A STUDY IN THE TREATMENT OF MALARIA,
WITH SPECIAL REFERENCE TO
THE ARMY IN INDIA.

by

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INTRODUCTION.

For the last 500 years, the Cinchona Alkaloids have reigned supreme in the treatment of the intermittent Fevers of the Tropics, and the word Malaria would not be complete without mentioning its unfailing and specific remedy, Quinine.

But, although it has always been looked upon as probably the greatest specific of all, in recent times, Quinine has not had the whole hearted support of tropical workers. They have recognised that, although it is a wonderful drug for curing the attack of Malaria, in preventing relapses, it falls very short of the ideal. As a result of this, numerous drugs have been tried as substitutes for Quinine, but with no success, and this ancient remedy has always held sway.

In the last decade, two new drugs have sprung into prominence, and are threatening to oust Quinine from the throne it has held for such a long time.

Malaria is practically a world wide disease, and is so important, that it would be folly to abandon carelessly a drug which has proved itself by long use, for two new drugs, without a thorough trial of the new, and comparison with the old.

In this Thesis, I propose to make a study of the treatment of Malaria, starting with a short historical
account, and then describing the results of treatment by different workers, with the various Cinchona Alkaloids, and other drugs which have been tried as substitutes. From there, I shall go on to the new drugs, Plasmoquine and Atebrin, and I shall pay particular attention to the treatment of Malaria in the Army in India.

I then propose to describe the results of treatment with the new drugs, carried out by myself at Kohat, in the North West Frontier Province, finishing up with a summary and conclusions.
HISTORICAL ACCOUNT.

Malaria has probably been in existence since the infancy of the human race.

The Ancient Egyptians possessed some knowledge of Malarial Fevers. It is said that the letters A A T, which are found among the inscriptions of the Temple of Denderah, referred to a disease, doubtless Malaria, which recurred yearly at the same time.

More than 1000 years B.C. Malarial diseases were mentioned in the Orphic Poems.

Some of the early plagues mentioned in the Bible, and the vast epidemics which assailed the Assyrian and Babylonian Armies, were possibly Malarial.

According to Herodotus, the fishermen on the Nile, used their fishing nets to prevent the attacks of mosquitoes.

Hippocrates, 5th Century B.C. gave a fairly complete description of Malaria. He differentiated Malarial from Continuous Fevers, and observed the periodicity of the paroxysms. He divided Malarial Fevers into Quotidian, Tertian, and Quartan.

The darkness and superstition of the Middle Ages retarded all advances in our knowledge of disease, and it was not until the 17th Century that the first real stage of the history of Malaria was entered upon.

The first great advance was made in the therapeu-
tics of Malaria, and this provides a fascinating chapter in the history of the disease.

In 1630, Don Francisco Lopez Canizaris, the Spanish Corregidor of Loxa, is said to have been cured of a fever by use of the bark from a tree. In 1638, hearing of the illness of Ana de Osorio, wife of the Count of Chinchon, Viceroy of Peru, Canizaris sent to the palace at Lima, a parcel of the bark. Her physician Don Juan de Vega used it to cure her Tertian Fever. It was after this, known as Cinchona Bark. In Belgium and Holland, it was known as Jesuit's Powder.

The various methods of treating Malarial Fevers with Cinchona Bark in these early days, are interesting and instructive. The Jesuits are said to have adopted the following line of treatment. Eight grams of powdered Cinchona Bark were given immediately before the paroxysm was expected to begin, and the administration was repeated until the patient recovered, the dose being gradually reduced. (Trousseau 1872).

Sydenham (1624-1689) commenced treatment when the paroxysm was over, and gave thirty-two grams of Bark in twelve divided doses, at intervals of four hours. This course was repeated from one week to a fortnight later. This was found to be superior to the Jesuit's method of treatment, and it was recognised that fewer relapses occurred.

Robert Talbor used Cinchona Bark with Port Wine
as a vehicle, which made his treatment a very popular one. He became a fashionable physician, and Louis XIV purchased at a large price the secret of his specific. He incurred the displeasure of the College of Physicians, but Charles II appointed him one of his physicians, and saved him from medical ostracism.

It is interesting to compare the dosage used in these days with the present day doses of Quinine. The average alkaloidal content of the Cinchona Bark is about five per cent. Therefore, 30 grams of Bark would yield about 1.5 grams or 22 grains of alkaloid. Sydenham's course of treatment corresponded, therefore to about two grains of Quinine every four hours for twelve doses. This course was repeated once later, so the entire treatment consisted of the administration of only about forty eight grains of Quinine. It is known, of course, that this is quite enough to stop the febrile paroxysm.

Stephens and his co-workers have shown that, in Benign Tertian Malaria, the oral administration of Quinine Sulphate, in doses of ten grains, on each of two consecutive days, causes the cessation of febrile paroxysms and the temporary disappearance of all stages of the Malarial Parasite from the blood. (Stephens 1917).

The relapse rate in Sydenham's cases must have been very high.
The discovery of the Cinchona Alkaloids marked the next great advance in Malarial therapeutics. Bernardino Antonio Gomez, a Portuguese Naval Surgeon discovered in 1810, the first of the Cinchona Alkaloids and named it, Cinchonin. In 1820, two chemists, Pelletier and Caverton, isolated Quinine. Henry and Delondre discovered Quinidine in 1833, while Cinchonidine was discovered by Winckler in 1847.

In the history of the use of Cinchona Bark in India, there is also a dark "Middle Age", during which, owing to ignorance, this wonderful discovery was deliberately ignored, and physicians returned to the useless treatment of earlier days.

The earliest writers on the Fevers of India were Ship Surgeons, who visited the principal ports of the country, and wrote about the use of Cinchona Bark. It was first used in Calcutta, in 1657, by Doctor Bogue. Doctor James Lind, who divided Fevers into Intermittent, Remittent and Continued, tried the Cinchona Bark on about 500 cases, using over 140 pounds. In his series of cases, there were only two fatalities, neither of which had taken the bark. His treatment was, first of all, to bleed the patient, then give a strong purge, followed by an antimonial draught to produce sweating, or a remission. Then he gave the bark in doses of one to two drachms every
two hours. (Lind 1808).

Then came the period of darkness and ignorance, in which the use of the bark was practically given up. Doctor James Johnson came out to India as a ship's Surgeon, and arrived at Calcutta during the height of the malarial season of the year 1804. In his book, he describes his first attempt to cure a patient, who was suffering from a severe attack of Bengal Remittent Fever, with Cinchona Bark. Owing to obstinate vomiting, the remedy failed, and the patient died on the third day of the disease. Doctor Johnson, his reasoning faculty completely upset by this fatal case, never tried Cinchona Bark again, but copiously bled his next case, which recovered. "Henceforth", he said, "I carried the evacuating plan with a high hand. If I gave a purgative, I always added to the mercurial frictions to prevent a halt in the pursuit of my ulterior and principal object, ptyalism". Doctor Johnson returned to London, and in 1813, published his book on Tropical Diseases. (Johnson 1813).

Resulting from this, Cinchona Bark was almost entirely given up in India, and even when Quinine was discovered, it was for many years used only as a tonic in small doses, after the fever had ceased. Some even forbade its use until the tongue had become clean.

In 1816, Doctor Halliday published some cases
in which eight to nine hundred grains of Calomel had been administered during a single attack of fever.

Doctor Annesley used Cinchona Bark in 1828 after having "promoted the discharge of morbid secretions and faecal accumulations, and removed local congestion by blood letting", "otherwise", he said, "it will fail to produce its febrifuge effects. But this difficulty is happily got rid of, since the introduction of Sulphate of Quinine into practice". (Annesley 1828).

Quinine was first used in India in 1826, but did not come into general use for another quarter of a century.

William Twining, 1832, was a great advocate of venesection, and stated that it nearly always cured the attack of fever, but he bowed to modern opinion, and used Quinine. His scheme of treatment was -

First a purgative. Then during the cold stage, he took away from twelve to sixteen ounces of blood. He followed this by Quinine Sulphate two grains every three hours for four doses, during the intervals of the paroxysms. He also gave two ounces of the following mixture every three hours, until three stools were procured.

R/
Decoct. Cinchonae 1 pound
Mag. Sulph. 1 ounce
Tr. Rhei Co. ½ ounce

He recognised Chronic Malaria, and treated it with the
He was the first to treat chronic cases of Malaria with Arsenic. He said, "The Liquor Arsenicalis is also very effective in slighter cases of the intermittent fevers of this country.

It was Edward Hare, who, by keen observation and therapeutic research, established the use of Quinine in India. He came out to India in 1839, and encountered the deadly Terai Fever, which was prevalent at the foot of the Nepal Himalayas. He treated them according to the standard practice, but all his cases died. He cast aside these unscientific remedies, and used Quinine in all his subsequent cases, with excellent results. One year's trial of his Quinine method was made at the hospitals in Calcutta, with such good results, that a report was sent to every medical officer in India. Hare subsequently treated 6882 Fever cases in different Regiments, with only one death in 211 cases, or one half per cent mortality. (Hare 1847).
THE CINCHONA ALKALOIDS.

The chief source of Cinchona Alkaloids is at present the island of Java. The average alkaloidal content of dry commercial Bark of the Cinchona Calisaya Ledgeriana is:

- Quinine Alkaloid: 4.143 %
- Cinchonidin: 0.542 %
- Cinchonin: 0.381 %
- Quinidin: 0.170 %
- Amorphous: 0.288 %

Since the discovery of the Cinchona Alkaloids, numerous workers have tested and compared the efficacy of each in treating the intermittent Fevers, with a view to discovering the best.

In 1821, Chomel and Double compared the virtues of Quinine and Cinchonin, and concluded that Cinchonin cures intermittent Fevers but slowly, and in larger doses than is necessary with Quinine. Pepper (1853) considered Cinchonin equal to Quinine. Turner in 1864, used Cinchonin in one hundred cases, in doses of three grains every hour, with a total dose of twenty grains, and said that in slightly larger doses, it was equal to Quinine, and in these days, it cost from one half to one tenth the price of Quinine. (Dawson W.T. 1930).

The first elaborate investigation into the relative virtues of the Cinchona Alkaloids was made by the Madras Cinchona Commission, and they published the report in 1868. They tried these alkaloids on 2472 cases, and their criterion of cure was, the cessation of the fébrile paroxysm.
The following were their results:-

<table>
<thead>
<tr>
<th>Remittent Fever</th>
<th>Tertian Fever</th>
<th>Quartan Fever</th>
<th>Total Cured treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinine 740</td>
<td>5</td>
<td>66</td>
<td>35</td>
</tr>
<tr>
<td>Quinidine 942</td>
<td>2</td>
<td>80</td>
<td>10</td>
</tr>
<tr>
<td>Cinchonidin 687</td>
<td>8</td>
<td>63</td>
<td>4</td>
</tr>
<tr>
<td>Cinchonin 872</td>
<td>6</td>
<td>26</td>
<td>5</td>
</tr>
</tbody>
</table>

These results are, of course, valueless, as the cessation of the febrile paroxysm is no criterion of cure, but they show that the alkaloids are equally effective in curing the attack of fever.

Following the discovery of the malarial parasite, and the separation of Malaria into simple (Benign Tertian), Malignant Tertian, and Quartan Fevers, further trials of the different Alkaloids were made.

Giemsa and Werner, using Quinidine Hydrochloride, in three grain doses twice a day, found that it caused the disappearance of parasites in three days, and of the Fever, more quickly. (Giemsa G. 1914.)

MacGilchrist (1915) ranked the common Alkaloids in order of effectiveness - Cinchonin - Quinine - Quinidine. In 1920, Acton carried out observations at the Dagshai Malarial Convalescent Depot in India. The criterion of cure was no relapse within two months following the cessation of treatment. The following are his results, which show Quinidine to be superior to Quinine.

(Activity H.W. 1920 1921).
<table>
<thead>
<tr>
<th>Drug</th>
<th>Treated</th>
<th>Cured</th>
<th>Plan of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinine Sulphate</td>
<td>663</td>
<td>52.6%</td>
<td>Four months oral treatment</td>
</tr>
<tr>
<td>Quinidine Sulphate</td>
<td>62</td>
<td>62.9%</td>
<td>Ten grains twice a day for 21 days.</td>
</tr>
<tr>
<td>Cinchonidine Sulphate</td>
<td>46</td>
<td>63.1%</td>
<td>- do -</td>
</tr>
<tr>
<td>Cinchonin</td>
<td>14</td>
<td>42.8%</td>
<td>- do -</td>
</tr>
<tr>
<td>Cinchona Febrifuge</td>
<td>110</td>
<td>51.8%</td>
<td>Twentyone grains a day for 21 days.</td>
</tr>
</tbody>
</table>

Sinton and Bird were unable to confirm this work. Following five years investigation on 1300 patients, they came to the conclusion that: "The four chief Alkaloids showed almost an equal value in preventing relapses in chronic Benign Tertian Malaria; Quinidine gave the worst results. Their criterion of cure was - absence of parasites in blood samples taken every week for eight weeks following cessation of treatment. (Sinton 1929). Their results are tabulated on the next page.

Although the investigations of both Acton and Sinton tended to rank the other Alkaloids equal to, and in some cases, higher than, Quinine, the number of cases treated with the latter drug, was very much larger, with more scope for relapses.

Fletcher carried out an investigation in Malaya, with the Cinchona Alkaloids, and the following were his conclusions.

1. In doses of ten grains twice a day, the four crystallizable Alkaloids, Quinine, Quinidine, Cinchonine, and Cinchonidine, appeared to be of equal value in
<table>
<thead>
<tr>
<th>Alkaloid</th>
<th>Total Patients</th>
<th>Number lost sight of</th>
<th>Number not relapsing</th>
<th>Number of relapses</th>
<th>Observed</th>
<th>Possible Maximum</th>
<th>Observed Minimum</th>
<th>Average</th>
<th>Deviation from average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinine</td>
<td>667</td>
<td>66</td>
<td>184</td>
<td>417</td>
<td>69.4</td>
<td>72.4</td>
<td>62.5</td>
<td>68.0</td>
<td>-3.2</td>
</tr>
<tr>
<td>Quinidine</td>
<td>208</td>
<td>14</td>
<td>30</td>
<td>164</td>
<td>84.5</td>
<td>85.6</td>
<td>78.8</td>
<td>83.0</td>
<td>+11.8</td>
</tr>
<tr>
<td>Cinchonine</td>
<td>72</td>
<td>3</td>
<td>22</td>
<td>47</td>
<td>68.1</td>
<td>69.4</td>
<td>65.3</td>
<td>67.6</td>
<td>-3.6</td>
</tr>
<tr>
<td>Cinchonidine</td>
<td>107</td>
<td>24</td>
<td>23</td>
<td>60</td>
<td>72.3</td>
<td>78.5</td>
<td>56.0</td>
<td>68.7</td>
<td>-2.5</td>
</tr>
<tr>
<td>C. Febrifuge</td>
<td>110</td>
<td>25</td>
<td>19</td>
<td>66</td>
<td>77.6</td>
<td>82.7</td>
<td>60.0</td>
<td>73.1</td>
<td>+1.9</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>1164</strong></td>
<td><strong>132</strong></td>
<td><strong>278</strong></td>
<td><strong>754</strong></td>
<td><strong>73.0</strong></td>
<td><strong>76.1</strong></td>
<td><strong>64.7</strong></td>
<td><strong>71.2</strong></td>
<td></td>
</tr>
</tbody>
</table>
bring-ing about the disappearance of Malarial parasites in patients weighing about one hundred pounds.

2. In smaller doses of five grains a day, Cinchonine did not appear to be quite as potent as Quinine and Quinidine; Cinchonidine was definitely inferior.

3. Cinchonine did not cause any unpleasant symptoms when given in a dose about ten grains. If any-thing, it is less toxic than Quinine. A dose about twenty grains twice daily caused giddiness.
CINCHONA FEBRIFUGE.

Cinchona Febrifuge originally consisted of the total Alkaloids extracted from the bark of Cinchona Succirubra imported from the Andes. It contained a very small percentage of Quinine. When Quinine was separated, cultivators turned their attention to growing Cinchona Ledgeriana which has a much higher Quinine content. The residual Alkaloids were sold as Cinchona Febrifuge.

The approximate composition of Cinchona Febrifuge is:

- Quinine: 6.2
- Cinchonidine: 7.2
- Cinchonin: 28.8
- Quinidine: 8.7
- Amorphous: 45.0
- Ash: 4.2

Acton (1921) investigated the curative value of Cinchona Febrifuge in Benign Tertian Malaria. He gave twenty one grains daily for twenty one days to his first series—fiftythree cases, and twentyone grains daily for ten days to second series—fiftyseven cases. Both courses were followed by a three weeks Iron and Arsenic Tonic. His percentage cure was 50.9%, and none of his patients suffered from Cinchonism or Gastric trouble.

His conclusions were:

1. The administration of Cinchona Febrifuge in Benign Tertian Malaria is better than Quinine. The three weeks course gives the same curative results as a four months course of Quinine.
2. The amount of Cinchona Febrifuge used in a three weeks course is four hundred and fortyone grains.
The amount of Quinine in a four months' course is 1980 grains.

3. The cost of a three weeks' course of Cinchona Febrifuge is six and a half annas, as against Rupees eight annas four for a four months' course of Quinine.

4. Cinchona Febrifuge in tablet form is less toxic than Quinine.

At the present time, there is not a great demand for the Cinchona Alkaloids other than Quinine. Their chief use, especially Cinchonin and Cinchonidin, is as ingredients of popular "chill tonics". Although they may be as effective as Quinine in curing attacks of Malaria, their action is uncertain, and the composition of Cinchona Febrifuge is subject to considerable variation.

Their great advantage is their cheapness, and a standardised mixture of the Alkaloids would be a boon to communities of poor people, who cannot afford more expensive Quinine.

The Malaria Commission of the League of Nations recognised this, and suggested the preparation of a new Cinchona product to be called Totaquina.

This product was to be a mixture of all the Alkaloids of Cinchona Bark standardised to contain not less than seventy per cent of the crystallisable Alkaloids, of which, not less than fifteen per cent must be Quinine.

Two types of this preparation can be made.

1. By extracting and precipitating as an almost white powder, the total Alkaloids from the Bark of Cinchona
Succerubra or Cinchona Robusta which can be cultivated abundantly in almost every Malarious country.

2. This type is made by using the residues remaining after Quinine Sulphate has been extracted from Cinchona Ledgeriana, and bringing the preparation up to the required standard by adding sufficient Quinine and other crystallisable Alkaloids. These preparations are now on trial.

(Malaria Commission 1933).

Since Hare, in 1839, established the use of Quinine, the other Alkaloids of Cinchona Bark have not been used in the treatment of Malaria in the Army in India.
Quinine has the composition C20 H24 N2 O2, and is composed of two rings, a Quinoline ring, and a Piperidine ring, which are linked together by the group - CH(OH)-, and a side chain is attached to each ring.

The mode of action of Quinine on the Malaria parasite is still unknown, but since the treatment of General Paralysis of the Insane by Malarial inoculation was established, opportunities have been provided for studying the action of the drug.

When Quinine is given in full doses, its concentration in the blood does not exceed one part in one hundred thousand. Malarial parasites were inoculated for twenty-four hours in blood containing one part of Quinine in ten thousand. This blood was then injected into a volunteer, and a Malarial attack was produced. This experiment proves that Quinine in therapeutic concentration, does not kill Malarial parasites in vitro. The action of the drug is probably an indirect one.

Yorke and others made the following observations, based on investigations made during the treatment of General Paralysis of the Insane.

"In the treatment of Malaria, the train of events is, in our opinion, as follows.

Quinine given to a patient whose blood contains numerous parasites, invariably destroys directly, or more probably, indirectly, large numbers, if not all,
of the parasites, thus setting free a considerable quantity of soluble antigen. The antigen provokes, by stimulation of the host's tissues, the formation of immune body. This immune body, if present in sufficient amount, destroys the remaining parasites, thus resulting in sterilization of the infection, and in the cure of the patient. If for any reason, either of these things does not happen, the infection is not completely sterilized, and a relapse occurs.

The cells of the host, in response to the antigen stimulus, must be able to produce a sufficient quantity of immune body.

There is a considerable mass of evidence that man exhibits some degree of immunity to Malaria. Certain individuals are unable to produce sufficient immune body, and so have relapses." (Yorke 1924.)

The Malaria Commission of the League of Nations advanced the following theories to explain the parasiticidal action of drugs.

1. By direct toxic action of the drug after being absorbed into the blood stream.

2. By its conversion into a more powerful parasiticide after absorption.

3. By the stimulation of certain cells of the body to produce parasiticidal substances or antibodies.

4. By rendering the red cells resistant to the attack of the parasite.

5. By a combination of two or more of these factors.
Though it is still impossible to say how Quinine acts as a curative agent in Malaria, some workers, leaning towards the views that it functions as a sort of biological catalyst, assert that small doses are just as efficacious as large ones. (Carman 1935.)

Quinine salts are very bitter in taste, which makes them a very unpopular remedy with most patients, and when they are given continuously in large doses, they are liable to produce digestive disturbance. Quinine is believed to stimulate the Uterus, and large doses are stated to favour the occurrence of abortion. It must, therefore, be used with great caution in pregnant women. It has a specific action on the sense organs, and large doses cause ringing in the ears, accompanied by slight deafness. The eyes may also be affected, with diminution in the field of vision, and photophobia. There may even be temporary blindness. Cases have been recorded in which, the long continued administration of Quinine, has produced permanent impairment of the hearing, or of the sight. (Clark 1933.)

Occasionally, individuals are found, who show an idiosyncrasy to Quinine, and toxic symptoms are produced. These include dyspnoea, exanthemata, pruritis, and gastric disturbance.

The relation of Quinine to Blackwater Fever has long been a controversial problem.
Rogers and Megaw say that "Quinine is one of the common exciting causes of the disease, and therefore is likely to aggravate the haemoglobinuria. (Rogers 1930). Giglioli states that "In individuals infected with haemolytic strains of the Malarial parasite, the onset of haemoglobinuria may be determined by quinine. (Giglioli 1932.)

Professor Nocht of Hamburg, in a "Note on Quinine", in the League of Nation's Bulletin, says- "Quinine is not a medicament which has no effect on the human organism. After the prolonged daily use in large doses (for some weeks or more), apart from the well known secondary effects, it produces chronic poisoning, the chief symptoms of which are a lowering of the defensive and immunising capacity to such a degree, that fever and parasites occur, despite the administration of large doses.

In certain circumstances, Quinine may cause more or less copious skin haemorrhages, either in cases of idiosyncrasy, or as a result of the improper chronic use of large doses, or of the prolonged administration of small doses such as are employed, for instance, in Quinine Prophylaxis. In susceptible patients, Quinine may cause haemolysis or serious haemoglobinuria.

In the course of my investigation, I have found that Quinine stimulates to such a degree, a whole series of haemolytic antibodies, in the living organism of the animal and increases their activity so greatly, that even such small doses of haemolytic agents as would
not by themselves, cause intravascular haemolysis or haemoglobinuria, produce these effects when combined with Quinine. Such substances are - for example - haemolytic serum, cobra venom, lysocytine, and bile salts.

It is probable that, in certain cases of Malaria, particularly patients suffering from a chronic infection, haemolytic substances may be found and be activated by Quinine. I cannot admit, however, that it has so far been possible to prove the presence of such haemolysins."

Young says about Quinine- "It has even been said that Quinine is the cause of Blackwater Fever. Veretas (Greece) 1858, originated the theory, and Tomaselli (Italy) and Koch, later supported it. I have never seen any ill effects following the use of Quinine in the ordinary doses required for treatment- twentyfour to thirty grains a day, and in the course of his large experience, Sir Malcolm Watson has seen only one case of idiosyncrasy." (Young 1933).

Cases of Quinine idiosyncrasy must be rare but I have met with numbers of patients who refuse to take Quinine, owing to the extreme discomfort it produces.

It is a favourite device of patients, not to swallow the dose of Quinine, but to keep it in their mouths until they are unobserved, and then spit it out.

The objection is not so much to the taste but to the unpleasant secondary effects. This practice explains a number of those cases of
Malaria, which are supposed to be resistant to Quinine. It is obvious also, that, in patients with chronic Malaria, who are anaemic, and who have drifted into the stage of Malaria Cachexia, large doses of Quinine may precipitate an attack of Blackwater Fever, although it would be very unfair to accuse the drug of being the primary cause of the attack.

The treatment of Malaria with Quinine has been upto the last decade or two, somewhat haphazard. The cessation of fever, and the relief of the actual attack were the results aimed for, so, consequently, the doses were small, and courses of treatment were short. When it was recognised, that, in the treatment of Malaria, the removal of parasites from the blood, and the relief of symptoms, were only a preliminary to the ultimate goal - the prevention of relapses, various observers started investigations with different courses of treatment. The experience gained during the Great War, was also a stimulus to research into the best method of Quinine therapy.

Although oral administration of Quinine has long been the standard method of giving the drug, in recent years, the intravenous and intramuscular routes have had strong adherents, and there has been much discussion as to the relative value of these three forms of therapy.

Intramuscular therapy is not without danger. Quinine salts are protoplasmic poisons, and cause a great deal of pain, when injected under the skin. They also may cause destruction and necrosis of muscle
tissue, which provides a favourable nidus for the growth of the Tetanus Bacillus. There have been, and still are, great differences of opinion as to the advisability of giving Quinine intramuscularly. MacGillchrist stated, as early as 1911, that this mode of Quinine administration should be abandoned. Semple collected ten cases of Tetanus due to intramuscular injections of Quinine, and more recently, Acton and Chopra reported three cases. (Acton 1924).

On the other hand, this form of therapy has had strong adherents. Some observers looked upon it as a sheet and anchor in all obstinate/chronic cases of Malaria. They stated that, with careful asepsis, no bad results were generally observed and disagreed with Sir Ronald Ross who held that intramuscular therapy should be given up (Stephens 1917). Sir Leonard Rogers suggested the substitution of Cinchonine Bihydrochloride for the Quinine salt, in intramuscular therapy. He stated that it was absorbed more quickly, and did not cause local necrosis at the site on injection. (Rogers 1918).

In a discussion on intramuscular injections of Quinine Balfour stated- "There is something to be said for both sides. If proper precautions are taken, the risk of Tetanus may be ignored, while if a suitable salt in adequate dilution be used, necrosis and abscess formation need not be feared. They are indicated in cases which "hang fire," and in pernicious cases when intravenous injections are not indicated.

The intravenous method of giving Quinine, which was first used by Bacelli in 1890, although safer
than the intramuscular, is sometimes attended by alarming symptoms. If the drug is injected too quickly, an immediate fall of blood pressure may take place, resulting in circulatory failure. Thrombosis of the veins may also occur at the site of injection. In a series of one hundred and twenty-four injections, thrombosis of the veins occurred in four (Stephens 1917). Karamchandani in a discussion on intramuscular versus oral administration of Quinine, came to the following conclusions.

1. "Quinine administered orally is as efficacious therapeutically as Quinine by injection.

2. Intramuscular injections of Quinine are very liable to produce local necrosis and suppuration of the tissues.

3. The lesions from intramuscular injections afford favourable sites for the development of Tetanus spores because of the presence of lactic acid in the muscular tissues, and of deep seated pus, if suppuration occurs.

4. When oral administration is impracticable, as in comatose pernicious cases, Quinine should be given intravenously, but this may not be feasible under two conditions— in small children, and in obese patients whose veins are not prominent. Only in these conditions should parenteral injections be given, and the subcutaneous route is preferable to the intramuscular.

5. Dilute solutions should be used—five grains in ten c.c.s saline freshly prepared and sterile. Quinine-acid-hydrobromide is the salt of choice. (Karamchandani 1932).
Stephens (1917) and his co-workers investigated intramuscular and intravenous Quinine therapy, with special regard to the number of relapses which occurred after these treatments. They gave fifteen grains in two c.c.s of water intramuscularly on two consecutive days. Their conclusions were:

"These two injections cause the cessation of febrile paroxysms of Simple Tertian Malaria, and effect the disappearance of all stages of parasites from the cutaneous blood. The action is only temporary, a relapse occurring within two to three weeks."

Their results were the same in Malignant Tertian Malaria. (Stephens 1919).

In an Interim Report on the treatment of Malaria issued by the War Office in 1919, a combination of intramuscular and oral therapy was advocated by Sir Ronald Ross, and pronounced to be most successful by medical officers.

The above authors investigated this form of treatment. Fifteen grains of Quinine Bihydrochloride were given intramuscularly into each Deltoid, with ten grains orally three times a day, totalling sixty grains daily for twelve days. The patients remained in bed throughout treatment. Their conclusions were:

This treatment may be followed by eighty-seven per cent relapses within a post-treatment observation period of sixty days. (Stephens 1918.)

Their conclusions about intravenous therapy were:

In Benign Tertian Malaria, either one or a series of
six injections effect a temporary cure. Relapses occurred after approximately the same period from the end of treatment, whether one or six injections were given. In Malignant Tertian Malaria, neither a single nor a series of injections, caused the disappearance of parasites from the blood (Stephens 1917.)

In one hundred cases of Benign Tertian Malaria treated by Quinine intravenously in doses varying from five to ten grains, for five injections, the cure percentage was eighteen per cent. (Rennie 1921).

In Army Medical practice, intramuscular injections of Quinine are looked upon with disfavour. I have seen deep and extensive abscess formation produced by these injections, and consequently, have avoided them. I have given Quinine intravenously to all cases of Malignant Tertian Malaria with pernicious symptoms, and have never seen any ill effects following these injections. Oral administration is the method of choice, and it is only in special circumstances, that parenteral administration is indicated. Quinine should be injected intravenously in cases heavily infected with the Malignant Tertian parasite, especially in cases with hyperpyrexia or cerebral symptoms. Persistent vomiting may also be an indication for intravenous therapy. Intramuscular injections should only be resorted to in those urgent cases which require immediate treatment, and in which, intravenous injections are impossible.
When it was recognised that the ultimate aim in the treatment of Malaria, was the prevention of relapses, and the permanent cure of the disease, various "Courses" of Quinine were advocated. Anti-relapse therapy, as it was called, was investigated by different workers.

Ross (1918) suggested that the best doses in respect of relapses were - one thousand grains in four weeks, large doses being given during the first days of that period.

Stephens (1918) and his co-workers investigated the following different courses of treatment.

In 1907, Laveran recommended that Quinine Sulphate should be given for two consecutive days weekly, over prolonged periods, in Benign Tertian Malaria. The above workers tried this form of treatment, which gave the following results:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Duration</th>
<th>No. of cases treated</th>
<th>No. of cases relapsed</th>
<th>Percentage cases relapsed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grs.</td>
<td>Weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>8-16</td>
<td>17</td>
<td>10</td>
<td>41.2</td>
</tr>
<tr>
<td>45</td>
<td>8</td>
<td>21</td>
<td>6</td>
<td>28.6</td>
</tr>
</tbody>
</table>

The cases which were observed for less than sixty days were considered relapses, in calculating the maximum percentage.

The above workers concluded that, a dose of fortyfive grains was the best, and all patients were able to take this large dose without difficulty.

They then tried the oral administration of Quinine Sulphate daily over prolonged periods in Benign
Tertian Malaria, with the following results.

(See next page.)

They concluded that, of the various methods of continuous administration, that of grains forty-five was the best. Practically all the cases were able to take a daily dose of twenty to thirty grains for eight weeks or more. When, however, the daily dose reached forty-five grains, it was found that only seven of the nineteen cases were able to complete the full eight weeks course. In the remaining twelve, the treatment had to be stopped owing to tremors and vomiting.

Comparing the results of interrupted and continuous Quinine administration, they came to the following conclusions.

1. Tolerance— A daily dose of forty-five grains is not well borne by all patients, but in no case, did the administration of forty-five grains twice weekly, produce any intolerance; all cases completed the eight weeks course without difficulty.

2. Economy— The interrupted treatment required, over any given period, only two sevenths of the quantity required for the corresponding continuous treatment.

3. Interrupted treatment is preferable to continuous treatment.

The same workers tried the effect of one hundred and twenty grains of Quinine Sulphate orally on two consecutive days only. In five out of fifteen cases, it was impossible to continue the treatment owing to the development of serious symptoms—vomiting,
<table>
<thead>
<tr>
<th>Dose</th>
<th>Duration of treatment</th>
<th>No. of cases treated</th>
<th>No. of cases which relapsed</th>
<th>No. of cases not relapsing, but observed for less than sixty days</th>
<th>Percentage of relapse cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Minimum.</td>
<td>Maximum.</td>
</tr>
<tr>
<td>20</td>
<td>14 to 45</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>60.0</td>
</tr>
<tr>
<td>30</td>
<td>5 to 18</td>
<td>14</td>
<td>10</td>
<td>0</td>
<td>71.0</td>
</tr>
<tr>
<td>30</td>
<td>8</td>
<td>29</td>
<td>24</td>
<td>5</td>
<td>79.3</td>
</tr>
<tr>
<td>30</td>
<td>3</td>
<td>22</td>
<td>17</td>
<td>1</td>
<td>77.4</td>
</tr>
<tr>
<td>45</td>
<td>1</td>
<td>22</td>
<td>17</td>
<td>1</td>
<td>77.4</td>
</tr>
<tr>
<td>45</td>
<td>3 to 8</td>
<td>19</td>
<td>7</td>
<td>3</td>
<td>36.8</td>
</tr>
</tbody>
</table>
deafness, dimness of vision, and collapse, but in no case did the symptoms persist beyond one week. They came to the conclusion that this dose was the maximum amount of the drug which could be tolerated by the average case, and relapses occurred in sixty per cent of the cases who completed the treatment.

An investigation on similar lines was carried out by Rennie (1921), and his co-workers, and their results were as follows.

A. Continuous oral administration.

1. Long course - Quinine Sulphate grains thirty for twenty one days, followed by grains fifteen for ninety days.
   - Number of cases: 76.
   - Cure percentage: 52.6

2. Short course - Quinine Sulphate for ten days, followed by Iron and Arsenic for three weeks.
   - Number of cases: 190.
   - Cure percentage: 42.1

B. Intermittent oral Quinine.

1. Quinine Sulphate grains forty five on two consecutive days for eight weeks.
   - Number of cases: 90.
   - Cure percentage: 18.8

2. Quinine Sulphate on two consecutive days for eight weeks.
   - Number of cases: 113.
   - Cure percentage: 30.

C. Prolonged oral treatment - Quinine Sulphate grains thirty daily for a period of from two and a half to five months.
   - Average percentage of cures: 56.
These results show the intermittent administration to be much inferior to continuous administration, in preventing relapses. Rennie's investigations must be taken more seriously than Stephen's, and are more accurate, as the number of cases on which the latter judged his results, is much too small to be of any value.

The close resemblance between the Malarial paroxysm and anaphylactoid symptoms - protein shock, has been pointed out by various observers. (Rennie 1919 and Abrami 1919). The points of resemblance are -

The sudden onset, the fall by crisis, and the profuse sweating.

The marked fall of blood pressure.

In protein shock, there is a diminution of the alkali reserve - an acidosis.

Sinton (1923) found that the amount of alkali required to make the urine alkaline averaged twice as much in one hundred cases of Malaria, as among fifty normal persons. He found that another point of resemblance between the two conditions, was the leucopenia, with a marked shift to the left of the Arneth Index.

Acting on the above theory, Sinton tried the following treatment. He used two mixtures -

1. Alkaline mixture.

<table>
<thead>
<tr>
<th>Sodium Bicarbonate</th>
<th>grains 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Citrate</td>
<td>grains 40</td>
</tr>
<tr>
<td>Water</td>
<td>to ounce 1</td>
</tr>
</tbody>
</table>

2. Quinine mixture.

<table>
<thead>
<tr>
<th>Quinine Sulphate</th>
<th>grains 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citric acid</td>
<td>grains 30</td>
</tr>
<tr>
<td>Mg. sulphate</td>
<td>grains 60</td>
</tr>
<tr>
<td>Water</td>
<td>to ounce 1</td>
</tr>
</tbody>
</table>
On the morning after Malaria was diagnosed, the patient was given one dose of the Alkaline mixture at 7.30 a.m. and repeated at 9.30 a.m., 11.30 a.m., and 6 p.m. A dose of the Quinine mixture was given half an hour after each dose of the Alkaline mixture. For the following six days, the patient was given one dose of the Alkaline mixture three times a day, followed in half an hour by one dose of the Quinine mixture.

The course of treatment lasted seven days, and the results were excellent,—sixty per cent better than control cases getting Quinine alone. (Sinton 1923).

**QUININE IN MALIGNANT TERTIAN INFECTIONS.**

It has been recognised for a long time that Quinine is more effective in preventing relapses in Malignant Tertian Malaria, than in the Benign form.

Barlow (1915) estimated that one hundred per cent of Malignant infections were cured, if Quinine was administered for one month. Thomson (1917) stated that eighty per cent of these infections were cured by Quinine.

Acton and his co-workers investigated a series of cases of Malaria, at the British Malarial Convalescent Depot, Dagshai, in India, which was started on the twenty-third of March, 1918. Although Malignant Tertian Malaria was very common in the Punjab, very few cases arrived at the convalescent depot, and the above workers came to the following conclusions.—

1. **Quinine is a specific for Malignant Tertian Infection.**

2. In a small experience of thirteen cases of Malignant Tertian Infections, twelve were cured, and only one
relapsed, owing to a short intravenous course. (Acton 1921.) The above workers, with Rennie (1921), later tried the effect of Quinine on a much larger number of Malignant Tertian cases. They gave Quinine Bisulphate in doses of thirty grains a day for three days, followed by fifteen grains daily for one month. In a prolonged course fifteen grains twice a week were given for two more months. The patients were observed for periods varying from three to six months after the completion of treatment. The following were their results:

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Duration of treatment</th>
<th>Relapses</th>
<th>Cure %</th>
</tr>
</thead>
<tbody>
<tr>
<td>116</td>
<td>Less than one month.</td>
<td>116</td>
<td>0</td>
</tr>
<tr>
<td>246</td>
<td>One month.</td>
<td>91</td>
<td>63</td>
</tr>
<tr>
<td>218</td>
<td>Three months.</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

Sinton (1926) came to the following conclusions after the treatment of about eight hundred cases of Malignant Tertian Malaria, contracted in Northern India.

1. If the infection is treated for one week with thirty grains of Quinine daily, combined with alkaline treatment, at least eighty percent will be cured.

2. A week's course of thirty grains daily of Quinine or Cinchona Febrifuge, will probably cure about fifty percent of Malignant Tertian Infections.

3. Patients infected with Plasmodium falciparum are much more easily cured by the same doses of Quinine than those infected with Plasmodium vivax.

After oral administration of Quinine, its concentration in the Portal circulation is much
higher than in the peripheral circulation. The reason advanced for the comparative ease with which Malignant Tertian Malaria is cured by Quinine, was that, as the parasites sporulated in the portal circulation, they were more easily attacked by the higher concentration of the drug in this area. As the concentration of Quinine is low in the peripheral circulation, some of the parasites of Benign Tertian Malaria escape, and are able to carry on the infection.

The Army Medical Authorities in India considered that the continuous administration of Quinine, for a moderate period, was more likely to eradicate a Benign Tertian Infection, and, as a result of researches in the treatment of Malaria during and after the Great War, they instituted for the first time in 1924, a universal method of treatment for the Army in India. They decided that the normal post-hospital course of treatment for Malaria should consist of ten grains of Quinine Sulphate administered daily, preferably in the evening, for a period of eight weeks, followed by a three week's course of Iron and Arsenic tonic. (D.M.S. Circular 1924).

Early in 1924, the Malarial Treatment Centre was instituted in Kasauli, a hill station about six thousand feet above sea level, situated in the Simla Hills. All chronic relapsing cases of Malaria among British Troops were sent there, and researches were carried out, with a view to discovering the most satisfactory treatment for these cases.

As a result of experiments carried out there the Medical Authorities modified the treatment given
above, and, in 1925, adopted the following as a routine treatment for Malaria.

Benign Tertian Cases.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinine Sulphate</td>
<td>ten grains</td>
</tr>
<tr>
<td>Citric acid</td>
<td>thirty grains</td>
</tr>
<tr>
<td>Tr. Orange</td>
<td>qs.</td>
</tr>
<tr>
<td>Water</td>
<td>to one ounce</td>
</tr>
</tbody>
</table>

Routine.
First week - the above mixture three times a day.
Second week - Iron and Arsenic three times a day.
Third week - as in first week.
From the fourth to the eighth week, the above mixture once a day.

Malignant Tertian Cases.
The above mixture for ten days only; then Iron and Arsenic for a week or longer.

As regards the method of administration of Quinine, the Circular stated - "The vast majority of cases are amenable to treatment by the oral route. In cases where oral administration is too slow in its action, as in cerebral cases, or, where, for any reason, the oral route is impracticable, intravenous injection is the most suitable and efficient alternative; not more than five grains should be injected at one time. One half C.C. of Pituitrin, added to the Quinine, is sufficient to prevent collapse." (D.M.S. Circular 1925).

In a later Circular, they stated that the essential factor for success in the treatment of Malaria was, that it should be commenced at the earliest possible moment after the first appearance of symptoms. Recent work showed that the results obtained by late treatment did not compare with those obtained by early treatment. (D.M.S. Circular 1927).
A short account of some other drugs which have been tried in the treatment of Malaria.

The unpopularity of Quinine with a large number of patients, and its failure in many cases to prevent relapses, and completely eradicate Malarial Infection, led to a search for substitutes, which, either given alone, or in combination with Quinine, would prove more effective than the latter drug.

Arsenic, in different forms, was the chief claimant as an anti-Malarial remedy, and various workers studied its effects.

Stephens (1918) and his co-workers tried the effect of a single intravenous injection of N.A.B. in Benign Tertian Malaria. They found that, an intravenous injection in a dose varying from 0.45 to 0.9 of a gram, controlled the febrile paroxysm, and caused the disappearance of parasites from the cutaneous blood, as a rule, within one day. Parasitic relapses occurred on an average, in twenty-one days. The curative effect of a single dose was nil.

They also tried the effect of Liquor Arsenicalis by mouth, fifteen minims daily, and also, preceded by two intramuscular injections of Quinine Bihydrochloride, in fifteen grain doses. They concluded that Liquor Arsenicalis alone, failed to cause the disappearance of parasites, and to control symptoms, and did not suffice to prevent relapses in cases, in which parasites and fever had disappeared, as the result of the intramuscular injections of Quinine.

They obtained the same results in Malignant Tertian Malaria.
Sinton and Eate (1926) tried the effect of the oral administration of STOVARSOL in the treatment of Benign Tertian Malaria. Their conclusions were:

1. The administration by mouth of short courses of Stovarsol to patients suffering from chronic infection with Plasmodium vivax, has not prevented relapses in the majority of cases.

2. Stovarsol, by mouth, in doses of one gram daily, has caused Plasmodium vivax to disappear from the peripheral blood inside forty eight hours in about ninety eight percent of patients thus treated.

3. Our results would seem to indicate that Stovarsol may provoke an increased febrile reaction in some cases of chronic Benign Tertian Malaria.

Sinton (1927) tried SODIUM STOVARSOL intravenously in the treatment of Benign Tertian Malaria. He found that:

"The intravenous injection of Sodium Stovarsol in varying doses up to a total of four grammes during five days, has only produced a true cure in a very small percentage of cases. It will cause the disappearance from the peripheral blood of Plasmodium vivax, and a clinical cure in the majority of cases. The drug does not seem to have as rapid an effect in reducing splenic enlargement, as the Cinchona Alkaloids."

The same worker also tried Quinine and Stovarsol given together, in doses of seven grains of the former, and eight of the latter, twice a day, for twenty eight days. He concluded that Stovarsol was a useful adjuvant to Quinine in the treatment of Malaria, and he obtained similar results with QUININE TROPOSAN, the Quinine salt of 2 oxy-5-acetylamino-phenyl arsenic acid. (Sinton 1928).
TARTAR Emetic was recommended by Sir Leonard Rogers, who stated that it might prove of value in destroying the extra-corpuscular stages of the Malarial parasite thus preventing relapses, and also lessen the infectiveness of the patient by killing the crescents of Malignant Tertian Malaria. (Rogers 1917).

Stephens (1917) and his co-workers, after a series of experiments with this drug, found that:

1. Intravenous injections of Tartar Emetic do not cause the disappearance from the peripheral blood of any stage of the Malarial parasite, whether Plasmodium vivax or falciparum.

2. The injections do not control either the rigors or the fever of acute Malaria.

VON HEYDEN in doses of 0.3 of a gram, intravenously, every third day, for ten injections, was also tried, but with no success. (Large 1926).

Walker (1924), while working with the Swiss Red Cross Expedition in the famine districts of Russia, conducted a series of experiments in the treatment of Malaria with two new drugs, called PER&CRINA 303 and 304. He claimed that the former drug was a specific remedy against Malaria. Peracrina 303 is a compound containing specific albuminates combined with ten per cent Trypanflavine.

Sinton (1927) tried this drug on a number of patients in the Malaria Convalescent Depot, Kasauli. On the first three days of treatment, the patient took six pills daily, each containing 0.5 of a gram. From the fourth to the seventh day, the dose was increased to eight pills daily, and from the eighth to the tenth day, nine
pills daily. From then, the patient took twelve pills a day, and the course lasted one hundred and eight days. It was found that the drug was very uncertain, and Walker's good results were not borne out.

**METHYLENE BLUE** was recommended as a substitute for Quinine.

Thomson (1917) advised a three week's course of Methylene Blue in pill form, twelve grains daily, in patients who were intolerant to Quinine.

Pitschugin (1925) reported success in Benign Tertian Infection in children, with a centigramme of this Dye, for every year of age, three times daily, for a week.

Numerous other drugs and compounds have tried to supplant Quinine as a cure for Malaria, but like the examples quoted above, they have met with little success.

Although these enthusiastic trials of different remedies were unsuccessful, they indicated a definite line of research, and helped in the evolution of the two synthetic anti-Malarial drugs - Plasmoquine and Atebrin.
The search for a synthetic substitute for Quinine went on for about eighty years, until 1924, when Plasmoquine was discovered.

This important discovery was made by Schulemann, Schonafer, and Wingler, at the Elberfield Laboratories, in Germany. They, first of all, experimented with Methylene Blue, and found that, by a slight modification, its anti-Malarial properties were increased. They applied the same modification to the Quinoline Nucleus and by adding a CH-CH3 and CH2 group to the latter compound, evolved Plasmoquine.

The drug was then thoroughly tested by numerous workers. Roehl tried it in Bird Malaria; Sioli tried it on patients suffering from General Paralysis of the Insane, artificially inoculated with Benign Tertian Malaria, and Muhlens and his co-workers tested it, in the Hamburg Institute for Tropical Diseases, on patients suffering from Malaria. (Muhlens 1933).

These, and other tests, showed that, although Plasmoquine had a selective action on the Crescents of the Malignant Tertian Parasite, it had little or no action on the Ring forms and Schizonts, and thus fell far short of the ideal anti-Malarial drug.

Quinine acts on the asexual forms of the parasite, and is supposed to have no action on the sexual forms of Plasmodium falciparum, although Stephens (1919) found, in treating about ninety cases of Malignant Tertian Malaria, with thirty grains of Quinine daily, that Crescents did not persist in the cutaneous blood for more than three weeks.
The action of Plasmoquine on Malignant Tertian Crescents is a very rapid one. Patients suffering from Malignant Tertian Malaria, whose blood contained Crescents, were given 0.04 of a gram of Plasmoquine for five days. The changes in the parasites were observed by the wet cover slip method. On the second day, there was complete inhibition of the female gamete, and a curious partial inhibition of the male, which failed to proceed to exflagellation. On the third day, the Crescents appeared quite inert, and on the fifth day, none could be found. (Manson Bahr 1934).

The failure of Plasmoquine to act on the asexual forms of Malignant Tertian Malaria was a very serious disadvantage, and the manufacturers tried to overcome this defect by combining Quinine in the tablet with Plasmoquine. This product was called Plasmoquine Compound, and it contained 0.01 of a gram of Plasmoquine, and 0.125 of a gram of Quinine, or about two grains. This dose of Quinine was much too small, so a new product called Quino-Plasmoquine was introduced, which contained more than double the amount of Quinine.

Plasmoquine is a tasteless drug, and is made in tablet form. In the early trials, the dosage was much higher than is used now, and it was soon discovered that the drug had to be used with great caution, as it produced severe toxic symptoms in a number of cases treated.

Sioli (1927) reported several cases of poisoning among his patients. One, to whom he had given 0.075 of a gram daily for eight days, was seized with
pains in the abdomen, and passed black urine. His lips were livid, and his blood was the colour of chocolate. Both urine and blood showed the spectrum of Lethaemoglobin.

Manson Bahr (1927) described a case of Methaemoglobinuria after a daily dose of 0.12 of a gram, with a total dosage of 0.4 of a gram. The drug was stopped, and recovery was rapid.

The toxic effects of Plasmoquine are due to the conversion of Oxyhaemoglobin into Methaemoglobin, and the symptoms may arise suddenly, or more often, the onset is less abrupt. Cyanosis of the lips, or gripping pains in the abdomen, are warning signs, and if the Plasmoquine is stopped at once, the symptoms soon pass off. If it be continued, the cyanosis spreads to the palate, gums, and finger nails, the temperature rises, and an attack resembling Blackwater Fever develops, accompanied by destruction of red cells, haemolytic jaundice, and black urine containing Methaemoglobin. The examination of the liver in fatal cases, shows Hepatitis and fatty degeneration, or necrosis. (Fletcher 1933).

Fischer and Weise (1927) examined the cyanosis due to Plasmoquine from the point of view of Methaemoglobinaemia. Cases investigated were given 0.05 to 0.1 of a gram daily by injection for six or seven days. In Benign Tertian and Quartan Malaria, 0.05 of a gram was given orally, twice daily, for four consecutive days a week, the course lasting five weeks. Methaemoglobinaemia was examined in a layer of five per cent blood, four cms. thick, by which could be measured, spectroscopically, any quantity of Methaemoglobin from four per cent upwards.
Of twenty six patients tested daily, Methaemoglobinaemia was absent from one only. In the others, it ranged from four to twenty per cent. The earliest appearance of Methaemoglobinaemia was twenty four hours after the first injection, and the last evidence was ten days after cessation of treatment. Certain experiments suggested that the greater the initial anaemia, the greater the induced Methaemoglobinaemia.

With a daily dose of 0.03 of a gram, ten out of thirteen cases showed Methaemoglobinaemia. With a daily dose of 0.02 of a gram, seven out of seventeen cases showed it. With this dosage, it is held that there is no risk.

The first clinical trial of Plasmoquine in the Army in India, was made at the Malaria Treatment Centre by Sinton and Bird. (1928). All their patients were suffering from chronic Benign Tertian Malaria. The average dose given was, 0.08 of a gram daily, either continuously, or intermittently, with rest days. A compound of Plasmoquine and Quinine, containing 0.1 of a gram of the former, and 1.25 grams of the latter, was also tried in some cases. The following were their results:

1. Effect on relapses: - Of fifty one cases treated with Plasmoquine alone, the relapse rate averaged thirty per cent. Of thirty five cases treated with Plasmoquine Compound, the relapse rate was only eight point five per cent. The combination of Quinine with Plasmoquine, seems to be a distinct advantage.

2. Effect on the duration of Plasmodium vivax in the blood. : - The average duration of parasites in the Plasmoquine series, was 1.71 days; in the Plasmoquine
3. Effect on temperature: - The average duration of fever among the Plasmoquine cases, was .8 days.
   Among the Plasmoquine Compound series: -.3 days.
   Among one thousand one hundred and twenty seven cases treated by different Cinchona Alkaloids: -.31 days.

4. Effect on splenic enlargement: - The action is no more marked than with the Cinchona Alkaloids.

5. Effect on the relapse rate in Malignant Tertian Malaria: - Plasmoquine or the Compound was tried in only fourteen cases. Seventy one per cent relapsed.
   In seven controls treated with Quinine and Alkali, fourteen per cent relapsed.

6. Effect on the duration of Plasmodium falciparum in the blood: - Plasmoquine appears to have little effect on the asexual forms of P.falciparum. It has a distinctive action on Crescents, but they appear again during relapses.

7. Toxic manifestations: - Severe toxic symptoms may follow the use of Plasmoquine, and the margin of safety with the present dosage, seems to be comparatively small. Toxic symptoms appeared most frequently about the fifth day, and were usually, only cyanosis, and abdominal pains of varying intensity. Two cases were very severe.

Further researches were carried out in the treatment of chronic Benign Tertian Malaria, with Plasmoquine and Quinine, by Sinton, Smith, and Pottinger. (1930).

Their conclusions were:

i. The time has not yet arrived when Plasmoquine can be issued for use, except under the constant supervision and control of the Medical Profession.
2. The combination of Plasmoquine and Quinine is better than either drug separately, in the production of a permanent cure in chronic Benign Tertian Malaria.

3. The daily dose of Quinine should not be less than twenty grains.

4. Continuous treatment with Plasmoquine in small doses and Quinine, produces a greater number of permanent cures, than larger doses given by the interrupted method.

5. Doses of Plasmoquine greater than 0.04 of a gram, should not be given, and possibly, 0.03 of a gram or less, will be found to be the maximum safe dose.

6. Plasmoquine treatment should be stopped on the least suspicion of the occurrence of toxic manifestations. It should not be given, or only with extreme caution, to patients suffering from lesions of the liver, kidneys, and circulatory system.

As a result of the above researches, it was decided, in 1929, to try the Quinine Plasmoquine treatment, on a large scale, in the Army in India (D.H.S. Letter 1929). Twenty grains of Quinine, and 0.04 of a gram of Plasmoquine, were given daily, for a twenty-one days course.

Three thousand one hundred and eighty seven cases of Benign Tertian Malaria completed this course, with the following results (Manifold 1931).

**Toxic Symptoms.** Treatment was temporarily withheld for varying periods, owing to the appearance of toxic symptoms, in 21.4% of one thousand two hundred and ninety eight British cases, and 10.2% of one thousand nine hundred and fifteen Indian cases. In the great majority, the symptoms were not severe. Ninety nine percent of all cases completed the twenty one days course.
Epigastric pain occurred in 14.4% British cases, and 7.9% Indian cases. This would be lessened, if the drug could be taken immediately after a meal, or after an alkaline mixture.

Cyanosis occurred in 4.3% British cases, and 0.67% Indian cases. In 80%, it became apparent on, or after the seventh day. In 0.6% British cases, treatment was permanently stopped, owing to the cyanosis.

Dyspnoea was noticed in only two cases.

Vomiting. There were twenty six cases among the British cases, but this was probably due to the Malaria. Jaundice, which was mild, was noticed in two British, and four Indian cases.

Albuminuria occurred in five Indian cases.

There were three cases of Methaemoglobinuria, one of which, died, with an attack resembling Blackwater Fever. Pyrexia responded more rapidly to this treatment, than to Quinine alone.

Relapses. The period of observation was from four to five months. The average relapse rate was 5.2%. In a control series of cases treated with Quinine alone, the relapse rate was 42%.

Dixon (1933), in a report on six hundred cases of Malaria treated with Quinine and Plasmoquine, and observed over a period of two years, made the following observations.

In Plasmodium vivax primary infections, observed over a period of two years, the relapse rate was 4.1%.

In relapse cases, the relapse rate was 4.7%.

Malignant Tertian Malaria was treated with Quinine, thirty grains daily for twelve days, followed by 0.03 of a gram of Plasmoquine daily for five days, and then
ten grains of Quinine daily, for ten days. The relapse rate was two per cent.

Two cases of accidental overdose of Plasmoquine, occurred in 1928. They received 0.32 of a gram for two days. On the third day, deep cyanosis was present. On the fourth day, one case developed incessant vomiting with epigastric pain. On the fifth day, this patient appeared to have a transient attack of Nephritis. The urine contained granular and hyaline casts, with large quantities of albumin, and much haemoglobin. The urine was reduced in quantity. The clinical symptoms suggested an attack of Blackwater Fever.

In 1931, the universal treatment of Benign Tertian and Quartan Malaria adopted in the Army, was twenty grains of Quinine, and 0.03 of a gram of Plasmoquine daily, for twenty one days. The treatment of Malignant Tertian Malaria recommended, was, a short course of Quinine, followed by 0.03 of a gram of Plasmoquine daily, for five days, to kill the Crescents. (D.M.S. Letter 1931).

Amy (1934) reported eleven cases of Haemoglobinuria which had occurred in 1932 and 1933, among Indian Troops stationed in the North West Frontier Province, and among whom, there were seven deaths. All these were cases of Malaria, five of whom had Malignant Tertian Parasites in their blood, five, Benign Tertian Parasites, and one, whose blood was negative. They had all been treated with Quinine and Plasmoquine, the latter in a dosage of 0.03 of a gram daily. The smallest amount of Plasmoquine given before toxic manifestations set in, was 0.06 of a gram, in two days,
and the highest, 2.8 grams, in six days. It was found later, that three of the fatal cases had not been given Quinine.

The diagnosis in these cases lay between Blackwater Fever, and Plasmoquine poisoning. Amy presented the following points against a diagnosis of Blackwater Fever -

1. The Geographical distribution - No case of Blackwater Fever had been reported up to that date, west of Longitude 75 degrees (Amritzar). The North West Frontier is not a Blackwater Fever area.

2. All the patients were Indians. "This fact is dead against a Blackwater Fever hypothesis. Europeans are more susceptible than any other race."

3. Some of the cases showed cyanosis and Methaemoglobin-inuria.

Yorke (1935), in a criticism of Amy's paper, stated that the above points were doubtful, and he failed to discover any reason why the cases should be regarded as other than Blackwater Fever.

The fact that all these cases occurred in one region, the North West Frontier, and five, in the same station (Quetta), is against the theory of Plasmoquine poisoning. Patients all over India were receiving the same dosage, and it is very unlikely that eleven men with an idiosyncrasy to Plasmoquine, would be grouped in one small corner of India.

One theory of the causation of Blackwater Fever is, that it is due to special haemolytic strains of the Malarial Parasite, and, therefore, the epidemiology is governed by the geographical and local distribution of such haemolytic strains. (Giglioli 1932).
If this theory could be accepted, it would support the hypothesis, that the above were cases of Blackwater Fever, due to the introduction of haemolytic strains of the Malarial Parasite, into the North West Frontier. It would seem also, that Plasmoquine, like Quinine, might be the exciting factor in precipitating an attack of Blackwater Fever.

After the occurrence of the above cases, the dose of Plasmoquine for Indian Troops, was reduced from .03 to .02 of a gram daily. No similar cases have been reported since 1934.
ATEBRIN.

The failure of Plasmoquine to affect the asexual forms of Plasmodium falciparum stimulated the search for a drug which would destroy these forms, and therefore be a true substitute for Quinine.

Many compounds were tried, and finally, in 1930, Mietzch and Mauss, working in the Elberfield Laboratories, discovered Atebrin. It was tested in Bird Malaria by Kikuth, and in human Malaria by Sioli, Peter, and others.

Atebrin is a derivative of Acridin, and is a yellow powder, soluble in water. It has a bitter taste, but not nearly so marked as Quinine.

In the tests on Bird Malaria, it was found to affect the asexual parasites, but had very little action on the gametocytes. In human Malaria, it was found to be especially active in destroying the asexual forms of the Malignant Tertian Parasite, as well as the Benign Tertian, and Quartan.

With a single dose of 0.6 of a gram, the pigment of the Benign Tertian and Quartan Parasites becomes aggregated into clumps. The cytoplasm becomes thin and ragged, breaks up, and the nuclear vacuole is distended. The chromatin becomes opened out and diffuse, till finally, only a few lightly stained dots remain. (James 1934).

In Malignant Tertian Malaria, the effect of Atebrin was observed by means of blood culture and the wet coverslip method. The patient was given 0.3 of a gram of Atebrin daily for five days, and the blood was examined daily. On the first day, there was no change in the Ring forms, but on the second day, and after, there was no development in culture. Within four
days, all the Ring forms had disappeared from the blood but the Crescents were unaffected. (Manson Bahr 1934).

Atebrin is excreted slowly from the body, and has, therefore, a cumulative effect. It may be found in the urine for at least a week after the completion of treatment, and in some cases, may persist for a month. Part of the Atebrin which is absorbed, accumulates in the Liver, is excreted in the bile, and re-absorbed by the bowel. (Height 1933).

The treatment recommended for all three types of Malaria, was 0.1 of a gram three times a day, for five or seven days. With the above dosage, toxic symptoms are very rare. Atebrin does not cause the unpleasant symptoms of Cinchonism associated with the use of Quinine, or Methaemoglobinemia, which results from the taking of Plasmoquine. In a small number of cases, it may cause headache, abdominal pains, and a yellowish discoloration of the skin, which is due to the dyeing of the tissues with the drug.

Height (1933), experimenting on rabbits and cats, by oral and intravenous administration of Atebrin found that it caused a local stimulation of tissue, and in higher doses, irritation of the gastro-intestinal tract. It also affected the Nervous System, and especially the Cerebrum, which is stimulated by fatal doses. Intravenous injection caused a short fall of blood pressure, but the Heart was very resistant. A number of cases of "cerebral excitation" have been reported, following the use of Atebrin. The patient becomes mentally excited, and behaves in a foolish, hilarious manner, somewhat resembling alcoholic intoxication.
cation. Green (1934) described two cases, and found that the excretion of the drug was much delayed, Atebrin being absent from the urine on the fifth day of treatment.

Kingsbury (1934) described twelve cases of Psychoses, following the exhibition of Atebrin, after doses averaging thirteen tablets. The average interval between the commencement of treatment and the onset of symptoms, was five and a half days. The average duration of symptoms was one and a half days. He attributed the cause of these symptoms to one of three factors:

1. The condition might be due to the Malaria itself, especially a Malignant Tertian Infection.
2. It might be caused by an individual idiosyncrasy to Atebrin.
3. The drug might liberate toxins by its action on the Malarial Parasites.

The experiments on rabbits by Height have proved that Atebrin, in high doses, excites the cerebrum, and it seems quite likely that, in ordinary dosage, it may cause mental excitement in patients with an unstable nervous system.

Atebrin became available for general use in April 1932, but prior to that, it underwent a prolonged series of clinical tests, especially in the hospitals in Malaya. The Malaya Advisory Board of the Federated Malay States, in its 1932 annual report, made the following observations:

"A few patients complained of epigastric colic, and supra-orbital headache after Atebrin. It did not act so quickly in Sub-tertian Malaria, as Quinine, there-
Quinine was advisable in the first forty eight hours in severe cases. In Sub-tertian Malaria, it might lead to a provocative, in the first forty eight hours. It is superior to Quinine in preventing relapses. In twenty six cases of Benign Tertian Malaria treated with seven days Quinine, more than fifty per cent relapsed within three days. In thirty two cases treated with Atebrin, only one relapsed."

In Malaya, prior to the introduction of Atebrin and Plasmoquine, the relapse rate of Malaria amounted to half of the total number of cases admitted to hospitals. Until then, the treatment given was thirty grains of Quinine for three days, followed by twenty grains for seven days. The patient was then discharged and attended for ten grains of Quinine daily for thirty days. In 1931, a modification of Sinton's method was tried, with the addition of one quarter of a grain of Plasmoquine daily, for ten days. In 1932, the readmission rate rose to alarming proportions, so it was decided to try Atebrin. The results were as follows:

1. Effect on Parasites in the peripheral blood - In Benign Tertian Malaria, the parasites disappeared by the fourth day. In Malignant Tertian Malaria, they persisted for about eight hours longer.

2. Effect on the temperature - In Benign Tertian Malaria, the temperature dropped after two doses in fifty one per cent of the cases, and there was no subsequent rise. In forty two per cent, it dropped after two doses, rose again, but became normal within forty eight hours. In three per cent, the temperature did not drop to normal until after the second day. Three per cent showed a second rise on the third day.
In Malignant Tertian Malaria, all the temperatures reached normal by the third day, but it was a more gradual drop.

3. Haemoglobin Index - The percentage rose by an average of six percent during the Atebrin course.

4. Spleenic enlargement - Seventy seven point four percent with enlargement showed a marked decrease.

5. Relapse rate - In the first series of one hundred and sixty eight Benign Tertian cases, treated with Atebrin alone, the relapse rate was 10.7%.

In the second series of one hundred and sixteen Benign Tertian cases, treated with Atebrin and Plasmoquine, the relapse rate was just over 5%.

In the third series of Malignant Tertian cases, treated with Atebrin and Plasmoquine, there was only one relapse.

6. Toxicity - No toxic symptoms that could be attributed to Atebrin, have been noted in any case.

Skin discoloration became slightly apparent only in a very small proportion of Asians. It was more evident in Europeans.

In over fourteen percent of cases treated with Atebrin and Plasmoquine, abnormal symptoms appeared. Borrowman (1933) compared the results of different forms of treatment in various States in Malaya, with the following results -

1. Short course of Quinine - Quinine Bihydrochloride grains thirty daily, for ten days.

<table>
<thead>
<tr>
<th></th>
<th>Number treated</th>
<th>No. observed over 6 months</th>
<th>No. relapses in 6 months</th>
<th>% relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. Tertian</td>
<td>257</td>
<td>139</td>
<td>129</td>
<td>93</td>
</tr>
<tr>
<td>N. Tertian</td>
<td>155</td>
<td>96</td>
<td>84</td>
<td>87</td>
</tr>
</tbody>
</table>

(Duncan 1933)
2. Long course of Quinine - Thirty grains daily for ten days, followed by fifteen grains daily for three months.

<table>
<thead>
<tr>
<th></th>
<th>Number observed</th>
<th>No. relapses</th>
<th>% treated over 6 months in 6 months</th>
<th>No. relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. Tertian</td>
<td>227</td>
<td>528</td>
<td>180</td>
<td>20</td>
</tr>
<tr>
<td>M. Tertian</td>
<td>470</td>
<td>203</td>
<td>30</td>
<td>12</td>
</tr>
</tbody>
</table>

3. Quinine and Plasmoquine course - Fourteen grains of Quinine, with 0.02 gram Plasmoquine daily for twenty one days.

<table>
<thead>
<tr>
<th></th>
<th>Number observed</th>
<th>No. relapses</th>
<th>% treated over 6 months in 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. Tertian</td>
<td>774</td>
<td>583</td>
<td>10†</td>
</tr>
<tr>
<td>M. Tertian</td>
<td>262</td>
<td>172</td>
<td>51</td>
</tr>
</tbody>
</table>

4. Atebrin course - Atebrin 0.4 grain daily for four days, preceded by two days Quinine.

<table>
<thead>
<tr>
<th></th>
<th>Number observed</th>
<th>No. relapses</th>
<th>% treated over 6 months in 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. Tertian</td>
<td>339</td>
<td>175</td>
<td>21†</td>
</tr>
<tr>
<td>M. Tertian</td>
<td>404</td>
<td>194</td>
<td>10</td>
</tr>
</tbody>
</table>

5. Atebrin and Plasmoquine course.

<table>
<thead>
<tr>
<th></th>
<th>Number observed</th>
<th>No. relapses</th>
<th>% treated over 6 months in 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. Tertian</td>
<td>294</td>
<td>132</td>
<td>6†</td>
</tr>
<tr>
<td>M. Tertian</td>
<td>106</td>
<td>63</td>
<td>3†</td>
</tr>
</tbody>
</table>

The following were his conclusions -

1. The treatment of cases with Quinine only, until the disappearance of clinical symptoms, is useless, either as a means of cure of the individual, or as a sanitary measure.

2. In comparison with three months treatment with Quinine alone, treatment with Quinine and Plasmoquine for three weeks, is forty per cent more effective in curing cases of Benign Tertian Malaria, but is nearly sixty per cent less effective, in cases of Malignant Tertian Malaria.

3. Atebrin is less effective than Quinine, in rapidly removing the clinical symptoms of Malaria, but the
percentage of permanent cures is about four times greater than from a three months course of Quinine.

4. Treatment with Atebrin and Plasmoquine for one week is, in both Benign and Malignant Tertian Malaria, nearly six times as effective in providing permanent cures, than Quinine and Plasmoquine for twenty one days.

Hooper (1933), in a review of the published results obtained with Atebrin in the treatment of Malaria in Malaya, came to the following conclusions -

1. Atebrin is the best drug available for the treatment of all types of Malaria in Malaya.

2. It is as efficacious as Quinine in abating the clinical symptoms of the primary attack of Malaria.

3. It is infinitely superior to Quinine in the prevention of relapses. It may be expected to effect a radical cure in nearly ninety per cent of Benign Tertian, and ninety five per cent of Malignant Tertian cases.

4. The toxicity of Atebrin is low.

5. If Plasmoquine is used, it should not be administered until after the Atebrin course is finished.

Green (1934) found that in treating six hundred cases of Malaria with Atebrin, there were no toxic effects, or unpleasant symptoms. Among one hundred and thirty seven hospital patients, who were given somewhat higher doses, seven cases complained of abdominal pain, which was severe in three. Seven cases showed a yellow discoloration of the skin, which appeared between the first and eighth day after treatment. Four cases complained of headache, appearing from the fourth day of treatment. In all these cases, he found that the excretion of Atebrin in the urine was delayed.
He stated that it was essential to make certain that these symptoms were really due to the Atebrin, and not to the Malaria itself, or other causes.

Although Atebrin is usually given by mouth, in the form of tablets, it is sometimes given intravenously, and intramuscularly.

Eckhardt (1933) found Atebrin in a dose of 0.2 of a gram in five c.c.s of saline, given intravenously, very satisfactory, and he also claimed good results in Malignant Tertian Malaria, by giving a combination of 0.1 of a gram of Atebrin, and 0.01 of a gram of Plasmoquine, intramuscularly.

Recently, a soluble salt of Atebrin, called Atebrin Musonate, has been introduced for intramuscular and intravenous injection. It is supplied in ampoules containing 0.125 of a gram, which is equivalent to 0.1 of a gram of Atebrin, and the adult dose is the content of three ampoules, which is soluble in ten c.c.s of water. Two intramuscular injections are given at an interval of twenty-four hours.

This drug has been used in the Ceylon epidemic of Malaria, and it was found that two intramuscular injections brought the temperature down in the majority of cases, and caused the disappearance of the asexual stages of the parasites (whether Plasmodium vivax or falciparum) within three days.

Somasundram (1935) compared the immediate results of cases treated with two intramuscular injections of Atebrin Musonate, and two intramuscular injections of one gramme each of Quinine Bihydrochloride, followed by Quinine Sulphate, seven and a half grains in a mixture, by mouth, three times a day.
He did not consider that the Atebrin Musonate injections were superior to Quinine, as regards the immediate effects, but could not make any statement regarding the relative frequency of relapses, after the two treatments. The Atebrin Musonate injections were quite painless.

Wright (1935) found that Malaria Parasites disappeared very rapidly after two injections of Atebrin Musonate, especially in Malignant Tertian infections. In eleven Malignant Tertian cases, there were no parasites to be seen after forty eight hours. He also stated that the clinical results were excellent.

The treatment of Malaria with Atebrin was introduced into Army Medical practice, in India, in August 1932. Two forms of treatment were tried -

1. Atebrin 0.1 of a gram three times a day, for five days, followed by Plasmoquine 0.02 of a gram daily for five days.

2. In this form, Atebrin was given for seven days instead of five.

In July 1933, the dose of Plasmoquine for British Troops, was increased to 0.03 of a gram.

A number of alternate cases of Benign Tertian, and Malignant Tertian Malaria, were given the above courses of treatment. (D.M.S. Circular 1932 and 1933).

The results of these treatments were considered very good, as a considerable number of re-infections were included in the relapse percentage, and 1933 was a year of high infectivity, and high primary incidence.

The following lines of treatment were then adopted for the Army in India. (D.M.S. Circular 1934-5).
Benign Tertian Malaria.
Either 1. Quinine grains twenty, and Plasmoquine 0.03 of a gram, for twenty one days, or
2. Atebrin 0.1 of a gram three times a day for seven days, followed by Plasmoquine 0.03 of a gram daily for five days, the dose of Plasmoquine for Indian Troops being 0.02 of a gram.

Malignant Tertian Malaria.
Either the Atebrin-Plasmoquine course, as above, or a short course of Quinine, followed by five days Plasmoquine, to destroy Crescents. More drastic methods of treatment would probably be necessary, in severe cases of this type of Malaria.

Quartan Malaria.
The Atebrin-Plasmoquine course.

Some results of the Atebrin-Plasmoquine course of treatment, are given below:

<table>
<thead>
<tr>
<th>Cases</th>
<th>Relapses</th>
<th>Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases, British and Indian</td>
<td>2303</td>
<td>294</td>
</tr>
<tr>
<td>Benign Tertian</td>
<td>1600</td>
<td>218</td>
</tr>
<tr>
<td>Malignant Tertian</td>
<td>628</td>
<td>71</td>
</tr>
</tbody>
</table>

As was mentioned above, a number of the relapses were really re-infections, so these results are good.
In estimating the effects of different forms of treatment on the incidence of Malaria, in a large community like the Army in India, a number of factors must be taken into account.

1. One of the most important of these factors is, the differentiation between a fresh attack of Malaria, including a re-infection, and a relapse. This is a very difficult problem during the Malarial season, and the statistics from various hospitals must differ considerably, just as Medical Officers differ in their interpretation of Malarial attacks. There is also the danger that the Medical Officer in charge of Malaria Wards, who is also the Anti-Malarial Officer of the Station, may be prejudiced in his outlook, and look upon most of his Malaria cases as relapses, just as the clinician, who is testing a new form of treatment, in which he has great belief, may, in his enthusiasm, label all attacks as fresh. The varying opinions of Medical Officers in different hospitals, and even in the same hospital, on this subject, must influence considerably the Malaria Statistics of the Army in India, and in interpreting them, one should always think of this.

From time to time, a "time limit" has been fixed, to guide Medical Officers in the differential diagnosis of fresh and relapse Malaria. It was once the rule to label as fresh infections, any attack occurring six months after the first attack, all attacks within this period, being relapses. This period of time was elastic, and differed according to the fancy of the Medical Officer. The research workers also differed on this subject, some estimating as "cures",
cases, which had no clinical or parasitological relapse within eight weeks after the cessation of treatment, while others observed their cases for varying periods of from two to six months.

While it is impossible, in some cases, to differentiate between a relapse and a re-infection, the study of certain factors in relation to each case, will assist in attaining a fair degree of accuracy, and in putting the subject on a more scientific basis.

The type of Malaria the patient is suffering from, is a great help. Quartan Malaria is so rare, at any rate, in the Army in India, that a second attack may safely be looked upon as a relapse. Malignant Tertian Malaria is much less likely to relapse than Benign Tertian, especially if it is efficiently treated.

The time of year in which the infection occurs, is a very important factor. By a study of the rainfall, humidity, temperature, and the numbers and types of mosquitoes found, it should be possible to work out the seasonal incidence of Malaria in any particular station.

Thus, during the cold winter months, from December to April, in the North of India, during which, there are very few mosquitoes found, and the temperature is too low for parasites to breed, all Malarial attacks could be called relapses. There is one exception to this rule. A person who habitually takes small doses of Quinine during the Malarial season, may have a delayed primary attack during these Winter months.

Then, the incidence of Malignant Tertian Malaria is fairly definite, and can be worked out with a fair degree of accuracy in any station. In most stations in
India, this type of infection occurs during the Autumn months - August to November, and attacks occurring from December to June or July, may be looked upon as relapses.

During the height of the Malarial season, it is a difficult problem to decide whether an attack is a re-infection or a relapse, in a patient who has had Malaria sometime previously, but a study of various factors should help one to make a fairly accurate decision. If, in the patient's Regiment, a number of known fresh cases of Malaria occur at the same time, it is likely that he is suffering from a re-infection. A study of the blood smear may also be of some help. In a relapse case, the parasites are usually fairly numerous, and Gametocytes are present, whereas in a fresh case (including a re-infection) parasites are scanty, and Gametocytes are not commonly seen, in the early stages of the Fever.

The old rule that, if the spleen is definitely enlarged, and easily palpable, the attack must be a relapse, is not a reliable one. The spleen may be markedly enlarged in a fresh attack of Malaria, although it may be accepted that the chronically enlarged spleen is usually a sign of chronic relapsing Malaria.

A discriminating study of the above points in any case will be of great assistance in arriving at a reliable decision.

2. Another important factor affecting the incidence of Malaria in a community, is the type, and extent of Anti-Malarial work carried out in that community. The mosquito proofing of barracks, and the sending of troops to the "hills" during the Malarial season, lower the Malaria incidence considerably.
3. Climate is another important factor. A good climatic year, with little rainfall, results in a greatly decreased number of mosquitoes, and consequently, a lessened incidence of Malaria.

4. A Frontier war occurring during the Malaria season, during which large numbers of troops are moved about with inadequate protection from the mosquito, causes a large increase of Malaria cases.

Taking into account all the above factors, a study of the statistics shown on the next page, is interesting.

It will be seen that there was a marked fall in the Malaria incidence in the year 1928. The total number of Malaria cases in that year, was a little more than fifty per cent less than in 1926. If the new drugs, Atebrin and Plasmoquine had been in general use in the Army, during the two preceding years, enthusiasts would probably have pointed to the year 1928 as a record year, and acclaimed these drugs as a great success.

But Plasmoquine was not in general use in the Army, until 1929, and Atebrin, three years later, so they could not have been responsible for this marked decrease in the Malaria incidence.

The following factors were responsible for 1928 being a record year.

There was very little rainfall throughout India, and therefore, climatic conditions were against the mosquito.

A large number of barracks were mosquito proofed in that year, and major anti-Malarial measures had been
<table>
<thead>
<tr>
<th>Year</th>
<th>Strength</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>1922</td>
<td>20,186</td>
<td>2591</td>
<td>684</td>
<td>910</td>
<td>3</td>
<td>3937</td>
<td>970</td>
<td>1508</td>
<td>17</td>
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<tr>
<td>1923</td>
<td>21,139</td>
<td>3479</td>
<td>836</td>
<td>585</td>
<td>10</td>
<td>3950</td>
<td>783</td>
<td>174</td>
<td>8</td>
<td>30</td>
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<tr>
<td>1924</td>
<td>58,014</td>
<td>3293</td>
<td>748</td>
<td>440</td>
<td>21</td>
<td>6133</td>
<td>661</td>
<td>769</td>
<td>9</td>
<td>18</td>
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</tr>
<tr>
<td>1925</td>
<td>54,378</td>
<td>2228</td>
<td>543</td>
<td>281</td>
<td>8</td>
<td>4738</td>
<td>479</td>
<td>785</td>
<td>9</td>
<td>33</td>
<td>9,124</td>
</tr>
<tr>
<td>1926</td>
<td>56,498</td>
<td>2851</td>
<td>926</td>
<td>484</td>
<td>9</td>
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<td>404</td>
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<td>55,632</td>
<td>2914</td>
<td>587</td>
<td>318</td>
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<tr>
<td>1929</td>
<td>55,626</td>
<td>2554</td>
<td>1293</td>
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<td>3</td>
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<td>328</td>
<td>1</td>
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<td>1930</td>
<td>55,424</td>
<td>2361</td>
<td>429</td>
<td>409</td>
<td>19</td>
<td>2524</td>
<td>190</td>
<td>280</td>
<td>2</td>
<td>1</td>
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<tr>
<td>1931</td>
<td>55,336</td>
<td>1536</td>
<td>818</td>
<td>281</td>
<td>11</td>
<td>1615</td>
<td>121</td>
<td>186</td>
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</table>
carried out during the preceding year.
A much larger number of troops was sent to the "hills" during the Malarial season of 1928.

But, studying the "table" further, it will be seen that the year 1932 was even better than 1928, and a number of factors militated against a good Malarial in 1932.

Climatic conditions were bad, as the rainfall was fairly abundant over the whole country. Grants were reduced, and major engineering anti-Malarial work came to a standstill.

Owing to civil outbreaks, many more troops were kept in the "plains" during the Malarial season than in 1928.

Some other explanation of the marked fall in the incidence of Malaria, must be sought for, and it is evident that Plasmoquine, which was in general use during the two preceding years, must have played some, if not the major part, in this.

The average relapse rate for the whole of India over the quinquennium 1927-1931 was 277 per 1000.

In 1932, after the introduction of Plasmoquine, the relapse rate varied from 30.5 to 40.5 per 1000.

Although Medical Officers may have diagnosed fewer cases as relapses, in their enthusiasm for the new drug, such a marked fall in the relapse rate could not be explained by that.

The incidence of Malaria in 1933 was higher than 1932 and the enthusiasm of the upholders of the new synthetic drugs, was slightly damped.

The following are the figures for British Troops, and it will be seen that, although the primary incidence
is higher, the relapse rate is lower.

Malaria rate per 1000.

<table>
<thead>
<tr>
<th>Fresh cases</th>
<th>Relapse cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1932</td>
<td>1933</td>
</tr>
<tr>
<td>49.2</td>
<td>79.1</td>
</tr>
</tbody>
</table>

The conditions in 1933 militated against it being a good Malarial year, as the rainfall was in great excess, and the Mohmand Operations on the North West Frontier involved the moving about of a large number of troops.

The opinion has been expressed that, if the new drugs had not been in use, the year 1933 would have been a very bad one indeed.
THE PROPHYLAXIS OF MALARIA.

The term "prophylactic Quinine" has been used up till quite recently to signify the giving of Quinine in small doses, either continuously, or intermittently, to prevent an attack of Malaria.

With the advent of the new synthetic anti-Malarial drugs, and a more exact knowledge of their action, the term prophylaxis has been put on a more scientific basis.

First, there is the prophylaxis against Malarial Sporozoites injected by the infected mosquito. This has been termed Causal Prophylaxis.

Quinine, Plasmoquine, and Atebrin, are not causal prophylactics, as they have no action on the primarily injected sporozoite. Plasmoquine, in toxic doses, may delay the attack of Malaria for a considerable period, but in the ordinary dosage of .03 of a gram, it has no action as a causal prophylactic.

Clinical Prophylaxis. This consists merely in the suppression of the immediate clinical symptoms of malaria, and is not really a prophylaxis against Malaria. The usual practice is to give a daily dose of ten grains of Quinine to people who are occupying a bad Malarious area. This daily dose of Quinine helps to ward off the symptoms of the Malarial attack, but does not eradicate the infection.

In the Army, the term "prophylactic Quinine" has been abandoned, and it is now called "delayed action Quinine". Young (1933) carried out a large scale experiment with "delayed action Quinine" in Northern India.
His conclusions were :-
1. Delayed action Quinine effected a considerable reduction in the sickness, due directly, or indirectly to Malaria.
2. No ill-effects were noted, and ability for work or games was not affected.
3. The treatment of cases of Malaria, the severity of the attack, or the duration of stay in hospital, were not prejudicially affected to any material extent by previous delayed action Quinine.
4. There was no evidence that delayed action Quinine suppresses Malaria, nor that suppressed Malaria showed itself after the cessation of Quinine.
5. There was no evidence of the production of a Quinine fast parasite.
6. It should only be resorted to in epidemic years - ten grains five times a week from mid September to mid November.

Delayed action Quinine, as a routine measure, has fallen into disfavour in the Army in India, but it is very useful if troops have to enter a highly malarious area - for instance - in a campaign on the North West Frontier.

The value of Atebrin in delaying the clinical symptoms of Malaria, has not been proved, but, because of its cumulative effects, it might be unsafe to give it for long periods.

Gametocyte Prophylaxis. By this term is meant, the prevention of the spread of Malaria by Anopheline mosquitoes, resulting from the sterilization of the blood of the sexual forms of the Malarial Parasite.
Plasmoquine is the ideal gametocide, especially in Malignant Tertian Malaria, but, to rid a community of Malaria by this means, would be a very difficult problem. It might reduce the incidence of Malaria in an isolated community, if all the Crescent "carriers", including children, could be found, and treated with Plasmoquine, and the community would have to be under strict control. This ideal state is not often found, and in the Army, with its constant moving about, and fresh infections, gametocyte prophylaxis is not a workable proposition. It would also be impracticable to give Plasmoquine for any length of time, without the strictest supervision, because of its possible toxic effects.
MALARIA IN KOHAT.

Kohat is a military station in the North West Frontier Province, about forty miles south of Peshawar. The garrison consists of about 5000 Indian Troops, and 500 British.

The incidence of Malaria differs from year to year, and depends to a great extent on the rainfall, relative humidity, and temperature. In 1929, there were 2333 admissions for Malaria, in 1934, 589, and in 1935, 600.

The breeding of mosquitoes usually starts in April, and reaches its highest peak in August. The following table shows the different species of Anopheline Mosquitoes found breeding during the different months of 1935, and it will be seen that there was a steady increase from April to August, then a decline, until in November, no breeding places were found. This agrees with the number of mosquitoes caught during the year. No catches were made during the three months January to March, but during May, they started to appear, and the total catches during the period April to June were 3294, Anopheles stephensi, and Anopheles culicifacies, being the predominating mosquitoes. In the July to December period, the number of mosquitoes caught reached 11,351, the chief being Anopheles stephensi, Anopheles culicifacies, and A.
A study of the following charts gives a good picture of the incidence of Malaria in Kohat.

Chart A shows the number of Larvae breeding places found during 1935, with the rainfall, humidity, and temperature. It will be seen that, with the rise of relative humidity, and temperature, the number of breeding places increased. The mean maximum and minimum temperatures, and the relative humidity reached their peak in August, and in that month, the largest number of breeding places was found.

Chart B gives a comparison between the adult catches of mosquitoes, and the incidence of Malaria. Anopheles stephensi was caught in large numbers from May to August, and was responsible for the Benign Tertian Malaria during these months, while A. culicifacies, and A. listonii, which predominated during the months September and October, were responsible for the Malignant Tertian infection.

In Chart C, is shown the different types of Malaria, and the months in which they occurred. There were a few fresh cases of Benign Tertian Malaria in April and May, and June, but the real incidence commenced in July, and was highest towards the end of August, and September. Fresh cases of Malignant Tertian Malaria commenced in September, and reached their peak in
October.

Chart D shows the incidence of Malaria in Kohat, from 1931 to 1935.

The number of cases of Malaria admitted to the Military hospital at Kohat, in 1935, was 601. Of these, 233 were Benign Tertian Malaria, 232 Malignant Tertian, one was mixed Benign and Malignant Tertian, two were Quartan, and seventy one were clinical. The cases diagnosed clinical, were those which resembled Malaria clinically, but, in whose blood smears, no parasites were found. In this thesis, I propose to omit these clinical cases, and also the two Quartan infections, and describe the results of treatment in the Benign and Malignant Tertian cases.

The scheme of treatment adopted for these cases was as follows.

1. BENIGN TERTIAN MALARIA.

   A. 161 cases were treated with Atebrin 0.1 of a gram three times a day for seven days, followed, after three days' interval, by Plasmoquine 0.03 of a gram for five days, the dose of Plasmoquine for Indian patients being only 0.02 of a gram.

   B. 132 cases received Quinine, twenty grains, with Plasmoquine 0.02 of a gram, daily for twenty one days.

2. MALIGNANT TERTIAN MALARIA.

   A. 177 cases were treated as follows: - They were
CHART TO SHOW RATIOS PER 1000 OF STRENGTH.

- ADMISSIONS
- AVERAGE CONSTANTLY SICK

LARVAE FROM NUMBER OF BREEDING PLACES.

1. MEAN MAXIMUM TEMPERATURE
2. MEAN MINIMUM TEMPERATURE
3. MEAN RELATIVE HUMIDITY
4. RAINFALL IN INCHES

BY MONTHS
BY WEEKS
BY MONTHS

Shown thus:

Shown thus:

MEAN TEMPERATURE,
MEAN IQR.
MEAN IQR.
MEAN IQR.

MEAN RELATIVE HUMIDITY.
RAINFALL IN INCHES.

PER MEEK.

EMPIRE

Novenber
December

1935

Holoscinographed at the Survey of India Offices, Dehra Dun.
given Quinine twenty grains daily for twenty one days
with Plasmoquine 0.02 of a gram daily, for the last
five days, to destroy crescents.

B. 55 cases were given the Atebrin Plasmoquine
course as above.
Pernicious cases of Malignant Tertian Malaria, and
those with persistent vomiting, were given Quinine
intravenously. No intramuscular injections were given.
Quinine Sulphate was used for oral treatment, and
Quinine Bihydrochloride, in a dose of seven and a half
grains, for intravenous injection.

In judging the efficacy of the different forms
of therapy, particular attention was paid to the
clinical aspects of treatment. Some observers have
found that Atebrin is much slower in reducing the
temperature in Malaria, than Quinine, while others
have noted that it might have a provocative effect
on the temperature in Malignant Tertian Malaria.
The average time taken for the temperature to become
normal, and remain normal, after the commencement of
treatment, was noted in the above series of cases.
The average length of stay in hospital of patients
under the different treatments, was also noted, as
this is of importance to the Army.
All the patients were carefully observed for any
toxic symptoms arising from Atebrin or Plasmoquine,
and the urines of three hundred patients were examined spectroscopically for methaemoglobin, at the termination of the course of Plasmoquine. The blood and serum of patients who exhibited cyanosis, or complained of abdominal pain, were also examined with the spectroscope for methaemoglobin.

In estimating the relapse rate after the different treatments, a study was made of the various points outlined above regarding the differentiation between relapses and reinfections, and an attempt was made to obtain the true relapse rate. Fifty per cent of the cases were observed for a period longer than six months, some over a year, while the observation period of the remainder was less than six months, the majority being four.

The following are the results of the different treatments.

1. The average time taken for the temperature to become normal and remain normal after the commencement of treatment.

A. BENIGN TERTIAN MALARIA.

1. Atebrin Plasmoquine course 1.34 days.
2. Quinine Plasmoquine course 0.65 days.

B. MALIGNANT TERTIAN MALARIA.

1. Atebrin Plasmoquine course 1.8 days.
2. Quinine 0.77 days.
2. The average length of stay in hospital.

A. BENIGN TERTIAN MALARIA.
1. Atebrin Plasmoquine course 9.6 days.
2. Quinine Plasmoquine course 8 days.

B. MALIGNANT TERTIAN MALARIA.
1. Atebrin Plasmoquine 9 days.
2. Quinine 8.3 days.

2. Toxic manifestations.

A. Plasmoquine. None of the Indian patients receiving a dose of 0.02 of a gram showed any toxic symptoms after Plasmoquine, although a large number received a twenty-one days' course. Among the British patients receiving a dose of 0.03 of a gram, cyanosis of the lips was observed in five cases, and one complained of griping pain in the abdomen. These patients were only on five days Plasmoquine. The blood, serum, and urine of the above cases were examined spectroscopically for methaemoglobin, but none was detected. The spectroscopic examination of the urine of three hundred cases, after Plasmoquine, also proved negative. The cyanosis in the above cases appeared at the end of the five days Plasmoquine course.

B. Atebrin. Although not a toxic manifestation, yellow discoloration of the skin was observed in a large number of cases after Atebrin. In fact, it was
possible, after a little experience, to detect the cases who had been given Atebrin, and to distinguish them from the Quinine Plasmoquine group. In the majority of cases, the yellow discoloration was very slight.

As regards toxic symptoms, one had to be very careful in distinguishing between those due to Atebrin, and those caused by the attack of Malaria itself. Atebrin definitely took a longer time to control the temperature than Quinine, and therefore, patients receiving Atebrin seemed much worse in the first two or three days of the disease, than patients receiving Quinine, or Quinine and Plasmoquine.

In cases suffering from disease of the liver or kidneys, Atebrin seemed to have no effect on the temperature at all. In two patients with Malignant Tertian Malaria of a fairly mild type, but who gave a history of previous attacks of Hepatitis, which was aggravated by the attack of Malaria, the symptoms became so much worse and the temperature so high, after the first three doses of Atebrin, that an intravenous injection of Quinine had to be given. This effect may not be due to any toxic property of Atebrin, but to the failure of the liver, owing to the Hepatitis, to excrete Atebrin into the bowel after absorption. To produce its curative effect, Atebrin
may be broken down in the liver, and some other product formed, which is excreted into the bowel and re-absorbed. This would explain its failure when the liver is put out of action, either by an old standing affection, or a Hepatitis due to the Malaria itself. To support this hypothesis, it was noted that, when Quinine had controlled the temperature in the above two cases, and the attack of Hepatitis had cleared up, the administration of Atebrin for seven days caused no further ill-effects.

In five other cases, three Malignant and two Benign Tertian infections, Atebrin took such a long time to control the temperature, that three days' Quinine had to be given, after which the Atebrin course was continued.

In one patient who complained of severe abdominal pain after two days' treatment with Atebrin, a dose of castor oil caused the pain to disappear, and the Atebrin course was not interrupted.

Two patients complained of slight giddiness towards the end of the Atebrin course, but there were no cases of mental excitement or psychoses.

In one patient suffering from Nephritis, Atebrin had to be stopped, owing to persistent vomiting, and Quinine substituted.

The majority of patients preferred Atebrin, and were
delighted to escape the unpleasant manifestations of cinchonism associated with Quinine.

4. RELAPSE RATE.

A. Benign Tertian Malaria.
   1. Atebrin and Plasmoquine course.
   Of 161 cases who completed this course, eight relapsed, a percentage of 4.9.
   2. Quinine and Plasmoquine course.
   Of 132 cases who completed this course, five relapsed, a percentage of 3.7.

B. Malignant Tertian Malaria.
   1. Atebrin and Plasmoquine course.
   Of 55 cases who completed this course, none relapsed.
   2. Twenty one days' Quinine followed by five days' Plasmoquine.
   Of 177 cases who completed this course, six relapsed, a percentage of 3.3.
Temperature charts of Benign Tertian Malaria treated with Quinine and Plasmoquine. These and the following charts show when the treatment was commenced.
Temperature charts of Benign Tertian Malaria treated with Atebrin followed by Flasmoquine.
Temperature charts of Malignant Tertian Malaria treated with Quinine followed by Plasmoquine.
Temperature charts of Malignant Tertian Malaria
treated with Atebrin followed by Plasmoquine.
In this thesis, I have attempted to describe stages in the evolution of the treatment of Malaria, starting with a short historical account, then describing the results of treatment with the various Cinchona Alkaloids, and the substitutes which have tried to replace Quinine, and ending up with a description of the new synthetic drugs.

It was evident, from a study of the results of various workers, that the Cinchona Alkaloids were equally effective in reducing the temperature, and alleviating the symptoms, of the Malarial paroxysm. Of the Cinchona Alkaloids, Quinine was found to be the most reliable, and probably the least toxic. For over one hundred years, Quinine remained the sheet anchor in Malaria, and its reputation was well deserved. It quickly relieved the attack of Malaria, with its unpleasant symptoms, and in a considerable number of cases, eradicated the infection, if administered over a fairly prolonged period. In preventing relapses, and curing the disease, the continuous method of giving Quinine for a month or longer, was found to be superior to the short and interrupted courses.

It soon became evident, however, that Quinine suffered from three disadvantages. It failed to eradicate the
Malarial infection, in a large number of patients, who continued to suffer from relapses at short intervals, in spite of intensive courses of the drug. Its action on the sexual forms of the Malarial parasite, especially Plasmodium falciparum, was very slow, and therefore, it did not prevent the spread of infection by the mosquito. It was also distasteful to the majority of people, partly because of its bitter taste and also, owing to its unpleasant effects. Some people even insisted that they would prefer to suffer from Malaria, than endure the depressing symptoms of cinchonism. This was an unsatisfactory state of affairs, as numerous sufferers from Malaria were driven to experiment with proprietary preparations, a large number of which were useless. It also stimulated research workers to discover a substitute for Quinine but although a number of drugs were discovered, the chief being Arsenic, which would alleviate the Malarial paroxysm, and drive the parasites from the blood, they were all proved to be much inferior to Quinine.

The discovery of Plasmoquine, about ten years ago, marked the first real advance in the therapeutics of Malaria, since the time of the Cinchona Alkaloids. It was found to destroy the sexual forms of the Malignant Tertian parasite very quickly, a great
advantage over Quinine, but its failure to act on the asexual forms of the same parasite, and its toxic properties, prevented it from being a real substitute. But it was also discovered that, when given with Quinine in small doses, in Benign Tertian Malaria, it was much more successful in eradicating the infection and preventing relapses, than when the latter drug was given alone. The results of various workers bear this out, and my own results agree.

In the third general report of the Malarial Commission of the League of Nations, dealing with the therapeutics of Malaria, the opinion was formed that the combination of Quinine and Plasmoquine was of doubtful value. The Report stated that the mixture of Quinine and Plasmoquine does not form a new compound in the stomach, but that each drug exerts its specific action, and therefore the Commission did not see how the administration of both drugs could be more effective in preventing relapses in Benign Tertian Malaria, than Quinine alone.

There is no evidence that a new compound is not formed after absorption of both drugs, and the results of a number of workers prove that the combination is very effective in preventing relapses in Benign Tertian Malaria.

The Malaria Treatment Centre in Kasauli, to which all
the chronic relapsing cases of Malaria among British troops were sent, and which always accommodated two hundred patients, with a long waiting list, has had to close down since the introduction of Plasmoquine. The patients who relapsed at short intervals, some even in the middle of the Quinine course, have practically disappeared from the British Army in India, and there is no longer any necessity for a treatment centre. The toxicity of Plasmoquine was a very serious objection, but in small doses of .02 of a gram, it is effective and non-toxic. My own results show that in a dose of .03 of a gram, it produced cyanosis in quite a large percentage of British patients, while in Indian patients receiving .02 of a gram, no toxic symptoms were observed, although the latter received a twenty one days' course. I consider that the dose of Plasmoquine for British patients should also be reduced to .02 of a gram. I think that the margin of safety with a dose of .03 of a gram, is small, although no methaemoglobin was detected in the blood or urine of the patients exhibiting cyanosis. It is much more satisfactory to have a wider margin of safety with a drug which is used so universally.

Atebrin, which was discovered some years later, was the next advance towards the ideal anti-Malarial drug. It was found to destroy the asexual forms of
Plasmodium falciparum, P. malariae, and P. vivax, but has very little action on the sexual forms. It was also discovered that it was very effective in reducing the relapse rate in Benign Tertian Malaria, especially if it was followed by a short course of Plasmoquine. It is a relatively non-toxic drug, and is agreeable to take, without the unpleasant effects of Quinine, and the course of treatment is a short one, a great improvement on the prolonged Quinine course. My results show that it is very effective in preventing relapses, and also, that its toxicity is low. But it is not the ideal anti-Malarial drug. It has two disadvantages. It has very little action on the sexual forms of the Malarial parasites, and it is very slow in its action, which in a disease like Malaria, especially the type caused by the Malignant Tertian parasite, is not to be desired.

Atebrin Musonate intramuscularly acts more quickly than Atebrin given orally, but there is no evidence that it is better than Quinine given orally, and treatment by injection of a widespread disease like Malaria is not ideal.

The ideal anti-Malarial drug would be one combining the properties of Atebrin and Plasmoquine, with the rapidity of action of Quinine, and also be of low toxicity.
The Malaria Commission of the League of Nations, in their third General Report, recommended the following treatment for ordinary cases of Malaria. They said that the patient should be allowed to have two or three rigors, before treatment was commenced, and then, only a very short course of Quinine should be given. This treatment should be repeated at each relapse, and Quinine and Atebrin might be alternated. They recommended this treatment on the theory that the giving of drugs too quickly, destroys immunity. Although there is a lot to be said for this, their treatment has great disadvantages, especially in the Army. A disadvantage from the patient's point of view is that he has to suffer the unpleasant symptoms of the Malarial paroxysm longer than is necessary. In the ordinary Benign Tertian infection, it is perhaps safe to allow a patient to have a few rigors, but it is never safe to dally with a Malignant Tertian infection, and if a large number of blood smears have to be examined, there may be a mistake made in the type of infection present, or there may be a mixed infection, which is not diagnosed. The number of relapses during the above treatment would, in addition to being an extra expense to the Army because of the larger number of admissions to hospital, seriously interfere with the training of
troops.

In coming to any conclusion about the best treatment of Malaria, it must not be lost sight of that there are a number of factors which influence the therapeutic action of anti-Marial drugs. The species of parasite, and the particular geographical race or strain of the same species, affect considerably its virulence. For instance, the Rome strain of the Malignant Tertian parasite is much more virulent than the Indian strain, and requires about eight times as much Quinine to control the infection caused by it.

The dose of infection, and the degree of natural or acquired resistance to Malaria possessed by the patient, also influence the therapeutic action of drugs.

So, in suggesting a scheme of treatment of Malaria for the Army in India, it is recognised that the same treatment might not be so successful in some other part of the world, where a different strain of parasite has to be contended with.

For **BENIGN TERTIAN MALARIA**, I consider that the Atebrin Plasmoquine is the best - Atebrin 0.1 of a gram three times a day for seven days, followed, after three days' interval, by Plasmoquine 0.02 of a gram daily for five days. If the infection is a severe
one, twenty grains of Quinine should be given daily for three days, before Atebrin is started.

For **MALIGNANT TERTIAN MALARIA**, I advise the same treatment.

For pernicious cases, or if there is persistent vomiting, an intravenous injection of seven and a half grains of Quinine Bi-hydrochloride in ten cc. of freshly distilled water, should be given, and intramuscular therapy resorted to, only when an intravenous injection is impossible - in babies, or in patients whose veins are difficult to find.

For **QUARTAN MALARIA**, the Atebrin Plasmoquine is suitable.

Atebrin and Plasmoquine must always be given after meals, and never on an empty stomach.

The treatment should be preceded by a dose of Calomel three grains at night, followed by a saline in the morning.

Quinine will still continue to hold a place in the treatment of Malaria, and will not be relegated to the background, until a drug is discovered which is superior to Atebrin and Plasmoquine, and combines the action of the old and the new.
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