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MALARIA WITHOUT QUININE

ROBERT A. LEHMER

SENIOR THESIS PRESENTED TO THE COLLEGE
OF MEDICINE,
UNIVERSITY OF NEBRASKA, OMAHA, 1943

Any progressive man of Medicine, whether he be expertly schooled and exquisitely trained or for the first time seated in a freshman Anatomy lecture, is still a "Student of Medicine".

Such men are cognizant of the fact that this second World War is now and will continue to throw many burdens on the hypothetical shoulders of the Medical Profession; both in the guise of Supply and Demand of the present and in that of complicating changes necessary in the practice of medicine when our boys come back, accompanied by diseases (new or forgotten) and in the need of completely rearranged medical services (geographically).

In the last war, malaria took first place among the diseases responsible for casualties and our clever enemies took first advantage of this bit of knowledge, quickly acting to take the Netherland East Indies. When this conquest was accredited, we found that the source of practically the entire world supply of quinine was lost to the United Nations.

With Japan holding fast to the supply house of the only successful drug intimately known to the therapy of malaria there were only two avenues open for solution: reconquest of the said losses or substitution of a new and equally effective method of therapy which did not depend on any drug not easily obtained from raw materials readily accessible within our own possessive boundaries.

It is with this modern problem of Supply and Demand that we shall attempt to deal by presenting a survey of the literature to date, giving both sides of the various appraisals, and trimming repetitious articles into one sequential story.

First in line, however, to a working knowledge of any subject is a short history of the principal factor, which in this case is the disease malaria--so to those readers who would not care for the repetition of a spicey, different, and more descriptively, a "table-talk" type of history, we say that

the cold, bare facts begin with the article entitled, "Mosquitoes".

HISTORY (1)

In current usage during the past century the word malaria has come to designate any member of a group of chronic infections produced by several species of protozoan parasites belonging to the family of plasmodidae. The human infections are attributable to three or more species of these parasites, which for precision should be distinguished by the name of the causitive parasite as falciparum malaria, vivax malaria, and quartan malaria.

The origin of the term malaria is from the Italian, "mal" meaning bad, and "aria" meaning air, as well as the term miasma which designated a noxious exhalation in old terminology. These terms were used to designate the supposed exciting agent of these as well as other diseases.

In just this sense, malaria was introduced into English literature by Mac Culloch

(1829) who stated: "It has long been familiar to physicians that there was produced by wet lands, or by marshes and swamps, a poisonous and acriform substance, the cause, not only of ordinary fevers, but of intermittent ones and to this unknown agent of disease the term 'marsh miasma' has been applied...This is the unseen, and still unknown poison to which Italy applies the term that I have borrowed, 'malaria'". One of the last expressions on the old viewpoint was afforded by the following quotation from Sternberg (1884): "The various types of intermittent and remittent fever which are cured by quinine are by common consent recognized as due to malaria poisoning, and...we must insist that the prevalence of periodic fever be taken as the test of the presence of malaria."

It is unfortunate for students of modern medicine that they know little of the old terminology and are thus slightly, if at all, conversant with the old writers. For just this purpose with regards myself and other

readers, let us here present some synonymi:

Vivax malaria: tertian fever, benign tertian fever, simple intermittent fever, paroxysmal fever, tertian ague, chills and fever, fever and ague.

Quartan malaria: quartan fever, quartan ague, simple intermittent fever, paroxysmal fever, chills and fever.

Falciparum malaria: tertian fever, sestivo-autumnal malaria, malignant tertian fever, remittent fever, (including bilious, congestive and malignant types), continued malaria fever, pernicious fever, congestive intermittent fever, pernicious intermittent fever, congestive fever, congestive chills.

The diagnosis of remittent fever has been applied to many cases of typhoid, while yellow fever has masquaraded as bilious remittent fever. Regarding the history of immunity, Kalm (1770) in speaking of "fever and ague" in southern New Jersey said, "Strangers who arrive here are commonly attacked by this

sickness the first or second year of their arrival, and it acts more violently upon them than upon the natives, so that they sometimes die of it. But if they escape the first time, they have the advantage of not being visited again the next year or perhaps ever. It is commonly said here that strangers get the fever to accustom them to the climate." Cumming (1810) stated, "All newcomers are subject to what is called a seasoning, after which, though they may be annually attacked by this scourge of the climate, it rarely confines them longer than a few days."

Regarding the progress in basic scientific knowledge, confirmation of Laveran's discovery of the malarial parasite was affected by Sternberg in 1886, who demonstrated the parasites in the blood of an active clinical case. This was several years before effective staining techniques were introduced and in these early years microscopical diagnosis was commonly done with fresh blood.

Long before it became possible to differentiate between yellow fever and falciparum

malaria a number of physicians in America had come to suspect that mosquitoes were involved in the transmission of both diseases. Although nearly forty years previously, men had advanced such an idea, it was King, in 1883, who advanced the following propositions: 1. The malaria season corresponds to the mosquito abundance; 2. Malaria country is suitable to mosquito breeding; 3. Similar conditions afford protection against malaria and mosquitoes; 4. Exposure to night air means exposure to mosquitoes; 5. Soldiers, tramps and fishermen are particularly susceptible to malaria and are especially exposed to mosquitoes at night; 6. Turning up the soil or making excavations in previously healthy districts is often followed by malaria; 7. Coincidence of malaria and mosquitoes, increase of both in late summer and autumn.

Following the incrimination of mosquitoes in the transmission of yellow fever and malaria, studies emphasize the fact that

effective anti-anopheline work requires an extensive knowledge of the bionomics of local vectors and that controlled measures must be adapted to the character of the local problem arising from these peculiarities.

Progress in treatment and prevention may be traced from the tremendous importance of the disclosure to European medicine that the bark of a Peruvian tree could cure intermittent fever. It is alleged that as early as 1630, Don Juan Lopez had been cured of an intermittent fever by the use of this bark. The extent to which the bark came to general use as a febrifuge in the Americas during the next century and a half was obscure. The buccaneer surgeon, Lionel Wafer, 1699, appears to have become familiar with the Peruvian or Jesuit's bark in his cruise down the west coast of South America in 1680-81, as he speaks of observing it brought from the jungles on mule back for export in Africa and Peru. In the account of his adventures, we read, "We brought away with us several bundles

of this bark, and I found it to be the right sort, by the frequent use I made of it in Virginia and elsewhere."

As early as 1776, the Continental Congress ordered the medical committee to forward 300 lbs. of Peruvian bark to the Southern Department for the use of the troops. Jackson, 1791, a British army surgeon attached to one of the regiments of Lord Cornwallis' army, made extensive use of Peruvian bark in treating the abundant intermittent fevers from which the British army suffered in its southern campaign. At any rate, its use in the United States appears to have become wide spread subsequent to the Revolution.

Quinine was prepared commercially in Philadelphia three years after its isolation in 1820. The earliest report of its employment in the United States has come to our attention through Henry Perrine in 1826, who employed from 6 to 12 grains every two to three hours at any period of the fever, continued until its symptoms in pulse and skin

were subdued, repeating if the return of fever was suggested.

Quinine soon became an ingredient of proprietary fever remedies, one of the earliest of which, Dr. Sappington's "anti-fever pills", was extensively sold throughout the Mississippi valley and the southwest during the 30's and 40's. Dr. Sappington's advice to use quinine as a prophylactic did not attract much attention until the decade immediately before the Civil War. Merritt, (1861), surgeon to a mining company in Panama in 1850, obliged all employees to take a daily dose of 5 grains before breakfast. Soon the crews of the vessels operated by the Panama Railway Company were required to take quinine while in certain malarial ports. It was reported successful as a prophylaxis among the negro slaves engaged in the construction of the Charleston and Savannah Railway and was extensively, though not systematically, employed for this purpose during the Civil War.

Various study areas were located in the

early 1900's to determine the effects and dosages of quinine on the various populations in their respective areas. Work began to be done on the transformation of swamps to rice fields etc. in the late 19th century and thus attacks began to be made upon the habitats of the newly found etiological agents. Just when screening of doors and windows was introduced is uncertain although some screen wire was manufactured as early as 1865, and the amount now manufactured for domestic consumption and export is enormous, in 1927 exceeding five hundred millions square feet. Malaria will probably continue to be endemic in many regions of the world where any attempt to control this disease based upon the application of available measures is beyond local resources. The hope of cheaper methods depends upon the requirement of new viewpoints to the problem, the attainment of which necessitates an extension of our knowledge. Probably no better guide to the means and opportunities for research

in the field of malaria can be secured than through an inventory of existing knowledge of all the aspects of malaria fever known to man.

Although quinine and its use in the treatment of malaria is to be a dropped subject in this article it would be well to remember a statement made by Mumford (2) and to repeat his recommendations for the dosage of the drug. "Owing to a low toxicity, and the fact that careful medical supervision is not required, quinine is still the most valuable drug for malarial prophylaxis and the treatment of acute malaria." But it is claimed that quinine is much too valuable to be used as a prophylactic (to be saved for acute therapy) where there is doubt of the danger of becoming infected.

"Rx: Quinine; 1. Ordinary adult cases, a dose of 0.5 to 0.65 grm daily. 2. Acute malaria, 0.65 grm. orally two or three times daily for three or four days or until acute symptoms disappear. Then a dose of 0.65 grm.

is given every night for eight weeks. (Goodman Gilman 1941)".

Perhaps the location of our present theater of war will change, but unless it does so quite quickly and quite unexpectedly, we will do well to remember that this historical disease, malaria, is "believed to occur in all the islands between the equator and 20 degrees S., from New Guinea eastwards to 170 degrees E.." (3).

MOSQUITOES

Since King convicted the mosquitoes as the vectors and their presence is very nearly a necessity to the incidence of any type of malaria, let us make a very brief outline survey of the mosquitoe situation: For our present purposes we can begin by stating that true mosquitoes possess the following characteristics:

a. The arrangement of their wing-veins is characteristic.
b. They have a long proboscis which is adapted for sucking up fluids. In the female sex

of most, but not all, species the proboscis is also adapted for piercing the skin.

c. The veins on their wings are clothed with true scales.

Although in all true mosquitoes the proboscis is long (usually about the length of the abdomen) and is adapted for sucking up fluids, by no means are all species blood-suckers, and no male mosquitoes have this habit.

Many species feed on plant juices, and the members of one small genus have the very curious habit of living in association with ants which supply them with food.

In most countries one or two species are much more actively concerned with the spread of malaria than others. Major Christophers has compiled the following list of species which he considers, (on account of their known habits, carrying powers, relative prevalence and widespread distribution), may be regarded as the chief malaria-carrying species in the particular countries, but only those which

have been most frequently found to be responsible for the spread of the disease:

IN EUROPE AND NORTH AMERICA: A. maculipennis and its allied species A. quadrimaculatus and A. occidentalis.

IN SOUTHERN EUROPE: A. superpictus and A. bifurcatus.

IN UNITED STATES: A. quadrimaculatus and A. crucians.

IN CENTRAL AND SOUTH TROPICAL AMERICA AND THE WEST INDIES: A. albimanus and A. argyritarsis.

IN SOUTHERN SPAIN AND NORTH AFRICA: A. turkhudi.

IN GREECE, ASIA MINOR, PALESTINE, ETC.: A. superictus.

IN THE MEDITERRANEAN: A. pseudopictus.

IN MESOPOTAMIA: A. stephensi.

IN INDIA: A. culicifacies, A. listoni, A. stephensi; etc.

IN THE MALAY STATES: A. minimus, A. maculatus, A. ludlowi.

IN THE MALAY ARCHIPELAGO AND NEW GUINEA: A. leucosphyrus and A. tesselatus.

IN NORTH AUSTRALIA: A. annulipes.
THROUGHOUT AFRICA AND IN SOUTHERN ARABIA: A. funestus and A. costalis.
IN SOME FOREST REGIONS: A. plumbeus (Europe), A. lutzii (Central America).

One man (4) suggests the conviction of children as well as mosquitoes because they are responsible for the principal maintenance of malarial infection in hyperendemic areas. This, he contends, is explained by the fact that young children develop an immunity very slowly.

Congenital malaria, although a disputed fact by many, is presented as a proven fact and there are several cases reported in support of such a contention.

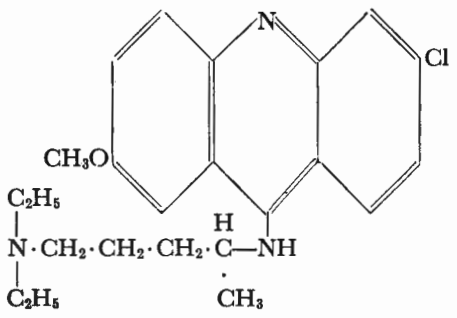
There are several considerable differences between child and adult malaria and their respective clinical pictures. The main of these are: 1. The frequent absence of fever; 2. Its irregularity, if present; 3. The predominance of digestive symptoms; 4. The common excitation into activity of latent conditions; 5. The

relatively large doses of quinine necessary to cure; 6. While a leukopenia is the rule, many cases of malaria (aestivo-autumnal) have a high leukocyte count with a high percentage of polys; 7. Attention is called to a pyelitis that often exists in a malarial patient possibly overshadowing the primary condition, but clearing quickly under proper therapy.

But now, on to a survey of the newer drugs, which for the sake of some order, we have divided into separate treatments of: 1. Atabrine, 2. Plasmochin, 3. Sulfonamides, 4. Combinations of these, and 5. Miscellaneous.

ATABRINE (5)

Chemistry. Atabrine, 2-methoxy-6-chlor-9- (α-methyl-δ-diethylaminobutyl) aminoacridine, is a substituted alkyl amino derivative of acridine. The side-chain in this compound is the same as that in plasmochin. Substitutions can apparently be made in this side-chain without seriously altering the antiplasmodial activity, but this does not seem to be true for plasmochin. The structural formula is as follows:



Atabrine

Atabrine is a yellow bitter powder. It is usually marketed as the dihydrochloride salt in yellow tablets, or as the powder which dissolves in water to the extent of three per cent to form a neutral fluorescent solution. The drug is not official and is not included in N.N.R.

In a recent article to the lay we find that this subject of ours has become a matter of public interest and the reasons, simply stated but completely inadequate for the conclusions drawn, warrant some quotation from a historical standpoint only.

"It was a prewar mistake of the Germans that their dye trust, I. G. Farbenindustrie, underestimating the ingenuity of American chemists, let us in on a hint of Atabrine's secret. German chemists had been working on synthetic quinine for years; their Nazi masters knew that no bid for world conquest could be made without a substitue for quinine, because malarial soldiers are just too sick to fight...

For Nazi warlords, concerned with transport, Atabrine had this enormous advantage: one ton of it would cure 600,000 malarious people, while the same amount of quinine would cure only 30,000. The Germans tried it out experimentally in Rumania, Italy, Spain, Africa and the East Indies. Back came a

roaring yes of scientific approval. With the new drug one could live in health despite swarms of deadly malaria mosquitoes. It was a German monopoly, a master weapon, and now Hitler's 'Wehrmacht' was ready and rarin' to go.

But at this point the German dye trust made its blunder. The Germans sold the secret of Atabrine to America! They thought they were driving a sharp bargain, because they deliberately left out vital pieces of the chemical jigsaw puzzle of the synthesis of Atabrine. They reckoned without the ingenuity of Dr. A. E. Sherndal of the Winthrop Chemical Company. Sherndal knew what the missing ingredients were, but could not obtain them in the United States. (Ironically, TNT and Atabrine, one the destroyer, one the health giver, are made from the same basic chemical.) Sherndal therefore devised a process of making Atabrine by using available American materials, and produced a medicine identical with the German chemical.

By 1939, Sherndal (who should have the highest military honors), succeeded in the mass production of an American Atabrine.

More than a year before Pearl Harbor, Dr. Parran not only forsaw the disastrous consequences of our lack of quinine but suggested to the Winthrop Chemical Company the urgency of stepping up Atabrine production. Not waiting for government orders or financing, the Winthrop Company, with the help of Merck and Company, shot Atabrine production up from 5,000,000 to 500,000,000 pills per year. Recently, the United States Army placed a giant order for 270,000,000 of the yellow pills--indispensable weapon in our global sturgle for victory. The American high command knows that Atabrine will keep our boys on their feet and fighting, wherever they may be. Millions of pills have been flown to Brazil, to make possible successful rubber production in the malaria-infested jungle. More millions have been flown to Turkey--for that nation made it a primary

consideration of its trade agreement that the United States should protect Turkey from malaria.

Characteristically, American mass production methods have lowered the price of this lifesaving victory chemical from its prohibitive German monopolistic high of $66 per 1,000 pills in 1933 to $4.50 per 1,000 today. This means that when the disease is tackled on a large scale an average case of malaria can be cured for just a little over six cents--the cost of an airmail letter!...

But the final glowing promise of these little yellow pills is not only for America, it is for the 800,000,000 malaria sufferers all over the world, with millions dying yearly. In the postwar tomorrow we shall be faced with a battered, maimed, starved, sick world. You cannot rebuild a world with half of its people drag-footed, shaking with malarial chills, burning with malarial fever--now curable at six cents per capita! And we shall meet at least part of our obligations toward

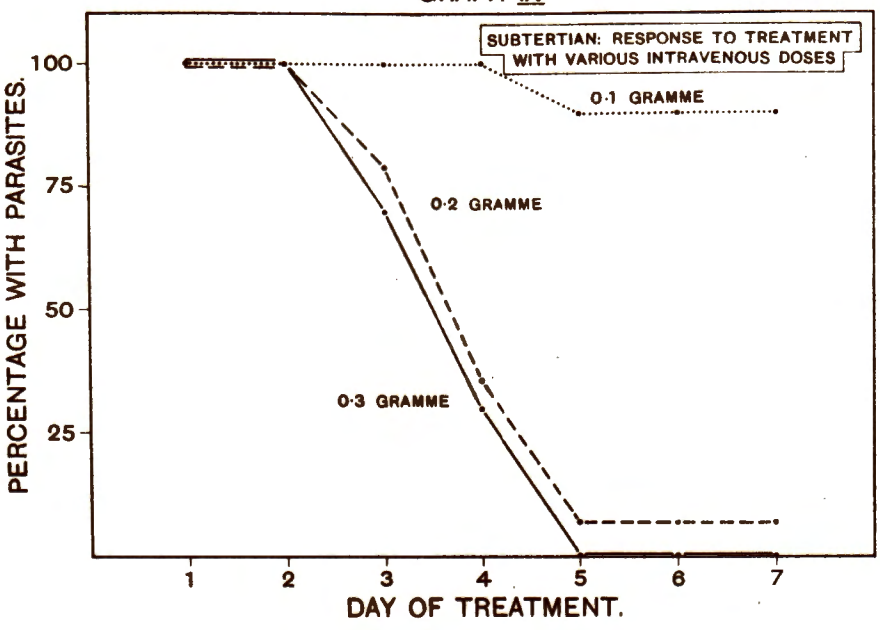
reconstruction by producing and distributing billions of yellow pills of Atabrine that will eventually conquer malaria."

From the standpoint of strict, scientific proof, we look first to the official report of the National Research Council (6) which states that Atabrine, now officially recognized under the nonproprietary name of Quinacrine, has assumed a role of unsurpassed importance as a strategic drug, and the American Atabrine has been now proven to be genuine, and comparable in every respect with that produced in other countires.

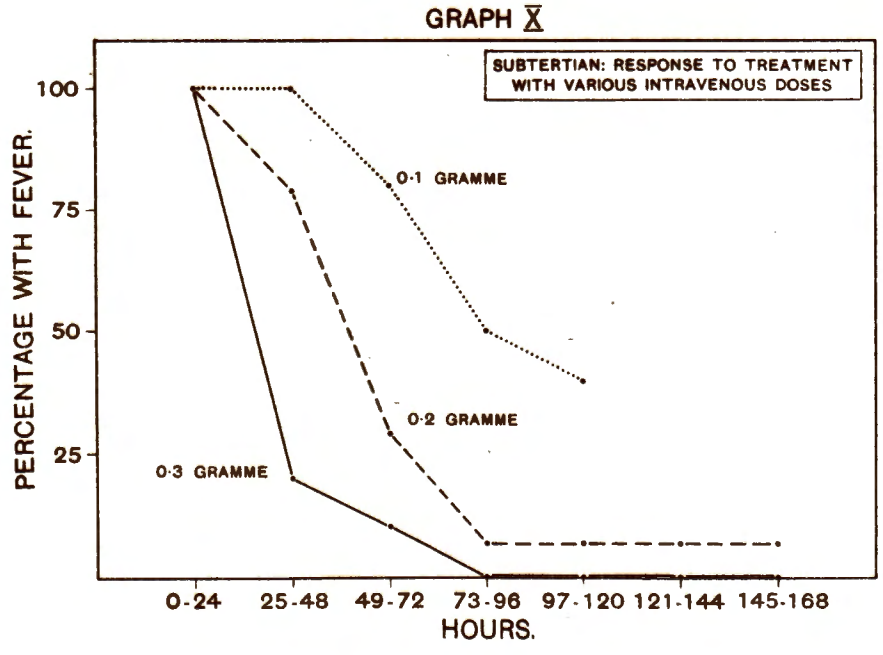
Experimental work has been done, not only on the dosage and effects of Atabrine by the oral route but also by the intramuscular and intravenous routes as well, and some of these reports lead to conclusions pro while others, though greatly in the minority, lead to conclusions con.

Owing to the very slow excretion or destruction of Atabrine in the body it seems unnecessary to exceed for intravenous

GRAPH IX



GRAPH X

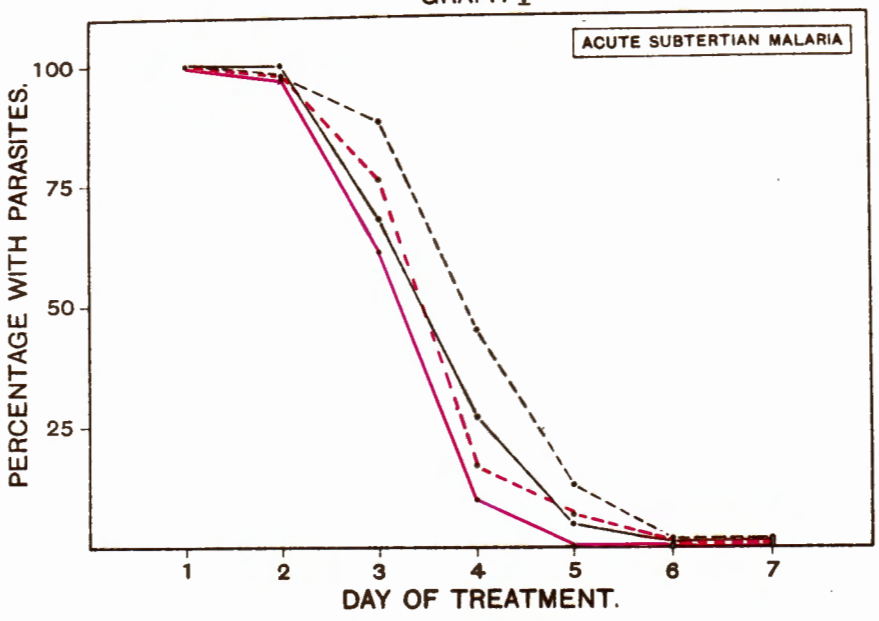


injection the dose of 0.1 gram, for an adult. The margin of safety is probably not great, and intravenous injection should be resorted to only in emergency. The injections should be made very slowly and timed to take several minutes for completion. The total injected over a period of twenty four hours should not exceed 0.3 grams.

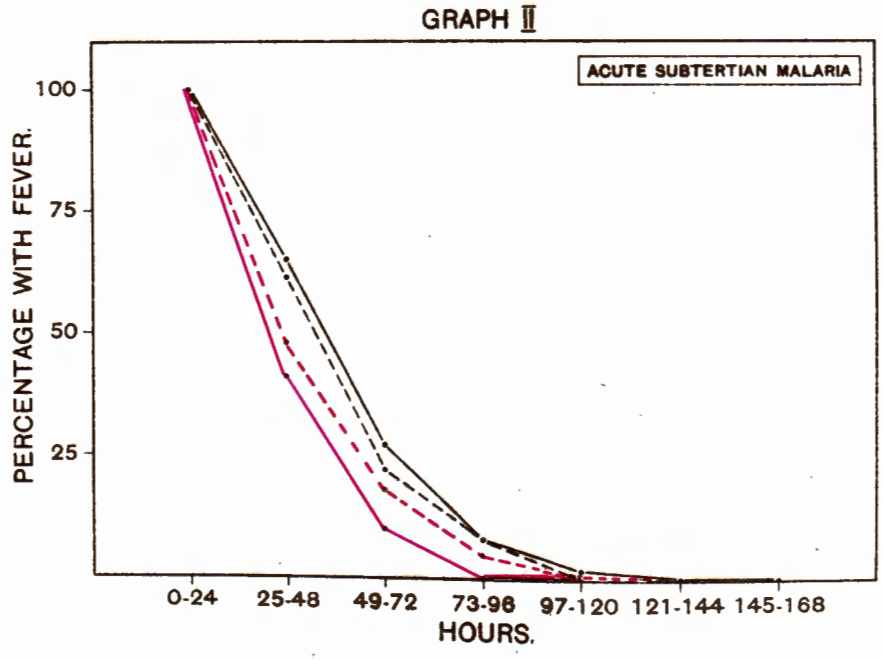
"In view of the very slow excretion or destruction of the drug in the body, it is reasonable to consider that a course of treatment with it should not be repeated within a period of say, eight weeks, and that the drug should be taken under supervision of a physician." (7)

Graphs IX and X (8) shown herewith, show the therapeutic responses to 0.1, 0.2, and 0.3 gram doses of Atabrine musonat when given intravenously. It will be seen that 0.1 gram is quite an inefficient dosage. In three cases, treatment at an effective dosage had to be given before the end of the customary seven-day observation period and therefore

GRAPH I



GRAPH II



QUININE BIHYDROCHLORIDE 2 GMS. PER 100 KG. B.W. ——

" " 1 GM " " " " - - - -

ATEBRIN MUSONATE AT 0.4 GM. DAILY DOSE ——

" " " 0.3 " " " " — — — —

no fever endpoint was obtainable so that the full seven-day curve could not be completed.

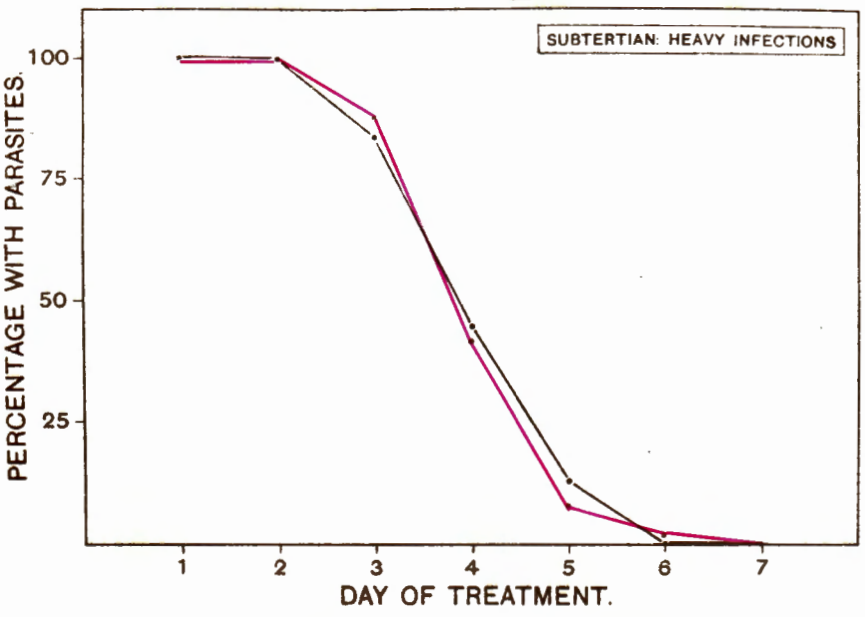
0.2 gram was found to be a fairly efficient dosage, though in one case, fever and parasites persisted throughout the seven days.

0.3 gram was still more efficient, a striking feature being the rapid fall in temperature--in eight out of the ten cases the fever had disappeared within twenty four hours.

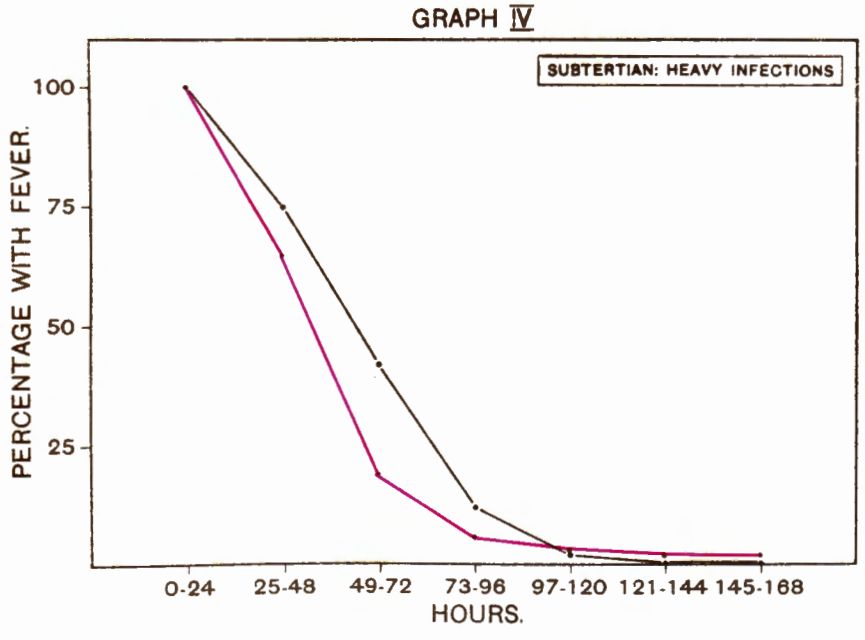
"Notwithstanding the ready response to intravenous treatment at efficient dosage, we are in full agreement with the makers that the route of choice is intramuscular. Intramuscular injections produce a rapid effect on trophozoites and fever, and the appearance of Atabrine in the urine within ten minutes of injection indicates a sufficiently rapid absorption into the general circulation." (8)

Graphs I and II it will be observed that, so far as the disappearance of parasites and of fever can be regarded as criteria of therapeutic activity, Atabrine musonat was slightly more rapid in its effect than

GRAPH III



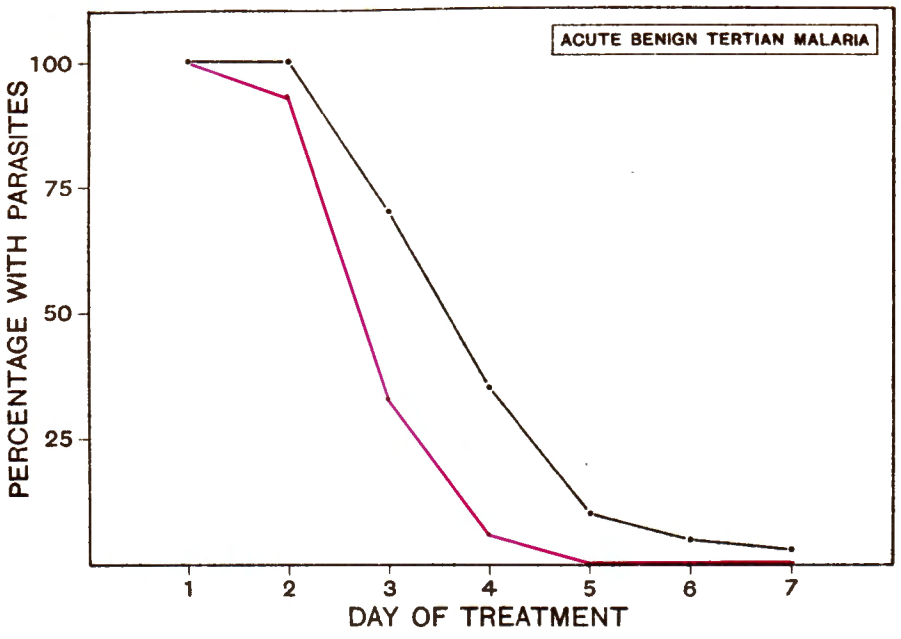
GRAPH IV



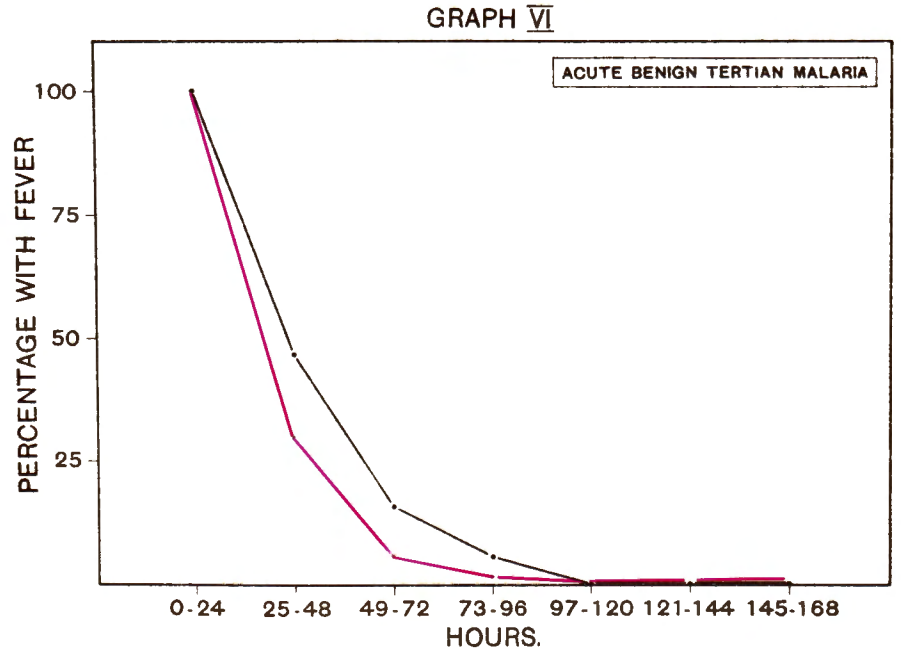
QUININE BIHYDROCHLORIDE ——————

ATEBRIN MUSONATE ——————

GRAPH V



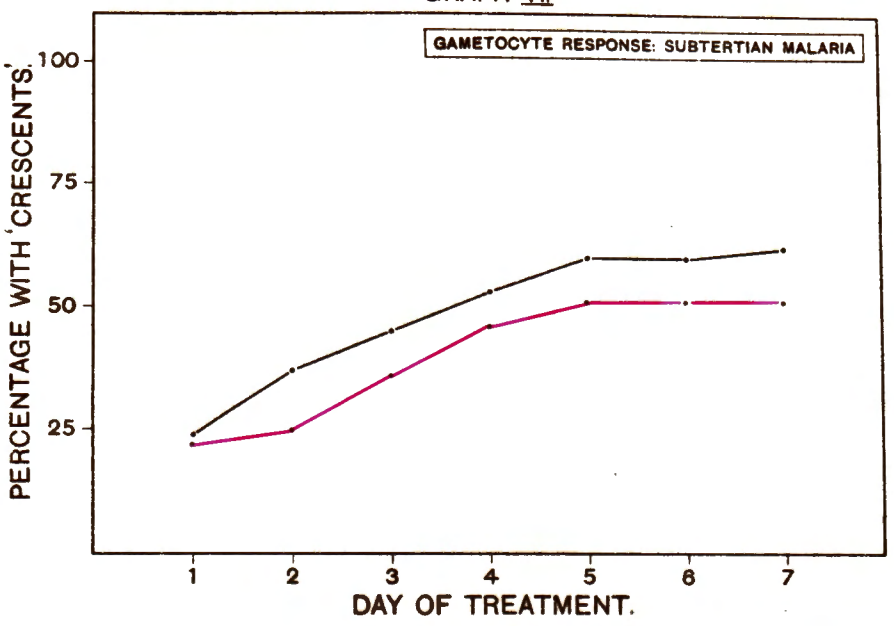
GRAPH VI



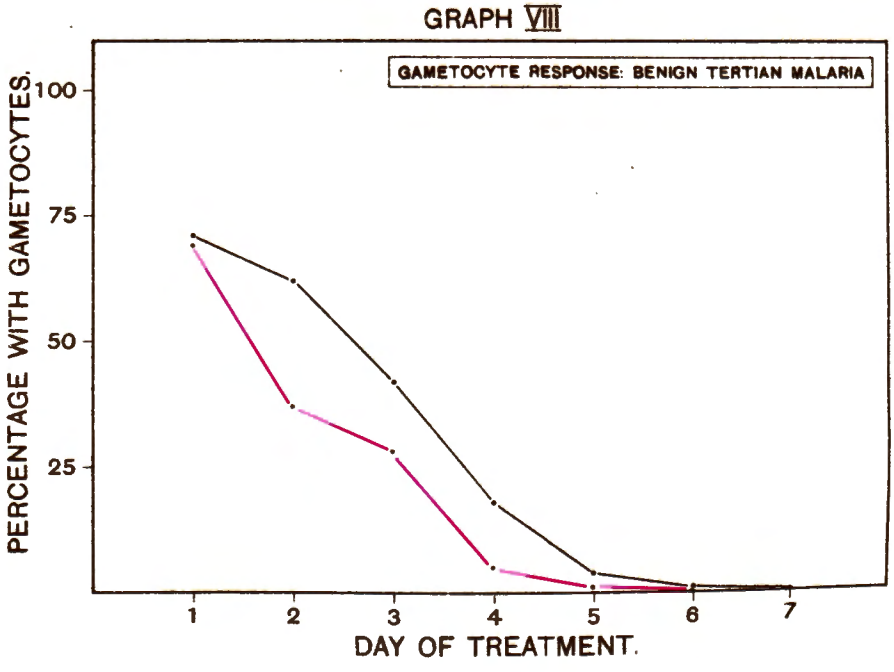
QUININE BIHYDROCHLORIDE ——

ATEBRIN MUSONATE ——

GRAPH VII



GRAPH VIII



QUININE BIHYDROCHLORIDE ——

ATEBRIN MUSONATE ——

quinine bihydrochloride.

Graphs III and IV (8) it will be seen that no significant difference in the schizonticidal effects of the two drugs was evident in these heavy infections, though Atabine musonat was distinctly more rapid than that of quinine bihydrochloride.

Graphs VII and VIII (8) from these graphs it is clear that Atabrine musonat, though it efficiently disposes of the sexual forms of the benign tertian malarial parasite, is not an efficient subtertian gametocide. Nor does it affect the viability of the gametocytes, for five out of six crescent carriers on whom mosquitoes were fed at varying times from the fourth to the tenth day were found to be infective.

Thus, the important conclusions to be drawn from the above piece of work are as follows:

1. The optimum daily dose is found to be 0.375 gram at Atabrine musonat. This dose efficiently controls an acute attack of malaria,

given on two successive days either intramuscularly or intravenously.

2. Five hundred samples of urine from both groups were tested for urobilin; the findings do not suggest that the urobilinuria associated with Atabrine musonat treatment is more than that of quinine treated controls.

3. Three cases of severe nervous disturbance following Atabrine musonat are recorded.

4. Although Atabrine musonat efficiently controls an acute attack of malaria, its routine administration is not advisable. Oral therapy is the method of choice in the majority of cases and the alarming nervous sequelae occasionally occuring after Atabrine musonat injections are a serious objection to its general use.

A brief summary of 21 cases in which the authors were dealing with unusally heavy infections in a poor and mostly underfed class of patients, showed us a few more points of interest. (9) They found that

crescents (gametocytes) were in no way influenced, and that these must be destroyed by plasmochin. In some cases there was a reappearance of parasites in the blood after a few days, but they disappeared spontaneously; and in no case observed was there any return of fever after two injections.

Prophylactic use of Atabrine has been worked with to quite some extent and one group of men (10) found that their observations confirmed the results obtained by other observers who had given prophylactic treatment for at least 10 days after exposure to infection; namely that Atabrine gives more constant protection than quinine, and that the prophylactic action of the drug on P. falciparum infection seems to be more constant than on P. vivax infection.

"The prevention of infection by a prophylactic treatment of 11 days, compared with our previous results obtained by a prolonged treatment during the incubation of malignant tertian malaria and the negative results of

other observers who did not go beyond an 8 day course of prophylaxis, is an indication--it seems to us--that the therapeutic action is upon the schizogonic forms of the parasite and not upon the sporozoites or any intermediate stages. We mention in support of this hypothesis our observations on the lack of infectivity of the blood during the first 5 days of the incubation period of malignant tertian malaria." (10)

Others (11) say that in the past, treatment of carriers and prophylaxis with quinine has been found to be unsuccessful. Investigations carried out upon the CCC enrollees have shown conclusively that the use of Atabrine as a prophylactic agent is successful so far as infection with P. vivax is concerned, but that it should not be concluded that Atabrine is put forward as a drug which would eliminate malarial infection as water does fire. "After administering Atabrine to some thousands of patients, it has been found that untoward actions are almost never encountered and when

encountered are of a transient character."

To be fair about any presentation and also that we, as physicians, shall not be taken by surprise at the occurence of untoward effects, though they be few and far between, we shall treat to some extent (but completely) the evidences found by reputable researchers and contrary to the very exuberant acceptance of Atabrine as "the newfound savior".

First, let us remind ourselves that Atabrine, according to the predominence of opinion, is non-gametocidal; and bring proof from the work of Sinton. (12) He reports from his work that Atabrine is known to produce morphological changes in both the sexual and asexual forms of P. vivax and P. malariae, and also in asexual forms of P. falciparum. On the other hand, it is reported by many workers to have no action upon the gametocytes of the last parasite. When the drug is given to a patient showing mature crescents in the peripheral blood,

these forms are apparently unchanged and are still capable of causing transmissal infection in mosquitoes. His conclusion is that although Atabrine brings about morphological changes such as clumping of the pigment and even the absence due to the extrusion of this substance in gametocytes, they still seem to be perfectly capable of undergoing their development in the insect host.

The untoward effects of Atabrine appear to include: gasping or accelerated respiration, circulatory failure, collapse, vomiting, possibly rise of temperature, psychoses, loss of appetite and of weight, abdominal pain, headache, diarrhea, yellowed sclera, rather persistent yellowing of the skin; and in view of the very slow excretion or destruction of the drug in the body, it is reasonable to consider that a course of treatment with it should not be repeated within a period of say, eight weeks, and that the drug should be taken under supervision of a physician only.

Overbeek (13) announces that in view of

a series of cases half o which were treated with quinine and the other half of which were treated with Atabrine, 34% of the quinine group harbored parasites after three weeks as compared to a low 5.6% from the Atabrine group. He did, however, bring out a point that we have seen before, namely and Atabrine-treated case followed by acute mental disorder which lasted fourteen days. A month later the patient had a second attack of malaria; anxiety and mental confusion followed the administration of 0.3 gram of Atabrine. The treatment was continued for three days but fever and parasites persisted. The administration of 1 gram of quinine reduced the temperature to normal and the patient became quieter.

Animal experimentation results have been culled from this presentation as nearly as possible, but one bit of work done by a group at the Albany Medical College warrants at least brief consideration even though its results have not been as yet upheld very strongly in clinical observations; for it is to be

remembered that we have very few, if any observations from the human necropsy table as yet.

An experiment carried on in dogs in the department of pharmacology of Albany Medical College showed the following to be true of Atabrine medication: 1. 33 or 66% of the acute minimum lethal dose daily for fourteen and four days respectively resulted in an impairment of hepatic function as measured by the bromsulphalein and bilirubin tests. 2. In contrast, daily medication with 17% of the minimum lethal dose for six weeks revealed no significant reduction in liver function. 3. Chronic doses of Atabrine ranging from 17 to 66% of minimum lethal dose administered daily for a period of 42 days gave no evidence of renal damage.

PLASMOCHIN *

After seeing that the effects of Atabrine are nearly wholly schizogonic our next question is, "Can we make our therapy more effective, more prophylactic and generally more

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* SEE PAGE 38 FOR CHEMICAL FORMULA, ETC..

complete by adding to Atabrine therapy a drug which has gametocidal powers? If so, are the two drugs compatible and under what conditions are they compatible?"

Plasmochin, according to the surveys to date, is our drug for this purpose and though the work has not been nearly so extensive as that on Atabrine, it gives, we believe, substantial experimental and clinical evidence to warrant its use for further exploration of its therapeutic value.

A very cautious bit of work was done (14) using, in one case a single, small dose of ½ cg. (0.005 gm.) of Plasmochin and observing a definite effect on the viability of crescents as measured by mosquito infection tests. Degenerative changes in crescents after the use of plasmochin did not appear to be definite enough to measure the early effects of small doses of Plasmochin, but the conclusion stated that it was probable that the general use in a population of such small doses of Plasmochin would be safe and effective in

reducing the transmission of malaria.

As with most other basic drugs, there are several forms and combination to be had and the same is true for Plasmochin. "Plasmochin compound", generally means 1/16 gr. Plasmochin and 2 grs. quinine and is put up in tablets to be given two or three times a day. "Plasmochin compound" is employed in malaria of all kinds: 1. For the acute symptoms, 2. To rid the blood of gametocytes.

"Pure Plasmochin" is employed in tertian or quartan, not aestivo-autumnal as: 1. A substitue for quinine in quinine idiocyncracy, 2. A tasteless substitute for quinine for children.

The toxicology of this new drug is manifest in nausea, vomiting, epigastric pain, splenic and liver tenderness, cyanosis, methemoglobinuria, mehemoglobinemia, hypo-glycemia, pallor, headache, dizziness, hemoglobimuria, and prostration. Bad effects, though usually mild, leave it suited for use under supervision only and not applicable for prolonged treatment or prophylaxis. It is used

with great caution on patients with kidney, liver or heart disease or marked anemia for severe symptoms may develop suddenly and without previous warning.

Imperial Chemical Industries Limited have synthesized a substance--Pamaquin--which they believe is chemically identical with Plasmoquine (Bayer). As Plasmochin is not a crystalline substance, and as there are no chemical tests by which certain isomers can be distinguished from Plasmochin, it was considered necessary, before placing Pamaquin on the market, to subject the substance to critical examination, in order to ascertain whether its biological effects were identical with those of Plasmochin.

Pamaquin tablets (Pamaquin methylene di-(2:3 hydroxynaphthoic acid)) were given to four adult men. (15) One of these was a normal, healthy individual, another was naturally infected with P. falciparum, and the other two were naturally infected with P. malariae. Each was given 3 tablets daily for 5 consecutive

days; one tablet containing the equivalent of 10 mgm. of Pamaquin dihydrochloride. The conclusion was that the biological action of Pamaquin (I.C.I.) had been compared with that of Plasmoquine (Bayer) and that the toxicity of the two preparations was the same, as was also their activity in canary, fowl, monkey and human malaria.

A brevified presentation of a series of opinions is boring to say the least but in this case it is the only way that we can find to present the evidence that we feel necessary to a complete-to-the-present knowledge of Plasmochin and some of its related compounds.

Strickland and Roy (1932a) broke all surprise records by noting that Atabrine administered to a patient suffering from malaria completely prevented the development in the mosquito of any gametocyte from that host, and that the parasite resumed its developmental powers three days after the discontinuance of the treatment. In the same year, the above authors (1932b) rectified their

statement by saying "...We have recently tried without success to repeat our experience regarding the influence of Atabrine on the development of malarial plasmodia in the mosquito, reported in the April number (of the Ind. Med. Gaz.) of this year."

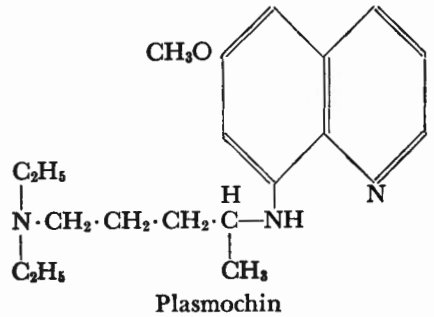
Simanin (1928) observed that the gametocytes continued their development in the mosquito unchecked, with the use of various drugs other than Plasmochin, and concluded that there was no drug which affects both the crescents and ring forms of P. flaciparum.

Barber and Komp (1927) showed that the gametocytes of malignant tertian and benign tertian would not develop in the mosquitoes fed on persons after two days' continued treatment with Plasmochin and quinine, and pointed out the importance of this finding in the possible control of malaria by treatment. In the authors' own language, "should it prove that small doses of Plasmochin may so cripple gametocytes or so far interfere with their normal development as the case may

be, that they are rendered incapable of forming healthy oocysts, the usefulness of Plasmochin combined with quinine, could be greatly extended."

The accompanying table shows the results of comparable work done by Chopra and Basu.(16)

Chemistry and Preparations. The synthesis of quinoline compounds of this type was suggested by the fact that methylene blue is somewhat plasmodicidal, and the introduction of aminoalkyl groups was found to enhance this property. *Plasmochin* is a quinoline derivative, 6 methoxy-8- (α-methyl-δ-diethylaminobutyl) aminoquinoline, and has the following structural formula:



Plasmochin

The drug is a tasteless white powder available as the hydrochloride salt in pills or capsules. It is also dispensed in tablets in combination with quinine sulfate in fixed doses.

SULFONAMIDES

The great enthusiasm shown for the sulfonamides on their arrival on the medical horizon was as prevalent in the field of Tropical Medicine as it was elsewhere, but the common concensus of opinion now is that this enthusiasm was a short-lived affair.

On the whole, we found this to be true, but there are some very definite reports voicing opinions too reasonable and too well founded to be ignored; it is not yet to be said that the sulfonamides are a closed issue in the treatment of malaria.

On reporting the efficacy of Promin, Coggeshall & Best (17) said that in a series of seventeen patients acutely ill with vivax and falciparum infections treated with sodium p, p'-diaminodiphenylsulfone N, N'-didextrose sulfonate (Promin), results revealed a definite effect on naturally acquired human malarial infections. The vivax infections were more resistant to therapy than the falciparum and the infections in the native Negro residents were more responsive to the drug than the same infections in the relatively nonimmune white patients.

Thirteen patients with vivax, falciparum and quartan malaria were treated with 2-sulfanilamido pyrimidine (sulfadiazine). There was a demonstrable effect in 10 cases but none

in 3. Although the effect of this drug was definite, it appeared to be less active than promin when given under the conditions described.

"From the observations cited, it seems apparent that there is ample evidence to show that these new types of compounds, unrelated to quinine or Atabrine, possess considerable activity against experimental and human malaria and, with related compounds, justify further study." (17)

These reports were enthusiastic enough but in the observer's own words: "It should be emphasized that at present there are no reasons for giving the drugs in preference to quinine or Atabrine for the treatment of malaria, and they should be regarded only as important substitutes."

Sulfathiazole (18) was used to terminate artificially induced malaria in nine patients; relapses occurred in five of this group and the antimalarial action of sulfathiazole was slower than that observed with quinine.

Prontosil, when reported (19) in ordinary therapeutic doses (3 to 4 gm. daily for five days) had an undoubted action in causing disappearance of malarial parasites from the peripheral blood and in controlling symptoms of the disease. It destroyed both asexual and sexual forms of P. vivax and P. malariae and only the asexual forms of P. falciparum, but had no action on the crescents. Its action on P. malariae appeared to be comparatively slower and less potent than that on P. vivax.

In smaller doses (1.5 to 2.0 gm. daily for five days) the symptoms of the disease abated and the parasites disappeared from the peripheral blood but recrudescence of the disease occurred within a fortnight. Prontosil undoubtedly possesses mild antimalarial properties in infections with Indian strains of malaria and may be worthy of trial when other antimalarial drugs are not available or are contraindicated.

Another report on the value of Prontosil,

given by Niven (20) affords the following quotation: "The present investigation has shown that Prontosil has some lethal action on malaria parasites, a fact that is of academic interest in view of the relatively simple structure of the drug. Somewhat surprisingly it appears to be more effective against P. falciparum than against P. vivax. As a practical addition to the therapy of malaria, however, the drug has no place. It is obviously much less than quinine, is more dangerous, and is much more costly." (THE UNDERLINING IS OUR OWN)

A translation of a report by Dr. Amonario Diaz de Leon and thought to be the first report on the use of sulfonamide compounds in the treatment of malaria, brought out the following favoring facts.

First case: P. vivax demonstrated, underwent three fever attacks before given the medicine, five days later returned for consultation feeling perfectly well and having suffered no attacks during that period.

Second and third cases: Two brothers suffering an attack of fever on the same day (P. vivax demonstrated in each case) and both patients suffered only the initial attack, before treatment. Seven days after the first consultation no parasites could be found in the blood.

Fourth case: A woman who had had an abortion followed by general malaise, lack of appetite and headache. Soon came chills, fever and copious sweat. Benign tertian parasites demonstrated. Last attack appeared the day after the initial dose and was light with only a slight chill and temperature rising only to 38 degrees C. disappearing in three hours, in contrast to the former attacks which had lasted eight to ten hours. "After having treated fifteen cases of benign tertian fever with complete success, I am sure that rubiazol is an effective, specific drug for this form of malaria..." (RUBIAZOL IS THE SAME AS PRONTOSIL AND PRONTYLIN)

Sulfapyridine (2 sulfanilylamino pyridine)

was used in experimentation on monkeys and some encouraging results reported but the work was so brief that the only conclusion was that the drug was worthy of trial in human cases. (21)

One of the most encouraging reports on this group was one on the use of Soluseptasine, (22) a white crystaline powder of well refined chemical constitution. It is readily soluble in water to give a solution of approximately neutral reaction. Concentration selected by the manufacturer for clinical use is 5%. A solution of this strength is very nearly isotonic with the blood and is, according to the manufacturers, well tolerated by subcutaneous, intra-muscular or intravenous injection by all common laboratory animals and also by man. It is said to be much less toxic in the experimental animals than the other sulphonamide derivatives and no serious, untowards effects have been reported following the use of soluseptasine.

One of the monkeys suffering from a low-grade infection with P. knowlesi was injected with 2 ccm. of soluseptasine, i.v. It had been showing a fair number of parasites (both schizonts and gametocytes) in the blood but 24 hours after the injection no parasites could be demonstrated even in thick blood films. To waiver the question of spontaneous disappearance of the parasites as is common with monkeys with a chronic infection, a fresh monkey was innoculated with 3 ccm. of monkey blood showing an infection with P. knowlesi. On the 14th day after innoculation a few parasites appeared in the blood films and when the parasite count was very high the monkey developed hemoglobinuria and looked very ill. At this stage, 2 ccm. of soluseptasine were injected, i.v.; next day the animal looked better and there was not only a considerable fall in the parasite count bu there were also definite degenerative changes in the parasites. The same dose was repeated 24 hours later, i.m., and after the two injections no parasites

could be found.

COMBINATIONS

It seems reasonably evident with the information that we have up to the present, that no one drug is completely adequate to do the complete job all by itself. Atabrine worked on the schizonts, the Sulfas seem to be effective in much the same way and Plasmochin is the only one that has a dependable and marked effect on the gametocytes which are the beginning of the sexual cycle and are also just what the mosquito's proboscus is hunting as he drills it though the outer layer of a malaria patient or carrier.

Now to the question, are combinations of schizonticides and gametocides compatible and effective as they would seem to be theoretically?

Matilla, Fabrega and Vich (23) prescribe for persons over 10 years, Atabrine 0.3 gm. daily for seven days, a pause of three days, then Plasmochin 0.03 gm. daily for 5 days. They claim, from 100 cases, rapid cure and

protection from relapses in benign and malignant tertian malaria. This treatment is not contraindicated in pregnancy, and Atabrine is the drug of choice in blackwater fever, followed by Plasmochin if gametocytes are present.

During the years of 1933 and 1934, another bit of work was done using Atabrine as a schizonticide, and Plasmochin as a gametocide. (24) Throughout two malarial seasons there was satisfactory control of gametocyte productions, believed due to Plasmochin. Atabrine was found to be particularly effective in the sterilization of carriers and in the short course of treatment necessary, the effectiveness of Atabrine as a schizonticide and the efficacy of Plasmochin as a gametocyde were proved to the satisfaction of the author.

Results (25) of treatment with Atabrine, Plasmochin and quinine, singly and in combination, in 1,696 cases in a group of military personel, using the recurrence rate in

those cases observed for six months or more following an attack as the sole criterion of the success or failure of a treatment. The following conclusions were drawn:

1. Atabrine alone, has failed to prevent recurrences to a greater extent than any other type of treatment.

2. Quinine, in the large and continued doses given here, has somewhat greater relapse preventing properties than has Atabrine in vivax malaria and markedly greater ones in falciparum malaria.

3. Plasmochin, in the daily doses commonly used, given concurrently with or following Atabrine, has a very definite and pronounced effect upon the relapse rate in all types of malaria. This effect is especially noticable in the vivax cases in this series. This finding is in absolute agreement with the recent conclusions of the Malaria Commission of the League of Nations Health Organization.

Another extensive experimentation was

done on a patient infected with P. falciparum giving Atabrine 0.1 gm. (t.i.d.) for the first five days at the end of which time the ring forms (schizonts) had completely vanished but the crescent forms (gametocytes) had remained absolutely unchanged. For the second five days Plasmochin was given .02 gm. (b.i.d.) with the result that the crescents vanished from the blood on the fifth day and had shown diminution in number on the fourth day. (26)

Drugs may be tried for three purposes: preventing infection from developing in the human; preventing development of sporozoites in the mosquito; or sterilizing the parasites in the human carrier.

Prophylactically speaking, quinine controls the clinical attacks but does not prevent infection of the patient; Plasmochin definitely hits the gametocytes of P. falciparum and has been credited for prevention of the sporogenous cycle in the mosquito; and Atabrine (prophylactically) is in question to its power to control the infection of the

patient, but it definitely does prolong the incubation.

A new, scientific system has been recommended (27) for prevention of relapses and here is the idea with no attempt made to give treatment for the prevention of relapses during the primary attack. One waits until the first recrudescence and then one uses the specific remedies in such a way that they will assist, rather than hinder, the development of the patient's natural defensive forces...by repeating this plan with the same watchfulness during the second recrudescence (using the specific drug at a later period and more sparingly than in the first recrudescence) and again, if necessary, during a third recrudescence, it happens in most cases that the patient becomes fortified or premunized against the disease to the extent that he not only ceases to suffer relapses, but fails to have an attack when he is reinfected.

In order that we may avoid repetition let

it be said that out of 192 cases treated with Atabrine and Plasmochin in dosages the same as we have encountered in most of the previous reading, the results were reported good, there was no drug intolerance and no relapses. The same workers, (28) using these drugs prophylactically found only 3 cases of malaria out of 242 persons treated as compared with 126 cases out of a series of 854 persons tried prophylactically on quinine.

Before dropping the subject of using combinations of schizontocides and gametocides it would be well to add our words of warning as we have gathered them during the course of this compilation. It is inadvisable, in an attack of malaria, to use mixtures of different schizontocides, or mixtures of schizontocides and gametocides. A mixture of Atabrine plus Plasmochin should be particularly avoided. These two substances, if administered simultaneously, produce a high percentage of toxic disturbances.

It appears to be clearly superfluous to

administer a daily sub-toxic dose of Plasmochin in order to devitalise the gametocytes. A single dose of 0.02 gm. repeated if necessary, every five days (but only in the rare cases in which the gametocytes still persist), will have the same effect. The administration of this sub-toxic dose of Plasmochin during five days, notwithstanding certain cyanotic disturbances, may be continued without further incident.

MISCELLANEOUS DRUGS

Certuna (Cilional) is a new drug with a gametocytocidal action resembling that of Plasmochin, and has been reported by Kikuth (1938) from the Eberfeld Laboratories of Messrs. Bayer. (29)

The drug was well tolerated in every instance and even when large doses were given did not produce any unpleasant or abnormal manifestations but the proof of the experiment is only against certuna when used with the Rumanian strain of P. falciparum. The conclusion was that certuna, even in doses

as great as 0.06 gram t.i.d. for 7 days commencing the day before infection, produces no true prophylactic action against the dosage of sporozoites of the Rumanian strain of P. falciparum.

Another group found that a total dosage of 0.35 to 0.4 gram of cilional administered as a dose of 0.03 gram three times a day, is usually sufficient to eradicate practically all gametocytes of P. falciparum from the blood and even this high dose has been borne by the patients experimented upon, without any ill effects. (30) In the author's own words: "On considering the points discussed above we cannot, however, help arriving at the conclusion that Plasmochin is preferable to cilional, inasmuch as a much smaller dose of the former effects the eradication of crescents in a comparatively short time, and as the dosage of Plasmochin (as advocated by Knowled and Das Gupta) is not at all toxic and perhaps cheaper than its rival."

The sharp limitation of the field of

effective action to the gametocytes of P. falciparum implies that certuna is inferior in its plasmocidal range to Plasmochin and cannot replace Plasmochin as a general gametocide. Combined with a schizontocide, the drug might be of value in the treatment of sub-tertian malaria were it less toxic than Plasmochin and yet equally effective. Whether the drug is entirely harmless or not is uncertain. The use of certuna in effective prophylaxis would necessitate more accurate species diagnosis than is usually possible in the field of practice.

Clark (31) reports that Cilional, belonging to the Plasmochin series of preparations, shows quite a potent action on the gametes of P. falciparum in doses far less than that which would produce toxic symptoms and is considered by him to be superior to Plasmochin as a gametocide in malignant tertian malaria.

"Malarian" or variance of this name, seems to be a popular term for proprietary

malarial remedies. "Malarian" is described as a nonpoisonous vegetable drug, which is cheaper than quinine and free from the unpleasantness associated with quinine treatment, and which has been used "with a large measure of success" by an English investigator. Its action in acute malaria was untried, and a request was made that the drug be put to a suitable test. Such was done (32) and though the number of cases treated was small, it was sufficient to indicate that this preparation is so far inferior to quinine bihydrochloride as to have no place in the treatment of acute malaria.

"Malario", a new preparation received from a Singapore firm was claimed to give satisfactory results in the treatment of malaria (types not specified)--rapid relief of symptoms with no recurrences over a period of months. The preparation was in the form of a brown powder with a slight chocolate taste. S.S. Government analysist reported, that it contained two parts of arsenic per

million and no trace of any other deleterious substance and did not contain Atabrine or quinine. Tests made on 47 cases (32) of acute malaria with the following conclusions: "Malario is of no value in the treatment of acute P. falciparum malaria and a very low efficiency in acute P. vivax malaria."

Sulfonamide conclusions drawn from the same reports are the same as those that we have stated before and the general conclusion was that they have no place in the practical treatment of malaria from its low efficiency and high cost.

In an attempt to facilitate administration to young children the manufacturers have prepared a new compound, allied to Atabrine and called "A. Granulate". It is made in the form of yellow granules with a slightly sweetish taste and has not appeared on the market, as yet. Work done with a small quantity sent to the Institue indicate that the drug is inferior to Atabrine for the treatment of acute malaria. (32)

Malaria has always been a serious problem in the southern part of China. The root-bark of an indigenous tree under the native name of Pai-chi'ang-kan or Ken-yen-yao has been used by the southern Yunnanese for the last thirty years as a remedy for the relief of intermittent fever and also as a mild laxative. Concerning its medical application, no literature in any form is obtainable. For the sake of convenience we shall denote it as the sinine tree.

"In the summer of 1939 we tried the powder of the root-bark on 34 malaria patients of Hsiao-ku-lang District, Kunming. Most of them were children. On the average, they came to our institute about eleven days after the onset of symptoms. We treated them with 3 grams of dried powder t.i.d. after meals for adults, and corrected doses according to Young's rule t.i.d. for children. Within eight days, parasites disappeared from the blood smears from acute subtertian, acute and chronic tertian or quartan cases. For

chronic subtertian cases it seems to be less effective. After several days the enlarged spleen became much smaller. Equivalent doses of fluid-extract of the root-bark were just as effective. At the beginning of this year, we again examined the blood of the treated patients. All blood smears were negative, indicating that there was no recurrence. Stem, bark and leaves are also effective.

With children, however, sinism was produced by large doses, either double or even 40% over the normal amount. Some developed either vomiting or tinnitus aurium. The latter symptom in one case lasted nearly three weeks after cessation of treatment. Only one case developed slight diarrhea with the powder of the root-bark; thus its laxative action was not marked.

In conclusion, this drug may be said to be more potent than, and just as satisfactory as, quinine for the treatment of all kinds of malaria. It takes on the average, four days to kill malarial parasites

in the blood. Its pharmacological actions, side effect and toxicological properties are very similar to those of quinine. Since this species is very widely distributed and can be grown everywhere very easily, on the limestone mountains in the southern part of Yunnan province and even in Kunming through the long, windy dry weather, its economical value is undoubtedly much greater than that of quinine." (33)

Another drug which for the sake of convenience may be termed the chunine tree contains an active alkaloid chunine, with even greater antipyretic and infusoriacidal actions, very much like quinine and sinine.

Benign tertian malaria in a patient with acquired anaphylactoid reaction to quinine was successfully treated with quinidine, the dextrorotatory isomer of quinine, without discomfort to the patient. A positive skin test was obtained to quinine but not to its dextrorotatory isomer, quinidine. A son appeared to have inherited a form of quinine

intolerance, as he suffered from urticaria on the one occasion when it was given, but he gave a negative skin test to quinidine.

Quinidine sulphate, U.S.P., given in 10 grain doses once a day about two to four hours before the ordinary hour of the paroxysm, has given prompt and good results in a small series of patients with malaria. (34) The results strengthen the suggestion of Dawson and Garbade that quinidine may well be given a trial in the treatment of malaria in cases of quinine intolerance.

All four common cinchona alkaloids are of approximately equal value in chronic benign tertian malaria. In cases of quinine idiosyncrasy, taking the form of urticaria, coryza or dyspneic attacks, quinidine or cinchonine may be given a trial with fair prospects of avoiding the unpleasant side effects, and especially in the case of quinidine, security as to therapeutic efficacy of the treatment.

Preliminary observations (35) indicate

that hydrocinchonidine and hydrocinchonine as well as hydroquinine and hydroquinidine possess definite antimalarial activity, a result of some theoretical importance.

An experiment testing the use of calcium chloride as treatment for the chills occuring in malaria reveal the following: (36) 1. Three patients suffering from malaria (induced in the treatment of neuro-syphilis) were available for study. In this group calcium chloride was administered on five occasions. Immediate relief from the chill was obtained in all five instances, but in two instances the injection caused nausea and had to be discontinued, after which the chill recurred. The preparation of calcium chloride used was a 10% aqueous solution. The usual quantity injected was 10 cc. although as much as 20 cc. has been given. The solution should be injected very slowly as it has been found that if given too rapidly the chill manifestations, although initially relieved may recur.

Very briefly, let us present some newer

and less important forms of treatment: (37)

1. Antimony tartrate--after small doses the patient cannot infect mosquitoes.

2. Dr. J. Lavergne stated that synthetic drugs (quinacrine for five days followed by rhodoquine for three days) gave better results than quinine.

3. Tibourskaja reports from Moscow the use of quinoline as a gametocide--eliminated subsequent infection of mosquitoes that were fed on the patient 24 hours after the last dose was given.

4. Mass prophylaxis in a malarial region of Tunis using premaline in tablet form. A table of this drug contains quinacrine 0.01 gram, rhodoquine 0.005 gram, and praequine 0.005 gram. Symptoms of intolerance were rare and cost was only half the cost of that of what daily quinine administration would have been. The authors were enthusiastic about the results.

SUMMARY

In conclusion, it seems that all evidence points to the use of both Atabrine and Plasmochin. As to the time of administration of each, perhaps the safer course is the better so we should recommend not a mixture of the two drugs (several reports of severe toxic manifestations) but a five day course of Atabrine (0.1 gm. t.i.d.) followed by a second five day course, this time using Plasmochin (.02 gm. b.i.d.).

If Atabrine is not available, it may be well to remember the sulfas and some of the other fairly effective schizonticides, but the only effective gametocide is Plasmochin.

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