago Frerichs likewise attached much importance in the causation of cerebral symptoms to accumulations of pigment and the formation of coagula within the cerebral vessels. It appears, however, to the writer that, aside from certain general pathological considerations and analogies with similar conditions in other diseases, this mechanical explanation is inadequate, and that here too the toxic products of the parasite are operative. The promptness with which the grave cerebral symptoms may subside after administration of quinine is not easily reconcilable with the theory that they are due to plugging of the vessels.

Even the focal necroses which are common in the liver in pernicious cases, and may occur in the spleen, the kidneys, and elsewhere, are best interpreted as due to the toxic products of the parasite, rather than as the result, as is claimed for the liver by Guarnieri, of plugging of the bloodvessels. These necroses do not differ from those observed in diphtheria, typhoid fever, and streptococcus and other infections, and that they may be purely toxic in origin has been demonstrated by Welch and Flexner.[1]

The capillary hemorrhages which have been observed in the brain in the comatose form of pernicious fever, and which may occur elsewhere, may be referred to the hyperæmia and stasis resulting from plugging of the vessels. The interesting fact has been observed that in these capillary hemorrhages the extravasated red corpuscles are without parasites, while the neighboring bloodvessels are filled with red corpuscles containing parasites. The explanation of this which is given by Marchiafava and Bignami and adopted by others is that the corpuscles containing parasites on account of their greater adhesiveness stick to the walls of the vessels and thus are prevented from escaping. The writer offers another explanation as the more probable. The examination of these small hemorrhages shows that they are the result of diapedesis, and not of actual rupture of the vessels (rhexis). It is not difficult to comprehend that red corpuscles altered by the invasion of parasites would not participate in the process of diapedesis, whereas it is not easy to understand why they should not escape from ruptured vessels.

It is evident from what has been said that, while occlusion of vessels and consequent disturbances of the circulation are common in severe malarial affections, and are doubtless of importance in causing some of the lesions and symptoms, the more important and characteristic symptoms and lesions are, in the opinion of the writer, with our present

[1] *The Johns Hopkins Hospital Bulletin*, March, 1892.

knowledge, better explained by the toxic theory of the pathogenic action of the malarial parasite than by any mechanical theories which have yet been offered.

We have, however, no positive demonstration of the existence of specific malarial toxins. The investigations as to the toxicity of the urine of malarial patients will be described on page 123. They have not led to any positive results as to the detection of specific malarial poisons.

It is a very old conception that the febrile reaction of the malarial paroxysm is conservative in the sense that this response of the body to the presence of pyogenic agents in some way aids in the elimination or destruction of injurious substances. This conception is not altogether without support from the parasitological study of malaria. The fever begins at the time of the birth of a new generation of parasites. These young organisms before they have entered the red blood-corpuscles are, of all phases of development of the parasite, in the most vulnerable condition, as has been shown by investigations of the action of quinine. That a large number of them perish during the febrile paroxysm seems to be demonstrated, at least in quartan and tertian infections, by the contrast between the number of sporulating forms and the number of succeeding infected corpuscles. Especially suggestive of increased potency of parasiticidal agencies during the febrile paroxysm are cases, especially of quartan or tertian infection, in which, after a sharp paroxysm, the symptoms and the parasites disappear, perhaps permanently, but often to return after a long interval as a recrudescence of the fever (page 121).

Similar Hæmatozoa in the Lower Animals.

Great interest attaches to the presence in the blood of certain lower animals of protozoan parasites closely resembling the malarial parasite. Attention was first called to this resemblance by Danilewsky (1885–86), who described more fully certain forms which were previously known, and added the discovery of new forms, especially that of hæmatozoa in birds which bear close resemblance to the human malarial parasite. Since Danilewsky's first publications there have been a number of investigations on this subject by Kruse, Celli and Sanfelice, Grassi and Feletti, Laveran, Labbé, and others.

In the blood of frogs, turtles, lizards, and some other cold-blooded animals hæmatozoa presenting some points of resemblance to the malarial parasite are not uncommon. Of these the best studied and most interesting is the Drepanidium ranarum (Lankester), identical with Gaule's "Würmchen," in the blood of frogs. It is, however, certain hæmatozoa in birds which bear such close resemblance to the malarial parasite that their identity with the latter has been assumed by Danilewsky and Grassi and Feletti, who speak of the existence of malaria and of malarial parasites in these animals. Most of the observations thus far reported have come from Russia and Italy, but the parasites have been found in birds also in Germany and France, and recently in the United States.

In birds thus infected have been found forms similar to those of the malarial parasite in man—viz. unpigmented and pigmented hyaline

bodies (which, however, in distinction from similar bodies in man, manifest little or no amœboid movement), sporulating forms, crescents, and flagellated bodies. The bird's hæmatozoa are also parasites of the red blood-corpuscles, from which they produce black pigment: they pass through the same stages of development as the latter, and the same diversity of views exists as to the origin and significance of the crescents and flagellated bodies. The name HÆMOPROTEUS was introduced by Kruse to designate these so-called malarial parasites of birds, and various other names have also been suggested. Grassi and Feletti adopt the same names and the same classification for these parasite of birds as for the human parasites (page 38). There are differences between the hæmatozoa found in different species of birds, and in the same species apparently different varieties of the parasite have been observed, but there are at present no definite classification and no certainty as to the number of varieties which may exist.

Although these hæmatozoa of birds evidently belong to the same class of organisms as the malarial parasite, there are several reasons which indicate that they are not identical with the latter. They present certain morphological and physiological differences which it would lead too far here to describe. Although found thus far chiefly in birds from malarial regions, it is not proven that they may not exist in birds elsewhere. The inoculation of uninfected birds with the blood of birds containing the parasites has been, in a large preponderance of the experiments, unsuccessful in the result. The inoculation of birds with blood from human beings affected with malaria, and the inoculation of human beings with the blood of birds containing the hæmatozoa, have been uniformly without positive result (Di Mattei). Large doses of quinine have no influence upon the parasites in birds. The presence of the hæmatozoa in birds is usually without recognizable disturbance of the health of the birds, although it may cause a chronic or an acute affection. While, then, we must admit a close relationship between certain hæmatozoa of birds and the human malarial parasite, the existing evidence is opposed to their identification.

DESCRIPTION OF PLATES I. AND II.[1]

The drawings were made with great care and skill by Mr. Max Broedel, with the assistance of the camera lucida, from specimens of fresh blood. A Winkel microscope, objective, 1-14 (oil-immersion), ocular, 4, was used.

Figs. 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 pseudopodia. 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.—Degenerative form simulating a segmenting body.

16, 17.—Precocious segmentation.

18, 19, 20.—Large swollen and fragmenting extracellular bodies.

22.—Flagellate body.

23, 24.—Degenerative forms showing vacuolation.

The Parasite of Quartan Fever.[2]

25.—Normal red corpuscle.

26.—Young hyaline form.

27–34—Gradual development of the intracorpuscular bodies.

35.—Full-grown body. The substance of the red corpuscle is not visible in the fresh specimen.

36–39.—Segmenting bodies.

40.—Large swollen extracellular form.

41.—Flagellate body.

42.—Degenerative form showing vacuolation.

PLATE II.

The Parasite of Æstivo-autumnal Fever (*Hæmatozoön falciparum*).

1, 2.—Small refractive ring-like bodies.

3–6.—Larger disk-like and amœboid forms.

7.—Ring-like body with a few pigment granules in a brassy, shrunken corpuscle.

8, 9, 10, 12.—Similar pigmented bodies.

11.—Amœboid body with pigment.

13.—Body with a central clump of pigment in a corpuscle showing a retraction of the hæmoglobin-containing substance about the parasite.

14–20.—Bodies with central pigment clumps or blocks. Presegmenting forms.

21–24.—Larger bodies with central pigment blocks. Presegmenting bodies. Seen in the peripheral circulation during a severe paroxysm.

25–28.—Segmenting bodies from the spleen. Figs. 25–27 represent one body where the entire process of segmentation was observed. The segments, eighteen in number, were accurately counted before separation, as in Fig. 27. The sudden separation of the segments, occurring as though some retaining membrane were ruptured, was observed.

29–37.—Crescents and ovoid bodies. Figs. 34 and 35 represent one body which was seen to extrude slowly, and later to withdraw, two rounded protrusions.

38, 39.—Round bodies.

40.—Pseudo-gemmation, fragmentation.

41.—Vacuolation of a crescent.

42–44.—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. 42. At 4.27 the flagella appeared; at 4.33 two of the flagella had already broken away from the mother body.

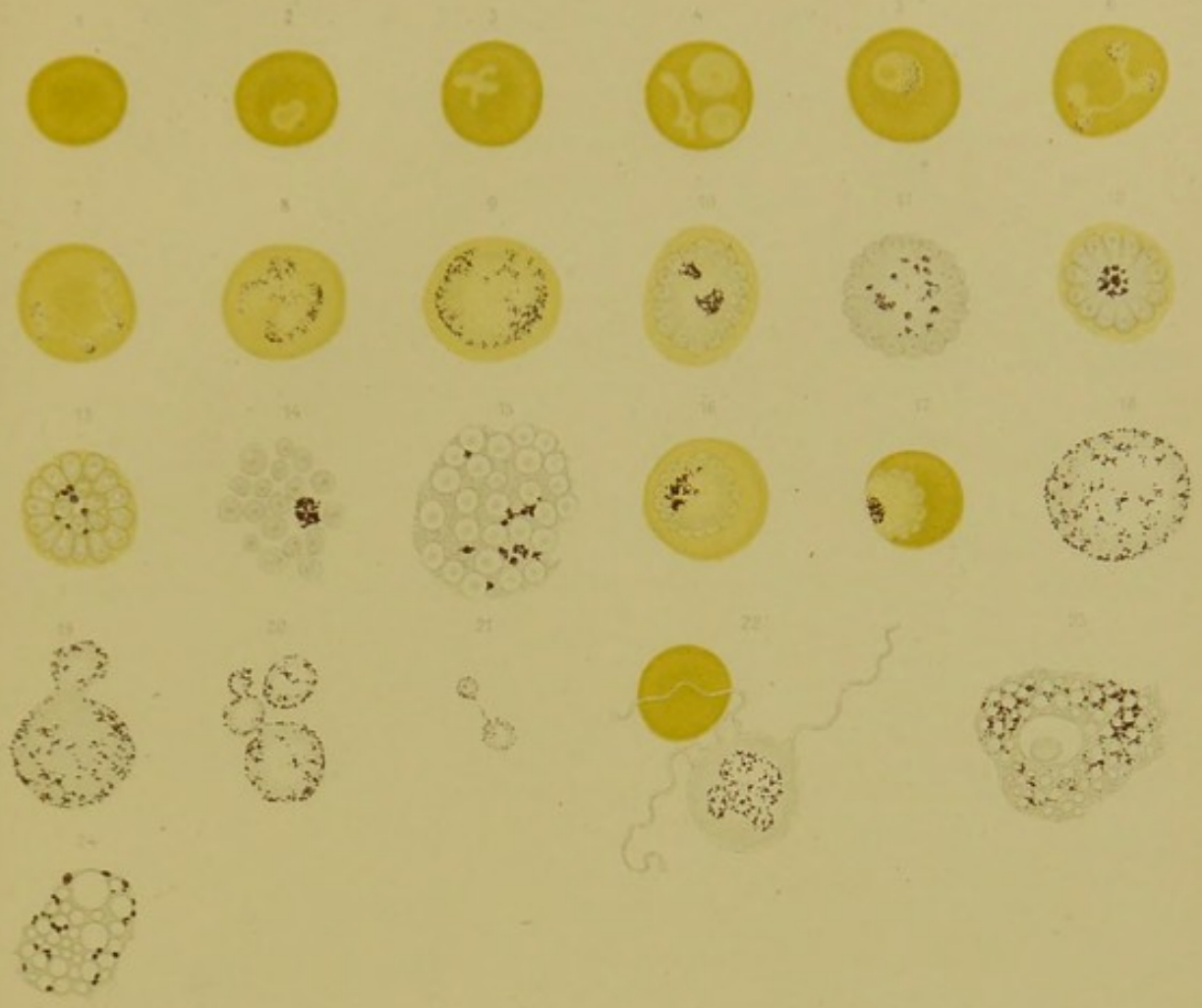
45–49.—Phagocytosis. Traced with the camera lucida.

[1] These plates are taken by permission from *The Johns Hopkins Hospital Reports*, vol. v., 1895. Four figures—viz. Figs. 21, 22, 23, and 24—have been added to Plate II., and are also from the drawings of Mr. Max Broedel.

[2] The color of the pigment in these figures of the quartan parasite has too much of a reddish tint.

PLATE I.

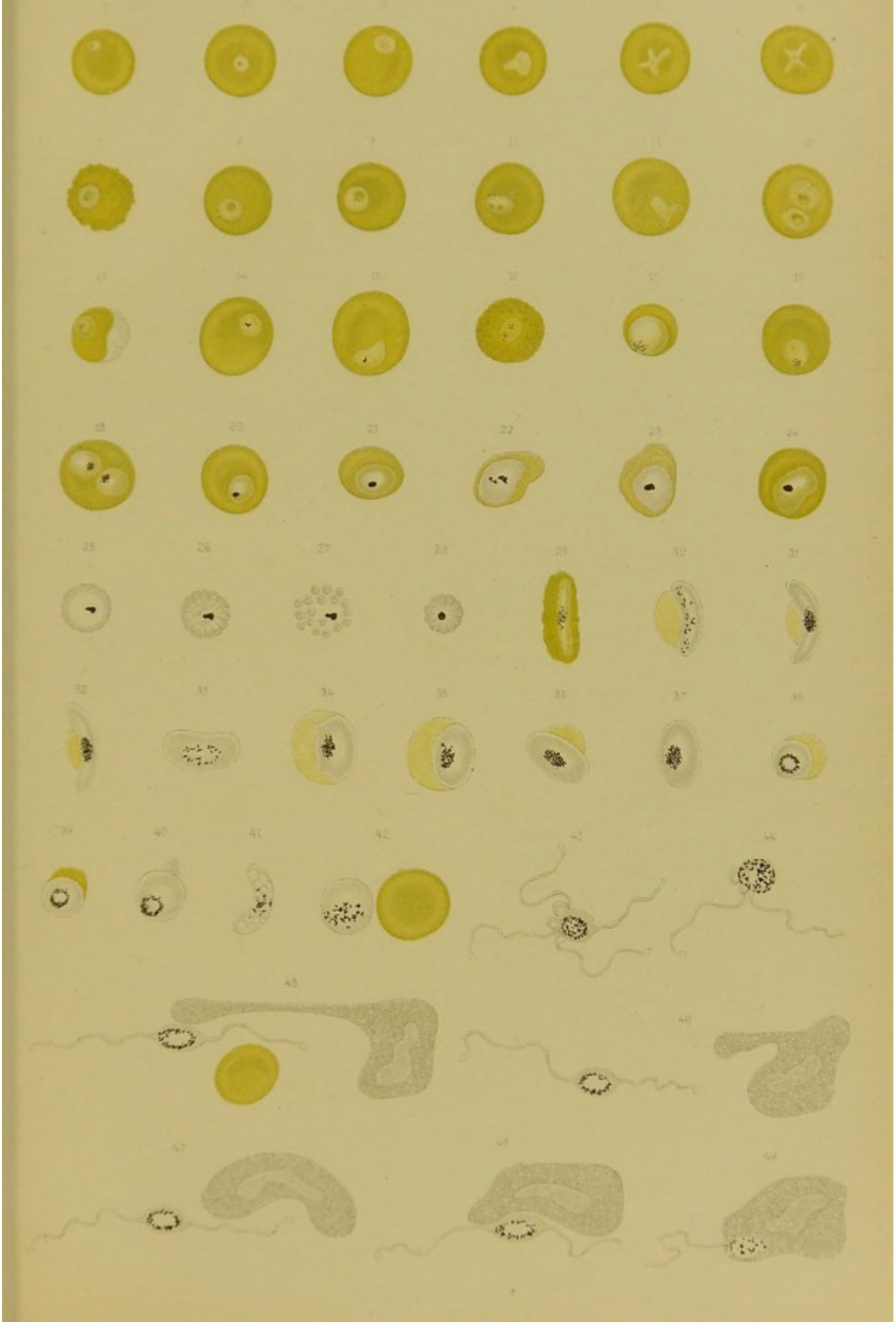
The Parasite of Tertian Fever.



The Parasite of Quartan Fever.

PLATE II.

The Parasite of Aestivo-Autumnal Fever.



ETIOLOGY, PATHOLOGICAL ANATOMY, SYMPTOMS, DIAGNOSIS, PROGNOSIS, AND TREATMENT.

By WILLIAM S. THAYER, M. D.

Etiology.

Distribution.—The malarial fevers are widely distributed, occurring in almost all regions of the earth. There are, however, certain principal foci where the disease is permanently endemic. These regions are chiefly in the warmer temperate and tropical countries. Generally speaking, the farther one departs from the equator the less common are the malarial fevers. A sharp line of delimitation cannot, however, be drawn. Occasionl cases have, according to Celli,[1] been observed as far north as Irkutsk in Siberia, Haparanda in the Gulf of Bothnia (65° N. latitude), Juliushaab, Southern Greenland, and New Archangel in Alaska, while to the south malaria has been reported to exist as far as the isotherm of 60°. It must, however, be remembered in considering any statistics concerning the distribution of malaria that the diagnosis of malarial fever has been, until very recently—and is, alas! far too frequently today—made upon a very insufficient basis. In many regions today an intermittent fever with chills is without further investigation assumed to be of malarial origin, and even at the present time, in some of the large cities of this country, there are official statistics of mortality due to malaria—statistics showing thousands of deaths every year—which are almost absolutely incorrect.

About the main foyers of malaria there is, however, little doubt. In Europe the disease is common in the low lands about the coasts of Italy, Sicily, Corsica, Greece, the Black and Caspian Seas, and in the lands bordering upon the Po, the Tiber, the Danube, and the Volga. About the coast of certain parts of France, Spain, and in Denmark and Sweden, an occasional case is seen. In Holland and Belgium the milder forms of the disease are not uncommon, while a few cases of the same nature are seen in Germany about the mouth of the Elbe and along the Baltic coast of Prussia, in Silesia, the plain of the river Mark, and in Pomerania. In tropical Africa the disease appears in its most severe forms, especially along the West Coast. The chief foyers of the disease in Europe are in Italy and Southern Russia. In India, Ceylon, and in the East Indies it is particularly common, while in Southern and Southwestern China it is also endemic. In Japan the disease is rare. In the Western Hemisphere malaria is seen in the lowlands about the coast from New England to Florida, though above Virginia the severe forms are rare. In the Gulf States and along the banks of the Mississippi and its tributaries, in most of the Southern States, the disease is almost always present. About some of the Great Lakes, both in the United States and Canada, malarial fevers are occa-

[1] *Verhandl. d. X. Internat. Med. Cong.*, Bd. v. Abth. xv. p. 68.

sionally seen, while a certain number of cases are reported from the Pacific coast.

In Cuba, Mexico, and Central America some of the most fatal forms of the disease are met with. The much feared Chagres fever of the Isthmus of Panama is a pernicious malarial infection. About the lowlands of the eastern coast of South America, particularly in the Guianas and in Brazil, the disease is endemic in its most malignant forms. On the west coast it is less frequent, though its occurrence in Peru and Bolivia has been known for years. Indeed, it is from the Peruvian Indians that we learned the value of the specific remedy for the disease. In Australia, New Caledonia, and the islands of the Pacific the disease is very rare, and in some regions, such as Hawaii, Samoa, New Zealand, and Van Diemen's Land, notwithstanding the existence of extensive low marshy tracts, it is quite unknown.

In cases of malarial fever which occur sporadically in regions where the disease is uncommon the infection may often be traced to a previous sojourn in a malarious district. Extensive epidemics and pandemics of malarial fever, spreading over the greater part of the earth, have been described. In most of these instances, however, considerable uncertainty exists as to the true nature of the process.

Physical Geography.—The physical geography of the country has much to do with the prevalence of malarial fever. In the words of Laveran, "The principal foyers of paludism are situated on the coast or along the banks of large rivers." High altitudes are usually free from malarial fever, and the mountains and plateaus in the neighborhood of malarial districts are often used as sanitaria by the inhabitants. The high altitudes may not, however, be a protection, as, according to Hertz,[1] fevers occur in the Tuscan Apennines at a height of 1100 feet, in the Pyrenees at 5000 feet, on the island of Ceylon at 6500 feet, in Peru at from 10,000 to 11,000 feet. It is, however, by no means improbable that many of these fevers which have been called "malarial" are, in reality, of some other nature. This has been shown to be true in the case of the "mountain fever" of the Western States, which is for the most part, probably, typhoid fever.

The Soil.—Low, marshy regions are particularly likely to be malarious; hence the term "paludism" which is so generally used. Mixed salt and fresh water marshes seem to be particularly favorable for the development of the disease. Low, moist, ill drained lands, rich in vegetable matters—lands which have been allowed to fall out of cultivation—are particularly dangerous. All marshy regions, however, even in tropical countries, are not of necessity malarious, an example of this being shown in some of the South Pacific islands, as already mentioned. And, while the disease is particularly common in marshy districts, it may occur in other regions in sandy or clayey soil, or, indeed, in rocky regions. An impervious subsoil is believed to be particularly dangerous.

Effects of Turning up the Soil.—In many instances the denudation of a soil covered by forests or rank vegetation, or the turning up of the soil in a district which was previously free from the disease, may be followed by an outbreak of malarial fever, while in other regions where

[1] *v. Ziemssen's Cyclopædia of the Practice of Medicine*, vol. ii.

the disease already exists similar interference with the vegetation or the soil may greatly intensify the severity of the process. An example of this latter condition is shown in the severe outbreak of malarial fever which was associated with the excavation of the Panama Canal. In Paris, which for many years had been free from paludism, the digging of the Canal Saint Martin, and again, in 1840, the excavations for the fortifications, were, in each instance, followed by an outbreak of characteristic intermittent fever. Irrigation of low lying districts without proper drainage has been followed by an outbreak of malaria or an increase in the severity of the cases. Such a condition of things has been noted in some of the irrigated districts in Southern California.

Effects of Drainage.—Efficient drainage of marshy districts which have been rich in malarial fevers has a marked effect upon the frequency and severity of the manifestations of the disease. Years ago malaria was common in the surroundings of London, which were marshy and ill-drained; today, thanks to good drainage, the disease is unknown. The low lands of Holland used to be the seat of very severe malaria; today, only occasional cases of the mildest forms of the disease occur. The effect of good drainage upon the Roman Campagna has been very striking, the severity of malarial fever diminishing materially.

Cultivation.—The cultivation of many marshy, malarious districts has been followed by a marked improvement in the sanitary condition. The planting of trees has been supposed to have a particularly good effect, possibly because of the drainage of the soil which is thus accomplished. For some time it was supposed that certain trees, particularly the *eucalyptus globulus*, had an almost specific effect in protecting the neighborhood against malarial fever. The advantages of this particular tree have, however, been much exaggerated. Malarial fever never originates at sea. Those cases which have been reported date their infection, unquestionably, to some period before the voyage. There is much to suggest that the soil has some intimate connection with the development of the contagium of paludism.

Variations in Distribution.—One of the most striking characteristics of malarial fever is the manner in which it leaves one region in which it has existed for some time, to appear in another which may, for a considerable period, have been quite free from any manifestations of the disease. This change in the distribution of the disease is in great part due to the activity of man. On the one hand, an outbreak may follow the abandonment or neglect of richly cultivated areas which have been well drained and taken care of, as, for instance, the Roman Campagna in the time of Augustus, while, again, in other regions the turning up of the soil may bring about an outbreak where it is least expected. But this explanation does not answer all cases. The appearance of malarial fevers in the New England States during the past fifteen years, after a long period of almost entire quiescence, is a striking example of these inexplicable changes in location. Again, in districts where malaria is permanently endemic there are often cycles in the severity of the disease which are impossible to explain.

Climate.—Heat and moisture are important for the development of the fever. In malarious districts a very dry season is usually more

healthy. Laveran[1] states that in Algeria the rainy years show a more severe endemic than the dry, while the first "rains of the autumn give rise, almost always, in Algeria to a recrudescence of the fever."

Season.—In tropical countries malaria exists usually throughout the year, but it is almost always most severe in the summer and fall. As one approaches the temperate climate the cases in winter and spring become very rare. Along the eastern coast of the United States, just as in Rome, the cases in the winter are very few, while with the spring a certain number of infections begin to appear. It is, however, not until July that the real malarial season begins. The height of the malarial season is reached in the months of August, September, and October. The following table, showing the number of cases of malarial fever treated at the Johns Hopkins Hospital between January 1, 1890, and January 1, 1894, gives a good idea of the variations in the occurrence of the disease to the seasons of the year:

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

The earliest cases show also the mildest types of infection. Thus, in the spring the first cases are usually tertian or quartan infections. As the season advances double tertian infections become more frequent, while at the height of the malarial season the majority of cases are of the æstivo-autumnal type, the most severe form of malaria. Thus, out of 542 cases analyzed by Hewetson and the author,[2] there were—

	First half year.	Second half year.
Regularly intermittent fevers	113	230
Æstivo-autumnal fevers	5	183
Combined infections	3	8
	121	421 = 542

At the height of the malarial season, during the months of September and October, there were—

Regularly intermittent fevers	109
Æstivo-autumnal fevers	120
Combined infections	5

This observation concerning the variation of the types of the fever with the times of the year is as old as Hippocrates. It has long been popularly supposed that the early cases of fever in the winter and in the spring represent, *in toto*, relapses from infections of the preceding fall, the fevers of first invasion beginning only with the summer months. The analyses of our cases at the Johns Hopkins Hospital tend, however, to show that, while the proportion of fevers of first invasion is less in the spring than in the summer months, yet they do occur.

Winds.—There is much which tends to suggest that the infective agent may be carried by the wind. It has been asserted, for instance, that along the banks of a stream in a malarious district the fevers are often more frequent and severe on the side toward which the prevailing winds blow. Again, in other instances it has appeared that strips of

[1] *Traité des Fièvres palustres*, Paris, 1884, p. 8.

[2] "The Malarial Fevers of Baltimore," *Johns Hopkins Hospital Reports*, vol. v.

forest land have arrested the spread of the disease, suggesting that some infectious substance may be filtered out by the trees. Thus, Lancisi believed that it was through the influence of the winds that the Roman Campagna became more unhealthy after the removal of the sacred groves. These, he believed, acted as a protection by filtering from the air infectious substances carried by the winds which blew over the Pontine marshes.

ALTITUDE.—It has been repeatedly observed that in malarious districts the dangers of infection are much greater close to the ground. Sleeping upon the ground is particularly dangerous. The upper stories of a house are safer than the lower. Infection appears to take place more readily by night than by day.

DRINKING WATER.—Many have laid, and still do lay, much stress upon drinking water as the source of the disease. The experiments, however, of Celli,[1] Marino,[2] and Zeri,[3] who caused individuals to drink in large quantities water which was obtained from the most malarious districts, without any bad effects, and of Grassi and Feletti,[4] who fed individuals upon dew collected from malarious regions, with similar negative results, are strong arguments against this idea. It should be remembered, however, that while these experiments are strong evidence that the malarial poison is not introduced through the drinking water, yet it is no proof that water may not contain the parasite, or, indeed, form an actual culture medium for some forms of the organism. We are wholly ignorant of the manner of entry of the parasite into the system, of the form in which it exists outside of the body, or of the changes which it may pursue in other media than the circulating blood. It is not impossible to imagine a body which might pursue a part of its development in water, reaching its truly infectious form only in a later stage and in some other medium.

Grassi and Feletti have shown that the living parasite from the circulating blood does not, when ingested, cause fever. Thus, they caused an individual to drink the fresh blood of a malarial patient without result, while inoculation experiments with similar blood are almost always positive. (See page 34.)

RACE.—In many malarial districts the natives—negroes, Arabs, Indians, Tamils—appear to have a relative insusceptibility to the disease, the degree of which varies in different localities and according to different authors. Our observations in Baltimore would tend to show that here the susceptibility of the negro is only about one third that of the white.

OCCUPATION.—The occupation has much to do with susceptibility to the disease. Soldiers and tramps who sleep upon the ground in malarious districts are particularly susceptible. Fishermen in the bays and inlets along the southern coast of the United States, as well as farmers and berry pickers in the same regions, are particularly open to infection.

AGE has apparently no effect upon the susceptibility, excepting in so far as the very young and the very old are less likely to be exposed.

[1] *Bull. d. Soc. Lanc. d. Roma*, 1886, vi. 1, 39 (5 Dec., 1885).
[2] *Riforma Medica*, 31 Oct., 1890, No. 251, 1502.
[3] *Bull. d. R. Acc. Med. di Roma*, 1889–90, xvi. 244.
[4] *Centralblatt für Backt.*, 1891, ix. 403, 429, 461.

Predisposing Causes.—It is generally believed that in malarious districts almost anything which tends to diminish the vitality of the patient acts as a predisposing cause to malarial infection. It is often asserted that where a previous attack has existed injuries of various sorts are particularly likely to be followed by a relapse of the malaria. It has been asserted, for instance, that an injury to the spleen in a patient who has formerly had malarial fever may call forth a relapse. With regard to the effects of traumatism, the observation of nearly a thousand cases during the last five or six years has not given any positive answer, while the complications of malaria with other acute diseases have been, perhaps, rather surprisingly infrequent. It seems reasonable that trauma or operation, by reducing the condition of the patient, should render him more susceptible to a fresh malarial infection or more liable to a recrudescence of an already existing process. The fact, however, that in nearly seven years not a single case of post-operative malaria has occurred in the Johns Hopkins Hospital has led us to believe that many of the chills occurring under these circumstances, generally supposed to be malarial, are probably, in reality, septic in origin.

Manner of Infection.—The discoveries of Laveran have revealed to us the infectious agent in malaria, while its specific action has been abundantly demonstrated by clinical observation and inoculation experiments. And yet it must be confessed that we are wholly ignorant as to the manner in which the parasite exists outside of the body or how infection takes place. The most important points of entry into the system which have been suggested are—

(1) The respiratory tract;
(2) The digestive tract;
(3) The skin (insect bites, etc.).

(1) There is a very general belief that infection may take place through the respiratory tract, though positive proof of its occurrence is as yet wanting. In favor of this view are the observations of Lancisi and others concerning the winds.

(2) Many observers, as has been said, still believe that the parasite is introduced chiefly through the digestive tract. The observations, however, of Celli, Marino, Zeri, Grassi and Feletti, already referred to, are very suggestive evidence against this idea.

(3) The inoculation experiments referred to in the description of the parasites have given positive proof that infection may take place when the parasite is introduced beneath the skin. This renders more plausible the old idea that insect bites may sometimes serve to convey the contagium. In this connection one may remember the remarkable observations of Theobald Smith,[1] who has shown that the hæmocytozoön of Texas fever in cattle (*Pyrosoma bigeminum*) is conveyed from animal to animal by means of the cattle tick (*Boöphilus bovis*).

Experimentally it has been shown that although infection through the alimentary tract is improbable, subcutaneous infection is possible, while clinical observation is strongly in favor of the view that infection through the respiratory tract may occur.

[1] U. S. Dept. of Agriculture, Bureau of Animal Industry, *Bull. No. 1*, Washington, 1892.

In Summary.—The malarial fevers flourish in low, moist, hot regions, the borders of rivers and marshes, places where the water is brackish being particularly dangerous. High, dry, sandy, or rocky regions are rarely malarious. In a malarious district there is greater danger of infection near the ground, by night than by day. There is suggestive evidence that the contagium may be carried by the winds. Age has no marked influence on the susceptibility. The negro is relatively much more insusceptible than the white. The manner of existence of the parasite outside the body and the manner in which the infection takes place are still wholly unknown.

Pathological Anatomy.

(1) Anatomical Changes in Acute Malarial Infections; (2) Changes following Repeated or Chronic Infections.

Cases of the regularly intermittent fevers are so rarely met with upon the autopsy table that our knowledge of the pathological changes present in the internal organs are largely based upon a study of the cases of pernicious æstivo-autumnal fever. Our knowledge of the pathology of the malarial fevers has been greatly increased in late years by the investigations made since the discovery of the parasite by Laveran, Councilman and Abbott, Guarnieri, Dock, Bignami, Barker, and Monti. One of the most interesting points which at once strikes the careful observer is the extreme variation in the distribution of the malarial parasites in the body, and the anatomical changes produced by them in different cases. This difference in the localization of the parasites and in the seat of the important anatomical changes may bear, as has been pointed out in the description of the parasite, a direct relation to the symptoms which have existed during life.

The most striking point in the appearance of the organs in malarial fevers is the melanosis which gives a characteristic slaty gray color to many of the organs. This results from the accumulation of the pigment produced by the parasites from the hæmoglobin of the blood-corpuscles, and, while almost invariably present, its distribution, as in the case of the parasites, and the degree in which different organs are affected, varies considerably in different cases.

The Brain.—The most striking changes in the brain are to be met with in the cases of comatose pernicious fever. The brain may be the seat of but few macroscopical changes. Melanosis may be entirely absent. At times, however, there may be a slight subpial œdema with hyperæmia of the cerebral substance, and perhaps punctate hemorrhages; more commonly, however, the gray cortex shows a slaty or chocolate color, which may be quite deep. The vessels are markedly injected, and in places, as has been said, punctate hemorrhages may be found. In these instances the microscopical appearances are most striking. The cerebral capillaries are crowded with parasites, which are, for the most part, within red corpuscles, and may form an actual complete injection of many of the cerebral vessels. This is generally most striking in the gray substance. These parasites (usually of the æstivo-autumnal type) may be in all stages of development, though generally one of the stages is most marked. Sometimes in cases where

death has occurred during the paroxysm actual thrombi of segmenting organisms may exist. Sometimes the organisms may not be so numerous, but evidence of their previous existence is found in free clumps of pigment and swollen pigmented endothelial cells, as well as leucocytes containing pigment and red blood-corpuscles. There is usually decided granular and fatty degeneration, and often pigmentation of the endothelium of the vessels—a change upon which the punctate hemorrhages probably depend. Some endothelial cells may be greatly swollen, almost occluding the lumen of the vessels: these, as has been demonstrated, especially by Monti, may contain a considerable number of apparently well preserved parasites in various stages of development; they may be within shrunken or brassy corpuscles or full grown and free. Occasionally large macrophages are seen almost occluding the capillary, which appear, according to Monti, to be endothelial cells which have broken loose and are free in the current.

These lesions are particularly marked in the comatose form of pernicious malaria. In some instances different parts of the central nervous system may be differently affected. In one case, for instance, studied by Marchiafava,[1] where the patient died with symptoms of bulbar paralysis, a special localization of the changes was noted in the medulla. In other instances the cerebral lesions may be slight; the collections of parasites in the capillaries, as well as the degenerative changes in the endothelium, are not to be made out.

Monti[2] has recently studied the changes in the nerve cells in the gray cortex in pernicious malaria, according to Golgi's method, with interesting results. In some cases these elements were, so far as could be made out, quite normal, while in others interesting changes were noted: these cases were chiefly those showing grave nervous symptoms, such as coma, during life. The alterations were not uniformly diffused throughout the cortex, and never affected all the elements in a given zone. Usually cells more or less profoundly altered were found among other cells and fibres which were quite normal, although a tendency to a focal arrangement of these changes could be made out. The alterations affected chiefly the protoplasmic prolongations of the nervous cells of the cerebral cortex. Sometimes the prolongations appeared thinned and studded with fine nodes. Not infrequently these alterations were limited to the more delicate and distant branches, though it was not difficult to find cells of which all the dendrites presented the beaded appearance which is so well observed in the nerve cells of animals dead of inanition. In other points the alterations consisted of simple irregularities of contour in dendrites which were much thinned, extending from cells the bodies of which were sometimes normal, more often swollen, rarely thinned, shrunken, or atrophic. Coarser alterations were, however, not wanting. Cells were found whose dendrites showed coarse varicosities and very marked constrictions, so that they appeared as if formed of masses of protoplasmic matter connected only by the finest filaments of protoplasm. Similar changes were observed in the brains of animals in which embolisms were produced by the injection of lycopodium.

[1] *Lav. del. III. Cong. del. Soc. Ital. di Med. Int.*, Roma, 1890, 142.
[2] *Bull. d. Soc. Med.-Chir. di Pavia*, 1895.

In most of Monti's cases the axis cylinders were well preserved; the principal lesion appeared to consist in alterations of the protoplasmic prolongations. In some cases, however, especially in one severe case of comatose pernicious fever, certain alterations were to be made out in the axones. In this case the alterations of the nervous elements appeared more marked throughout the brain than in the other cases; the alterations in the dendrites were more frequent and marked, while the nervous prolongations also, had, in many points, lost their normal character. Instead of being smooth and regular as usual, they presented sometimes small nodes, more rarely larger swellings. Also, among the axones, as well in the cerebral cortex as in the cerebellum, there were occasionally varicosities. The alterations of the nervous fibres were, however, always less marked than those of the dendrites.

Monti believes that these changes are due to the grave circulatory disturbances, the occlusion of capillaries, lesions of their walls, the stasis, and the hemorrhages produced by the malarial parasites. It may be noted that many of these changes are not dissimilar to those described by Dr. Berkley in animals after the injection of ricin.

THE SPLEEN.—The spleen is always enlarged; there is a pronounced "acute splenic tumor." The capsule is tense. The parenchyma is cyanotic and sometimes is of a markedly slaty gray color; it is soft and is often almost diffluent. In acute malaria death may occasionally occur from rupture of an enlarged spleen. Microscopically, the pulp contains enormous numbers of red corpuscles, many of which contain parasites. These parasites may be in various stages of development. Sometimes, in the same organ, different areas show separate groups of parasites in different stages of development. Generally the pigmented and segmenting forms may be found in large numbers. Free forms of the parasite are relatively rare. One of the most striking appearances in the splenic pulp is, however, the presence of great numbers of phagocytes, some smaller and apparently leucocytic in nature, others very large cells, rich in protoplasm, containing a single large nucleus and occasionally a coarse granulation. These cells may reach an enormous size. They are laden with pigment, either in large clumps or spheres, in rodlets, or in very fine granules; the granules sometimes present the same arrangement which they had in the body of the parasite. The fine pigment may be distributed in delicate lines throughout the whole mass of protoplasm of the phagocyte; it often seems to vary in its color in different parts of the cell, but on focussing this appearance is found to be due to differences in plane. These large cells also contain red corpuscles, which are often partially or completely decolorized and contain parasites; and, finally, entire smaller phagocytes with their included pigment or corpuscles, as well as clumps of hæmoglobin of the color of old brass and fragments of degenerated red corpuscles. Golgi and Monti have called particular attention to the frequency with which these macrophages contain apparently well preserved parasites in different stages of development. They believe that the shrunken and brassy parasitiferous red corpuscles are engulfed in the phagocytes as would be any foreign body, while the included parasites continue their development within. Some of these macrophages may show evidences of necrosis. In some cases one may find in the pulp actual focal necroses, very much

like those which may be seen in typhoid fever. These changes have been well described by Barker.[1]

There may be malarial pigment free in the intercellular spaces in the pulp. Pigmented polymorphonuclear cells are relatively rare; the small mononuclear elements and the lymphocytes of the follicles never contain pigment. The capillaries are usually filled with corpuscles containing parasites, while the splenic veins show relatively few, though they always contain phagocytes containing pigment and fragments of blood-corpuscles.

The Liver.—The liver is often of an intense slaty gray color, which depends upon the enormous numbers of parasites and of pigment contained in the capillaries. The distribution of the pigment is different, as will be pointed out later, in this acute malarial infection from that characteristic of repeated attacks. There is always a marked cloudy swelling. Microscopically, the capillaries are often crowded with leucocytes and contain numerous phagocytes; some of the largest macrophages are here observed. Not infrequently the endothelial cells may be also observed to show evidences of phagocytic action. The perivascular tissue in the portal spaces may show numerous pigment bearing cells, while frequently liver cells may be found to contain clumps of pigment derived from the blood and altered red corpuscles. This condition, similar to that observed in pernicious anæmia, accounts, doubtless, for the polycholia and the subicteric hue so commonly observed in the malarial fevers. Ordinarily relatively few parasites within red corpuscles are to be found within the vessels: these are more numerous in the interlobular branches of the portal vein. In the intralobular veins one more often sees the macrophages.

Among the most interesting changes to be noted in the liver are occasionally occurring disseminated areas of local necrosis of the liver elements with fragmentation of the nuclei, wandering in of leucocytes, and sometimes with evidences of proliferation of cells in the surrounding tissue. These changes are very similar to those already noted in typhoid fever and other acute infectious diseases, and proven by Welch and Flexner[2] to be produced in diphtheria, and by Reed[3] in typhoid fever, by a circulating toxic substance. The occurrence of these foci in the liver was first described by Guarnieri,[4] who ascribed them to the cutting off of the nutrition by the extensive blocking of the intralobular capillaries with pigment bearing phagocytes. Barker[5] describes and pictures capillary thromboses in association with many of these areas.

The Lungs.—The alveolar capillaries show, generally, large numbers of phagocytes, which are, however, smaller than the largest macrophages of the liver and spleen. Their substance may show evidence of necrosis. Occasionally pigment may be found in the endothelial cells of the capillaries and small veins, but much more rarely than in the capillaries of the brain or of the liver. Leucocytes containing malarial pigment are seldom found in the interior of the alveoli. Mononuclear phagocytes are much more frequent than ordinary polymorpho-

[1] *Johns Hopkins Hospital Reports*, vol. v., 1895.
[2] *The Johns Hopkins Hospital Bulletin*, No. 20, March, 1892.
[3] *Johns Hopkins Hospital Reports*, vol. v., 1895.
[4] *Atti della R. Acc. Med. di Roma*, 1887, s. ii. v. iii. 247–266. [5] *Loc. cit.*

nuclear leucocytes, which, when present, contain, usually, finer, smaller particles of pigment. The macrophages are generally collected about the periphery of the smaller veins. The endoglobular parasites show, usually, all stages of development. The endothelium of the capillaries and small veins rarely contains pigment, in sharp contrast to the condition existing in the brain. It is striking that the areas of bronchopneumonia, which are not infrequently found, contain only the ordinary polymorphonuclear leucocytes and alveolar epithelial cells, pigmented elements being very rarely present. The capillaries of the septa may, however, be filled with pigment and macrophages. Bignami suggests that this fact is due to the diminished vitality of the pigment bearing cells, which have, to a certain extent, lost their motile power and are thus less able to pass through the vessels.

The Kidneys.—The changes in the kidneys in acute malaria are usually much less marked than in the liver and spleen. Their gross appearance varies but little from the normal. Evidences of pigmentation are usually wanting on gross examination. The malarial parasites and phagocytes are usually present in smaller numbers, the quantity being disproportionately small in comparison to the alterations of the parenchyma which are sometimes to be found. The glomeruli, however, are ordinarily considerably pigmented, the pigment at times being seen within large white cells within the vessels, sometimes in the glomerular endothelium. Endoglobular parasites are rarely seen in the capillaries of the glomeruli; they are more common in the intertubular vessels, but are rare even there. The most important lesions consist in exfoliation and degeneration of the epithelium lining the capsules. Albuminous exudates within the glomeruli were found by Bignami only in algid pernicious fever. At times, however, there may be marked alterations in the parenchyma—to wit, focal necroses of the epithelium, especially that of the convoluted tubules.

The changes in the kidneys in cases of hæmoglobinuric fever have been described by Pellarin,[1] Benoit,[2] Kiéner, and Kelsch.[3] The kidneys are somewhat increased in size, the color varying from a deep reddish brown to a light yellowish brown coffee color in more anæmic individuals. When the color is pale, irregular pinhead points and blotches of a maroon color are to be seen upon the surface, some as large as several millimetres in area. They are also scattered throughout the cortex. These have been shown by Kelsch and Kiéner to be due to pigment deposits; they are not visible in more congested kidneys. The pyramids are of a deep red color from intratubular hemorrhages. The capsule is easily detached; the consistency of the gland is normal.

Microscopically, the epithelium of the convoluted tubules and of the large branches of Henle's loops are very opaque, the nuclei being scarcely visible. This is due to an infiltration of the protoplasm with a diffuse coloring matter and fine pigment granules which are rendered more evident by KOH. These granules are extremely small, and separately appear of a yellowish color, while *en masse* they have a brown shade. The epithelial cells are swollen and bulge into the lumen of the canal. Occasionally a cell shows a hyaline protrusion which seems on

[1] *Arch. de Méd. nav.*, 1865. [2] *Ibid.* [3] *Arch. de Phys.*, 1882.

the point of escaping. In some tubes the epithelial covering is represented only by a thin protoplasmic layer with a homogeneous surface, appearing as if eroded down to the level of the nuclei. The lumen of the tubule is filled with clumps of amorphous material or casts mixed to a greater or less extent with this pigment. The brown specks and blotches seen macroscopically represent groups of tubules, the epithelium and lumina of which are crowded with similar masses of pigment; but pigment may also be found in larger granules—granules nearly as large as a red blood-corpuscle, and more or less spherical; they are refractive, of a color varying from a yellow ochre to a deep brown, and are sometimes accumulated in epithelial cells which bulge so as to almost occlude the lumen. Sometimes they occupy the lumen and form conglomerations, taking the shape of casts; sometimes they are fused into a vitreoid mass. Between the opaque dark casts formed by the fine brown granulations and the almost vitreoid casts composed of the large orange colored granulations every intermediate stage may be seen in the same preparation. Generally this pigment gives no reaction for iron, though Kelsch and Kiéner have obtained this reaction from certain granules in one case. The finely granular substance is found, according to these authors, more particularly in cases where death has occurred in a pernicious paroxysm, while the larger forms of pigment are more frequent in cases of longer duration. In the glomeruli, as well as in the blood, Kelsch and Kiéner have never seen the large variety of granules, though the finer granules are numerous. Between the glomerulus and capsule, usually near the mouth of the tubule, there is often quite a collection of granules, which are also found sometimes in epithelial cells, sometimes free. In the glomerulus itself one may see fine granulations disseminated in its substance and apparently included in the cells of the capillary walls. More rarely granulations may be accumulated in a capillary loop. In some cases there are small interstitial hemorrhages. The pyramids show few changes. The same varieties of casts as noted above may be found, and the same pigment collections. The epithelium is usually intact, though sometimes protruding and vesicular cells suggest that they may take part in the formation of hyaline material. Almost invariably a number of the tubes are found filled with blood-corpuscles.

The Gastro-intestinal Tract.—The stomach and intestines show, under ordinary circumstances, few changes beyond the melanosis. It is to be remembered, however, that the intestinal mucous membrane may be of a dark steel gray color in conditions other than malaria. Microscopically, one may see a considerable number of parasites, especially of the full grown and segmenting varieties, in the capillaries of the mucous membrane, together with numerous pigmented cells and apparently few pigment clumps. In most cases, however, the gastro-intestinal mucous membrane is not particularly sought by the parasites.

In other instances, as pointed out by Marchiafava and Bignami, this region may be the seat of the main localization of the affection. Macroscopically, there may be intense hyperæmia with punctate hemorrhages in the gastro-intestinal mucosa. In one instance observed by the author there was a distinct dusky slaty tinge as well. Here the capillaries throughout the gastro-intestinal tract may be crowded and blocked

with parasites, free and contained in the red corpuscles or in phagocytes. As in the case of the brain, actual thromboses may exist with necrosis of the epithelial covering and ulceration. Cases of this nature are associated frequently with marked gastro-intestinal symptoms, some showing a clinical picture very similar to that of Asiatic cholera.

The Bone Marrow.—The marrow is generally of a dark slaty color; it is often almost black. The small vessels are filled with endoglobular pigmented parasites, while numerous macrophages containing pigment and red blood-corpuscles may be found about the periphery of the lumina of the vessels. At times, between the corpuscles, Bignami[1] found numerous ovoid or round bodies which, from their size and staining propensities, he believed to be free spores. Not only in the vessels, but also outside of these, the parasites are to be found in greater or less number. The macrophages are, however, especially numerous, even in the pulp. At times also free pigment clumps are apparently to be made out.

The adrenal glands may be the seat of pronounced alterations. There are irregular areas of vascular dilatation, parasites being numerous in the distended vessels. Macrophages with varying contents may be present in considerable numbers. The endothelial cells of the vessels may be phagocytic, and malarial pigment and infected corpuscles may even be enclosed by true adrenal cells.

In the other organs there is little that is characteristic.

(2) Changes following Repeated or Chronic Infections.—Chronic Malarial Cachexia.

While the above mentioned changes are found in the acutely fatal cases of malaria, interesting pathological changes may occur in various organs as the result of long continued or frequently repeated attacks. The most important of these changes occur in the spleen, the liver, the bone marrow, and the circulating blood.

The Spleen.—The spleen is always considerably enlarged; it may be enormous, reaching beyond the umbilicus and as low as the pubes. It is firm and hard; the border is sharp. The capsule is usually much thickened, and white fibrous cartilaginoid plaques occur upon the surface. On section it has often a somewhat slaty color, while the trabeculæ are very prominent.

The minute anatomy and development of the changes in the viscera, following repeated malarial attacks, has been followed with particular care by Bignami,[2] upon whose valuable work we shall largely trespass in the following description. The acute splenic tumor is caused chiefly by the aggregation in the pulp of the spleen of an enormous number of red corpuscles which have become either shrunken and brassy colored or decolorized, and are found included in the colorless elements of the spleen as brassy colored fragments or hyaline masses; by the continuous aggregation of colorless elements containing pigment, red corpuscles, or parasites, which collect from all parts of the body, and many of which are necrotic; and, thirdly, by great numbers of red corpuscles containing parasites, some of which apparently pass through the vessel walls

[1] *Atti d. R. Acc. Med. di Roma*, Anno xvi. v., 1890.
[2] *Bull. d. R. Acc. Med. di Roma*, 1893, Anno xix. f. 4, p. 186.

by diapedesis and seek the columns of the pulp, where they are for the most part enclosed by the epithelioid elements. While, as a result of this proceeding, a considerable number of the proper elements of the spleen become necrotic, others, as well in the pulp as in the follicles, undergo karyokinetic division, while all this is followed by a marked hyperæmia and acute tumor of the splenic pulp. Thus the spleen is converted into a place for the deposit of cadavers, while at the same time, during the same infection, processes of regeneration have begun to appear.

When the actual infection is at an end and the acute hyperæmia of the spleen has ceased, the tissues in the neighborhood of these collections of necrotic elements, or those surrounding the necrotic areas of the splenic pulp, show certain changes which, on the one hand, tend to produce permanent alterations, and on the other to lead to a partial reparation of the part. In those parts where a considerable portion of the splenic tissue becomes necrotic or disappears, being carried away by the lymphatics, the splenic vessels become considerably dilated, forming a network of venous lacunæ which are separated by thin layers of pulp. This results in a tissue simulating that of an angioma. In those cases where a more marked destruction of the splenic tissue has occurred, and where every trace of the pulp is gone, parts become represented by extensive areas of tissue which consist of wide cavernous sinuses, the septa of which are composed of a very delicate connective tissue, rich in giant cells, similar to that of the bone marrow. Some of the follicles become necrotic and fibrous. While this occurs a process of regeneration yet more extensive takes place, starting for the most part from the follicles, but also sometimes from the splenic pulp. The follicles become hyperplastic, reaching sometimes three or four times their normal size. This new form of lymphoid tissue, starting from the follicles, may be sometimes seen to surround necrotic areas of splenic tissue which become smaller and smaller and finally disappear. In the neighborhood of these hyperplastic follicles occurs a hyperplasia of the true elements of the pulp, while the reticulum becomes thickened so as to give rise, in preparations, to very beautiful and clear figures, such as are not to be seen in the normal spleen. The pigment and probably the greater part of the necrotic elements are carried on toward and collected about the periphery of the follicles, so that the diffuse melanosis of the pulp is followed by a perifollicular melanosis. The pigment then passes on into the lymphatic vessels of the sheaths of the arteries and of the connective tissue of the septa. This results, on the one hand, in thickening of the vascular sheaths and of the septa, and, on the other hand, in the appearance of single or multiple lymphatic cysts, giving sometimes the picture of a lymphangioma and resulting in chronic lymph stasis.

When we consider that after each new infection fresh processes similar to these must occur, it is easy to understand the gradual development of the enormous splenic tumors, in which, sometimes, it is difficult, even histologically, to recognize the original structure of the organ.

The Liver.—The changes occurring in the liver in chronic malaria may in the same manner be traced from those occurring in the acute infection. In the acute infection an enormous number of phagocytes, pigmentiferous or globuliferous, coming in great part from the spleen,

invades the capillary network of the liver, while the parasites are generally scanty. The circulation is slowed, the capillary network becomes dilated, while a certain amount of pigment is taken up by the endothelial cells of the vessels, and later by Kupffer's cells. The pigmented endothelium becomes swollen and in part necrotic. These vascular changes are followed by new areas of blood stasis. At the same time, as has been noted, many of the liver cells suffer alterations, either undergoing an acute atrophy from pressure or a coagulative necrosis. These areas are sometimes quite extensive. In other instances many cells are found to be filled with blocks of yellowish iron-containing pigment, resulting from the early death of many red corpuscles. At the same time a certain number of liver cells, Kupffer's cells, and endothelial cells multiply by karyokinesis. The result of all this is the acute hepatic tumor and the increase in functional activity—polycholia.

But a small part of the great number of pigmented elements which enter the liver escape, passing through the branches of the suprahepatic veins. The greater part is taken up by endothelial and perivascular cells, so that the melanæmia is followed by a melanosis of the vessels. The pigment then passes forward out of the capillary network into the perivascular lymph channels, where it is collected in large blocks enclosed in white cells. These carry the pigment following the lymph channels to the periphery of the lobules, and perilobular melanosis follows thus the interlobular melanosis. This process then extends, and the masses of pigment are to be found three or four months after the end of the infection in large blocks, for the most part endocellular, in the perivascular lymphatic tissue of Glisson's capsule.

While this migration of pigment is going on in the lobule there occur, on the one hand, permanent alterations, and on the other hand regenerative processes. Where the dilatation of the lymph and blood-vessels and the degeneration and pigmentation of the vascular elements is most marked and extensive, no regeneration may follow the atrophy and necrosis of the endothelial and liver cells. The dilatation of the vessels increases and becomes permanent. The greater part of the remaining liver elements disappears; only a few remain in an atrophic condition, the tissue showing an angioma-like appearance consisting of ectatic vascular network, about which may be recognized a stroma consisting of Kupffer's cells. Where the dilatation of the lymph vessels is most marked there may occur small lymphatic cysts.

In all parts of the liver, when the normal blood current has been restored after the disappearance of the pigment and the necrotic masses in general from the endothelial cells of the vessel walls, an active regeneration of the tissue elements occurs about the atrophic or necrotic liver cells. The young hepatic cells become arranged with great regularity in long rows on both sides of the old elements. Thus, when the stroma remains intact, an interlobular regeneration may occur. These regenerative processes are accompanied by the appearance of giant cells with budding nuclei, just such as are found in the embryonic liver. The regeneration never appears in parts of the liver that have not been entirely freed from the collections of pigment and parasites.

The migration and collection of the pigment in the perilobular tissue is followed by a hyperplasia of this tissue, so that the surroundings of

the lobules are more distinct. These de- and regenerative changes result, then, in a marked increase in the size of some lobules and a diminution in size and an atrophy of others. As this process accompanies each acute infection, one can readily understand the chronic perilobular, monolobular hepatitis of malaria, which is characterized by the presence of zones of hyperplasia or of atrophy of the parenchyma, by chronic blood and lymph stasis, by the formation of areas of angiomatoid tissue, by lymphectases and lymphatic cysts. In this manner the large liver tumors which are so well known, with smooth surface and lobules of irregular size, have their origin.

Bignami divides the processes in the liver into four stages:

(1) The liver appears congested, while the lobules are not sharply distinguishable and show in severe cases a decreased melanosis. The macroscopical characters are about the same as those of the liver in acute malarial infections. Microscopically, at this period, a little after the termination of the acute infection, it may be noted that the parasites have disappeared from the capillaries of the liver, the pigmented endovascular macrophages have in great part gone, and the pigment is entirely collected in the endothelium and in Kupffer's cells. Those parts of the hepatic lobules in which necrosis or degeneration has occurred undergo a marked atrophy; the necrotic and degenerate elements are carried away in the phagocytes, while the vascular network becomes dilated.

(2) In a more advanced stage on gross examination the lobules are distinct. The melanosis continues to be diffuse throughout the lobule, but is more marked at its periphery. The organ is still congested. The particular features of this stage are that, on the one hand, the hepatic lobule frees itself from the accumulation of pigment and the necrotic remains, which become collected toward the periphery of the lobule, while, on the other hand, an active process begins which tends toward a partial regeneration of the parenchyma.

(3) In this stage the diffuse melanosis of the lobule, with the greater prevalence of pigment toward the periphery, is succeeded by an exclusively perilobular melanosis. The liver is enlarged, the consistency somewhat increased, the surface smooth. On section one may see that all the lobules are surrounded by a slate colored line, in the neighborhood of which the coloration of that part of the lobule is somewhat brown. In general, the slaty lines marking out each lobule form an exquisite network. The size of individual lobules varies greatly: some are two or three times the normal size, others are markedly diminished. Microscopically, it may be observed that the degenerative alterations of some lobules have led to the formation of false angiomata and of lacunæ or cysts of lymphatic nature. Other lobules, by the process of regeneration already described, have increased notably in volume. The pigment has become extravascular; its transport through the capillaries and perilobular lymphatics is brought about by white mono- and polymorphonuclear cells.

(4) In cases in which the acute infection has passed for several months (in one case three months only) the pigmentation is greatly diminished and scarcely visible to the naked eye. The liver is notably enlarged and congested. The surface is smooth. On section one may see the lobules distinctly marked, surrounded by a most delicate red-

dish brown border; the consistency is somewhat increased. Microscopical examination shows that the melanosis has become exclusively perivascular.

(5) Lastly, one arrives at the definite terminal form of the chronic malarial hepatic tumor. The macroscopical characters are the following: The liver is increased in size and in weight, sometimes enormously; the surface is smooth, the capsule a little thickened. On section the appearance is finely granular, the lobules are distinct, a little prominent, and surrounded by a zone of slightly pinkish tissue. Microscopical examination shows the disappearance of all malarial pigment. The alterations of the parenchyma are similar to those described in the last two stages. The lobules of varying size are surrounded by a hyperplastic perilobular connective tissue. The connective tissue of the larger septa is, on the other hand, of about normal volume. A notable dilatation of the capillaries, with stasis of the colorless corpuscles, persists. The hepatic cells are altered in form in the zones where the dilatation is most marked. There is considerable difference in individual cases in the extent of these various lesions. There are cases, for example, in which, despite the enormous increase in the weight of the organ, there may be no very marked dilatation of the capillaries, nor are false angiomata or lymphatic cysts to be found, while, on the other hand, the hyperplasia of the perilobular connective tissue and the increase in volume of many lobules may be more marked: there may be an evident hyperplasia of the parenchyma (hepatic cells with many nuclei and nuclei rich in chromatic substance). In other cases, on the other hand, the cysts and false angiomata may be enormously developed, so as to constitute one of the chief factors in the enlargement of the liver.

The Bone Marrow.—In individuals who have had numerous relapses of malarial fever the marrow of the long bones—for example, of the femur in the upper and lower fourths—is usually red and of a consistency greater than is generally seen in acute infections. The microscopical alterations are various; generally the signs of an active proliferation of the proper elements of the marrow are present. This leads to an increase in the hæmatopoietic activity. There are factors, however, such as the degenerative and destructive alterations which take place in the bone marrow during acute infections, which injure, to a varying extent and through a varying length of time, the hæmatopoietic functions of the marrow. In other cases, very rare indeed, the bone marrow presents the macroscopical and microscopical features which exist in acute pernicious anæmia, particularly the presence of a considerable number of megaloblasts. Lastly, there may be cases in which the new formation of the hæmatoblastic marrow is wanting or entirely insufficient. In these cases the post-malarial anæmia is of necessity progressive.

The Blood.—Corresponding to the change in the bone marrow, Bignami and Dionisi[1] distinguish four types of post-malarial anæmia:

(1) Anæmiæ in which the examination of the blood shows alterations similar to those observed in secondary anæmiæ, from which they differ only in that the leucocytes are diminished in number. The greater part

[1] *Cent. f. Allg. Path. u. Path. Anat.*, 1894, V. No. 10, 422.

of these cases go on to recovery; a few, without any further change in the hæmatological condition, pursue a fatal course.

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

(3) Anæmiæ which are progressive, as a result of 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 anæmiæ 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.

The Kidneys.—The kidneys in chronic malaria show usually no great changes. Kiéner, however, describes two forms of kidneys met with in chronic paludism: (1) the congested form, and (2) the atrophic form.

(1) The engorged kidneys are voluminous, increased in weight; the surface is smooth, the consistency firm, the color of a deep red. The congestion is especially marked in the pyramids. All the vessels are distended, and the congestion is sometimes so extreme that interstitial hemorrhages may result or hemorrhages into the interior of the tubules. The epithelium of the tubules is granular; there is often desquamation, and hyaline casts may be found.

(2) The atrophic kidneys are small and irregular in surface. The capsule is adherent, the consistency increased. The kidneys show a maroon or mahogany color or a blotchy appearance. Small cysts are often to be found. The microscope shows alterations as well in the connective tissue as in the epithelium of the tubules.

Amyloid degeneration occasionally follows chronic malaria. This has been noted in the kidneys by Laveran[1] in two instances, but in both of them the malarial cachexia was complicated with chronic bronchopneumonia and bronchiectasis. Frerichs[2] describes three cases, while Marchiafava and Bignami[3] have carefully studied several instances. The clinical history of these cases showed that after a long period of febrile attacks (æstivo-autumnal or obstinate quartan) there followed the symptoms of nephritis and a rapid cachexia, in which the patients died in a few months. On autopsy the principal changes that were found were a grave anæmia, a marantic condition of the organs, a chronic nephritis, and a diffuse amyloid degeneration. The distribution of the amyloid substance in their cases was as follows: The degeneration was most prevalent in the *kidneys*, where not only the vessels of small and medium size and glomeruli were affected, but also, to a considerable extent, the walls of the renal tubules. The alteration of the

[1] *Traité des Fièvres palustres*, p. 94. [2] *Lehrbuch der Leberkrankheiten.*
[3] *Riforma Medica*, 1891, vol. i. p. 571.

interstitial tissue and the degenerations of the renal parenchyma are very grave.

After the kidneys the amyloid degeneration is most severe in the *intestines* and the *spleen*. In the *intestine* the degeneration affects chiefly the vessels of the villi, but also the vessels of the submucosa, and to less extent those of the other intestinal coats. In the *spleen* the vascular network of the periphery of the follicles is particularly affected. Here one sees usually the deposition of great blocks of amyloid substance, while in the trabeculæ of the pulp the process is in its beginning or is entirely wanting. In the *liver* there is a less extensive and diffuse deposition of amyloid substance than in the kidneys. The degeneration affects islands of hepatic tissue which are irregularly disseminated, so that, for example, one may see an island of the size of a lobule or larger from which the hepatic tissue has entirely disappeared, the vascular network showing a most grave amyloid degeneration, while about this the hepatic tissue has a normal appearance. The first small zones of degeneration, according to Bignami, seek by preference the periphery of the hepatic lobules, from whence the process spreads.

Malarial Cirrhosis.—The Relation of Chronic or Repeated Malarial Infections to Cirrhotic Processes.

For many years certain authors have associated cirrhosis of the liver, certain chronic renal changes, and, in some instances, chronic inflammation of the lung, endocardium, and central nervous system, with malarial fever. Indeed, in almost all works upon medicine malarial fever is included as one of the etiological factors in ordinary atrophic cirrhosis of the liver. This statement has been based almost entirely upon rough clinical observation, no one having definitely traced the development of the cirrhosis from the changes following acute or chronic malaria. Frerichs[1] noted the rarity of cirrhosis in patients dying with chronic malaria, though in five instances this was the only etiological cause which he could discover. Laveran[2] in his considerable experience has seen but two cases of atrophic cirrhosis following malarial fever. Welch has seen but one case of atrophic cirrhosis which appeared to follow malaria.

Kelsch and Kiéner give a longer description of hepatitis in malaria, distinguishing three forms of chronic malarial hepatitis and two groups of malarial cirrhoses: (1) Insular cirrhosis with nodular hepatitis and insular cirrhosis with diffuse parenchymatous hepatitis; (2) annular cirrhosis with nodular or diffuse parenchymatous hepatitis. The general appearance of the liver in these cases is that of ordinary atrophic cirrhosis.

Bignami has recently discussed this subject in a very thorough manner. He concludes that there is little evidence to show that ordinary atrophic cirrhosis is a frequent follower of malarial fever. After describing the development of the ordinary chronic hepatic tumor of malarial cachexia, he says: "It is easy to understand from this that it is not difficult to make a differential diagnosis between this form of chronic tumor—or of chronic hepatitis, as one might say—from the other forms

[1] *Loc. cit.*

[2] *Traité des Fièvres palustres*, p. 90.

of cirrhosis. There are not facts or reasons sufficient to cause us to believe that ordinary cirrhosis can follow a chronic tumor. The structure in the two cases is absolutely different. In the one we have an extensive new formation of connective tissue, multilobular in nature, retracting about the included lobules; in the other, a more scanty formation of perilobular connective tissue about a single lobule, not contracting, together with grave alterations of the lobules themselves, especially of their vascular and lymphatic system, not depending, as we have seen, upon the new formation of perilobular connective tissue, but due to lesions primarily local. Atrophic conditions of the liver exist in malaria, but are simple atrophies, and occur in patients who are exhausted, for example, by profuse diarrhœa, etc., or in cases which I have described as progressive post-malarial anæmia. They depend upon the complete want or almost complete absence of any process tending toward regeneration, resulting from grave and diffuse regressive alterations."

Barker[1] has recently ably discussed the relation of malarial infections to cirrhotic processes, and has emphasized the fact that many conditions exist in the organs in malarial fever which might well be the starting-point for extensive growth of connective tissue. Flexner,[2] after the injection of blood serum from one animal into another, has seen the development of characteristic cirrhosis of the liver and of the kidneys in rabbits, following focal necroses not dissimilar to those found in the liver in acute malarial infections.

In conclusion, then, it may be said that secondary sclerotic processes of greater or less degree in the liver, spleen, and bone marrow are not uncommon after repeated malarial infections. The question of the possibility of the development of a *true atrophic cirrhosis* of the liver, of malarial origin, is not settled; the development has never been actually traced and the condition, if it exist at all, is probably rare. The possibility of its occurrence cannot, however, be denied.

Symptoms.

Period of Incubation.—In the absence of definite knowledge as to how malaria is acquired, the ideas concerning the period of incubation have varied very greatly. It has undoubtedly been observed that characteristic malarial fever may appear very shortly after exposure in a malarious district, many observers believing that this may occur within a shorter time than twenty-four hours. It is possible that the febrile attacks which occur sometimes immediately after exposure at night in damp, marshy, malarious districts may have some other cause than malarial infection. Thus, Plehn describes cases where, after exposure at night in very malarious districts in West Africa, there was an immediate paroxysm similar to a malarial attack, which, however, did not recur until the appearance, ten days later, of a true malarial fever, which doubtless dated its infection from the night of exposure. At the time of the first paroxysm the blood was negative, the parasite (æstivo-autumnal) not appearing until ten days later. The hypothesis of Plehn that the initial paroxysm was due to the absorption of some toxic sub-

[1] *Johns Hopkins Hospital Reports*, vol. v. [2] *The Medical News*, Philad., Aug., 1894.

stance produced, perhaps, by the parasite outside of the body, is ingenious, but seems a little far-fetched. More commonly an interval of one or two weeks may be made out between the time of exposure and the time of the breaking out of the disease. Maillot[1] considered the mean period of incubation to be from ten to twelve days, while Sorel[2] estimated it at from seven to nine days. Hertz[3] states that the period of incubation is commonly reckoned at from six to twenty days, but believes that the disease may appear immediately after the reception of the injurious influence.

A number of instances of prolonged incubation have been reported, many of which are open to doubt. Some of these, however, are hard to explain. Such, for instance, is the case of Blaxall,[4] where, after spending five days in the harbor of Port Louis, two of the crew of a man-of-war were attacked, at the end of, respectively, twelve and fourteen days, with quotidian intermittent fever, while two others developed tertian fever at the end of, respectively, forty-eight and one hundred and eighty-four days after embarkation. It is probable, in view of our present knowledge, that many cases of prolonged incubation represent relapses of earlier attacks, the manifestations of which have been present and would have been evident on more careful examination.

Of recent years, since the discoveries of the malarial parasite and the inoculation experiments of Gerhardt,[5] Mariotti and Ciarrochi,[6] Marchiafava and Celli,[7] Gualdi and Antolisei,[8] Angelini,[9] Di Mattei,[10] Calandruccio,[11] Bein,[12] Baccelli,[13] Sacharov,[14] the subject has been considered in a much more intelligent manner. The period of incubation in these cases where the blood of one malarial patient was introduced intravenously or hypodermically into a healthy individual, have varied greatly. In individual cases there was a variance in the period of incubation of from six to eighteen days, while the average duration was from eleven to twelve days. Recently, Bastianelli and Bignami[15] have contributed four new cases to this list and have made a careful study of this subject. In their words, the period of incubation in these cases of artificial inoculation represents "the time necessary for the inoculated parasites to arrive, by multiplication, at the quantity necessary to determine the fever." . . . . "The period of incubation with a given variety of parasites varies inversely to the quantity of material inoculated." . . . . "The mean and minimum period of incubation under equal conditions varies with the various groups of the fever: it is least with æstival fevers, a little longer with tertian fever, and yet a little longer with quartan fever." They believe that they are justified in concluding that "the period of incubation in experimental malarial infections is not a constant quantity, but varies in the same group of fevers and in different groups. In a given group of fevers it depends primarily upon the

[1] *Traité des Fièvres*, p. 263.
[2] *Arch. de Médecin milit.*, 1884, t. 3, p. 273.
[3] *Ziemssen's Cyclopædia*, vol. ii. p. 588.
[4] Quoted from Hertz, *loc. cit.*
[5] *Zeitschr. f. klin. Med.*, 1884, 375.
[6] *Lo Sperimentale*, 1884, s. iv. t. liv. 263.
[7] *Fortschritte d. Med.*, 1885, iii. Nos. 11 and 14.
[8] *Rif. Med.*, 1889, Nos. 225, 264, 274.
[9] *Rif. Med.*, 1889, Nos. 226 and 227, pp. 1352, 1358.
[10] *Ibid.*, 1891, p. 544, and *Arch. für Hyg.*, 1895, 191.
[11] Cf. Grassi and Feletti; *Cent. für Backt.*, 1891, ix. 403, 429, 461.
[12] *Charité Annalen*, 1891, 181.
[13] *Deutsch. med. Woch.*, 1892, No. 32, 721.
[14] *Cent. für Backt.*, 1894, xv. p. 158.
[15] *Bull. d. R. Acc. Med. di Roma*, 1893–94, Anno xv., v. xx. 151.

quantity of material inoculated. In different groups of fevers it varies with the rapidity of the cycle of development of the parasites and with the special capacity for reproduction of the parasitic variety."

They have constructed the following table from an analysis of all cases of experimental malarial infection which they could collect:

Period of Incubation.	Maximum (days).	Minimum (days).	Mean (days).
Quartan fever	15	11	13
Tertian fever	12	6	10
Æstivo-autumnal fever	5	2	3

These researches, especially those of Bastianelli and Bignami proving that the incubation period in æstivo-autumnal fever may be as brief as two days, are of a great deal of interest. It is striking to see how well their conclusions agree with the deductions which have been drawn by other observers before the discovery of the malarial parasite. It is with the æstivo-autumnal variety of the parasite, that variety which is associated with the pernicious fevers, that the short periods of incubation have been observed, while the older clinical observations of short periods of incubation relate usually to the same class of cases. We cannot, however, positively assume that these figures represent the period of incubation in infection as it ordinarily takes place, for we do not know how or in what form this occurs.

The general results, however, of inoculations in tertian and quartan fevers agree quite closely with what might have been expected from clinical observation, while the demonstration that after small intravenous inoculations in æstivo-autumnal fever the disease may appear in forty-eight hours makes it very easy for us to believe that, however the infection may occur, the true incubation period in some very malignant fevers may be extremely short.

Plehn[1] advances an ingenious hypothesis to account for certain early manifestations of fever. He asserts, as has been stated above, that he has noticed in several instances a well marked febrile reaction occurring within a few hours after exposure in a malarious locality and simulating a single malarial paroxysm. The examination of the blood was negative. From nine to twelve days later, however, characteristic malarial fever developed, the parasites being readily found in the blood. He suggests that by exposure in extremely malarious districts the individual may absorb a sufficient quantity of a pyrogenic toxine to cause immediately a single paroxysm days before the true incubation period has been passed through; there is, however, little which can be advanced as proof of such an hypothesis.

Basing our conclusions, then, upon the comparison between clinical deductions and the accurate observation of inoculation experiments, we may say that it seems likely that the ordinary period of incubation in tertian fever is about ten or twelve days, in quartan fever a little longer, while in æstivo-autumnal fever the period may range from twenty-four hours or even less to ten days or two weeks, averaging probably a somewhat shorter time than in the case of tertian or quartan fever.

Types of Fever.—The malarial fevers may be divided into two

[1] *Virch. Archiv*, 1892, cxxix. 285.

main classes: (1) The regularly intermittent fevers, occurring throughout the malarial season; (2) the more irregular, often more or less continued fevers, occurring in temperate climates, only at the height of the malarial season, the late summer and early fall.

And under these two main classes one may separate three distinct types of fever, depending in turn upon infection with one of the three types of the malarial parasite which have been described previously. Thus, the first class, the regularly intermittent fevers, includes (*a*) *tertian fever*, with its combinations (double tertian fever), and (*b*) *quartan fever*, with its combinations (double and triple quartan fever). The second class of fevers, that including the more irregular varieties, depends upon infection with the third variety of parasite above described. Occurring, as it does, at the height of the malarial season (August, September, October), it justly deserves the name (*c*) *æstivo-autumnal fever* applied to it by the Italian observers.

Tertian fever is common in almost all malarial regions. Quartan fever is, however, rare in many districts where the other forms of infection are frequent. In the United States quartan fever appears to be rare; in the last seven years, out of nearly a thousand cases observed at the Johns Hopkins Hospital, only nine cases of quartan fever have been seen. On the other hand, there are certain regions in which quartan fever is particularly common, as the neighborhood of Pavia in Italy and in certain parts of Sicily.[1]

These types of fever are the same wherever they exist. In tropical countries the severer types of æstivo-autumnal fevers are in excess. As one passes away from the equator only the milder tertian and quartan fevers are to be seen in the earlier part of the malarial season, while the æstivo-autumnal fevers appear in the later summer and early autumn. Lastly, in districts where malaria is very uncommon the milder forms, tertian and quartan fever, alone prevail.

Tertian Fever.—(1) *Single Infections—Tertian Intermittent Fever;* (2) *Double Infections—Quotidian Intermittent Fever.*

(1) *Single Infections—Tertian Intermittent Fever.*—This type of fever depends upon infection with the tertian parasite, an organism which, as has been described, possesses the remarkable characteristic of existing in the blood of the infected individual in great groups, all the members of which are approximately at the same stage of development and pass

[1] The interesting fact that districts closely adjoining one another and presenting the same general physical conditions may be each the *foyer* for a distinct type of malarial fever was noted by Trousseau some years before the discovery of the parasite. In discussing the types of regularly intermittent fevers the great clinician says (*Clinique médicale*, vol. iii. p. 425, 2d. ed., 1865): "The types seem to depend upon the nature of the miasm, and especially upon the locality which it infects, rather than upon conditions relative to the individual who is affected. Tours and Saumur, both situated on the left bank of the Loire, appear to me to present the same climatic and telluric conditions, yet one observes at Tours only tertian fevers, while the several cases of quartan fever which I have met with there were individuals coming either from Saumur or Rochefort or from other regions where they had contracted it. One of the examples which has most impressed me in connection with the subject is the following: Fourteen soldiers imprisoned at Saumur came to Tours to testify before a court-martial. They had been scarcely ten days in the last town when nine of them were compelled to enter the hospital, affected with quartan fever, the germ of which they had evidently contracted at Saumur, since all the fevers which we observed with the inhabitants of Tours and the neighborhood were of the tertian type."

through their cycle of existence together, all the organisms composing the group undergoing segmentation within a period of several hours; it requires, as has been said, approximately forty-eight hours to complete its cycle of development. In infections, then, with a single group of parasites segmentation occurs at intervals approximately forty-eight hours apart. As Golgi so clearly showed, the febrile paroxysm is always associated with the segmentation of a group of malarial parasites, and, as one might expect, the chief characteristic of this type of fever consists in intermittent febrile paroxysms occurring every other day. The regularity with which these paroxysms recur is truly remarkable, the onset sometimes taking place at almost exactly the same hour day after day. More frequently there are slight differences, generally, however, of not more than two hours, between the time at which succeeding paroxysms recur. Our observations of nearly a thousand cases would lead us to believe that slight anticipation in the hour of onset is more common than retardation.

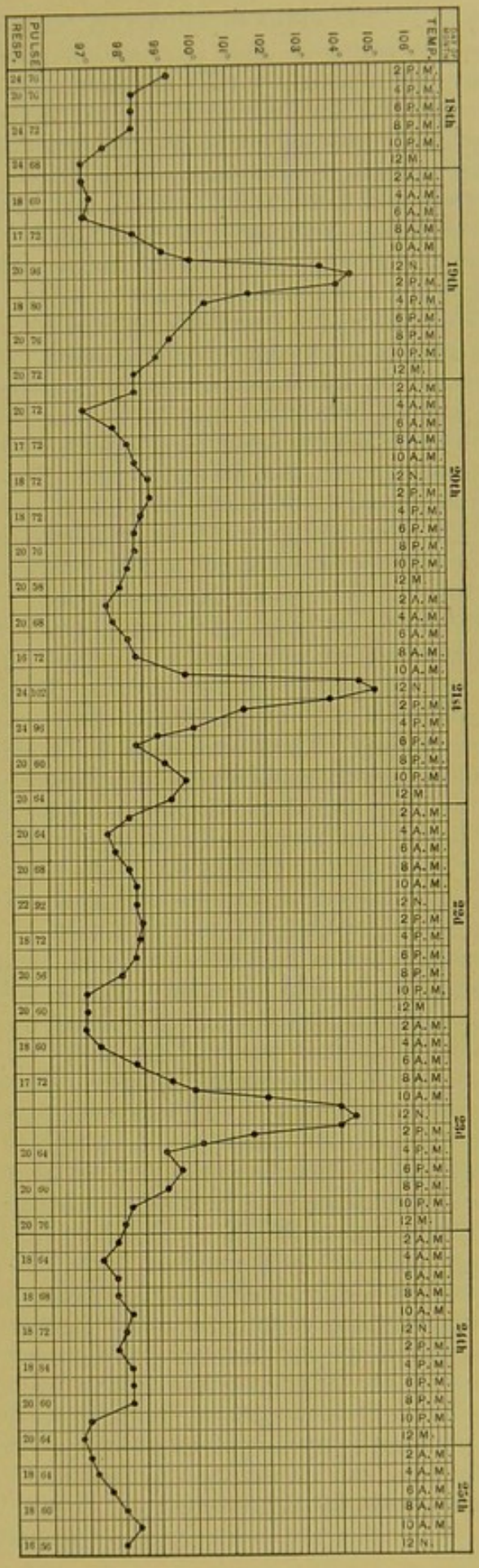
The Paroxysm.—The paroxysm is usually divided into three classical stages: (*a*) the *chill;* (*b*) the *fever;* (*c*) the defervescence or *sweating* stage.

(*a*) *The Chill.*—This may begin without any premonitory symptoms. More commonly, however, for a period of from a few minutes to half an hour the patient complains of uneasy sensations, a slight headache, or perhaps a little giddiness or fatigue. Not infrequently the onset is preceded by yawning. If the temperature is carefully noted during this period, it will usually be found that a slight elevation has already begun to appear. Immediately after this the patient begins to complain of chilly sensations, usually up and down the back; these increase, the patient begins to shiver, and soon a general shaking chill follows. The chill is often extremely violent: the teeth chatter; the whole body is thrown into so violent a tremor that the bed and often surrounding objects in the room are shaken. The skin is pale or often somewhat cyanotic and cool, though wholly disproportionately so in comparison to the intense feeling of cold complained of by the patient. It is often moist, while the erection of the hair follicles gives rise to the characteristic "goose flesh." The pupils are usually dilated. The patient complains often of headache, buzzing in the ears, vertigo, and sometimes of troubles of vision. The pulse is small and rapid and often of rather high tension. There may be nausea and vomiting. The duration of the chill varies materially in different cases; it may last as long as an hour, though usually the period is considerably shorter —from ten minutes to half an hour. Not infrequently no actual shaking occurs, the patient complaining only of chilly sensations. Occasionally, though very rarely in this type of fever, the chill may be entirely absent. Thus out of 339 cases classified by Hewetson and the author at the Johns Hopkins Hospital, chills or chilly sensations were present in 95.5 per cent. of the cases. During the period of the chill the temperature of the patient rises rapidly, and at the end of the chilly sensations may have reached almost its height. Generally, almost the maximum point of temperature is reached within two hours after the onset of the paroxysm.

(*b*) *The Febrile Stage.*—After a certain length of time the chilly sen-

sations become less marked and are interrupted by flushes of heat, which become more frequent, and finally wholly replace the chill. Then begins the second or febrile stage of the paroxysm. The patient complains of an intense burning heat; the skin is flushed, hot, and dry, the conjunctivæ injected, the pulse becomes fuller, but remains rapid; it may be dicrotic. The patient complains bitterly of headache and often of vertigo and buzzing in the ears. The coverings for which but a short time ago he had begged are now thrown aside. Often there is intense thirst. The patient is frequently restless, throwing himself from one side of the bed to the other. In some instances there is active delirium. A case observed by the author jumped from the window of the ward during the febrile stage of a double tertian paroxysm, killing himself by the fall. In other instances the patient is dull, drowsy, and typhoidal in appearance, complaining upon inquiry only of intense headache and aching pains in the back and the extremities. Not infrequently there is a slight cough. Sometimes there is vomiting or diarrhœa. Bleeding from the nose occasionally occurs.

On physical examination the face is flushed, the conjunctivæ are injected; the tongue is often dry and coated. There is often a dusky, yellowish-gray color



Tertian intermittent fever.

Fig. 1.

to the skin, while the lips and mucous membranes are pale. Herpes on the lips and nose is very common. Various cutaneous eruptions have been noted, usually erythematous in nature. In several instances the author has observed an extensive general urticaria. The respiration is not particularly accelerated, though the pulse is often rapid and sometimes dicrotic. The lungs are generally clear on auscultation and percussion, though, not infrequently, evidences of a general bronchitis—sonorous and sibillant râles—may be heard throughout the chest, more frequently in the back. The heart sounds are usually clear, though a soft systolic murmur may be heard over the body of the heart. The abdomen is generally natural in appearance. The area of hepatic dulness is often somewhat increased. There is frequently tenderness on pressure in the region of the spleen, while the area of the splenic dulness is almost invariably increased. In most cases the spleen is easily palpable. This has been the case in 73.4 per cent. of our cases in which notes were made. In fresh cases the border is rounded and soft; in older cases, where there have been numerous previous attacks, the border is often sharp and firm, reaching sometimes a considerable distance below the costal margin. The splenic tumor is particularly striking in children. The most marked splenic enlargements occur, however, in the more irregular æstivo-autumnal fevers. Massuriany[1] noted the presence of a soft souffle over the splenic area, which Bouchard has compared to the uterine bruit. During this period the temperature reaches its maximum point. Temperatures as high as 108° F. have been noted. The duration of the febrile period is usually four or five hours, though, not infrequently, considerably longer.

(*c*) *The Sweating Stage.*—After the stage of fever has existed for four or five hours it is usually followed quite suddenly by the third or sweating stage of the paroxysm. The patient begins to feel relief from the sensation of oppressive heat from which he has been suffering, and then, quite suddenly, breaks into a profuse sweat. The sweating is often excessive; the night-clothes and bedding may be soaked. In association with this the temperature falls, usually quite rapidly. The pulse, which has been rapid, becomes slow and full, and the patient often passes into a refreshing sleep. The temperature falls, almost invariably to a subnormal point. The duration of the sweating stage varies considerably. The defervescence is generally somewhat longer than the rise of temperature, though it may be very short and sudden; it commonly lasts from two to four hours, though often somewhat longer.

The average length of the entire paroxysm from the time the temperature passed 99° F. until it reached this point again averaged, in 173 cases observed by the author, about eleven hours. The paroxysms occur more frequently during the day than during the night, the onset being, perhaps, more commonly noted between midnight and noon, though it may occur at any hour of the day or night; indeed, paroxysms beginning in the afternoon are not at all uncommon.

In *children* the paroxysm differs often from that observed in adults. Very commonly in young children both the first and third stages, the chill and the sweating, may be absent or abortive. The first stage is then generally represented by a slight restlessness. The face looks

[1] *St. Pet. med. Woch.*, 1884.

pinched, the eyes are sunken; the finger-tips and toes become cyanotic and cold, while the child may yawn and stretch itself. Nausea, vomiting and diarrhœa are particularly common. These may be the only manifestations of the first stage. Commonly, however, these symptoms are followed by grave nervous phenomena. The chill in malaria, as in other acute diseases, is not infrequently represented in the young child by general convulsions. These begin usually with a slight spasmodic twitching of the eyelids or of the extremities, the spasm soon becoming general. The febrile stage and the whole paroxysm are often shorter in the child than in the adult. The sweating stage may be wholly absent. In many instances, besides a slight coldness of the hands and blueness of the finger-tips, and a somewhat pinched expression of the face in the first stage, the first and third stage of the paroxysm may be entirely lacking.

The Intermission.—In the period of intermission the patient often feels quite well, so much so that it is not uncommon for patients to pass through a number of paroxysms before consulting a physician, believing after each that the disease is at an end. The temperature after the sweating stage becomes almost invariably subnormal, and often remains so during the greater part of the next day. About forty-eight hours after the onset of the first paroxysm the fresh group of parasites proceeding from the segmentation of two days before having reached maturity and entered again upon segmentation, a fresh paroxysm begins. Often, as has been said, the time of onset of several successive paroxysms is almost exactly the same. More commonly, though, there are slight variations of an hour or two, anticipation or retardation. In these instances the parasite passes through its cycle of existence a little quicker or a little slower than in the typical forty-eight hours. Slightly anticipating paroxysms are very common, more so than retardation.

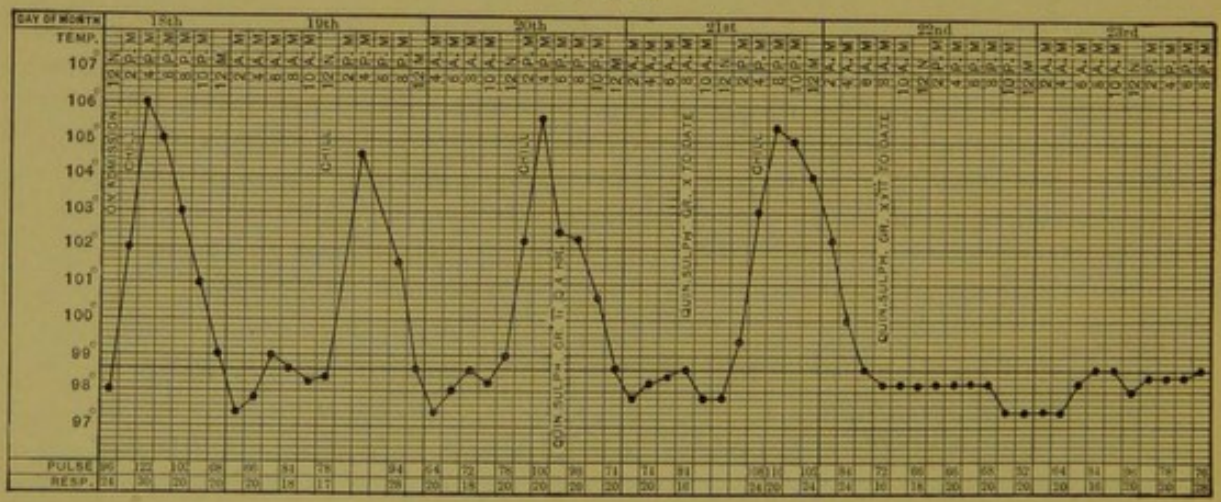
The Blood.—The blood shows the presence of one group of the characteristic tertian parasites. These organisms are to be followed through all the stages of their development. They are most striking and most readily observed several hours before the paroxysm, when they are large and contain most pigment. At the time of the paroxysm and immediately before this the picture may not be so striking, as many of the parasites which, earlier in development, are to be found with great frequency in the general peripheral circulation, become accumulated in certain of the internal organs, where they remain during the period of segmentation. Segmenting parasites are usually to be found in the peripheral circulation, the first being seen several hours before the onset of the paroxysm; at times they may be present in large numbers. Large swollen forms of the organism with very active pigment granules, or deformed and vacuolated forms, are also common during this period. Often the fragmentation of these bodies may be seen, and numerous small pigmented extracellular forms resulting from this fragmentation may be found. These swollen vacuolated and fragmented forms appear to be more common where recovery is taking place, and there is every reason to believe that they represent full-grown parasites which, failing to undergo segmentation, have become degenerate and sterile. During and just after the paroxysm the process of phagocytosis may often be observed under the microscope, and

pigmented leucocytes are always present. The elements taken up are for the most part the free pigment clumps from segmenting forms, the segmenting form itself, fragmented extracellular bodies, and flagellate forms.

(2) *Double Infections.—Quotidian Intermittent Fever.*—Single tertian infections are among the mildest forms of malarial fever which are observed in temperate climates; more commonly the individual shows an infection with two groups of the tertian parasite. These groups reach maturity on alternate days. Segmentation, then, of a group of parasites occurs every day, and, as one might expect, daily paroxysms, *quotidian intermittent fever*, result. The paroxysms in these instances are similar in every way to those of single tertian infections. The manner of onset and duration are the same, while during the periods of intermission the temperature is likewise almost always subnormal. It is common, however, for the paroxysms on successive days to show slight constant differences in their hours of onset, one group of parasites arriving at maturity at an hour slightly different from that of the other. These differences are usually not great, though they may be considerable, one paroxysm beginning in the morning, that upon the following day in the afternoon. Very commonly one set of organisms is more numerous than the other, causing thus a more severe paroxysm. The chart then shows alternate mild and severe attacks. These facts alone might lead us to recognize the dependence of this quotidian fever upon a double infection without the confirmation obtained by examination of the blood.

The *blood* shows the presence of two groups of the tertian parasite in different stages of development. Thus at the time of the paroxysm,

FIG. 2.



Double tertian infection (quotidian fever).

while one group is full grown and in the stage of segmentation, the other is represented by smaller, slightly pigmented, actively amœboid bodies. The question of the origin of these double tertian infections is interesting and by no means wholly clear. Very commonly the first several paroxysms are tertian in nature, daily chills appearing only later on in the course. This may well be, and probably is due to the fact that at the time of the original infection there were two groups of

parasites, one of which was so much smaller than the other as to take materially longer to reach a size sufficient to produce a paroxysm. On the other hand, some observers have suggested that the origin of double infections may be due to the lagging behind of certain parasites out of an originally single group, these retarded forms eventually forming a group of their own. If this be the case, however, it is remarkable that the retardation should be almost exactly twenty-four hours behind that of the original group. Indeed, the remarkable similarity in the hours of the paroxysms due to two different groups of the parasite is striking and not easily explained.

Infections with multiple groups of parasites have been described. These result, naturally, in more irregular subcontinuous fever. This is, however, extremely rare. Only one doubtful case of this nature has been observed by the author. The examination of the blood in these instances shows organisms in all stages of development; there is great difficulty here in distinguishing separate groups.

Quartan Fever.—(1) *Single Infections.—Quartan Intermittent Fever;* (2) *Double Infections.—Double Quartan Intermittent Fever;* (3) *Triple Infections.—Quotidian (Triple Quartan) Intermittent Fever.*

(1) *Single Infections.—Quartan Intermittent Fever.*—This type of fever depends upon the presence in the blood of the quartan parasite, an organism which, just as in the case of the tertian parasite, possesses the remarkable characteristic of existing in the blood in great groups, all the members of which are, approximately, at the same stage of development. The cycle of development of the quartan parasite lasts approximately seventy-two hours, segmentation occurring every fourth day. The characteristics, then, of single quartan infections are quartan intermittent paroxysms, two days of complete intermission existing between. The paroxysm in quartan fever resembles in all its features that observed in tertian infection. The duration in the cases seen by the author averaged between ten and eleven hours. The same periods of subnormal temperature, lasting often during the greater part of the two days of intermission, are observed. The regularity of the paroxysms in quartan infection is the most remarkable characteristic of the disease. A tendency toward anticipation or retardation in the paroxysms is less often noted than in tertian infection.

The blood shows the presence of a quartan parasite. The development of the organism may be readily followed. It is most clearly demonstrated just before and during the paroxysm when the parasites are full grown. The tendency of the full grown and sporulating forms to accumulate in the internal organs—a tendency which has been noted in tertian fever, and exists, as will be stated later, to a greater extent in æstivo-autumnal fever—is not to be observed in the case of the quartan organism; all stages of development may be seen with equal frequency in the peripheral circulation. At the time when the parasite reaches maturity swollen, fragmented, and vacuolated forms may be seen as in tertian fever. They are, however, less frequent, as are also the flagellate bodies.

(2) *Double Infections.—Double Quartan Fever.*—Often more than one group of quartan parasites may be present in the blood at the same time. When two groups are present segmentation usually occurs on two suc-

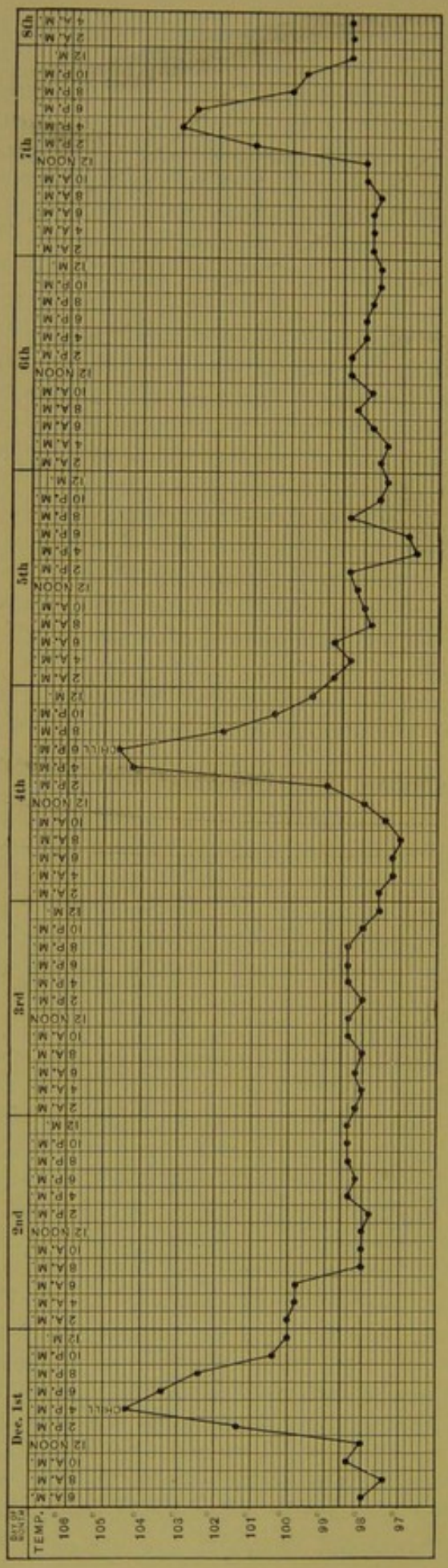


FIG. 3.

cessive days, with a day of intermission following. Clinically, therefore, these double infections are characterized by chills upon two successive days, with a day of complete intermission following. The paroxysms in these instances are exactly similar to those observed in single infection. The examination of the blood, however, shows the presence of two groups of the quartan parasite.

(3) *Triple Infections.*—*Triple Quartan Fever.*—Very commonly three groups of the quartan parasite may be present in the blood at the same time. These groups reach maturity on successive days, and cause, therefore, quotidian intermittent fever. The symptoms of quotidian fever depending upon a triple quartan infection differ often in no wise from those depending upon a double tertian infection. Daily paroxysms, exactly similar in nature, occur in both instances. The same period of subnormal temperature may be noted, and the diagnosis, without the examination of the blood, may be impossible. Examination of the blood in these instances shows, however, the presence of three groups of the quartan parasite, each in different stages of development.

ÆSTIVO-AUTUMNAL FEVER.—This type of fever differs materially from the regularly intermittent fevers of the early part of the malarial season. It depends upon the presence in the blood of the smaller organism first described by Marchiafava and Celli, the æstivo-autumnal

parasite. This parasite, as has been previously stated, possesses to a much less marked degree the characteristic of existing in large sharply defined groups, while, as has also been noted, the length of the cycle of existence appears to vary considerably. At the beginning of many infections an arrangement in groups may, however, be made out, and this arrangement may exist for a certain length of time. Usually, however, before the process has lasted very long organisms in different stages of development may be found at any time during the fever. In some instances groups of parasites with a cycle lasting about twenty-four hours have apparently been made out, while in others fairly distinct groups appear to pass through a cycle lasting considerably longer, as long as forty-eight hours or even more. Clinically, æstivo-autumnal fever appears in very varied forms.

Not infrequently it may be seen in the form of *quotidian intermittent fever*. Here the paroxysms may resemble very closely those of tertian or quartan fever, and in some instances, without the examination of the blood, the distinction from double tertian or triple quartan infections cannot be made. In these instances the process begins with a sharp chill and ends with a well marked sweating stage, the duration of the paroxysm being perhaps exactly similar to that in the regularly intermittent fevers. More commonly, however, the paroxysms are longer and more drawn out, lasting perhaps as long as twenty hours. Here the first stage often differs greatly from that in tertian or quartan fever. While in the regularly intermittent fevers the onset is rapid and usually associated with a chill, in these instances the rise may be much more gradual, while the chill is not infrequently altogether lacking. Often a slight transient chill may be observed some time after the beginning of the rise in temperature. The chill in æstivo-autumnal fever can by no means be called the *initial* symptom in the paroxysm ; the fever has often become well marked before the onset of the rigor. Usually, after a certain number of paroxysms, a distinct irregularity in the fever becomes evident. Either from the lengthening out of one of the paroxysms or from the anticipation of the following paroxysm the intermission between the two becomes, perhaps, completely obliterated or indicated only by a slight drop in temperature, until finally there results an irregular continued fever in which all trace of the paroxysm has disappeared.

Not infrequently the early paroxysms recur at greater intervals one from the other. These intervals are frequently forty-eight hours, more or less (*"Æstivo-autumnal tertian fever; malignant tertian fever"*—Marchiafava and Bignami). In these instances the paroxysms are usually particularly long, lasting sometimes as much as thirty-six hours. The very gradual rise in temperature, which is often unaccompanied by a chill, and the slow fall, are in striking contrast to the chart of an ordinary tertian fever. Marchiafava and Bignami, who, as has been before stated, believe that they can distinguish two separate types of the æstivo-autumnal parasite, the quotidian and the tertian, have described minutely the fever curve in these cases with longer intervals. This class of cases they term *"malignant tertian fever,"* in contradistinction to the milder regularly intermittent tertian fever. They describe what they believe to be a characteristic fever curve, the more or less sudden onset of the symptoms, a pseudo-crisis, a precritical elevation

of temperature, which often reaches a point higher than has been previously attained, and, finally, the actual crisis. Charts similar to this

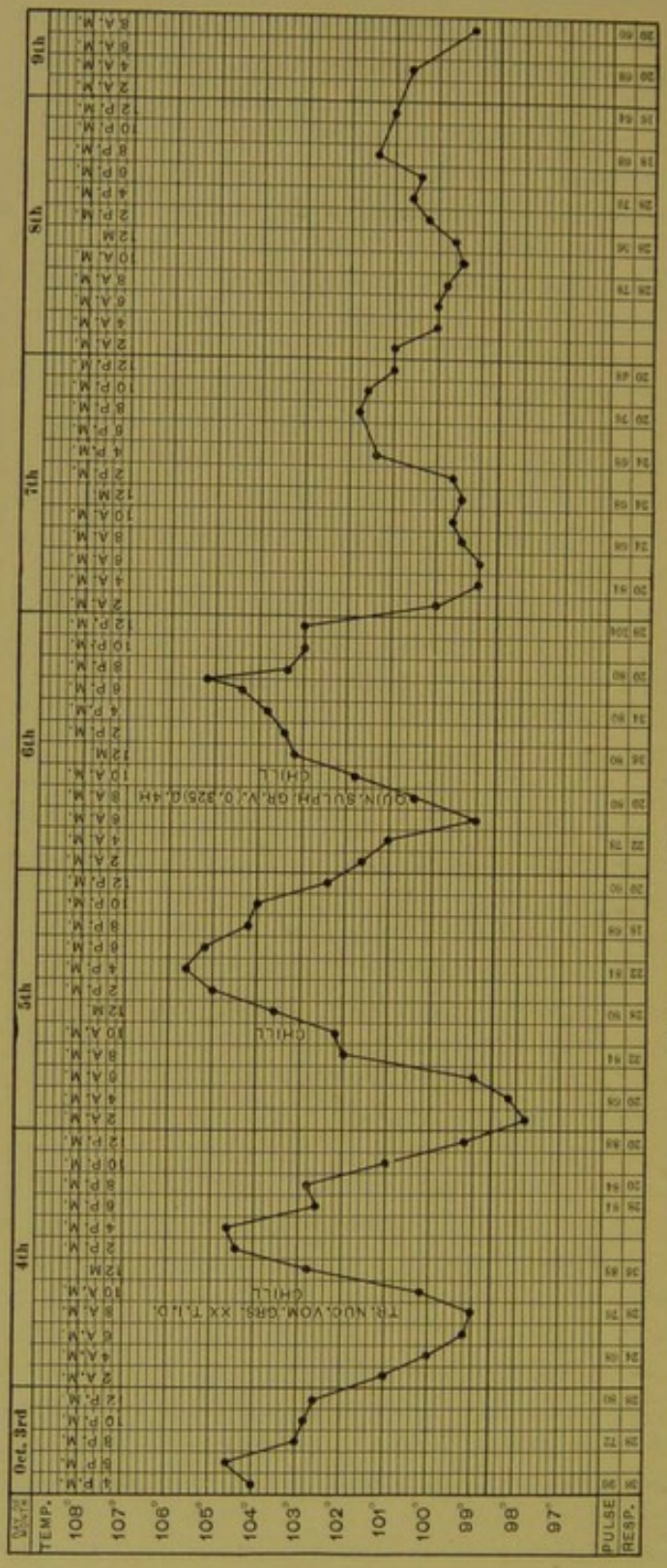


FIG. 4. Æstivo-autumnal fever (quotidian paroxysms).

have been observed by the author and reproduced in a recent publication (see Fig. 5), though he has not seen a sufficient number of instances to justify him in believing that such a curve is characteristic of a particular, separate type of parasite. It is certainly true, however,

that irregular oscillations in the curve of the fever produced by these parasites are very common. The periods of intermission between par-

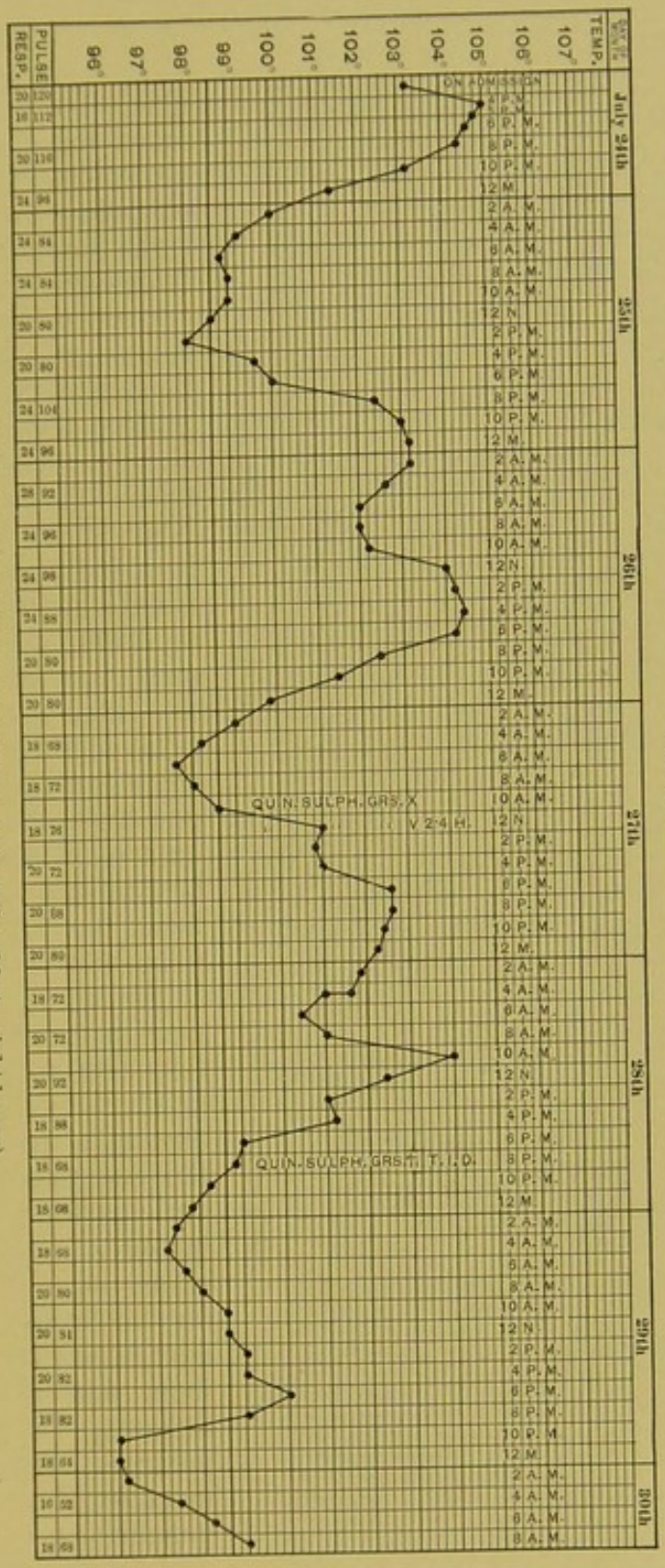


Fig. 5.

Æstivo-autumnal fever (paroxysms at intervals of forty-eight hours).

oxysms show, usually, a subnormal temperature. The periods of apyrexia are, however, very brief, as one may readily conceive when he considers the length of the paroxysm, lasting, as it often does, thirty-six hours or over.

In those cases in which the paroxysms occur at intervals of approximately forty-eight hours, one from another, the irregularity in the hour of onset of the paroxysms is particularly striking. In some cases there is marked retardation, intervals of considerably more than forty-eight hours occurring between the beginning of one paroxysm and that of its successor. More frequently, however, there is anticipation, the paroxysms recurring at intervals of less than forty-eight hours. Now, if, as already stated, the individual paroxysm should last thirty-six hours or more, it may be readily seen how short the period of intermission in these cases would be. Often, then, there is an almost continuous high temperature, with occasional remissions or intermissions lasting, perhaps, less than an hour—"*malarial remittent fever.*"

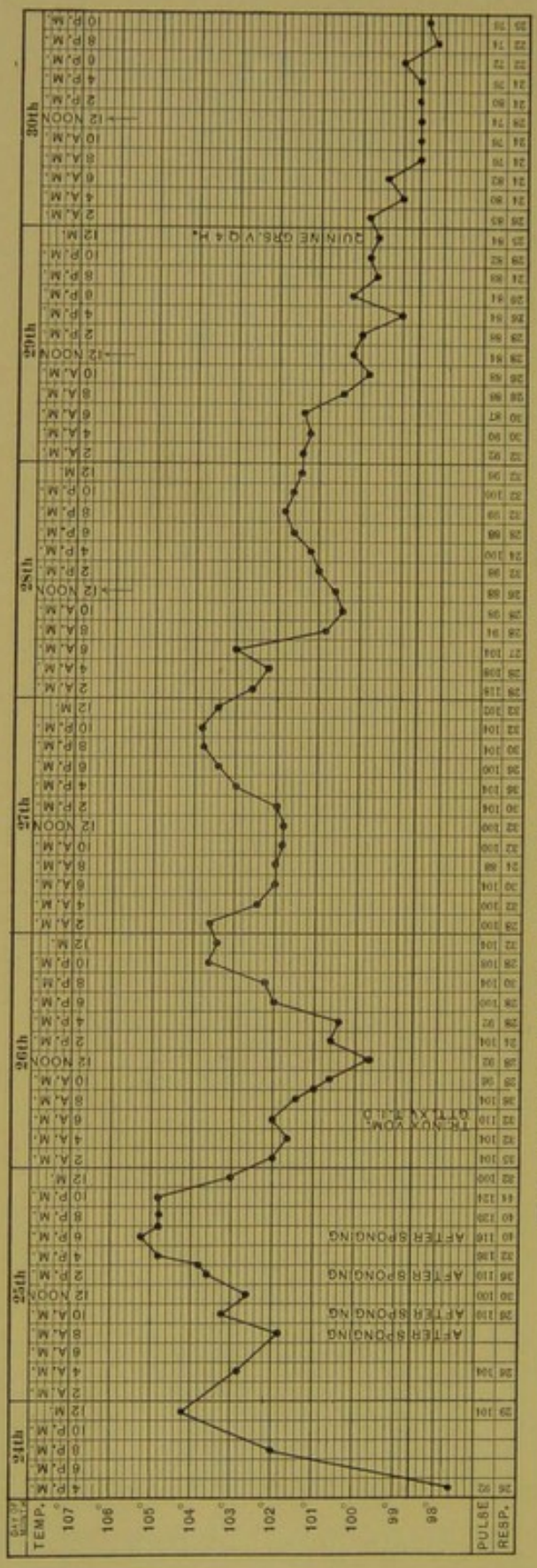


FIG. 6.

Æstivo-autumnal fever (showing the development of remittent and continued fevers).

In many instances the new paroxysm begins before the previous one has finished, owing either to an excessive prolongation of the first paroxysm or to an anticipation of the succeeding one. In these cases the result is, of course, a *continuous* fever. Usually, the continuous fevers resulting from æstivo-autumnal infections, though the temperature may never reach the normal point, yet show indications of the paroxysms and sometimes occasional abortive chills. In some instances, however, all evidence of paroxysms may be absent, the chart closely simulating that of typhoid fever. Such cases are probably often due to infections

with more than one group of parasites. It is probably true that the long duration of some of the paroxysms is accounted for by the fact that the segmentation of a given group of parasites occurs through an appreciably greater length of time than in the regularly intermittent fevers.

The result of all this is that the chart of æstivo-autumnal fever presents very commonly somewhat the following picture: At the onset there are several intermittent paroxysms occurring at intervals of from twenty-four to forty-eight hours or a little more. After a few of these attacks the fever becomes irregular or continued. This may occur, as has been said, in several ways: (1) *Through modifications of the curve in the individual paroxysm;* (2) *by modification in 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 slow and continuous manner; (*b*) the occurrence of a 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.

(2) *The modifications in the succession of the paroxysms may be* (*a*) the anticipation of the paroxysms; (*b*) the retardation of the paroxysms; (*c*) the prolongation of the paroxysms, by which apyrexia is made incomplete; (*d*) the occurrence of slight oscillations in temperature during the period which ought to be one of apyrexia; (*e*) the reduplication of the attack.

Very often when the case first comes under observation it is already one of "remittent" or continued fever. The chills are frequently absent; the patient complains bitterly of headache and general pain in his back and extremities. He is usually dull, drowsy, and apathetic, though there may be marked delirium. The face is flushed, the conjunctivæ are injected, the tongue dry and coated; there is sordes upon the lips and teeth; the patient remains continuously in a condition similar to that described in the febrile stage of the ordinary paroxysm. In these instances it is often absolutely impossible, without examination of the blood, to distinguish the case from one of typhoid fever. The writer has repeatedly seen patients with æstivo-autumnal malaria placed under treatment as cases of typhoid fever, the attention being first drawn to the true condition of things by a sudden fall of the temperature to normal, or by the discovery of the small amœboid hyaline parasites within the red corpuscles. Grave cerebral or abdominal symptoms develop, often early in the course of these subcontinuous fevers, which frequently tend to become pernicious. Careful observations may show that these symptoms are paroxysmal. Delirium, drowsiness, stupor, coma, grave cerebral symptoms, local spasms, general convulsive seizures may occur, or perhaps profuse vomiting or a choleriform diarrhœa with collapse. In fact, any of the symptoms which will be discussed under the Pernicious Fevers may suddenly develop in the course of subcontinuous æstivo-autumnal infection.

These instances of more or less continued fever are occasionally referred to as "*malarial remittent fever.*" They have been admirably described by Baccelli, who recognized their true malarial nature, under

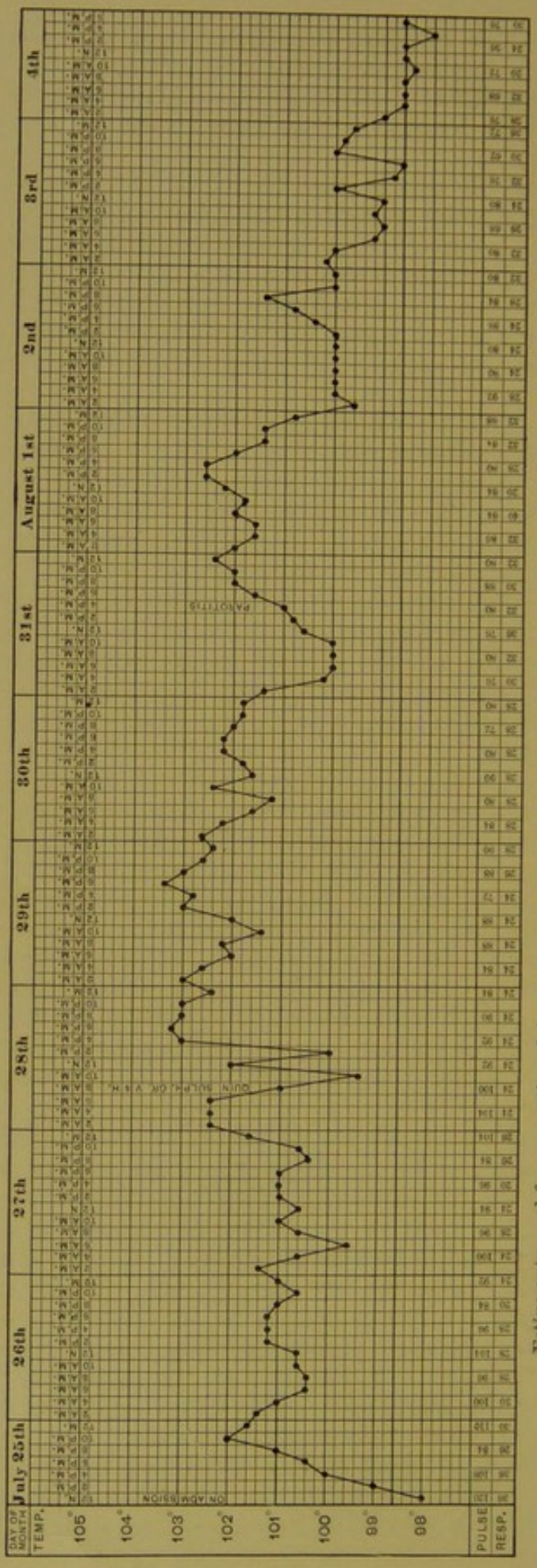


FIG. 7.

Æstivo-autumnal fever; continued fever; "subcontinua typholdea." (The fever after the 31st was due to an acute parotitis.)

the name of "*subcontinua typhoidea.*" As has been previously stated, the tendency of the regularly intermittent fevers, when left to themselves, is toward spontaneous recovery after a certain number of paroxysms, and, while relapses are common and productive, perhaps, of grave secondary disturbances—anæmia, nephritis, etc.—the tendency to become pernicious is rarely observed. This is not true of æstivo-autumnal infections as a class. In many instances, to be sure, when placed under hygienic conditions the same tendency toward spontaneous recovery, usually with relapses, is to be observed. Often, however, an untreated infection becomes steadily more aggravated, until, finally, so-called "pernicious" symptoms appear and a fatal result ensues.

In other instances an æstivo-autumnal infection may be associated with but *slight irregular rises in temperature;* there may be no sharp paroxysms, the patient complaining only of languor, anorexia, headache, pains in the back and limbs. Such instances may easily lead to errors in diagnosis. There is usually, if the case has existed for any length of time, a certain degree of anæmia, with the characteristic sallow hue to the skin, while the spleen is almost always enlarged. Such cases probably often pass into the condition which will be later described as "chronic malarial cachexia."

Pernicious Malarial Fevers.—These very malignant forms of malarial fever have, in this and other languages, generally acquired the name "*the pernicious fevers.*" It is quite true that the term "malignant fevers" used by the translators of Marchiafava and Bignami's[1] work is, in the abstract, better, but the word "pernicious" is so firmly implanted in the general usage that its eradication appears to the writer injudicious.

Pernicious fever depends, almost invariably, upon infection with the æstivo-autumnal parasite. In temperate climates these fevers are rare, but in the tropics they are extremely common. The pernicious nature of an attack depends, generally, as has been shown in the section on *Pathological Anatomy* (page 83), upon several causes: (1) The great numbers of parasites present and their capacity for rapid multiplication; (2) the special involvement of certain vital organs by the parasites, which, as has been pointed out, show a remarkable tendency toward accumulation in certain definite organs, varying in different cases; (3) possibly upon the greater or less virulence of the parasite. This latter statement is based upon the assumption that the malarial parasites produce a specific toxic substance. Certain authors thus believe that, in the case of infection with a very malignant parasite, pernicious symptoms may result, while but a small number of parasites are present, particularly if the chief seat of development of the parasite be localized in a particularly vital spot. This is, however, doubtful. While it is probable that a specific toxic substance may be produced by the parasite, and while there is very good reason to believe that there is a difference between the malignity of the parasites in different instances, yet, in a general way, the severity of the symptoms, as demonstrated long ago by Golgi, appears to depend largely upon the number of parasites present. And in a general way it may be definitely stated that per-

[1] *The Parasites of Malarial Fevers*, New Sydenham Society, 1894.

nicious fever never occurs without the presence of a considerable number of parasites, though in some of these instances very few organisms may be found in the peripheral circulation.

Bastianelli and Bignami in a recent article[1] well say: "The conditions through which a malarial infection becomes pernicious are: (1) That the infection be produced by one of the varieties of the æstivo-autumnal parasite. On this condition all today are agreed, and we shall not insist further.[2] (2) The second condition relates to the abundance of the parasites, and it may be stated as follows: In pernicious fevers, if one takes into consideration not only the examination of the blood from the finger, but also the condition in the vessels of the various organs (Marchiafava, Celli, Bignami), it is a striking point that, however the distribution of the parasites may vary in individual cases, their total number is always considerable. As regards the distribution, one may make the following distinctions: There exist (1) cases in which the number of parasites is most abundant, yes enormous, while all the organs are uniformly invaded. These are the most common forms of pernicious fever, and are usually accompanied by coma. There are some cases in this category in which the number of parasites in the blood of the finger, of the spleen, of the bone marrow, etc. is enormous, while the number in the brain is scanty; clinically, the absence of cerebral phenomena is noted. (2) Cases in which the number of parasites is absolutely and relatively scanty in the bone marrow, in the spleen, in the liver, while there may be relatively few in the blood of the finger, yet other organs are crowded with parasites. Among these the following localizations are to be made out: (*a*) The brain and the meninges are filled with parasites either in sporulation or in all their stages of development; in such cases it is difficult to find not only sporulating forms, but even young parasites in the spleen. Clinically, there are cerebral phenomena. (*b*) The stomach and intestine are chiefly invaded; in these organs the mature forms of the parasite are usually found; these are the cases of pernicious fever which present, clinically, ... intestinal phenomena."

The pernicious symptoms may come on quite early in the course of the infection, though usually several paroxysms have existed before their appearance. In very malarious districts, however, almost the first paroxysm observed may be pernicious in nature.

The Comatose Type.—The commonest form of pernicious malaria is that accompanied by coma. Here, in the earlier part of the paroxysm, the patient may be slightly delirious, but he soon becomes drowsy and somnolent, passing finally into a condition of profound coma. Not infrequently, in grave malarious districts, the patient comes for the first time to the observation of the physician while in this condition. He is profoundly unconscious; the respiration is often stertorous, and occasionally of the Cheyne-Stokes type. The pupils may be contracted or dilated, sometimes perhaps unequal. There is often—a not unimportant point—a slight jaundice. Not infrequently there is hiccough; the pulse

[1] *Bull. d. R. Acc. Med. di Roma*, 1893–94, Anno xv., v. xx. 186.

[2] There are exceptions, though rare, to this rule. Dr. Walter Reed of the Army Medical Museum in Washington has recently communicated to me his observation of specimens from a case of characteristic comatose pernicious fever due to a double tertian infection. This case has since been reported by Dr. Wm. B. French of Washington (*N. Y. Med. Journal*, 1895, vol. lxiii. p. 674).

may be full and slow and of high tension, though toward the end it is often rapid, irregular, and feeble. Local spasms of certain muscles may occur. Thus, in one of the author's cases there was a well marked spasm of the lower facial muscles on one side, which disappeared with the paroxysm. Recovery may result after the gravest symptoms, but without treatment the paroxysm is usually followed rapidly by a second, which generally proves fatal.

Other Cerebral Manifestations.—In other instances most decided cerebral symptoms of a different nature may occur. *Delirium* which may be maniacal may be observed. Active *delusions* and *hallucinations* are not uncommon, while in some instances *tetanic convulsions* have been noted. In a number of instances *hemiplegia* has been associated with the paroxysm, disappearing after the attack. At times distinct symptoms of bulbar paralysis may occur. In one of these cases carefully studied by Marchiafava[1] the special localization of the parasites in certain foci in the medulla was confirmed post-mortem.

Hemorrhagic Type.—In some instances of pernicious fever grave hemorrhagic symptoms may occur—epistaxis, hæmoptysis, extensive cutaneous hemorrhages. Several of these cases are described by Marchiafava and Bignami.[2]

Algid Type.—This is sometimes extremely insidious and fatal. After several paroxysms which are in no way remarkable the patient very suddenly passes into a condition of extreme collapse. This does not occur at the beginning of the paroxysm, but at the time when the stage of fever should exist. The temperature may be but slightly elevated; indeed, in some instances it is subnormal. The condition is not unlike that in Asiatic cholera. The mind is clear, there is little suffering, but extreme collapse. The eyes are sunken; the features drawn and pinched; the face expressionless; the tongue dry; the skin moist and covered with a cold sweat. The patient may be so quiet and uncomplaining that it may be, as Laveran states, only through an accidental examination of the pulse that the true state of affairs may be discovered. The pulse is very rapid and feeble and thready, almost impalpable, becoming imperceptible at the wrist before death. Physical examination of the thorax is negative excepting for the feeble action of the heart. The second sound at the base may be quite inaudible. The abdomen is usually retracted; there is often tenderness on pressure in the region of the spleen, which is palpable.

Sudoriferous Type.—A sudoriferous type of paroxysm has been described, in which, during the last stage, the sweating becomes excessive and the patient passes into a condition of collapse with a thready pulse and cold extremities. Without vigorous interference the case may end fatally.

Bilious Type.—A type of paroxysm has been described by certain observers, the chief symptom of which is the vomiting of large quantities of bile-stained fluid; this is usually associated with stools of a similar nature.

Gastralgic and Cardialgic Types.—Severe gastralgic paroxysms associated with profuse vomiting, and often with hæmatemesis,

[1] *Lav. d. III. Cong. d. soc. It. d. Med. Int.*, Roma, 1890, 142. [2] *Loc. cit.*

may occur without the existence of striking intestinal symptoms. An attack of this nature is well described by Laveran.[1]

Choleriform Type.—In certain instances in which the chief localization of the parasite is in the stomach and intestines the patients present a clinical picture strongly resembling that of Asiatic cholera. These cases have been particularly studied by Marchiafava.[2] The paroxysm usually begins with profuse vomiting and diarrhœa; the discharges may resemble those of cholera. The skin is cold, moist, and clammy. There is cyanosis of the lips and extremities; the pulse is rapid and thread-like. There may be cramps in the extremities. The condition closely resembles the algid stage of Asiatic cholera. If the paroxysm be not fatal, profuse sweating may follow, with an intermission in the symptoms. Anatomically, the mucous membrane of the stomach and intestines is found to be filled with malarial parasites. These may produce actual thrombosis of the vessels of the mucous membrane with superficial necroses and ulceration.

Pneumonic or Dyspnœic Type.—Baccelli[3] and others have described a type of paroxysm the symptoms of which suggest strongly a pneumonia. This admirable observer, however, as long ago as 1866 recognized this condition to be distinct from a true complicating pneumonia. There is intense thoracic pain, great dyspnœa, and a painful cough. There may be moderate dulness over the affected lung with coarse, sonorous, and sibilant and finer moist râles. Laveran[4] has seen a fairly abundant hæmoptysis following an acute dyspnœic paroxysm. In other instances, despite the extreme dyspnœa, physical examination may be quite negative. The sputum is mixed with dark fluid and clotted blood. The condition is certainly not a pneumonia; it is more probably an active congestion of the pulmonary vessels. In the absence of autopsy records in cases of this nature one can but suspect that they represent a special localization of the parasite in the pulmonary capillaries.

Hæmoglobinuric Type—"*Malarial hæmaturia.*"—Hæmoglobinuria is a not uncommon symptom in the graver fevers in certain malarious districts. In temperate climates it is rarely seen. The ultimate cause of its production is not yet settled. A continual destruction of the red blood-corpuscles is going on throughout every malarial infection. This occurs in various ways: (1) The parasites, developing within the corpuscles, form the black pigment, melanin, at the expense of the corpuscles in which they grow, the corpuscles becoming gradually decolorized and destroyed. (2) In many instances the red blood-corpuscles containing the parasite undergo a premature necrosis, becoming brassy colored and shrunken. (3) Sometimes the decolorization of the corpuscles containing the parasite occurs quite suddenly, the corpuscles bursting, as it were, and setting free their hæmoglobin in the blood current. Thus, during an ordinary malarial attack there is always a certain amount of hæmoglobin set free in the serum, but, as this amount does not pass beyond the limit of the quantity which can be disposed of by the liver, it does not appear in the urine.

[1] *Traité des Fièvres palustres*, Obs. xxxviii.
[2] *Cent. f. Allg. Path. u. Path. Anat.*, 1894, V. No. 10, 418.
[3] *Studien über Malaria*, Berlin, 1895.
[4] *Traité des Fièvres palustres.*

It is doubtless, in part, to this constant destruction of the red corpuscles, with the liberation of their hæmoglobin, that the polycholia and slight jaundice so commonly observed in malaria are due. Ponfick estimates that up to one sixth the total number of the red blood-corpuscles may be destroyed and disposed of in the economy without the hæmoglobin appearing, as such, in the urine. If this destruction of the red blood-corpuscles becomes unusually great, and the quantity of hæmoglobin separated from the disco-plasma of the red blood-corpuscles exceeds the amount which can be taken care of by the liver, hæmoglobinuria will result. It is not, however, only the infected corpuscles which lose their hæmoglobin in these instances; great numbers of their uninfected fellows are equally affected, just as in the ordinary paroxysmal hæmoglobinuria. Some substance excessively toxic to the disco-plasma of the red blood-corpuscles must be present in the circulation, or some change has taken place in the blood serum by which it has lost its isotonicity, but what these changes are and to what they are due are by no means clear. There is much which might lead us to believe with Baccelli that some toxic substance, produced perhaps by the parasite itself, may be at the bottom of these changes. Why, however, hæmoglobinuria should be so common in certain regions—as, for instance, Greece and West Africa—and so infrequent in many other more malarious districts is quite inexplicable in the present state of our knowledge.

Clinically, these cases are among the severest forms of malarial fever. The same condition is known in Western Africa as "*black water fever.*" By many observers, particularly by the French, the term *bilious hæmoglobinuric fever* has been used. Not infrequently the term "*hæmaturic*" is used, and, indeed, as the interesting researches of Joseph Jones show, actual hæmaturia often occurs. The hæmoglobinuric attack is rarely the initial symptom of the infection. Usually the patient has had repeated attacks of malaria, the hæmoglobinuria appearing suddenly with a relapse, or, if it be the first infection, the hæmoglobinuric attack is preceded by several intermittent paroxysms. In cases where either in a relapse or in a primary infection the hæmoglobinuria appears with the first actual paroxysm, there are often prodromal symptoms lasting for from several hours to sometimes several days. It is probable that these are associated with moderate fever and often represent abortive paroxysms. There are loss of appetite, headache, indefinite pains in the extremities and back. It may be remembered that in many paroxysms of the more ordinary types of æstivo-autumnal fever the gradual onset of the paroxysm without chill is frequent: this is not true in the case of the hæmoglobinuric paroxysm, which begins almost invariably with a severe shaking chill. This is followed by intense pain in the back, head, and extremities, and by profuse vomiting; the vomitus consists of a deeply bile-stained fluid. The face is flushed; the conjunctivæ are injected; the pulse is rapid; the patient is usually in a condition of great anxiety and apprehension. There is a well marked icteric hue to the skin. There is usually profuse diarrhœa.

The first *urine* that is passed, in the early stage of the paroxysm, has a somewhat rosy reddish hue. This, however, rapidly becomes deeper, and is finally an intense brownish black color with something of a greenish tinge, and a greenish yellow foam on shaking. The vomitus

becomes of a deeper color, at first yellow, then green, finally sometimes almost black. There may be diarrhœa, the dejecta being green or brown in color, while in other instances there is constipation. During the stage of fever the patient generally becomes jaundiced. There is usually little delirium, the patient being quite conscious and in a condition of great anxiety and agitation. He often complains of severe epigastric pain, which is possibly associated with repeated vomiting; in other instances the pains in the loins may be extremely severe, bearing, possibly, as Kelsch and Kiéner[1] suggest, some relation to the intense renal congestion. The fever is often high, the temperature touching, in some instances, 41° C. (106° F.) or even higher.

The *urine* at the height of the process is of a deep brownish black color, and deposits on standing an abundance of reddish brown sediment. The amount varies considerably in different instances, in some being extremely scanty, in others amounting to as much as 1000 or 1500 c.c. The specific gravity varies inversely to the amount of urine passed. As the amount is generally somewhat reduced, the specific gravity averages above normal. The reaction varies; it is generally feebly acid. There is usually an abundance of albumin. In some instances a test for the biliary coloring matters may be obtained. Kelsch and Kiéner assert that this is the rule at the height of the process, while Plehn[2] in eight instances was unable to obtain this test. The sediment consists of mucus, bladder epithelium, numerous granules and masses of pigment, renal epithelial cells, and, almost invariably, hyaline and granular casts with epithelial cells adherent. In many instances blood-corpuscles may also be found, actual hemorrhages taking place into the kidney. Often, however, besides the profuse sediment of a brownish granular material, occasional epithelial cells, and casts, not a sign of a red corpuscle may be found, the condition being a true hæmoglobinuria.

In the simplest and mildest attacks the temperature remains elevated nine or ten hours, and then falls quite suddenly to normal, the urine at the same time clearing up, excepting for a slight trace of albumin with occasional casts. In some instances a paroxysm of this nature is the last manifestation of the process, complete recovery following. In other instances there may be repeated intermittent hæmoglobinuric paroxysms, ending perhaps in recovery. Very frequently, however, the condition is more severe. The fever lasts much longer; the vomiting and diarrhœa continue; the jaundice becomes more intense; there are perhaps occasional slight intermissions, but in the main the attack is continuous. The urine, as well as the fever, may show occasional temporary changes for the better, but these are of short duration, fresh exacerbations rapidly following. The urine becomes often scanty and more albuminous; the patient becomes emaciated and pale; the eyes are sunken, the tongue is dry, the pulse rapid and feeble, and eventually a fatal result follows. In some instances, however, recovery may occur when the patient is apparently almost beyond hope.

Certain cases pursue an extremely rapid fatal course. The initial chill, fever, vomiting, and diarrhœa are associated with almost complete suppression of urine; that which is passed, often but a few drops, is intensely bloody. There is great agitation, intense prostration, the patient

[1] *Maladies des Pays chauds.* [2] *Deutsch. med. Woch.*, 1895, Nos. 25, 26, 27.

falling into a condition of profound collapse and dying within several days. Nephritis almost invariably follows the hæmoglobinuric attack. In the milder cases it is transient and slight. In many more severe cases, however, the end of the paroxysm is followed by the symptoms of a well marked nephritis, lasting sometimes for weeks and possibly even for months. In a certain number of instances this condition pursues a rapidly fatal course. The albuminuria and casts persist; the quantity of urine remains steadily below normal; the patient becomes uræmic; and delirium, coma, and convulsions ensue with a fatal result.

Malarial hæmoglobinuria does not occur in all malarious districts. In some regions where pernicious fevers are relatively common hæmoglobinuria is rarely seen. The cause for this is not apparent. In Rome, for instance, the disease is uncommon. It is not very frequent in most of the malarious districts of the United States. In Greece it seems to be unusually common, while in certain parts of Africa it is seen in its most fatal forms.

The *blood* generally shows the æstivo-autumnal parasite.[1] Predisposing causes appear to be any over-exertion or exposure, indeed anything which reduces the vitality of the individual. Extremely interesting is the widespread idea in certain regions that quinine, which has so specific an action upon the parasites, may yet have an unfavorable influence, indeed be the determining cause of the hæmoglobinuric paroxysm. In Joseph Jones' interesting memoirs[2] a number of assertions of this nature appear. More recently Plehn[3] in a valuable article upon the black water fever of Cameroon records his belief that in that climate, at least, the development of hæmoglobinuria is often brought about by the administration of quinine, while the records of his cases of hæmoglobinuric fever treated with and without the specific malarial remedy show that the more favorable course was pursued by those cases which were treated expectantly. This view, however, is not held by the majority of observers. The tendency toward spontaneous recovery in many of these cases suggests, certainly, that the presence of the hæmoglobinuria, dependent on whatever it may be, may have an injurious effect upon the life of the parasite.

The Blood in the Æstivo-autumnal Fevers.—The blood in the æstivo-autumnal fevers shows the presence of the small form of the parasite described first by Marchiafava and Celli ("Hæmatozoön falciparum," Welch). As already noted in the description of the parasite, only the earlier forms in its cycle of existence are generally found in the peripheral circulation. These are the ring-like or amœboid hyaline bodies, which are often quite free from pigment. As the later stages in the development of the organism are rarely found in the peripheral circulation, it is natural that the period shortly before and during the early part of the paroxysm should be that in which the smallest number of parasites is to be found on clinical examination of the blood; and this

[1] This has been the case in those instances observed by the Roman authors, and the descriptions of Plehn and others seem to point in the same direction. Owing, however, to the remarkable distribution of these fevers, to which reference has been made above, we should perhaps bear in mind the possibility that there may be certain fine differences between the parasites of the ordinary irregular fevers and those of the hæmoglobinuric variety, which may be brought to light by further study.

[2] *Medical and Surgical Memoirs*, vol. ii., New Orleans, 1887.

[3] *Loc. cit.*

is the case. There are cases of æstivo-autumnal fever where, at this period, a prolonged search must be made before parasites are to be found. Always, however, in the experience of the writer, parasites are present after a few hours have passed by. And I believe that it may be emphatically stated that there are no dangerous forms of malaria in which the parasite is not to be found after reasonably careful search.

After the infection has existed for a week or two the crescentic and ovoid pigmented forms of the organism are usually observable. Phagocytosis is very commonly to be noted, and pigment-bearing leucocytes are to be found throughout almost all periods of the fever. The periodicity in the phagocytic action is much less marked than in the ordinary intermittent fevers. This is due in part to the presence at all times of parasites in different stages of development, and in part to the early necrosis of the red blood-corpuscles which is so common in these fevers the dead fragments are speedily engulfed and carried away by the colorless elements. Occasionally, true macrophages, such as are seen in the spleen, may be found in the peripheral circulation; these may be enormous, ten times the size of an ordinary leucocyte. They sometimes contain coarse granules, much larger than any ordinarily seen in the blood, having somewhat the appearance of eosinophilic granules. These cells may contain not only parasites, but red corpuscles, usually shrunken and brassy colored, including a parasite, and also entire smaller phagocytes with their included pigment or parasites or corpuscles.

Fevers with Long Intervals.—From the earliest times there have been described, besides the ordinary quotidian, tertian, and quartan intermittent fevers, other fevers with intermissions considerably longer; thus fevers with intervals of five, six, seven, eight, nine, ten, eleven, and twelve days, or even longer, have been believed to exist. Celsus, who distinguished quotidian, tertian, and quartan fevers, referred to the occasional occurrence of fevers with longer intervals, but noted their rarity.[1]

After Golgi's first researches concerning the life history of the quartan and tertian parasites, and after the fact became settled that a third variety of parasite existed, whose cycle, under some circumstances, lasted but twenty-four hours, the fever in every instance being definitely connected with the segmentation of a group of parasites, it is but natural that many observers should have suspected the existence of other varieties of parasites which in turn might be related to these rare fevers with longer intervals. And Golgi in 1889[2] advanced the hypothesis that the crescentic bodies which we know to be connected with the æstivo-autumnal parasite might bear a definite relation to these forms of fever. He believed that they represented a form of parasite which underwent a long, slow development, lasting from seven to twelve days—that, finally, segmentation of the crescentic forms occurred and paroxysms followed, just as in the case of the regularly intermittent fevers. This variety of parasite, however, differed in the greater length and the irregularity of the cycle of development, while the paroxysms, in like manner, recurred at irregular intervals, from seven to twelve days apart

[1] "Interdum etiam longiore circuitû quaedam redeunt, sed id raro evenit."
[2] *Ziegler's Beiträge*, 1890, vii. 647.

or even more. Canalis[1] believed that the æstivo-autumnal parasite possessed two separate cycles—a shorter, lasting from one to two days, and a longer, associated with the crescentic and ovoid bodies, lasting an indefinite length of time, three or four days at least. Antolisei and Angelini[2] also believed that this variety of parasite was associated with fevers with longer intervals.

Clinically, however, one very rarely observes cases showing a *regular* recurrence of paroxysms at intervals longer than every fourth day. On the other hand, it is not so very unusual to meet with cases where a number of paroxysms have recurred at intervals of, *approximately*, six to fourteen days. In all these instances one is generally compelled to depend largely upon the statements of the patient. An analysis of those cases which have been observed since the recognition of the parasite and its different varieties shows that these fevers with long intervals may be associated with any of the varieties of parasite which we now know. Golgi noted the existence of such paroxysms in patients whose blood showed the æstivo-autumnal parasite. Bignami[3] and Pes[4] described cases occurring in connection with the tertian parasite, while Vincenzi[5] has shown that they may be associated with the presence of any of the varieties of parasites which we now know, alone or in combination.

The manner in which these fevers arise was described first by Bignami. As stated in the description of the parasite, the mere presence of the organism in the circulating blood is not sufficient to produce subjective symptoms. These appear first only when, from steady multiplication, the number of parasites contained in the circulation has reached a certain necessary quantity. With every period of segmentation their number appreciably increases. Not every fresh segment, however, continues to develop. Were this the case, every infection would become pernicious within a short period. With each paroxysm a very considerable number of young parasites is destroyed—so great a number, in fact, that many, indeed the majority, of cases of tertian and quartan fever tend toward spontaneous recovery, though, to be sure, relapses often occur. To what this destruction is due is as yet a matter of doubt. In how far it may depend upon the protective power of the blood serum or upon an active defensive phagocytosis on the part of the leucocytes, or, possibly, upon the deleterious effects of some toxic substance produced, perhaps, by the parasite itself at the time of segmentation, is as yet wholly a matter of speculation. It is, however, not an infrequent occurrence to see, more particularly in tertian or quartan infections, a severe paroxysm followed by a complete disappearance of the symptoms, while the blood shows a disappearance of the group of parasites. The author has previously published charts of this nature.[6] In such instances, through some means or other, the greater part or an entire group of parasites is destroyed at the time of segmentation. In these cases the result is usually complete apyrexia for a certain length of time, from several days to two weeks or even more, and then, after, perhaps, a little warning, a repetition of the paroxysms.

[1] *Fortschritte d. Med.*, 1890, Nos. 8 and 9. [2] *Riforma Medica*, 1890, 320, 326, 332.
[3] *Ibid.*, 1891, No. 165, p. 169. [4] *Ibid.*, 1893, vol. ii. p. 759.
[5] *Bull. R. Acc. Med. di Roma*, 1891–92, p. 631; *Arch. per le Sc. Med.*, vol. xix. f. 3, p. 263. [6] *The Malarial Fevers of Baltimore, loc. cit.*

In some instances the first paroxysm may be followed by a period of apyrexia, lasting, as in one of the author's cases, eight days before the development of a second febrile attack, and that, in turn, by another intermission of approximately the same length of time, and so on, the chart thus showing an intermittent fever with intervals of, perhaps, eight or ten or twelve days. And yet the examination of the blood shows the characteristic parasites of tertian or of quartan fever.

The explanation, then, of these fevers with long intervals is not to be found in a parasite whose cycle of development lasts an unusually great length of time, but in the fact that the first sharp paroxysm is followed by the destruction of so great a number of the parasites that a long period—sometimes practically that of the period of incubation of the disease—must be passed through before the group again reaches a size sufficient to produce symptoms. The recurrent attacks represent, as Bignami pointed out, recrudescences from attacks from which complete recovery has not taken place. Single paroxysms with long intervals, or, more commonly, one or two paroxysms occurring together with long intervals between them, may exist for a very considerable length of time in tertian or quartan infections. Thus, the author has had occasion to observe an individual who for over two years had had occasional chills at irregular intervals of two or three weeks, more or less, due to an untreated tertian infection. One or two paroxysms were almost invariably followed by an apparent complete spontaneous recovery, only to be succeeded in the course of from two to four weeks by another relapse.

In another class of cases the paroxysms with long intervals are due to imperfectly treated malarial fever. Many patients living in malarious districts are in the habit of taking large single doses of quinine immediately following any outbreak of fever. Thus in an instance observed by the author a lady asserted that she had had paroxysms at intervals of ten days. The third or fourth paroxysm occurred under his observation, the blood showing the characteristic tertian parasites. In this instance the patient, by taking a single dose of quinine after each paroxysm, had accomplished the same end which nature accomplishes in the other class of cases—viz. the destruction of the greater part of the group of parasites; and in each instance a relapse occurred about ten days after the previous attack. The same explanation is probably true in the cases occurring in æstivo-autumnal infections. There is no evidence to show that there is any such thing as a regular type of fever occurring at intervals longer than every fourth day. The paroxysms in these instances differ in no way from those in tertian, quartan, or æstivo-autumnal fevers according to the variety of infection.

Combined Infections with Different Varieties of Parasites.

Combined infections with two or more varieties of the malarial parasites may occur, though they are rather uncommon. In 542 cases of malarial fever classified by Hewetson and the author there were only 11 such instances. Clinically, these cases present usually the features of an ordinary tertian, quartan, or æstivo-autumnal infection, and without examination of the blood the presence of two varieties of parasites

would often remain unsuspected. This is due to the fact that the two different varieties of the organism are rarely present each in sufficient number to produce symptoms at the same time. One type of the parasite almost always predominates, and is responsible for the clinical symptoms. Certain cases have been noted where a distinct alternation of symptoms has occurred; a period of quartan fever, for instance, being followed by spontaneous recovery, and succeeded by a period of tertian fever, which, if untreated, pursues the same course, and gives way finally to a relapse of the quartan infection; the parasites of both varieties are present at the same time. In rare instances complicated fever curves may arise from a combined infection. This is, however, very unusual. The commonest combination in this climate is æstivo-autumnal and tertian fever.

THE URINE.—The urine in the malarial fevers has no special diagnostic features. There are no constant changes in the *amount* or in the *specific gravity* of the twenty-four hours' urine. The *color* of the urine is somewhat increased, due probably to the increased quantity of urobilin which is derived from the hæmoglobin of the red blood-corpuscles destroyed by the parasites. The amount of *urea* excreted during the paroxysms is increased, just as it is during any other acute febrile condition. *Albumin* is usually present in serious cases. Thus, out of 284 cases examined by Hewetson and the author, albumin was present in 133 instances, nearly one-half. In many of these instances casts of the renal tubules may be found. Actual *acute nephritis* may occur. Thus in 4 instances out of 335 of our cases evidences of a severe acute nephritis were present—a nephritis which, apparently, owed its origin directly to the malarial infection. In 3 of these instances the nephritis was hemorrhagic in nature; in the other case, which resulted fatally, there was an extensive acute diffuse nephritis. Ehrlich's diazo reaction may be present; it was found in 5.5 per cent. of our cases.

The Toxicity of Malarial Urine.—Extremely interesting researches have lately been made concerning the increased toxicity of the urine during malarial fever. Brousse,[1] studying the effects following the injection of the urine of cases of malarial fever into animals, arrived at the following conclusions: "(1) The urotoxic coefficient calculated by Bouchard's formula, the mean coefficient being 0.464, rises during the paroxysm, and the physiological effects observed are those which usually follow the injection of urine—dyspnœa, myosis, falling of temperature, exophthalmos, and furthermore convulsions; (2) this toxicity is diminished during the period of convalescence in intermittent fever, very much below that of the urine during the paroxysm, and moreover below that of the normal urine."[2]

Roque and Lemoine[3] studied the urine in 3 cases of malarial fever—one a case of tertian fever and two cases of pernicious comatose malaria. Their conclusions were as follows: "(1) The pathogenic agents of paludism form, in the blood, a large quantity of toxic products, a great part of which is eliminated by the urine. This elimination is at its maximum immediately after the paroxysm, and lasts, generally, twenty-

[1] Quoted from Laveran, *Du Paludisme, etc.*, Paris, 1891.
[2] *Société de Méd. et de Chir. pratiques de Montpellier*, 14 Mai, 1890.
[3] *Revue de Méd.*, 1890, p. 926.

four hours, at least in the paroxysms of tertian fever. (2) Sulphate of quinine acts by favoring the increase of this elimination. (3) Certain pernicious fevers, showing a complete absence of toxicity in the urine, depend probably upon alterations in the kidneys and liver, and the return of the urinary toxicity should be considered a good prognostic sign. (4) Finally, it may be noted that in two cases recovery has followed a more increased elimination of toxines than that observed after the preceding paroxysms." In discussing this paper Lépine justly remarked that injections should be made not only with the pure urine, but also with a solution of the salts of the urine made after calcination. This alone can give a reliable idea of the toxicity of the urine dependent upon organic compounds.

More recently Botazzi and Pensuti[1] have made an elaborate control research, and, while finding the same general results as Roque and Lemoine, dispute their conclusions. Their studies were carried out in ten cases. They collected urine during and after the febrile periods. They found that during the paroxysm the urine showed a less intense color than afterward. During the febrile periods examination of the urine with the ordinary reagents which are used in qualitative analysis showed always a diminished amount of alkaline and earthy phosphates, while that voided after the paroxysm showed sometimes a considerable quantity. The specific gravity of the urine passed after the paroxysm was higher than that during the paroxysm. They state that under other conditions the urotoxic coefficient has been shown to run parallel to the elimination of the potassium salts, while the presence of peptones in the urine increases appreciably its toxicity. Both these substances they found present in increased quantities in the urine passed after the paroxysm. The urobilin, as already stated, is present in increased quantities in the urine of malarial fever, and especially so in that following the paroxysm. The toxicity of this substance has been demonstrated by these authors, who found that the urine passed after the paroxysm, when decolorized, lost half its toxicity. They assert, in opposition to Roque and Lemoine, that "there is no need to suppose the presence of special toxic substances of the nature of leucomaïnes to account for the toxicity of malarial urine" [after the paroxysm]; "the potassium, the phosphoric acid, the peptones, the urinary pigments, and especially urobilin, which are found in this urine in markedly increased quantities relatively to the normal urine and to that of the febrile period, are of themselves a sufficient explanation." The cause of the increased presence of these substances is not difficult to appreciate. The potassium salts and the pigments which they believe to be the chief cause of the hypertoxicity result from the destruction of the red blood-corpuscles, and the phosphoric acid and peptones are doubtless due to the disintegration and combustion of the albumins and nucleins of the cellular elements of the tissues. They have not found evidence of a marked retention of toxic substances owing to disease of the kidneys, as asserted by Roque and Lemoine.

In conclusion, they state: "We think that we have demonstrated (1) that in the malarial fevers the febrile urine is less toxic than that emitted during the apyretic stage; (2) that the urine emitted during the period of apyrexia is more toxic than normal urine; (3) that the

[1] *Lo Sperimentale*, Firenze, 1894, xlviii. 232, 254.

toxicity of the urine of malarial patients augments constantly with the succession of febrile attacks, though in some cases this augmentation appears in the form of unexpected and irregular exacerbations; (4) that, as there is nothing specific in the course of the intoxications produced in rabbits with malarial urine, there is no need to suppose the presence of specific toxins or substances of the nature of leucomaïnes, for the salts of potassium, phosphoric acid, the urinary pigments, the peptones, all of which substances are eliminated in increased quantities, are a sufficient explanation; (5) that the injection of febrile urine is followed by a slower intoxication, characterized by sopor, by increased diuresis, by diarrhœa, and mydriasis, while the apyretic urine produces a more acute effect, sometimes fulminating, characterized by clonic and tonic spasms and myosis, '*exhorbitisme*,' spastic expiration; (6) that to explain this different picture one may suppose that with febrile urine the polyuria and diarrhœa are due chiefly to the increased richness in the urea, while the peptones may contribute to the production of sopor. In the afebrile urines the salts of potassium, the phosphoric acid, the urinary pigments, and especially the urobilin, manifesting themselves as substances essentially convulsive, determine hypertoxicity. (7) Finally, besides the hæmocytolysis and the destruction of the cellular elements of the tissues, and the formation and elimination of toxic substances, there must exist intermediate factors which account for the absence of increased toxicity after the first febrile paroxysms and the irregular elevation and diminution in the urotoxic coefficient in some other cases." Laveran speaks also conservatively concerning these experiments as a proof of the existence of a specific toxin.

In conclusion, then, one may say that while a distinct increase in the toxicity of the urine has been shown to be present after malarial paroxysms, there is as yet no proof that this is dependent upon specific products of the action of the malarial parasite.

The Blood.—Besides the presence of the parasites, the examination of the blood in malarial fever reveals certain other changes which are at times valuable from a diagnostic point of view.

(*A*) *The Regularly Intermittent Fevers.*—An actual *anæmia* always occurs in malarial fever. Kelsch,[1] Kalindero,[2] Dionisi,[3] all noted that a considerable fall in the number of *red blood-corpuscles* to the cubic millimetre occurred after each paroxysm, while similar results were obtained by Dr. Kirkebride in some counts made under the author's observation in 1893. The fall in the number of red corpuscles may be quite considerable, though in tertian and quartan fever the restitution to normal is very rapid. Always, however, after several paroxysms have occurred there is a certain degree of anæmia, which, if the disease be allowed to continue, may become quite marked.

The percentage of *hæmoglobin* falls with the number of corpuscles, but usually to a somewhat greater extent, while the return to the normal point, as noted by Rossoni,[4] takes place more slowly than that of the red corpuscles.

[1] *Arch. de Phys.*, 1876, ii. s., t. iii. 490.
[2] *Jour. de Méd. et de Pharm. d'Algérie*, 1889, xiv. 123.
[3] *Lo Sperimentale*, 1891, t. iii. and iv. 284.
[4] *Lav. d. Cong. d. Soc. Ital. d. med. Int., II° Congresso*, Roma, Oct., 1889, 121.

The behavior of the *colorless corpuscles* in malarial fever has been noted especially by Kelsch,[1] Kalindero,[2] Bastianelli,[3] and Billings.[4] It has been shown that the number of leucocytes in malarial fever is almost invariably subnormal. The smallest number of leucocytes is seen just after the paroxysm when the temperature is subnormal. From this time there is a gradual, slight increase, which becomes accentuated just before the paroxysm. A rapid diminution in number occurs again during the paroxysm. At no time is there leucocytosis.

(*B*) *The Æstivo-autumnal Fevers.*—The changes in the blood in the æstivo-autumnal fevers are very similar to those in the regularly intermittent forms, differing only in their intensity. The red corpuscles show a marked diminution with each paroxysm. When the parasites are numerous this reduction amounts, sometimes, to as much as a million corpuscles during a single paroxysm. Between the attacks the corpuscles do not show the same tendency to return to the normal number which is observed in the regularly intermittent fevers. The restitution is imperfect and incomplete. The number, however, rarely falls below one million to the cubic millimetre, although Kelsch has seen as small a number as five hundred thousand. The *colorless corpuscles* are almost invariably reduced in number. The changes in number follow the same course here as in the regularly intermittent fevers. There is a diminution after the paroxysm, a slight rise just before the beginning of the succeeding attack, with a fall again later on. The *hæmoglobin* follows the same curve as do the red corpuscles, falling, however, generally to a slightly greater extent.

In certain instances a well marked leucocytosis has been noted in pernicious paroxysms. Bignami has noted the unfavorable inferences that one may draw from this symptom. In some instances this, very possibly, depends upon a secondary mixed infection. In other instances, however, it may occur where cultures from the organs are quite negative. Thus, in one of the author's cases of the pernicious algid type the blood contained, one hour before death, sixty thousand leucocytes to the cubic millimetre. The leucocytes in malarial fever show certain other changes which are quite characteristic and interesting. Just as in the case of typhoid fever, where the number of leucocytes is ordinarily subnormal, so in malarial fever, one finds upon a differential count a well marked reduction in the percentage of the polymorphonuclear neutrophiles, with a corresponding relative increase in the percentage of the large mononuclear forms. Thus the average numerical proportions of the various forms of leucocytes in sixteen cases analyzed in this clinic by Billings were as follows:—

Small mononuclear	16.9
Large mononuclear	16.9
Polymorphonuclear	65.04
Eosinophilic	0.96

In the pernicious case above referred to, observed by the author, the relative proportions of the different varieties of leucocytes, notwithstanding the leucocytosis, were as follows:

[1] *Arch. de Phys.*, 1876, ii. s., t. iii. 490. [2] *Loc. cit.*
[3] *Bull. d. R. Acc. Med. d. Roma*, 1890, Anno xviii., f. v. 297.
[4] *Johns Hopkins Hospital Bulletin*, 1894, No. 43, 105.

Small mononuclear	23 per cent.
Large mononuclear and transitional forms	18.4 "
Polymorphonuclear	58.6 "

The changes in the blood in malarial hæmoglobinuria have been already referred to.

The grave anæmiæ which may follow malarial fever will be considered later among the sequelæ.

Sequelæ and Complications.

There is no one point in the history of the development of our knowledge concerning the malarial fevers where so much confusion and misapprehension has existed as in the appreciation of the nature of the sequelæ and complications. The relation of chronic cachexia and grave anæmia to malaria has long been recognized, as well as the existence of an acute post-malarial nephritis. The grave cerebral, nervous, gastro-intestinal symptoms which may occur with acute malaria have been already referred to. Many observers, however, do, even today, ascribe to the malarial poison the capacity of producing of itself a considerable number of other complicating processes ordinarily dependent on other specific causes. These observers have in particular described a characteristic "malarial pneumonia," "malarial dysentery," etc. That such misapprehension should have arisen is not remarkable when we consider the many ways in which the simple malarial process may be masked or complicated.

Ascoli[1] states clearly the main possibilities in this direction as follows: "Finally, in conclusion, we may distinguish the following clinical forms: (1) Malaria which simulates another pathological process. (2) A disease, the [ordinary] course of which is known, which, in an individual suffering with chronic malaria, progresses and develops anomalies in its course according to the stage of the cachexia.[2] (3) A fresh malaria develops in a subject who is at that time in an apyretic stage of the disease or suffering from the remains of a former infection (*combinata*). (4) Different varieties of the hæmatozoa exist in the blood of a patient suffering from malaria alone (*mista*). (5) Two febrile diseases exist together and contemporaneously (*concomitanti*): (*a*) exerting a reciprocal influence detrimental to the organism (*proporzionate*); in certain of these cases the reciprocal influence is not manifest throughout the entire course; (*b*) each preserving its more constant and common symptomatology (*associata*). (6) The malaria may prepare the ground for the development of another acute infection, or it may follow after another infection has run itself out (*consecutiva*)."

The sequelæ and complications of malarial fever may be divided into—(1) Those sequelæ or complications due directly to changes produced by the malarial parasites or their toxic products; (2) true complications, mixed infections.

1. **Sequelæ and Complications due directly to Changes produced by the Malarial Parasites or their Toxic Products.**—In the section upon the pernicious fevers the acute symptoms produced by the special

[1] *Bull. della Soc. Lanc. d. Osp. di Roma*, An. xii., 1891–92, 103.

[2] "Una malattia di processo morboso noto che, attacando un malarico chronico, assume andamento e parvenze variabili secondo lo stadio della cachessia."

localization of the parasites in the brain, lungs, or gastro-intestinal tract have already been discussed. It is therefore unnecessary to refer again to the acute choleriform and comatose cases which might so readily suggest a mixed infection.

Relapses.—The extreme frequency with which relapses are met in malarial fever has been referred to in the section on fevers with long intervals. Most cases, unless treatment be thoroughly carried out, show recrudescences in the course of one or two or three weeks. These are clearly proven to be due to the fact that all the parasites have not been destroyed by the treatment. The few which escape form a nucleus for the development of new groups, which in the course of a week or two arrive at a degree of development sufficient to result in a fresh outbreak of the symptoms. The recrudescences are, ordinarily, in every way similar to the original attacks. There is, however, another variety of relapse which has been recognized for many years—viz. the reappearance of an infection many weeks or months after all symptoms have disappeared. Undoubtedly, many such cases are fresh infections. There are, however, cases where a fresh infection can be definitely ruled out, while the malarial nature of the process is undoubted. An interesting example of the reappearance of fever after a long period of perfect health is the case of a friend of the author, a physician himself, wholly familiar with malarial fever, clinically and pathologically. During the fall of 1880 Dr. —— suffered from a prolonged attack of tertian fever which reduced him to rather a cachectic condition. Recovery followed full doses of quinine. For twenty-one months after this the health was perfectly good, the patient living in non-malarious districts. On a hot afternoon of August, 1882, while making a pedestrian tour in the Tyrol, after a prolonged walk, during which the patient was subjected to great changes of temperature, there was a well defined characteristic malarial paroxysm. The true nature of the attack was not suspected, but on the third day, at the same hour, while travelling in a railway-carriage, there was a second paroxysm. On the fifth day, again, at the same hour, a third characteristic paroxysm occurred. Convinced then of the malarial nature of the attacks, treatment with quinine was begun, which resulted in the immediate and permanent disappearance of the paroxysms. In the words of Dr. ——, "In this case there can be no question of a second infection. I had not been in a country where there was any malaria for two years, and for three weeks before the appearance of the first chill I had been in the mountains of the Tyrol."

The absolute proof—the discovery of the parasite—is here wanting; there can be little doubt, however, as to the nature of the case. The explanation of these cases is difficult. It is highly improbable that the parasite has remained present in the blood, passing through its ordinary cycle of development, and yet some form of the parasite must exist throughout this time. Bignami, as was noted in the description of the parasite, suggests that some form of the organism—which perhaps we have not yet been able to discover, possibly a non-staining spore—may persist in some of the internal organs, possibly within the protoplasm of some of the cellular elements.

Chronic Malarial Cachexia.—The commonest sequel to malarial fever is that which is generally known as chronic malarial cachexia.

In malarious districts many patients allow an infection to continue for weeks, months—nay, in some instances, even for years—without ever attempting a systematic or thorough treatment. The result is, naturally, a serious drain upon the vital resources of the individual. The course of such a case is commonly as follows: The patient has several paroxysms, and takes a few doses of quinine, which are followed by a disappearance of the fever, or after a week or so of paroxysms which have been untreated the fever disappears spontaneously. Frequent relapses occur which are improperly treated or allowed to take their own course. In some instances of æstivo-autumnal fever a patient may remain for a long period of time with a slight, irregular fever, no sharp, definite, malarial paroxysms being observed. The first result of a continued process of this nature is the gradual development of an anæmia which usually becomes marked, and is sometimes extremely grave. The patient has a sallow, grayish yellow color; the lips and mucous membranes are blanched; the tongue is often coated; there is frequently œdema of the dependent parts. The spleen is usually greatly enlarged, sometimes reaching to the right of the median line. Indeed, some of the largest splenic tumors which occur may be seen in these cases. The hepatic flatness is increased in extent; the border is often palpable, reaching sometimes a considerable distance below the costal margin. The patient suffers greatly from exhaustion, severe headache, pains in different regions of the body. Severe supraorbital neuralgia may exist. Sudden motion or exertion is followed by vertigo or fainting. The gait is tottering and unsteady; there may be a marked general tremor.

The examination of the *blood* during an afebrile stage may be quite negative, excepting for the anæmia. More commonly occasional parasites or pigmented leucocytes may be found, while in æstivo-autumnal infections the characteristic crescentic or ovoid pigmented bodies are usually to be seen. Chronic cachexia may follow any variety of infection. In the majority of instances, however, it represents an untreated æstivo-autumnal infection, and in these instances the crescentic and ovoid forms of the parasite may be found. The same condition also follows frequently repeated attacks, even though the individual attack has been actively treated. The tendency toward dropsical transudations is generally decided, and at times may give rise to confusion. Thus, in several instances the author has observed cases of moderate anæmia with quite marked œdema of the dependent parts and complete absence of fever, where, owing to an unsatisfactory history and the failure to find parasites in the blood, the true nature of the process was wholly unsuspected until the appearance, within several weeks, of a relapse. Gastro-intestinal disturbances are very common in malarial cachexia, and the grave anæmia, with diarrhœa, œdema of the dependent parts, the enormous splenic tumor, reduce the patient to a most distressing condition of marasmus, where he is an easy prey to complicating infections of all sorts.

Chronic malarial cachexia is not uncommon in children, where, owing to the irregularity of the symptoms, the true nature of the process is often unsuspected. It may lead to the most intense grade of infantile atrophy. The child becomes greatly emaciated; the sallow,

grayish yellow, parchment-like skin hangs in folds; the mucous membranes are blanched. There are occasionally slight febrile attacks, the child becoming cold and blue, or, perhaps, showing now and then a slight eclamptic attack. There are persistent gastro-intestinal disturbances, vomiting, diarrhœa, as well as, perhaps, diffuse bronchitis. The spleen is always enormously enlarged.

Post-malarial Anæmia.—The anæmia associated with malarial fever may assume various forms. Thus, Bignami and Dionisi[1] have distinguished four types of post-malarial anæmia.

(1) Anæmia, in which the examination of the blood shows alterations similar to those observed in ordinary secondary anæmia, differing from these cases only in that the leucocytes are diminished in number. These cases often show well marked oligocythæmia; oligochromæmia relatively greater; more or less poikilocytosis; nucleated red corpuscles (normoblasts). The leucocytes, as already stated, are diminished in number, while the relative proportion of the large mononuclear forms is increased at the expense of the polymorphonuclear cells. The greater number of these cases go on to recovery; a few, however without any change in the hæmatological condition, pursue a fatal course.

(2) Anæmia in which the blood shows changes or alterations similar to those common in pernicious anæmia—*i. e.* marked oligocythæmia; oligochromæmia relatively less; marked poikilocytosis; nucleated red corpuscles, for the most part gigantoblasts; leucocytes, diminished in number with an increase often in the small mononuclear forms, and a diminution in the polymorphonuclear varieties. These cases end fatally.

(3) Anæmia showing the ordinary characteristics of secondary anæmia, excepting for the complete absence of regenerative forms (nucleated red corpuscles). These cases are progressive and fatal, the marrow, at autopsy, showing, as has already been stated, no evidence of regenerative activity.

(4) Chronic secondary anæmiæ occur in prolonged cases of malarial cachexia, and are remarkable for the small number of nucleated red corpuscles present and the marked reduction in the number of the leucocytes, particularly of the polymorphonuclear variety. There are, however, post-malarial anæmias which do show after the clearing up of the infection a leucocytosis similar to that in ordinary secondary anæmia. This is probably a favorable sign, pointing to a rapid regeneration.

Malarial Nephritis.—The grave damage which the kidneys may suffer in certain acute malarial infections, either from the direct action of some toxin produced by the hæmatazoa or from the presence in the circulation of injurious substances, due indirectly to the action of the parasite, is most strikingly brought to one's notice in the intense acute nephritis which, as described in a previous section, may follow malarial hæmoglobinuria. The kidney, however, rarely escapes a certain amount of damage in any severe malarial infection. Thus, out of 284 cases analyzed by Hewetson and the author, albumin was found in nearly one-half, while severe acute nephritis was present in 4 instances. The nephritis following malarial fever is usually a mild acute, diffuse process similar to that observed in any infectious disease. In some instances, as stated in the section on malarial hæmaturia, the course

[1] *Loc. cit.*

may be rapid and fatal; in the majority, however, the prognosis is favorable and complete recovery occurs. It is not impossible that, in some instances, a fatal chronic diffuse nephritis may owe its origin to the malarial poison; however, definite proof of this is as yet wanting. There is nothing absolutely characteristic, clinically or pathologically, in these instances of malarial nephritis.

Amyloid Degeneration.—Amyloid degeneration is an occasional sequel to malarial fever. Two cases were reported by Frerichs,[1] and several others have recently been studied by Marchiafava and Bignami.[2] These cases have followed after a long series of febrile attacks, those which have been carefully studied having been æstivo-autumnal or obstinate quartan fever. The clinical symptoms are those of nephritis accompanied by an extremely rapid cachexia, ending fatally, as a rule, within several months. The blood in these cases may show the condition first noted by Ehrlich as of grave portent—viz. complete absence of nucleated red corpuscles and eosinophilic cells, and reduction in the number of the leucocytes, with an excess of lymphocytes, while at autopsy the marrow of the long bones is found to be entirely fatty, showing no evidence of an attempt at proper regeneration.

Atrophy of the Gastro-intestinal Mucosa.—Pensuti[3] has reported a case of extensive atrophy of the gastro-intestinal mucosa following, apparently, an acute malaria. Constant diarrhœa followed the attack, resulting in great exhaustion and death from broncho-pneumonia in three months. Though Baccelli was inclined to believe that the change was directly due to the action of some toxic substance connected with the malarial infection, the case cannot be said to be wholly convincing.

Malarial Hepatitis; Malaria and Cirrhotic Processes.—As has been stated in the section on *Pathological Anatomy*, many observers insist upon the occurrence of a true atrophic cirrhosis of the liver as a sequel to malarial fever. There are many reasons which would lead us to believe that this may, in some instances, occur, but clinically, in this climate at least, such cases are rarely met with. In few instances does one meet with a true atrophic cirrhosis of the liver in which other important etiological factors have not also been present. No such case has come under observation in the Johns Hopkins Hospital in the seven years since its opening. On the other hand, chronic hepatitis, resulting usually in an increase in the size of the liver, is commonly observed in malarial cachexia and following repeated malarial infections. Distinct clinical symptoms due to the hepatic changes do not apparently exist.

Malarial Paralyses.—*Cerebral Paralyses.*—Various paralyses have been described in association with malaria. The different forms which may occur in acute pernicious malaria have already been referred to. They are usually transitory, disappearing under treatment, and are due probably to circulatory disturbances induced mechanically by the parasites: they are almost always cortical in nature. The nervous symptoms in acute malaria are more commonly irritative than paralytic.

Occasionally symptoms suggesting involvement of the *spinal cord*

[1] *Loc. cit.* [2] *Loc. cit.*
[3] *Gaz. Med. di Roma*, 1893, xix. 121.

may occur. Several Italian observers have reported cases where the symptoms strongly suggested *disseminated sclerosis*. In all these instances the parasites were found in the circulating blood, and recovery followed treatment by quinine. In one of Torti's[1] cases there was, however, no fever, notwithstanding the presence of active parasites in the blood. In such instances it is easy to conceive that without examination of the blood a diagnosis would be quite impossible. DaCosta[2] has also reported a case of paraplegia with intention tremor, severe headaches, bitemporal hemianopsia, and mental symptoms, where the blood showed the æstivo-autumnal parasites. Recovery occurred under quinine. The cases of "acute ataxia" reported by Kahler and Pick[3] were probably truly malarial. Bastianelli and Bignami[4] have reported a case showing symptoms of the so-called "*electric chorea*" or "*Dubini's disease*." This was associated with a continued fever, the nature of which was not, at first, determined. Examination of the blood later showed it to be due to an æstivo-autumnal malarial infection. Recovery occurred under quinine. They believed that the process was due to "lesions secondary to the cerebral localization of the parasites."

All of these processes coming on with acute malarial fever are essentially favorable in their course if treatment be begun in time. According to Boinet and Salibert, however, permanent paralyses, both cerebral and spinal in nature, may follow malarial fever.

Cases of *peripheral neuritis* following malarial fever have been reported, though definite proof that they were malarial in origin has not been obtained. From what we know, however, of the pathogenesis of the disease, we may readily believe that malarial fever as well as other acute infectious diseases, may be followed by acute degenerative lesions in the peripheral nerves.

Some observers have believed that there was some predisposing relation between malarial fever and *Raynaud's disease* (symmetrical gangrene), though this is by no means proven. Poncet has described a retinitis and a *retino-choroiditis*, due to emboli of melaniferous leucocytes in the capillaries.

Mental Diseases.—Various mental affections may follow malarial fever, just as may be the case with any acute infection. There is nothing especially characteristic in these cases. Thus, one of our instances of tertian malaria was followed by an attack of paranoia lasting for several months.

True Complications and Mixed Infections.—Malaria, like any other acute disease, is subject to various complications, many of which are a result of mixed infections with other pathogenic agents. As stated before, many of the symptoms caused by mixed infections were believed by the older observers to be due directly to the malarial poison. Of late, however, with our increased facilities for study and appreciation of these conditions, it has been recognized that in the majority of instances the complication is dependent upon a true mixed infection.

Pulmonary Complications.—Pneumonia.—As has been stated

[1] *Bull. d. Soc. Lanc. d. Osp. d. Roma*, 1891, xi. 217.
[2] *International Clinics*, Philada., 1891, iii. 246.
[3] *Beiträge z. Pathologie u. Pathologischen Anatomie des Centralnervensystem*, Leipzig, 1879.
[4] *Bull. d. R. Acc. Med. di Roma*, 1893-94, Anno xx. p. 221.

in an earlier section, many observers have described pernicious fevers which during the paroxysm showed well marked pulmonary symptoms, dyspnœa, pain, hæmoptysis. These symptoms, dependent probably upon the special localization of the parasites in the pulmonary capillaries, are to be sharply distinguished from true pneumonia, which may, and not unfrequently does, complicate a malarial attack. Again, in certain instances an ordinary acute pneumonia may present an intermittent fever which simulates quite closely the chart of intermittent malarial fever. These cases, however, may be readily recognized by the absence of the parasite from the circulating blood. Such cases have been described by Wunderlich, Jaccoud, Bertrand, and Andrew Clark, while Ascoli[1] gives an excellent chart. True acute pneumonia and malarial fever may, however, coexist. In these instances the course of the pneumonia may be but little influenced by the coexisting malarial fever, while in other instances the exacerbations and remissions of temperature may be quite marked. Here the pulmonary process is a genuine croupous pneumonia, due, as has been shown by Marchiafava and Guarnieri,[2] to infection with the diplococcus lanceolatus. Its course is quite uninfluenced by the administration of quinine, and its connection with malarial fever is purely accidental, unless, as it may be in some instances, a preceding malaria has prepared the ground for the pneumococcus infection by reducing the vital forces of the individual. Pneumonia occurring in individuals suffering with chronic malarial cachexia appears to pursue an unusually malignant course, owing, doubtless, to the reduced condition of the patient. Retarded resolution and "organization" of the exudate are not uncommon in these instances (Ascoli). *Broncho-pneumonia* is also occasionally observed in association with malaria. The infection, however, is purely secondary, in no way directly related to the malarial process.

Pleurisy.—Certain observers have described symptoms in acute pernicious malaria suggesting pleural involvement where, on autopsy, nothing was to be found. In other instances pleurisy and malarial fever may coexist, although there is nothing whatever to show that this pleurisy is not an entirely separate process from the malarial infection. There is nothing abnormal in the clinical or pathological course of such a pleurisy; it is uninfluenced by the administration of quinine. These cases are not to be confounded with the pleural transudations which may occur in cachectics. Quinine has no influence upon the process.

Typhoid Fever.—The relations between malarial fever and typhoid fever have been much discussed, and are today probably more generally misunderstood in this country than any one point in connection with the febrile diseases. Since the discovery of the malarial parasite, with our modern means of diagnosis, there is no reason for the existence of any such confusion at the present day. The great similarity between the symptoms in certain cases of æstivo-autumnal fever with typhoid fever has been pointed out in earlier sections. There is, however, no excuse whatever for the physician who today fails to recognize the malarial nature of such a fever after a few days' observation. The simple examination of the blood will invariably settle this question, the parasite being always present.

[1] *Loc. cit.* [2] *Bull. d. R. Acc. Med. di Roma*, xv. 1888–89, 355.

Few are unfamiliar with the term so commonly employed, "typho-malarial fever." It was supposed that in malarious districts there existed a continued fever which depended upon the combined action of two poisons, that of malaria and that of typhoid fever—true "*proportionata*," in the sense of the old Italian observers. This fever was supposed to be markedly resistant to quinine and to betray its malarial nature by the frequency with which rigors occurred. We know today that "typho-malarial fever" as a distinct entity does not exist. Rigors occurring in the course of typhoid fever are by no means uncommon, but are of themselves wholly insufficient evidence on which to base a diagnosis of malaria. We know, on the other hand, that there exist, in this country at least, no malarial fevers which resist for more than three or four days the action of quinine. True complications of typhoid fever and malaria may occur, but they are rare, only one doubtful instance having been observed in seven years in the Johns Hopkins Hospital, where both typhoid fever and malaria are, unfortunately, very common. Typhoid fever may be acquired by a patient suffering from acute or chronic malaria. A fresh malarial infection may break out or a slumbering infection may come to life again during the course of typhoid fever. But this condition is uncommon, and in no way justifies the term *typho-malarial fever*. There is little doubt that the enormous majority of cases referred to today as "typho-malarial" fever in this country and elsewhere are cases of typhoid fever, pure and simple. Too much stress cannot be laid upon this point, for the groundless assumption that there exists in this country a fever due to the combined action of typhoid and malarial poison, pursuing a fairly characteristic course and calling, from its malarial nature, for the continued use of quinine, has exercised in the past, and is exercising today, an extremely injurious influence upon the medical practice of this country. This influence cannot fail to be appreciated by the intelligent observer who has occasion to note the quantities of quinine which are systematically administered to many cases of uncomplicated typhoid fever in various districts of the United States.

In the instances of true mixed infection of typhoid and malarial fever the picture may be most varied. If a fresh malarial attack or a relapse break out during the course of typhoid fever, well marked indications of the paroxysms, varying according to the type of parasite present, may be observed, as shown admirably by the charts recently published by Gilman Thompson.[1] In these instances the blood shows the presence of the parasites; these, with the symptoms dependent upon them, disappear immediately after ordinary doses of quinine. If, on the other hand, the typhoid fever develop in the course of latent or chronic malarial infection, the symptoms on the part of the malarial parasite may be almost absent.

Intestinal Complications.—The occurrence of diarrhœa, particularly in children, during acute paroxysms is well known. The changes produced by the malarial parasite in the intestine in certain acute pernicious cases have already been considered; the acute choleriform pernicious paroxysm is truly malarial in nature. There is nothing, however, to show that the more chronic dysenteries and diarrhœas often

[1] *Trans. Ass. Am. Phys.*, 1894, 110.

associated with cachexia are in any way directly connected with the action of the malarial poison, excepting in so far as this may have prepared the ground. It is not impossible to conceive that severe infections might follow directly upon an acute choleriform attack. Particularly interesting are several cases noted in the medical clinic of the Johns Hopkins Hospital, where the *Amœba coli* has been found in the dejecta of patients suffering simultaneously with acute malaria and dysentery. In all of these instances the intestinal process might well have been directly ascribed to the malarial poison. The frequency with which the Amœba coli is associated with tropical dysenteries makes it exceedingly probable that many of these post-malarial intestinal affections in tropical climates may be in reality due to a mixed infection with the two protozoa, as in our instances.

Tuberculosis.—Numerous observers, and particularly Boudin,[1] have asserted that tuberculosis was directly antagonistic to malarial fever and the converse. Boudin pointed out that tuberculosis was rare in countries where malaria existed, and that where tuberculosis was common malaria was rare. This assumption has exerted a certain influence on the minds of many. Experience, however, has shown that it lacks foundation. In many of the districts where malaria is common it is true that tuberculosis is unusual, owing to certain climatic influences. In the northern regions, where tuberculosis is more common, malaria, as is well known, is relatively infrequent. In other regions we find malarial fever and tuberculosis side by side, intimately associated, occurring, by no means infrequently, in the same patient. Marchiafava,[2] indeed, is inclined to believe from his observations that chronic malaria is not an unimportant predisposing cause to pulmonary tuberculosis. It is, however, really interesting that among the 614 cases analyzed by Hewetson and the author in not a single instance was pulmonary tuberculosis present.

Other Infections.—Infection with the other pathogenic organisms is not so very rare; thus the author has observed *furunculosis*, *parotitis*, *tonsillitis*, and *acute rheumatism*, while in one fatal case, admirably studied by Barker, there was a general infection with the *Streptococcus pyogenes*. Antolisei and Laveran have observed cases of *variola* complicated during convalescence by characteristic malarial fever, while Baccelli has observed the same in cases of other *exanthemata*.

Post-partum and Post-operative Malaria.—One hears not infrequently of post-partum and post-operative malarial fever, and it is, alas! only too common today to ascribe elevations of temperature during the first few days after operation and during the puerperium to malarial fever. This condition is probably rare. There are few such instances in literature where the malarial nature of post-partum paroxysms was definitely proven. In the seven years since the opening of the Johns Hopkins Hospital not a single case of post-operative malaria has occurred. Undoubtedly, the reduced condition of the patient during these periods might, and probably does, favor a recrudescence of the latent malarial infection. It is, on the other hand, probable that the majority of instances of supposed post-partum and post-operative malaria have no

[1] *Traité des Fièvres intermittentes*, Paris, 1842.
[2] *Bull. d. Soc. Lanc. d. Osp. d. Roma*, 1891, Anno xv. 186.

connection whatever with true malarial fever, but represent simply a septic infection. This has been the case in every instance of suspected post-operative malaria which has come under the author's observation.

Insolation.—The complication of an active or chronic malarial fever with insolation is probably not very uncommon. Bastianelli and Bignami[1] have recently demonstrated in an interesting manner the frequency with which such cases have, in Italy, been considered as essentially malarial in nature. The pernicious malarial fevers are particularly common at the hottest season of the year, while the individuals most subjected to malarial infection are also often those who work bareheaded in the fields, exposed directly to the sun's rays. These observers called attention to the fact that a number of instances of what has been considered pernicious comatose malaria have been reported in which, at autopsy, only cerebral hyperæmia, pulmonary hypostasis, and slight degenerative changes in other organs were observed. In some of these cases no malarial parasites were to be found; in others, evidences of a recent infection; in others, perhaps the evidence of a recent infection with the presence of a small number of active parasites—far too few, however, to account under ordinary circumstances for such grave symptoms. Cases of this nature have led some observers to assume that a very small number of parasites might give rise to severe pernicious symptoms, owing to their excessive malignancy. It is much more probable, as Bastianelli and Bignami state, that the process represents a complication of malarial fever with insolation which might occur in an individual with active malarial fever or in one who has recently recovered from an attack. Indeed, it is not impossible that a preceding malarial infection, by reducing the strength of the individual, may render him more subject to such attacks.

Diagnosis.

(1) The Regularly Intermittent Fevers.—The diagnosis of the regularly intermittent, tertian, and quartan fevers is generally a relatively simple matter. The regular paroxysms with their three stages of chill, fever, and sweating are so characteristic as to leave little doubt in most instances concerning the nature of the process. The anæmia and the enlarged spleen which are present in the vast majority of instances are also important from the point of view of differential diagnosis. Occasionally paroxysms very closely similar to the malarial access may occur from other infectious causes, and sometimes the regularity with which the individual paroxysms may succeed one another may lead to errors in diagnosis. The paroxysms, however, in malaria differ in certain respects from those occurring in most other acute infections. Thus, the average duration of the malarial paroxysm, if we estimate the course from the time the temperature passes 99° until it again falls below this point, is from ten to twelve hours, while in other infections the course is often materially shorter. There may, of course, be mild malarial paroxysms which last but four or six hours, but in these the temperature is correspondingly moderate. One rarely observes in malarial fever temperatures of 104°, 105°, or 106° in a paroxysm lasting as short

[1] *Bull. d. R. Acc. Med. d. Roma*, 1893–94, Anno xx. p. 151.

a time as six hours or even less. The writer has seen cases of septic infection in which, for a considerable length of time, chills closely simulating those of malarial fever occurred, while the anæmia and enlarged spleen were also present. The chief difference to be noted was the marked difference in the length of the paroxysms, which were sometimes as short as four or five hours, the temperature reaching, perhaps, within this time a point as high as 106°. The same may be true of the chills which are not so infrequently seen during the course of typhoid fever—chills caused, doubtless, by auto-intoxications as yet not understood. Whenever the temperature rises as high as 104° and the paroxysm lasts no longer than six hours, one is justified in the suspicion that the fever is not malarial in origin.

At times, however, other infections may give rise to paroxysms most closely simulating those of malarial fever. Thus, in two instances the writer has observed typical quotidian paroxysms lasting from ten to twelve hours, and beginning nearly at the same hour on two successive days, which were considered to be malarial in nature, but which, upon examination, turned out to be due to acute otitis media (in one instance due to the diplococcus lanceolatus).

The intermittent fever which is most commonly confused with malaria is that associated with *pulmonary tuberculosis*. It is probably no exaggeration to say that the majority of cases of pulmonary tuberculosis arising in the malarial districts of this country are, at some time in their course, mistaken for malarial fever. Intermittent fever, recurring often at fairly regular hours on succeeding days, is the rule at some stage, earlier or later, of pulmonary tuberculosis, while actual chills may occur. It is natural that the patient should ascribe such symptoms to malaria; there is, however, no excuse today for such error on the part of the physician. The sallow color, the anæmia, the enlarged spleen will serve to distinguish the malarial process from the tuberculosis, where, though the face be pale, the lips and mucous membranes show usually a good color, while splenic enlargement is rare. The examination of the lungs, sputa, and blood will determine the diagnosis.

The chills which often occur in the course of *gonorrhœa* or those following catheterization or the passing of sounds may be confused with malarial fever. The urethra should always be examined in doubtful cases. In some cases of grave septicæmia following gonorrhœa there may be little or no evidence of an actual urethritis. Here the examination of the blood will immediately settle the question. In the one instance there is leucocytosis without malarial parasites; in the other, a normal or reduced number of leucocytes with the presence of the malarial organism. In all these cases the final decision must be arrived at from an examination of the blood. It is through this alone that a positive diagnosis of malarial fever can be made.

Method of Examination of the Blood.—For the satisfactory examination of the blood an oil-immersion lens is absolutely necessary. No physician today can consider himself equipped for practice without a good microscope and an oil-immersion lens. Though much valuable work has been done with dry lenses and lower powers, it is folly to attempt careful work without better means. The simplest and best method of studying the malarial parasite is in the fresh blood at the

bedside or in the consulting room. The steps toward the preparation of the specimen are quite simple, though 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 the lobe of the ear is perhaps preferable, inasmuch as it is less sensitive and more readily 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 in children. The ear is first thoroughly cleaned; the lobe is then punctured with a small knife or lancet. For the most careful procedures it is advisable to wash the ear with soap and water, and afterward with the alcohol and ether. But, practically, it is often advisable to make as few preparations as possible, and unless the ear or finger be extremely dirty one may proceed at once. A pin or needle will, of course, answer the purpose, but it is well to remember that a stab made by a round blunt-pointed instrument is much more painful than that by a sharp cutting edge, while a considerably deeper stab is required to draw a given quantity of blood. If a very sharp spear-pointed lancet be used, and the lobe of the ear taken firmly between the fingers so that the skin is held tense, very slight pressure with the tip of the lance will cause an incision deep enough for all purposes. This process is almost without pain to the patient. By proceeding carefully blood may often be obtained in this manner from a sleeping infant without its awakening.

After the first several drops of blood have been wiped away the freshly cleaned cover-glass is taken in a pair of forceps and allowed to touch the tip of a minute drop of blood. It is then placed immediately upon a 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 cover-glass. The spreading out of a drop of blood will be thus considerably facilitated. If the slide and cover be perfectly clean, the blood will immediately spread out between them, and, unless the drop of blood be 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 be very anæmic, and care should also be exercised that the tip of the drop only 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 at the edge of the drop 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. The specimens will remain in good condition for a considerable length of time, an hour or more—long enough to be thoroughly examined. If one desire to observe the specimen for a greater length of time, the periphery of the glass may be surrounded by paraffin or vaseline. In this manner we may see the parasites living and in active motion, while

the most exquisite examples of phagocytosis may be observed. By enclosing the specimen in paraffin or vaseline the preparations may, if handled carefully, be carried from the residence of the patient to the consulting room and there examined, but under these circumstances one must generally rely upon dried and stained specimens.

The preparation of specimens for staining is quite simple, requiring only a little experience and practice. Stained specimens are of especial assistance in the detection of the unpigmented hyaline bodies, particularly the pale tertian forms and those of the æstivo-autumnal parasites. A small drop of blood flowing from the lobe of the ear or the finger-tip is collected upon a perfectly clean cover-glass, which is immediately placed upon another glass. The drop of blood, if the two covers be perfectly clean, spreads out immediately between the glasses. The cover-glasses are then drawn apart. If neither glass be lifted or tilted during this process, they will slide apart readily without sticking. If the glasses have remained together so long that they have begun to adhere, one may be sure that the specimen will be no longer perfect. The glasses, thus prepared, are allowed to dry in the air, which they do usually in the course of a few seconds, and may then be preserved for an almost indefinite length of time. To prepare them for staining the glasses should be heated upon a copper bar or in a thermostat at a temperature of 100° to 120° C. for two hours, according to the method of Ehrlich, or they may be placed in absolute alcohol and ether, equal quantities, for two hours or more (Nikiforov's method).

The malarial parasite is readily stained by most of the basic nuclear dyes. The simplest method is perhaps to stain with a concentrated aqueous solution of methylene blue or *Löffler's methylene blue*:

Concentrated alcoholic solution of methylene blue,	30 c.c.
Solution of caustic potash 1 : 10,000	100 "

In either instance, the specimens should be stained for from thirty seconds to a minute, washed in water, dried between filter papers, and mounted in oil or balsam. The red corpuscles then will be unstained, while the nuclei of the leucocytes and parasites will be stained a clear blue.

A contrast stain may be obtained by the following method: The cover-glass specimen, after fixing in absolute alcohol and ether from four to twenty-four hours, is placed for a few seconds (thirty seconds to five minutes) in a 0.5 per cent. solution of eosin in 60 per cent. alcohol, washed in water, dried between filter papers, and placed for from thirty seconds to two minutes in a concentrated aqueous solution of methylene blue, or in Löffler's methylene blue, washed in water, dried between filter papers, and mounted in Canada balsam. The red corpuscles and the eosinophilic granules are stained by the eosin, while the nuclei of the leucocytes and the parasites take a blue color.

Admirable results may be obtained by a modification of *Romanovsky's* method. Two solutions are necessary—a saturated aqueous solution of methylene blue and a 1 per cent. watery solution of eosin. The older the methylene blue solution the better the results. The staining mixture should be 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 and poured into a watch-glass; it should not be filtered after the mixture has been made. The cover-glasses, fixed according to the methods above described or by hardening in alcohol for from ten minutes upward, are allowed to float upon the top of this fluid. The specimens are covered by another inverted glass, and the whole by an inverted cylinder which is moistened on the inside. In from half an hour to three hours—best in two or three hours—good specimens are obtained.

For quick work in the consulting room the simple stain with methylene blue alone is perfectly satisfactory, though the observer must of course have sufficient experience to be able to distinguish precipitates which may be present in the staining solution from parasites.[1]

The discovery of malarial parasites in the red blood-corpuscles is, of course, a positive sign of the malarial nature of the process. In some instances where the parasites may be very scanty or absent the presence or absence of a leucocytosis is an important diagnostic sign. As will be remembered, the leucocytes in malarial fever are normal or diminished in number, whereas in almost all processes with which the acute intermittent malarial fever may be confounded there is a well marked leucocytosis. This is the case in all the septic infections which are most likely to be confounded with tertian and quartan fever; it is also true of tuberculosis, at least when accompanied by intermittent fever. The presence of a marked leucocytosis is strong presumptive evidence against the existence of malarial fever. In some instances where very few parasites are present the finding of pigment-bearing leucocytes may be an important aid in diagnosis. Tertian and quartan infections where multiple groups of parasites are present may occasionally be confounded with typhoid fever. Well marked remissions and, almost invariably, actual intermissions, usually occur, while the examination of the blood will readily clear up the diagnosis.

The differential diagnosis between tertian and quartan infections may be readily made in the fresh specimen, less distinctly in the stained. The larger and more actively amœboid, pale tertian parasite with fine brownish, actively dancing pigment granules may be readily distinguished from the smaller, less active, more refractive quartan parasite with its coarser, more slowly moving, darker granules. In the case of the tertian parasite the red corpuscles may be seen to become expanded and pale with the growth of the organism, while in the quartan parasite the corpuscle is shrunken and of a deeper, more brassy color. If the blood be examined just before or during the paroxysm, the more irregularly segmenting tertian organisms with their numerous (twelve to thirty) segments may be clearly distinguished from the smaller regular forms in quartan fever with their fewer (six to twelve) segments. The presence, in either instance, of one or more groups of parasites may usually be readily determined. Combined infections with quartan and tertian parasites—which, though very rare, do exist—may also be readily made out.

In the stained specimen the size of the pigment and the parasite

[1] The experienced observer may obtain sufficiently good specimens for diagnosis in many instances by rapid heating of the cover-glass over the flame for a few minutes; the results, however, are uncertain.

and the behavior of the red corpuscle, pale in one instance, taking a deep eosin stain in the other, and the characteristics of the segmenting forms, should enable us also to make a differential diagnosis.

If it be impossible to make a microscopical examination of the blood, the therapeutic test is usually sufficient; thus, in the regularly intermittent fevers there is rarely any recurrence of the fever after forty-eight hours from the beginning of the administration of quinine. In the majority of instances of tertian infection in this climate all traces of fever disappear within twenty-four hours.

(2) The Æstivo-autumnal Fevers.—While the diagnosis in the regularly intermittent tertian and quartan fevers is a relatively simple matter, the same is not true of the more irregular æstivo-autumnal forms of malaria. In some instances, where the paroxysms are of shorter duration and occur at regular intervals, usually quotidian, the diagnosis may be as self-evident as in the regularly intermittent fevers. The longer paroxysms, occurring at intervals of approximately forty-eight hours one from another, with their less rapid rise, but with a complete intermission between them, are also generally easily recognized when we take into consideration the anæmia, the enlarged spleen, and the herpes labialis which are so commonly present. When, however, from any of the various causes above mentioned the separate paroxysms become more or less complicated or merged one with another, so that at first but slight transient intermissions, then perhaps only irregular remissions, and finally a continued high fever, result, the diagnosis becomes often more difficult. Such a case often presents itself in the form termed by Baccelli "*subcontinua typhoidea.*" The general clinical appearances are so similar to those of *typhoid fever* that a distinction without examination of the blood may be quite impossible. In a certain number of instances vestiges of the paroxysms still may be made out, a well marked acme in the fever being reached at approximately the same hour at quotidian or tertian intervals, though in other instances all traces of the individual paroxysms may have disappeared. Sometimes the history of several sharply intermittent paroxysms in the beginning of the illness may lead us to a correct diagnosis. Again, the prodromal symptoms are much less frequent and severe, as a rule, in malaria than in typhoid. Herpes is common in æstivo-autumnal malaria, unusual in typhoid fever. Delirium may appear quite early in a malarial attack; it is rare during the first few days of a typhoid. Bronchitis is more common in typhoid than in continued malarial fever. Marked abdominal symptoms, though they may occur, are unusual in malaria; the rule in typhoid fever. Certain erythemata, and especially, urticaria, may be present in malarial fever, while the characteristic typhoid roseola does not occur. In both instances the spleen is usually enlarged. An important diagnostic sign is the anæmia which is almost invariably present if the malarial fever has lasted more than a few days, while in typhoid fever anæmia during the first two weeks is rare. Another important sign is the slight icteric hue which is usually present in malaria; rare in typhoid. Ehrlich's diazo reaction is unusual in the urine in malarial fever; it was found in but 6 per cent. of the cases classified by Hewetson and the author, while it is almost invariably present in typhoid.

Here, however, as in all other forms of malaria, the final decision

is to be reached only by examination of the blood, where the small, amœboid, and ring-shaped, hyaline æstivo-autumnal parasites are to be found. If the process has lasted a week or more, the pigmented ovoid and crescentic bodies are also usually present. In rare instances quite severe febrile symptoms may be present, while the peripheral circulation may at times show but a small number of parasites. Here the discovery of pigment-bearing leucocytes may often be of assistance. The diminished number of leucocytes which one finds under these circumstances does not help us in the differential diagnosis from typhoid fever, where also the leucocytes are almost invariably subnormal in number. If the case occur in a neighborhood where it is impossible to obtain the aid of the microscope, the diagnosis may be definitely made by the therapeutic test. No malarial fever now known resists good doses of quinine for more than three or four days. It is generally safe to say that if the process be malarial the temperature will be practically normal by the fourth day. If quinine fails to influence the fever, we may rest assured that the process is either non-malarial or a mixed infection.

The confusion with typhus fever might occur in some instances, but here, again, the examination of the blood will settle the question.

As in the case of the regularly intermittent fevers, the process may be confounded with tuberculosis or other various septic infections. The one safe method of differential diagnosis is the examination of the blood.

Pernicious Malaria.—The diagnosis in some pernicious paroxysms may be at times confusing.

Comatose Pernicious Fever.—This type of fever must be distinguished from sunstroke, uræmia, cerebral hemorrhage. The differentiation of such an attack from sunstroke is by no means simple. As Bastianelli and Bignami have pointed out, individuals who are subjected to malarial infection are often those working in the fields and most exposed to the rays of the sun at the hottest season of the year, while the clinical symptoms of the two processes may be closely similar. It is interesting to note that the case of comatose pernicious fever referred to above as occurring in a tertian infection was at first mistaken for sunstroke. The slight jaundice, the anæmia, the enlarged spleen would serve to suggest the malarial nature of the process, while the examination of the blood gives a positive clue to the diagnosis. In the *tetanic, meningeal, eclamptic,* and *hemiplegic* types the same symptoms may lead to a correct diagnosis.

The Algid Type.—In this type of paroxysm, where the temperature may be normal or subnormal, and where often (from the actual condensation of the blood) the anæmia may not be as apparent, the diagnosis may be considerably in doubt. Here, however, icterus and enlarged spleen are suggestive, while examination of the blood will give positive diagnosis. It is in cases of this nature that the physician who makes systematic blood examinations in all doubtful cases will be enabled at times to gain information which will save the life of his patient.

The Hemorrhagic Type.—The diagnosis in some of the instances of this nature must be made between malarial and yellow fever. The early appearance of albumin and casts in yellow fever is suggestive, while the spleen is often but little enlarged in this affection.

The examination of the blood may in some cases be the sole reliable method of differentiation.

Malarial Hæmoglobinuria.—The diagnosis here lies usually between yellow fever, the ordinary paroxysmal hæmoglobinuria, and acute nephritis from some other toxic origin. And here, again, the chief reliance must be placed upon the examination of the blood.

Post-partum and Post-operative Malaria.—A diagnosis of these conditions can only be made upon examination of the blood. The malarial paroxysms differ from the paroxysm due to septic infection chiefly by their greater regularity and by their average longer duration. The blood, apart from the presence of the specific parasites and pigment, shows in the one instance diminution in the number of leucocytes, and in the other well marked leucocytosis.

Chronic Malarial Cachexia.—The diagnosis of chronic malarial cachexia is usually relatively easy. It is chiefly to be confounded with grave primary or secondary anæmia or with leukæmia and pseudo-leukæmia. The malarial process may usually be distinguished from splenic anæmia by the presence of pigment and parasites in the blood. In some instances, however, where these are not to be found, the enlarged spleen, the grave anæmia, the hemorrhagic tendency, the dropsical effusions present in both conditions may render the diagnosis almost impossible without appealing to the history of the patient. The progress of such cases under proper treatment is usually, however, decisive. The malarial cachexia responds generally, slowly but progressively, to treatment. Thus, the author has seen a spleen which reached beyond the umbilicus and almost to the pubes diminish under treatment until it was only just palpable, while the blood returned from 1,000,000 red corpuscles to the cubic centimetre to the normal condition, the patient remaining in perfectly good health in a non-malarious district. The diagnosis from leukæmia is readily made by examination of the blood.

Post-malarial Anæmia.—An absolute differential diagnosis between post-malarial anæmia and some other secondary anæmiæ is impossible. The tendency, however, in the post-malarial anæmia to a diminution in the number of leucocytes is always marked, while a relative increase in the large mononuclear elements is very suggestive. As has been said before, there is nothing characteristic in the *nephritis* which follows malarial fever.

Other Complications and Mixed Infections.—In some of the mixed infections to which reference has been made above a certain diagnosis can only be made by the discovery of the parasites and the persistence of the complicating process after the disappearance of the organisms under quinine. Thus, the diagnosis of *typhoid fever* may be made if the characteristic symptoms continue after the clearing up of the complicating malarial process.

In the case of *pneumonia* the diagnosis depends more upon the physical examination, knowing as we do that the malarial parasite is of itself incapable of producing actual pneumonic consolidation. The same is true of *pleurisy*.

The occurrence of *diarrhœa* or *dysentery* during the active malarial process may or may not be directly due to the malarial poison. The

presence of the Amœba coli in the stools is evidence of a complicating process, while in other instances of diarrhœa in acute malaria the result of the specific treatment must be awaited before one can form a definite diagnosis.

Parotitis, tonsillitis, acute rheumatism, the *exanthemata*, occurring in connection with malarial fever, may be recognized by their usual symptoms.

Prognosis.

The Regularly Intermittent Fevers. — The prognosis in tertian and quartan fevers as for ultimate recovery is almost invariably good. The writer knows of but one instance in which actual pernicious symptoms were present in tertian or quartan infection. Without systematic and careful treatment relapses and grave cachexia may, however, follow— a cachexia which may well lay the patient open to the gravest secondary complicating processes. It is not improbable that in certain of these instances a fatal chronic nephritis may follow repeated malarial infections.

Æstivo-autumnal Fever.—In ordinary cases of æstivo-autumnal fever which come early under treatment the prognosis is perfectly good. Treatment must, however, be more active and longer carried out than in the regularly intermittent fevers. Imperfectly treated cases are more likely to be followed by cachexia and grave post-malarial anæmia.

Pernicious Fevers.—Wherever pernicious symptoms have developed the prognosis is extremely grave, and, unless active treatment be instituted, usually wholly unfavorable. In a patient first coming under observation in a pernicious paroxysm an entirely favorable prognosis can never be given for at least forty-eight hours after the beginning of treatment. It is always possible that a single pernicious paroxysm may be succeeded, despite treatment, by another upon the following day. If active treatment has been begun during a pernicious paroxysm and no succeeding paroxysm has occurred within forty-eight hours, the prognosis is usually favorable.

Malarial Hæmoglobinuria.—The prognosis here is always extremely grave; indeed, the dangers of a fatal outcome are not past until several days after the complete disappearance of fever and of symptoms on the part of the urine.

Chronic Malarial Cachexia.—In the milder grades of chronic malarial cachexia the prognosis is good if the patient can be compelled to adopt a properly hygienic life. In the more severe grades recovery is extremely slow, and at times almost impossible, unless the patient be transferred into a more healthy region.

Post-malarial Anæmia.—The anæmiæ following malaria are often extremely grave. In those instances where the nucleated red corpuscles are scanty or absent and the leucocytes are diminished in number, and in those cases where the blood shows the characteristics of true pernicious anæmia, the prognosis is extremely grave.

The prognosis in the various *complications* of malaria is influenced only by the possible unfavorable effect of the coexisting malarial infection. Secondary infections occurring in individuals suffering from malarial cachexia appear to pursue an unusually unfavorable course.

Treatment.

General Measures.—Certain general hygienic measures are advisable, and sometimes very important, in the treatment of malarial fever.

Rest in Bed.—It is always prudent, if possible, to keep a patient with malarial fever in bed for twenty-four or forty-eight hours; in the more severe æstivo-autumnal fevers it is absolutely necessary. The simpler regularly intermittent fevers often show a temporary and sometimes permanent spontaneous recovery following rest in bed, without further treatment. In hospital practice it is our rule to keep a patient with malaria in bed until the entire disappearance of fever, whether it be intermittent or subcontinuous. It is not impossible that the more satisfactory results of hospital treatment may, in part, depend upon the fact that the patients are so much more readily kept at rest.

Change of Surroundings.—If the patient's dwelling be in a malarious district, it is always important, if possible, that the individual be removed into more healthy surroundings. Thus, recovery from chronic cachexia is greatly favored by the removal into higher, more healthy regions. In some instances of advanced cachexia the removal may be absolutely necessary. In the ordinary acute malarial fevers it is, however, generally perfectly possible to treat the case in the malarial district itself. The patient should be kept, while under treatment, in one of the upper stories of the house; he should be warned against remaining out of doors at night during convalescence, and prevented, as far as possible, from subsequent exposure to infection.

Diet.—In the simple intermittent fevers the patient may be given an ordinary nourishing general diet. During the paroxysms, which last but ten or twelve hours in all, the patient need not be forced to eat; it is, however, generally well that liquids, milk, broths, soups, should be taken in small quantities. Stimulants may be administered symptomatically. In the more severe subcontinuous fevers, where there is usually complete anorexia, the patient may be given liquids of all sorts, soups, milk, broths, at short intervals; while, if he be hungry and there be no gastro-intestinal symptoms, there is no contraindication to soft solids and eggs. In cases where there are marked gastro-intestinal symptoms great care must, of course, be exercised with the diet. Easily digested liquids, such as boiled milk, albumin-water, and broths should alone be given.

Exposure to the Air.—There are districts where experience has led the inhabitants to believe, probably justly, that exposure to the night air is injudicious. It may be unwise in such regions for the patient to be allowed to sleep with his window open. If, however, the patient be in a healthy district and be accustomed to living and sleeping with open windows, there is no reason why a change should be made during the existence of the fever. There is no fever which we know today which is unfavorably influenced by fresh air and open windows, provided the individual be accustomed to such air beforehand.

Quinine.—Malarial fever is one of the few diseases against which we possess a remedy which truly deserves to be called specific. This remedy, in the form of cinchona bark, was introduced into Europe in 1640 by the countess del Chinchon (wife of del Chinchon, the Spanish governor of Peru), who had recovered from a severe attack of intermit-

tent fever after taking a powder administered by a *corregidor* of Loxa. As far as is known, this substance was first used by the Indians in this region as a remedy against malarial fever. The powder, which was known at first as "the powder of the countess," and afterward as "the Jesuits' powder" for the reason that it was introduced into general use by the Jesuits in Rome in 1649, was prepared from the bark of a Peruvian tree. This was for years known as Peruvian bark, though its officinal name, Cinchona, is derived from that of its introducer to the Eastern hemisphere. It was at first administered in the form of the pulverized bark, the cinchona powder, which contains, in addition to various alkaloidal substances, a considerable quantity of tannin. Today, however, the pulverized bark is no longer in general use, its place having been taken by various salts of its active principle, quinine.

Action of Quinine on the Malarial Parasite.—For centuries after the introduction of quinine and after its specific action in malarial fever had been noted the exact mode of action remained unknown. As long ago as 1867, Binz[1] correctly concluded that the efficacy of quinine in paludism depended upon its action as a protoplasmic poison upon some lower organism which he assumed to be the cause of the process. The extremely toxic action of quinine upon the infusoria was at that time clearly demonstrated. Since the development of our knowledge concerning the malarial parasite it has been possible to study, to a certain extent, the direct action of quinine upon the hæmatozoa. Laveran noted the immediate disappearance of the parasites following the administration of quinine, and in 1881 asserted that "it is because it destroys the parasite that quinine causes the disappearance of the manifestations of paludism." 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, as they are upon subjecting the organism to any other protoplasmic poison.

Golgi[2] has studied the action of quinine on the tertian and quartan parasites. He noted that after the administration of quinine the quartan organism, 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 present a large transparent swollen condition with very active movements of the pigment granules. Sometimes the pigment may collect toward the periphery, leaving an hyaline space in the middle. Mannaberg[3] asserts that three hours after the administration of 0.5 of quinine the amœboid 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

[1] *Centralblatt f. d. med. Wiss.*, 1867, p. 308.
[2] *Deutsch. med. Woch.*, 1892, 661, 695, 707, 729.
[3] *Loc. cit.*

are fragmented, resulting in the presence of several separate spherules in the red corpuscle. Full grown forms show a cessation of the movements of the pigment, the body having a somewhat refractive homogeneous appearance. Large hydropic forms with active pigment may also be seen. These two latter forms may occur normally during the paroxysm, as Golgi and Mannaberg also assert; they are probably degenerate forms. The writer has also observed in the case of the tertian parasite the somewhat greater refractiveness of the organism, the collection of the pigment into clumps, and the cessation of active movements, as well as the presence of a greater number of fragmenting forms.

Romanovsky[1] and Mannaberg[2] have made interesting studies with stained specimens. Both observers note the loss of affinity for coloring matters in the chromatin substance of the nucleus. They also note that in the segmenting forms, after quinine has been given, the greater number of the segments show no nucleoli. These changes in the nucleus they believe to be evidence of a necrotic process. The segments without nucleus Mannaberg terms "still-born." Baccelli[3] noted that in æstivo-autumnal fever after the intravenous injection of quinine there was an increase in the activity of the small amœboid forms, which, often inside of twenty-four hours, disappeared without showing any outward signs of degeneration. Marchiafava and Bignami,[4] studying the æstivo-autumnal fevers, note that the administration of quinine is followed by an increase in number of shrunken, brassy colored corpuscles. They believe that the included parasites are incapable of further development.

Most observers who have been able to test the action of quinine upon the malarial parasite will agree with Golgi that in tertian and quartan fever quinine acts most markedly on the free young segments, 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 the paroxysm, it will not prevent segmentation, but it will destroy the new group of parasites, the fresh segments. Segmentation takes place, toxic substances are produced and enter into the blood serum, and the chill follows, being at most a little modified or retarded. The further development of the new group of organisms is, however, prevented, and on the following day no parasites whatever may be observed. Marchiafava and Bignami[5] arrive at the same conclusion in the case of the æstivo-autumnal parasite. They state "that the maximum and most rapid action of the remedy is exercised on that phase of the extraglobular life of the parasite which follows the completed segmentation." They note, as does Golgi in the case of the tertian and quartan organisms, that the segmentation cannot be prevented if quinine be given when the parasite has reached the preparatory stages. "Quinine," they say, "acts on the amœba of malaria during those phases of its life in which it absorbs nourishment and develops; when the nutritive activity comes to an end, the transformation of hæmoglobin into black pigment having been accomplished, and the phase of reproduction begins, then quinine becomes inefficacious against this process."

[1] *Cent. für Backt.*, 1892, xi. Nos. 6 and 7, 219; and *St. Pet. med. Woch.*, 1891, Nos. 34 and 35. [2] *Loc. cit.*, and *Cent. für klin. Med*, 1891, No. 27.
[3] *Deutsch. med. Woch.*, 1892, No. 32, 721. [4] *Loc. cit.* [5] *Loc. cit.*

To best combat the further development of a group of malarial parasites quinine should be in solution in the blood at the time of the setting free of the fresh parasites—*i. e.* during and several hours before the paroxysm. In ordinary tertian or quartan fevers, with moderate regular daily doses of quinine, the parasites will usually wholly disappear from the peripheral circulation inside of three days. In æstivo-autumnal fever the time may be a little longer. All observers agree that the crescentic bodies are affected slowly if at all by quinine; they remain in the blood long after all other forms of the parasite have disappeared.

Effects of Quinine upon the Human Being.—In small doses, such as are ordinarily required therapeutically, quinine causes no subjective symptoms. In somewhat larger doses, however, it produces at times a ringing in the ears, roaring or sometimes tinkling noises, and, finally, more or less deafness. Larger doses are followed by a dimming of the vision, even to complete blindness. Ringer has noted that this may sometimes begin in one eye, and, indeed, exist for considerable time upon one side alone. The pupil is usually dilated. In larger doses a severe frontal headache, with giddiness and staggering gait, delirium, and great muscular weakness, may follow, and, finally, in still larger doses, convulsions and death. At times large doses of quinine are followed by certain cutaneous disturbances. Ringer describes an intense general erythema similar to a scarlet fever rash and followed also by desquamation. Urticaria also at times occurs.

Manner in which Quinine should be Given.—Like another commonly used and extremely valuable drug, digitalis, quinine, which is our main stay in malarial processes, is very frequently abused. Laveran well says: "In a general way it may be said that in malarial districts far too much sulphate of quinine is given to patients who have no need of it, while a sufficient quantity is not given to patients suffering from paludism." The very degree of its efficacy, as in the case of mercury and iodide of potassium in syphilis, is probably accountable for the lax manner in which it is frequently given. When one or two doses are followed by a complete disappearance of symptoms, the immediate relief is so great that the patient fails to recognize the importance of continued treatment, and, by abandoning the regular régime, lays himself open to repeated relapses.

It is of considerable importance to determine in an individual case how and in what form quinine should be given. The following tables, taken from Laveran, show the percentage of quinine which the different salts contain, as well as their relative solubility:

Salts of Quinine classified according to the Percentage of the Alkaloid which they contain.

	Quinine.
100 parts of the basic muriate of quinine contain	81.71 per cent.
" " neutral " " "	81.61 "
" " basic lactate " "	78.26 "
" " " hydrobromate " "	76.60 "
" " " sulphate " "	74.31 "
" " " sulphovinate " "	72.16 "
" " neutral lactate " "	62.30 "
" " " hydrobromate " "	60.67 "
" " " sulphate " "	59.12 "
" " " sulphovinate " "	56.25 "

Salts of Quinine classified according to their Solubility in Water (Regnauld and Villejean).

							Water.
1 part of	the	neutral	hydrochlorate	of	quinine	is soluble in	0.96
"	"	"	sulphovinate	"	"	"	0.70
"	"	"	lactate	"	"	"	2.
"	"	basic	sulphovinate	"	"	"	3.30
"	"	neutral	hydrobromate	"	"	"	6.33
"	"	"	sulphate	"	"	"	9.00
"	"	basic	lactate	"	"	"	10.29
"	"	"	hydrochlorate	"	"	"	21.40
"	"	"	hydrobromate	"	"	"	45.02
"	"	"	sulphate	"	"	"	581.00

The ordinary method of administering quinine is by the mouth; the common form in which it is given in this and most countries is as the *sulphate*. The *sulphate of quinine* is very slightly soluble in water, but quite readily soluble in dilute acids. The best manner to administer this form of quinine is in water containing a sufficient quantity of dilute hydrochloric or sulphuric acid to hold the salt in solution.[1] The extremely bitter taste is sometimes an objection in sensitive patients: this, in the case of the quinine powder, may be partly obviated by mixing with an equal quantity of powdered ginger. The drug may also be administered in the form of pills or in capsules. Quinine pills are convenient, but are open to the common objection that in many instances the commercial pill is an highly insoluble object. Thus, it is not at all infrequent in dispensary practice for the physician to be consulted by patients with simple intermittent fever who have taken quinine pills[2] without effect, while the solution or the powder has an immediate result. For more rapid action the quinine may be administered hypodermically or, according to the method of Baccelli, intravenously. For these purposes more soluble salts than the sulphate must be used. Thus, for subcutaneous use the *neutral hydrochlorate of quinine* is an excellent salt. De Beurmann and Villejean[3] use the following formula:

℞. Bihydrochlorate of quinine, 5.
Distilled water, q.s. ad 10.
1 c.c. (ℳxv) of this solution contains 0.5 (gr. vijss) quinine.

If the hydrochlorate of quinine is not to be obtained, one may make use of the ordinary sulphate, as follows:

℞. Sulphate of quinine, 1.
Tartaric acid, 0.5
Distilled water, 10.

The officinal *bisulphate of quinine* is soluble in about 9 or 10 parts of water, and may be used hypodermically if a more soluble salt cannot be obtained.

[1] The druggist customarily adds about 1 drop of the dilute acid to 1 grain (0.65) of the salt.

[2] My colleague, Dr. L. F. Barker, has actually observed the discharge of well preserved quinine pills from fæcal fistulæ in three instances.

[3] Quoted from Laveran, *Du Paludisme, etc.*

Baccelli[1] uses, as an intravenous injection, the following mixture, which he has found to act with the greatest rapidity and the most marked effect:

℞. Quininæ hydrochloratis,	1.0
Sodii chloridi,	0.075
Aquæ destillatæ,	10.0

The solution is perfectly clear and should be injected lukewarm. The procedure is described by Baccelli as follows: "After the veins of the forearm have been made turgescent by means of a circular tourniquet above the elbow, we introduce a Pravaz needle in a direction from below upward into the lumen of the vein. We select a small one in order to avoid hemorrhage afterward. Generally, we are accustomed to select one situated upon the flexor side of the forearm. The syringe holds 5 c.c., and is filled according to the dose which is to be given, and connected with the needle before its introduction." The most rigid antisepsis must be observed. The stab wound is closed with collodion after the needle has been withdrawn.

The *bimuriate of quinine and urea*, which contains nearly 80 per cent. of quinine and is soluble in less than its own bulk of water, is another convenient form in which to administer the drug.

The hypodermic use of quinine is attended by considerable pain and real danger of a subsequent abscess or necrosis. If the solution and the instruments be carefully sterilized, there is little danger of abscess, but at times a considerable area of necrosis may result. It is always important to introduce the needle well into the subcutaneous tissue; if this be neglected and the solution be introduced into the deeper part of the cutis, necrosis usually follows. Quinine may be given by rectum; this is, however, a last resort, and is practically never necessary excepting, at times, in children.

The Time at which Quinine should be Given.—If one but remember the studies of Laveran, Golgi, Mannaberg, and others concerning the effect of quinine upon the parasite, and then consider the close relation between the development of the parasite and the symptoms of the malarial infection, one may readily perceive the time at which, theoretically, the drug should be best administered. Inasmuch as it has been shown that quinine acts most effectually upon the young extracorpuscular parasite, it would seem fair to conclude that the period just before or during the paroxysm should be that at which quinine might be administered with most effect, and, as has been clearly shown, this is the case. A dose of quinine shortly before a paroxysm in the regularly intermittent fevers will not affect that paroxysm, but will prevent a recurrence of the succeeding one dependent upon that group of organisms. Thus, a single moderate dose of quinine given just before or during a paroxysm in single tertian or quartan infection will cause generally a total disappearance of the symptoms, while in the case of a double tertian infection it may often be seen to change the type of the fever from quotidian to tertian. Thus, in such an instance the paroxysm expected upon the following day will occur, but that expected

[1] *Studien über Malaria*, Berlin, 1895.

in forty-eight hours will not appear, the greater part of the group of parasites having been destroyed. The same has been shown to be true in æstivo-autumnal fever, though the parasites are much more resistant to the action of quinine than those of the regularly intermittent fevers.

Administration of Quinine in the Regularly Intermittent Fevers.—Here it is generally best to place the patient upon regular continued treatment with quinine. If it be possible to keep the patient in bed, very small doses will often be sufficient. Thus, 0.065 (gr. j) three times a day will, in many instances, be followed by a disappearance of the symptoms. In practice we may give, according to the severity of the case, from 0.13 to 0.325 (gr. ij–gr. v) three times a day. If in tertian fever the patient be seen on the day between the paroxysms, 0.325 (gr. v), three times a day will generally, if the patient be confined to bed, prevent even any succeeding paroxysm. One may predict, almost with certainty, the entire disappearance of the fever after this. If the patient be seen first just before an expected paroxysm or during the attack, it may be well to give a single large dose, 0.325–0.65 (gr. v–gr. x), and follow this by smaller doses, 0.13 (gr. ij), three times a day. If the paroxysms have been severe, it is sometimes wise to give large doses of the drug (0.325–0.65 (gr. v–gr. x)) during the first days of treatment at the hour when without treatment the paroxysm might have been expected. The parasites in tertian and quartan infections disappear from the blood generally within three days, but treatment with small doses, 0.4 (gr. vj), in twenty-four hours should be continued for at least three weeks.

Æstivo-autumnal Fevers.—In the treatment of æstivo-autumnal fever larger quantities of quinine must, as a rule, be given. In ordinary cases where no pernicious symptoms have developed one may start treatment with 0.325 (gr. v) every four hours. In most cases under such treatment fever will entirely disappear inside of three days. If symptoms of cinchonism develop, the dose may be reduced. If the patient come under observation during a paroxysm, or if the history be obtained of a severe paroxysm having recently occurred, it may be well to begin with larger single doses. Thus, during or just before a paroxysm 0.65 (gr. x) may be administered, followed by 0.325 (gr. v) every four hours. If severe nervous manifestations accompany the paroxysm and the development of pernicious symptoms be feared, it may be well to administer the quinine hypodermically or intravenously. It is rarely necessary to give doses larger than 1.0 (gr. xv). It may rarely be necessary to give several doses of this size at intervals of several hours during a long-continued paroxysm ; usually two or three doses at intervals of four hours are sufficient, while afterward it will be possible to give smaller quantities (0.325) every four hours. Such doses will usually prevent the recurrence of a paroxysm due to this group of parasites. It is, however, possible that a second large group of parasites, which all treatment has failed to influence, may on the following day produce a fatal paroxysm. The same course should be pursued during the succeeding paroxysm. It has long been a well recognized fact in malarious districts that if the patient survive the second paroxysm after the beginning of treatment, ultimate recovery is usually assured. In true *pernicious* paroxysms the experience of Baccelli would seem to show that intravenous injections of quinine are by far the most efficacious.

Baccelli has used successfully the solution of quinine described on page 150. It is apparently unnecessary to use doses larger than 1.0 (gr. xv).

Malarial Hæmoglobinuria.—The same general rules which apply to the treatment of the other pernicious fevers hold good in the case of malarial hæmoglobinuria. It should, however, be noted that certain observers believe that large doses of quinine exert a distinctly injurious influence upon the blood, aggravating often the destruction of the red corpuscles. Thus, Plehn[1] in a recent article goes so far as to advise an expectant treatment in these cases, asserting that recovery is more likely to result under careful nursing and general treatment than under the administration of quinine. This view is not held by the majority of observers.

Cinchonism.—*Contraindications to Quinine.*—There is a great difference in the susceptibility of different individuals to quinine. Relatively small doses produce cinchonism in some individuals, while others are extremely tolerant of the drug. In the majority of instances, however, in which complaint is made it is based upon the fact that the drug has been administered in injudiciously large doses. The writer has never observed but one case in which it was impossible to administer quinine in sufficient doses to combat ordinary malarial manifestations without serious symptoms. In this instance, occurring in a colleague, the symptoms produced by quinine or other cinchona derivatives are interesting enough to mention here. After taking 0.13 (gr. ij) of the sulphate of quinine, in half an hour the patient had a feeling of oppression in the epigastrium, followed by nausea, vomiting, and then soon by "a hot prickling sensation over the entire skin." On one occasion, without extreme itching, there was an intense scarlatinoid erythema, lasting for hours and followed by desquamation; on another occasion, after 0.195 (gr. iij) of salicylate of cinchonidia, a most intense general urticaria. Cases of this nature are extremely rare, and there are few instances probably in which individual susceptibility is any true contraindication to the administration of quinine in malarial fever. The prejudice against the drug is very strong in the mind of some individuals, and it is not infrequently wise for the physician to introduce quinine in a form unfamiliar to the patient.

Other Cinchona Derivatives.—Various other cinchona derivatives have been used as substitutes for quinine in the treatment of malarial fever. Thus, *cinchonin*, *cinchonidin*, *quinidin*, and *quinoidin* have been recommended. The efficacy of these drugs is, however, so far below that of the various salts of quinine that their employment is inadvisable.

Methylene Blue.—Next to quinine, the most valuable remedy in malarial fever is, probably, methylene blue. This substance was first employed in 1891 by Gutmann and Ehrlich,[2] who were led to its use by the observation of Celli and Guarnieri that the malarial parasites were stained while yet living by this substance. They found that in small doses quite a marked effect was obtained in several cases of intermittent fever. Since this time the drug has been used by a number of different observers, most of whom agree in the conclusion that methylene blue

[1] *Loc. cit.*

[2] *Berliner klin. Woch.*, 1891.

possesses a well marked antimalarial action, the parasites often disappearing from the blood and the patient recovering after its administration. As an antimalarial agent it is, however, as the observations of the author[1] have shown, far below quinine in efficiency, while the parasite acquires, apparently, a certain tolerance to the drug after its continued use. In certain mild cases of the regularly intermittent fevers it may be given in doses of 0.13 every four hours in capsule, with possibly a curative effect. Larger doses have been given without ill effect—doses as high as 3.0 (gr. xlv) in twenty-four hours. The only unpleasant symptom following its use is, apparently, strangury, which may be prevented by the administration of small quantities of powdered nutmeg at the same time. After ingestion of methylene blue the urine has a deep blue color; the fæces become blue on exposure to the air. While in certain instances methylene blue may have a curative effect, it is so far inferior to quinine that its value is certainly extremely limited.

Phenocoll.—Within the last few years several Italian observers have reported moderate successes from the treatment of malarial fever with the hydrochlorate or acetate of phenocoll, a derivative of phenacetin. It may be given in doses of 1.0 (gr. xv). It has been prescribed in the treatment of malaria in children.

Other Remedies.—A large number of other drugs have been at one time and another employed in the treatment of paludism. Thus iodine, strychnine, sulphur, arsenic, alum, preparations of eucalyptus and helianthus have been recommended. With the exception of arsenic, which, as will be said, is often of use in anæmia and chronic cachexia, the value of these substances is slight.

Further Treatment.—Besides the treatment with the specific drug, certain accessory and symptomatic measures are often important. The value of purgation has long been insisted upon, and the old custom of beginning the treatment of malarial fever by administering a mercurial purge is probably in some instances of value. In cases where there are grave intestinal symptoms it should be avoided. Profuse *vomiting* or *purging* during a paroxysm should be controlled, as far as possible, by morphia administered hypodermically. Excitement and active *delirium* during the fever may also at times require the use of morphia. In the *collapse* in pernicious fevers most active stimulation must at times be resorted to; alcohol, strychnia, and ether may be freely administered hypodermically. In the algid forms external heat should be applied, as well as enemata of warm water. In *continued high fever*, particularly if there be delirium, cold sponging or the actual cold bath may be of value.

During convalescence the most serious symptom with which we have to deal is the *anæmia*. In these cases iron and arsenic are our mainstays. In most instances iron alone, either in the form of Blaud's pills or as the tincture of the chloride, in full doses, will be followed by good results. In severe cases *arsenic* may be resorted to; it is best given in Fowler's solution (liquor potassii arsenitis). It is well to begin with small doses (gtt. iii, *t. i. d.*), and to increase the dose steadily, one drop every other day, until the physiological effect is observable—slight suffusion and injection of the conjunctivæ, gastro-intestinal symp-

[1] *Johns Hopkins Hosp. Bulletin*, 1892, No. 22, 49.

toms. The dose should then, after a few days' pause, be reduced and maintained at the highest possible limit. Some very grave anæmiæ which closely simulate true pernicious anæmia and react but little to iron may show marked improvement after vigorous treatment with arsenic. It should be borne in mind that in rare cases arsenical neuritis may follow. In some instances it is well to continue the use of strychnia in some form as a bitter tonic during convalescence.

Treatment of Chronic Malarial Cachexia.—The treatment of chronic cachexia is often a very difficult matter. Active treatment by quinine will readily remove the parasite from the circulation and put an end to acute symptoms, but the extreme debility and the grave anæmia are often very obstinate. Owing to the great susceptibility of such patients to fresh infections or to a reappearance of an old infection after the cessation of treatment by quinine, it is sometimes almost necessary to remove the sufferer to a non-malarious district. The anæmia, which is usually the gravest symptom, should be treated according to the suggestions given above. It is in these cases that persistent and vigorous treatment by arsenic is especially valuable. The patient should be kept from all undue exertion; if the anæmia be very grave, rest in bed is important. The diet should be most nourishing, and the patient should be allowed to sit in the sun and fresh air in the middle of the day if the climate be not too hot. Bitter tonics are often valuable, particularly strychnia. Most cases of this nature will recover, even in a malarious district, if treatment be properly carried out. The majority of cases of malarial cachexia owe their origin to the carelessness of the patient, who does not carry out proper treatment with quinine and fails to observe the ordinary prophylactic measures.

Prophylaxis.—General public prophylactic measures, such as proper drainage, cultivation of the soil, and so forth, cannot be considered here. The individual, however, may adopt certain measures which may protect him in the most malarious districts. If it be necessary to visit, temporarily, notoriously malarious districts, let him, so far as possible, choose the season at which the fevers are least prevalent. The dwelling should be sought upon ground as high and dry as possible. Exposure at night in damp or marshy districts should be avoided; the sleeping apartment should be an upper story of the house. Despite the experimental evidence against the idea that infection occurs through the gastro-intestinal tract, it is prudent to boil all drinking water coming from malarious districts. Medicinally, quinine in small doses will often prevent infection. If the district be extremely malarious, the various simple wines containing cinchona are insufficient protection, and it is prudent to take several grains of quinine daily. Monti[1] has recently reported good results from the administration of the sulphate of quinine in doses of 0.40 (gr. vj) every other day. Sezary[2] believed that a smaller quantity, 0.15 (a little over gr. ij), daily was sufficient to protect the individual under most circumstances.

[1] *Loc. cit.* [2] *Médecine moderne*, 1892.