The Treatment of Malaria including the Important Indications.

Importance of the Subject. Malaria is a very widespread disease. Schulte, in his Diseases of Warm Countries (p. 98), says: "The geographical region of distribution of malarial disease is extraordinarily large. In this respect no other infectious disease can compare with it." Apart from its wide distribution, the vast amount of disease, ill health, and mortality due to malaria should be considered. Dr. Creighton, in his article on Malaria in the Encyclopaedia Britannica (18th edition), makes the following statement: "Malaria has been estimated to produce one-half of the entire mortality of the human race, and inasmuch as it is the most frequent cause of sickness and death in those parts of the globe that are most densely populated, the estimate may be taken as at least rhetorically correct." Manson, writing of the malarial parasite, says, "Directly and
indirectly it is the principal cause of morbidity and death in the tropics and sub-tropics. A third consideration which makes the subject of malaria one of great importance is that the disease is preventable.

Important Indications - The important indications for the treatment of Malaria may be divided into aetiological, pathological, diagnostic, and clinical or symptomatic.

Aetiological Indications - It has been clearly proved that the essential cause of Malaria is a minute protozoic blood-parasite, the Plasmodium malaecae, belonging to the order Haemopordia of the class Phorozoa. This parasite exhibits an alternation of generations passing its asexual life-cycle in the blood of man and its sexual life-cycle in mosquitoes of the Anopheles genus. Most writers agree in stating that there are at least three species of the malarial plasmodium, but the view is also held that the different forms met with are only varieties of a single pleomorphous species. The parasites live mainly in man and at the expense of the red...
Blood corpuscles. They destroy the red blood corpuscles, liberating hæmoglobin, pigment, derived from the hæmoglobin, and waste products. The onset of the febrile paroxysm corresponds in time with the maturation and sporulation of the parasites. The fever is believed to be due to the liberation of a febrigenetic substance, probably one of the waste products of the parasite, when sporulation takes place. An important characteristic of the parasite is its capability of remaining quiescent or latent in the system for long periods of time. This is exemplified by the occurrence of first attacks after the patient has left a malarious region, by the frequency of relapses, by the occurrence of malarial cachexia without definite previous attacks of fever, and by masked forms of malaria. Finally, it should be mentioned that the fevers may be acute or chronic, and that in the latter condition the disease may be masked or latent for a considerable period. What exactly happens
to the parasite during this time is now the only obscure part of its life-history. (Lankester’s Zoology, Pt I, fasc. II, p. 242). The malarial parasite has a tendency to retreat to and accumulate in the more sluggish circulation of the deeper parts, such as the spleen and bone marrow. The latent periods of malaria may be explained by the probable supposition that, as in the case of Pathogenic Bacteria, the virulence and power of multiplication of the parasite are markedly diminished for a time by unfavourable conditions, the parasite living in the blood in smaller numbers and with less vital activity than are sufficient for the production of fever. This supposition would also explain the phenomena of Malarial Cachexia such as the Anaemia, debility, etc. The relapses would be explained by the parasite becoming more virulent and multiplying rapidly under more favourable conditions, such as are brought about by predisposing and exciting causes of malarial fever e.g., depression of vitality and natural resistance in
the host. It is also possible that resisting spores may be formed which under favourable circumstances give rise to repetitions of the asexual cycle (vide Landerer’s Zoology W. f. 77, p. 263). Malarial infection is conveyed only or mainly by the bites of infected mosquitoes of the Anopheles genus. The evidence for this mode of infection is, I think, conclusive. Celli says, “as to now, of all supposed vehicles of malaria, this of the mosquitoes is the only one that has been directly and undoubtedly demonstrated” (Celli’s Malaria, p. 94 – See also Schenké’s Diseases of Warm Countries, p. 118 and other systematic works on medicine). As corroborative evidence I may here give my own experience in the tropics. In a malarious country in Burma in 1901 and 1902 I found the ponds and rice fields were swarming with mosquito larvae, a fairly large proportion being Anopheles larvae. After measures were carried out in 1902 for filling up some pools with earth and treating others with kerosene oil, there was an appreciable
fall in the number of mosquitoes and in the
number of cases of malaria admitted to
the local hospital. During the early part
of 1907, in a dry region with a small
rainfall just beyond the North-west-front
of India, I observed that all the stagnant
pools in the dry beds of the hill streams
contained large numbers of mosquito
larvae, nearly all of the Anopheles genus.
A large majority of the patients admitted
to hospital in this region were suffering
from severe types of malarial fever.

The air theory of the mode of infection
of in malaria has little evidence in its
favour. The evidence formerly adduced
in proof of it is now better explained by
the mosquito theory. The drinking-water
theory has some evidence in its favour
and a good deal of evidence against it.
(vide Davidson, Schenbe and Cellès works on
Malaria). Manson says “man, I conjecture,
may become infected by drinking water
contaminated by the mosquito, or, and
much more frequently, by inhaling the
dust of the mud of dried up mosquito-haunted 
ponds; or in some similar way.” (Tropical 
Diseases, 1898, p. 17). An argument in favour 
of these latter modes of infection is the 
possibility of the existence of a resisting 
spore or cyst, by means of which dissemina 
tion may take place. Dissemination by 
resisting spores or cysts occurs in other 
Haemosporidia and in the Cecidia (vide 
Lankester's Zoology, pt. 1, fasc. ii, p. 263). I find 
by microscopic examination that the stagnant 
water and sediment of a tank in the Rangoon 
Cantonment gardens contain besides Algae 
and Fungi (diatoms, bacteria etc.), numerous 
Amoebulae (2-5 or 6 μ in diameter), Infusoria 
( monads etc.) and a few cecidomyia and oral 
boles (from 0.5 to 10 μ in length). This 
tank contains numerous mosquito larvae 
of the Anopheles and Culex genera. I have 
obtained four or five species of Anopheles 
mosquitoes from the larvae taken from 
the tank (Anopheles barbirostris, nigerrimus, 
Culicifacies, tectorum or festinarius, fuliginosus). 
The minute organism discovered by Klebs and
Tommasi Undechi in the soil and air of the Roman Campagna is described as "a microscopic fungus consisting of numerous shining spores of a longish oval shape, and nine micromillimeters in diameter" (Omnis's Dictionary of Medicine 1883, p. 914). The ameboblast mentioned above may be the ameboid stage of monads or the ameboid and plasmodium stages of mycosomes. But it seems to me probable, or at least possible, that the ameboblasts and crescentic and oval bodies may be stages in the life history of the malarial plasmodium.

I cannot help thinking that the original natural home or source of the malarial parasite is in nature, I mean as apart from the higher animals, and that the particular part of nature is the stagnant water and organic matter (living and dead) of collections of still and slowly running water. (vide paragraph on Malaria in uninhabited regions in Scheuch's Diseases of Warm Countries p. 114–115). On the whole the evidence points to the conclusion that infection by air and drinking water are occasional and secondary modes of infection. The telluric
and atmospheric conditions, such as a certain degree of heat and moisture and the presence of organic vegetable matter in the soil, are of importance because they are favourable to the life of malarial parasites and Anophiles mosquitos. The most important condition is the presence of collections of more or less stagnant water. These are found all through the tropics and in some temperate regions, even in the driest localities. The chief predisposing cause of an attack of malarial fever is a previous attack. The disease is said to be more common and more severe in young children than in adults. All influences that depress vitality and diminish natural resistance, such as fatigue, chill, overwork, malnutrition, and exposure to a tropical sun, act as predisposing and exciting causes. Pathological indications. Fever is the chief feature of the disease and the most important pathological process but is mainly a subject of general pathology.
Apart from fever, the most important pathological process is the destruction of the red blood corpuscles by the parasites. This gives rise to Anaemia, often severe, and to deposition of pigments and other waste products in and congestion and enlargement of the Liver, Spleen, and other internal organs. In chronic cases and in malarial cachexia the congestion becomes permanent and is associated with more or less fibrosis, hypertrophy and degeneration. These changes are most marked and advanced in the Spleen and Liver. In pernicious cases, especially of the comatose type, the malarial parasite is found in large numbers in the circulation of the brain and other organs, sometimes blocking the capillaries. Malaria is said sometimes to give rise to ulceration and sloughing of the mucous membrane of the intestines not distinguishable from those of dysentery. (Encyclopaedia Britannica, 15th Ed., article Malaria.)

Diagnostic indications. Periodicity and
The remedial effect of Quinine are important when indications of Malaria are taken with the clinical course of the disease suffice for a diagnosis. tertian and quartan periodicity occur only in Malaria. periodicity occurs in other fevers, but the rise of temperature, as a general rule, takes place later in the twenty-four hours than in Malaria. Quinine sometimes fails in Malarial fevers. Periodicity and the remedial effect of Quinine are valuable but not conclusive indications of Malaria.

The discovery of the malarial parasite and its pigment in the blood by microscopic examination is the most conclusive evidence of Malaria. Parasites and pigments are not always found in the peripheral circulation. In such cases, Schenke says, "blood for examination must be extracted from the spleen by means of a Pavang syringe with the application of antiseptic precautions." (Diseases of Warm Countries, p. 156). Explicit directions are given Manson's and
Other works on Tropical Diseases and Medicine for microscopical examination of the blood. Manson states that a microscopical examination of the blood should be made in every case in which the slightest doubt exists (Gibson’s Text Book of Medicine p. 311). Useful information on the microscopical examination of the blood in Malaria will be found in articles by Manson and Ross in the Lancet, May 17, 1902, p. 1379, and Jan. 10, 1903, p. 86. In six consecutive cases of Malarial Fever of the remittent and continued types I had no difficulty in finding the malarial parasite in the blood by microscopical examination. For the differential diagnosis of Malaria from other diseases such as Typhoid and Typho-Malaria, signs pathognomonic of the latter (e.g. rose spots and the presence of Typhoid Bacilli) should be looked for. The presence of the malarial parasite or pigment in the blood will prove conclusively that there is a malarial element in the case.
Clinical or Symptomatic indications—It is important to remember that, though commonly associated with malignant parasites and the corresponding types of fever, pernicious symptoms may arise in any case of malarial fever. Ross states that "as a rule, pernicious attacks are associated with very large numbers of parasites, not necessarily found in the peripheral blood, but present in the body as a whole, or in certain organs (Dunin’s Dictionary of Medicine, 3rd Edn. Art: Malaria). Pernicious attacks are generally preceded by repeated attacks of malarial fever. Double, triple, and mixed infections occur. The paroxysms may anticipate or postpone, the life cycle of the parasite not always running its course in exactly the same period of time. Paroxysms may be unusually prolonged. Special symptoms are associated with different types of fever, e.g., bilious vomiting with bilious Remittent Fever. These facts account for the numerous irregularities in the Symptoms and Course of Malarial Fever. The general conclusions to be drawn
from the clinical manifestations are (1) that no case of malarial fever should be trifled with, (2) that perilious symptoms should be prevented, if possible, and be treated early and energetically when they arise, and (3) that the special symptoms associated with different clinical types of malarial fever always require special attention and treatment.

Prophylactic Treatment

Personal prophylaxis. Protection from the bites of mosquitoes is the most important means of prevention of malarial fever. More or less complete protection may be obtained by avoiding altogether, or as far as possible, malarious localities, by the use of mosquito curtains for beds and of wire gauze screens for doors and windows, by keeping indoors before sunrise and after sunset, and by similar measures. The choice, when possible, of a residence on a healthy site, far removed from sources of infection.
including both mosquitoes and infected human beings, and possessing good sanitary arrangements, is advisable. The carrying out of measures on a small scale for the destruction of mosquitoes and removal of their breeding-places by residents individually is very desirable, as more extensive measures, which might or ought to be carried out by public authorities, are either imperfectly carried out or in many cases not even attempted. Great in importance to the prevention of malarial bite is the destruction of the malarial parasites in the blood. This object is effected by the administration of prophylactic remedies, especially Quinine, and by hygienic and therapeutic measures directed to restore and maintain the general health and natural resistance to disease. There is abundant evidence that Quinine is a valuable prophylactic. It is obvious that if Quinine kills the parasites when the latter have already entered the blood and multiplied sufficiently to produce fever, it
will also do so, and if in the same dose probably more efficiently, if it is already in the blood when the parasites enter or enters soon after them; just, for instance, as the administration of the antidote to a poison along with the latter or soon after prevents toxic effects. Manson advises the administration of 3 to 5 gns daily, or two or three five grain doses in one day once or twice a week. (Tropical Diseases, p. 125). Davidson advises the administration of 2 to 5 gns daily when the residence in a malarious country extends over a period of two or three weeks, and 20 to 30 gns in divided doses daily when the residence is only of a few days duration. A dose of 7½ to 15 gns every five to eight days is recommended by German Authorities. This plan, Menke says, decidedly merits the preference because larger doses have more chance of destroying the malarial parasites. (Diseases of warm Countries, p. 161). Koch's method is the administration of 1 to 1½ gms of Quinine on two consecutive days at intervals of eight or ten days. (vide Medical Annual for 1907, p. 367). vide also Gibbon: Text Book of Medicine, 1877, p. 316.
Protection from mosquito bites if complete ensures the prevention of malarial fever. When its prevention from mosquito bites is not complete and certain, Quinine should be taken according to one of the plans mentioned, the larger doses being taken when there is much exposure to infection in very malarious regions or when there are prodromal symptoms of malarial fever. A good reason for the prophylactic use of Quinine is the uncertain and sometimes prolonged incubation period in malaria, which may, according to Manson, extend to years. (Gibson's Textbook of Medicine Vol. 1 p. 303)

There is no doubt that Arsenic, owing to its tonic action, is an indirect prophylactic. Italian observers find Arsenic of some value as a prophylactic (Celle's Malaria pp. 214-215). It probably acts only by toning the system and by improving the general health, thus increasing the natural resistance of the body to disease. Amongst prophylactics, Manson mentions Tea, Coffee, very small doses of Alcohol and Lemon
Decoction (Tropical Diseases, 1878, pp. 125-126). These agents, like Arsenic, have no specific prophylactic power. They merely fortify the system and increase the natural resistance. As water is a possible vehicle of infection and bad water is likely, apart from malaria, to be injurious to health, all drinking water from doubtful sources should be boiled. It is advisable to avoid sleeping near the ground in malarious regions, in order to avoid mosquitoes, dampness, and miasma in the air.

General Prophylaxis. The principles underlying measures for general prophylaxis are (1) The destruction of the essential cause, the malarial parasite, within and outside of human beings and (2) The prevention of the entrance of malarial parasites into human beings. (1a) Measures for the destruction of malarial parasites in man. Most of these measures have already been dealt with under the head of personal prophylaxis. The administration of Quinine as a prophyl...
lactic to all the members of a community has
been recommended by Koch, but other
authorities do not consider it practicable
(vide art. Malaria, Encyclopaedia Brittanica, 8th
ed. and Celli's Malaria, p. 193). In favourable
circumstances, e.g., for limited period of
time, such as the most unhealthy season of the
year, in small communities, and in con-
junction with other measures, this plan
might prove of great service (vide Medical
Annual for 1907, pp. 366-367). The administra-
tion of Arsenic on a large scale has been tried
with some success (vide personal prophylaxis
and Article Malaria in the Encyclopaedia Brittanica
8th ed.). A combination of Quinine, Arsenic
and Iron has been found useful as a
prophylactic by Professors Grassi (vide Quin.
for July 5, 1902, p. 37).

17. The destruction of the malarial parasite
outside the human body can only be effected
by the removal of the conditions favourable
to its life and that of its alternative host
and carrier, the Anopheles mosquito, and
by the destruction of the latter. The chief
measure under this head is the removal of all collections of stagnant water. This may be affected by drainage by drainage, by filling up stagnant pools and collections of water with earth, by covering marshy soil with healthy soil, and by cultivation, especially of trees that absorb much water (e.g. Eucalyptus, the melon tree, etc.). Rank vegetation and undergrowth should be removed, as they promote dampness of the soil and harbour mosquitoes. An important point in drainage on a large scale is “to avoid interfering with the natural drainage of a district in constructing railways and so forth.” (Frazer’s Tropical Diseases, 1898, p. 123). The cultivation of rice, owing to the stagnant water of the rice fields, is favourable to the life of the Anopheles mosquito and to malaria. Rice fields should not be allowed within several miles of towns, villages, and human habitations. In Burma they may be seen within a stone’s throw of inhabited houses, even those of government officials and well-to-do residents.
In Italy the cultivation of rice within four miles of human habitations has been forbidden.

(\textit{Lancet}, August 22\textsuperscript{nd}, 1903, p. 544). Drainage and the other measures mentioned above will exterminate or reduce the number of mosquitoes by removing more or less completely their breeding grounds. When stagnant pools and tanks cannot be filled in they may be made unsuitable for breeding grounds of the Culicidae and other mosquitoes by deepening and cleaning and by treating them at short intervals (weekly) with petroleum oil, and other culicidal substances. The application of a thin layer of petroleum or oil to the surface of stagnant pools destroys all the mosquito larvae and nymphs in them in a few hours. Other culicidal substances recommended are saturated water infusion of Tobacco leaves, powdered Chrysanthemum flowers, Witches' Broom, certain Aniline dyes (at Cells’ Malaria Jy. 191-201). For the destruction of mosquitoes in houses tobacco smoke, the fumes produced by burning powdered Chrysanthemum flowers, Eucalyptus leaves,
Pyrethrum powders, Sulphur Dioxide, and other gases are recommended (vide Collie's malaria pp 203-209).

(2) The prevention of the entrance of malarial parasites into man. This is, in the main, the prevention of the transmission of malarial parasites from the sick to the healthy by Anopheles mosquitoes. The measures and precautions, such as the use of mosquito nets and wire gauze, the administration of Quinine as a prophylactic, etc already described under the head personal prophylaxis and the preceding heads 11a and 11c are useful and necessary for this purpose. Thorough treatment of every case of malaria promotes the same object. The most effective and necessary for the prevention of infection is the destruction of Anopheles mosquitoes. The methods of destroying mosquitoes have already been dealt with, the chief and most important method being the removal of all collections of stagnant water. By these
various measures much may be done to rid a country or locality of Malaria. Favourable results have been reported from Havana, Jamaica, Freetown, and other malarious centres (vide Ross’s Mosquito Brigades and reports in the medical journals from 1896 onwards.) The difficulties are mainly due to the wide extent of country to be dealt with and the carrying out of irrigation and other public works without regard to the question of malaria, but quite as much to the ignorance, indifference, unwillingness to incur expense, and obstruction for similar reasons not only of the public but also of those chiefly responsible, the sanitary, executive, and other governmental and public authorities (vide Enlightened St. Lucia in Lancet, Jan 4, 1902, p 55; Ross’s Mosquito Brigades, pp 57-60, and Gibson’s Text Book of Medicine, Vol 1, p 316). “In spite of the difficulties, however, there is no doubt that a great deal can be done to reduce, if not stamp out, Malaria by the methods indicated, which should be applied according to circumstances.” (Article
Treatment

The most important fact for guidance in treatment is that Malaria has a specific and essential, viz., the malarial plasmodium. The essential cause, the malarial plasmodium, and the conditions favourable and unfavourable to its life, activity, and proliferation, are the important facts to be considered in adopting remedial and preventive measures. The preventive measures have already been dealt with. The therapeutic agencies, such as drugs, hygienic precautions, etc., available are to be carefully considered and studied in order that a judicious choice of the most suitable and effective may be made. The constitution of the individual, his history, and the condition of his vital powers and organs, as in other diseases, are to be taken into account and the treatment should be modified or supplemented accordingly.
The conditions unfavourable to the life and multiplication of the malarial \textit{plasmodium} are in health, bodily vigour, and a sufficient degree of natural resistance in the individual. Of drugs, \textit{quinine} is a specific, attacking the \textit{malarial parasite}, and by far the most important and effective. Other drugs which have been used as \textit{specifics} are \textit{methylene blue}, \textit{Andresine}, \textit{Phenocol hydrochloride}, \textit{Carbonic acid} and some others. \textit{Methylene blue} is the only one of these drugs that has any clinical evidence in its favour as a specific. Drugs which counteract the injurious effects of the \textit{malarial parasite} and maintain or restore bodily vigour and natural resistance, and drugs which in other ways aid the action of the \textit{specific} drug are useful and more or less necessary in the treatment of \textit{malaria}. The \textit{mode of action}, advantages, and disadvantages of the \textit{specific} drug, \textit{quinine}, may be considered in this place. \textit{Quinine} has
a specific effect on amoeboid organisms, arresting their movements and finally killing them. The resistance of the malarial parasite is said to be diminished at the approach of the febrile attack and during its development and to reach its maximum degree during the period of apyrexia (Cetti's Malaria p. 190). Quinine is said to have no influence on the crescents and gametocytes, but reduces the formation of gametocytes (Cetti's Malaria pp. 192-193).

Craig concludes that, excluding the gametocytes, quinine exerts an injurious influence during all stages of the human life cycle of the parasite, except just prior to sporulation. He advocates the administration of quinine in divided doses at regular intervals, rather than the giving of one or more large doses. I carried out some experiments with solutions of quinine and perchloride of mercury on the protozoic and other minute organisms in the stagnant water mentioned on page 7 and give the results in the subjoined tables. The doses given in the tables are such as would give in the human subject the same dilution.
or strength in the blood as was obtained by mixing the Quinin and Perchloride of Mercury solutions with equal parts of the stagnant water. The minimum times given are the periods in which the solutions showed a marked influence on the movement of the organisms; the maximum times are the periods in which the solutions killed or arrested all movements of the organisms. There were occasional slower movements, in a few cases at the ends of the longer periods, but the organisms showing them appeared to be moribund and were mainly of members of higher groups (e.g., minute crustaceans) or the larger protozoic animal scales (such as paramecium).

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<tr>
<th>Quinin</th>
<th>30 grs</th>
<th>20 grs</th>
<th>15 grs</th>
<th>10 grs</th>
<th>7 1/2 grs</th>
<th>5 grs</th>
<th>Series of Experiments</th>
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<td></td>
<td>4 mins</td>
<td>5 to 6 mins</td>
<td>8 to 25 mins</td>
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**Bichloride of Mercury**

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<tr>
<th>½ gr dose</th>
<th>1 gr dose</th>
<th>¼ gr dose</th>
<th>⅛ gr dose</th>
<th>Series of Experiments</th>
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<tr>
<td>2 to 7 minutes</td>
<td>10 to 45 minutes</td>
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<td></td>
<td>125 1st water containing much organic debris and numerous organisms, 1 to 2000 dilution destroyed all living forms in 5-6 minutes</td>
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<td>3 to 10 minutes</td>
<td>8 minutes</td>
<td>8 minutes</td>
<td>15 minutes</td>
<td>2nd water containing much sediment and fewer organisms</td>
</tr>
<tr>
<td>2 to 5 minutes</td>
<td>5 minutes</td>
<td>5 minutes</td>
<td>8 to 10 minutes</td>
<td>3rd clear water with less sediment and fewer organisms</td>
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</table>

The strongest solutions or doses of Quinine and Bichloride acted with the greatest rapidity and certainty. Medium doses acted with almost the same degree of certainty and rapidity. The smaller doses acted more slowly and on the whole with less certainty and completeness. Apart from its specific action, the antipyretic and tonic actions of Quinine are of value in the treatment of malarial fevers. The advantages of Quinine are summed up in its specific, antipyretic, and tonic actions. The
The disadvantages of Quinine are its toxic effects and its bitter taste. The latter is of little consequence and may to some extent be overcome by administering it in milk or coffee. In Lander Brunt's Pharmacology (Ed. 1893, p. 577), excess of acid is recommended to cover the bitter taste. Quinine may also be given in cachets or as the cabinet preparation Eugenin.

The toxic effects of Quinine are the result of large doses. A slight degree of Quinism may not be dangerous and is recommended in severe cases of Malarial Fever, but a greater degree may result in dangerous or fatal depression of the heart and respiratory centre. Altogether the physician should ask himself in every case where he considers large doses of Quinine desirable, whether an existing or threatening weakness of the respiration or circulation might prove an objection to his prescription. Speedy death has been observed in Typhoid Fever in patients or convalescents after about twenty grains of Quinine, and even less may prove dangerous. In such cases one should not go higher than ten
grains, and at the same time give good wine in moderate doses and frequently (Bi-gin Artich. Oxinum in Quain’s Dictionary of Medicine, 1845). In pregnancy the possible abortifacient action of Oxinum should be kept in mind and Oxinum should be avoided. The authority quoted above is of opinion that abortion and premature birth are mostly due to the illness for which the Oxinum has been given. Other undesirable effects of Oxinum are certain skin eruptions, the most important being urticaria and purpura, and irritation of the kidneys and bladder, which may cause albuminuria, color of the bladder and possibly hematuria. Albuminuria and Haemoglobinuria are also said to be produced by large amounts of Oxinum. (See Art. Oxinum in Quain’s Dict. of Medicine and Hale White, Pharmacology and Therapeutics). The antiperiodic dose of Oxinum is usually stated to be from 5 to 20 grains. In Craig’s Botanical Table, in the British Pharmacopoeia, and the Extra Pharmacopoeia of Martindale and Woollcott the dose is given as 1 to 10 grs. But the general principle of Mitchell Peale’s Materia Medica and Therapeutics, 1905.
as to dosage given in the Preface to the British Pharmacopoeia is as follows, "The doses mentioned in the Pharmacopoeia are intended to represent the average range, in ordinary cases, for adults. They are meant for general guidance, but are not authoritatively enjoined by the Council. The medical practitioner must act on his own responsibility as to the doses of any therapeutic agents which he may administer." (p. xviii). In Landor Brunton's Pharmacology (1888) 2-5 gcs of Quinine Sulfate, repeated every 2-4 hrs (i.e. up to 60 gcs in the 24 hrs in divided doses) is the direction for the administration of Quinine as an antipyretic and 15-20 gcs is said to be a large dose. In the same work a little larger doses of the Bisulfate are recommended. Remembering the toxic effects of Quinine, it is as well not to exceed 10 gcs in ordinary cases, as a general rule. In urgent and pernicious cases and in the case of the primary dose large doses (15-20 gcs), when not contraindicated, may be given. In the Italian hospitals 31 gcs is usually given in two
doses, with a two or four hours' interval and 15-23
gas every twelve hours." (Hale White's Practical
Pharmacology and Therapeutics, Art. Anichmond
its Alkaloids). The most soluble salts of
Quinine, the hydrochloride, bichloride, and
bismuthate are the best salts for
administration, the two former being preferable,
as they are the most powerful curare
in the form, a chloride, in which Quinine
is absorbed from the stomach. Pills and
tablloids are slowly and often not completely
absorbed, and are therefore to be avoided
during the attacks of Malarial Fever.
Methods of administration. (1) Quinine is
usually given by the mouth. As a general
rule this is the best method of administra-
tion. In cases where there is vomiting a
small dose of Picrot or Opium may be
given with the Quinine. I have found
this a useful plan. In addition to eradicating
nausea and vomiting, the small doses
of Opium appear to aid the action of
Quinine by their stimulating and
diaphoretic properties.
2. Administration per rectum. This method and the following are to be resorted to when owing to persistent vomiting and inability to swallow from coma, convulsions, etc., administration by the mouth is impossible. A small dose of laudanum, ten minims or so, should be added to the enema of quinine.

3. Hypodermic injection. This method is indicated in the conditions mentioned above under (2), when the rectum is irritable and when the symptoms are grave and alarming. It is preferable to the preceding method, provided careful antiseptic precautions can be taken. "In all cases in which life is in imminent danger, and in which the earliest possible action of the drug is of importance, it must be given hypodermically." (Manson's "Principles of Tropical Diseases," 1898, p. 114). The hydrochloride and acid hydrochloride dissolved in distilled water in doses of 7½ to 15 grs., and the Sulphate dissolved in distilled water by the aid of half its weight of Tartaric Acid are the best.
salk for administration by this method. The
sulphate dissolved by the aid of dilute sulphuric
acid is also used. Manson states that the
solution of Quinine should be boiled before
being used. Intra muscular injection is re-
commended as preferable to subcutaneous
injection, as it causes less irritation.
(4) Intravenous injection of a solution of the
hydrochloride has been advocated by
Bacelli in desperate pernicious cases. He
uses the following solution: Hydrochloride of Quinine,
1 gm; Chloride of Sodium, 75 ceps; distilled water
10 ceps. Half of this quantity slightly warmed is
injected. (vde Gibson's Pract. Book of Medicine, p 314).

Intermittent Fever. In simple intermittent
Fever the usual practice is to give a dose of 5-
to 10 or 15 gms. of Quinine in the sweating stage,
or in the intermission and 5-grain doses sub-
sequently at regular intervals up to a daily
amount of 15 to 30 grains. In mild inter-
mittent attacks three 5-gr. doses daily after
the initial dose are generally considered
sufficient. Manson says, "A fever fit,
once begun, cannot be cut short by Quinine, and
Manson's Tropical Diseases. II., Daniel's Breezer,
Ward.
To give Quinine during the early stages aggravates the headache and general distress. (Diseases, 1970, p. 111). But, as pointed out by Ross, and as a study of the histology of malaria indicates, "the object is not to reduce a given attack of fever but to rid the system of the parasites entirely" (Art. Malaria, Quain's Dictionary of Medicine, 3rd ed.). Fayer also says, the objection to Quinine in the pyrexial stage is groundless for it reduces temperature and often produces diaphoresis (Fever of India, p. 111). I should therefore recommend that the initial dose, varying from the average full dose of 10 grs to the usual maximum medicinal dose of 20 grs, be given immediately, the contra-indications for larger doses (15-20 grs) being carefully considered. By the immediate administration of the initial dose of Quinine young amastigotes are killed and the formation of gametocytes or resistant forms of the parasite is reduced or entirely prevented. I have repeatedly given Quinine to patients during the Fever and always with benefit. I have seen the Fever pass off rapidly and not
return after the administration of Quinine in this way. After the initial dose has been given, the usual plan of administering 15- to 300- or 400 grs. of Quinine in divided doses of 5 to 7 1/2 grs. may be followed. Considering the main object of treatment, as moderately large daily dose of Quinine, 25 to 30 or 40 grs., would be better than a smaller amount, for a few days, Ross recommends that a mild degree of Aethromia, singling in the ears, be kept up till the fever has passed off. (Art. Malaria, Quinins Dictionary of Medicine, 3rd ed.). The intermission may be taken advantage of for the administration of the greater part of the daily dose of Quinine. The best time for the administration of Quinine is said to be a little before, or directly after, the expected paroxysm. This is explained by the facts that the maximum effect of Quinine occurs about five hours after its administration, and that it acts most injuriously on the young plasmodia or Amoebula. As a practical illustration of this method of administration I may mention that I have found it of advantage in Celli; malaria p. 191-192, Hale White's Pharamacy and Therapeutics, Schimel; Diseases of Warm Countries, 1864, P. 147-148.
to give the greater part of the daily dose of Quinine in the early morning hours, the paroxysm as a general rule, coming on in the late morning or early afternoon hours. The continuous treatment by Quinine should be kept up for some time, two or three days according to Manson, three weeks according to Ross, after the subsidence of the fever, the daily dose being gradually reduced. The longer period would no doubt give a better permanent result. Ross states that the drug should not be entirely abandoned for three months after an attack. (Quain's Dictionary of Medicine, 5th Ed.). A relapse may occur for two or more years after an attack; it would probably be of advantage, whenever possible, to treat patients intermittently with Quinine for a year or two, when there is a probability that the disease, i.e., the malarial parasite is latent in the system.

Remittent and Continuous Malarial Fevers. In all severe types of Malarial Fever it is necessary to give Quinine as early as possible and in larger doses than those commonly given in simple intermittent fever. Authorities
differ as to the dose and time of administration of Quinine; but in the severest types of malarial fevers, all authorities agree that Quinine should be given at once in a full dose and continued at intervals in moderate or full doses. "In Remittent Fews the periods of remission are chosen for the administration of Quinine." (Schmuke's Diseases of warm Countries p. 165). This is the usual plan recommended by writers on Malaria. Mackan says not less than half-adram of Quinine should be given during the remission. The same authority also mentions the plan of giving Quinine in the hot-stage. "American Physicians appear, in treating this disease, to follow chiefly the second plan mentioned, and, trusting to the known property of Quinine to diminish and not to increase temperature, they give it during the hot-stage." (Ouin's Dictionary of Medicine p. 641). Schmuke recommends 1.5 to 2 grammes of Quinine once daily, 1 gramme every twelve hours, or 0.5 gramme every 6 hours in pernicious cases and in cont- 

linued fevers when a high temperature has
permitted for two days. Manson, writing on The Treatment of Bilious Remittent Fever, says, "In all grave fevers a full dose of ten or fifteen grains should be at once administered," and in another place, he says, "But in continued fevers, or in the presence of dysentery, Quinine should be given at once in 10 gr. doses every six hours or oftener, and irrespective of the stage of the disease." I think one may safely conclude that the best plan is to administer of 10 to 15 or even 20 grs of Quinine at once in all the severer types of Bilious Fever, including Remittent Fevers. Saides states that "a dose of 15 or 20 grains is often required in grave or pernicious attacks." Subsequently to the administration of the initial dose Quinine should be given at regular intervals as recommended by Manson or Schenke or on some similar plan. I think Manson's plan of giving 10 grains every six hours or oftener would meet the indica-

In the Remittent Fevers, the administration of Quinine & Tropical Diseases, 1872, p. 117, and Gibson's Text-Book of Medicine Vol. 7, p. 313.
in doses of 5 to 7½ or 10 gns at regular intervals of 3 to 6 hours according to the severity of the particular case appears to me advisable. The remissions may be taken advantage of if of sufficient duration, but they are often short. Manson recommends 5 gns of Quinine every 3 to 6 hours in Bilious Remittent Fever. (Tropical Diseases, 1878, p. 117). As to the daily dose in the severe types of Malarial Fever, Remittent, Continued, and Remittent Schenkel is of opinion that it is useless even dangerous to exceed 30 grains in the twenty-four hours. This appears to me to be far too strict a limitation of the daily amount of Quinine, involving the risk of losing the beneficial effect of a larger amount in cases requiring energetic treatment with Quinine. Forty to sixty grains in less and grave cases, at least for a few days, would probably be required to cure the fever and prevent a long illness or fatal result. Forty grains in the twenty-four hours is generally considered a safe amount. (M. Burney's Manual of Medical Treatment, Vol. II, p. 672).
The largest single and daily doses should be reserved for the gravest and most urgent cases, the contraindications being first carefully considered. I have found that two or three grain doses, given at short interval of half an hour or one hour, are borne better than a single dose of 10 or 15 grs by patients suffering from great weakness and prostration. When there are marked remissions, the may be taken advantage of for the administration of large single doses or for the greater part of the daily dose given in divided doses. For hypodermic injection 7½ to 15 grs of the Hydrochloride of Quinine may be given. Schenke states that in this method of administration half the internal dose is sufficient. Manson recommends that in severe pernicious cases 15 grains of the Hydrochloride should be administered at least thrice daily (Gibson’s Text Book of Medicine, Vol 7 p 314). The following advice given by Dr. J. Robertson (Theory and Practice of Medicine, 25 Ed., p 338), appears to me to be sound and well worth quoting in regard.
to the treatment of malarial fevers. "In localities and during seasons in which serious cases of malarial fever are likely to occur, it is of great importance to treat even mild attacks promptly and actively by quinine, in order to prevent its more grave developments. When these have actually occurred, both in the administration of this remedy is imperatively demanded under all circumstances. It should be given in from 10 to 20 grain doses or more every two hours, until cinchonism has been produced, which may then be kept up by smaller doses, due care being exercised against producing serious symptoms." Ross says, "Quinine must be well pushed in paroxysmal attacks." (Quine, Dictionary of Medicine, 3rd Edt., Art. Malaria.) Quinine acts better when a purgative, especially a cholagogue purgative, has first been given. Davidson says, "a purgative is in most cases of undoubted service." Fayrer say the administration of an aperient consisting of aloes and blue bill to relieve constipation and
Congestion of the portal system is generally the first and important step (Fever of India).

The administration of an emetic also, when indicated by a loaded stomach, nausea, and retching, biliousness, etc. is also of service in aiding the action of Quinine. The following pharmacological explanation and advice are given by Lander Brunton in his Text Book of Pharmacology (1889, p. 359). "If Quinine forms with the bile a salt which is sparingly soluble, except in excess of bile, hence before giving Quinine in malaria, clear out the liver by administering an emetic and a choloagogue purgative. The administration of the purgative should not be allowed to interfere in turn delay the administration of Quinine. The best purgative for the purpose is Epsom salts, followed, if necessary, by a saline, especially in cases of Bilious Reulent Fever.

Symptomatic Treatment. Warm coverings are required in the cold stage, and a moderate amount of some warm drink, such as weak tea, may be given. Hot fomentations to the extremities
and friction of the skin with the hand or hot flannels may be called for in some cases. It is desirable to discontinue the application of warmth as soon as the cold stage is over. The temperature is often raised by the too prolonged use of warm coverings by patients. When the hot stage sets in the patient should be lightly covered. In this stage cool refrigerant drinks, such as lime juice, and sponging with tepid water are soothing and beneficial. In the sweating stage perspiration should be encouraged by keeping the patient warm and by administering hot drinks. Constipation should be treated with aperients, the bowels being made to act regularly and freely throughout the course of the illness. Diarrhea should be treated on general principles and should only be checked when excessive and exhausting. Vomiting is often a troublesome symptom. It may be mitigated or prevented by the administration of a simple emetic (Specacular or mustard and water) at the onset of the
attack of fever. The administration of a
mixture emetic in certain cases, when the stomach
is loaded with food, when there is much nausea
and retching, and when the fever is of the
Diabatic Remittent type is recommended
by Davidson (Diseases of Warm Climates, 201).
The usual remedies for vomiting, such as
effervescent drinks, ice, morphine and
opium, analgesics to the epigastricum, etc., may be
employed. For headache the application
of cold to the head by evaporating lotions,
iced water, etc., is the best method of treatment.
Schulze recommend 5-grain doses of anti-
pyrin for headache and pain in the limbs;
but as a general rule, it is best to
avoid depressant analgics and antipyretic
remedies. Bromide of potassium is recommend-
ed for sleeplessness, restlessness, and con-
vulsive seizures. In algid attacks treat-
ment by linaments and turpentine stripes
to the extremities, friction of the skin with
rubefacients, and the internal administra-
tion of diffusible stimulants, such as
ammonia, ether, brandy by the mouth, and
Ether and strychnine by hypodermic injection, is required. In cerebral types of malarial fever, counter-irritation to the extremities, the administration of a drastic purgative, cold baths and douches and the application of cold to the head, and bleeding by leeches over the mastoid process, are the chief measures indicated. Hyperpyrexia is treated by the application of cold, by means of the cold bath etc., and by similar measures for the reduction of high temperature. This is one of the cases in which the prompt and active administration of the specific remedy Quinine is most urgently indicated and necessary. Not only the Specific but also the antipyretic action of Quinine is of service in these cases. Manson says Antipyrin and similar antipyretics are absolutely useless and that Quinine must be injected hypodermically, or into a vein in full doses, and repeated every three hours until thirty or forty grains have been given. "(Tropical Diseases p.118). In the Treatment of malarial dysentereia
Symptoms and of Dysesthesia associated with or complicated by malarial fever. Quinine is required. In the treatment of Malaria complicated by Pneumonia, Quinine must be given in somewhat smaller doses than in other cases, in order to avoid its depressant effect on the circulation and respiration. Alcoholic and Cardiac Stimulants will be required in severe cases of Malarial Fever, especially Syncopeal and Algic attacks and cases complicated by Pneumonia. In other cases the usual indica followed in administering Alcoholic Stimulants in Fevers, may be acted on. On the subsidence of the fever, tonic remedy, especially Iron, Arsenic, and Quinine, should be given. Iron is always clearly indicated and necessary. A liberal diet of good nourishing, digestible food is obviously essential.

Treatment of Haemoglobinuric Fever. Opinions differ considerably as to the treatment of this fever, being founded on different views of
its causation. Some authorities believe the condition is entirely malarial, some that it is due to Quinism, and others that both causes are concerned in its production (Gibson's Text Book of Medicine, vol. 7, p. 315). The last view, I think, is best supported by the facts and by reason. The evidence points to the conclusion that Malaria is the chief cause and Quinine an occasional and supplementary cause (vide Year Book of Treatment for 1898, p. 425 and Lancet, July 11, 1903, p. 104, and Manson's Tropical Diseases, p. 119). It is easy to understand that when more Haemoglobin is liberated in the circulation than the Liver is able to deal with by conversion into pigments &c., some unaltered Haemoglobin must escape by the Kidneys. That large doses of Quinine are frequently given in Malarial Fever, without producing Haemoglobinuria is a well attested fact, especially in India (for an instance see Lancet, June 13, 1903, p. 1662). Schenke says: "It is only permissive to give Quinine after the disappearance of the Fever and the nephritic symptoms, and when patients have been feeling well for
Several days.” (Diseases of Warm Countries, p. 165-166.)

Roberts states that “Full doses of Quinine and

Tincture of Iron have been found of most

service in the Treatment of Premonogal

Haemoglobinuria.” (Theory and Practice of

Medicine, 7th Edn. 1877, p. 1039.) The opinion

is held that Quinine should be given only

when malarial parasites are present in

the blood. On the whole a judicious and

careful administration of Quinine is in-
dicated. Some useful rules for the admin-

istration of Quinine, formulated by Bartlett,

and based mainly on the presence or absence

of malarial parasites in the blood, will

be found in The Year Book of Treatment

for 1878, page 426. Quinae is should be

promoted by liquids (barley water, water,

milk etc.) and by mild non-irritating diuretics,

such as Chlorate of Potassium. The patient

should be kept warm, and warm applications

to the loins may be tried to relieve congestion

d of the kidneys. Other remedies employed are

Colonel in moderate or full doses, Taninie

Acid in doses of 15 grains every eight hours,
Chloroform in frequent small doses, and
transfusion of blood. These remedies
appear to be used empirically. The after-
treatment is the same as for other forms
of malaria, special attention being
paid to protection from exposure to
cold and chills.

Treatment of Chronic Malaria and
Malarial Cachexia. In these conditions
the Anemia and debility, and the change
in internal organs have to be remedied;
as completely as possible, by therapeutic
measures. For the Anemia and debility,
Hematinics, Iron and Arsenic especially,
A nourishing digestible diet, and
tonics, such as Ferrum, Arsenic, and
Picrohurmine should be given. A
change to a dry, cool, equable, tracing
climate is a valuable therapeutic measure
and often necessary. Hepatic disorders
are best treated by Cholagogue and
Aperient Salines. The best of these is
Carlsbad Salts or Waters. Others recommend
ed are the mineral waters of Kissingen, Bombay.
and Wiesbaden. When they cannot be obtained at the drugs or elsewhere, substitutes for them may be prescribed. Other cholagogues, calomel, also do to stimulate the functions of the liver and relieve portal congestion are of service in treatment. The enlargement of the spleen is treated by counter-irritants and red soles of mercury, ointment externally and mercurial and iodic preparations internally, by malarial remedies such as quinine, iron, and arsenic internally, and by drugs which relieve congestion of the portal system, such as chologogue and other aperients and purgatives. In all cases removal of the patient from the malarious locality is beneficial, and is said to be in many cases the only means of treatment.

General Conclusions on Treatment.

1. Prophylaxis (a) Personal: The means for personal prophylaxis (1) those which protect individuals from the bites of mosquitoes, such as the use of mosquito nets, (2) the
prophylactic use of Quinine (3) measures for the maintenance of a high degree of natural resistance such as living in accordance with the laws of hygiene and avoiding predisposing causes of malaria and other diseases, and (4) the carrying out of the measures adapted for general prophylaxis on a small scale by individual residents in malarious localities.

(1) General prophylaxis. This is, in the main, the destruction of mosquitoes and of malarial parasites. The measures may be tersely summed up in the words used by Ross as a motto for mosquito brigades and anti-malarial campaigns, viz., "No stagnant water" (vide Mosquito Brigades, p. 43). Next in importance, but a measure of less permanent value and not so practicable, is the use of Quinine and other prophylactic remedies on a large scale.

Treatment. The treatment of Malaria means the most efficient administration in each case, of the Specific remedy Quinine.
in as full or large doses, single and daily, as can be used without producing dangerous toxic symptoms. All other remedies, though useful and often necessary, are only adjuvants and supplemental to the chief therapeutic measure, the administration of the specific remedy Quinine.

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Appendix to Thesis for M.D. Degree.

As Quinine appears to have little or no influence on the gametes and crescents of the Malarial Parasite, I would suggest that a stronger internal disinfectant, namely, Perchloride of Mercury, in doses of \( \frac{1}{8} \) - \( \frac{1}{4} \) gr., be tried. This idea suggests itself to me from a knowledge of the powerful disinfectant action of Perchloride of Mercury and from the consideration of the results of the experiments with Perchloride of Mercury and Quinine on Protozoic organisms described in my Thesis. The Perchloride of Mercury, apart from its possible injurious action on the gametes and crescents of the Malarial Parasite, would prove useful in removing congestion and other pathological conditions of the Portal System and other parts of body associated with Malaria.