The action of Quinine on the blood-corpuscles.

M. D. 1911.

The most important and useful action of Quinine is its antagonism to the malarial parasite, to which it acts as a direct poison.

Any further effects it has on the blood are therfore of the highest importance, particularly in the East, where Quinine is indispensable and given frequently and sometimes for long periods.

The action of Quinine on the blood, and particularly on the White Corpuscles, has been studied for many years. As early as 1867 the destructive action of Quinine on protozoans and bacteria was first investigated.

C. Binz paralysed unicellular animals in a few seconds with a .2% solution of Quinine, and observed that they became rounded, granular, and with darkened protoplasm. .1% Quinine Hydrochloride gave similar changes with amoeba ranicula. The white blood corpuscles of cats under the influence of a .05% solution of Quinine at 38° C were seen to lose their movements, to become granular, and sometimes to divide unequally.

In 1873 Binz, having found that in a cat killed by Quinine there was an almost

entire absence of white blood corpuscles, also found that all white blood corpuscle migration was stopped through a frog's mesentery when acted on by Quinine. He explained that this loss of motion was probably due to the Quinine holding, more firmly than normal, the Oxygen in the Red Blood corpuscles.

Grltowsky in 1872 published a series of experiments to determine the amount of Quinine necessary to check white blood corpuscle movements. He found the corpuscles tended to retract their prolongations, to become coarsely granular, and to be permanently round. His conclusions were, that Quinine checks the white corpuscle movements in a 1-800 solution, that the solution acts equally well in water or in serum, that the corpuscles of animals enfeebled by loss of blood in previous experiments resist with less power than those of fresh healthy animals, and that the corpuscles of the female resist longer than those of the male. He used Quinine Hydrochlorate and newt's blood. With the guinea-pig, he found a solution of Quinine in serum 1-2000 caused corpuscle movements to cease.

The Practitioner June 1872 "On the action of Quinine on the Colourless corpuscles". - Grltowsky.

With human blood, a solution of 1-2,100 was required to stop the movements, while a 1-4000 solution had no action at all. These Experiments were done with glass slides and coverglass.

Injections of Quinine into a frog and a guineapig, followed by a blood-slide being taken, resulted in no changes of white corpuscles being seen, in shape, size, or normal movements.

It was concluded that although Quinine possesses the power to stop white corpuscle movements, yet perhaps this action can only be obtained on the microscopic stage; and Quinine injected into the blood Even in doses sufficient to cause the death of the animal does not affect the corpuscles.

Goltowskī Explained the diminution of leucocytes in the treatment of leucaemia by Quinine, by its action on the nervous system or on the glands.

In 1873, experiments on the same lines were carried out by Baxter, who also used newt's blood and Quinine hydrochlorate. He found that the migratory movements of the white corpuscles were arrested by a 1-1500 solution, in 10 minutes, while the movements of the pseudopodia went on for 6 hours; and that to arrest all movements in 10 minutes, a 1-700 solution was required.

The Practitioner Nov. 1873 "The action of the Cinchona alkaloids ... on colourless blood corpuscles" by R.B. Baxter M.D

About the same time, it was stated that Quinine, in accordance with experiments on animals made by Briquet in Paris, increases greatly the proportion of fibrin in the blood, and slightly the proportion of water, and diminishes the amount of the red globules, thus rendering the blood chlorotic. Later experiments gave the well-known Guiac ozone test, showing a diminished power of the Red corpuscles to give up their Oxygen.

Dict. encyclopéd. des Sciences méd. Paris. 1874 3rd series vol I. p. 215

In more modern times, Experiments became more definite and accurate.

Quinine was shown to arrest the two movements of White corpuscles:- of pseudopodia and of migration. A frog's mesentery showing inflammation, i.e., with white corpuscles passing through the capillary walls, was treated with Quinine locally. This results in arrest of the movements of those corpuscles which have already emerged, while the leucocytes inside the vessels are not prevented from emerging, and form a dense accumulation round the vessel.

Text book of Pharmacology - 1885 - Lauder Brunton p. 48.

Injection of Quinine in the circulation, on the other hand, prevents leucocytes in the vessels from emerging, while those which have already

emerged continue to wander outwards among the tissues, leaving a clear space outside the vessel.

The size of Red Corpuscles appeared to be individually increased, and their power of giving up Oxygen to be diminished.

Quinine has power to diminish both the amount of Oxygen absorbed, and the CO_2 given out, by the blood. p. 58.

In 1886, Hare concluded that a course of Quinine caused a considerable increase in the total number of red corpuscles. His figures were as follows:- The Boston Med. & Surg. Journal - 1886 Vol. CXIV 22-4-86 p. 372 H. A. Hare

Quinine Sulphate gr X per diem —

1st day -	morning,	5, 750, 000	afternoon	5, 640, 000
2nd day -	"	5, 940, 000	"	6, 000, 000
3rd day.	"	6, 120, 000	"	5, 940, 000
4th day.	"	6, 180, 000	"	6, 120, 000
5th day.	"	6, 840, 000	"	6, 380, 000
6th day.	"	6, 540, 000	"	6, 420, 000
7th day.	"	6, 500, 000	"	6, 340, 000

These figures show a progressive increase in the total number of red corpuscles per c. mm.

Bartholow, however, quoting Cutler and Bradford, states that Quinine, while

it increases the relative proportion of the white corpuscles, diminishes the total number of the red. He thinks that as Quinine can reduce the size of a malarial spleen, it follows that the diminution in the reds and the increase in the whites may be due to this action. Barthelow also observes that no amount of Quinine short of a fatal dose can affect the movements of the white blood corpuscles of a living warm-blooded animal. He gives, however, no account of any experiments on which he has based these observations.

Practical Treatise on Mat. Med - R. Barthelow 1888 p. 183.

Bocelli is quoted about this time to have shown Experimentally that Quinine can be injected into the blood current of animals without damaging or causing any change in either the red or the white corpuscles.

Annuaire de Thérapeutique 26. 6. 90

Quinine is stated by Mitchell Bruce to enlarge the individual red blood corpuscles, after internal administration, and in large doses to paralyse the white corpuscles, checking diapedesis, while it lessens the capability of the red corpuscles for giving up $O \times 4 \frac{1}{2}$.

Mat. Med. and Therapeutics - Mitchell Bruce p. 314

In several experiments on rabbits carried out by Mauriel in 1902, much emphasis is laid on the fact that when leucocytes are acted upon by Quinine, their spherical shape precedes their death. He found that a proportion of 1 in 100 of Quinine in blood killed leucocytes at once, while a proportion of 1 in 1000 allows some leucocytes to live for over twelve hours, these first becoming spherical. The red corpuscles remain intact, having more resistance to Quinine than the leucocytes have. Quinine injected so as to reach the pulmonary circulation causes the spherical leucocytes to act as emboli, which results in death. Quinine injected into e.g. the renal artery will cause some loss of muscular power in the legs, but this may be only temporary, and will not necessarily cause death.

The result of certain leucocytes sticking as emboli in the pulmonary circulation will be that the total number of leucocytes will be diminished in the general circulation.

Mauriel worked out the varying blood-counts of a rabbit injected with Quinine,

Compt. Rend. hebd. des séances et mémoires de la Soc. de Biol. Vol. LIV
M. E. Mauriel.
8.11.02
p. 1202

14.3.03
p. 367

with the following results.

		RBCs	WBCs
At 2 p.m.	The rabbit's blood-count was	5,223,500	10,230
3 pm	Quinine hypodermic injection (10 centigm per Kilogm of the animal) solution 1-20		
3.30 pm	rabbit benumbed.	4,743,000	6,510
11.15	Quinine hypodermic injection (25 centigm per Kilogm of the animal)		
11.30	rabbit comatose	4,619,000	5,270
2	" "		4,030
4.30	Increasing coma.	5,285,500	1,860

Mauvel concludes :-

(1) that Quinine in certain doses diminishes the number of white corpuscles in the peripheral circulation

(2) that the doses causing spherical formation of the leucocytes have a relation to the doses causing leucopenia.

(3) that the leucopenia is due to the spherical leucocytes being retained in the capillaries, the diameter of the leucocyte being greater than the diameter of the capillary.

An important series of experiments was carried out by Wilson in America, which included the effect of Quinine on the phagocytic powers of polymorphonuclear leucocytes. Wilson prevented blood-coagulation by defibrinating and centrifugalizing 1 cc blood in a tube of such diameter

American Journal of Physiology 1907 Vol XIX "The action of Quinine Sulphate a human blood" - T.M. Wilson. p. 445.

that the 1 cc had a length of 100 mm.
The serum is then syphoned off, and the upper third of the sediment collected and washed with 20 cc. Salt solution. The fluid is removed and the sediment washed as before till a greatly concentrated accumulation of white corpuscles is obtained. 40% of washed corpuscles are mixed in a fine tube with 20% serum and 40% Streptococci, the latter having been inoculated in approximately equal quantities and into the same volume of bouillon, and grown for 24 hours at 37°C. The suspension is then incubated for 60 minutes at 37°C, and coverslip smears made and stained. The bacteria are counted in 50 polynuclear leucocytes and an average for one calculated.

For the actual experiment, Quinine Sulphate gr XV in gr III doses in 24 hours was given to 10 men, whose blood was examined both before the Quinine and 24 hours after. The virulence of the Streptococci was tested with each man without Quinine, virulence being taken as = 1, if 60 bacteria are engulfed during 60 minutes' incubation at 37°C by one polynuclear in the presence of

20% serum, the number of bacteria being ·5 to 5 millions per cub. mm of the medium. The virulence varies inversely as the number of bacteria taken up in a unit of time, and also varies inversely, as the percentage of serum present. The figures are as follows:-

	Coagulable time	Serum percentage	Haemoglobin percentage	RBCs in thousands	WBCs	P.N.ud.	Lymph.	Hyal.	Eosin.	Bas.	Phagocytosis per PN	Virulence of Streptoc.	
1a	–	45	–	5736	7900	63·8	29·2	4	2·5	0·5	29·9	2	Quinine for IX. only.
1b	-	46	–	5568	7400	66·5	29	2	1·5	1·0	38·2		
2a	3·5	46	–	5296	6600	53·3	39·3	4·6	0·6	2·0	21·3	2	
2b	3·9	46	–	5480	6500	60	33	4·0	2·0	0·6	24·1		
3a	5·0	51	–	6148	6050	62·5	24·3	11·3	1·3	0·6	31·8	2	
3b	3·0	53	–	6304	6500	49·0	43·0	5·0	2·0	1·0	30·2		
4a	3·2	44	100	5796	6500	56·4	36·4	2·4	4·4	0·4	19·7	2	
4b	3·5	47	95	5552	6050	51·6	36·8	7·2	4·0	0·4	18·1		
5a	3·0	40	100	6336	5500	46·8	36·4	7·6	2	2·8	12·1	4·9	
5b	4·2	49	105	6848	6200	50	42	4·8	·8	·4	12·6		
6a	5·0	45	95	6150	5050	65	28	4	1	2	8·6	4·9	
6b	3·7	45	85	6000	5350	67	38	2·5	1·5	1	8·9		
7a	3·5	43	-	5824	6900	75	21	2·5	1	·5	7·4	4·9	
7b	2·5	45	–	6048	6800	54	41	4	1	0	11		
8a	3·5	33	100	6264	6200	61	33	5	1	0	10·8	4·9	
8b	4·6	36	94	6116	6400	68	25·3	3·6	2·6	·5	13·5		
9a	3·6	44	101	5128	5350	73	21·5	2·5	1·5	1·5	8	4·9	
9b	4·0	38	107	5648	5750	65·5	25·5	4	1·5	·5	10·7		
10a	4·5	50	92	4392	6500	60	30·8	3·2	5·6	·4	8·3	8·2	
10b	4·5	48	98	4976	6000	48·4	42	1·2	7·2	1·2	12·1		

This experiment, showing the action of Quinine on human blood in vivo, was followed by another, in which Wilson worked out the effect of Quinine on the opsonic index of polymuclears in vitro. A graduated series of Quinine Sulphate solutions in salt solution are made, giving dilutions of 1 in 200, 1 in 400, 1 in 800 and so on, up to 11 solutions. ·2 cc of each ~~was~~ added to 11 test-tubes respectively, each test-tube containing ·15 cc blood and ·15 cc suspension of streptococci from a 24-hour bouillon culture. A twelfth tube was used as a control, and in it ·2 cc normal salt solution was added to the blood and the suspension, instead of Quinine solution. The test-tubes were then placed in an incubator for 30 and 60 minutes at 37°C and smears taken and stained. The control showed 8·7 bacteria per polymuclear in 30 minutes and 16·9 in 60 minutes. The first six test-tubes showed a marked inhibition of phagocytosis with the strong solutions – those stronger than 1 in 20,000, while the weaker solutions increased phagocytosis.

The figures of this experiment are as follows:-

Test-tube		Number of bacteria in each polymuclear after 30'	after 60'	in cultivation.
1st.	Quinine ·2 % or 1 in 500.	·35	·2	
2nd.	Quinine 1 in 1,000	·45	1·1	
3rd.	" 1 in 2,000	2·8	7·4	
4th.	" 1 in 4,000	3·9	11·9	
5th.	" 1 in 8,000	6·4	16·4	
6th.	" 1 in 16,000	7·6	19·6	
7th.	" 1 in 32,000	7·9	21·7	
8th.	" 1 in 64,000	11·5	23·8	
9th.	" 1 in 128,000	7·5	18·1	
10th.	" 1 in 256,000	8·9	18·4	
11th.	" 1 in 512,000	8·9	17·3	
Control.	·2% normal salt solution.	8·7	16·9	

Suspensions containing more than 1 in 20,000 Quinine not only showed diminished phagocytosis, but their polymuclears showed a marked absence of granules, a contour frequently ragged, vacuoles present in most, and markedly diminished staining powers.

Taking a gr X dose of Quinine Sulphate as representing in the blood of an average man a proportion of 1 in 7,500 if entirely absorbed, or rather a gr XX dose if half absorbed, then 2-4 gr. will represent the dose for Quinine Sulphate best

fitted to give the maximum phagocytic effect. A larger dose than gr iv will decrease phagocytosis.

But this effect of Quinine on phagocytosis may be really due to its rendering the bacteria more susceptible to the action of the polymuclears.

Wilson concludes that Quinine Sulphate gr xv in 24 hours given to healthy men appears to cause a slight increase in their opsonic indices; and that Quinine Sulphate in vitro has an inhibitory effect on phagocytosis in strong solutions; but apparently a stimulating influence in dilutions from 1 in 15,000 to 1 in 1,000,000.

Experiments on the same lines were carried out recently, to ascertain whether Quinine inhibits phagocytosis and is therefore contra-indicated in septic conditions. These were carried out by Lyon Smith, who used the Acid Hydrochloride of Quinine as being very soluble, less irritating than the Sulphate, and containing 8% more Quinine. Morphia Hydrochloride was added, 1/8 gr., to each gr x of the Quinine salt. Four counts were taken,

The Lancet
The influence of Quinine & Morphia upon phagocytosis.
H. Lyon Smith.
5. 11. 10

of the phagocytic index in four experiments.

One volume each of washed human blood corpuscles, human serum, and a fresh emulsion of living B Coli, were mixed with an equal volume of a solution as stated below, sealed in a Wright's pipette, and incubated at 37°C for 15 minutes, when films were made, stained, and the bacteria in each corpuscle counted. The above mixed with

(A) a 1 in 7500 solution of Quinine and Morphia showed an average of 4·28 bacteria in each Polymuclear.

(B) a 1 in 30,000 solution of Quinine and Morphia gave an average of 3·21

(C) a ·85% solution NaCl " " 1·64

(D) no solution used - " " 2·61.

(A) The 1 in 7500 solution represents a gr ¼ for Acid Quinine Hydrochloride dose, giving (compared with D) a 64% increase of Phagocytosis.

(B) The 1 in 30,000 solution representing a 2½ gr dose gives a 23% increase.

The 1 in 7,500 solution was then used in a series of 11 experiments with different bacteria, of which 9 showed a marked increase. The figures are as follows:-

1. With Streptococci the increase of Phagocytosis was 30 %
2. " B. Coli " " 64 %
3. " Pneumococci " " 80 %
4. " Tubercle Bacilli there was a diminished phagocytosis
5. " Staphylococci " " " " 50 %

whereas a gr 1 dose solution gave a very slight increase.

6. " Streptococci (another strain) the increase of Phagocytosis was 90 %
7. " B. influenzae " " 20 %
8. " a pseudo-diphtheriae B. " " 20 %
9. " B. Coli (another strain) " " 30 %
10. " Pneumococci (another strain) " " 30 %
11. " B. Coli (a third strain) " " 250 %

Smaller doses in all the groups were less effective, while very large doses (30 to 40 gr.) diminish phagocytosis, sometimes over 50 %.

This action of Quinine might be due to a directly bactericidal effect - but as it takes a 1 in 400 solution of Quinine to inhibit the growth of certain bacteria (e.g. Staphylococci), the bactericidal effect of any Therapeutic dose must be nil.

The action might be due to stimulation of the polynuclears - but in this case it is difficult to understand why

a diminished phagocytosis was obtained with the staphylococci groups (no 5 preceding page), which differed so much from the rest.

The phagocytic increase therefore appears due to the Quinine acting as an opsonin to certain bacteria. It has been stated before that in a patient who has been taking Quinine Hydrochloride, his plasma acts as an excitant to healthy leucocytes. Re Lancet 16.1.09

Quinine therefore in moderate doses, gr V to X, appears likely to benefit in the initial stages of a bacterial invasion.

In the above experiment, the increase in phagocytosis is in no way due to the Morphia. It has been shown by Experiment that the phagocytic powers of the polynuclears of a guinea pig are diminished in a marked degree after the hypodermic administration of Morphia. Re Lancet 26.2.10 p. 569.

Hence the fact that the combined action of Quinine and Morphia results in raising the phagocytic index, shows the more clearly the action of Quinine in this respect.

The above Experiments are conclusive on several points. It appears to be definitely proved that Quinine in vitro has a destructive action on the life of white blood corpuscles, and lessens their movements and their powers of ingesting bacteria. Quinine in vivo increases the number of red corpuscles with no loss of haemoglobin; while it appears to cause a constant if slight diminution in the number of white corpuscles, and in small doses to increase the phagocytic power of each polynuclear. This last action is important when looked at as a defence against bacterial invasion, and more than counterbalances the weak point involved in the diminution in the total number of leucocytes.

Taking the leucopenia as an established fact, it is not easy to explain why it should follow Quinine administration. Three theories may be advanced.

(1) Actual destruction of leucocytes by Quinine.

(2) Quinine causing an alteration in the concentration of the blood.

(3) Quinine changing the distribution of corpuscles in the vascular system.

(1) There is some evidence in vitro of leucocyte-destruction. Any solution of Quinine stronger than 1 in 20,000 causes marked degenerative changes in polymuclears (p. 12). But such a strength of Quinine represents a dose which would never be administered therapeutically, while after therapeutic doses no evidence can be obtained of leucocyte destruction or degeneration.

(2) Quinine does cause a distinct increase in serum percentage, and this might be held to explain the leucopenia. In that case a corresponding diminution in the total number of red corpuscles would be expected. The latter are, however, increased in number.

(3) There is no direct evidence that Quinine can modify the different

vascular areas so as to cause a varying distribution of leucocytes, but this explanation is a possible one. Quinine in large doses lowers the blood-pressure, and it is possible that owing to the diminished velocity of the blood-stream the leucocytes remain in their peripheral position in the deeper vessels, and therefore reach the superficial capillaries in diminished numbers. We may compare the physiological leucopenia caused by a change from the recumbent to the erect position. Lauret 21. 1. 11 p. 181

In small doses Quinine by dilating the vessels of the stomach walls may possibly cause stagnation of the leucocytes in the gastric vascular area, and consequently an apparent leucopenia in the superficial capillaries.

There is no evidence that Quinine in therapeutic doses can so arrest the movements of leucocytes as to cause their accumulation in the deeper vessels. There is similarly no evidence of Mauel's theory (p. 7)

that leucocytes becoming spherical accumulate in the pulmonary capillaries, as this could only happen in the administration of Quinine in lethal doses.

Differential blood-counts show a constant diminution in polynuclears and an increase in hyalines and lymphocytes. Here the difficulty is to ascertain which changes are primary, and which are relatively dependent on the primary change.

In the differential count quoted above (p. 10), there is an increase in polynuclears in five cases and a decrease in five; lymphocytes are increased in seven, and hyalines decreased in seven, out of the ten cases. These figures, however, are all based on the results of only one day following the administration of Quinine.

The following differential counts show the changes following the administration of Quinine for some days, and also for some days after Quinine had been stopped.

Action of Quinine on own White Corpuscles.

1908.		Percentage of Polynuclears	Lymphocytes	Hyalines	Eosinophiles
Nov. 26.	7 a.m.	65·4	24·7	6·8	2·8
27.	"	67·4	24·1	6·4	2
28.	"	66·4	25·5	7·4	1·1
Average without Quinine:		66·4	24·7	6·8	1·9
28.	11 pm.	Quin. Sulph gr X.			
29.	7 am.	63·5	29·3	6	1·5
30.	" gr X noctè	60·9	29·2	6·4	·8
Dec. 1.	" gr X noctè	64·4	28·1	7·1	·8
2.	" gr X noctè	60·5	27·4	8·1	3·5
3.	"	64·4	25·3	7·9	2·3
	Stop Quinine.				
4.	7 am.	65·3	27·8	6·8	·4
5.	"	66	26·4	7	1·1
6.	"	68	24	6·5	2

The above shows a decrease in polynuclears, a distinct increase in lymphocytes, and a slight increase in hyalines, all recovering their normal proportions.

The hyalines during ~~after~~ the first day of Quinine administration have decreased, and take a longer period to increase than the lymphocytes.

Action of Quinine on own blood.

1909	Total RBCs.	Total WBCs.	Percentage of Polynucl.	Lymphoc.	Hyal.	Eosin.
12 a.m. daily						
Feb. 4.	5,200,000	7,960	68·5	22·3	8·7	·3
8.	4,940,000	7,750	67·5	23·2	7·6	1·6
18.	5,046,870	8,340	69·5	22	7·5	1·5
25.	5,450,000	7,860	69·5	22·6	6·5	1·3
Average Without Quinine:	5,159,380	7,977	68·7	22·5	7·5	1·2
25. 11 p.m. Quin. Sulph gr X.						
27.	5,510,000	7,230	66·9	23	7	2
27th → 28th 11 p.m. Quin Sulph gr X.						
March 1.	5,288,000	6,500	65·6	23·3	8·2	2·7
2.	5,500,000	6,428	64·5	25·3	8·8	1·7
3. 11 p.m: Quin. Sulph. gr X						
4.	5,480,000	5,850	63·3	26·3	10·3	0
Stop Quinine.						
5.	5,500,000	5,170	62·9	24·5	10·7	1·7
6.	5,460,000	5,710	64·2	25·5	10·2	0
7.	5,800,000	5,400	65·6	21·6	10·3	2·3
9.	6,000,000	6,100	67·5	20	11·5	1
10.		6,250				
11.		7,500				
15.		7,800				

Here the Red corpuscles increase and continue to increase.

The White corpuscles decrease and recover.

The Polynuclears decrease, Lymphocytes increase, both recover.

Hyalines increase slowly and continue to increase.

Rifleman Samardhoj Rai, 10th Gurkha Rifles,

in hospital for conjunctivitis.

1909		Total RBCs.	Total WBCs.	Percentage of — Polynucl.	Lymphoc.	Hyal.	Eosin.
Without Quinine (12 grs. daily)	March 9.	4,600,000	8,060	65	23·6	8	3·3
	9. 2 p.m.	Quin. Sulph. gr X T.I.D. for 6 days.					
	10.	4,700,000	7,600	65·8	25·9	6·9	1·3
	11.	4,575,000	7,436	64·2	24·6	8·2	1·8
	12.	4,680,000	6,750	64·4	25·2	8·9	1·3
	13.	4,875,000	7,000	64·5	23·5	9	3
	14.		7,650				
	15.	4,700,000	7,000	63·6	26·3	9·6	·3
Stop Quinine.							
	16.	5,225,000	7,630	63·5	25·8	10·7	·8
	17.	5,580,000	8,060	65	23·6	10·3	1
	20.	6,350,000	8,000	64·5	23·5	9·6	1·8

The Red Corpuscles increase and continue to increase.

The white Corpuscles decrease and recover.

Polynuclears show a slight decrease,

Lymphocytes a slight increase. Both recover.

Hyalines increase by the third day after Quinine was begun, and have not recovered by the third day after Quinine has been stopped.

Recruit Nardhoj Rai, 10th Gurkha Rifles.

in hospital for enlarged spleen. History of 'fever' 6 months previously.

1909	Total RBCs.	Total WBCs.	Percentage of Polynucl.	Lymphoc.	Hyal.	Eosin.
12 a.m. daily						
Without Quinine } March 9	5,350,000	9,500	60·9	29·2	5·4	4·3
9. 2 p.m.	Qui. Sulph. 8r X T.i.D. for 6 days.					
10.	5,300,000	9,300	61	27·2	6·2	5·8
11.	5,200,000	8,670	54·7	29·5	11·5	4·8
12.	5,712,000	8,800	59·5	27	11·3	2·2
13.	5,475,000	8,530	55	30·4	10·3	4
14.		9,110				
15.	5,865,000	8,400	53	32	13·3	1·6
Stop Quinine.						
16.	5,112,500	8,090	55·4	33	11·3	1·4
17.	5,262,500	8,930	53	34	9·3	3·3
18.	5,712,500	9,120	57·1	26·5	11·1	5·1
19.	4,900,000	9,060	55·5	29·6	8·3	6·4
20.	5,300,000	10,430	55·5	32·2	5	6·1

Red corpuscles show a temporary increase.

The White corpuscles decrease and recover.

Polynuclears are decreased, lymphocytes are increased, a change in this case continued in both. Hyalins show a considerable increase, and recover.

The following series of 6 counts are from men of the 61st Pioneers of over two years' service whose "medical history sheets" show no attacks of fever of any sort. Their spleens were not palpable.

(1) Privat Rangasami. In hospital for cut on shin.

1910	Total RBCs.	Total WBCs.	Percentage of Polynucl.	Lymphoc.	Hyal.	Eos.
8 a.m. daily						
Without Quinine — Oct. 2.	5,350,000	8,220	68	23·2	6·5	2·2
Without Quinine — 3.	5,470,000	8,410	68·5	22·8	6·3	2·3
3. 12 a.m. Quin Sulph. gr. X T.I.D. for 7 days						
4.	5,460,000	8,540	67·2	25·2	5·1	3·4
5.	5,215,000	8,760	68·1	24·7	5·8	2·3
6.	5,915,000	8,320	67·9	25·2	6·4	·4
7.	6,450,000	8,070	66·8	25·1	6·9	1·1
8.	5,746,500	7,540	67·3	26·1	6·3	·3
9.	6,325,300	7,860	64·7	23·6	7·8	3·6
10.	6,430,200	7,340	62·9	27·6	9·4	·2
Stop Quinine.						
11.	6,840,500	6,980	63	24·4	9·3	3·2
12.	6,750,000	7,850	61·3	28·2	6·3	4
13.	5,980,500	7,540	68·1	25·1	7·3	·2
14.	6,123,650	7,970	65·5	27·2	6·1	1·1
15.	5,875,000	8,110	67·1	24·8	8·5	1·2

Red corpuscles increase, White corpuscles decrease, both recover. Polynucleans decrease, lymphocytes increase, both recover. Hyalines increase more slowly and appear to continue to

(2) Private Muthusami. In hospital for fistula in ano.

1910 8 a.m. daily		Total RBCs.	Total WBCs.	Polymucl.	Lymphoc.	Hyal.	Eosin.
Without Quinine	Oct. 2.	4,850,000	8,060	73·4	21	5·2	·3
	3.	4,570,000	8,250	75·7	19	4·9	·1
	3.	12 am. Quin. Sulph. gr X T. I. D. for 7 days.					
	4.	4,685,740	8,370	75·2	18·5	5·6	·5
	5.	4,364,000	8,110	73·7	20·6	4·2	1·8
	6.	4,742,000	7,860	75·3	19·5	4·5	1·2
	7.	4,657,000	8,320	72·1	21·1	5·8	·8
	8.	5,345,000	7,240	74·3	20	5·5	·1
	9.	4,973,000	7,570	68	23·2	7·4	1·2
	10.	5,470,000	7,150	70·3	22	6·9	1·6
	Stop Quinine.						
	11.	5,320,500	7,370	67·4	24·3	7·7	·4
	12.	5,542,000	7,210	72·1	20·5	6·3	1·1
	13.	5,312,000	7,940	69·4	23	7·1	·3
	14.	5,120,500	7,660	71·2	21·3	7·1	·3
	15.	4,970,600	7,870	71·8	20·6	7·5	·2

The Red Corpuscles show a continued increase.

The White Corpuscles show a decrease, followed by recovery.

Polymuclears show a slight decrease,

Lymphocytes a slight increase. both recovering.

Hyalines show a continued increase.

Eosinophiles are slightly increased.

(3) Private Tungawha, in hospital for Sciatica.

1910 8 a.m. daily	Total RBCs.	Total WBCs.	Percentage of Polynucl.	lymphoc.	Hyal	Eosin:
Without Quinine — Oct. 17.	4,953,000	9,100	64·5	27·1	9·2	·3
18.	5,270,000	8,870	68·4	26·2	5·7	·1
18. 12 a.m.	Quin. Sulph gr X T.I.D. for 7 days.					
19.	5,129,000	8,620	65·8	25·6	7·5	·7
20.	5,482,000	8,800	63·6	27·7	5·9	2·4
21.	5,316,700	8,300	64·7	26·4	6·5	2·1
22.	6,182,400	8,860	60·3	31·1	9·2	·2
23.	5,769,000	7,940	61·5	28·6	7·7	1·8
24.	6,289,000	8,520	63·3	25	10·5	·7
25.	6,120,300	8,120	57·6	31·4	9·1	1·5
Stop Quinine.						
26.	6,450,600	7,720	52·7	33·9	11·3	1·8
27.	6,342,000	8,650	62·3	23·4	8·4	·6
28.	5,760,800	7,980	58	30·2	11·1	·5
29.	6,129,000	8,430	65·2	23·3	11	·2
30.	5,420,000	8,960	62·5	25·1	12·2	·1

Red Corpuscles increase and recover partially.

White Corpuscles show a very slight decrease.

Polynuclears decrease and recover.

Lymphocytes increase and recover.

Hyalines show a continual increase after the 5th day's Quinine.

(4) Private Ponnasami. In hospital for Conjunctivitis.

1910 8 a.m. daily	Total RBCs.	Total WBCs.	Percentage of Polynucl.	Lymphoc.	Hyal.	Eosin.
Without Quinine Oct. 17.	5,700,000	8,700	71·3	21·6	6·1	·8
18.	6,120,500	8,560	73·5	19·4	6·4	·6
18. 12 am.	Quin. Sulph. gr X T.I.D for 7 days.					
19.	5,870,000	8,690	73·4	19·1	7	·3
20.	5,959,000	8,120	70·7	20·8	8·2	·3
21.	6,230,400	7,860	71·1	23·3	5·1	·4
22.	6,143,700	8,340	68·5	21·6	8·9	·6
23.	6,342,000	7,950	70·1	22·3	7	·3
24.	6,027,490	7,720	68	25·4	6·4	·1
25.	6,352,000	7,810	67·3	25·2	7·3	·1
Stop Quinine.						
26.	6,450,000	7,620	64·7	27	8·1	·1
27.	6,129,000	7,930	65·5	26·2	7·7	·4
28.	6,275,000	8,240	67·1	23·3	9·5	·2
29.	6,570,000	7,980	71	20·5	8·3	·1
30.	6,360,500	8,560	70·3	22·1	7·3	·2

The Red Corpuscles show a continued increase.

The White Corpuscles. decrease and recover.

Polynuclears decrease and recover.

Lymphocytes show a slight increase. and recovery.

Hyalines show a slight increase after several days, Quinine administration.

(5) Private Muttaya Dewar. In hospital for boils.

1910 8 a.m. daily	Total RBCs.	Total WBCs.	Percentage of Polymnel.	Lymphoc.	Hyal.	Eosin:
without Quinine Nov. 6.	6,750,000	8,420	79·2	14·6	6·1	0
7.	6,290,000	8,960	76·1	15·3	7·9	·5
7.	12 am. Quin. Sulph. gr X T.I.D. for 7 days.					
8.	6,825,000	8,540	77·6	12·2	9·2	0
9.	7,146,700	8,120	75·8	14·7	8·5	·8
10.	7,426,000	7,560	79·2	12·3	8·2	·2
11.	6,940,000	7,930	73·1	16·2	10·3	·3
12.	7,520,300	7,420	78·7	11·3	9·6	·2
13.	7,340,600	7,840	70·6	15·6	12·8	·7
14.	7,876,000	8,110	77·8	10·5	11·2	·3
Stop Quinine.						
15.	8,420,000	7,560	73·5	13·2	13·2	0
16.	7,830,000	7,330	76·4	15·7	7·2	·5
17.	8,123,000	7,890	82·3	11·1	6·4	0
18.	7,760,000	8,460	73·1	16·5	9·9	·4
19.	7,570,000	8,110	70·2	20·9	8·3	·5

The Red Corpuscles increase and continue.

The White Corpuscles decrease slightly and recover.

Polymuclears show a slight decrease, and recovery.

Lymphocytes in this case are not definitely increased. Hyalins show a marked increase at once and tend to recover.

(b) Private Narayan. In hospital for injury to muscles of back.

1910. 8 a.m. daily	Total RBCs.	Total WBCs.	Percentage of Polymucl.	Lymphocs.	Hyal.	Eosin:
without Quinine Nov. 6.	6, 254, 000	7, 640	68·4	20·7	9·8	·8
7.	5, 873, 000	8, 120	75·1	16·5	7·5	·6
7.	12 a.m. Quin. Sulph. gr. X T.I.D. for 7 days.					
8.	5, 329, 000	7, 850	72·3	17·7	9·2	·7
9.	5, 974, 000	7, 540	70·6	19·2	10·1	0
10.	5, 635, 000	8, 110	73·2	20·1	6·5	0
11.	6, 478, 000	7, 730	68·5	21·4	10	0
12.	6, 289, 000	7, 310	65·1	23·3	11·4	0
13.	6, 873, 000	6, 460	70·7	18·5	10·5	·2
14.	6, 435, 000	7, 120	63·2	23·3	12·5	·6
Stop Quinine.						
15.	6, 798, 000	7, 350	59·5	25·6	14·1	·5
16.	6, 328, 000	6, 860	69·3	21·2	9·3	0
17.	5, 964, 000	6, 340	61·2	24·1	13·9	·6
18.	6, 342, 000	6, 970	55·6	26·3	17·4	·5
19.	6, 574, 000	7, 450	64·1	20·9	14·8	0

Red corpuscles show a slight increase with recovery.
White corpuscles are decreased and recover.
Polymuclears are decreased and continue.
Lymphocytes increase and recover.
Hyalines show a marked increase which continues.

These counts show various constant changes following the administration of Quinine. The total number of red corpuscles is definitely increased, and this increase continues after the Quinine administration has been stopped. The action of Quinine as a tonic will explain this, as the red corpuscles increase in number in proportion to the improvement in general health. No alteration in the size of the individual red corpuscles was observed.

There is also a constant decrease in the total number of white corpuscles, which is slight and corresponds definitely to the period during which the patient is under the influence of Quinine. No loss of staining power or other degenerative change was noticed in the leucocytes.

There is an almost constant diminution in polynuclear percentage, and an increase in lymphocytes and hyalines. The hyalines in each case appear to

increase in percentage more slowly, and to continue this increase for a longer time, than is the case with the changes observed in the other leucocytes. Eosinophiles do not appear to undergo any constant change. It is probable that there is an actual absolute diminution in the polynuclears, in which case the increase in lymphocyte and hyaline percentages would be a relative and proportional one. The discrepancy between the hyaline percentages of the preceding series and those on p. 10 is explained by the fact that the increase in hyaline percentage does not occur till the third or fourth day after Quinine has been administered. The figures on p. 10 are from blood-counts taken 24 hours after Quinine was begun, before the hyalines had time to show an increase, or the polynuclears to show a decrease in more than half the cases.

As the chief use of Quinine is anti-malarial, it is of importance to ascertain what changes malaria itself effects in the blood before treatment by Quinine has been begun — apart from the actual changes in the individual red corpuscles caused by the attacking parasite. In this way it can be seen how Quinine, apart from its direct action on the malaria parasite, can affect the blood of a malarial patient.

The chief changes in the blood brought about by an attack of malaria are those of anaemia. There is a diminution in the total number of red corpuscles, and a diminished haemoglobin value of the surviving corpuscles.

There is also a marked increase in the number of hyalines, both absolutely and relatively. These have marked phagocytic powers and frequently contain malarial pigment. Pigment may be also observed, but less frequently, in the lymphocytes. "Transitionals" are very common.

Occasionly the increase in hyalines only occurs immediately after the malarial pyrexia subsides, and this is followed by a diminution in their number as convalescence goes on.

Stevens and Christophers Pract. Study of Malaria. 1908 p. 43

p. 219

In the actual fever attack, there is a transient leucocytosis during the rigor, up to the height of the fever, – i.e. corresponding with the time of setting free a number of spores ~~of~~ the malarial parasite into the blood-stream. This is followed by a leucopenia which is at its maximum before the onset of the next attack. The leucopenia is therefore ~~also~~ ~~also~~ best marked in the periods of apyrexia, and the increase in the number of hyalines is also best marked at that time.

The number of hyalines at fever-height may show no increase at all, because of the increase in the number of polymuclears at that time. For this reason, the hyalines in a benign tertian attack will show a much greater increase in number than they will in a malignant tertian attack, because the apyretic period is longer.

All the varieties of the malarial parasite have this effect on the leucocytes during the pyrexial period.

But the malignant tertian parasite appears to have a special effect in causing a definitely active phagocytosis of infected red corpuscles. Such a phagocytosis is exceedingly rare, and probably non-existent, in Quartan and in benign tertian infections. In the case of the malignant variety, this phagocytosis frequently occurs, and is allied to a tendency to an accumulation of the infected red corpuscles in the visceral capillaries, especially in those of the spleen and liver.

New Syd. Soc. p.181 and Lancet 4.9.08 p.16

The malignant tertian parasite therefore acts on the red corpuscle which it inhabits, to render it specially susceptible to being held up in the visceral capillaries, and to destruction by phagocytosis.

This action can be reproduced experimentally. By immunising an animal of species A against injections

Christophers + Bentley
Bombay Med Congress
Jan. '09.

of the red blood corpuscles of an animal of species B, a haemolytic serum is produced in A capable of dissolving the red corpuscles of B. Injection of this serum into B results in anaemia and death. The anaemia is due to a phagocytosis of the red corpuscles in the visceral capillaries produced by certain doses of the serum.

A similar effect can be produced from two animals both of the same species.

It is suggested that a malignant infection may result in the production of an auto-lysin, the patient being "immunised against his own blood-cells." The primary phenomenon in such immunising processes is one of phagocytosis, the injected red corpuscles being attacked like foreign substances.

This is of importance in relation to the fact that the malignant parasite is the one concerned in the causation of blackwater fever.

In addition to this phagocytosis which occurs in relation to malignant infections, there appears to be a constant diminished resistance of the blood of a chronic malarial patient to haemolytic action. The isotonic point of normal human blood may be taken to be about 0·41% salt solution, a strength below which there will result a solution of haemoglobin. The isotonic point of a chronic malarial patient was found to be 0·44% salt solution, his blood having a resistance to haemolysis which was less than normal.

Stevens & Christian p. 225

p. 242

These various changes in the blood resulting from a malarial infection are, according to Plehn, completely absent during the primary incubation period which varies from 3 to 12 days according to the variety of parasite causing the infection.

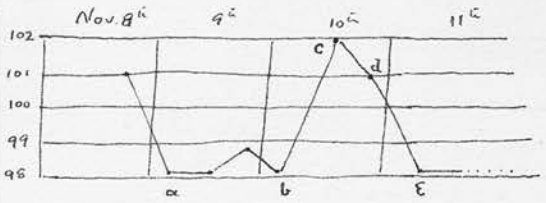
The modifications of the above changes caused by the ingestion of a Quinine salt may now be considered.

The action of Quinine in increasing the total number of red corpuscles and their haemoglobin is especially useful in the case of the anaemic malarial patient; and in chronic cases of long standing malaria when the anaemia is well-marked, the benefit of continued doses of Quinine becomes apparent.

The increase in the hyaline percentage which follows Quinine administration may also be of considerable benefit, as the hyalines, with their powers of ingesting the malarial parasite, are already increased in a malarial attack, and this increase will be further reinforced by the Quinine.

Quinine does not appear to modify the varying leucocyte counts which occur during the malarial pyrexia. In the following cases, there is a leucopenia in the apyrexial intervals, and a leucocytosis corresponding to the height of the fever.

Sepoy Alam Din, 93rd Burma Infantry.

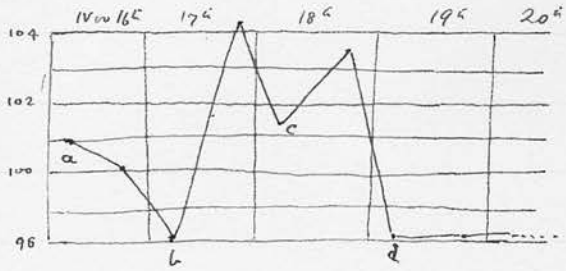


Malignant Tertian.

Nov. 9th. Numerous small rings, some red corpuscles showing Maurer's dots.

		Total WBCs.	Polynucl.	Lymphoc.	Hyal.	Eosin.
(a)	10 a.m.	10,000	72·6	12	15·3	0
Nov. 10th.	8 a.m.	Quin Sulph. gr XX.				
(b)	10 a.m.	6,500	56·6	13·2	30	0
(c)	2 p.m.	8,000	60·4	12·6	26·9	0
(d)	7 p.m.	9,500	72·6	11·7	15·4	0
Nov. 10th.		Quin Sulph. gr X T. I. D.				
(e)	9 a.m.	11,000	74·1	11·7	14·1	0

The leucopenia is most marked at the end of the apyrexia. The variations in the leucocytic counts are those of the usual malarial fever, and do not appear to be modified by the Quinine. That the Quinine was quickly absorbed was shown by the malarial rings at (b) definitely losing their stains and showing as faint brownish-red instead of the blue and red of the Leishman stain.



Sepoy Bisher Singh

25th Mountain Battery,

Malignant Tertian.

Nov. 16th. 8 a.m. Numerous crescents. Quin Sulph gr X T.I.D.

		Total WBCs.	Polynucl.	Lymphoc.	Hyal.	Eosin.
	(a)	8,500.	62.5	14.3	22.6	.6
Nov. 17th	(b)	7,500.	47.5	17.3	34.1	.6
Nov. 18th.	(c)	11,000	71.4	12.2	16.2	0
19th.	(d)	10,000	70.5	14.7	14.7	.3
20th.			61.2	17.8	20.6	.7
21st.			53.1	21.9	24.9	.1
22nd.			43.4	26.9	26.9	2.6
23rd.			42.5	20.7	31.1	5.5
26th			37.3	23.3	35	5.3
29th			45.1	20.1	30	4

HERE The leucopenia at (b) marking the beginning of a rigor is not repeated at (d), as the temperature remained normal after (d).

The increase in hyalines is relatively apparent at (b), as would be expected in any malarial attack, and is again observed from the day following the last attack, when the increase is actual and continuous, only decreasing as convalescence proceeds.

It appears then that Quinine has no effect on the leucocytic variations that occur during a malarial attack.

Of the other changes mentioned above brought about in the blood by the malarial parasite, the active phagocytosis of those red corpuscles which are infected by the malignant tertian parasite is not likely to be influenced by Quinine, which is given in cases of malignant malaria in much larger doses than the "moderate" doses (p. 16) which were found to result in an increased phagocytosis.

The action of the malarial parasite, mentioned above, in raising the isotonic point of a patient's blood, is intensified by Quinine, administration of which to a malarial patient still further diminishes the resistance of his red corpuscles to haemolysis. The isotonic point of the patient mentioned on p. 37, suffering from chronic malaria, which was raised to 0·44 % NaCl, went up to 0·46 %

one hour after taking Quinine, and the patient began to show signs of haemoglobinuria.

It may be concluded that the action of Quinine on the blood resulting from its internal administration has various definite advantages, apart from its antimalarial action.

We have seen that Quinine taken internally increases the total number of red corpuscles and their haemoglobin, this increase continuing for some time after the administration of Quinine has ceased. This action is of special benefit in the after-treatment of malaria, as well in the treatment of other secondary anaemias.

Quinine also increases the phagocytic powers of the individual polymuclears. The maximum increase, according to Wilson, follows doses representing a 1 in 64,000 solution Quinine Sulphate, or according to Lyon Smith, doses representing a 1 in 7,500 solution Quinine Bihydrochloride. But the latter experimenter, although he

worked with the more soluble salt, used it in combination with Morphia. As Morphia diminishes phagocytosis, the combination required a larger proportion of Quinine.

The "ideal" dose of Quinine Sulphate, causing the maximum amount of phagocytosis, may be taken as about gr IV, and that of the acid hydrochloride as rather less.

Quinine as used in the after-treatment of malaria is therefore of further benefit in decreasing the liability to a bacterial invasion. This is the more necessary in view of the absolute leucopenia which follows Quinine administration, with its relative decrease in the number of polymuclears.

The relative increase in hyalines following Quinine may possibly be of benefit in the treatment of malaria, by adding to the existing increase of hyalines.

These various indirect actions of Quinine on the blood in malaria are of little importance compared with the direct

action of Quinine on the parasite, with which however we are not now concerned.

With regard to malignant tertian infection, Quinine is not likely to influence the phagocytosis of infected red corpuscles, which is looked on as an illustration of an autolysis; while by further raising the isotonic point of a malarial patient's blood it may possibly be a factor in blackwater fever, which appears to occur in direct association with a malarial infection. But this is no argument in favour of abstaining from Quinine in a malignant infection, as its adequate administration will prevent that recurrence of the attacks which induces the haemoglobinuric state.