A Statistical Investigation

OF
RECORDS OF TREATMENT AND BLOOD
EXAMINATION IN 18,731 CASES OF

MALARIA.

BY J. PRATT JOHNSON, M.C., M.B., B.S. LOND.,
D.P.H. OXF.,

D.A.D.M.S. (PATHOLOGY), MAJOR, S.A.M.C.;
AND

KENNETH GILCHRIST, M.C., M.B., CH.B. EDIN.,
MAJOR, S.A.M.C.

THESE investigations were carried out during the war on cases of malaria returned from the German East African campaign and admitted for treatment into military hospitals in South Africa. A routine system of blood examination was instituted, each man's blood being examined by the thick-film method on admission and subsequently at weekly intervals. Special malaria cards on which laboratory reports and records of treatment were kept were taken out for each man, and provided ample material for statistical research. These cards on sorting gave the following groups :—

Classification of Series.

- 1. Total cards analysed 18,731
- 2. Total cards clinically diagnosed malaria with negative smears ("negative cards") 9,943
- 3. Total cards diagnosed malaria with positive smears ("positive cards") 8,788
- 4. Total smears carried out in series 74,022
- 5. Positive cards—
  - (a) Benign tertian ... .. 5,393, or 61%
  - (b) Malignant subtertian ... .. 1,977, or 23%
  - (c) Mixed infections (B.T. and M.T.) ... .. 1,418, or 16%

The large number of mixed infections indicates that infection with one type of malaria in no way protects against invasion with another. The converse is more likely to be true; the debility produced by malarial infection naturally reduces the effectiveness of the protective mechanism.

ROUTINE TREATMENT OF MALARIA.

The earlier records of this series showed marked variation in the actual dosage of quinine employed and in the duration of quinine treatment. A dosage of quinine of 5 or 10 gr. daily was frequently recorded, and was commonly associated with repeated relapses and progressive anæmia. Whatever may be said for the successful employment of such doses in mild cases of malaria, they were found to be totally inadequate for the severe massive and mixed infections commonly observed in troops invalided from the German East African campaign. Apart from the necessity of controlling infection as early as possible from the point of view of the ultimate cure of the disease, the question arose of undue pressure on the hospitals owing to the increased period in hospital of each case inadequately treated.

In November, 1917, definite instructions for the routine treatment of malaria were issued. All ordinary cases, irrespective of type, were ordered 10 gr. of quinine in solution three times daily for three weeks, followed by the same dose twice daily for one month and then 10 gr. daily for two months.

The beneficial effects of the increase of quinine employed in all cases of malaria is reflected in Chart 1. It will be observed that an increase in the number of days on which quinine was administered and the average daily dose of quinine is associated with a reduction in the number of days in hospital, and that the percentage number of days in hospital on quinine in October, 1917, rises from 67 per cent. of the total stay in hospital to over 92 per cent. in March, 1918. The average amount of quinine administered in all cases of malaria similarly rises from 16 gr. per case per day in October to 23 gr. per case per day in April. The gradual rise in these factors is accompanied by a gradual fall in the average period in hospital of all cases.

Period in Hospital of Each Type of Malaria.

It should be borne in mind that the same standard of clinical fitness and two consecutive negative smears at weekly intervals was required of all cases before discharge, irrespective of the particular type of malaria recorded. Furthermore, with regard to treatment, although the average daily quinine employed shows a gradual rise the increase applies generally to all cases

CHART 1.

Showing the beneficial effect of increase of quinine dosage on the length of malaria attack as evidenced by the number of days in hospital. Upper line = percentage number of days in hospital on quinine. Middle line = average number of days in hospital per case. Lower line = daily average grains quinine per case. The figures below the chart give the actual number of cases.

of malaria. Under these circumstances, for the same period the average duration of treatment of each type of malaria before discharge reflects—with a considerable degree of accuracy considering the large number of cases in each group—the relative resistance of each type of malarial infection to treatment. It should also be remembered that practically every man admitted to hospital had suffered at some time or other during the campaign from attacks of malaria. Table I. summarises the results of analysis in each type of case.

TABLE I.—Relation between Quinine Treatment and Days in Hospital in 4905 Different Infections.

Type of case.	No. of cases.	Average daily quinine (gr.)	Average days in hospital.
Benign tertian	1670	24.7	45.4
Malignant subtertian	473	25.2	43.6
Mixed infection (B.T. and M.T.) ...	318	24.2	63.1
Total positives	2461	24.7	47.3
"Negative" cases	2444	22.5	32.3
All cases	4905	23.9	39.9

In reviewing the above figures it is clear that: (1) Mixed infections are more resistant to treatment than either B.T. (benign tertian), or M.T. (malignant subtertian); (2) B.T. is as resistant or even more resistant than M.T., when the question of parasitological and clinical relapse is taken into consideration.

Benign tertian and malignant subtertian infections.—The ready response of B.T. infections (excepting chronic resistant cases) to quinine administration is reflected more in the rapid disappearance of parasites from the finger blood than in the freedom from relapses. M.T. infections, although in the first place more obstinate and difficult to eradicate from the finger-blood, once controlled, are far less prone to relapse. It should be noted that the occurrence of a parasitological relapse prevented the discharge of a patient in military hospitals until two consecutive negative blood reports had been recorded, although negative tests may have been recorded previous to the relapse. The long period of detention of benign tertian cases is largely due to the high percentage of relapses both clinical and parasitological which occurred in this infection.

Mixed infections.—The prolonged treatment required in mixed infection (M.T. and B.T.) is due partly to the resistance of these infections to the action of quinine, and partly to the frequency with which relapses of either one or the other (usually benign tertian) infection takes place. Almost without exception the occurrence of two types of malaria together in the same patient increases enormously the difficulty of control and eradication of either infection, and indicates a less favourable prognosis than in the case of pure infection with any one type.

Syphilis and malaria.—The resistance of malarial infections, even when involving one type only of malaria, in syphilitic subjects is very marked. Relapses are frequent and anæmia severe. The natural protective forces of the body are reduced in effectiveness by any debilitating influence. The chronicity of malaria in syphilitic subjects, in spite of thorough anti-syphilitic and of antimalarial treatment, emphasises the importance of the natural protective mechanism of the body in combating malaria and in rendering effective the administration of quinine.

PARASITOLOGICAL RELAPSE UNDER QUININE TREATMENT.

Viewed in the somewhat indefinite light of ordinary clinical interpretation the word "relapse" would appear to imply a recurrence of acute symptoms in a resolving pathological condition which otherwise might reasonably have been expected to proceed to complete cure. The "relapse" of malaria, however, does not admit of such simple and precise interpretation, for it need not imply the presence of subacute or even chronic symptoms prior to the onset of the more acute manifestations; nor need it imply that a complete cure might reasonably have been expected. Relapses in malaria are the acute exacerbations of an otherwise continuous, and it may be entirely latent, systemic infection, where sooner or later the recurrence of acute manifestations is the invariable rule. Moreover, the term "relapse" is used not only where the latency interval is ten days to two or three weeks, but similarly to indicate an acute attack supervening after a latency interval free of all malarial symptoms extending over a period of from one or two months to one or two years.

Classification of Relapses.

(1) *Clinical or pyrogenic relapse.*—A recurrence of fever and its associated acute symptoms after a period of quiescence constitutes the true clinical relapse of malaria. Parasites are present in the peripheral blood.

(2) *Parasitological relapse.*—The reappearance of asexual parasites in the peripheral blood after one or more consecutive negative findings constitutes "parasitological relapse," which frequently occurs without clinical relapse, but will include any clinical relapse which may take place, its recorded duration being longer. For the parasitological relapse, based entirely on parasitic findings, embraces the whole period of the persistence of asexual parasites in the peripheral blood, and parasites can be demonstrated in the blood for some days before the onset and for a varying period after the subsidence of clinical symptoms. Frequent relapse is a clear indication that the host's defensive mechanism and any remedial measures adopted have failed to control the vegetative activities of the parasite. It is most prone to occur in untreated infections, in massive multiple, and particularly in mixed infections, in conditions of low vitality, and especially in the presence of a debilitating disease, such as syphilis. During the interval between attacks the parasites may either fall below the "detectable limit" or persist in numbers well above this limit.

In quiescent chronic malaria there exists a condition of armed neutrality—of temporary adaptation of host to parasite, of parasite to host. The extraordinary power of persistence exhibited by malarial infections, in spite of sustained and vigorous treatment, is a characteristic of the disease—a characteristic single, significant, dominant; a characteristic which demands cautious acceptance and careful investigation of all so-called "cures" of malaria. It is common knowledge that all

other protozoal diseases of man and the lower animals exhibit tenacious persistency and are difficult of eradication.

Variations Presented by a Subclassification of Parasitological Relapse.

- (a) Relapses to same type—simple infection:—
  1. Malignant subtertian to malignant subtertian.
  2. Benign tertian to benign tertian.
  3. Mixed (M.T. and B.T.) to mixed (M.T. and B.T.).
- (b) Relapses to different type—mixed infections:—
  1. Benign tertian to malignant subtertian.
  2. Malignant subtertian to benign tertian.
  3. Mixed to benign tertian.
  4. Mixed to malignant subtertian.
  5. Malignant subtertian to mixed.
  6. Benign tertian to mixed.
- (c) Relapse from negative smears:—
  1. Negative to malignant subtertian.
  2. Negative to benign tertian.
  3. Negative to mixed.

In examining the following tables it should be remembered that (1) these final figures are obtained by reduction from numerous preliminary detailed tables (unpublished). It is not possible to employ the results in one table in association with the results in any other table; and that (2) the total number of cases investigated vary in different tables owing to the fact that the data available in some cards are not sufficiently complete for all investigations, but may provide facts which can be utilised for statistical purposes. For example, a card may show full records of the various blood examinations made, but the records of the treatment given during the whole period of stay in hospital may be incomplete. Such a card would be of service for an investigation of parasitological relapse, but would be of no value in a correlation of relapse incidence and quinine dosage.

TABLE II.—Final Analysis of 1281 Relapses under Quinine to Same Type of Cases Positive on Admission: Analysed Totals.

Type of relapse.	Before parasite relapse—	
	Average interval under treatment.	Average daily quinine.
M.T. to M.T. (156 relapses)	17 days.	21 gr.
B.T. to B.T. (1112 relapses)... ..	18 "	23 "
Mixed to mixed (13 relapses)	18 "	21 "
1281 relapses	18 "	23 gr.

TABLE III.—Final Analysis of 399 Relapses under Quinine to Different Type of Cases Positive on Admission: Analysed Totals.

B.T. to M.T. (116 relapses)	15 days.	20 gr.
M.T. to B.T. (144 relapses)	16 "	22 "
Mixed to B.T. (62 relapses)	21 "	20 "
Mixed to M.T. (24 relapses)	20 "	17 "
M.T. to mixed (22 relapses)	12 "	18 "
B.T. to mixed (31 relapses)	18 "	20 "

All positive cases relapsing to different type (399 relapses)...	17 "	21 gr.

TABLE IV.—1276 Cases Negative on Admission Relapsing under Quinine to Different Types: Analysed Totals.

Malignant subtertian. (232 cases)	12 days.	20 gr.
Benign tertian. (995 cases)	14 "	20 "
Mixed infections. (B.T. plus M.T.) 49 cases ...	14 "	21 "
All cases negative on admission relapsing under treatment (1276 cases)	13 "	20 gr.

Frequency of Relapses Under Quinine in Each Type of Malaria.

The final results arrived at from an analysis of 2649 relapses occurring in a series of 14,802 cases of malaria under treatment in military hospitals are as follows.

- Percentage Relapse Incidence.
- 1. All relapses in series—2649 out of 14,802 cases, or 17·9 % relapsed.
  - 2. Of cases with initial negative smears... .. 14·1 % ..
  - 3. Of cases with positive smears ... .. 23·7 % ..
  - 4. In benign tertian malaria—
881 out of 3877 cases, or 23·8 % ..
  - 5. In malignant subtertian malaria—
143 out of 1565 cases, or 11·2 % ..
  - 6. In mixed B.T. and M.T. malaria—
393 out of 1232 cases, or 39·4 % ..

An examination of these figures indicates that the most intractable type of malaria from the point of view of control and prevention of relapses is a mixed infection of benign tertian and malignant subtertian. Moreover, the chances of relapse are more than twice as great in benign tertian than in malignant subtertian. The lower percentage incidence obtaining in cases with initial negative smears indicates that this group included the lighter infections, which were more easily controlled by the routine treatment employed in all military hospitals. The percentage of relapses in cases diagnosed clinically but not microscopically as malaria approximates sufficiently to the percentage relapses in malarial cases in which the diagnosis was proved microscopically to support the conclusion that the negative cases included in this series are cases of malaria. If cases wrongly diagnosed as malaria had been included the percentage relapses would be reduced to a figure markedly below that for known positives. All cases included in this series were troops returned from the German East African campaign; practically all had at some time suffered from malaria.

TABLE V.—Relapse Analysis in Different Infections (6674 Cases) under Quinine.

Infection.	Total cases positive on adm.	Total cases relapsing.	Av. No. relapse per case.	Cases relapsing per cent.	Av. relapse interval (days).	Av. daily quinine per case during interval.	Av. No. of days in hospital.
B. T.	3877	881	1·3	23·8	17·9	23·0 gr.	47·5
M. T.	1565	143	1·2	11·2	16·4	21·3 ..	45·5
Mxd.	1232	393	1·1	39·4	16·7	20·6 ..	66·3

The relapse-rate in each type per week is as follows:—Benign tertian, 3·5 per cent.; malignant subtertian, 1·7 per cent.; mixed infection (M.T. and B.T.), 4·1 per cent.

TABLE VI.—Correlation of Quinine Treatment, Period in Hospital, and Relapses under Quinine.

(A) Cape Coloured Corps (All Types of Malaria).

Period of observation.	No. of cases.	Per cent. relapses.	Average daily quinine.	Average period in hospital.
June-July, 1918	124	32·3	21·8	70
August, 1918	223	19·7	26·9	42
September-October	345	17·6	27·1	46
—	693	21·0	25·0 gr.	49 days.

(B) Europeans (All Types of Malaria).

January to March, 1918..	1871	18·8	23·8	38
April to June, 1918	919	11·1	23·5	31
July to September, 1918..	520	11·9	25·9	36
—	3310	15·6	24·0 gr.	36 days.

(C) Benign Tertian Malaria: in Cape Coloured and Europeans.

Race.	No. of cases.	Per cent. relapses.	Average daily quinine.	Average days in hospital.
Cape coloured	334	36	26 gr.	51
Europeans	1080	32	25 gr.	40

The relapse statistics in regard to the Cape Coloured Corps are of interest in view of the fact that an increase in daily quinine dosage from 21·8 gr. to 27·1 gr. is associated with a fall in the average period in hospital from 70 to 46 days and a reduction in the percentage relapses from 32·3 per cent. to 17·6 per cent. It will be observed that for the same type of malaria (benign tertian) the relapse incidence and average stay in hospital are greater for the Coloured Corps as compared with the

European figures. This divergence would appear to be partly accounted for by the lessened resistance exhibited by coloured races to infectious diseases.

Relapse Interval.

It is necessary to emphasise that the relapse interval of these records refers only to parasite relapses under quinine, which may be considered to be more reliable data for study than records of clinical relapses unsupported by microscopical examination. The average number of days of the relapse interval are as follows: Benign tertian relapse: from initial negative smear, 14 days; from initial positive smear, 17·9 days. Malignant subtertian relapse: from initial negative smear, 12 days; from initial positive smear, 16·4 days. Mixed infection (M.T. and B.T.) relapse: from initial negative smear, 14 days; from initial positive smear, 17 days.

PERSISTENCE OF ASEYUAL PARASITES.

Before discussing the question of the persistence of asexual forms in the peripheral blood it is necessary to state that in all cases under examination included in this investigation the *thick film* was used throughout. The information available from weekly analyses, apart from its interest from a research point of view, supplied valuable indications as to the results obtained in each area from the treatment administered. In view of the almost universal prejudice of the soldier against quinine, and the firm belief held by some that quinine is distinctly harmful and liable to cause heart disease, it was necessary to exercise the greatest vigilance in regard to its administration. The persistence of parasites in the blood over a long period focussed attention on these cases, and resulted in either an alteration or modification of treatment, or discovery of a patient who was deliberately but covertly avoiding his doses of quinine. The fact that except in unusually chronic cases asexual parasites are not found in thick smears after a few days' administration of quinine raised the question as to what proportion of these cases in which asexual parasites persisted indefinitely in the blood were due to avoidance of quinine. Accordingly a system of recording each dose administered to each patient was instituted in one hospital, the quinine being administered in solution; each dose was actually seen to be swallowed and was then noted.

The results obtained in this hospital were in accordance with those generally obtained in the treatment of malaria in military hospitals in South Africa. Records of presence or absence of parasites in finger blood were available at about weekly intervals; cases responding to treatment were separated from resistant cases, and especial attention was thus secured for the latter group.

It should be noted that in each type of malaria the interval between blood examinations is less than the average relapse interval, so that although records of daily blood examinations were not available it is reasonable to assume the presence of parasites in the blood on the days intervening between two positive examinations, especially in view of the large proportion of heavy and resistant infections.

Final results of analyses of the records with regard to persistence of asexual parasites are set out in the following tables:—

TABLE VII.—Persistence of Asexual Forms under Quinine.

Type of malaria.	Total of cases.	Average interval between blood examinations.	Cases positive on re-examination.		Average persistence of asexual forms in cases positive on re-examination.
			Num-ber.	Per cent.	
Malignant subtertian	591	8 days (21·4 gr.)*	82	14	16 days.
Benign tertian	3171	8 .. (23·2 gr.)*	710	22	19 ..
Mixed M.T. and B.T.	281	8 .. (20·6 gr.)*	155	55	22 ..
All types positive on admission... ..	4043	8 .. (22·7 gr.)*	947	23	19 days.

* Average daily quinine in interval.

Owing to continued pressure on the "small dosage" school the average daily quinine in all cases showed a gradual rise. This desired result was further assisted by the issue of definite instructions laying down a "standard" treatment for malaria. Table VIII. is an analysis of 4043 cases indicating that the rise in quinine was associated with a marked reduction in the number of positive cases remaining positive at the end of eight days' treatment.

TABLE VIII.—Results in 4043 Malaria Cases Admitted to Hospital with Positive Smears on Re-examination After an Average Interval of Eight Days' Quinine Treatment.

Three months ending—	Number of cases.	No. of cases positive on re-examination.	Per cent. positive on re-examination.	Average daily quinine.
Dec. 29th/17 ...	1081	313	29%	18 gr.
March 30th/18	1491	368	25%	23 ..
June 29th/18 ...	909	160	19%	27 ..
Oct. 5th/18 ...	562	106	19%	27 ..

Showing how a rise in quinine is associated with reduction in the number of positive cases remaining positive at the end of eight days' treatment. Hatched line = average daily quinine in interval between examinations. Continuous line = percentage cases positive on re-examination.

It will be observed that of 4043 cases of malaria admitted into hospital with positive parasite findings 23 per cent. show parasites persisting in the blood on the 8th day in spite of an average daily dose of quinine of 22.7 gr. The average persistence of parasites in the finger blood in these cases was 19 days. This fact indicates the severe nature of the malaria cases admitted to military hospitals, and demonstrates the ineffectiveness and slow action of quinine in destroying malaria parasites in unhealthy and debilitated individuals.

Recent publications viewed from the point of view of the specific action of quinine disclose a certain degree of shaken confidence in the parasitotropic value of this drug. Quinine is undoubtedly the most valuable single remedy at present known, but its repeated failure to eradicate malaria, even when exhibited in doses and amounts limited only by the toxicity of this drug, indicates that unless it is aided by the natural protective mechanism of the body frequent relapses and long-continued illness occur, as was clearly shown in recent campaigns in malarial countries; the exigencies of military service gave rise, especially in the tropics, to conditions in which the individual's natural resistance to disease is reduced to the minimum. In the German East African campaign, owing to the extreme exhaustion of the troops admitted to field hospitals for treatment, the action of quinine could not be described as more than palliative, most cases progressing to massive infections, frequently relapsing, which were not reduced until better health conditions—as on return to South Africa—gradually engendered a more effective natural resistance. It seems highly probable that the latter is largely represented by "phagocytosis."

It is possible that the action of quinine in malaria analogous to the action of opsonins on bacteria

in infected tissues. Parasites damaged but not destroyed by quinine may then be actually ingested and destroyed by phagocytosis. There appears to be no doubt that the leucocyte is of paramount importance in the prevention and cure of malaria. Perusal of published works on malaria, particularly those of the earlier writers, leaves the impression that parasites disappear from the finger blood soon after the administration of quinine. The above figures show that on an average in 4043 cases parasites could still be demonstrated in 23 per cent. of cases when examined after an average interval of eight days, and that the parasites in these resistant cases persisted for an average period of 19 days, treatment being 22.7 gr. of quinine per day. In considering this apparent anomaly it is necessary to bear in mind the following points: (1) In this series the thick-film method is used for diagnosis which increases the chance of a positive result by about 30 times, and in the publications referred to the usual method of examination is presumed to be the thin-film method. (2) The bulk of available literature refers to quinine treatment carried out amongst civilians reasonably fed and acclimatised and for the most part protected from mosquitoes, exposure, and fatigue.

The resistant cases in this series were often severe massive infections, frequently of mixed type occurring in non-acclimatised individuals recruited from South Africa; owing to exigencies in warfare in German East Africa they were subjected to severe physical strain and hardship involving exposure to tropical sun and rains and unsuitable or insufficient food. In such cases the therapeutic effects of quinine are more slowly produced.

THE SEXUAL PARASITE OF MALIGNANT SUBTERTIAN MALARIA.

The gametes of subtertian malaria are sausage-shaped bodies, longer than the diameter of a red corpuscle showing pigment aggregated into a clump near the centre. These bodies are commonly known as "crescents" in view of their characteristic appearance. The importance of this phase in the life-history of *P. falciparum* is that its presence in sufficient numbers in the peripheral circulation renders the individual infective and a danger to a community in which malaria-transmitting anopheles are present.

Frequency of crescents in peripheral blood.—Considerable difference of opinion prevails as to the frequency with which crescents are found in malignant tertian infections. Deaderick states that, in his experience,

"Crescents are very rarely seen in blood obtained from the superficial circulation. They are also infrequent in the experience of Plehn, Stephens, Christophers, Ziemann, Wellmann, Annett, Dutton, Elliott, Kendall, and others."

Craig states that:—

"It often requires a long and patient search to demonstrate the presence of crescents in the blood of individuals who have suffered from æstivo-autumnal infections, and while I believe that a prolonged search would show crescents in 50 per cent. of such cases, still in the study of several hundred cases I have only been able to demonstrate this form in a little over 33 per cent. Rogers found that crescents were present only in 10 per cent. of the cases he observed in Europe. Mason believes that crescents are more frequently observed in cases of malaria which have been contracted in the tropics, but have returned to temperate regions, and that in the tropics it is much more rare to observe this form of plasmodia."

Craig does not agree with Mason, as he has found that the percentage of cases showing crescents in the tropics is practically the same as in temperate regions.

With regard to the frequency of crescents in the peripheral blood it is necessary to consider the following points: (1) method of examination (thick or thin blood smears); (2) number of consecutive examinations; (3) stage of disease at time of observation (acute, convalescent, or chronic); (4) influence of previous treatment; (5) influence of treatment at time of observation; and (6) defensive mechanism of patient (general health).

The statistical records in regard to crescents available from these investigations refer only to the results of examination of thick blood smears, the average number of consecutive examinations being four in each

case, each separate examination taking up a maximum of about five minutes. The treatment laid down for all cases of malaria has been previously noted. The thick film method of examination increases the chances of finding crescents by about 30 times when compared with half an hour's examination of a thin blood film. The original infection in these cases was usually contracted several months previously in German East Africa under active service conditions. During this time quinine prophylaxis was usually carried out, and there was generally a history of repeated attacks necessitating admission to field hospitals. The cases were therefore usually admitted to union hospitals with an acute or subacute attack occurring in a more or less chronic infection associated in the more severe cases with a markedly debilitated condition characterised by anorexia, wasting, shortness of breath, and anæmia. (Tables IX. and X.)

TABLE IX.—Classification of Cards Showing Crescents During Period in Hospital under Quinine Treatment.

Three months ending—	Total cards showing C.	Cards showing C only.	Cards showing first C's then R's, or R's & C's.	Cards showing first R's then C's, or R's & C's.	% C cases showing R's during period in hospital.	% C cases showing C's only during period in hospital.
Dec. 29/17 ...	576	495	60	21	14.1	85.9
March 30/18	760	475	79	206	37.5	62.5
June 29/18 ...	469	346	64	59	26.2	73.8
Oct. 5/18 ...	167	126	15	26	24.6	75.4
Total all cases...	1972	1442	218	312	26.9	73.1

R = ring form of parasite ; C = crescent.

TABLE X.—Frequency of Crescents in Peripheral Blood.*

Three months ending—	M.T. infection	Mixed infection	Total cases with M.T. infection.	Total cases showing crescents.	Per cent. M.T. infections showing crescents in peripheral blood.
Dec. 29/17...	790	487	1277	576	45.1
Mch. 30/18...	662	497	1159	760	65.6
June 29/18...	334	290	624	469	75.2
Oct. 5/18 ...	191	144	335	167	49.8
Total ...	1977	1418	3395	1972	58.1

* Average period of observation 52.4 days.

The production of crescents in sufficient numbers in the peripheral blood to enable their presence to be discovered in a thick film indicates that an environment has been created (usually by quinine treatment) sufficiently unfavourable to menace the existence of the asexual generation, the presence of the sexual parasites being an effort on the part of the parasite to prevent total eradication by transference by means of a mosquito to a more favourable environment. So long as the parasite is able to maintain its numbers by a vegetative cycle this method of propagation is selected and preferred by the organism. This is indicated by the fact that crescents are not found in acute stages or in untreated cases of the disease.

The continuous exhibition of inadequate doses of quinine appears to favour the production of crescents owing to the fact that while an unfavourable environment is produced the dosage of quinine employed does not reduce the crescent-forming "rings" sufficiently to prevent the detection of the crescents produced. The presence of numerous crescents in the blood suggests that the asexual generation has been damaged and reduced but not eradicated. The disappearance of crescents shows that progress has been maintained in reducing the infection.

It will, therefore, be seen that crescent formation occurs in infections resistant to treatment in which the destruction of parasites has been slowly effected. The formation of crescents may be prevented in malignant subtertian infections by vigorous and effective quinine

treatment in suitable cases owing to the rapid reduction and destruction of the asexual generation, thereby cutting off the supply of "ring" forms destined to develop into crescents. Crescents do not appear similarly in the peripheral blood in untreated infections or markedly resistant infections inadequately treated owing to the fact that the measures adopted for treatment do not menace the asexual generation or establish an unfavourable environment. The appearance of crescents is not an unfavourable sign in the treatment of malignant subtertian malaria in which "rings" only are present in the finger blood, as it is an indication that the therapeutic measures employed are to some extent effective against the asexual generation. Disappearance of all "ring" forms from the peripheral blood and failure to produce crescents indicates that the infection has been hard hit and so reduced in numbers as to justify a favourable prognosis.

CASES UNDER TREATMENT: TIME OF APPEARANCE OF CRESCENTS IN PERIPHERAL BLOOD.

With regard to the time of appearance of crescents in the blood the results of treatment with varying doses of quinine in cases of malignant subtertian malaria showing at first "rings" only in the peripheral blood are indicated in the following summarised tables:—

TABLE XI.—Quinine Treatment and Time of Appearance of Crescents in Blood.

Series. (Daily quinine treatment).	No. of cases.	Days of treatment until appearance of crescents.	Average daily quinine.
10 gr.	26	11	10 gr.
11 gr. to 20 gr. ...	110	11	16 "
21 gr. to 30 gr. ...	164	9	28 "
31 gr. to 45 gr. ...	12	9	39 "
	312	9.5	22 gr.

It will be observed that the time of the appearance of crescents is a shorter period in the case of the larger doses of quinine, but that the average time of appearance of crescents is 9.5 days, with an average daily dose of quinine of 22 gr. The shorter interval suggests that an unfavourable environment was more quickly established in the case of the larger doses of quinine.

DURATION OF CRESCENTS IN PERIPHERAL BLOOD.

The crescent is a form of the malignant subtertian parasite particularly resistant to the action of drugs. Quinine has no obvious direct action on crescents, but indirectly it is the most powerful remedy at present available for ridding the blood of them. Its action in these cases is entirely on the ring forms of the parasite which are controlled, reduced, and destroyed, thereby eliminating the forms of the parasite from which crescents are produced. In one series of 1798 crescent infections in which the average daily quinine administered during the persistence of crescents was 25 grains, the average persistence of crescents in the peripheral blood was 15 days. It is therefore clear that crescent infections are not formidable, and tend to clear up in the ordinary way on adequate quininisation. In cases where quinine is insufficient to control the infection and prevent relapses, as in very debilitated individuals, supplementary treatment with organic arsenic preparations, especially "606," given intravenously, has proved useful in breaking down the resistance of the asexual parasites to the action of quinine. These preparations do not appear to exercise any direct destructive action on crescents. A series of 27 cases was treated with intravenous injections of tartar emetic without any definite action of this preparation on crescents being demonstrable. Tartar emetic also has no influence in preventing relapse in malarial infections.

The following figures indicate that so long as an adequate dosage of quinine is employed no obvious advantage as regards persistence of crescents is gained, in ordinary cases of malignant subtertian malaria in which crescents are present in the finger blood, by the addition of intramuscular injections of soamin or intravenous injections of "606" preparations. It

should be noted (see Table XII.) that in 1577 cases treated with an average dose of quinine of 24 gr. daily the crescents persisted in the blood for 15 days for all treatments.

TABLE XII.

No. of cases	Average daily quinine.	Duration of crescents.	Treatment series.	No. of injections per case.
952	25 gr.	15	Quinine only.	—
506	21 „	15	Quinine and inorganic arsenic.	—
56	23 „	16	Quinine and soamin.	3
63	24 „	21	Quinine and "606."	3
1577	24 gr.	15	All treatments.	—

It is therefore clear that the eradication of crescents is satisfactorily secured by the control of the asexual generation of the malarial parasite by adequate quininisation. The same is true of the sexual forms of the benign tertian parasite.

This paper is included in a report by the Director of Medical Services to the Minister of Defence, Union of South Africa, on "Malarial Research in South Africa during the War." Acknowledgments are due to Colonel P. G. Stock, Director of Medical Services, and Colonel G. H. Knapp, Deputy Director of Medical Services, for sympathetic support in sanctioning the necessary arrangements for carrying out malarial researches; to Lieutenant-Colonel Andrew Balfour, and Lieutenant-Colonel J. W. W. Stephens, for valuable criticism and advice; to the commanding officers and medical officers of S.A.M.C. hospitals, and medical officers of S.A.M.C. laboratories, Lieutenant-Colonel G. W. Robertson, Majors Targett-Adams, D. Pullon, J. C. Venniker, Captains Pearson, Impey, Luke, Garrow, and Walker, without whose keenness and coöperation it would not have been possible under war conditions to carry out these researches.

THREE CASES OF INFLUENZAL PNEUMONIA

WITH SEPTICÆMIA AND EXTENSIVE MEMBRANOUS COLITIS.

By E. CRONIN LOWE, M.B.E., M.B., B.S. LOND.,
PATHOLOGIST TO SOUTHPORT INFIRMARY; BACTERIOLOGIST TO EYE
INFIRMARY, LIVERPOOL; LATE CAPTAIN, N.Z.M.C., AND
PATHOLOGIST TO NO. 2 N.Z.G.H.

THE cases here recorded occurred among a series of severe influenzal pneumonia cases during the winter of 1919 at the No. 2 N.Z. General Hospital, Walton-on-Thames. The details of history and of bacteriological and pathological findings are given as fully as possible, because the post-mortem examinations revealed a condition of the alimentary canal which has, as far as I know, not been definitely recorded or frequently observed.

The interest centres about the following points:—

- (1) The cases were not in any way associated with one another before or during their illness.
- (2) They were all apparently definite respiratory infections in which an initial "influenzal" attack developed a rapidly progressive broncho-pneumonia, becoming markedly septicæmic.
- (3) Alimentary symptoms were practically absent in each of the cases, and any marked pathological condition of the gut was not anticipated from the slight clinical symptoms observed.
- (4) Vaccinal prophylaxis had not been undertaken, except in one case, where a single dose had been administered five days previously to the commencement of the illness.
- (5) Treatment during illness varied in each case. In Case A, two doses of 1 12th gr. corrosive sublimate in 1 c.cm. of saline had been given intravenously on the fifth day before death; some abdominal discomfort was complained of the same night and following day, and seven evacuations occurred during this interval, but there was not any violent intestinal disturbance, and during the last three days semi-normal stools were passed. It was very largely because of interest attaching to several influenzal cases in hospital at the same time, in whom more violent intestinal disturbance had followed the intravenous use of corrosive sublimate,

that especial attention was directed to the alimentary condition in this case at the post-mortem examination, for no other case which had received intravenous mercury died. In Case B no mercurial or other intravenous medication was given, and in Case C intravenous corrosive sublimate was not given; a mixture of urotropin 25 per cent. and phenol 1 per cent. in saline, a total dose of 8 c.cm., was given intravenously on three occasions on the fourth and second day before day.

(6) Blood culture was attempted four days before death in Case A only, but proved negative. Cultures made at the post-mortem examination from heart, blood, and spleen gave pure streptococcal cultures in each case; the organisms were also present in direct film examinations from the spleens of Cases A and B.

(7) The pathological condition of the respiratory organs of Cases A and C were practically identical. A patchy broncho-pneumonia, becoming confluent through associated oedematous infiltration of intervening lung tissue, was most marked in the lower lobes of both lungs, extending discretely in the upper lobes. Bronchial secretions were not markedly purulent, but fairly profuse and frothy. The bronchi, trachea, and larynx were deeply injected. These broncho-pneumonic areas caused an obvious dark coarse mottling where they reached the pleural surface, but no obvious pleurisy occurred, nor was there excess of pleural effusion.

Definite hæmorrhagic areas, varying from microscopic sizes to extravasations of about $\frac{1}{2}$ inch across, were irregularly distributed throughout the more intensely infected lower lobes. Film preparations of the bronchiole secretions of the more confluent areas showed the presence of pneumococci, streptococci, and *Micro. catarrhalis*, the two former predominating. A few *B. influenzae* were present, with *M. catarrhalis* and a smaller proportion of streptococci and pneumococci in the less markedly inflammatory areas. Streptococci (markedly hæmolytic), pneumococci, and a few *B. influenzae*, as well as *M. catarrhalis*, staphylococci, and *B. proteus*, were obtained by culture from the lung tissue.

Detailed Conditions.

Lungs and pleura.—The lung condition of B differed considerably from those of A and C. In this case, accompanying a less intense broncho-pneumonia of the right lower lobe and a still slighter condition of the left, there was an abscess cavity situated near the lower border of the right upper lobe, about 1½ inches in diameter, its wall reaching but not perforating the pleura at one point; its cavity was full of pink-coloured pus and masses of necrotic tissue; the wall was ill defined. An extensive pleurisy was associated with this abscess, thick, lightly adherent flakes of purulent exudate covering the whole pleural surface, and a fair amount of purulent fluid being present in the pleural cavity. The left pleura was normal. Smear preparations and cultures made from the pleural fluid indicated pure streptococcal infection, while those from the abscess a mixed infection, in which streptococci largely predominated. In all cases the bronchial and tracheal glands were enlarged, congested, and oedematous, being most marked in B, where evidence of early suppurative change was found in the larger glands.

Heart.—The heart in each case was of normal size, the evidence of disease being only found in the dark congestive state of the muscle walls, some small endothelial hæmorrhages occurring around a more general endothelial injection and a pinkish coloration of the aortic cusps, most evident in A. Pericarditis or excess of pericardial fluid was absent in each case. Blood-smears and cultures were made; in each case streptococci were recovered by culture in A and B, a heavy growth in C sparingly. Film preparations showed the organism present in A only.

Spleen.—The spleen of each case showed the usual signs of an intense septic infection, being slightly enlarged, abnormally pink in colour, soft and friable in consistency. Numerous small hæmorrhages occurred in A, and a single abscess about the size of a pea in B. Smear preparations gave evidence of streptococci in B only, but by culture streptococci were recovered from both A and B.

Kidneys.—The kidneys showed the usual pathology—acute septic infection in each case, more intensely congested in A and C than in B, and by microscopic section showing cloudy swelling, acute parenchymatous