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ON THE PARASITES OF MALARIAL FEVER.*

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Although the infectious nature of the malarial fevers has been suspected from the earliest times, as testified to by the varied and interesting hypotheses and theories as to its origin from that of Varro to those of Mitchell and Salisbury and Klebs and Tomassi Crudelli, the discovery of the specific parasite has been one of the more recent advances in the modern study of the infectious diseases. To-day, however, thanks to the discovery of Laveran, we know that malaria is a specific infectious disease. We further know that the causal agent, as pointed out by him, is a protozoan parasite of the class of the sporozoa, which inhabits the red corpuscles of the infected individual.

Once entering the red corpuscle the parasite, by its growth, destroys its host, and, on reaching maturity, breaks up by a process of fission into a varying number of fresh young organisms, each one of which is, in turn, ready to attack a new red corpuscle and pursue again its cycle of existence.

Within the bodies of these developing parasites the hæmoglobin of the containing corpuscle is transformed into the dark brown pigment which has been recognized for many years as characteristic of malarial infections. The intracorpuscular development of the parasites accounts for the grave anæmia which has also so long been recognized as an important concomitant of the disease.

Following upon the work of Laveran in Algiers and Marchiafava and Celli in Rome, Golgi of Pavia made the discovery that, in the regularly intermittent forms of malaria, the parasites exist together in enormous groups, all the members of which are approximately at the same stage of development; and, moreover, that the development of these groups of organisms bears a direct relation to the clinical symptoms of the case. It

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was shown by Golgi that the malarial paroxysm invariably coincides with or immediately follows the sporulation of one of these great groups of parasites.

Golgi further noted the remarkable fact that distinct morphological and biological differences are to be made out between the organisms associated with the different types of fever. The parasite, for instance, of tertian fever, passing by for a moment its morphological characterisics, requires forty-eight hours to complete its cycle of development. Thus, in infection with a single group of parasites, sporulation occurs every other day, resulting in tertian paroxysms, while in infections with the quartan parasite, whose cycle of existence lasts seventy-two hours the paroxysms occur every fourth day.

The researches of Golgi have been confirmed by a large number of observers, and in addition both he and many others have distinguished a third type of organism which is associated with distinct clinical manifestations. This third parasite is believed to be associated with the more irregular types of malarial fever which are commoner in the tropical and more severely malarious districts—the "*æstivo-autumnal fevers*" of the Italian observers, the "*tropical malaria*" of the Germans, the "*Febris meridionalis*" of Sacharov.

Laveran, however, and some of his followers, persistently deny the justice of such a division, adhering to the view that the parasite is a single but polymorphous organism. Laveran does not deny that certain of these forms may be found more commonly in connection with certain types of fever, but that there is any definite relation between the types of organism and the types of fever, he is unconvinced.

Shortly after coming to Baltimore in 1890 I became deeply interested in the question of the unity or multiplicity of the malarial parasites, and the results of the observations of several years were published by Dr. Hewetson and myself in the reports of the Johns Hopkins Hospital for 1895. Since that time we have accumulated a large number of observations which have tended in many ways to support, and in others to extend the conclusions reached in our earlier communication. During the seven years up to the first of January, 1897, we have had the good fortune to observe over 2,000 cases of malarial fever; two or three hundred of these cases, occurring in the out-patient department, were so hastily and incompletely studied that they have been left out of consideration. However, 1,719 cases have been carefully studied and tabulated. Our observations have led us to

distinguish three separate types of the parasite which are in turn associated with three distinct types of fever:

1. The tertian parasite.
2. The quartan parasite.
3. The æstivo-autumnal parasite (*Hæmatozoon falciparum* of Welch).

We have never observed any indication of transitional forms between these different varieties of organisms, and our observations would lead us to adhere to the view that these bodies represent three distinct species of parasites.

1. The tertian parasite. The tertian parasite is represented in the earliest stages by a small, pale, hyaline body which is possessed of active amœboid movements. It lies clearly within the red corpuscle. It is so pale and its index of refraction is so like that of the including corpuscle that its outlines are often distinguished with considerable difficulty; but it may be readily detected by the trained eye even in the fresh unstained specimen. As the parasite grows it accumulates fine yellowish brown pigment granules which may be seen to have a dancing motion, probably communicated to them by active undulations of the including protoplasm. These granules lie very frequently collected in groups at the extremities of the pseudopodia of the amœboid parasite. As the organism grows the surrounding red corpuscle becomes expanded and decolorized. By the end of thirty-six hours the parasite has accumulated a large number of pigment granules which have also become somewhat coarser and darker, while the amœboid movements of the body become much less active. Finally, at the period of complete development, the parasite has arrived at a size approaching that of a normal red corpuscle, while the pale expanded rim of the containing element is scarcely to be made out. The pigment granules then begin to collect in a small mass or clump at one point, usually about the middle of the organism; often they become apparently fused into a single distinct block. At the same time the protoplasm of the parasite which has begun to assume a slightly cloudy and more opaque appearance, begins to show evidence of a radial striation, while small glistening spots may be observed just within the periphery of the sphere, as well as often at different points in the interior of the parasite. Shortly after this, evidences of division of the parasite are to be made out along the lines of these radial striations. Sometimes the division may take place into regular symmetrical leaflets, each stria extending from the periphery to the centre of the parasite. More commonly, however, there is an inner layer of segments

more or less irregularly arranged; so that, when separation is fully completed, we have a central pigment clump surrounded by a morula-like mass of small round hyaline bodies. These hyaline bodies represent complete young parasites, ready to attack a fresh corpuscle.

The parasites in tertian fever exist in great groups, all of which are approximately at the same stage of development, and entire groups undergo sporulation within the course of a few hours. The result, then, in an infection with a single group of tertian parasites is sporulation every forty-eight hours; and with the sporulation of one of these groups of organisms occurs, invariably, the febrile paroxysm. The paroxysm follows, usually, within several hours after the observation of the first sporulating forms in the blood.

2. The quartan parasite resembles the tertian organism in many respects though it is readily distinguishable by the practiced eye. In the very earliest stages the organism is almost exactly similar in appearance to the tertian parasite, but soon differences are to be noted. It is less actively amœboid, while the substance of the parasite is more refractive, its outline more distinct. The pigment granules which begin early to appear are larger, darker, and more inclined to a peripheral arrangement. As the parasite grows, the red corpuscle instead of becoming decolorized and expanded, becomes rather diminished in size, contracting, as it were, about the parasite, often assuming a somewhat deeper, slightly brassy color. The amœboid movements become lost earlier in the life history of the parasite and the full-grown form is somewhat smaller than that of the tertian organism. When the parasite has reached full growth which occurs in the course of about sixty-five hours after the paroxysm the pigment tends to collect in the centre flowing in toward the central point in more or less distinct radial lines, a point which, in our experience, is characteristic of the quartan organism. After the collection of the pigment the sporulation of the parasite takes place just as in the case of the tertian body, with the exception of the fact that here absolute symmetry is the rule, the parasite dividing into from six to twelve regularly arranged radial leaflets, resulting in a beautiful marguerite-like picture. The quartan parasites also exist in the blood in enormous groups, but the cycle of development of these organisms, as pointed out by Golgi, lasts approximately seventy-two hours, so that in infections with a single group sporulation and the paroxysms occur every fourth day.

Very frequently, however, in both tertian and quartan infec-

tions more than one group of parasites may be present; double tertian infections and double or triple quartan infections are extremely frequent. It is an interesting fact that when two groups of the tertian parasite are present they segment, almost invariably, on successive days, causing a daily chill, while in case of double quartan infection chills occur on successive days with a day of intermission between, and, in triple quartan infections, quotidian fever, which from the chart alone, may be indistinguishable from a double tertian infection.

3. The æstivo-autumnal parasite—hæmatozoon falciparum. This variety of organism is associated with fevers which differ distinctly in their clinical manifestations from the regularly intermittent tertian and quartan fevers. In some instances the paroxysms may, for a certain length of time, show marked regularity, occurring at intervals of from twenty-four to forty-eight hours more or less, but soon after the onset of the symptoms an irregularity usually becomes manifest and often the fever may pursue a continued course (the so-called remittent fever). This type of fever, as has been already mentioned, is rarely seen in the milder malarious districts. It is, however, common in Baltimore at the height of the malarial season and forms the majority of the cases occurring in the severely malarious districts.

The parasite here begins, as in the other instances, as a small, amœboid, hyaline body; it has, however, a marked tendency to take on a ring-like appearance. The body is not a true ring, but probably represents a bi-concave disc with a well marked central depression. It is also, in its earliest stages, distinctly smaller than the early forms of the tertian and quartan organisms. As it develops the pigment granules which are accumulated are scanty and extremely minute. The adult forms are materially smaller than those of the parasites of the regularly intermittent fevers, some organisms sporulating when scarcely more than a third the diameter of a red cell, though usually the diameter is approximately two-thirds that of the including element. The sporulating bodies resemble those of the tertian parasite.

This organism, however, shows several distinct differences from the forms already described.

The tertian and quartan parasites are found at all stages of development in the peripheral circulation, though, to be sure, in a case of the tertian organism the adult forms are found with greater frequency in the blood of the spleen. In the case of the æstivo-autumnal parasite, however, only the earlier stages are to

be made out in the circulating blood. These are the small hyaline bodies which may or may not possess a few very minute pigment granules. Occasionally, just before or during a paroxysm, larger forms with a central pigment block are to be made out. Actual sporulating bodies we have observed in only three instances out of 633 cases of æstivo-autumnal fever. To properly study these latter stages of development it is necessary to aspirate the blood from the spleen, which is by no means a safe procedure unless done with the utmost precaution.

After a certain length of time, from five days to two weeks, there begin to appear in the circulation other bodies which are quite characteristic of this form of infection. These are large crescentic elements with sharp refractive outlines, containing a ring or clump of dark pigment granules arranged in the middle of the organism. These crescentic-shaped bodies may often be seen to change, under observation, into ovoid or round forms which are somewhat smaller than the normal red corpuscle. The round bodies in some instances lose their refractive character, and from them there develop, not infrequently, the flagellate elements which were early described by Laveran.

These flagellate forms which constitute one of the most interesting appearances to be made out in the malarial blood may develop from large full-grown parasites either in tertian or quartan fever, or from the above named round bodies in æstivo-autumnal infections. Their manner of origin is interesting. While observing such a body, at a period, usually of about ten to twenty minutes after the slide of blood has been made, the pigment may be seen to become excessively active. The entire parasite is shaken, the periphery showing protrusions and undulations suggesting the efforts of some contained body to escape. And suddenly there appear from one to four or five delicate, actively motile filaments. These filaments are commonly of very regular size, measuring about twice the diameter of a red cell and usually showing at one extremity a slight clubbing. Sometimes one may observe bits of pigment on the extremity or along the course of a flagellum. Not infrequently the flagella may be seen to break away from the mother body and rush off alone across the field showing an active serpentine motion.

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Another characteristic in which the æstivo-autumnal parasite differs from the tertian and quartan organisms is in that it is not, as a rule, arranged in groups, each organism of which is

at the same period of development. Though this would appear to be the case at the beginning of many infections, multiple generations rapidly develop, and often the arrangement of parasites in definite groups is entirely lost. Sporulation thus occurs more or less continuously, or at periods rapidly succeeding one another, so that the result, not unnaturally, is an irregular or continued fever.

It is very remarkable that while in tertian fever, for instance, infections with two groups of parasites segmenting on successive days and causing quotidian fever are very common, it is most unusual to find *more* than two groups present at the same time, or to find two groups segmenting within the same twenty-four hours. To be sure it is not infrequent, as Gotyé has also noted, to find in a single or in a double tertian infection, organisms which, morphologically speaking, would appear to be somewhat separated from the main group or groups present. It is, however, extremely rare to find a sufficient number of such parasites to constitute a generation large enough to produce febrile manifestations on its own account.

This indeed would appear to constitute one of the main biological differences between the parasites of the regularly intermittent fevers and those of æstivo-autumnal fever, where, as is well known, the tendency to the development of multiple groups would appear to be a striking feature.

As has been pointed out by Antolisei and Bastianelli and Bignami, infections with the tertian parasite may give rise to irregular and even continued fever. This is, however, rare. Out of 931 cases of tertian infection we have observed but three instances of continued fever. Here, we have been led to believe that the parasite, as in æstivo-autumnal infections, was present in multiple groups, the segmentation occurring at intervals so frequent as to result in a practically continuous fever.

The accompanying chart will show the relation of the different types of infection to the different times of the year:

	Jan.	*Feb.*	*Mar.*	*Apl.*	*May.*	*Jun.*	*Jul.*	*Aug.*	*Sept.*	*Oct.*	*Nov.*	*Dec.*	*Tot.*
TERTIAN, - - -	12	12	28	51	76	68	131	161	153	168	54	17=	931
QUARTAN, - - -	3	1	0	1	0	0	3	0	2	1	4	2=	17
ÆSTIVO-AUTUMNAL,	5	1	2	5	2	3	37	99	191	203	63	22=	633
COMBINED, - - -	0	1	1	0	0	1	3	3	4	11	6	2=	32
TOTALS, - - -	20	15	31	57	78	72	174	263	350	383	127	43=	1613

Infections with the tertian parasite form the majority of all the cases of malarial fever observed in temperate climates.

Quartan fever is rare in Baltimore. We have observed but seventeen instances out of 1,613 cases. Of these, eight were single quartan infections; two were double quartan infections; seven were triple quartan infections. We have never observed continued fever in infections with the quartan parasite. The paroxysms in tertian and quartan fever average between ten and twelve hours in length, estimating the period of time elapsing while the temperature remains about ninety-nine.

Æstivo-autumnal fever is very frequent with us at the height of the malarial season; rare, however, in the early part of the year. Of 633 cases of æstivo-autumnal fever but eighteen occurred in the first half of the year and of these seven were imported from tropical regions, while most of the other cases were relapses from autumn infections, occurring in the first months of the year. In the second half year, however, the æstivo-autumnal infections amounted to nearly one-half of all the cases. In the months of September and October, that period at which malaria is most common in Baltimore, there were 394 cases of æstivo-autumnal fever to 339 of all other forms of infection. Adding to the æstivo-autumnal fevers fifteen cases of combined infections we have 409 cases of æstivo-autumnal fever against 324 cases of tertian and quartan fever.

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The existence of these distinct types of parasites and their specificity have not only been proven by clinical observations; they have been controlled by a large series of careful inoculation experiments. These have shown that the introduction of fresh blood from an infected patient under the skin or into the veins of an healthy man will invariably produce the same type of disease with the same type of organism.

These facts impress us as interesting and wonderful, but there is nothing new under the sun, and on consulting the literature of malaria it is astonishing to find that they but confirm an hypothesis expressed more than sixty years ago by Rasori, who said, in a conversation with Bassi, "For many years I have held the opinion that the intermittent fevers are produced by parasites which bring about the paroxysm by the act of their reproduction which follows more or less rapidly according to their species."

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But the recently acquired proofs of the accuracy of this hypothesis by no means clear up entirely the question of the ætiology of the malarial paroxysm. Why should the process of

sporulation cause fever? The question has been answered differently by different observers. The weight of evidence, however, tends to support the view that during the act of sporulation some toxic substance is produced—set free, probably, by the parasites themselves—which, entering into the general circulation, is the direct exciting cause of the febrile paroxysm. This idea is supported by the fact that the sweat and the urine during the malarial paroxysm show a markedly increased toxicity, while the clinical sequelæ and the anatomical changes found after severe malarial infections go far in its support. Clinically, there exist a number of complications and sequels, such as albuminuria, nephritis, neuritis—entirely analogous to those which so commonly follow other severe general infections, changes which, in many instances, we know to be due to the presence of circulating toxic substances. The strongest support of the theory of the toxic origin of the fever is afforded in the anatomical changes, especially the extensive focal necroses in various internal organs, as described by Guarnieri, Bignami, Barker, Monti, and others, changes which Flexner has recently shown to be pathognomonic of general intoxications.

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Among the more interesting and disputed points in connection with the malarial parasite has been the question which has occupied a prominent position since the discovery of the organism as to the nature of the flagellate bodies. Laveran has held from the beginning that the parasite represents a sort of cyst within which the flagella develop. The flagella, according to him, represent a certain phase in the evolution of the hæmatozoon. He has more than once hinted his belief that they represent an important stage in the history of the parasite.

Most of the Italian observers, however, (Golgi, Antolisei, Grassi and Feletti, Marchiafava and Celli, Bignami and Bastianelli), believe that they represent degenerate forms, basing their opinion upon the fact that they develop in tertian and quartan fever from the large, swollen parasites, which have, apparently, failed to sporulate, forms in which, beyond flagellation only degenerative changes have been seen; while in æstivo-autumnal fever they develop from the round bodies derived from crescents. But all evidence goes to show that these crescents are, while left within the organism, sterile elements. Experiment also has shown that crescents are incapable of transferring the infection.

On the other hand, Danilevsky, who studied the closely similar hæmatozoa of birds, Dock, Mannaberg and Manson all agree

with Laveran in so far as they regard the flagella as active phases in the life history of the organism. Mannaberg and Manson believe that they represent a form of the parasite capable of preserving its existence outside of the human body. Sacharov advanced an ingenous hypothesis which has, until very recently, at least, commanded little attention. He believes that he has demonstrated that the flagella represent chromatic filaments of the nucleus which break loose from the organism.

The argument of the Italian observers has much in it that is tempting and yet we have always felt with Laveran that the extraordinary activity of these forms, their singular regularity in shape and size, is hardly to be reconciled with the idea that they are products of fragmentation and degeneration. They impress one as preformed bodies.

Within the last four months, however, an observation has been made which, in all probability, will clear up this long disputed question. And it is with considerable pride that I am able to say that this work has come from our clinic. Dr. W. A. McCallum in connection with Dr. Opie, undertook two years ago, the study of the parasites of the blood of birds, the great similarity of which to the malarial organisms has long been known. Opie was able to distinguish two separate varieties of parasites—varieties which had also previously been recognized by continental observers, and especially described by Labbé. These organisms grew within the blood corpuscles of the birds and developed pigment exactly as do the malarial parasites in the blood of man. And in both forms of the parasite, flagellation of the organisms may be observed. In one type, that which has been termed by Labbé the "Halteridium Danilevskyi," the flagellation occurs very rapidly after the preparation of the specimen, within a few minutes. And as many organisms are often seen in one field, a very large proportion of which develop flagella, the process is to be observed to a much greater advantage in birds than in man.

Opie, in a very careful and satisfactory morphological study of the parasites, had already noted a previously undescribed distinction between two forms of the Halteridium—forms which are found together in almost every specimen. In one of these the substances of the organism is completely clear and hyaline, while in the other the protoplasm has a somewhat granular appearance in which larger distinct hyaline points are to be made out. The staining reactions of these organisms are also different. The more granular forms take up basic dyes with

considerable avidity, the small clear points remaining unstained, while the clearer hyaline bodies stain but faintly.

Last summer, McCallum, continuing the studies of Opie, was able to confirm these observations and noted further the fact that the pigment is generally somewhat finer in the granular bodies.

McCallum took upon himself especially the problem of the nature of the process of flagellation, and while studying one day the behavior of a granular and hyaline form lying close together in the same field of the microscope, he observed an interesting phenomenon. Several flagella breaking loose from the central body, made their way directly to the granular non-motile form which they immediately surrounded, wriggling actively about it. Finally one of the flagella penetrated the granular sphere which appeared to put forth a process to meet it. The remaining flagella persisted in their attempts to enter but met with no success. Immediately after entrance of the flagellum the pigment of the young body became actively agitated. This was followed by a period of quiescence, after which the body changed into a fusiform element with the pigment at one end, and took upon itself a steady, sliding, forward motion. These elongated motile bodies had been repeatedly observed and described as *pseudo-vermiculi* by Danilevsky. Their significance is not known. They do not occur in human blood. This very remarkable phenomenon MacCallum was able to observe repeatedly, and to demonstrate at the meeting of the British Association in Montreal last August.

The conclusion is almost inevitable that this represents a process of fertilization. It is, as MacCallum points out, somewhat analogous to the sexual process as it occurs in some lower plants under unfavorable conditions. "In *spirogyra* and *œdogionus* when their circumstances have become such that the ordinary reproduction by fission can no longer result in a successful preservation of life, a more resistent body is formed by the conjugation of the adjacent cells. But so long as the conditions of growth are favorable we may look in vain for this process."

In various amœbæ conjugation has been observed, though, as far as I know, the formation of spermatozoa has never been noted.

Are we justified in a similar interpretation of the process occurring in the malarial parasites of human beings? It is too early to express an absolute opinion, but from recent observations in the medical clinic at the Johns Hopkins Hospital, it is extremely probable that we can. Any one who has studied the

fresh blood in malarial infections has noted repeatedly that only a certain proportion of the round forms of the æstivo-autumnal parasite develop flagella. Many others, especially forms in which the pigment assumes a very regular ring-like appearance, remain unchanged. About a month ago Dr. MacCallum was able to observe the penetration of one of these round bodies by a free flagellum; I had the good fortune to see this form shortly after penetration. The round body was surrounded by two flagella which were wriggling about the parasite, bunting their heads against it, and making, apparently, every effort to enter. The picture was striking—almost convincing of itself. Dr. Pancoast and Dr. Mactier Warfield have also been able to see the process of penetration within a few days of the time of writing. Beyond the immediate agitation of the pigment granules after the entrance of the flagellum no further change has yet been observed in these fertilized (?) forms in the human blood.

As has been before stated it is too early to draw definite conclusions as to the entire significance of this important discovery. This much may be said: It is in every way probable that the flagella of the malarial parasite represent, as Laveran originally held, important constituent parts of the organism; the view held by so many observers that the flagella are degenerate elements must be definitely abandoned; it is probable that the process of flagellation and penetration represent a sexual act, a process of fertilization which may well result in the development of more resistent forms of the organism, forms which under certain circumstances, possibly after escape into external conditions, may undergo changes rendering them capable of again infecting human beings.

How might such an escape take place? In what form does the organism exist outside of the body? How does infection occur? These questions remain as yet unanswered.

Certain observations by MacCallum suggest that in birds, the fertilized form may escape into the intestinal canal and thence reach the external medium. But the point needs further study. And indeed positive proof that flagella develop while the parasites are in the circulation of the living animal has yet to be obtained.

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In what form does the malarial parasite exist outside of the body and how does infection take place? It must be confessed that we are still sadly ignorant with regard to both these questions.

The subject has been admirably discussed in a paper by Dr. Norton of Washington and by Laveran in his most recent work. As to the form in which the parasite exists when it leaves the body, or, to speak more carefully, before it enters the body, for that it leaves the body we have no proof, we are absolutely ignorant.

As to its manner of entry many views have been held. The most popular and ancient has been that infection takes place by the inhaled air. Hence indeed the name of the disease, which is but a joining of two Italian words, "mal'aria." There are, it must be said, certain facts which speak in favor of this hypothesis. A second idea, long held, has been that infection may take place through the drinking water, while a third and, at present, very popular view is that the disease may be conveyed by the bites of insects.

The water-born theory of malaria must be said to rest upon an insufficient basis.

A number of careful experiments have been made in relation to this question, all with negative results. Celli and Marino and Zeri administered water from the Pontine marshes, regions which are the seats of most pernicious malaria, by the mouth, by the rectum and as inhalations, and in none of these instances did fever develop, although the patients were subjected to this treatment in some instances for months. Grassi and Feletti fed healthy men upon dew collected from malarial regions as well as upon the fresh blood of infected individuals, blood which, as we have seen before, invariably conveys the infection when introduced hypodermically or intravenously; infection did not follow. They further failed to convey infection in birds by feeding birds of prey upon corpses of other birds dead or suffering from avian malaria. Dr. Norton's interesting study has shown how unfounded are many of the statistics tending to prove this theory.

In the absence of proof of the theory that malarial infection might take place through the gastro-intestinal tract one has commonly fallen back upon the idea that it must be conveyed by the inhaled air, and indeed there is considerable evidence in favor of this theory. Certain it is that simple exposure, especially to the night air in severely malarious regions is commonly followed by infection. There are also observations to the effect that malaria prevails especially upon that side of a swamp or stream toward which the prevailing winds blow; one has, however,

usually arrived at the assumption that this is the common mode of contagion by a process of exclusion.

Of recent years there has been a strong tendency toward the idea that, in some instances, infection might occur through the agency of the bites of insects, more especially the mosquito. We possess abundant evidence that the disease is readily transferable hypodermically. Moreover, the recently discovered fact that certain closely analogous protozoan infections of the blood may arise through the agency of insect bites has led one to regard this hypothesis with considerably greater favor. Especially the discovery that Texas fever, or as Celli has termed it, "Bovine malaria," is a disease caused by an hæmacytozoon closely resembling that of malarial fever, an organism introduced into the infected animal through the agency of the cattle tick, is extremely suggestive. This discovery was the brilliant achievement of Professor Theobald Smith of Boston. More recently also the interesting disease "Nagana" has been shown by Bruce to be due to the presence of an animal parasite, a *trypanosoma* which is introduced by the bite of the Tsetse fly. Laveran, as has been said, has always favored the idea that malaria might arise from mosquito bites, and more recently Bignami has contributed an interesting plea in favor of this hypothesis.

The districts in which malaria prevails, moist, hot, swampy, tropical regions are exactly those in which mosquitoes usually abound. In temperate climates malaria is most common during the latter summer and early fall, exactly the period at which mosquitoes are most numerous. In a malarious district the dangers of infection are generally greater by night than by day, at the very periods when mosquitoes are most numerous and active. A strong breeze is unfavorable to malarial infection, and during a strong breeze the mosquito is less dangerous. Furthermore, Bignami notes that in malarious districts the measures adopted by the inhabitants to protect themselves from infection are in great part such are also adopted to protect them from mosquito bites; namely, sleeping on upper stories of the house, closing of the windows. Again, he asserts that in certain very malarious districts, workmen who live in small conical huts with only one means of ventilation—an opening at the apex which serves as an outlet for the smoke of the small fire, are commonly free from malarial infections, while those about them may be almost without exception subject to the disease. Emin Pasha was so convinced of the danger of bites of mosquitoes that throughout his African travels he slept under a netting and never suffered from

the disease. These are interesting and suggestive arguments; positive evidence, however, of their justice we have yet to obtain.

The *rôle* of the mosquito in malarial infections has also been discussed by Manson who believes that this insect forms the intermediate host of the malarial parasite and points out in his interesting papers a supposititious method by which the mosquito might infect drinking water. But his ideas can be said to be little more than ingenious hypotheses; moreover, the possibility of infection through drinking water is, to say the least, very doubtful.

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The diagnostic importance of the malarial parasite is in many ways parallel to that of the tubercle bacillus in pulmonary tuberculosis and of the Klebs-Lœffler bacillus in diphtheria. The diagnosis of tuberculosis and diphtheria and malaria can be made in many instances without examining for the specific micro-organism, but on the other hand, how many, perhaps fatal, mistakes may be avoided by the physician who examines his blood and sputa and takes cultures from suspicious throats.

It may be urged that in malaria we have additional diagnostic assistance in the possession of a true specific. All malarial infections it is true, yield to quinine; there is no evidence in literature to the contrary; fevers which do not break within four days after the onset of the treatment are not uncomplicated malaria. In this connection it cannot be denied that in many cases in tropical districts the patient may be beyond help when first he comes under observation, though even here, perhaps, many might be saved by the intravenous administration of quinine according to the method of Baccelli. The anæmia and debility also following long continued or repeated malarial infections—chronic malarial cachexia—may be little influenced by the drug alone. But who would seek to deny that iodide of potassium is a specific in syphilis because, in some instances, a cerebral or hepatic lues may have reached a stage before the initiation of treatment, so advanced that the patient may die before the drug has had time to act? And who would be so unreasonable as to demand that iodide of potassium or mercury, in order to deserve the name "specific", must possess the power to restore degenerated nervous tracts or regenerate destroyed liver substance?

But the disappearance of the symptoms after quinine is only suggestive proof of the malarial character of the affection—more or less suggestive according to the nature of the case.

The discovery of the parasites in the blood is the only diagnostic sign of malarial infection.

Gentlemen: You may feel that all these facts are interesting, but of little practical importance in a community such as this, where, as a rule, the milder forms of malarial fever alone prevail. It is true that it will not frequently fall to the lot of a New England physician to save the life of a patient with pernicious malaria as a result of the happy discovery of the parasite, for pernicious malaria probably does not exist here. But while these capital cases do not occur, and while in some regions even the milder forms of the disease are uncommon, there is none the less considerable need of a clearer understanding of the manifestations of the malady. There is a grave and general misapprehension as to the nature and frequency of malarial fever throughout the Northern States. I have within a few years known a conscientious physician in a non-malarious district of a Northern State, to treat for several weeks a case of typhoid fever, who died from intestinal hemorrhage, with heroic doses of quinine, under the belief that it was an instance of continued malaria. Examination of the blood would have cleared matters up instantly. A realization of the fact that *malarial fever resistent to quinine does not exist either in the North or in the South* would have prevented such a misapprehension.

The intermittent fever of early tuberculosis here, as elsewhere, is often confounded with malaria, and the frequency with which the term is still applied to a variety of nervous manifestations which are common in the North, as everywhere, is notorious. I remember well, for instance, the ideas with which I entered into practice with regard to the frequency of supraorbital neuralgia of malarial origin. In the study of over 2,000 cases of malaria during somewhat over seven years, it has never fallen to my lot to see even a single case of this nature. One instance of supraorbital neuralgia I have observed in a case of post-malarial cachexia where the patient suffered also from an inflamed lachrymal duct. The parasites had long since disappeared from her blood. A variety, also, of ocular phenomena are still, without a shadow of foundation, referred to this disease.

The term malaria has, in times past, served as a cloak to cover our ignorance. It cannot be denied that we have made good use of it.

Laveran, by his discovery, has rendered this much affected garment unfit for further application.

Let us be thankful that he has delivered us from temptation!