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THE MALIGNANT TYPE OF MALARIA

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INTRODUCTION

Malaria is classed among the so-called "Tropical Diseases." While found most frequently in the tropics these diseases are by no means limited to these regions. Of all the diseases in this group none is more truly universal than malaria.

A glance at a map showing the vast distribution of this disease will immediately disclose its universality, and it will also point out as Bass (4) has shown that malaria was quite widespread even before any history records it. Probably it is because of this wide distribution and its harmful affect upon so many of the world's races that the malarial episode in the romance of medicine has become of such interest and concern both to the medical profession and to the layman as well.

Because of its economic significance and bearing upon the morale of a people, the study of malaria and its control has become of vital interest to leaders in state and national affairs, as well as heads of large corporations having interests in malarial districts.

Many exhaustive books have been written on this subject by men who have spent long years in diligent research. It shall not be my object in this paper to vie with them in a field wherein I have not entered experimentally. I merely propose to glean from their labors and from others who have made less extensive contributions on the subject,
information dealing with one of the phases of the disease, namely, the malignant type of malaria.

I shall seek to enumerate the various manifestations of malignant malaria, and to call attention to certain findings associated with this type of disease. The question of Blackwater Fever will be dismissed from consideration because it is probably a disease entity in itself, and while associated with malaria Whipple (54) believes it may be classed as malaria plus some as yet unknown factor.

In spite of all that has been done in the way of research and control of malaria, the problem is far from solved. Dr. Hoffman, (22) consulting statistician to the Prudential Insurance Company, in a survey of thirty countries, says it is only in a few cases where there is any marked reduction in the incidence of malaria. This statement is all the more striking when we consider the country whose people carry life insurance. Hehir (21) estimates that there are 100,000,000 cases of malaria annually in India alone. Gaines (18) notes 29,022 deaths from malaria in Georgia alone in six years ending 1924.

However, Bass (2) points out that the incidence of malaria in the last hundred years has been on the decline in such places as Northern United States, England, Wales, Scotland, Southern France, Holland, Germany and to some extent in Southern United States. His explanation for this decline is three-fold.
1. "Advancement of civilization with its clearing affect on natural habitat of the mosquito."

2. "The widespread knowledge that malaria is spread by the mosquitoes.

3. "Intelligent and more extensive use of quinine."

During the last fifteen years the greatest decline in the United States has been due to the extensive control campaign and widespread propaganda in the south for treatment with quinine after clinical symptoms have ceased and until the patient is cured.

At the present time the chief problem confronting those engaged in malarial work is the problem of control, and closely associated with this is finding a plan of treatment which will rid the blood of crescents. I shall, therefore, seek to state what progress has been made and try outline the best plan to date for ridding the blood of the sexual forms.
Before considering the malignant type of malaria in detail it might be well to consider briefly some of the historical background of the subject as a whole. Many deciding factors in the shaping of a nation's destiny are never recorded in her written history. Progress and decline are usually centered around some decisive battle, some great personality, or some outstanding invention, etc. Along with many other factors disease has played a very prominent part in the downfall of many nations. Oliver (40) has pointed out that the chronic diseases, and not the epidemics, are the ones which have had the greatest influence in changing history. The story of malaria is woven into the historical fabric of various nations of the past, and even today the economic and political program in nations where malaria is prevalent are being molded by it. This is because of the large number of people affected, and the extreme difficulty associated with the control of the disease. Ross (40) points out that in the tropics about one-third of the population suffers from malaria every year, and that about one-third of all hospital patients come in because of malaria.

Many authors have written about the glories of Greece, and have sought in various ways to explain her downfall. In his interesting and most instructive book, "Malaria and Greek History," Jones (1) has shown that about the time of Hippo-
crates malaria was becoming an endemic disease, and that it most likely had been introduced into Greece shortly before that time, but as to its mode of entrance, or just how long it had existed in Greece no one knows. Tait (47) believes that malaria was quite prevalent in the time of Hippocrates upon the evidence of universal prevalence of large spleens in those days and quotes from Hippocrates, "When the body flourishes the spleen wastes." At any rate, Hippocrates gave accurate descriptions of the quotidian, tertian, and the quartan types of malaria, and expressed that they are associated with low and swampy places. An interesting quotation from Hippocrates' treatise, "Airs, Waters and Places", is given by Bass: "Those who dwell in the hollow, hot districts where the winds and water are warm are neither tall nor straight. If they drink the water of the place they have diseases of the spleen and stomach. They are stout and fleshy, dark-colored and bilious. By nature they are neither courageous nor of great power of endurance. But there are no ill effects when the water is drained off."

Along side other explanations given for the downfall of Greece, such as immorality, decline in religion, decline in patriotism, Jones (25) has shown that malaria was becoming an outstanding menace in the progress of the nation. It crippled the farming classes so that they fled from their rural homes in desperation. The Greeks began to lose interest
in their homes, in the state, in the arts, and in the care of their physiques. The fact that there was a marked change for the worse in Greece between the fifth and third centuries, B.C. with no consensus of opinion as to the cause has led Jones (24) and others to believe that the prevalence of malaria, as a new endemic disease, was the cause. The degradation of medicine from the rational school of Hippocrates to the miracle-working charms and snakes of the Esculapian temples was due not only to the mental enfeeblement caused by malaria, but also to the absence of quinine as a cure for the disease. Probably one of the reasons for laying aside the scientific principles laid down by Hippocrates was the "increase and spread of the disease against which rational medicine was at a disadvantage as compared with religion, magic and empiricism, and such a disease is malaria." Jones (1).

The mode of entrance is probably to be explained by the wide contact which Greece had to the rest of the world through her extensive maritime traffic. Yet Ross (44) quotes Strabo (1st century, B.C.) as saying that "Alexandria in spite of its site was free from marsh fever in his time."

While the early Italian writers have very little to say about malaria the later writers do. Oliver (40) calls attention to the fact that malaria was present in Italy about 50 B.C., and was probably brought in by its mercenary
soldiers. That they were acquainted with malaria is evidenced by their use of mosquito nets. It was even endemic in Rome and the Campagna at that time. Rome was a hotbed of malaria and people were leaving the rural places for the cities due to the successes of the Roman conquests. This only complicated conditions because of the increased breeding possibilities for the mosquitoes when the land lay untilled.

Bass (2) has shown that interwoven into the history of Rome and of Ceylon, as in the case of Greece, is the role played by malaria, and it is perhaps the greatest single factor in the downfall of these great civilizations of the past.

From the time of Galen in the second century, A.D. who described with accuracy the malarial seizures with their quotidian and tertian characteristics, and until in 1640 when cinchona bark was introduced into Europe there is a period of marked silence. The actual history of malaria itself seems to be divided into three stages. 1. The stage of observation led by Hippocrates, and culminated by Morton, 1697, and Torti, 1753, who used cinchona bark as a means of differentiating the malarial fevers from the other types. 2. The stage of theory when explanations as to the cause of malaria were sought. 3. The stage of achievement led by Laveran.
The most outstanding early contribution to the study of malaria was the introduction of cinchona bark. Historical records of the Missouri Botanical Garden in St. Louis show that in 1630 Juan Lopez Canizares, the Spanish corregidor of Loxa, was the first to demonstrate the use of the bark of the cinchona tree in treating malaria. Ross (44) tells that the Countess d'El Cinchon, wife of the Viceroy of Peru, had been cured of fever by the use of it in that country. And Bass (4) shows that she, together with her physician-in-ordinary, Juan del Vego, introduced the cinchona bark into Europe in 1640. In 1820 Pelletier and Caventou extracted the alkaloid quinine from the bark.

We have considered malaria's effect upon history and the stage of observation led by Hippocrates. Let us, therefore, consider some of the theories given to explain the cause of malaria. Thayer (48) shows that Varro (118 to 29 B.C.) believed that malaria fever was caused by parasites. Morton in the 17th century thought that marsh air contained heterogeneous particles which caused malaria. Lancisi in 1717 believed the disease due to animalculi arising from putrificactive factors in swamps which when inhaled entered the blood stream where they multiply and give rise to symptoms. Rasori in 1846 held the idea that intermittent fevers were produced by parasites which renew the paroxysms by the act of their reproduction which occurs
more or less rapidly according to the variety of their specie. Virey thought the disease due to certain infusoria. Boudin attributed the disease to the inhalation of certain volatile poisons given off by certain marsh plants. The association of the disease with marshes was quite evident and hence, the name palustral disease. Mitchell in 1849 suggested spores found in large number in marsh districts as the cause of the disease. Lemaire studied vapor collected above the surface of the marshes in Sologne and found it to contain a large number of micro-organisms, and held that this was the cause. Bauchardat thought the disease due to poisons produced by animalculi resident in marshes. Salisbury in 1866 described small vegetable cells of the family of Palmella, which he asserted he found in urine and sweat of patients with malarial fever. These, he held as the pathogenic agents. This was successfully controverted by Wood in 1868. Lanzi and Terrigi in 1875 described bacteria thought to cause malarial infection. Klebs and Tomassi-Crudeli in 1879 created quite a stir in medical circles by announcing experiments where they injected animals with certain bacilli found in the soil around marshes and reproduced malaria.

Besides these various theories there were striking observations made by certain investigators which are significant. Thayer and Hewetsen (49) show that Meckel in
1847 first noted pigment in the blood of an insane woman at autopsy, who had died of malaria, but did not suspect it as the cause. In 1850 Hirschl recognized the connection between pigment and intermittent fever. Planer in 1854 noted pigment in the circulating blood and believed it arose during fever, and was the cause of many symptoms. Ross (44) showed that Gerhardt discredited the idea that paludic pigment in the red blood corpuscles was due to paludic miasma by infecting healthy individuals by the inoculation of blood from a patient suffering from paludism and reproducing the disease.

All these observations of malarial pigments were forerunners as to speak of the great discovery of Laveran which paved the way for a large number of successful studies. In 1878 Alphense Lavoran, a French army surgeon, commenced his work at Bone in Algeria by following up the granules of pigment described by the other observers. Ross (44). Then, on November 6, 1880 at Constantine in Algeria Laveran made his memorable discovery. Thayer (48) says that in the same month he sent a preliminary communication to the Academy of Medicine in Paris. This was to insure his priority to the claim of discovery as well as to announce his great finding. In 1881 he published a small monograph which describes his observations at length.
His observations were confirmed by another French surgeon, Richard, studying in Philippeville in Algeria, who went further than Laveran in that he recognized the youngest forms of the parasites as a small, clear, non-pigmented spot in the corpuscle. He also described the rosette form, and differed with Laveran in asserting that the parasite developed inside the red corpuscle, rather than on the outside. Thus, we see that Richard made an important contribution to Laveran's original study.

It was not without hard and diligent work that Laveran's discovery was made. A quotation given by Sequeira (46) discloses some of the care and precaution observed by Laveran before he announced his discovery.

"On the 20th of October last, while examining by microscope the blood of a patient suffering from malarial fever I observed in the midst of the red blood corpuscles the presence of elements which appeared to me to be of parasitic origin. Since then I have examined forty-four cases, and in twenty-six have found the same elements. I have searched in vain for these elements in the blood of patients suffering from diseases other than malaria. I have described the elements as bodies No. 1, No. 2, and No. 3. Bodies No. 1 are elongated elements, more or less tapering at the extremities, often curved into crescents, sometimes of oval form. These measure eight to nine thousandths
of a millimeter. They are colorless except for the central part, where there exists a blackish spot formed of a series of rounded granulations, which appear to be pigment granules. Some of these bodies show on the concave side a pale curved line which appears to tie together the extremities of the crescent. Bodies No. 2 show different aspects in rest and in motion. At rest they are spherical and show a circle of granules of pigments. In motion there is a rapid change; very transparent filaments animated by actual movement are seen outside the body. The filaments are symmetrical. A free filament of one of these bodies is figured. Bodies No. 3 are generally spherical but larger than No. 2 and show alterations in shape."

It was about this same time that the theory of the bacterial etiology was proclaimed by Klebs and Tomassi-Crudeli and many were led to believe in this theory. Thayer and Hewetson (49) tell how even Marchiafava and Celli were not convinced of the protozoal cause until 1885. In Celli's own words in speaking of Laveran's fundamental discoveries he says, "they, however, were not accepted until Marchiafava and I had demonstrated that melanin which is characteristic of this infection, was formed within the parasite, and pointed out the semblance which these bodies have in ameboid movement, and cell structure to protozoa, and that they multiply by fission."
They propose the name "plasmodium malariae" which Thayer (46) believed an unfortunately chosen name. These observers and Canalis published almost simultaneously articles describing the life history of the organism found in estivo-autumnal fever.

To Golgi working in Pavia in 1885 is accredited the discovery of life cycles in quartan and tertian fevers. His studies led to the conclusion that these two forms of fever were caused by specific and different organisms, and he was able to demonstrate and describe these forms. Although he recognized another form of parasite he was unable to fully describe it, probably because of its rare occurrence in Pavia. This was the parasite worked out by Marchiafava and Celli and Canalis. Osler (42) in 1889 felt that the Klebs and Tomassi-Crudeli bacillus theory of the etiology did not seem as plausible as the protzoa described by Laveran. However, he recognized the doubts and differences of opinion which were present. Up to that time Laveran's work had been confirmed in Italy, America, and India, but the bacilli theory of malaria had not. Among the American observers to confirm the work of the French students were Councilman, Abbot, Sternberg, Osler and James.

As Laveran was the leader in the studies of the
causitive organism in malaria so Ross stands out in the
work on the mode of the passage of the parasite from man
to man. Up to the time of Ross's discovery he (3) notes
that the suspicion that mosquitoes might be the cause was
held by several outstanding observers like Laveran, Manson,
Koch, and others.

Sir Ronald Ross (45) began his medical work as an
army physician in India in 1889, and it was during this
service that he became interested in the study of malaria.
Returning to England on leave in 1894 he met Sir Patrick
Manson and heard his hypothesis that "the flagellate bodies
are stages in the Laveran's parasites which produce
motile spores for the purpose of infecting mosquitoes which
happened to suck the patient's blood." Contrary to certain
statements, Ross states in his "Memoirs" that he chose to
verify Manson's hypothesis and that Manson did not select
him for the task. Ross consulted Manson freely and told
him of his plans. Manson in turn gave him helpful counsel
and much encouragement. In 1895 Ross returned to India to
take up his chosen task. On board ship and at the island
of Malta where he stopped for a while he did a large amount
of research work. And the correspondence carried on between
Ross and Manson is a beautiful example of sympathetic,
scientific cooperation, and it also reveals the struggle
Ross had before he was able in 1898 to announce his great discovery. Ewing (13) says that Ross found that the blood of birds infected with Proteosoma, a species of parasite closely resembling the malarial ameba, reaches the stomach of the mosquito, and there many of the organisms become flagellated. A few days later in the stomach wall of the mosquito there are large encysted pigmented bodies containing many rodlike structures, and some black spores, which on the rupture of the cyst, gain entrance into the general circulation. He was able to demonstrate these "germinal rods" in large numbers in the salivary glands of the mosquito, and was able to infect young birds by exposing them to these mosquitoes. Grassi, Bignami, and Bastianelli working in Italy confirmed Ross's observation. They succeeded in conveying the estivo-autumnal infection from one human being to another by means of a particular variety of mosquito, aopheles claviger, the "dapple-winged" mosquito described by Ross.

These were the pioneers in conquest of the malarial parasites and following them a host of workers have continued the pursuit of the final solution of the problem.
GENERAL CONSIDERATIONS

The term malaria had its origin from the supposed relation, as the derivation of the word would indicate, from the Italian "mal" meaning bad and "aria" meaning air, and according to Bass (4) was first used by Torti in 1753 in his treatise on these fevers. Malaria is a general term used to describe that group of fevers caused by the animal parasite termed plasmodium, and which before the discovery of the organism responded to quinine therapy.

These organisms live and multiply in the blood stream, invading or living on the red blood corpuscles, and are transmitted from man to man through the agency of mosquites belonging to the subfamily anophelene. It is characterized by the periodicity of symptoms, enlargement of the spleen, pigmentation of the spleen, liver and bone marrow, and is amenable to treatment with quinine.

Most authorities agree that there are three main types of malaria, and that each type is caused by a distinct organism. This was also concluded at the International Congress of Malaria held in 1925 as shown by Marchiafava. These organisms are Plasmodium Vivax, the cause of tertian malaria, Plasmodium malariae, the cause of quartan malaria, and Plasmodium falciparum, or praecox.
the cause of malignant malaria. That these three types are specific entities like Diphtheria, Tetanus, or Cholera is proven by the thousands of cases of Paresis inoculated for therapeutic purposes with Plasmodium Vivax chiefly, with the production of identical symptoms in each case, and the recovery of the same type of parasite later. Wagner-Jauregg (53) using tertian parasites has transmitted from one paretic patient to another so that he reached the 37th transmission of the same strain in over 200 cases, and through it all kept a pure tertian organism. Similar results have been obtained by many other neurologists. Marchiafava (35) cites a case of a woman age 37 in whose family malaria had appeared ten days previously and she with three others died in the fourth paroxysm of a choleriform attack. The estivo-autumnal parasite was found in her blood.

The mode of spread of these various types from man to man is the same, namely, by the bite of the female mosquito, of the subfamily anopheline. Various members of the anopheline group seem to have a specificity for a certain malarial parasite. Thus King (26) has shown anopheles Punctipennis is efficient for tertian and estivo-autumnal parasites, anopheles Crucians is efficient for estivo-autumnal parasites, and anopheles quadrimaculatus
is efficient for the estivo-autumnal and tertian parasites.

Craig (18) calls attention to the fact that such men as Grassi and Feletti, Mannaberg, Manson, Marchiafava, Bignami, Bass and himself have described differences in Plasmodium falciparum which lead them to believe that there are at least two varieties, and that these may account for the variation in the manifestation of disease. However, Marchiafava and Bignami (37) think the forms of estivo-autumnal parasites are to be differentiated from each other not so much by their morphological characteristics as by the mode of their pathogenic action on man. Lawson (30) who has made extensive studies of the estivo-autumnal parasite feels that there is no convincing morphological basis yet established for making a distinction of varieties of Plasmodium falciparum. Ziemann after studying 210 cases of estivo-autumnal infection was unable to find sufficient grounds for subdivision of this group. Koch (27) believes the estivo-autumnal parasite is one parasite and that in fresh cases is uniformly tertian and later becomes more and more irregular. And Hewetson and Thayer (49) believe all the organisms described by the above men are a single variety of parasite whose cycle of development varies between 24 hours or less and 48 hours or more according to circumstances depending
partly on the organism and partly on the affected individual.

While there are these two views as to the morphology of the Plasmodium falciparum it is quite universally held that some manifestation of this parasite is the chief cause of the malignant type of malaria.

Inasmuch as there is no final word on the subject, for the sake of simplicity, it might be well to hold to the single parasite idea.

That this parasite is always the cause of pernicious malaria is also disputed. Certain writers from time to time have described cases presenting pernicious symptoms and caused by plasmodium vivax. Gaines (18) reported three patients with mental symptoms, one with amnesia, one with neuresthenia and another with melancholia. Forrester (15) in discussing 116 admissions to the mental department showing some mental symptom plus malarial history gave both benign and malignant tertian parasites as the cause. He states that in Macedonia malaria was reckoned far and away the biggest factor in the causation of mental diseases amongst British troops. On a group of purely mental patients the certainty to which the symptoms might be attributed directly to the malarial organism is quite doubtful. Bass (4) believes that both tertian and quartan may produce pernicious symptoms and even death.
When the asexual forms of the estivo-autumnal organism find conditions unfavorable in the blood they develop crescents, but if favorable to their production and growth, crescents are not at all, or only slowly formed. If the blood of a patient is examined at the time when the latter is true, a differentiation between the estivo-autumnal and the tertian parasites is difficult to make. Probably some such condition existed in these cases of pernicious malaria reported as due to plasmodium vivax. The previous condition of the patient before the attack of tertian malaria may have been so poor that only something additional was needed to produce a condition of extremus. Also the fact that the cases presented by Forrester were purely mental patients makes their classification among the cases of pernicious malaria somewhat doubtful. Marchiafava (35) who was one of the first men to describe the estivo-autumnal parasite in relation to its life cycle, and who has actively studied the disease produced by this organism for over forty years, states that he has never seen pernicious malaria occurring in any other type of parasite.

Several names are used synonymously to express the malignant type of malaria. For the organism causing these more serious manifestations the names subtertian, malignant-tertian, Laveranian parasite, and the estivo-
autumnal parasite, have been given. The latter term is used in this country and by most of the Italian writers. From the clinical manifestation it is called malignant-malaria, "Tropical form of malaria" by Corradini, (9) "tropical fever" by Koch (27), and probably most frequently it is called pernicious malaria.

Malaria may be considered malignant when the life of the patient is definitely endangered. Cases infected with the estivo-autumnal parasite Manson (34) says may at any time become pernicious. It is not the height nor the form of the fever curve but the gravity of symptoms threatening life that determines the malignant character. Therefore, every patient infected with this type of organism is in great potential danger both to himself and to others. Symptoms in treated cases of quartan and tertian infections have a tendency to decrease in intensity and to practically disappear in time, while in the malignant type the symptoms become progressively worse.

Character of the Fever. While the fever curves in tertian and quartan types of malaria are almost clocklike in their course, the fever in estivo-autumnal malaria is apt to be irregular. Wright (55) says the fever is usually remittent in character, and where it is
intermittent it sooner or later becomes, or assumes, the remittent characteristics. The characteristic febrile curve is described by Marchiafava (35) as consisting of five stages; the onset of fever, the static period with oscillations of temperature, the pseudo-crisis, the pre-critical rise, and the true crisis. (See figure 1). Koch (27) holds that the fever in malignant malaria is intermittent and tertian in character early in the disease, and then becomes more and more irregular. An explanation of this might be made on the ground that early in the disease the meshes of the capillary net work in the internal organs have not become crowded with organisms and cellular debris. Marchiafava (35) offers three explanations for the change: (1) Prolongation of paroxysms so that they run into each other; (2) Exceleration of the rythm so that a new attack commences before the preceding one is over; (3) Double attacks due to two parasitic generations.

Certain other explanations have been given to account for these changes in the febrile manifestations. Probably the same factors operating to produce these irregularities in the febrile curve are the ones which produce the pernicious symptoms. Dock (11) in accounting for the production of the paroxysms in the tertian
and quartan types believes toxic substances produced by the growth and destruction of the malarial parasites act in some way on the nervous system. But he was confused when he sought to explain the more severe types because they presented these irregularities in manifestation. Ewing (13) cites Golgi as concluding that "the parasites in the blood of the estivo-autumnal cases are only an index of the infection and have little to do with the real pathogenesis of the fever, and that they represent early phases of a cycle which is much longer than has been believed." It is common knowledge that sporulation in this type occurs chiefly in the capillaries of the internal organs, and probably there is a smaller amount of the immune bodies in the blood plasma bathing the parasites in these regions. Hence, more of these organisms survive to reproduce. Certain observations that the estivo-autumnal parasites have the tendency to stick together and that they are more resistant to pressure may account for their clogging the capillaries.

Marchiafava (36) says it is possibly a modification of their physico-chemical quality that is the cause of the multiplication of the plasmodium in the smallest vessels of the internal organs. Von Egdorf (52) with many other writers has called attention to the fact that the sporulation in this type is not so regular. All phases of
development of the organism have been found in the same patient at autopsy. The biological characters upon which Marchiafava (35) is able to judge the malignancy of this organism are: 1. its greater power of multiplication. 2. its greater toxicity. Its greater power of multiplication may be induced from: (1). the parasitic density is often enormous in pernicious cases if one takes into account both the peripheral blood and the parasitic content of the viscera. (2). the shorter incubation period, which in his experience in spontaneous inflections runs from eight to ten days, while it is longer in ordinary tertian and quartan. (3). the greater number of spores, 24 to 32 in Plasmodium falciparum, 16 to 20 in Plasmodium vivax, and 8 to 10 in Plasmodium malariae. And the greater toxicity is largely proved by the gravity of the syndrome, by the frequent sequela of severe anemia, by the syndromes involving the central nervous system, and by the regressive alterations: as those of the red blood corpuscles principally exemplified in the "brassy cells," and degenerative changes to the point of necrosis in the parenchyma of such organs as the liver, kidneys, heart and central nervous system. Another indication of malignancy is its resistance to the salts of quinine as compared to the other species.
We have seen that the fever curve of the estivo-autumnal malaria begins as an intermittent type, and for various reasons becomes subcontinuous, (continuous fever with incomplete intermittence) or remittent in character. According to these variations in the fever curve there are certain clinical manifestations. For simplicity in describing these clinical manifestations three main groups will be observed.

Group one deals with the intermittent fever, where the blood shows parasites all or nearly all of the same stage of development. In this type there seems to be but one parasitic generation. This is the group which Castellani and Chalmers in their classification call simple subtertian. And if there is intermittent fever with a quotidian interval they classify it as double subtertian. This group is usually short in duration and often develops into one of the following two forms.

Group two deals with a subcontinuous fever, in which the blood shows parasites in varying stages of development, indicating that there is more than one generation of parasites. This group of cases Marchiafava classes as subcontinuous or simple pernicious fever because in this group the pernicious character is determined by the
intensity of the infection with a rapidly progressing aggravation of all the symptoms which accompany it. This form of manifestation may stimulate some general morbid conditions, and when so receives a term descriptive of that condition, such as typhoid, bilious (icteric), or pneumonic. From the classification of Castellani and Chalmers the following forms may be classed as coming under this heading: the irregular, the remittent, the bilious remittent, and the pernicious fevers not showing local symptoms such as the algid, diaphoretic, hemorrhagic and scarlatiniform forms of manifestation.

Group three deals with the comitant form, and arises from the intermittent form and at times from the subcontinuous group. It is so named because it is accompanied by an outstanding or dominant symptom or syndrome of particular gravity which suddenly imposes its own distinctive character upon the attack. In this group are those conditions which Castellani and Chalmers class as the pernicious fevers with local symptoms, and they group them according to the region involved, as the cerebral, spinal, gastro-intestinal, cardiac, and pulmonary. The pulmonary symptoms will be discussed in connection with the subcontinuous group.

The discussion of these three groups will be based chiefly upon materials obtained from the works of Marchiafava (35), Castellani and Chalmers (6), and Thayer (48).
with other writer's findings brought in occasionally.

The manifestations of the intermittent fever group most closely approach the typical paroxysms shown in the tertian and quartan types of malaria. It may take on either a tertian or a quotidian character. In the tertian variety the cold stage is variable as the attack may begin with a warm stage with severe pains in the limbs, back, and head, and there may be gastro-intestinal disturbances like vomiting and diarrhea, and a coated tongue. The sweating stage is always present, and the spleen is tender. The temperature remains up for about four hours at 104 to 105 degrees, oscillating about one degree, but just before the crisis the oscillation is greater, and that is called the pseudo-crisis. After this the temperature rises to its highest point (pre-critical elevation) and then suddenly falls to below normal where it remains until the next paroxysm. The length of the attack is longer than in the benign tertian malaria. In the quotidian type of manifestation the fastigium is very short and the cold stage is less marked. This form of manifestation is usually seen early in the disease, and at any time may precipitate into a fulminating, comitant attack. It may also become subcontinuous.

The second group is distinguished by the subcontinuous type of fever and a steady, gradual progression of the
malignant symptoms which are more generalized in character. The Typhoid form of manifestation in this group is characterized by the patient appearing dull and drowsy; face flushed, conjunctiva injected, tongue dry and brown; pulse often soft and dicrotic. The chest is usually quite clear except probably for a slight generalized bronchitis; somnolent and sibilant rales. The abdomen is negative, though there may be tenderness over the spleen. The spleen is usually palpable; soft and round in fresh infections, and hard with sharp margin in old continued attacks. There is marked anemia, a distinct, yellowish-gray hue to the skin and conjunctiva, and herpes on the nose and lips. Subjectively, there is severe headaches and intense aching and roaring in the ears with vertigo. Delirium is quite common at the height of the attack, ranging from a mild and muttering variety to a violent and maniacal type. Drowsiness may increase to actual coma. Nausea and vomiting may be severe and in children diarrhea occurs. Epistaxis is at times present. Thayer said that this condition was formerly frequently mistaken for typhoid fever in this country.

In the way of differential diagnosis between these two conditions, we note that in malignant malaria there are positive blood findings of the malarial organisms, a leucocytosis as compared with the leucopenia in typhoid,
and the negative findings of B. Typhosus and the negative Widal. In malaria, the fever frequently shows an intermittency in the early stages, the temperature is high from the first day, and there are irregular remissions of fever, the initial subicteric tint, the rapid onset of cerebral phenomena, the absence of diarrhea, or, if it should exist, would show marked differences from typhoid diarrhea, the enlargement of the liver accompanying that of the spleen, the non-cyclic course of the disease, and herpes around the nose and mouth which are rarely seen in typhoid.

The Bilious (icteric) form begins as an ordinary remittent fever, usually high, but is associated with jaundice, bilious vomiting, and usually diarrhea, and there may be constipation. There is pain and tenderness over the stomach and liver. After a few days of illness the symptoms may gradually subside, with or without hiccough, epistaxis or hematemesis. The temperature may rise considerably and the patient become comatose. The patient is dull and apathetic, face sunken and expressionless, respiration feebly, and the pulse almost impalpable. There is at times a curious intermission in the symptoms, unfortunately of short duration, after which a high fever ensues, quickly followed by coma and death. There is great blood destruction, and consequently much bile production
with a backing up of bile into the ducts, and reabsorption. Associated with this there are dark colored stools, and a highly colored urine, containing urobilin and bilirubin as well as albumin.

In the rare Pulmonic form there is usually a painful cough, great dyspnea, and severe pain in the chest, while there may be moderate dullness over the affected lung. On auscultation coarse, sonorous and sibilant râles together sometimes with fine, moist sounds may be heard. At times the physical examination is negative, even in the face of severe dyspnea. It resembles more a broncho-pneumonia, and there is bloody expectoration in which the red blood corpuscles contain malarial parasites. It is not a true pneumonia, but rather more probably an active congestion of the pulmonary vessels by the localization of parasites, because it is noted that the symptoms are better during the remissions of fever and worse during the attack. It may be complicated by true pneumonia due to the pneumococcus.

Closely associated with the above form is the pleuritic type which has been described with sharp prickling pain, dry cough, and friction sounds which improve in remissions and become worse during an attack.

The Irregular form is said to occur when several
broods of the estivo-autumnal parasites exist together in the blood so that sporulation occurs irregularly. This causes the paroxysms produced by each brood to overlap, and thereby produces an irregular type of fever. This form is commonly met with on the West Coast of Africa. This type closely simulates the intermittent, but because of the amount of infection and the high potential danger which such a patient is in, it is included in this group.

The Remittent form, instead of having several broods of parasites, is characterized by prolonged paroxysms produced by single infections, so that by anticipation or sub-entrance two attacks become continuous, that is, the onset of the second attack begins before the first is concluded. In the symptomatology there are a few days of prodromal symptoms consisting of malaise, lassitude, pains and sensation of chilliness, and gradually the fever begins to come on without any preceding chill. The skin becomes hot and dry and takes on an icteric tint. Headaches may be severe, and pains in different parts of the body may give considerable trouble to the patient. The tongue is dry and coated as in the intermittent form, and thirst is sometimes intense. It may be associated with vomiting and purging together with pains in the stomach, liver and spleen. There may be mental irritation, sleep-
lessness, restlessness, and delirium due to continued temperature above the normal; or this may be due to toxic substances acting on the brain.

The time of the remission is by no means certain. It may be at morning or evening. The remissions are preceded by high temperatures. In this type the parasites seem to be scattered throughout the capillaries of all the visceral organs so that although the peripheral blood may be comparatively free from parasites after treatment, the symptoms and remissions often continue. General symptoms vary directly with the amount of infection present.

In the Diaphoretic form there may be drenching sweats so as to form pools under the bed of the patient. This form is rare and has its danger in the great exhaustion and prostration from which dangerous collapse may ensue. While the symptoms are general their pathogenesis may be due to certain localization of parasites in and around the heat regulatory center in the brain.

The Hemorrhagic form is rare and is characterized by hemorrhages from the skin, mucosa of the nose, bronchi, intestines, stomach and generative organs during the attacks, but not during the remissions. There is a rapid production of anemia which may be grave, and associated with a thready pulse, coma, delirium, convulsions and death.
In the Scarlatiniform type a scarlatiniform rash appears all over the body with desquamation of the horny layer and erythema of the fauces. This condition may be followed by typhoidal state in which the patient dies. This manifestation may be evidence of severe toxemia produced by a more malignant strain of organisms.

Of all the manifestations of malignant malaria none is more striking and serious than the Algid form. This type produces the saddest expression and once seen can never be forgotten. The patient is, as a rule, first seen in such an extreme condition as to suspect cholera. The nose is sharp, eyes sunken, the features are drawn, the lips and extremities are cyanotic, the nails are livid, the pulse is small, soft, becoming thready and imperceptible, while on auscultation the heart sounds are very rapid and feeble, and the second sound being, perhaps, entirely absent. The skin is blue, cold and clammy, and the respirations are labored. The patient may be conscious and complain in a weak voice of thirst. Great prostrations is a marked symptom, the patient being unable to raise his hands. The temperature is often little, if at all, elevated. The mind is usually clear almost to the end and the voice is often extremely weak and husky. This is a very serious and fatal form of malignant malaria.
and generally kills its victim in a few hours. The patient falls into a condition of profound prostrations, indifference and apathy, as though resigned to his fate. During the early stages of an algid paroxysm, owing to the quiet, listless condition of the patient, the severity of the case may fail to be appreciated. Thayer (48) cites a case illustrating this point. A man walked into the out-patient department at 11 o'clock A. M. and took his seat among the others waiting to be seen by the doctor. Dr. Smith noticed the cyanosis and apparent illness of the man and upon examination found an imperceptible pulse at the wrist. His blood showed numerous estivo-autumnal parasites. He was sent to the ward and even after hypodermic injections of quinine and all stimulation the man died one and one half hours from the time of admission.

The duration of the subcontinuous group of conditions is largely dependent upon the treatment instituted. They respond, as a rule, quite readily to the ordinary treatment of malaria. The symptoms disappear in a few days.

The Comitant type of manifestation appears on the scene ruthless and unanticipated, as shown when a laborer in the field is struck down, sickle in hand, by a pernicious attack; or as a case Marchiafava (35) cites of a laborer
who arrived at the railroad station in Rome from the Campagna on the 12th of January 1911, and falling to the sidewalk, was found by the police in a stupor and taken to the hospital, where he died twenty-four hours later in coma. The autopsy showed an intense hyperemia of the nervous centers, the spleen only slightly enlarged with a tense capsule so thin that as to reveal a slatey-red color of the pulp, the liver diffusely melanotic, with the gall-bladder full of dense and highly colored bile. Microscopic examination disclosed an enormous parasitic localization in the nervous centers, in the spleen, in the bone marrow, and to a lesser degree in the other organs. The parasites were adult forms, ready to divide, with little blocks of pigment, and the capillaries of the brain could be seen crowded and distended with red cells containing parasites all in the same stage of the life cycle. In the peripheral vessels were a few parasites containing little granules of pigment, some with black central masses. Death came at the end of a paroxysm when a new generation was maturing for an attack.

In this group the place of greatest localization of the parasites determines the outstanding symptom. A number of forms is recognized when certain portions of the central nervous system are involved. Among the
forms most clearly recognized are the comatose or lethargic, the apoplectic, the delirious, the tetanic, the meningitic (cerebral) especially in children, the hemiplegic, the cerebellar, the ataxic and the bulbar forms.

Symptoms referable to the central nervous system in patients living in malarial districts should be checked by examination of the blood in order to rule out malaria as the cause, because almost any mental or nervous symptom may be due to the malarial parasites.

The Comatose or lethargic form is the most common of all manifestations. It may begin suddenly with a period of excitement and possibly delirium. There are frequently nausea and vomiting and these are followed by drowsiness, somnolence and coma, or it may begin slowly, when it begins with weakness, sleepiness, headache, disturbance of vision, stupor, or delirium, which ends in coma. The patient is usually brought to the hospital quite comatose. There is commonly a slight jaundice of the skin and conjunctiva which when present is an important symptom. There may be also local spasms pointing to localization of organisms in one part of the brain, but as a rule the patient lies flat on his back with usually no paralysis and no alteration in the reflexes. The pupils may be contracted and give the idea of opium poisoning, and while the patient
cannot be aroused to answer questions, he will usually only frown or groan.

Hemorrhages may be found in the skin and retina. The urine which may have casts and a little albumin, is usually passed involuntarily. The heart is dilated and the pulse at first slow, soon becomes quick, and towards the fatal termination very quick, thready and feeble. Respiration may be quiet or noisy. If death is to take place, the patient becomes colder and colder, tongue becomes dry and thick and respiration ceases.

In the more favorable cases the temperature, after remaining elevated for a certain length of time, begins to fall more or less rapidly, sometimes in association with sweating. While the coma gradually passes away he will be able to answer questions when aroused and after a time gradually recovers consciousness. Speech is most peculiar, being scanning in character.

The coma may be present one day, but the next day the patient may be slightly better, with a subnormal temperature and a slower, fuller pulse and a clearing of the sensorium; towards evening, however, the temperature rises, and the coma returns. The second attack is, as a rule, fatal. Quinine treatment by injection or given otherwise appears to be of no avail at times, and after two or three days of coma, even when the parasites have
disappeared from the peripheral blood, the person may die.

Special localization of parasites in the cerebral cortex is not always made out in every case of comatose malaria. In many instances the organisms are found about equally distributed throughout the general circulation. The underlying pathogenic agent then may be said to be toxic in nature.

The Delirious form has as its outstanding symptom, as the name implies, delirium. This is soon followed by exhaustion, coma and death. Most of these cases end fatally and are mistaken often for drunkeness, sunstroke or mania. They are characterized by high fever.

The Tetanic form may begin with a drewsiness and mild delirium. There is trismus, contraction of the limbs and apisthotonos with retraction of the abdomen and conjugate deviation of the eyes. The contractures may show remissions during the paroxysms but not fully relax. There may be priapism. The attack may slowly resolve into restful sleep or end in death with a high temperature. At moments of exacerbation rigidity of the trunk increases with the apisthotonos. Marchiafava (35) (page 27) tells of a tetanic attack in a robust baker of 20 years who after having had two attacks of fever, was seized by a paroxysm while at his work, and died on
the second day. The microscopic examination of the brain shows copious invasions of parasites in the capillaries. Only one generation of parasites was concerned, since both in the brain and in the other organs, no forms were found except those containing pigment in blocks.

The Meningitic form is seen chiefly in children and the picture is that of meningeal irritation with opisthotonus and a positive Kernig sign. The symptoms diminish between attacks and promptly clear up when proper treatment is instituted. In the Hemiplegic form there is a sudden attack of fever and symptoms of hemiplegia. There may be partial or complete paralysis of the upper motor neuron type. The paralysis is only temporary and disappears with control of the case. The Cerebellar form is characterized by the drunken cerebellar ataxia, vomiting and severe headaches. In the Ataxic type there is slow scanning speech, ataxia and vomiting. This type shows a good response to quinine. Another form often seen in children is the Eclamptic form. These children have tonic-clinic convulsions with stertorous respiration and then go into stupor, coma and death. Dr. Elizabeth Nelson of India reported two such cases to me. A girl, age 7 years, had a few paroxysms of chills, fever, and sweating, with the chief symptoms consisting of delirium and tonic-clinic convulsions and she died in one of the attacks. At
autopsy the blood vessels of the brain and meninges were crowded with malarial parasites. Another girl, age 5 years, and a sister to the above girl, developed similar symptoms with convulsions being the most prominent. Intravenous and intramuscular injections of quinine brought her out of the attack while these measures were ineffective with the 7 year old girl.

Another manifestation which is quite common, and one which is difficult to diagnose is the form simulating the bulbar syndrome. The syndrome fades at the end of each attack. The principal symptoms are dysarthria or anarthria, weak voice, half open mouth from which saliva flows freely, difficulty or inability to swallow, and all the symptoms due to paralysis of the muscles of the lips, tongue, soft palate, pharynx, and larynx. Ocular symptoms also often occur. If the paroxysm is about to have a fatal termination, there may be also stupor, difficult and stertorous respirations, rapid and arrhythmic pulse and a viscid sweat. If recovery is to follow, the bulbar symptoms will gradually vanish. The dysarthria seems to be one of the last conditions to clear up. In this syndrome one symptom may be more prominent than others. There may be a motor aphasia with or without any paralysis. There may be a sudden amaurosis. Sight may
be regained under treatment, and occasionally blindness may result due to thrombosis of the retinal vessels followed by retinal hemorrhage and optic neuritis. It may involve only one eye. This form of amaurosis must be differentiated from that due to quinine. In the malarial type the pupils react to light, and vision is usually not completely lost. In cinchonism the pupils are dilated, there is no reaction to light and there is associated tinnitus and deafness.

Almost every gastro-intestinal condition has been reproduced symptomatically by the malignant type of malaria. Appendicitis, gall-bladder disease, acute obstruction, peritonitis, cholera, dysentery, hemorrhagic pancreatitis, and typhoid fever have been simulated.

Perhaps the most common gastro-intestinal picture is the Choleric form of manifestation. There may be merely an exaggeration of the ordinary malarial gastro-intestinal symptoms, but more likely this form is due to localization of parasites in the gastric mucosa as shown by Marchiafava (35). There is vomiting, abdominal pain, and sudden severe, profuse watery diarrhea at times rice-water in character, associated with intense prostration going on to algidity. During the attack, the patient is pale or cyanotic, eyes sunken, skin cold and clammy; but
the temperature may be raised. There is hiccough, severe thirst, and painful cramps in the lower limbs. Urine is scanty or suppressed. Collapse, delirium, or coma may precede death, or the patient may be sensible to the end. If the patient is to recover, the algidity diminishes, diarrhea ceases, and after a long sleep he awakens refreshed and convalescence sets in. Without treatment practically all cases prove fatal. The case mentioned in connection with specificity of the malarial organisms illustrates this type of manifestation. A woman, age 37, in whose family malaria had appeared ten days previously was seen in her third paroxysm. Three persons had already died in the fourth paroxysm of a choleriform attack. She came to the hospital fearing that she too might die during the fourth paroxysm. She was treated immediately with injections of quinine but too late, for shortly afterwards she had a choleriform paroxysm in which she died. The examination of her blood during life, and the findings at autopsy, made the diagnosis of malaria unquestionable. Besides illustrating choleriform malaria, this case also shows that malignant symptoms appear early in the disease. Marchiafava has called attention to this, and has noted that the pernicious manifestations very rarely occur during the first paroxysm, but they very
often occur during the second or in the next few paroxysms. Glynn & Matthews (19) report a fatal case of malignant tertian malaria in a girl, age 18 years, who was admitted moribund to the Royal Infirmary at Liverpool and who died two hours later. There was a history of just a few days illness and on account of delirium the case was diagnosed meningitis. The authors class this case of the algid variety.

In the Cardiac group of cases the right heart has been noticed to be enlarged in attacks of malarial fever and sometimes these symptoms become marked, with severe pain in the cardiac region, accompanied with vomiting of blood. And the patient may pass into an algid condition and die.
Because of the protean manifestations of the malignant type of malaria the clinician is often taxed to his limit in making an accurate diagnosis. The unusual or slightly variable factors and manifestations of a disease are the elements which take the practice of medicine out of the strictly scientific pursuits and places it among the arts. These are the things which make medicine fascinating and the recognition of which mark the alert and astute practitioner. These variable factors are particularly peculiar to this type of malaria. While the above is clearly recognized, there is no disease which can be so easily confirmed or ruled out, when once it is suspected as the cause of a given condition.

**CLINICAL HISTORY:**

In the malignant type of malaria the clinical history does not give as much assistance in making a diagnosis as the benign tertian and quartan types because of the protean character of its manifestations. However, certain factors when determined may aid greatly in making the diagnosis. If the patient comes from a locality where malignant malaria is prevalent, this condition must be suspected in all diseases associated with or preceded by fever. Family history may be of value because in many
instances the same type of malaria has occurred in several members of the same family, probably due to the exposure to the same mosquitos. The type of occupation may be a vital factor in the causation of the disease. For example, those engaged in work around swampy, wooded areas and where their work keeps them late in the evening are liable to contract this disease.

The type of onset and later progress may be of value because while the fever may occur at regular intervals for a few times, there soon may be irregularities. The chill may be absent, the sweating may not be regular, or the temperature may not rise very high. Whenever there is a marked irregularity in the malarial syndrome of the cold stage, fever, and sweating stage a malignant infection should be suspected.

PHYSICAL FINDINGS:

Physical findings may be negative in the first few days of the disease. However, with the increased blood destruction there will be noticed an icteric tint to the skin.

In the gastro-intestinal type there may be some abdominal tenderness, especially over the spleen and liver. The tongue in these cases is usually furred and thick.
In the malignant type the spleen is usually not as large as in the benign types. Simmons - St. John (84) after making a survey of the prevalence and distribution of malaria on the island of Corregidor concluded that the splenic index gave only an approximate indication of the number of persons infected with malaria.

LABORATORY FINDINGS:

There is a great tendency in the tropical countries to consider all cases of fever as malaria and administer quinine immediately. Except in those cases where the clinical picture presents the typical periodic chill, fever, and sweat such a practice is unscientific and unwarrantable, because no accurate diagnose can be made of malaria without finding the parasites in the blood. These are positive in all stages of the infection. To those familiar with these organisms malaria can be diagnosed with the utmost certainty. Marchiafava (35) points out two practical morphological differences between the estivo-autumnal parasite and the tertian and quartan types: (a) Non-pigmented endoglobular forms appear early and are found at the height of the paroxysm; (b) The parasitized red cells shrivel up forming the "brassy red cells" first described in 1884; while in the quartan type the red blood corpuscles remain normal in size, and in the terian type the red blood corpuscles get larger
than normal.

The blood of the estivo-autumnal fever, as described by Thayer (48). During the early part of an estivo-autumnal infection the only forms which are seen in circulating blood are small ring-shaped or ameboid hyaline bodies. These are often smaller and somewhat more refractive than younger forms of tertian and quartan parasites. They frequently show a very marked ring-like appearance, though they may be disk-shaped and actively ameboid. Shortly before the onset of a paroxysm certain of these bodies are seen to have a very minute, dark-brown pigment granules, often only one or two. These are very commonly situated near periphery or about the central lumen-like spot. Just before and during the paroxysm organisms may be seen which are a little larger than others, containing in the middle, collections of fine, dark-brown pigment granules, or a single pigment block. Actual segmenting organisms are rarely seen in the peripheral blood. After process has existed from five days to two weeks the large ovoid and crescentic forms, with collections of coarse, centrally arranged pigment granules are usually to be found.

When the crescents and ovoid forms are to be found we may often see also round ovoid bodies which develop
from them, and wherever these round bodies are present changes similar to those observed in full-grown tertian and quartan organisms may often be followed out.

Marchiafava (35) notes that when the peripheral blood contains motionless rounded parasites with a central or an eccentric block of pigment, and at the same time numbers of brass-colored red cells containing parasites are observed, an imminent attack can be predicted which will begin upon maturation of a new parasitic generation.

In the malignant type of malaria Lippencott (32) has shown that there is a leucocytosis and a marked increase in the number of large monocytes.

DIFFERENTIAL DIAGNOSIS:

Manson is quoted by Gaines (18) as giving the following erroneous diagnoses purely on clinical grounds without examination of blood in cases which were proven later to be due to the estivo-autumnal parasite.

(1) Cerebral forms: Sunstroke or heat stroke, mental derangement, hysteria, alcoholism, aphasia, epilepsy, and meningitis. Thayer (48) includes in this list uremia, and cerebral hemorrhage and points out that a differentiation from sunstroke may be very difficult. The jaundice, anemia and a large spleen would immediately suggest malaria. It
should be remembered that there may be a hyperpyrexia in malaria closely simulating sunstroke which Manson believes is due to malarial toxins affecting central nerve elements.

(2) Abdominal forms: Dysentery - amebic or bacillary, intestinal obstruction, appendicitis, biliary colic, cholecystitis, hemorrhagic pancreatitis, and liver abscess.

(3) Pulmonary forms: (Malarial pyrexia with pulmonary congestion and myocarditis) Bronchitis, pneumonia, and valvular heart disease.

(4) Cases with cutaneous petechia have been mistaken for measles, endocarditis, and purpura. Thayer (48) includes Yellow Fever as simulating this group of cases. In Yellow Fever the spleen is often but little enlarged while albumin and casts usually occur early in the urine.

(5) Icteric cases have been confused with obstructive jaundice.

(6) Cachectic cases have been diagnosed as acute nephritis, pernicious anemia, and tuberculosis.

(7) Edematous forms: A general edema may be the only outstanding sign of a heavy sub-tertian infection. This may be confused with cardiac decompensation, or acute nephritis.
PATHOLOGY

The primary pathology in malignant malaria exists in the blood stream. There is great destruction of red blood corpuscles and there is, as a result, a production of pigments and debris. Lawson (31) has shown that by the migration of parasites from one red cell to another each parasite may destroy many red blood cells. A check on the amount of anemia during and between paroxysms has shown that it is greatest between paroxysms. This accounts for the marked anemia, and to a large extent the icterus and cachexia especially noticed in this type of malaria.

The secondary pathology is due either to toxic products or else mechanical factors associated with the debris and large numbers of parasites. Forrester (15) believes that where cases have persisted for some time individual nerve cells and cells of the higher nervous centers are affected by the malarial toxins, even to the point of necrosis in some cases. For example, when the sympathetics or vagus are involved there are abnormalities of pulse, tachycardia, palpitation, and shortness of breath on exertion. He has shown where in four cases single nerve paralyses occurred. Dock (11) thought that the toxins
probably acted on the nervous centers to produce the paroxysms.

The mechanical factors may operate to produce necrosis because of pressure or by blocking the blood vessels so as to impair the nutrition to a part. Organs supplied chiefly by end-arteries where collateral circulation is poor may suffer more acutely because of these vascular blocks in their capillary beds. Not all these organs suffer equally in each case because it is often noted that one organ may be more involved than the others. When this occurs, the clinical picture is seen to simulate diseases usually involving that particular organ. Together with the degenerative changes noticed in the parenchyma of various organs, a progressive and proliferative process has been noted by Marchiafava (35) which seems to be a defense and reparative phenomena.

FINDINGS AT AUTOPSY:

The Central Nervous System alterations may be classed as endovascular and extra vascular. Dudgeon (12) reports cerebral changes in a case which died in coma, illustrative of endovascular changes. Throughout the white matter the vessels were thrombosed and congested and there were numerous hemorrhages. The thrombi which consisted of infected red cells, masses of dot parasites,
particles of malanin, and mononuclear cells could not be removed from the vessel walls without injury to the tissues. There was no perivascular exudate present. The reasons for this congestion, as has been noted before, are probably some physico-chemical attraction, some sticky material peculiar to the estivo-autumnal parasites, mechanical factors such as multiple infection, extra-cellular attachment of the organisms, and increased multiplication of the parasites, etc. The normal red blood cells probably pass through these capillary meshes leaving behind the parasites and debris.

Marchiafava (35) calls attention to alterations in the lining epithelium of the blood vessels. These changes occur in all vessels of body but most markedly in the capillaries. The endothelial cells contain varying amounts of pigment and also present regressive changes. And he suggests that these changes may contribute to the slow progress or arrest of the parasitized red corpuscles in the capillary beds. Sometimes these endothelial cells become detached and appear in the peripheral blood.

As to the extravascular alterations attention has been called to the punctiform hemorrhages scattered throughout the white matter of the brain, cerebellum, in the
trunk of the brain and in the medulla, but not in the gray matter. These small hemorrhages may be seen under the microscope at the center of which there is a blood vessel choked with parasitized red cells and pigment, and its endothelial cells swelled and pigmented. Around and into these hemorrhagic areas neuroglia cells proliferate producing small whitish areas. As a rule, the signs of inflammation are absent. Localized areas of punctiform hemorrhages have been described in cases showing symptoms of localization.

Gastro-intestinal changes are described by Marchiafava (35) as being chiefly two in number, and which occur in the wall of the intestines: (1) accumulation in the capillaries of the mucosa and especially of the intestinal villi, of red cells containing parasites, (2) diffuse necrosis of the epithelium of the superficial of the mucosa, which explains the cholera-like diarrhea in the choleraform type of manifestation.

In the spleen and bone-marrow there is an accumulation of detritus, parasites and pigment which produce both degenerative and proliferative changes. The pigment imparts a distinct brownish color and this varies with the amount and duration of the infection. The enlargement of the spleen may be explained on these grounds. According to
Bass (4) the gametes in the bone marrow show all stages of development, if they are present at all. An outstanding microscopical finding in these two places is the presence of gigantic mononuclear cells at times containing enormous amounts of pigment.

The liver is always enlarged and congested and on gross appearance has a slatey-red color indicating its melanotic content. Microscopic examination reveals the dilatation of the capillaries with their pigmented endothelial cells distended by parasitized red blood corpuscles, and by pigmented and necrotic macrophages—the pigmentation of the star cells of Kupffer, the regressive as well as progressive changes in the hepatic cells whose protoplasm contains little lumps of ochre-colored pigment which give the iron reaction, and proceed in a large part from corpuscles precociously affected, the so-called brassy red cells. The black and ochre pigmentation of the endothelial and Kupffer cells is often so intense as to offer the best histological illustration of so-called blocking or saturation through the accumulation in their protoplasm of granules and particles of black pigment, ochre pigment, fragments of red cells and white cells and parasites. This ochre pigment owes its origin to phagocytosis, by the macrophages of the spleen, of the red
cells with young unpigmented parasites and also from
the breaking up of sporulating red cells with their
residue of hemoglobin. This also explains the richness
of the bile found in malignant infections, the dense and
highly colored bile in the gall bladder and bile passages,
and also the frequent jaundice.

The kidneys are peculiarly affected in malignant
malaria as shown by the conclusions reached by Ewing (14)
from autopsy findings in a case which died from malarial
nephritis. There is acute degeneration of toxic origin,
often reaching a degree in which exudation of blood serum
into the tubules is added. This type of condition accounts
for the albuminuria in malaria. Together with the acute
degeneration there may be focal necrosis, numerous hemor-
rhages, and exudation into the tubules of blood serum and
blood pigments. This is the picture seen in cases of
hemoglobinuria. Then, there is massing of parasites in
the renal capillaries, with extreme degeneration of the
parenchymal cells, multiple hemorrhages, and exudation
of blood serum into the tubules. With these possibilities
of pathology in the kidneys, it is not difficult to see
how albuminuria, hematuria and even total suppression of
urine may occur in severe estivo-autumnal infections.

The lungs may be discolored grossly by pigment and
on microscopic section the capillaries often show parasitized red corpuscles as found in other organs.

Bass (4) points out that it has been shown at autopsies on cases of pregnancy dying of acute malaria or in cases of abortion from malaria, that large numbers of malarial parasites occur in the maternal vessels of the placenta. Ljachowetsky (57) concluded that direct transmission of malaria from mother to child occurred in some cases he had studied. In these cases of so-called congenital malarial cases the transmission most probably occurred through a rent in the membrane separating the maternal from the fetal circulations.
TREATMENT

PROPHYLAXIS:

In the way of prophylaxis there are several rules to be observed by those entering malarial districts. Inasmuch as the mosquito is night worker, ample protection to the uncovered parts of the body is needed, when it is necessary to travel at night. A better rule is not to go out at nights. Houses should be well screened. According to Fort (16), King (26) and others it takes from ten to twelve days for the malarial parasites to develop in the mosquito. Hence, a mosquito is non-infective for ten or twelve days after a malarial blood meal. Therefore, Le Prince's method of preventing malaria by destroying all mosquitoes in the house daily is a good one.

As to the matter of giving prophylactic quinine there is a difference of opinion. Thomson (50) believes that it is a bad practice to give quinine in small doses of 5 grains daily, or irregularly, even though the doses be larger, for such treatment tends to increase the power of crescent formation. He (51) advocates 20 gr. of quinine daily for three weeks, four times a year; or 20 gr. of quinine daily for three weeks, four times a year to those having positive blood on thick blood smears. According to Hoffman (22) quinine prophylaxis is an insufficient means
of combating malaria.

Regarding the matter of control the Malarial Commission of the League of Nations concluded that there is no single method which can be adopted for every country, James (23). Hence, it is a local problem to be worked out according to the needs of the individual locality. Not until this fact is realized will the various agencies at work show progress in their work. The various species of anophelines differ in their habitats and even the same anopheline has been shown by Hackett (20) to behave differently in different situations. They may harbor the organisms over winter, according to Ottolenghi (43). The larvae exist over winter and if the mosquitoes are to be reduced the larvae should be attacked in fall after first frost and the first thing in the spring as advocated by Griffitts (56). Thus it is evident that each locality must study its own problem and institute control measures accordingly. Barber (1) believes that a historical study of malaria in a country may afford useful information as to the best means of combating the disease.

The biological difficulties which have to be met in the matter of malarial control as described by Buise (43) are: (1) plasmodia may persist in the body for years
after recovery of symptoms; (2) plasmodia may persist in the body of female anopheles for a few months at least; (3) malaria is widespread in its distribution; (4) anopheline species are more or less wild in their breeding habits, hence, the larvae are hard to reach; (5) anophelines travel quite far from their native places where they were hatched and reared, even as far as from one-half to two and one-half miles.

While the above conditions apply to malaria as a whole they also apply for Malignant Malaria. After the disease has been contracted the best and safest way to avoid pernicious symptoms lies in prompt and energetic treatment. Such treatment when effective will relieve the patient of symptoms in a few days and check the progress of the disease. Thomson (5) believes that early administration of 20-30 grains of quinine daily for a period of three weeks will render a patient non-infective. Bass (58) outlines a procedure of 30 grains a day for 3-4 days given in 10 gr. doses t.i.d., and should be commenced as soon as case is diagnosed. Thereafter, 10 gr. daily should take care of all residual parasites and prevent recurrence of symptoms and should be given for about 12 wks. Eight weeks of treatment is sufficient to
cure 90 - 95% of cases. While serving as a general guide the above measures may need to be modified in various countries, and as to whether one is dealing with the native population or foreigners.

The oral method of administration is held by most men as being the best. Some men advocate giving quinine in oil by rectum to those unable to take it by mouth. Craig (10) believes the intramuscular administration should not be used routinely but only in certain cases where oral administration is impossible, for young children, and where the intravenous method is not possible. It should be borne in mind that the intramuscular injections produce necrosis of tissue. Knowles & Senior-White (62) condemn general use of intramuscular injections of quinine in no uncertain terms. The International Congress on Malaria (59) concluded in 1930 that the intravenous administration of quinine salts is contra-indicated except in cases of pernicious abscesses. When the proper method of administration is selected a sufficient amount of quinine must be given to kill the crescents otherwise, according to Clark (8) that patient is a carrier and a potential danger for transmitting severe infection in another person.

In order for quinine to exert its affect it must be absorbed. Krauss (60) quotes Sinton as believing that
alkalis aid absorption. Cases reported as being resistant to quinine may merely represent conditions where the drug is not being absorbed. Rolleston (61) reports some cases where the patients did not respond to the sulphate salt of quinine. The drug was not absorbed and excreted in the urine, but by using the hydrochloride salt, good results were obtained. Craig (10) does not believe that any malarial plasmodium is resistant to quinine even during relapses. One should make sure that the quinine is being absorbed by the patient.

USE OF ALKALIS. Krauss (60) reports the favorable use of intravenous injections of soda bicarbonate in pernicious cases. He claims it opens up the blocked vessels and allows the solution to go through, and thus breaks up the attack. In any case he advocates the use of alkalis. Together with this, the bowels should be kept open. Knowles, and Senior-White (62) advocate alkali being given with quinine to avoid acidosis and because of the greater toxicity to the plasmodia.

Other drugs besides quinine have been used with apparently good results. That a new drug is needed is evidenced by the fact that quinine is ineffective against the crescent forms of parasites, and that at the present time Netherlands has a monopoly on quinine so that the
output is held to one-tenth of the demand. She produces about nine-tenths of the world's output and is thereby able to control prices. India with her 100,000,000 cases of malaria annually cannot at present be supplied with an adequate amount of quinine for her needs. Surely, every search for a new specific drug should be encouraged.

Sodium Cacodylate has been favorably reported by several investigators: Murphey (63) believes 20-30 gr. by intravenous injection in 24 hrs. will by itself produce a permanent cure. He claims it is less toxic than intravenous quinine, more effective than arsphenamine and less apt to produce rash than stovarsal. The author also claims that quinine therapy alone is not the solution for the cure of Malaria. After treating hundreds of cases of malignant malaria with Sodium Cacodylate over a period of ten years in Macedonia where the most malignant form is prevalent, Ullmann-Apostolon and Apostolon (64) report that not only the attack but also the entire course of the disease was modified. They gave 20-30 gr. of quinine sulphate a day by mouth during the first 10 days of disease and also gave subcutaneous injections of Strychnine sulphate (2 mg.) with the large doses of intravenous Sodium Cacodylate (from 1-2 gm). They note that the only disturbances are a slight diarrhea in 10-15% of
cases, and in 3-5% of the cases, after five or six injections, an eruption occurs with enlargement of the parotids. An accurate evaluation of the Sodium Cacodylate in this last series of cases cannot be made owing to the extensive use of other drugs. Its apparent effectiveness in so many cases warrants its being recognized among the antimalarial drugs.

Another drug has been introduced which has caused considerable comment, and has been subjected to a vast amount of research. It is plasmochin, a quinaline derivative first used on the human by Muhlens. It has been used with good results on birds but has received both good and bad comment as regards its use in the human.

Mühlens (39) found that this drug was more effective on the crescents than on the schizonts in estivo-autumnal infections and therefore when combined with quinine, it gives good results. Manson-Bahr (33) has subjected this drug to rigid tests and has obtained some good results. He feels that it should be regarded as the beginning and not the climax of a new series of anti-malarial drugs.

Krauss (28), who also has used the drug extensively, in a resume of his studies, he gives four different lines of treatment, using plasmochin, all of which seem to work satisfactorily. He believes that it is quite equal to
quinine in the benign types of malaria but when given alone in malignant malaria, it is not effective because while the crescents are destroyed by the drug, the schizonts appear but little disturbed. When the plasmochin compound, put up in tablets containing one centigram of plasmochin and 0.125 gm. quinine is used, it is very effective in destroying both the sexual and asexual varieties. Miller (38) believes it is the greatest addition to the armamenture against malaria since quinine was extracted from cinchona bark in 1820. He notes that the blood is freed from sexual forms in 2-9 days and that by destroying these forms the patient cannot infect mosquitos. This makes plasmochin a powerful prophylactic agent.

The chief objection to this drug is the toxic symptoms it produces, of which cyanosis is the first and the one most marked. Plasmochin compound is much less toxic than plain plasmochin and if given in the proper manner its toxicity will not be noticed. The line of treatment for malignant malaria, as outlined by Manson-Bahr (33) is here given.

For 5 days Plasmochin compound (Two tablets t.i.d.)
For 4 days Rest
For 3 days Plasmochin compound (Six tablets daily)
For 4 days Rest
For 3 days Plasmochin compound (six tablets daily)
For 4 days Rest
For 2 days Plasmochin compound (Six tablets daily)
For 5 days Rest
For 2 days Plasmochin compound (Six tablets daily)

The method of treatment used by the Medical Service of the United Fruit Co. (28) is two tablets of Plasmochin compound t.i.d. together with full doses of quinine sulphate for five days, then have the patient report for a blood examination. 96% of their cases were free from crescents. Follow-up treatment is given according to indications. It seems quite necessary not to give Plasmochin for more than five days in succession in order to avoid toxic symptoms. Krauss felt that the margin of safety with this drug was probably too small for general use. This was also recognized at the International Congress of Malaria (59) in 1930 at which time it was also decided not to use it as a substitute for quinine.

Other new drugs besides quinine seem to be effective only in the tertian and quartan types and are of no avail in malignant malaria.
CASE REPORTS

The cases being reported were described to me by Dr. Elizabeth Nelson who has spent about twenty-five years in India as a Medical Missionary.

Case No. 1.

History: A man, age 36 years, returned to his home with his wife and another lady after a short trip to a section of the country highly infested with Plasmodium falciparum. It was a level country where trees and shrubs abounded to which they went. Their camping equipment was inadequate and they all came down with malaria. He had had attacks of benign tertian malaria formerly. He lived in an area where sporadic cases of benign malaria occurred chiefly and where malignant malaria was rare.

Description of Patient: Before this exposure, the patient was apparently well and strong.

Clinical Description: The condition began with a rather characteristic chill and fever, together with aching in various parts of the body. The fever was not high at any time. After two paroxysms of a somewhat tertian character the patient went into coma, from which he could not be aroused. After 48 hours he woke up complaining of severe thirst.
Treatment: He was given quinine intravenously which proved to be effective. He was a patient who was unable to take large doses of quinine.

This case illustrates the suddenness with which an attack may develop, and that severe symptoms may occur in a previously healthy individual. It would be classified under the comatose form.

Case No. 2:

History and Clinical Description: A girl age 7 years had been sick but a short time. Prodromal symptoms of malaise, and a feeling of weakness, headache and pains in the limbs were followed by chills, fever and sweating. Temperature rose to 103 degrees. She had several attacks before delirium set in. The delirium advanced to tonic and clonic convulsions. These symptoms would diminish in intensity between paroxysms. After two or three convulsive seizures she died.

Description of Patient: The patient was a well developed and well nourished girl. She was perfectly well before the attack of malaria.

Treatment: Intravenous and intramuscular injections of quinine were of no avail.

Autopsy Findings: Blood vessels of the brain and meninges especially were packed with malarial organisms.
Case No. 3.

History and Clinical Description: A girl, age 5 years, sister of the girl above. They were taken sick about the same time. She had been well up to the time of the attack. Prodromal symptoms were quite similar to those of her sister. The malignant character in this case was not marked by delirium, but the convulsions were severe.

Treatment: Under intravenous and intramuscular injections of quinine she promptly recovered.

These two cases illustrate how malignant symptoms may occur in young children. It has been observed that the meningitic form occurs most frequently in children, and the convulsions may have been due partly to meningeal irritation. It reveals that intravenous quinine is not always effective.
SUMMARY AND CONCLUSIONS

Malaria seems to have had a very definite bearing on the downfall of various nations of the past. Its harmful effect upon the people of the tropics is very evident even today.

While there is a difference of opinion as to the number of types of malarial organisms, most authorities agree that there are three distinct types. These three types are based both upon the morphology of the organisms and upon the clinical manifestations produced by them.

That the Plasmodium falciparum is the chief cause of malignant malaria is held almost universally. My opinion is that it is the only cause for the truly malignant form, and in those cases of benign tertian malaria showing pernicious symptoms the Plasmodium vivax is only the precipitating factor in an already serious condition.

Malignant symptoms are due chiefly to mechanical plugging of the capillaries in the various internal organs, and the symptoms are dependent upon the greatest localization. Toxic agents unknown in character are thought also to play a part in the pathogenesis of malaria.

While a patient may harbor the estivo-autumnal parasite in the blood for varying lengths of time without
developing malignant symptoms, such a patient not under active treatment may at any time develop a fulminating attack which may prove fatal. And although the symptoms may be checked by treatment such a patient may be the cause of a fatal case of malaria because of the presence of crescents in the blood.

Quinine still is the specific drug in the treatment of malaria, although it is being supplemented chiefly by the drug plasmochin.

Plasmochin destroys the sexual but not the asexual forms of Plasmodium falciparum. Therefore, in order for it to be effective in malignant malaria, it should be combined with quinine and should not be given more than five days in succession.

Various theories are given to explain relapses after a period of latency: Rejuvenescence of parasites within the red blood corpuscles by a process of conjugation (union of two hyalin ring forms or two hyalin bodies) is held by Craig(65). A renewal of vitality on the part of the asexual forms after insufficient treatment, and aided by a lowered resistance of the patient, is held by James(66). Mackenzie(67) does not believe that relapse is due to parthenogenesis, but rather to a break-down of immunity to long-surviving parasites in the viscera due to fatigue, etc. That relapse may be due to seasonal variations in the diffused light rays from the sun at various geographical areas affecting photodynamic materials of the
blood by way of the eye-ball capillaries is suggested by Consouloff (68).
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ILLUSTRATIONS

Fig. #1 Malignant tertian

Fig. #2 Malignant tertian

Fig. #3 Subcontinuous fever

(From Marchiafava)
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