QUININE PROPHYLAXIS

in

NORTHERN INDIA.

by

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A R R A N G E M E N T.

Quinine Prophylaxis in Northern India.

Introduction.

1. of all the diseases which affect mankind Malaria is probably the commonest, and its ravages are widely distributed throughout the world. It is estimated (1) that 80,000,000 cases of malaria occur annually in India and that about 4,000,000 die from "fevers," in a third (2) of whom the cause is considered to be malaria. Apart altogether from the mortality of the disease, malaria exacts a high toll from the country in which it is widespread and severe, for its saps the vitality of its people, destroys the life of the country and is a potent factor in high infantile mortality. Its economic importance is enormous and delayed development in every line of progress can safely be attributed to it. It would be a mammoth task to endeavour to estimate the economic loss on account of malaria to a country such as India. Hospital treatment of cases, nursing, medicines, invaliding, training men to take the place of those invalided, work days lost owing to this malady and other ailments directly and indirectly attributable, anti-malarial measures, are some of the items which would help to make up the bill.

Dr. Andrew Balfour (3) estimated the direct annual cost of sickness and death resulting from malaria as between fifty and sixty million pounds exclusive of the further vast loss due to industrial inefficiency.

The economic importance of this disease is also evidenced by the results of anti-malarial measures in Preston, U.S.A., since 1926 (4) These measures included the use of quinine as a cure (in lay hands in all but serious cases) and the use of plasmochin as a preventative of mosquito infection.

Figures are as follows:-

	1925.	1926.	1927.	1928.	1929.
Hospital Admission Rate for Malaria --- Primary diagnosis only.	242	135	100	37	18

Average cane cut per man per day.	less than 1 ton	less than 1 ton	1.23 tons	1.39 tons	1.61 tons

Not only has the sick rate been steadily reduced but there has been a progressive increase in the work output per man.

Again in 1906 in Malay, Watson (5) found that in certain estates, the economic effect of quinine administration was that the small labour force was able to maintain the estate in perfect order. The improvement in health was not due to other causes.

Even in the British Army in India the sick wastage from malaria is very high. In the year 1929 (6) out of an average strength of 55,628, 6,454 cases were admitted to hospital, a ratio of 116 per 1,000, and this is the lowest figure, with one exception, viz: 1928, since the Great War. Happily in such a highly selected body of men so well fed, housed, clothed and medically treated, the death rate is small - 0.13 per mille in 1929. Nevertheless the disease is of very serious moment, and in the malarial season in an epidemic year the possibility of a campaign in certain areas on the Frontier would be viewed with the gravest concern.

Many cases are on record where malaria has decimated an expeditionary force. The ill-fated Walcheren expedition of 1809 is a well-known example. In spite of protests from the medical authorities a force was despatched in late summer and autumn when the malaria season was at its height. Soon an epidemic of appalling magnitude was in progress so that by the middle of September it was estimated that two-thirds of the force was sick. (7) The Army which left about 12,000 strong returned to England in December, decimated and broken. There were only 247 casualties from fighting but over 4,000 died of malaria.

The French Madagascar Campaign of 1895 suffered a similar fate. It lasted but ten months and in that time 5,600 died of disease, chiefly malaria. The strength of the force was 18,000, and only 7 were killed in action.

It is abundantly clear, therefore, that the success of a campaign in a malarious country is largely dependant on the efficacy of the anti-malarial measures adopted. The truth of this was again brought home during the Great War, when in Salonika in the first season there were over 30,000 cases amongst British Troops. (8) Also in Palestine during the last great advance from the River Auja, the sick wastage due to malaria was enormous.

For months before the advance the line had been more or less stationary and an intensive anti-malarial campaign had been in progress, consisting chiefly of anti-mosquito measures and protection from the bites of mosquitoes by the use of mosquito nets. When the advance began, mosquito nets were carried but often not used, and the troops suffered heavily in their passage through intensely malarious country, till then in enemy occupation, and where anit-mosquito measures were unknown.

In 1926 I was faced with a malaria problem and fortunately on this occasion I was in a position to test the efficacy of Quinine Prophylaxis.

I was stationed in a small "outpost of Empire" in the North West Frontier of India with a strength of about 1,700 British and 3,000 Indian Troops. The number of British Troops was reduced to about 600 throughout the hot weather, as many as possible being sent to "cold storage" in the hills to save them from the heat of the plains and to reduce as far as possible the numbers exposed and the period of exposure, to malarial infection. Early in the season I commenced a malaria survey and opened an intensive anti-malarial campaign. The work proceeded well and mosquitoes and malaria were negligible. During August and the first ten days of September, however, 16 inches of rain fell (the average annual rainfall is 15 inches) and when I returned from leave early in September the Cantonment was flooded and Anopheles, including the noted carrier A. culicifacies, were breeding everywhere. No stone was left unturned in our efforts to reduce mosquito breeding, but it was obvious that a severe epidemic was probable.

This was brought home during the last ten days of September when 58 cases of malaria were admitted to hospital out of a total British garrison of about 600 strong. All anti-malarial measures known to us and available locally were being tried. Pools were drained or filled in where possible. Otherwise cresol was added, paraffin-crude oil mixture sprayed on the surface, or Paris Green distributed with a blower. Routine oiling of wells was carried out, and diggies and tanks were emptied weekly or treated with oil. Numerous traps were set for mosquitoes, and barracks were sprayed or fumigated periodically. Individual protection was afforded the troops by forbidding the use of shorts and short-sleeved shirts after sundown, by the liberal use of P.C. Oil (Paraffin & Citronella) on all exposed parts and by strict mosquito net discipline both as regards use in bed and condition of repair. But in spite of all our efforts there was no reduction in the number of malaria cases admitted to hospital or in the number of variety of Anopheline mosquitoes caught in traps.

The use of quinine prophylaxis was then considered. It was useless to ask for permission. Quinine prophylaxis has been thrown overboard so far as official military medicine was concerned, chiefly, as a result of the failure of the process in Salonika during the Great War. Also time would be necessary. So I decided to carry out a controlled experiment during October on just under 500 men and to report the result afterwards. Local combatant opinion was very favourable, though considerable persuasion had to be used before the necessity for a control was fully appreciated. The results duly reported, though admittedly the trial was on a small scale, were considered sufficiently encouraging and I was officially instructed to continue the experiment the following year and on a larger scale.

Towards the end of the second season I was given an appointment in which I had control of the health organisation of troops in a larger area. So in 1928 the scope was further extended. We gained further experience in 1929 when my area was affected by a severe epidemic of subtertian malaria, and it was hoped that

the knowledge then acquired would be put to a final test in 1930. However the opposition to controls, which had been gaining strength throughout, eventually outweighed my efforts for a final test and orders were received that all troops were to be given "prophylactic quinine" and that controls would not be allowed as it was considered that the process was definitely beyond the experimental stage and the case for "quinine prophylaxis was quite definitely proved. While it was satisfactory to know that one's superiors were convinced, I would infinitely have preferred to have used controls, even in small numbers only, for another year. My protests, however, were in vain.

The whole subject of quinine prophylaxis is a very controversial one and different opinions are expressed by different authorities in no uncertain fashion, often, it seemed to me, on scanty evidence.

The experiment about to be described has been carried out over a period of four years during which it has been fully controlled. In the fifth year there were no controls. Many thousands of troops - British and Indian - were affected. Some were new arrivals, others were old campaigners. Commencing in one station the scope was extended to many stations, with widely different climates, in the plains and hills of two districts of the North West Frontier Province.

It is hoped that from the evidence produced it will be possible to arrive at a conclusion as to whether Quinine Prophylaxis has, in certain circumstances, a definite place in our war against malaria.

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Historical.

11. Malaria is probably as old as man. It was well known to Hippocrates in the 5th century. He recognised three types of fever, tertian, quartan and quotidian, and differentiated these types from continuous fevers. It is interesting to note that as early as the first century it was suggested by Varro that these fevers might be caused by swamp air. The term malaria (It. "mal" bad and "aria" air) was not introduced till early in the 18th. century when it was firmly believed that the disease was due to MIASMATA.

Though malarial fevers were well known to physicians and writers through out all the intervening centuries, material additions to our knowledge have only been made during the past hundred years. In 1847 Mickel demonstrated that the dark colour of internal organs in malaria was due to pigment and in the following year Virchow showed that the pigment was contained in cells. Kelsick in 1875 observed pigmented bodies in malarial blood and later (1880) concluded that these pigmented cells (Melaniferous Leucocytes) were diagnostic of malaria.

Meanwhile the first step towards the discovery of the parasites was made by Lancaster who in 1871 was the first to discover a protozoan parasite living within a red blood corpuscle - in a frog.

This was followed in 1889 by the most important discovery in the history of malaria, when Laveran, a French Army Surgeon, described a number of the stages in the life history of the malaria parasite viz. the amoebula, merozoite, and "flagellate" bodies.

The next step was in 1897 by MacCallum who, working in Baltimore on Haemoproteus columbae, the parasite of pigeon malaria, was fortunate enough to see a microgamete break off from a "flagellate" body, swim rapidly towards a spherical body and conjugation take place.

Meanwhile Manson had in 1884 traced the earlier stages of the development of Microfilaria bancrofti to its infective form in the thoracic muscles of Culex fatigans, and as a result had formulated the hypothesis of the mosquito transmission of malaria.

Major Ross showed that Manson's view was correct. In 1897 he demonstrated that in certain dappled-wing mosquitoes (Anopheline) fed on cases of malaria, malaria parasites with the characteristic pigment could be seen in the stomach wall. The following year, working in India with a malarial disease of sparrows (Proteosome) Ross found that if Culicine mosquitoes are fed on the blood of infected sparrows, the parasite enters the stomach wall grows and sporulates there with the production of sporozoites which subsequently enter the salivary glands. The insect is then capable of infecting other birds.

Rose's observations on bird malaria were soon confirmed on human parasites by Grassi.

The story was finally completed by Schaudinn who observed the penetration of a sporozoite into a red blood cell.

As is so often the case in the science of medicine, the cure for malaria was discovered before the cause. In 1638 Countess del Cinchon, wife of the Viceroy of Peru, was cured of intermittent fever by "Jesuits' bark," which was introduced into Europe in 1640. Hence the name "cinchona."

Morton and Sydenham noted the action in certain fevers of cinchona, and in 1753 Toyti wrote his classic account of malarial diseases and showed by the use of cinchona how to differentiate clinically those fevers which were cured by cinchona from those which did not yield to this specific.

It was not until after 1820 that quinine was introduced, and its use did not become general till the second half of last century. Even now we have still much to learn regarding the chemistry and pharmacology of the different alkaloids and derivatives of cinchona bark, and also as regards their absorption, metabolism, method of excretion from the body, and their action on malaria parasites. Not until these points are settled will we be able to express definite and reliable opinions on many of the problems affecting the administration of quinine in the cure and prevention of malaria.

In spite of the number of substitutes which have been tried in recent years, quinine remains our sheet anchor in the fight against malaria. India without quinine would be in a sorry plight. In endemic areas the death rate from malaria would be far above the present high figure and many of the survivors would be physical wrecks suffering from malarial cachexia and endeavouring to build up a natural immunity. Meantime they swell the reservoir of infection.

Quinine has its limitations, but according to Professor W. E. Dixon, F.R.S., (9) we are only touching the fringe of the pharmacology relating to quinine derivatives. The chief shortcomings of quinine are -

1. that, however thorough the dosage many cases of malaria subsequently relapse.
2. that frequently in primary cases of malaria the temperature does not fall for several days though the Acid Tanret test of the urine shows that the quinine is being absorbed.
3. that quinine appears to exert no effect on the sexual forms of the parasite.
4. that in many cases quinine will not cure an attack unless the patient is confined to bed.

Apart from the above limitations, failure to obtain good results is usually due to faulty administration, e.g., use of unsuitable salts or insoluble tablets, dose of drug ordered not being consumed, or non-absorption by the patient.

Laverans' statement is as true to-day as when it was made many years ago "If quinine is given in adequate doses properly administered, the diagnosis is at fault if the fever does not yield by the fourth day."

"Very little quinine is absorbed in the stomach; no matter what salt is swallowed it passes on into the duodenum where it is precipitated as amorphous quinine base and is absorbed by the aid of the bile" (10) From the alimentary canal it passes into the blood where most of it is rapidly taken up and destroyed by certain organs e.g., Liver, spleen, kidneys, suprarenals and brain.

A proportion of the quinine is exereted unchanged in the urine, where it may appear within ten minutes of consumption. Concentration in the blood is at its maximum after four to six hours. It is rapidly eliminated for the first six hours and the bulk, probably about three quarters, has been excreted within twelve hours. The more soluble salts are relatively more rapidly absorbed and also more rapidly excreted from the body.

Quinine prophylaxis is the regular taking and absorbing of quinine in such a manner as to prevent paroxysms of malaria.

Strictly speaking this is not prophylaxis for as Yorke and Macfie (11) demonstrated in G.P.I. cases experimentally infected with malaria, quinine given before the infecting feed is useless. The process would be more correctly designated "Early Treatment." Yorke & Macfie showed that unless quinine was continued for 10-14 days after an infective feed, infection develops. They considered that there was good reason for believing that quinine fails to destroy all, if any, of the sporozoites.

Infection is not prevented. It is cured or restrained. The multiplication of malaria parasites is prevented or retarded. In many cases an attack may be prevented, in others cessation of quinine may be closely followed by a paroxysm, and in some the "prophylaxis" may appear to be ineffective or the check on the propagation of the parasites is too slight to prevent the occurrence of malaria attacks while quinine is being administered.

Many years before the discovery of the malaria parasite and of mosquitoes as carriers of malaria, quinine prophylaxis was recognised as an effective preventative of intermittent fevers. As long ago as 1760 Europeans living on the coast of Guinea used Cinchona bark powder continually during the rainy season when fevers were prevalent.

Most residents in tropical countries, planters and big game hunters lay great store by Quinine Prophylaxis and in some parts of Africa where malaria and blackwater fever take a heavy toll of life,

every European infant receives 2 grains of quinine daily from birth, seemingly with benefit and certainly without appreciable hurt.

The measure, however, fell into disrepute during the Great War chiefly as a result of its apparent failure to check malaria in Macedonia. (12).

This is partly explained by the failure of the French, recorded by V. Nicolet, that widespread evasion occurred, for the lessening of which medical units had to be organised to detect the culprits by surprise examinations of their urines for the excretion of quinine.

Throughout the war on the different fronts where malaria prevailed, quinine was extensively used as a prophylactic. There appears to have been no consensus of opinion as to its value, but the evidence generally was against the practicability of its use as a prophylactic under war conditions where bodies of men may be dispersed and unprovided with the necessary supervision to ensure that the drug is actually taken.

In the Navy, however, during the war, P. Bassett Smith records the undoubted value of prophylactic quinine, if only to enable the infections to be so reduced as to lessen materially the loss of man power.

The results obtained by some authors are in marked conflict with those obtained by others.

Stitt (13) records the following:- "398 marines served in 1906 for about one month on the Isthmus of Panama during which time they were given 9 grs. of quinine daily as a prophylactic.

"During this month there was only an occasional case of malaria among the men. At the end of the month 298 of the original 398 returned aboard ship and sailed for the North. Two days later 20 cases of malaria developed, followed the next day by 53 and the day following by 45. The medical officer then resumed 10 grain prophylactic doses for those not down with malaria, but notwithstanding this there were 215 acute malarial paroxysms, some of them of pernicious type, among 298 men.

"It was noted that these men did not respond satisfactorily to quinine treatment even when the drug was administered intra-muscularly."

The fate of the hundred men who remained in Panama is not stated. It is interesting also to speculate as to what would have been the effect of continuing the quinine prophylaxis from embarkation for a period of ten days.

Stott's observations (14) are very interesting. From 1/10/11 to 30/9/12 he carried out a controlled experiment in the 91st Punjab Regiment using the odd halves of each double company as the experimental group and the even halves as control. For the first two and a half months fifteen grains of quinine sulphate in acid solution was given thrice weekly. During the next two months, the non-malarial season, no quinine was given. For the remainder of the period ten grains of quinine was given thrice weekly. The results showed:-

1. There was no material difference in the malaria incidence in the two groups.

2. The course exercised no practical influence on the severity of a subsequent malarial attack.

3. Exhibition of quinine did not render the diagnosis of cases more difficult.

4. If prophylactic quinine fails when its issue is as carefully administered as is ordinarily possible in a regiment, this particular method cannot be expected to succeed when distributed broadcast amongst an undisciplined rural population.

Hanschell (15) with 29 men in the Belgian Congo in 1915-16 found five grains of quinine daily (bisulphate tablets) ineffective in preventing malaria, while none of the remaining nine who slept under 3 feet nets caught the disease.

Twenty slept under 18" nets and all contracted malaria

More recently (1930) Boyd (16) at Ferozepur had unsatisfactory results, and Harris (17) at Hong Kong did not observe any beneficial results during the administration to troops in camp in the season 1930-31, of ten grains

of quinine sulphate nightly and for ten days after their departure from camp. It is not stated whether this latter experiment was fully controlled, but a feature of interest noticed was that ten grains of quinine can be taken daily for a period of six weeks with practically no opposition and without the least ill effect by men doing very hard physical work.

While admitting that quinine will control the case rate in actual malaria sickness, Williams (18) considers that the results are not sufficiently striking to warrant an extension of its use, on account of its unpopularity and the fact that it needs much time and supervision.

In an investigation of a small number of cases Treadgold (19) concluded that in Macedonia quinine alone was quite unable to prevent malaria. The same observer analysed 201 original papers and found that 134 of the writers favour quinine prophylaxis, 27 favour it with reservations, and 40 are against it. Those who advocate its use include such well known and experienced workers as Celli, Koch, Ross and James, to mention only a few.

"Week end prophylaxis" was advocated by H. Seidelin (20) in the Belgian Congo. He gave one gramme of Quinine Bihydrochloride on each of two successive days each week and concluded that sickness due to malaria was diminished, that not only was the incidence of the disease decreased, but that the infections occurring were milder, and that only 0.3% of working days were lost.

Other observers in the same district report similar findings. P. Walravens (21) advises that all children in that region should be given quinine from September to April and F. van den Branden and L. van Hoof found that considerable benefit accrued to those who took quinine once weekly, even with some irregularity, throughout the season. In Sumatra, J. A. Hendriks lays much stress on quininisation of the people especially as applied to schools. Rogers also records that in an extremely malarious part of New Guinea during an expedition, quinine failed to prevent infection, but the general mild nature of the attacks was considered to be due ~~to the drug~~ to the drug, enabling the work to be completed.

Gosse (22) had good results from a small but well controlled investigation in Mesopotamia. He suggests that good or bad results may depend on the intensity of infection, small doses of quinine being of more apparent value when the number of infected bites daily is small.

Watson (23) voices a similar opinion and Rosenau (24) states that good results have been obtained on the Isthmus of Panama by the use of moderate doses, 3 to 6 grains daily. When the disease increases in prevalence or virulence the amount is raised to 8 or 10 grains per day, then dropping off to 4 or 5.

Italian opinion is strongly in favour of Quinine Prophylaxis. Thompson (25) in an interesting description of various schemes of "bonification" and "integral bonification" shows that the state arrangements for quinine treatment and prophylaxis brought about a rapid and continuous decline of malaria mortality, from about 500 per million in 1900 (the year in which the State Quinine Law was promulgated) to only 61 in 1923.

Grasse (26) has recorded good results in marshy parts of Tuscany, and in North Italy and Switzerland Galli-Valerio records that the main element in bringing about the disappearance of malaria from certain foci was the administration of quinine.

In Palestine Kliger (27) reported that the regular administration of 30 grains daily for five days followed by ten grains daily till the end of the malaria season in November reduced the loss of working days to less than 1/6 of that of those not taking the drug, but a fourth showed parasites four days after ceasing quinine, the infections being masked and work impossible.

The Sergent (28) brothers, as a result of their great experience in Algeria, concluded that although prophylactic quinine is not an absolute protection against infection, still it should be taken daily as it renders the attacks milder and the infected less dangerous to their fellows. They found its wholesale use to be readily acceptable, not troublesome and sufficiently effective.

Probably the success or lack of success is largely determined by the thoroughness with which the quinine administration is carried out. In certain jail experiments in India (29) very good results were obtained where the administration was rigidly controlled.

The case for prophylactic quinine may be fittingly concluded by a reference to the work of Watson (30) who, working in Malay, found after twenty years experience, that quinine given regularly reduces the sick rate and death rate if given in sufficient doses (less than 6 grains daily are of little value where malaria is intense) but that the use of quinine does not cause any material reduction in the liability to infection. He considers, however, that quinine systematically given, probably assists the infected to acquire a natural immunity.

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The Theory of Quinine Prophylaxis.

111. Quinine is not regarded as a true prophylactic to malaria. It does not prevent infection of the red blood cells by the parasites, but, if given in sufficient doses and over a long enough period it may prevent an attack of malaria in an individual who has been bitten by an infective mosquito, and allow him to carry out his normal duties.

If there were ever any real doubts on the subject these have been laid to rest as a result of the celebrated work of Yorke and Macfie already referred to. They established that in order to prevent attacks of malaria developing quinine had to be continued for 10 days at least after the infective bite, and they considered that quinine failed to destroy all, if any, of the sporozoites. The reason for this failure is shown by the work of Acton ((31) who found that, after a single dose of ten grains of quinine, the maximum concentration of quinine in the blood was only 1 in 250,000, a very much weaker concentration than is necessary to kill off all parasites.

Warrington Yorke[32] (in collaboration with Macfie) has confirmed the work of Muhlens and Kirschbaum (1924) that quinine in concentrations considerably greater than can ever occur in the blood stream does not "in Vitro" destroy all the malaria parasites. He found that a mixture of simple tertian blood and of a 1 in 5,000 solution of quinine is infective after incubation at 37° C. for 2½ hours. Evidence is produced to show that the susceptibility to treatment in the induced malaria is bound up with the fact that in these cases one is concerned with the treatment of primary infections. The mechanism by which a cure is obtained in malaria is considered at length and the conclusion reached that the essential factor for the production of cures is the capacity of the host to produce immune body in response to antigen formation resulting from the destruction of a considerable number of merozoites - whether due to quinine treatment or to the natural powers of the patient. If for any reason the immune body formation is insufficient the infection is not sterilized and a relapse occurs. The failure of treatment in chronic relapse cases is explicable on the same hypothesis.

The parasites in such cases are not quinine resistant but immune body resistant. In primary cases on the other hand treatment does produce a cure, firstly because the immune body, normally present to some extent in the blood of all patients, is augmented as the result of the antigen formed by the action of the quinine on the parasites, and secondly, because the parasites have not yet become immune body resistant.

Interesting though this hypothesis may be it should be borne in mind that it is still only a hypothesis and that the evidence adduced in its favour is all indirect.

Whether we accept the hypothesis of Yorke or not it would appear from the above that quinine prophylaxis is merely a form of early treatment given in the incubation period before there are sufficient parasites present to cause a paroxysm, and that the quinine assists the natural defences of the body.

In whatever form quinine is administered it circulates in the blood as quinine base. It is present in the plasma is adsorbed on to the surface of the erythocytes but not within them. Hence such parasites as may have become intracellular escape its action. When the infected red cells burst, setting free in the blood plasma swarms of little merozoites, these merozoites attach themselves to fresh red blood corpuscles to initiate again the schizogony cycle. The malarial parasites are therefore extra cellular in their earlier trophozoite phase. Most malariologists, however, affirm that early in the process of development the trophozoite penetrates into the interior of the cell and that both the schizont and gametoyte are intracellular.

M. Rowley-Lawson does not agree and in a series of papers (1912-1919) beautifully illustrated, she maintains the view that the parasites are extracellular throughout the whole of the cycle in their human host, and that they wander about in the blood stream from one blood cell to another applying themselves to the surface of the cells but never penetrating into them.

Stephens and Gordon (33) hold similar views and, as a result of their studies on the relationship of the

crescent to the erythrocytes, formed the opinion that the crescents were extra cellular and applied only to the surface of the red cells.

Also, Sinton (34) by shrivelling erythrocytes with hypertonic saline and swelling them with hypotonic, believes that he has seen the parasites in the various extra corpuscular positions observed by Lawson.

The question as to whether or not the parasite is extra cellular during most of its life in the human body is interesting from the point of view of treatment. If the extra corpuscular theory is correct, then the parasite, from the injection of the sporozoite by the mosquito throughout the whole of the schizogony cycle and during that part of the sporogony cycle up to the formation of the gametocytes, is exposed to the action of quinine circulating in the blood; whilst if the view of the majority is the correct one, the parasite can only be affected by quinine during the sporozoite stage, the merozoite stage and the early trophozoite phase; and it is in the merozoite stage that the parasite is generally held to be most susceptible to the action of quinine.

Therefore it would appear that the weak concentrations of quinine present in the blood during treatment or during a course of prophylactic quinine exercise their lethal or weakening effect on the parasite during the sporozoite, early trophozoite and merozoite stages at least, and if the extra corpuscular theory is correct throughout the whole of the rest of the life of the parasite in the human host besides.

It follows that our aim should be to maintain in the blood a concentration of quinine sufficient to destroy all parasites directly or indirectly, and to determine the minimum dosage for this purpose. The dose will require to be higher where the number of infected Anopheles is high, during epidemic years, and when other measures of protection are ineffective.

The process will be less efficacious if circumstances exist which tend to lower the resistance of the individual e.g. stress and strain of active

service, exposure to climatic extremes. The well known fact that a mild attack of malaria adequately treated with quinine will often not clear up till the patient retires to bed, is a very good indication that factors other than quinine play their part in the cure of malaria.

Another factor influencing the dosage is the arrival in the station of batches of non-immunes. Their advent in the ordinary way during the malarial season is often the signal for a great intensification of the malaria, and not only the new arrivals but the old residents suffer. The non-immunes get infected, the percentage of infected Anophelines increases and the degree of immunity in the old residents is now insufficient to protect them. This is well exemplified after the return to the plains stations in India of parties of troops who have been spending part of the hot weather in the hills.

Watson (35) observed the same phenomenon after the arrival of recruits for labour gangs on the estates of Malay.

Whatever the environmental conditions, the dose should be sufficient not only to prevent the number of parasites rising above the febrile threshold, but, if possible, to destroy all parasites. The exhibition of quinine must be continued for at least 10 days after the latest possibility of infection. We may picture the state of affairs when the body defences and quinine in circulation are just sufficient to scotch but not to exterminate the infection. Perhaps fresh infections are constantly being superimposed. The schizogony cycle persists for very long periods, but the number of parasites in the blood stream is kept at a low level.

At the end of the malaria season, no further fresh infections occurring, the continuation of the quinine for 10 days may kill off the infection. On the other hand the infection may persist till some cause reduces the individual's power of destroying parasites, the schizogony cycle flares up, the total number of parasites rises above the febrile threshold and an attack of malaria ensues.

It is often argued that quinine prophylaxis only masks malaria infection and that when the quinine is stopped the mask is removed and an outbreak of malaria necessarily follows. Such has not been my experience. If the dose has been sufficient to keep an outbreak of malaria in check, and if the course of quinine is continued for 10 days or a fortnight after the danger of further infection has ceased, it is maintained that "masked" cases are the exception, not the rule.

Even in individuals taking no quinine it is well known that cases occur where the disease does not manifest itself till long after infection has taken place.

I will quote two cases within my knowledge.

1. E. C. H. had his first attack of malaria five months after returning to England following a prolonged spell of residence in India.

2. S. M. R. A. returned to England from India on 5/2/31. During six years in India he had kept perfectly fit and had not had a single day's sickness. He was posted to Catterick (Yorks) and later (September - 1931) developed a typical attack of Malaria B. T. He had a rigor on 6/9/31 followed by another on 8/9/31 when B.T. parasites were found in the blood. The condition rapidly responded to treatment with Quinine.

The question of susceptibility to infection is very imperfectly understood. Some individuals appear to be immune, whether mosquitoes will not bite these or whether actual resistance to infection exists is hard to say. I know of one officer (R.T.H.) who slept outside without a net or any other protection in an area where it was impossible for the ordinary individual to sit in comfort after dark. He stated he was never bitten. Another officer (J.N.) had been stationed in many intensely malarious parts of India over a period of 17 years and had escaped infection though he took no precautions against malaria. His resistance against other diseases and his general physique were poor, but repeated and thorough investigation failed to show any trace of malaria.

A further difficulty is the fact that a proportion of any group to whom quinine is given will not absorb the drug in the form usually given i.e. the sulphate, for it is well known that cases of malaria will frequently re-act to the bihydrochloride after treatment with sulphate has failed.

It is also necessary to ensure the efficient action of the liver by occasional sharp purges. Otherwise in many cases the quinine administered may not be fully absorbed.

Another drawback put forward against the use of quinine prophylaxis is that there is the possibility of producing an immunity to quinine on the part of the parasites, so that the action of quinine when required in curative doses is reduced or lost. The evidence, however, that quinine-fast parasites are produced by the prolonged administration of quinine when given either as a prophylactic or curative is far from being convincing, and Acton (36) and his colleagues of the Dagshai Malaria Hospital are of the opinion that the parasites do not become quinine-resistant.

Much has been written of the so-called dangers of quinine administration. It is well known that in large doses quinine depresses the heart, lowers the blood pressure and causes depression of the nervous system with a sense of misery and dejection. Atrophy of the optic nerve may follow. In a few particularly susceptible individuals quinine may produce severe symptoms e.g. haemoglobinuria, skin eruptions and severe abdominal colic. Such cases are extremely rare, however, when we consider how much quinine is consumed (The annual consumption in India is about 160,000 pounds) (37) It has even been said that quinine was the cause of Blackwater Fever. Veretas (Greece-1858) originated the theory and Tomaselli (Italy) and Koch later supported it. Much harm was done before this view was discountenanced, and it is now known that Blackwater Fever may develop without the previous administration of quinine.

I have never seen any serious ill effects following the use of quinine in the ordinary doses required for treatment, viz 24 to 30 grains a day, and in the course of his large experience Sir Malcolm Watson (38) has

only seen one case of idiosyncrasy.

Cinchonism does not persist for more than a few days, and in cases of indigestion a change of salt or an increase in the dosage usually cures the condition.

Quinine, however, is admittedly an unpleasant drug to take, and care must be exercised in choosing the best time and the most suitable method of administration in order to minimise its effects. Largely also on account of its taste, it is unpopular, and in dealing with large groups the closest supervision is required to ensure its consumption, for otherwise results will be disappointing. A soldier has been known to place a sponge in his mouth to soak up the quinine he was supposed to swallow.

The supervision required must extend to the preparation of the drug, and frequent examination must be made to ensure that the dose ordered is actually being administered. A Solution labelled as containing 10 grains to the ounce has been shown to contain only one grain (39) and quinine tablets have been found undissolved in the stools. In cases of doubt the urine should be examined for its presence.

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Indications and Technique.

lV. Among the many methods described for administrating quinine prophylactically are the following:-

Koch's - This is known as the "long interval prophylaxis" and consists of giving 15 grains on the 10th. and 11th. days.
Plehn's - "double prophylaxis" consists of giving 7 or 8 grains of quinine every fourth and fifth, or fifth and sixth days.
Indian Method - A medium size dose - 10 grains - is given twice a week on two consecutive days.
Ziemann. - Gave 15 grains every 4 days.
Deeks (40) found that prophylactic doses of 15 to 20 grains twice a week greatly reduced the number and severity of the admissions by limiting the parasitic development sufficiently to prevent severe symptoms and to establish tolerance.
Stott (41) gave 10 grains thrice weekly with unsatisfactory results.

In these methods the drug is given in fairly large doses intermittently, the object being to have the quinine in the blood in sufficient concentration to kill off easily and quickly any parasites which may have entered the body meanwhile and commenced their schizogonic cycle. The argument against this "large dose" method is that in a person bitten immediately after the effect of a dose has passed off, the parasite has a considerable time to multiply before the action of the second dose is felt.

The oldest method of giving quinine is by small doses daily, and originally it was hoped that with a small quantity of quinine constantly circulating in the blood any malaria parasites introduced into the body would be immediately destroyed. We now know that this is not the case. This method, however, continues to be the favourite, and it is generally held that the small amount of quinine always present in the blood exercises its effect on the malaria parasites after they have commenced multiplying by preventing or inhibiting subsequent schizogonic cycles. In Italy a dose of 2 to 3 grains daily has accomplished good results.

In Panama good results have been reported with a daily dose of 3 - 6 grains increased or decreased according to prevalence or virulence of the disease.

Celli's method is to give 3 grains of quinine each morning and 3 grains each evening. He holds that harmful effects from quinine are thus avoided and that quinine immunity does not occur.

Perhaps the most approved method is to give 5 grains daily in the evening. James recommends a further dose of 5 grains about midnight where a mosquito net is not being used. Castellani gives 5 grains daily and a double dose once a week.

Hehir (42) recommends 5 grains daily in stations where malaria is comparatively mild, and an extra 5 grains on the 7th day where the disease is moderately severe. Where severe, or very severe, 10 grains is given daily for 6 days and 20 grains on the 7th. Watson (43) agrees that doses of less than 6 grains daily are of little value where malaria is intense - say where the spleen rate is over 60. Where the malaria is intense and the population consists of immigrants he recommends 10 grain doses 6 days out of 7 and 20 grain doses when suffering from pyrexia, or not at work on account of ill health. He states that 20 - 30% of those taking quinine will be found to have parasites in the peripheral blood.

The Experiment in the North West Frontier Province.

The reasons for the trial have already been discussed.

When considering the question of quinine Prophylaxis originally in 1926 certain points were kept in mind:-

1. That Quinine Prophylaxis was officially discountenanced, probably as the result of experiments carried out in Salonika during the war.

It was felt that conditions obtaining in Salonika might differ in essential factors from those affecting the N.W.F.P.

In Salonika, in addition to the

trials and tribulations incidental to residence in a bad climate, the troops were exposed to the rigors and privations of a campaign. They were continuously under fire, life, apart from its dangers, was deadly monotonous, and the vitality of the troops and their resistance to disease became lowered. Also, it was appreciated that the type or the intensity of the infection might not be the same. In Nowshera, to which the trial was confined for the first two years, the malaria season is very short and we can state quite definitely that, for practical purposes, infection takes place in the period between the second or third week of September and the first few days of November. (This is specially marked in an epidemic year). There is quite a sharp line of demarcation, for while troops returning from the hills the last week in October usually contract a few cases of malaria, parties returning in November escape.

The same is true with certain modifications for other stations with which this paper deals. In Peshawar, it was found later, the season is not so well defined and is slightly earlier In the Khyber stations the season is decidedly earlier.

In ordinary years the infection is mainly Benign Tertian, in epidemic years Malignant Tertian is the prevailing type.

Though malaria infection is intense it has been attended by very little mortality in recent years. In Nowshera the morbidity rate has varied between 255 per mille in 1925 and 491 in 1922, whereas in Peshawar the worst year recently has been 1923 with an admission ratio per thousand of 479 and the best, 1922, with a corresponding figure of 371.

Hangu and Thal which are included in the experiment in 1929 have an even worse record.

2. That there was a firm belief in the lay mind, particularly among planters, that Quinine Prophylaxis was efficacious and that this belief was shared by many eminent and experienced malariologists.

3. That in cases where Quinine Prophylaxis had been employed with

success, there was considerable variation in the method of administration.

4. That prolonged administration of quinine might have disadvantages e.g.

(a) it might be harmful
(b) quinine might lose its effect
 (i) either by being absorbed in decreasing quantities or
 (ii) by the parasites becoming quinine-fast.

Controls

In view, therefore, of the strong body of opinion, in the service and outside, opposed to this method of combatting malaria, it was realised that the experiment must be well controlled. In Nowshera in 1926 the British Troops selected for the trial occupied ten barrack rooms. These were old buildings with electric punkahs in the main rooms and electric overhead fans in the verandahs. All the troops used mosquito nets. From each room half of the occupants were selected for a course of quinine and the remainder were kept as controls. Both groups lived under identical conditions as to work, play, messing and accommodation. Nominal rolls of both groups were drawn out - in 1926 the Quinine Group numbered 210 and the Control Group 228. Admissions to hospital for both groups were recorded as were also attendances at Quinine Parades of the Quinine Group.

Particulars of the Trial

The chief mosquito breeding ground was the stoney, gently shelving bed of the Kabul River slowly receding from its banks after the summer floods. It was found impossible to deal effectively with the mosquito breeding in the River, which ran parallel to barracks and at a distance of about 400 yards. During October and November larvae of A.stephensi, A. subpictus, A. culicifacies, A.maculatus, A.gigas, and A. turkhudi were all taken in this situation in large numbers.

It is interesting to note in this connection that in 1927 as late as 3rd December, the Kabul yielded larvae of A. stephensi, A.turkhudi and A. culicifacies - the maximum and minimum dry bulb temperatures being 79°F. and 39°F. respectively and the temperature of the river water at the time of

collection 56°F.

Another phenomenon in connection with this river, which I have not been able to explain, occurred in 1928. The river fell and the mosquito breeding began as in previous years; and one awaited the commencement of the usual outbreak of malaria. Suddenly, for no apparent reason, mosquito breeding ceased and did not recommence. There was nothing to account for this in rainfall, humidity, temperature or wind, but the explanation may lie in some alteration in the chemical content of the water or in the failure of some necessary food supply. A welcome freedom from Malaria resulted and the year 1928 showed the lowest incidence of Malaria on record.

In addition to the river, other sources of breeding occurred all around in the immediate vicinity of barracks e.g. wells, diggies, irrigation channels, pools after heavy rains. These, however, compared with the river, were comparatively easy to deal with.

The reservoir of infection was immense, for numerous bazaars, large and small, encroached on the barracks on all sides.

It was realised, therefore, that if the trial was to be successful a comparatively large dose of quinine would be essential on account of the intensity of the infection to be dealt with. Watson's method, with certain modifications was adopted.

Dose and Salt. -

10 grains of quinine sulphate. It was appreciated that quinine sulphate is not so readily absorbed as other salts and that in treatment it sometimes fails to bring down the temperature, rendering a change of salt necessary. On the other hand it is cheaper and it is more slowly excreted than other salts and so its action is continued over a longer period.

The drug was made up in solution with the addition of Citric Acid.

Frequency of Dosage. -

Daily for three weeks except Saturdays when a purge was given with a view to stimulating the liver and increasing the power of the body to

absorb quinine. It was hoped with this short course and one rest day per week that any disadvantages which might accrue from prolonged administration would not be encountered.

Time of Administration. -

Evening between 6 and 7 p.m. - exact time arranged so as to interfere as little as possible with games. This time also allowed for the maximum concentration of quinine in the blood during the period when the men were most likely to be bitten.

Method of Administration. -

Quinine Stations were established on a verandah in barracks. The parades were not held in hospital, so as to take up as little as possible of the time available for recreation. Bottles of Quinine Solution, a supply of 1 oz. gallipots and a basin of clean water were laid out on a table and a bucket was placed alongside on the floor. One Orderly filled a gallipot with quinine solution and handed it to the first soldier who drank it down and then called out his name (this ensured that the quinine was actually drunk). An N.C.O. recorded the attendance.

The soldier handed the gallipot to a second Orderly who washed it. 100 men could pass through each such station in less than ten minutes.

In the case of the R.A. units the Orderly officer was present at quinine parades. The C.O. of the infantry attended his own parade. A medical officer was present at the earlier parades and frequently later.

Absentees were accounted for and attended later, and arrangements were made for men on guard etc: to receive their dose.

All cases of fever were admitted to hospital and no quinine was given in barrack (outdoor) treatment except as part of the routine post-hospital malarial course. On admission, the urine of fever cases was subjected to the Acid Tanret Test to determine the presence, or absence, of quinine. A routine treatment was carried out. A diaphoretic mixture was given and a sharp purge. Thereafter salicylates were administered until the diagnosis had been definitely established. Two blood films (a thick and a thin) were taken, stained and examined on admission and twice daily thereafter until malaria parasites were found, when quinine treatment was commenced.

In the case of B.T. infections this consisted of Quinine Sulphate grs. X t.d.s. in acid solution, during the first and third weeks, an iron and arsenic tonic only being given in the second week. During the fourth to eigth weeks inclusive the case received Quinine Sulphate grs.X once daily. The patient was discharged from hospital as soon as he was fit enough and he continued the course of treatment in barracks, all doses being marked up on a treatment card. M.T. cases received treatment on the same lines but for three weeks only.

As soon as a diagnosis of malaria was made, the fact was entered up in the duplicate Quinine or Control Roll kept in hospital. The rolls were again checked as cases were discharged.

In 1926 records were maintained till the end of November, though quinine prophylaxis was only given for three weeks in October viz: 4th. to 24th. inclusive.

It was thought that any malaria "suppressed" by the Quinine exhibited during the three weeks in October would reveal itself before the end of November.

The results of 1926 were considered encouraging and instructions were received to continue the trials on a larger scale, and so in 1927 the scope of the experiment was extended to include Indian Troops, as well as British, in Nowshera. The quinine mixture was given for three weeks during September and again for three weeks during October with an interval of ten days between the courses. Owing to the commencement of training camps, manoeuvres etc: it was not considered practicable to continue observations during November. With these exceptions the conduct of the trial and the procedure carried out were exactly similar to those obtaining the previous year. The ten-day interval was adopted to eliminate or diminish any tendency for the production of quinine fast parasites and to avoid any possible harmful effects which might result from ingestion of quinine by a large body of troops over a long and continuous period. It was recognised that the subjective effects of consumption of quinine pass off in a few days and it was felt that the action of quinine on the parasites might be correspondingly reduced for

some reason other than the parasites becoming resistant to quinine.

In 1928, in addition to British and Indian Units in Nowshera, certain British and Indian units in Peshawar were included in the experiment. The procedure was exactly the same as in the previous year except that the dates were different, quinine being given from 24th. September to 13th October and, after a ten day interval, from 24th October to 14th November. Actually from the 1st November, onwards, owing to training - practice camps etc: the issue of quinine became unreliable and records were not kept. This experiment, therefore, was considered to terminate on 31/10/28.

In 1928 also, advantage was taken of the fact that the two-yearly relief of Chitral was taking place. On the outward journey one company of the 3/1st. P ----- R ----- and one company of the 4/6th. P ----- R ----- received prophylactic quinine. On the return journey the same company of the 3/1st. P ----- R ----- and one company of the 3/8th. P ----- R ------ received prophylactic quinine. The remainder of the force acted as a control.

The drug - (bihydrochloride of quinine - 2 tablets of five grains each) was given in the evening during the concentration period at Dargai, during the march from Dargai to Chakdara and for 3 days thereafter. On the return journey, the tablets were given during the march from Chakdara to Dargai and for three days after the troops left Dargai. The Dargai Chakdara zone was heavily infected with Malaria. There was very little Malaria in Chitral itself or in the country between Chitral and Chakdara.

Tablets of Quinine were given because it was impracticable either to make up the solution or to carry it on the line of march. The bihydrochloride was used because of its greater solubility.

Diagnosis of Malaria was on clinical grounds only, the detachment of a Field Ambulance accompanying the column having no facilities for microscopic examination.

In 1929 a total of 701 British and

3560 Indian troops at Nowshera, Peshawar, Shagai, and Landi Kotal in the Peshawar District and Hangu and Thal in the Kohat District were involved in the test which extended from 1st. September to 4th. December, over three months. During this time quinine was only given for two periods each of three weeks. There was an interval of 10 days between these periods. The last six weeks of the experiment served for observing whether any "suppression" of malaria had taken place as a result of the administration of quinine.

The procedure adopted was similar to that already described, with minor local modifications. In certain Indian units the quinine mixture was poured out of a gallipot into the open mouths of the Sepoys as they squatted on the ground in rows, and in most stations, magnesium sulphate was added in the preparation of the quinine mixture already described.

The quinine group was numerically between two and three times the size of the control group.

Observation was kept to see whether the finding of parasites was more difficult in blood films from cases admitted from the quinine group, and whether the cure of the disease (as evidenced by the duration of stay in hospital) was delayed.

The effect of the experiment on two groups of soldiers was also watched. One group was composed of young soldiers fresh from the United Kingdom and not previously exposed to Malarial infection, and the other of slightly older men who had spent one or more seasons in India and many of whom had suffered from malaria.

With a view to forestalling the suggestions (provided that the results turned out to be satisfactory) that quinine might simply have confused the diagnosis and caused malaria to be returned as some other disease, or that some enthusiastic protagonist of quinine prophylaxis might have assisted the production of good results, by unconsciously misdiagnosing cases of malaria in the Quinine Group, it was decided in all cases to record "Total Admissions from All Causes" from both groups. Numbers of admissions from causes other than malaria could, therefore, be closely scrutinised

and any material difference in the two groups investigated.

It should be clearly understood that during the whole period covered by the experiment, viz: four years, there was of course, not the slightest relaxation in the other anti-malarial measures at our disposal which were everywhere prosecuted with the customary vigour and method.

Early in 1930 arrangements were made and details worked out for a final test covering all troops, British and Indian, in the two areas. It was thought that 30,000 men would be involved in the experiment and as events turned out this number would have been greatly exceeded. It was proposed to endeavour to determine among other points, an optimum dosage and whether or not an interval between courses was really necessary or even advisable.

However, the experiment was forbidden by "higher authority" on the grounds that the case for quinine prophylaxis had been completely proved; and orders were received to issue 10 grains of quinine (acid solution) daily, five days a week, for a period of ten weeks from the beginning of September to the middle of November to all troops in malarious stations. This was done and a questionnaire was submitted to all hospitals asking for information on the following points:-

(a) Opinions of Commanding and other officers and medical officers as to the efficacy of quinine prophylaxis as practised.

(b) Popularity with the men.

(c) Any defects noted in the method of administration e.g. dose, time, frequency, duration etc.

(d) Percentage of fever cases to total admissions during period quinine has been administered this year and two previous.

(e) Proportion of B.T. to M.T. cases during period under review and during corresponding period in previous years.

(f) Any evidence ~~of~~ that quinine prophylaxis renders the recognition of malaria parasites in the blood stream more difficult.

(g) Any evidence of quinine-fast parasites.

(h) Any evidence that quinine prophylaxis "masks" malaria or that the cessation of quinine is followed by an outbreak of these "suppressed" cases (say within a month of the cessation of the course).

With a view to the further reduction of malaria in the districts, quinine was given daily for ten days to all arrivals in healthy stations from malarious stations.

In addition, all troops on the line of march were given quinine, and this was continued for ten days after the termination of the march.

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Results.

V. Tabulated results are shown in Appendices as follows:-

Appendix 1 - Summary of Results of Quinine Prophylaxis in Northern India, 1926 to 1929.

Appendix 11 - Results of Quinine Prophylaxis 1926.

Appendix 111 - A. Results of Quinine Prophylaxis (British Units) 1927.
B. Results of Quinine Prophylaxis (Indian Units) 1927.

Appendix 1V - A. Results of Quinine Prophylaxis Experiment, British Troops, Peshawar District, September, October & November, 1929.

" " - B. Results of Quinine Prophylaxis, Indian Troops, Peshawar District, September, October & November, 1929.

Appendix V - Graph to show relative daily incidence (ratios per mille) of malaria in quinine and control roll in 20 units (British and Indian) in 6 stations in Peshawar and Kohat Districts from 1st September to 4th December, 1929.

Appendix V1 - Table giving summary of admissions for "Malaria" and for "All Causes" in drafts from United Kingdom and Jubbulpore to determine the relative effect of Quinine Prophylaxis on troops previously free from infection and troops who had been constantly exposed.

Appendix V11 - Summary of answers to Questionnaire
(vide page 31 of text.)

1926 (vide Appendix 11).

Out of 210 troops who received quinine for three weeks from 4th to 24th October there were 17 cases of malaria during the whole of the month, corresponding to a ratio per thousand of 80.95. During the same period 68 cases occurred in the control group 225 strong, representing a ratio per thousand of 302.22. The incidence of malaria, therefore, in the control group was almost four times that in the quinine group.

The numbers are too small to allow of a detailed analysis but it would appear that the third unit shown (an R.A. Unit) did not re-act to the treatment as well as the other units and that the infantry unit's response was considerably above the average. The interest shown by this infantry unit's commanding officer and the personal supervision given by him may afford the explanation of the difference.

It will also be noted that of the total of 17 cases from the Quinine Group, 6 occurred in the week immediately following the termination of the Quinine Course. This suggests a temporary suppression of malaria during the exhibition of the quinine. That such suppression, if it did occur, was of no material significance is evidenced by the fact that during the following month i.e. November, the incidence of malaria in the two groups was practically identical viz 161.9 ‰ in the quinine Group and 160‰ in the Control Group.

The value of carrying out the Acid Tanret Test on admission to hospital was nil, for it was practically always negative, many hours usually having elapsed since the last dose of quinine.

During this year I was present in the station during the whole period of the experiment and was therefore in a position to give direct personal supervision and to carry out the statistical and other work involved.

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1927 (vide Appendix 1 and Appendices 111a & 111b).

Quinine was given during September from the 5th to the 25th inclusive and during October from the 6th to the 26th inclusive to 194 British Troops and 443 Indians.

British. During the whole of September the malaria admissions from the Quinine Group numbered 6, representing a ratio of 30.93 per mille. and there were 26 admissions from the 270 controls, a ratio of 96.29 per mille. During October there were 3 admissions from the Quinine Group (15.46‰) and 37 cases of malaria among 353 controls (104.81‰).

Indian Troops. No cases of malaria occurred during September or October among the 443 Indian Troops who received the Quinine Course. Among the 441 constituting the controls there were 4 cases (9.07‰) during September and 5 cases (11.34‰) during October.

While, therefore, no cases of malaria were recorded during the course of the experiment in the quinine group of Indian Troops, among British Troops the incidence in September in the Control Group was over three times and in October nearly seven times that of the Quinine Group.

Examining the detailed figures by units it is seen that the R.A. units show better results in comparison with the Infantry unit than was the case in 1926.

The question of suppression could not be investigated owing to the intervention in late October and November of training camps and manoeuvres.

During August and September of this year I was absent from the station carrying on research work for a brother officer who was ill and so the experiment was supervised in September by another officer. The scheme was, however, organised by me, was under my direct control in October, and the figures and results were collected and worked out by me.

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1928 (Appendix 1).

At Nowshera Quinine was given to 371 British and 1142 Indian Troops from 24th September to 13th October and again, after an interval of 10 days, from 24th October to 31st October when owing to training etc., the experiment was terminated. Besides, owing to the low incidence of malaria, the test was of very little value.

Two cases of malaria (5.39 per mille) occurred among the 371 quinine group (British Troops) during the last week of September as against 2 (7.66 per mille) among the control group of 261. During October there were again 2 cases in the quinine group against 9 (31.14%) among the control group of 289.

As regards the Indian Troops there were no cases in either quinine or control groups during the first part of the experiment. During October there were 6 cases in the Quinine Group of 1142 representing a ratio per thousand of 5.26, and 11 cases in the Controls 1018 strong - a ratio of 10.81 per thousand.

Quinine was also given during the Chitral Reliefs. On the outward journey 469 Indian Troops received a dose for 6 to 8 days depending on date of their arrival at Dargai, and 538 received a dose on the homeward journey for 6 to 8 days depending on the date of their departure from Dargai.

The evidence, so far as Nowshera is concerned, ~~and~~ slender though it is, is quite decidedly in favour of quinine prophylaxis.

The figures for the Chitral Relief Column are, however, more convincing, and moreover it should be borne in mind that quinine was only given for a relatively short period of the whole march. On the outward journey the quinine roll of 469 had only 3 cases of malaria (incidence ratio per mille 6.39) whereas the control of 3202 suffered 57 cases (incidence ratio per mille 17.80) i.e. the controls had nearly three times as much sickness due to malaria. On the homeward journey the 538 who were on quinine had no malaria. The control, 3046 strong, had 26 cases representing a ratio of 8.53 per thousand.

During 1928 the experiment was under my administrative control only. Detailed instructions were issued on my initiative,

and the working out of the scheme was left to medical officers on the spot.

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1929 (vide Appendix 1 & Appendices 1VA. & 1VB.)

The scope of the experiment was greatly extended and included 701 British and 3560 Indian Troops in six different stations in Peshawar and Kohat Districts.

The experiment lasted for 95 days though quinine was only given for two periods of three weeks, viz, from 1/9/29 to 21/9/29 and again, after a 10 day interval, from 2/10/29 to 22/10/29. The test was thus divided into 4 distinct parts, viz:-

1. 1st. Quinine Course of 21 days (with one day's rest per week)
2. Interval of 10 days.
3. 2nd.Quinine Course of 21 days (with one day's rest per week).
4. Observation period of 6 weeks.

The detail of results is given by units and in the case of all important totals the ratio per mille has been worked out to aid comparison. Further, to facilitate comparison of the relative incidence in the different periods as indicated above, the equivalent annual ratios of admissions for malaria and admissions from all causes during each period have been added at the bottom of Appendix 1V A, and Appendix 1V B, for Quinine and Control Rolls. In addition, the last column of each of the Appendices referred to shows the estimated saving of admissions for malaria. This estimate is based on the malaria rate prevailing among the controls.

Following two good years, 1928 being a record good year, 1929 proved to be the worst year on record in the district for malaria.

Out of a total of 473 British Troops on the quinine roll 228 contracted malaria during the whole period of 95 days, giving a ratio per mille of 482.03. During the same period there were 145 cases of malaria among 228 controls - a ratio per mille of 635.96. The difference in favour of the Quinine Roll is 153.93 per mille. It is estimated that if the rate prevailing among the controls had prevailed among the Quinine Roll i.e. if no quinine had been given 85 more cases of malaria would have occurred. That is to say, there has been an estimated saving of 85 cases of malaria, calculated by units, or 27 per cent of the estimated total.

The total of admissions from all causes in the Quinine Roll was 302 (ratio per mille 638.48) and in the Control Roll 178 (ratio per mille 780.70), the admission ratio for all causes other than malaria being therefore 156.45 per mille in the case of the Quinine Roll and 144.64 per mille in the Controls. It is evident, therefore, that no great "masking" occurred and that misdiagnosis of malaria for other causes was at all events uncommon. There was a genuine reduction in the sick rate and it seems only reasonable to attribute this reduction to the Quinine Prophylaxis.

Similarly, with the Indian Troops, out of a total of 2455 on the Quinine Roll 854 contracted malaria - a ratio per thousand of 347.86. In the Control Group of 1105 there were 591 cases representing a ratio per thousand of 534.84. The difference in favour of the Quinine Roll is 186.98 per mille. The estimated saving, calculated by units, as a result of the quinine prophylaxis test is 665 cases of malaria or 44% of the estimated total i.e. the number which would have occurred had no quinine been given and assuming that the rate which actually prevailed.in the control would have occurred among the Quinine Group. The total admissions from all causes was 1143 or 465.58 per mille in the Quinine Roll and 810 or 733.03 per mille in the Controls, the admission ratio for all causes other than malaria being 117.72 per mille in the Quinine Roll, a figure little more than half that in the Controls, viz: 198.19 per mille. It is obvious, therefore, that not only did no "masking" or misdiagnoses occur, but that the administration of prophylactic quinine appeared to have a beneficial effect on the general health of these troops. I have often been impressed with this feature in Indian Troops. The reduction in admissions to hospital for diseases other than malaria is due, no doubt, to the fact that much of the sickness from which the Indian suffers is indirectly attributable to malaria or at least aggravated by that disease. So well recognised a fact is this that many authorities commence the treatment of pneumonia in Indians by giving an intravenous injection of quinine even though no parasites of malaria have been found in the blood.

I would like to stress the fact that the results given above cover the whole period of the experiment, viz: 95 days and that quinine was only given for considerably less than half this period viz: two courses of 3 weeks each including a rest of one day each week. Comparison of the results obtained during each of the four periods (vide Equivalent Annual Ratios in last line of Appendices 1V A & 1V B.) shows considerably better results during the periods when quinine was actually being issued, as is to be expected. In the Quinine Roll (British Troops) the equivalent annual ratios of admissions for malaria was 36.7 per mille for the first course and 2461.9 per mille for the second against 686.0 per mille and 3659.1 per mille respectively for the Controls.

Corresponding figures for Indian Troops were 247.7 per mille and 1946.7 per mille for the Quinine group, and 456.1 per mille and 2611.0 per mille for the Controls. Though these results are perhaps somewhat less dramatic in the case of the Indian Troops, the effect of the quinine appears to have been more sustained, for whereas in the case of the British Troops the admissions of the two groups for the 6 weeks period of observation were practically identical, representing equivalent annual ratios of 2627.4 per mille for the Quinine Roll and 2630.0 per mille for the Controls, in the Indian Troops the equivalent annual ratios were 1642.5 for the Quinine Roll and 2831.2 for the Controls. This appears to indicate that with the Indian Troops the beneficial effect of the quinine continued to be felt long after its administration had ceased.

The figures given for each period do not, of course, convey an exact representation of the results of the Quinine administration, for the effect of the quinine was felt for several days after its cessation and the full benefit of its recommencement was likewise not seen for a short period. A reference to the graph in Appendix V bears this out. This graph begins with a low incidence of malaria, the controls suffering somewhat more, and this difference is more marked towards the end of the 1st. Course and extending about 4 days into the interval when the general incidence has begun to rise. During the remainder of the first interval and for about the first 3 days of the 2nd. Quinine Course the full force of the epidemci began to

be felt and the two curves approximated and rose together. From this point for almost four weeks there was a steady fall in admissions from the Quinine Roll with no corresponding drop in admissions from the Controls for the first three weeks at any rate.

After a short respite there was in the last few days of October a sharp exacerbation of the epidemic in which the Quinine Group shared though not to the same extent as the Controls. It should be remembered, also, that the rise did not begin till about a week after the quinine had been stopped. In view of this sudden intensification of the epidemic it is unfortunate that the quinine should have been discontinued so early, for there is no doubt that infections continued heavily till at least the end of October. Little would have been lost by commencing the experiment two or three weeks later, say about the 15th. or 20th. of September, and the test would undoubtedly have been a better one.

Throughout November the sick rate due to Malaria was extremely high but the Quinine curve continued to be considerably below the Control curve till near the end of the month when the epidemic began to die out and the two curves came down together.

The graph fully bears out the tables in their showing that throughout all stages of the experiment there was a definitely reduced incidence of malaria and a definitely lower ratio of admissions to hospital for All Causes among those taking quinine, and that there was no evidence of "Suppression." An examination of the tables reveals that this reduction is shown not only by stations, but by every individual unit, with one small exception, viz: the first R.A. unit in Appendix IV A. The incidence in this unit in the 6 weeks period of observation was greater in the Quinine Group than in the controls, but this was due not so much to any undue sickness in the quinine group as to an unaccountable freedom from sickness in the Control 1 Group. A comparison of the sick statistics in the second R.A. Battery and in other units should make this clear.

Effect of Prophylactic Quinine on subsequent treatment.

Officers were asked to note whether any difficulty occurred in demonstrating parasites in the blood of cases of

malaria who had been receiving prophylactic quinine or whether any effect on treatment was observed. The general opinion was that parasites were quite as easily demonstrated in cases of malaria admitted from the quinine roll as in cases from the Control, and that treatment was in no way affected nor the stay in hospital prolonged. These findings were in keeping with my own experience.

More precise work was done in Nowshera, and Colonel James (44) recording his experience the following year (1930) with Indian Troops wrote "Of fever cases which eventually proved to be malaria during the last eight weeks of Prophylactic Quinine only six out of a total of forty-six were missed at the first blood examination."

During the experiment of 1929 the average stay in hospital of British Troops in Nowshera admitted for malaria was 5.90 days for Quinine Roll, and 5.08 for Controls. The duration of fever after admission was also worked out in 100 consecutive cases. For Quinine Roll cases it was 3.1 days and for Controls 3.4. N.B. The period after "Admission" included any period of "Detention" prior to actual admission.

One officer reported that many of his cases of malaria admitted from the Quinine Roll were afebrile. They complained of Malaise, headache, loss of appetite etc: and it was only when the blood examination proved positive that a definite diagnosis could be made. These cases rapidly cleared up on quinine.

It would appear, therefore, that prophylactic quinine in no way prejudiced the diagnosis or treatment of intercurrent malaria.

Influence of Temperature. The experience of the unit stationed at Shagai is of interest. There were 183 on the Quinine Roll and 93 Controls.

Up to the date of departure for Landi Kotal (normal inter-Khyber reliefs) about 10 days after completion of the second quinine course, there had occurred 6 and 5 cases respectively among the Quinine and Control groups. The day following the arrival of the unit at Landi Kotal a sharp outbreak of malaria began, and the curious feature is that the

control group were by far the heaviest sufferers, 32 cases occurring within the next 2½ weeks, a ratio per mille of 344.1, against 10 for the same period in the quinine group, a ratio per mille of 54.6. The only explanation I can offer is the following:- During the malaria season at Shaghai a large proportion of the troops became infected but the number of parasites present in the blood was in most cases insufficient to cause an attack. The fatigue of the march (completed in one day) may have had some effect, but it is thought that the sudden change to the much lower temperature at the higher altitude of Landi Kotal lowered the body resistance and allowed the malaria parasites to get the upper hand. Most of the infections occurring in the Quinine Group were destroyed as a result of the course of Quinine. The infections were not contracted at Landi Kotal, for apart from the fact that malaria cases began the day after arrival in Landi Kotal, units which had been continuously in the station during the malaria season had been practically free from malaria.

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Effect of Quinine Prophylaxis on troops previously free from infection compared with troops which had been constantly exposed to malaria.

A brigade of Artillery recently arrived from Jubbulpore, consisted partly of seasoned troops, all of whom had spent one season and most many seasons in a malarious cantonment, and partly of a draft from home. The opportunity was taken to observe the results in each group.

The detailed results are given in Appendix VI. The malaria admissions (both drafts) for the Quinine group represented a ratio per mille of 498 as against a similar ratio of 570 for the Controls, a difference in favour of the Quinine Group of 72 per thousand. Corresponding figures for Admissions for "All Causes" were 652 (Quinine) and 710 (Control) the Quinine group benefitting to the extent of 58 per thousand.

In both the Quinine and Control Groups a higher admission ratio is observed in the Jubbulpore Draft. The difference is more marked in the Controls viz: 94 per thousand. In the Quinine Group the difference is 69 per thousand. Again in the Jubbulpore group the incidence in the Quinine Roll is 538 per mille and in the Controls 608, a difference of 68 per thousand. Similar figures for the U.K. draft were 469 (Quinine) and 512 (Control) the difference being only 43 per thousand.

These results, thought the extent of the experiment was small, appear to indicate that malaria was more prevalent among the "old stagers" presumably owing to relapses of old infections, and that the "old stagers" also benefitted from the quinine to a somewhat greater extent than the new arrivals. This was in all likdihood due to the fact that the courses of quinine assisted in clearing up old standing infections.

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Cost of Quinine Prophylaxis.

Working out the net cost of the whole experiment would involve a large amount of clerical labour. Take, however, the Indian Troops in Nowshera as an example (vide Appendix IV B):-

(a) 1849 men were given 360 grains of Quinine Sulphate each (if they lasted the course).

The cost at Rs 18/ per lb. was Rs 1710/-

This is less than One Rupee per man.

This does not take in consideration the fact that many men failed to complete the course. Actually 438 out of the total of 1849 were admitted to hospital before the completion of the 2nd Quinine Course, so the actual cost of the quinine was considerably less than the figure given.

(b) The estimated saving in Malaria admissions was 585, calculated by units.

Take the average amount of quinine given to each case of malaria as thirty grains daily for three weeks (Actually B.T. cases got more, M.T. less).

Cost of Quinine @ Rs 18/ lb. was Rs 948/-

This is the cost of treatment with quinine alone, and when one considers the cost of other treatment (diaphoretics, soda salicylate, tonics etc.) and the expenditure incidental to the stay in hospital, not to mention the loss to the unit in working days for training, etc: the contraction of a disease so liable to relapse, a disease which plays no little part, direct or indirect, as a cause for invaliding, the cost of the preventive treatment seems amply justified.

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1930.

As already explained there was no controlled experiment, superior authority having ruled that the case for Quinine Prophylaxis in the District had been proved beyond a shadow of doubt. All ranks were to receive quinine 5 days a week from the beginning of September to the middle of November and no controls were allowed.

The malaria curve commenced to rise earlier than usual. This was due to relapses of infections contracted during the severe epidemic of the previous autumn. In July and August the incidence was unduly high, an example of the "flowering time" of malaria parasites recently described by Martini (45), but in September, soon after the commencement of Prophylactic Quinine the outbreak suddenly died out and in the months when the disease is usually at its height, the sick rate was extremely low. How far the quinine was responsible for this eminently satisfactory state of affairs it is impossible, in the absence of controls, to state with any degree of assurance. The malaria curve so far as Nowshera is concerned is illustrated in an article in the Indian Medical Gazette by Lt.-Col. J.F. James, (46)

If quinine has played no part in the welcome freedom from Malaria during September and October, 1930, the phenomenon is capable of explanation according to the Quantum Theory of Gill (47) in that immunity from Malaria has become extremely high as a result of the severe epidemic of 1929. It may here be observed that a similar freedom from malaria occurred in 1931, so there was still no loss of equilibrium between the quantum of infection. Quinine Prophylaxis was commenced, but soon discontinued.

A questionnaire was sent out to 13 hospitals. Details have already been given - see page 31 .

A summary of the answers is shown in Appendix VII.

The opinions expressed may be summarised as follows:-

(a) Commanding and other officers consider Quinine Prophylaxis, as practised in Peshawar District, effective in reducing materially sickness due to malaria. Commanding

Officers in particular have been enthusiastic, the difficulty in past years having been to secure a body of men to act as control. They naturally enough want the whole unit to benefit and do not altogether appreciate the scientific reason for the control.

Officers of the medical services, many thoroughly sceptical at first, became thoroughly convinced as to the efficacy of this form of preventive treatment.

(b) Apart from the objectionable taste of quinine which is generally disliked, the process was popular with the men on the whole, and particularly so with many Indian units,. Many Indian Other Ranks brought their children for quinine.

There appeared to be a general feeling of confidence in the beneficial effects to be derived from the course.

(c) The only suggestion made was that the full dose of 10 grains should be assured by using a measure slightly larger than one ounce or by making up the mixture somewhat stronger, say 12 grains to the ounce.

(d) In the epidemic year 1929 the percentage of fever cases to total admissions was in most cases extremely high.

(e) It will be noted also that in the epidemic year 1929 the incidence of M.T. malaria was relatively very high.

(f) There was no evidence of Quinine-fast parasites.

(g) With two exceptions, both very small hospitals, all agreed that quinine prophylaxis did not render more difficult the detection of malaria parasites in the blood stream.

(h) There was no evidence of "Suppression" of malaria.

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Is Quinine Prophylaxis Worth While?

I think it must be admitted, judging from the results obtained in the experiments during the 4 years to 1929, that quinine prophylaxis as practised in Peshawar & Kohat Districts did actually effect a considerable reduction in the Hospital Admission ratio. It is fully appreciated that the accuracy of the term "prophylaxis" as applied to the method adopted is open to argument. Perhaps "massed treatment of potentially infected troops" would be a more accurate, though somewhat cumbersome description. The choice of terms, however, is of little moment.

In addition to the reduction in malaria directly due to Quinine Prophylaxis, it appears to me that a further reduction may result indirectly. Fewer individuals becoming infected, there are fewer carriers to infect Anopheline mosquitoes, a smaller proportion of which become infective. Thus the risk of being bitten by an infected mosquito and so contracting malaria is diminished.

It is not contended that Quinine Prophylaxis is the best method of reducing sickness due to malaria. There are many drawbacks to its use which may seriously interfere with its effectiveness. Quinine has an unpleasant taste, its administration must be very carefully supervised to ensure that the dose is actually consumed and that it is absorbed. Also the expenditure entailed is of necessity a recurring one.

But it is not suggested that Quinine Prophylaxis should take the place of other anti-malarial measures of which probably screening holds out greatest promise, though up till recently in the districts concerned anti-mosquito measures (mostly anti-larval measures) have been chiefly relied upon, with very indifferent results. The large initial cost of screening is a very serious obstacle, however, and this method is seldom practicable under service conditions, and more especially with the type of campaign common on the Frontier. In such circumstances even the mosquito net has to be discarded, and the only defensive weapon remaining is quinine.

All the disadvantages of a prolonged course of quinine including the cost, which is rather less than eight annas a man for a three weeks' course must be weighed carefully to determine whether the benefits likely to accrue outbalance the disadvantages. In Appendix I.I have included a column which shows the estimated saving, year by year, of Malaria Admissions as a result of the quinine administered. This is, of course, a hypothetical figure which is obtained by assuming that the rate among the controls would have prevailed generally if no quinine had been given. This rate is applied to the quinine roll, and from the resulting figure is subtracted the total which actually occurred. This gives the "estimated saving " which affords a fair idea of the effect of the quinine prophylaxis. From the results for 1926 and 1929 the trouble and expense involved seem amply justified. In 1926 the administration of quinine to 210 men for three weeks at a cost of approximately one hundred rupees was a very small price to pay for a saving of 47 cases of malaria. In 1929, the estimated saving during the malaria season among British Troops was 73 cases. Against this saving must be debited the labour and energy expended in issuing quinine to 473 men for two periods of three weeks each, the organisation necessary and the collection of statistics. The cost in quinine was in the region of four hundred rupees. Surely this is not excessive? One must remember also that the organisation required and the statistical and other work involved in an "experiment" of this nature are very much greater than would ordinarily be the case. This fact was duly appreciated in 1930 when there was no experiment and although quinine was given over a much longer period than in any previous year. Again, in Indian Troops in 1929 for a sum of about Rs. 2000/ an estimated saving of 459 cases of malaria was effected. An even better return is shown if the figures for Nowshera alone are considered.

The expense may be thought high but one has to consider the large sums of money being spent on anti-mosquito measures (exclusive of screening,)- as much as Rs. 10,000/ per annum in one cantonment alone without any apparent reduction in the incidence of malaria.

The results cited above for 1926 and 1929 in my opinion justify the expense and work involved. In these years malaria was in epidemic form and chiefly M.T. in type.

The position as regards the rest of the experiment is different, however, With the exception of the case of British Troops in 1927 when quinine was given in September and October for three weeks each month to 194 men at a cost of not far short of Rs. 200/, the estimated saving being 30 cases of malaria, most people will conclude that the saving effected was not worth while e.g. a possible saving of six malaria cases was effected in Indian Troops in 1928 at a cost of about Rs.2000/ in quinine, not to mention the trouble and worry involved in distributing quinine to 1142 men of several units for two periods of 3 weeks each. The same can be said of the results for British Troops in 1928 and for Indian Troops in 1927 and the Chitral Relief Column in 1928, though in these instances, and particularly the British Troops in 1928, the case is not so marked.

My contention, therefore, is that while the value of Quinine Prophylaxis in reducing sickness due to malaria in British and Indian Troops in Peshawar and Kohat Districts in epidemic years has been proved one cannot make out a good case in support of its practicability in non-epidemic years, particularly in Indian Troops.

As a result of the experience gained during the years 1926-1930, I would confidently recommend the issue to all troops in malarious stations in Peshawar and Kohat Districts, during epidemic years, of prophylactic quinine - 10 grains daily in solution five times a week from mid-September to mid-November.

Epidemic Malaria can now be forecasted (48) with assurance, though it should be borne in mind that the conditions in different parts of India vary enormously. In 1929 the admission ratio for malaria for the whole of India was the best for any year except 1928, since the Great War, (49) yet the North West Frontier Province suffered by far its worst epidemic on record.

Though eminently satisfactory results have been obtained, I am convinced that these can be greatly improved on. The dose may require modification to suit

local conditions, intensity of infection etc:. A more suitable preparation may be substituted e.g. the experience gained during the Chitral Reliefs demonstrated that tablets could be given satisfactorily. If the disadvantages inherent in tablets could be successfully overcome, the increased popularity resulting from their use might outweigh the increased cost. During a campaign tablets may be the only feasible method of administration. There are other possible avenues for improvement. My own small experience of plasmoquine in treatment, and the recorded results of Williams (50), Deeks (51), Barber & Kemp (52), Whitmore, Ronnefeldt (53), and others, suggest a wide scope in the field of prophylaxis for this and similar drugs which attack the parasite in its sexual phase. Recently, James, Nichol and Shute (54) , have carried out an experiment in which 10 volunteers were given plasmoquine for 7 days. On the second day they were bitten by mosquitoes heavily infected with the sporozoites of B.T. Malaria. Not one became infected. Four control cases, one of whom was given quinine for 8 days, developed malaria within 14 days. Other trials by these workers have been equally successful.

It must not be forgotten, however, that plasmoquine sometimes produces alarming symptoms. But, if this disability can be overcome, a combination of quinine and plasmoquine may prove the ideal compound for both prophylaxis and treatment.

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Summary and Conclusions.

VI.

1. Quinine Prophylaxis, as put to the test in Peshawar & Kohat Districts in the years 1926 to 1929, effected a considerable reduction in the sickness due directly and indirectly to malaria. This was a true reduction which was reflected in a fall in the ratio of admissions from "All Causes."

2. There was evidence that a reduction in sickness due to causes other than malaria followed its use in Indian Troops.

3. Quinine Prophylaxis appeared to be somewhat more effective in troops previously exposed to infection than in troops not so exposed, due no doubt to its curative effect in some cases which, without the course, would have relapsed.

4. No ill effects attributable to Quinine Prophylaxis were noted, and ability for work or games was not affected.

5. 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 quinine prophylaxis, and in one hospital many cases admitted from the Quinine Roll were noteworthy for their mildness.

6. The recognition of malaria parasites in cases of malaria was not rendered more difficult by the fact that such cases had been taking prophylactic quinine.

7. There was no evidence that Quinine Prophylaxis suppresses malaria and that this suppressed malaria shows itself after the cessation of quinine.

8. There was no evidence of the production of quinine-fast parasites.

9. The "interval" (10 days' rest period between courses) was not only unnecessary, but actually detrimental.

10. Cold as a factor in lighting up latent cases of malaria was demonstrated. The same incident

revealed the power of "quinine prophylaxis" in destroying this latent malaria before it could give evidence of its presence.

11. The cost of quinine prophylaxis is considerable, viz: about eight annas per man for a three weeks' course. There is a great deal of work involved in the process, and constant supervision is necessary. It should be remembered also that these extra duties are thrust on hospital staffs depleted by the necessary calls of leave, exhausted after the strain of the hot weather, and working at full pressure with other anti-malarial duties as well as with the ordinary medical routine. Bearing these facts in mind the meagre beneficial results obtained during non-epidemic years can hardly justify the cost. In epidemic years, however, the outlay in money and energy has been amply repaid by the satisfactory outcome of the experiment described. I consider, therefore, that malaria forecasts should be carefully studied in malarious districts of the North West Frontier Province and that Quinine Prophylaxis should be given in years forecasted as epidemic. The method recommended is a ten grain dose five times a week from mid-September to mid-November, with a weekly aperient.

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VII.

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A P P E N D I X. I.

Appendix 1.

Summary of Results of Quinine Prophylaxis Experiment in Northern India 1926 to 1929.

BRITISH TROOPS.

Place.	Period of Experiment.	Received Prophylactic Quinine. Number receiving Quinine with Dates.	*Number of Cases of Malaria. (Incidence per ‰ in brackets.)	Received NO Prophylactic Quinine. Number receiving no Quinine.	*Number of Cases of Malaria. (Incidence per ‰ in brackets.)	Estimated Saving of Malaria Admissions among Quinine Roll. (Estimate based on rate prevailing among Controls.)	Total Numbers under experiment.
Nowshera.	October 1926	210 (4/10/26 to 24/10/26.)	17 (80.95‰)	225	68 (302.22‰)	47	435.
	November 1926.		34 (161.9‰)	-	36 (160 ‰)		-
do.	September 1927.	194 (5/11/27 to 25/11/27.)	6 (30.93‰)	270	26 (96.29‰)	13	464
	October 1927.	194 (6/10/27 to 26/10/27.)	3 (15.46‰)	353	37 (104.81‰)	17	547
do.	24th/30th.Sept. 1928.	371 (24/9/28 to 30/9/28.)	2 (5.39 ‰)	261	2 (7.66‰)	1	632
	October 1928.	371 (1/10/28 - 13/10/28 & 24/10/28 to 31/10/28.)	2 (5.39 ‰)	289	9 (31.14‰)	10	660
Nowshera & Peshawar.	1st.Sept.1929 to 4th.Dec. 1929.	473 (1/9/29 to 21/9/29 & 2/10/29 to 22/10/29.)	228 (482.03‰)	228	145 (635.96‰)	73	701

INDIAN TROOPS.

Nowshera.	September 1927.	443 (5/9/27 to 25/9/27.)	-	441	4	(9.07‰)	4	884
	October 1927.	443 (6/10/27 to 26/10/27.)	-	441	5	(11.34‰)	5	884
do.	24th.to 30th. Sept. 1928.	1142 (24/9/28 to 30/9/28)	-	953	-		-	2095
	October 1928.	1142 (1/10/28 to 13/10/28 & 24/10/28 to 31/10/28.)	6 (5.26‰)	1018	11	(10.81‰)	6	2160
Chitral Relief Column.	Outward Journey September 1928.	469 (6 to 8 days)	3 (6.39‰)	3202	57	(17.80‰)	5	3671
	Homeward Journey. October 1928.	538 (6 to 8 days)	-	3046	26	(8.53‰)	5	3046
Nowshera, Peshawar, Shagai, Thal, Hangu, Landi Kotal.	1st Sept.1929, to 4th.Dec. 1929.	2455 (1/9/29 to 21/9/29 & 2/10/29 to 22/10/29.)	854 (347.86‰)	1105	591	(534.84‰)	459	3560

* These totals include all cases of malaria admitted, not merely during the period when quinine was being given, but during the whole period of experiment (vide column 2.)

Appendix 11.

A P P E N D I X 1 1.

Results of Quinine Prophylaxis - 1 9 2 6.

Unit	Barrack Room. No.	Average Strenght during October.	Number who received prophylactic quinine 4/10/26 to 24/10/26.	Number who received no prophylactic quinine.	Malaria admissions during October. Number who received prophylactic quinine.	Malaria admissions during October. Number who received no prophylactic quinine.	Malaria admissions during November. Number who received prophylactic quinine.	Malaria admissions during November. Number who received no prophylactic quinine.
--Field Bty.R.A.	15) 16)	114	50	64	5 (A)	21	7	4
** Field Bty.R.A.	1) 2)	109	56	53	2	12	14	11
--Field Bty.R.A.	11) 12)	100	39	61	7 (B)	16	7	14
--F.A.C.,R.A.	19)	40	26	14	1 (C)	3	-	1
"A" Coy.---- Highlanders.	6) 7) 8)	72	39	33	2 (D)	16	6	6
Total.		435	210	225	17 (80.95‰)	68 (302.22‰)	34 (161.9‰)	36 (160‰)

Note. (A) One of these cases was admitted after the completion of the 3 weeks course.
(B) Four of these cases were admitted " " " " " " " "
(C) This case was admitted after the completion of the course(In this instance the course only lasted
(D) One case was admitted on the 2nd day of the course & the (7 days as the unit moved to Akora Training
other a week after completion of the course. Camp.)

A P P E N D I X. III A.

Appendix 111a.

RESULTS OF QUININE PROPHYLAXIS. B R I T I S H U N I T S - 1 9 2 7.

Unit.	Average Strength September.	Average Strength October	No. who received Prophylactic Quinine 5th. to 25th. Sept. & 6th. to 26th. Oct.	No. of Controls Sept. / Octb.	Malaria Admissions during September. Recipients of Prophylactic Quinine. Actual Nos.	Incidence per 1000	Control. Actual Nos.	Incidence per 1000.	Total Cases in Unit. Actual Nos.	Incidence per 1000.	Malaria Admissions during October. Recipients of Prophylactic Quinine. Actual Nos.	Incidence per 1000.	Control. Actual Nos.	Incidence per 1000	Total Cases in Unit. Actual Nos.	Incidence per 1000.
--Fd.Bty.R.A.	103	131	40	63 / 91	1 (a)		6		7		-		9		9	
--Fd.Bty.R.A.	101	134	41	60 / 93	1 (b)		8		9		-		10		10	
--Fd.Bty.R.A.	114	132	54	60 / 78	3 (c)		7		10		1(e)		10		11	
--Bde.F.A.C.	40	43	15	25 / 28	-		1		1		1(f)		2		3	
"B"Coy.2nd.Bn. X Fusiliers.	106	107	44	62 / 63	1 (d)		4		5		1(g)		6		7	
	464	547	194	270 / 353	6	30.93‰	26	96.29 ‰	32	68.96 ‰	3	15.46‰	37	104.81‰	40	73.13‰

(a) One case admitted hospital on 1st. day of 1st.course.
(b) " " " " " 2nd. " " " "
(c) " " " " " 3rd. " " " "
(-) " " " " " 6th. " " " "
(-) " " " " " 8th. " " " "
(d) " " " " " 3rd. " " " "
(e) " " " " " 3rd. " " 2nd " "
(f) " " " " " 8th. " " " "
(g) " " " " " 12th. " " " ".

Appendix 111b.

APPENDIX 111 B.

Results of Quinine Prophylaxis (Indian Units) 1927.

Unit	Average Strength Septr.	Average Strength Octr.	No. who received Prophylactic Quinine 5th to 25th Septr. & 6th. to 26th. Octr.	No. of Controls.	Malaria admissions during September.						Malaria admission during October.					
					Recipients of Prophylactic Quinine.		Control.		Total Cases in Unit.		Recipients of Prophylactic Quinine.		Control		Total Cases in Unit.	
					Actual Nos.	Incidence per 1000.	Actual Nos.	Incidence per 1000.	Actual Nos.	Incidence per 1000.	Actual Nos.	Incidence per 1000	Actual Nos.	Incidence per 1000	Actual Nos.	Incidence per 1000.
-/- Punjab Regt.	395	416	99	98	-	-	-	-	13	-	-	-	1	-	12	
-/- Punjab Regt.	456	513	116	120	-	-	2	-	5	-	-	-	1	-	2	
-/- Sikh Regt.	862	675	98	98	-	-	1	-	24	-	-	-	1	-	12	
-/- Sikh Prs.	489	508	80	87	-	-	-	-	-	-	-	-	1	-	1	
-/- I.B.T. Coy.	304	303	50	38	-	-	1	-	3	-	-	-	1		1	
Totals.	2506	2615	443	441	-	-	4	9.07‰	45	17.96‰	-	-	5	11.34‰	28	10.71‰

A P P E N D I X IV A.

RESULTS OF QUININE PROPHYLAXIS EXPERIMENT. - British Troops. Peshawar District.

September, October & November, 1929.

ADMISSIONS FROM QUININE ROLL.

Station Unit.	Strength.	1st Course.		Interval.		2nd. Course.		Next 6 Weeks.		T O T A L.	
		Mal.	Total.	Mal.	Total	Mal.	Total.	Mal.	Total.	Mal.	Total.
PESHAWAR.											
- (M) Bty. R.A.	30	-	4	2	3	3	4	8	10	13	21
- Fd. Bty. R.A.	36	-	5	2	3	2	3	6	10	10	21
Total Peshawar.	66	-	9	4	6	5	7	14	20	23	42
Ratio per Mille - do.		Nil		60.6		75.76		212.12		348.48	636.36
NOWSHERA.											
"B" Coy. 2nd. ——	130	1	2	5	8	20	23	50	59	76	92
Dett: Distt: Sig.	13	-	-	-	-	-	1	-	-	-	1
- Fd. Bty. R.A.	93	-	4	4	5	16	19	32	41	52	69
- Fd. Bty. R.A.	82	-	-	2	3	15	17	21	29	38	49
- Fd. Bty. R.A.	72	-	-	2	4	9	13	22	26	33	43
- Fd. Bde. F.A.C.R.A.	17	-	-	-	-	2	2	4	4	6	6
Total Nowshera.	407	1	6	13	20	62	75	129	159	205	260
Ratio per Mille Nowshera		2.46		31.94		152.34		316.95		503.69	638.82
Total Peshawar & Nowshera.	473	1	15	17	26	67	82	143	179	228	302
Ratios per Mille Peshawar & Nowshera.		2.11	31.71	35.94	54.97	141.65	173.36	302.38	378.44	482.03	638.48
Equivalent Annual Ratio per Mille.		36.7	551.1	1311.8	2006.3	2461.9	3013.2	2627.4	3288.8	181.7	2479.1

ADMISSIONS FROM CONTROL ROLL.

Strength.	1st Course.		Interval		2nd Course.		Next 6 Weeks.		Total.		Estimated saving of Malaria admissions among Quinine Roll. (Estimate based on rate prevailing among Controls.)	
	Mal.	Total.	Mal.	Total.	Mal.	Total	Mal.	Total.	Mal.	Total.	Numbers.	Percentage
30	1	2	3	3	4	4	1	3	9	12	- 4	44%
31	2	6	3	4	11	11	7	9	23	30	+ 17	63%
61	3	8	6	7	15	15	8	12	32	42		
	49.18		98.36		245.90		131.15		524.59	688.52		
50	1	2	6	6	10	12	31	36	48	56	+ 49	39%
5	-	-	-	-	1	1	1	1	2	2	+ 5	100%
40	1	1	2	2	10	10	11	12	24	25	+ 4	7%
32	1	7	2	3	6	7	7	9	16	26	+ 3	7%
35	3	4	3	3	5	5	10	13	21	25	+10	23%
5	-	-	-	-	1	1	1	1	2	2	+ 1	14%
167	6	14	13	14	33	36	61	72	113	136		
	35.93		77.84		197.61		365.27		676.65	814.37		
228	9	22	19	21	48	51	69	84	145	178	* +85	27%
	39.47	96.49	83.33	92.10	210.53	223.69	302.63	368.42	635.96	780.70		
	686.0	1677.1	1041.6	1861.8	3659.1	3887.8	2630.0	3201.7	2469.4	3881.4		

* N.B. This is the sum of the estimated savings of each unit and does not agree with the estimated saving worked out on the total incidence of malaria for the whole area.

A P P E N D I X. IV B.

RESULTS OF QUININE PROPHYLAXIS EXPERIMENT - Indian Troops. Peshawar & Kohat Districts.

September, October, November, 1 9 2 9.

ADMISSIONS FROM QUININE ROLL.

Station & Unit.	Strength.	1st. Course. Mal.	1st. Course. Total.	Interval. Mal.	Interval. Total.	2nd. Course. Mal.	2nd. Course. Total.	Next 6 Weeks. Mal.	Next 6 Weeks. Total.	Total. Mal.	Total. Total.
PESHAWAR.											
— Sikh Regt.	135	-	4	-	3	3	18	12	29	15	54
— D.T.T. Coy.	148	2	8	2	3	4	10	29	34	37	55
Total Peshawar.	283	2	12	2	6	7	28	41	63	52	109
Ratio per Mille Peshawar.		7.07		7.07		34.73		144.87		183.74	385.16
NOWSHERA.											
— Distt: Signals.	24	-	-	-	-	9	9	5	5	14	14
— Mountain Battery.	109	3	5	4	4	11	16	34	41	52	66
— Fd. Bty. R.A.	26	-	1	1	1	2	3	4	7	7	12
— Fd. Bty. R.A.	38	1	4	-	1	5	6	4	16	10	27
— Fd. Bty. R.A.	24	-	2	3	4	1	2	1	3	5	11
— F.A.C.	32	-	-	1	1	-	1	5	10	6	12
— Bombay Pioneers.	222	4	9	15	19	41	45	63	69	123	142
— Sikh Regt.	538	2	6	11	17	28	29	111	132	152	184
- Dogra Regt.	350	4	4	10	10	57	64	102	115	173	193
—Punjab. Regt.	175	3	5	13	14	16	18	19	51	51	88
- 1.B.T. Coy.	198	11	17	11	13	69	74	44	57	135	161
- D.T.T. Company.	113	-	1	6	8	25	25	16	34	47	68
Total Nowshera.	1849	28	54	75	92	264	292	408	540	775	978
Ratio per Mille Nowshera.		15.14		40.56		142.78		220.66		419.14	528.93
SHAGAI.											
Landikotal from 30/10/29.											
Raj: Rifles.	183	3	9	2	4	1	8	11	14	17	35
Ratio per Mille		16.39		10.93		5.46		60.11		92.89	191.26
KOHAT DISTRICT.											
Thal/Hangu from 9/11/29.											
Punjab Regt.	92	1	2	1	2	-	2	3	6	5	12
Ratio per Mille		10.87		10.87				32.61		54.35	130.43
Hangu up to 9/11/29.											
Jat Regt:	48	1	2	-	-	3	5	1	2	5	9
Ratio per Mille		20.83				62.50		20.83		104.16	187.50
GRAND TOTAL.											
PESHAWAR & KOHAT DISTTS.	2455	35	79	80	104	275	335	464	625	854	1143
Ratio per Mille		14.25	32.18	32.59	42.36	112.08	136.46	189.00	254.58	347.86	465.58
Equivalent Annual Ratio per Mille.		247.7	559.3	1189.4	1546.2	1946.9	2371.7	1642.5	2212.4	1350.7	1807.8

N.B. This is the sum of the estimated savings of each unit and does not agree with the estimated saving worked out on the total incidence of malaria for the whole area.
(1) Calculated on total incidence all Indian Units in Nowshera.

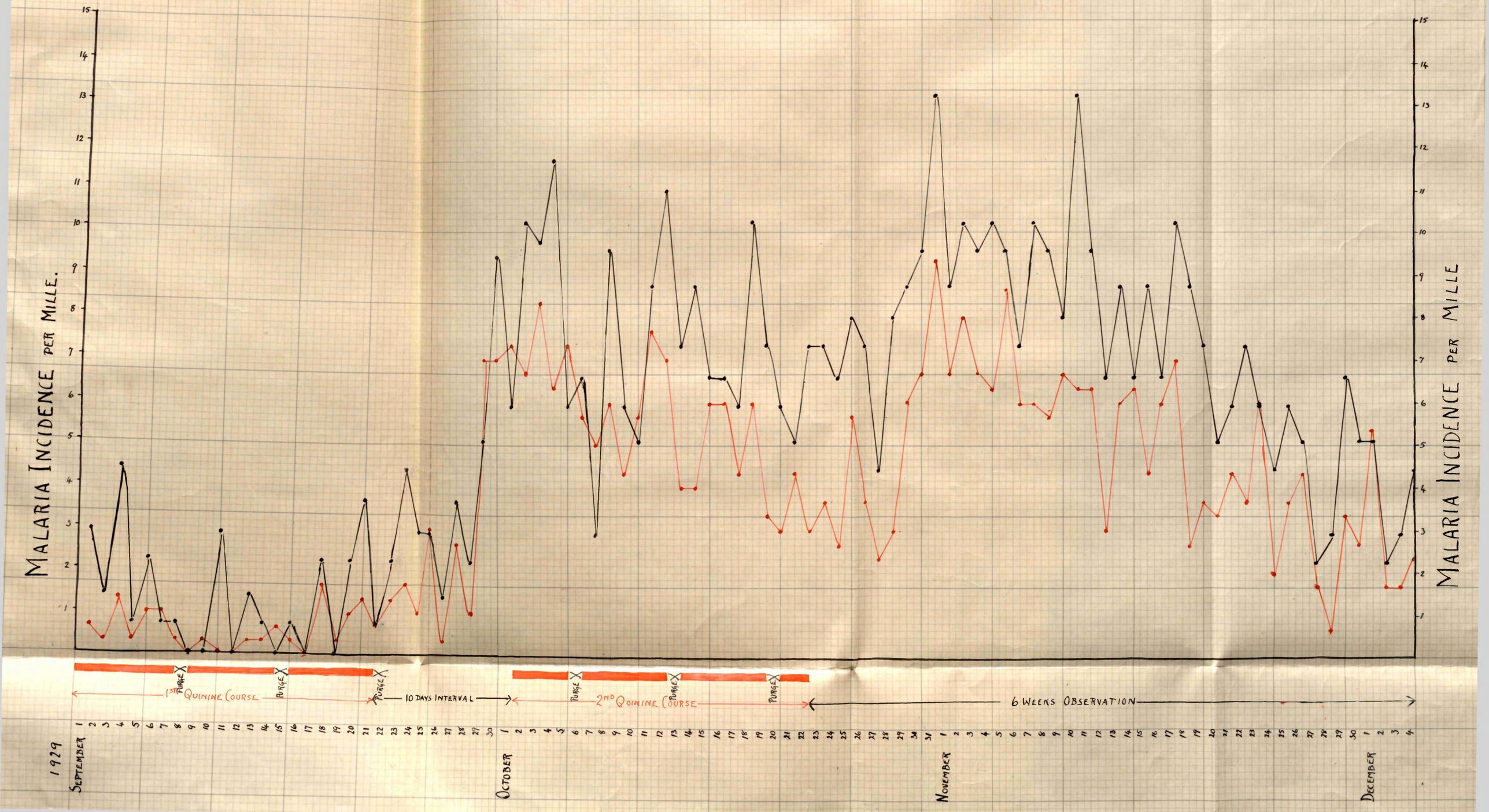
Strength	ADMISSIONS FROM CONTROL ROLL 1st. Course. Mal.	1st. Course. Total.	Interval. Mal.	Interval. Total.	2nd. Course. Mal.	2nd. Course. Total.	Next 6 Weeks. Mal.	Next 6 Weeks. Total.	Total. Mal.	Total. Total.	Estimated saving of Malaria admissions among Quinine Roll (Estimate based on rate prevailing among Controls.) Number.	Percentage.
138	1	7	4	4	23	30	21	48	49	89	33	69%
143	3	6	2	3	23	28	21	23	49	60	14	26%
281	4	13	6	7	46	58	42	71	98	149	47	47%
	14.23		21.35		163.70		149.47		348.75	530.25		
9	-	-	-	-	7	8	3	4	10	12	13	48%
36	1	1	2	3	6	9	26	28	35	41	54	51%
9	-	-	-	-	2	2	1	4	3	6	2	22%
13	2	3	-	-	6	6	4	4	12	13	25	71%
9	1	2	1	1	2	2	1	2	5	7	8	61%
11	-	-	-	-	2	3	2	5	4	8	6	50%
79	1	4	4	7	18	22	34	39	57	72	37	23%
141	1	3	3	4	12	16	61	76	77	99	142	48%
120	1	2	3	4	21	25	82	88	107	119	139	45%
55	3	3	5	5	13	20	15	30	36	58	64	56%
70	3	11	5	7	12	16	43	50	63	84	43	24%
38	-	3	3	4	11	13	11	25	25	45	27	36%
590	13	32	26	35	112	142	283	355	434	564	(1)(585	43%)
	22.03		44.07		189.83		479.66		735.59	959.53		
93	4	19	-	3	-	7	33	36	37	65	46	63%
	43.01						354.84		397.85	698.92		
92	2	3	4	4	5	9	1	4	12	20	7	58%
	21.74		43.48		54.34		10.87		130.43	217.39		
49	6	6	-	2	3	3	1	1	10	12	5	50%
	122.45				61.22		20.41		204.08	244.89		
1105	29	73	36	51	166	219	360	467	591	810	*	
	26.24	66.06	32.58	46.15	150.23	198.19	325.79	422.63	534.84	733.03	665	44%
	456.1	1148.2	1189.1	1684.6	2611.0	3444.8	2831.2	3672.9	2076.7	2846.3		

Quinine Prophylaxis Experiment ~ Peshawar & Kohat Districts - 1929.

Graph to show Relative incidence of Malaria in Quinine and Control Rolls of 20 Units (British & Indian) in 6 Stations.

Quinine Roll —— Strength 2928 Admissions - Malaria 1082. (369.34%) 1st Sept. to 4th Dec. Admissions - All Causes 1445 (493.51%) 1st Sept. to 4th Dec. (Not Charted.)

Control Roll —— Strength 1333 —— Do —— 736 (552.14%) —— Do —— 988 (741.19%)



A P P E N D I X. VI.

Appendix VI.

QUININE PROPHYLAXIS EXPERIMENT.

Summary of admissions for "Malaria" and for "All Causes" in drafts from U.K. and Jubbulpore to determine the relative effect of Quinine Prophylaxis on troops previously free from infection and troops who had been constantly exposed.

U N I T.	QUININE GROUP.							CONTROL GROUP.						
	Jubbulpore Draft.		U. K. Draft.		T o t a l.			Jubbulpore Draft.		U. K. Draft.		T o t a l.		
	Strength.	Malaria Admissions.	Strength.	Malaria Admissions.	Strength.	Malaria Admissions.	All Causes.	Strength.	Malaria Admissions.	Strength.	Malaria Admissions.	Strength.	Malaria Admissions.	All Causes.
-/- Field Battery.	45	25	48	27	93	52 (538‰)	69 (742‰)	17	15	23	9	40	24 (600‰)	25 (625‰)
--- Field Battery.	33	16	49	22	82	38 (464‰)	49 (598‰)	23	8	9	8	32	16 (500‰)	26 (813‰)
-*- Field Battery.	26	15	46	18	72	33 (458‰)	43 (597‰)	26	17	9	4	35	21 (600‰)	25 (714‰)
Totals.	104.	56	143	67	247	123	161	66	40	41	21	107	61	76
Ratios. per Mille.		538‰		469‰		498‰	652‰		606‰		512‰		570‰	710‰

Note 1. As is to be expected, the Jubbulpore draft, previously heavily infected, showed a higher incidence of malaria admissions than the draft from U. K.

Note 11. Both drafts appeared to share, the Jubbulpore Draft to a somewhat greater extent, the benefits of quinine prophylaxis, though the beneficial effect in R.A. units appears to be much less marked than in Infantry units.
Several reasons may be advanced in explanation e.g. (a) Ordinary Barrack Room discipline is generally not so good in R.A. units.
(b) Gunners are harder worked.
(c) Gunners during "Stables" are exposed to bites by mosquitoes which harbour in the lines and fodder sheds.

Appendix VII.

Summary of Answers to Questionnaire - (vide page 3/ of text.)

Hospital	(a)	(b)	(c)	(d) 1930	(d) 1929	(d) 1928	(e) 1930 BT/MT	(e) 1929 BT/MT	(e) 1928 BT/MT	(f)	(g)	(h)	Remarks.
B.M.H.------1.	Favourable	Unpopular owing to taste.	Nil.	63.27	75.25		7/I	1.5/I		No.	No.	No.	Suggests Quin.Bihyd. tablets during Aug. to October.
B.M.H.------2.	Favourable	Unpopular	Nil	53.78	39.52	31.08	12/I	14/I	23/I	No.	Yes	?	
B.M.H.------3.	Very Favourable	Popular	Nil *	71	84	56	4.5/I	.5/I	--/Nil	No.	No. When infection is severe	No.	*GrainsX should be assured by using a measure slightly larger than an ounce.
B.M.H.------4.	Favourable	Not Un-Popular	Nil	56	84	19	5/I	1.3/I	Nil	No.	No.	?	
C.I.M.H.----1.	Very Favourable	Very Popular	Nil		?			?		Nil.	Nil.	?	
I.M.H.------2.	Favourable	Very Popular	Nil		?		?	?		Nil	Nil	Nil	Suggests larger curative doses of Quinine necessary in cases of Malaria from Prophylactic Group. Marked influence of low temperatures on out-breaks of malaria.
C.I.M.H.----3.	Favourable	Very Popular	Nil	53	76	55	Nil	Nil	31/I	No.	No.	No.	
I.M.H.------4.	Favourable	Popular	Nil	53	45	42	1.4/I	.4/I	1.6/I	No.	No.	No.	Believes 50 grains of quinine weekly for 12 weeks may have some deleter-ious effect on the blood.
I.M.H.-----5.	Favourable	* Very Popular	Nil		?			?		No.	No.	?	Indian Other Ranks frequently brought their children for prophylactic quinine. *In one unit new to the district & in tents, C.O. stated it was unpopular & re-sponsible for giddin ess etc: There was very little fever in this regiment.
I.M.H.------6.	Favourable	Popular with about Half.	Nil	41	84	23	5/I	1.3/I	Nil/Nil.	No.	No.	No.	Indian Officers without exception were warm advocates.
I.M.H.------7.	Very little Malaria this year.	Unpopular.	Nil.	55	83	34	2.5/I	1/I	3/I	No.	?	No.	
I.M.H.------8.	Very Favourable	Popular	Nil.	56	94	82	1/I	3/I	1/I	No.	Yes.	No.	
I.M.H.------9.	Very Favourable	Popular	Nil.	75	81	74	15/I	6/I	2/I	No.	?	No.	