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# Section of Tropical Diseases and Parasitology

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## Clinical and Parasitological Observations on Induced Malaria

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(WITH NOTES ON THEIR APPLICATION TO THE STUDY OF MALARIA EPIDEMICS BY S. P. JAMES)

### (1) *The Clinical Severity of Epidemic Malaria*

IT is a matter of common knowledge, which was exemplified during the recent epidemic in Ceylon, that in every malarious country there is a striking clinical difference between ordinary endemic malaria and the epidemic disease. Why is it that ordinary endemic malaria, whether it is due to the so-called benign species or to the so-called malignant species, is comparatively mild and rarely followed by a fatal issue while epidemic malaria is always serious and is directly responsible for many deaths? The question is one that is seldom dealt with in textbooks and, when it is, the severity and fatality are usually attributed to factors other than those relating to the malaria parasite itself and the mosquitoes which transmit it. They are usually attributed to economic stress, hardship, famine, exposure, and other circumstances which sometimes happen to coincide with the epidemic. Reasons of this kind were emphasized by most writers on war-malaria in Eastern Europe and they have been prominently brought to notice in accounts of the recent epidemic in Ceylon. Contrary to this view we think that our work at Horton indicates that a type of malaria closely resembling epidemic malaria can be produced in the absence of any of those adverse circumstances which for this reason must be regarded, in our opinion, as playing only a minor role. We think that the leading role is played by the parasites themselves in the human host and in the mosquito. But in saying that the parasites play the leading role we do not mean that the strains responsible for the endemic disease cause the severe cases met with in an epidemic by becoming more "virulent." Certainly some geographical strains of *P. falciparum* seem inherently to be more "virulent" than others, as we showed in our paper on induced malignant tertian malaria which was published in 1932,[1] but we have no evidence that the inherent virulence of a particular strain can be increased or diminished. The

[1] *Proceedings*, 1932, **25**, 1153 (Sect. Trop. Dis. and Parasit., 37)

MADAGASCAR STRAIN.

BENIGN TERTIAN PRIMARY ATTACK INITIAL STAGE.

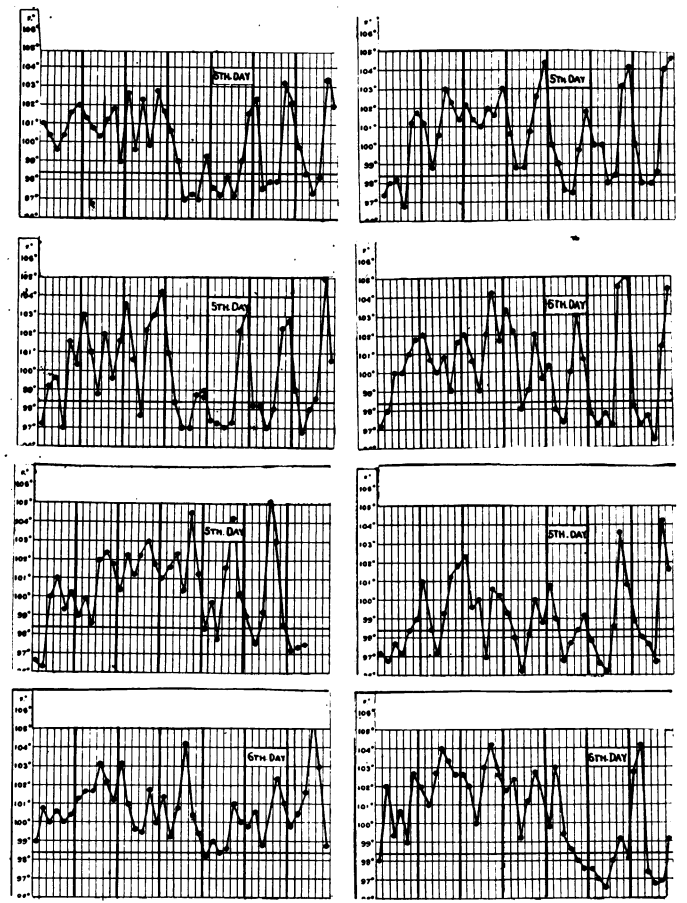


FIG. 1.

MALIGNANT TERTIAN PRIMARY ATTACK INITIAL STAGE.

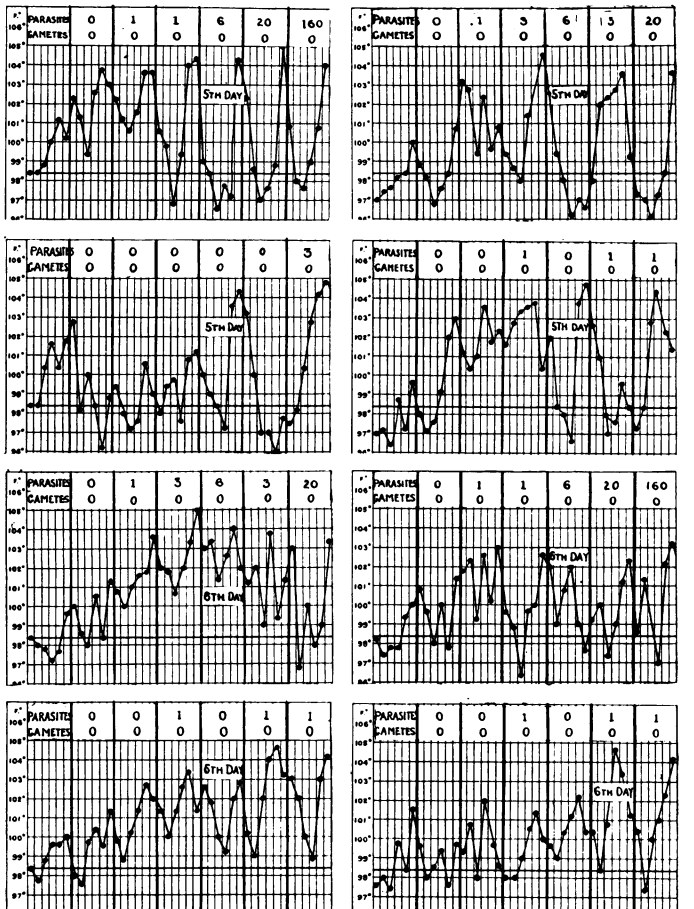


FIG. 2.

change in the parasites which we have observed at Horton (and which we think may be the change that is responsible for the severity of epidemic malaria) is not an increase of virulence but an increase of physical vigour and vitality, leading to the production of individuals which represent the species in its perfect form. In these individuals the normal processes of reproduction, sexual as well as asexual, are carried on in the most regular and complete manner of which the species is capable. One result is that the number of parasites which appear in persons infected with these healthy and vigorous parasites exceeds considerably the number which appear in persons infected with a less active strain. Susceptibility and other factors in the human host being equal, the number of parasites governs the severity of the case, and the result of using a strain which multiplies freely and vigorously is that non-immunes of normal susceptibility who are infected with it develop the severe "epidemic type" of the disease.

At Horton between 1925 and 1930 we succeeded in increasing the physical vigour and activity of an endemic strain of *P. vivax* from Madagascar to the degree in which it caused this severe "epidemic type" of the disease in 80% of our cases. We did so by using a particular procedure in passaging the strain through the human host and insect vector. The change was so definite that we came to consider that the strain at the height of its activity caused a more severe clinical type of malaria than was caused by any other strain of *P. vivax* which was being used for

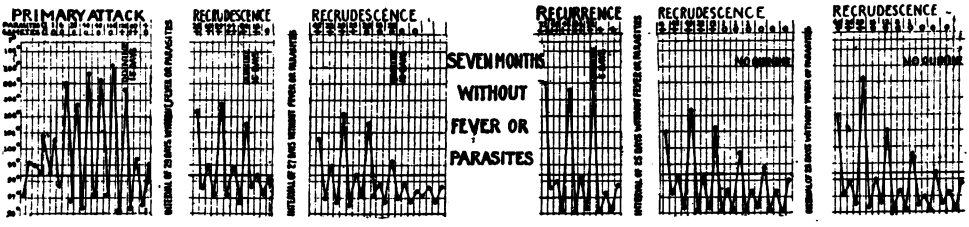


FIG. 3.

the practice of malariatherapy anywhere in the world. The mode of onset of the primary attack in cases infected with it is illustrated in fig. 1. It will be seen that the attack begins with a subcontinuous or remittent type of fever which does not become frankly intermittent until the fifth or sixth day. Rigors are usually absent during this stage and in other respects the mode of onset resembles that of cases due to infection with *P. falciparum* illustrated for comparison in fig. 2.

The subsequent course of a case of this severe type is shown in fig. 3. After the initial irregular fever there is a paroxysm of fever every day. This stage is severe and always has to be terminated by quinine. Frequent blood examinations must be made to see that the parasites are not becoming too numerous and there must be careful nursing to keep the temperature within bounds. Where these precautions are not taken the case mortality directly due to the malarial attack may be as high as 10 to 14%. About three weeks after treatment of the primary attack there is a relapse (or recrudescence as we call it) and if this has also to be cut short by quinine there is usually a second and perhaps a third at about the same interval. Then there follows a long period (usually about seven or eight months) during which it seems as if the infection had completely died out. Then quite suddenly, without any apparent reason, there is a sharp "recurrence" which, like the primary attack, may be followed by several recrudescences at intervals of about a month.

Temperature charts showing how a relapse of this type of malaria differs from a primary attack are illustrated in fig. 4. A relapse, instead of beginning with gradually increasing fever, begins abruptly with a sharp attack ushered in by a chill or rigor and thereafter there is usually a febrile paroxysm every other day instead of daily as in the primary attack.

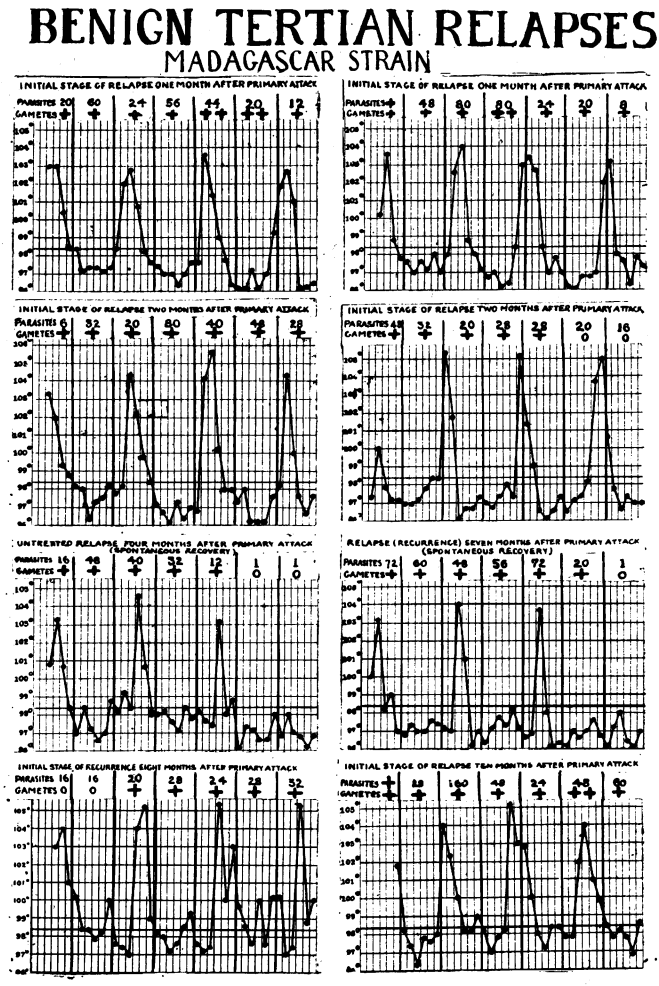


FIG. 4.

Parasitologically the change from the mild "endemic" type to the severe "epidemic" type is evidenced not only by an increase in the number of asexual parasites but particularly by the earlier appearance and greater number of gametocytes. When we first obtained the Madagascar strain of *P. vivax* in 1925 it was difficult to infect mosquitoes from it during the primary attack because gametocytes were seldom present in sufficient numbers before the day arrived on which it was the prescribed practice to terminate the course of therapeutic malaria, this day being

as a rule the tenth from the beginning of the attack. After adopting the particular procedure mentioned, the gametocyte-producing capacity of the strain became changed in the manner shown in fig. 5.

The difference in the *number* of gametocytes appearing in the blood of cases in the second series as compared with the first was as striking as was their earlier appearance but because actual counts were not made in all cases this result cannot belshown diagrammatically. The difference in numbers, however, was obvious from the results obtained in mosquitoes fed upon the cases. The number of oöcysts in mosquitoes fed when the strain was first obtained rarely exceeded ten, but the number in mosquitoes fed when the strain was at the height of its gameocyte-producing activity was often several hundred. In these insects sporozoites were so

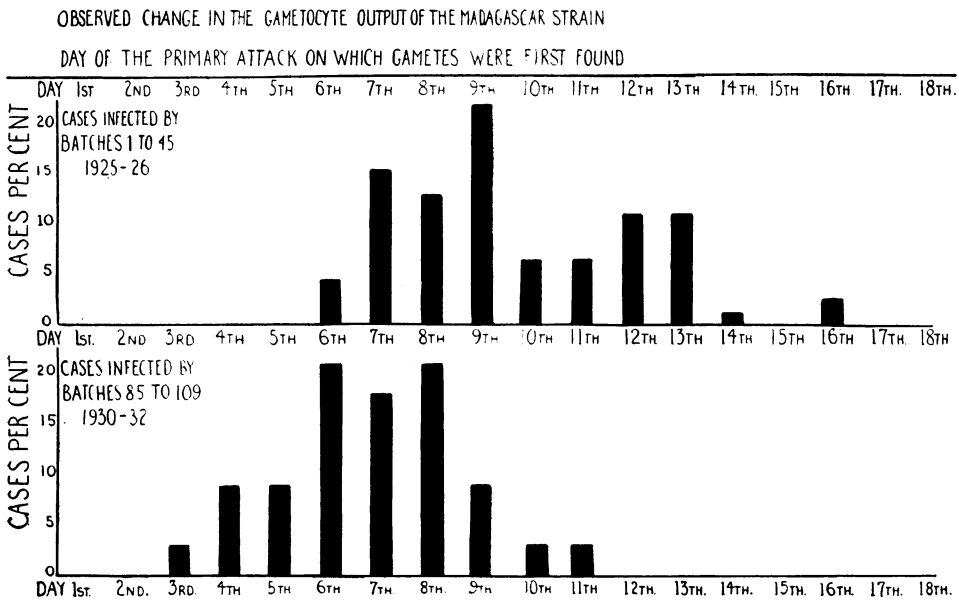


FIG. 5.

*Cases infected when the strain was first obtained.* Gametocytes were not found in any case before the sixth day: in 31% of cases they were not found before the twelfth day or later.

*Cases infected at the later period.* Gametocytes found in some cases as early as the third day: in *all* cases they were found before the twelfth day.

In the early series they were found on or before the eighth day in 30% of cases.

In the later series they were found on or before the eighth day in 82% of cases.

numerous that they could be found in every part of the anatomy of those which were dissected and they were still to be found in the salivary glands of insects which had infected as many as thirty persons.

### (2) *The Influence of the Dose of Infection*

At the end of the preparation of a batch of infected mosquitoes for the purposes of malariatherapy there are, let us say, 100 infected insects available. During the following two months or more, while they are being used for infecting patients, many of them die and the sporozoites in the glands of those that remain alive gradually become used up. Towards the end of the batch only two or three insects may be alive and there may be only a few sporozoites in their salivary glands. In

persons of normal susceptibility the result of infection by the bites of these two or three lightly-infected insects is usually quite different from the result of infection by the bites of many heavily-infected insects at the beginning of the batch. Some examples of the usual reaction are shown in fig. 6. In these cases the primary attack is represented by only two or three days of irregular fever from which the patient recovers without specific treatment or there may be no appreciable sign or

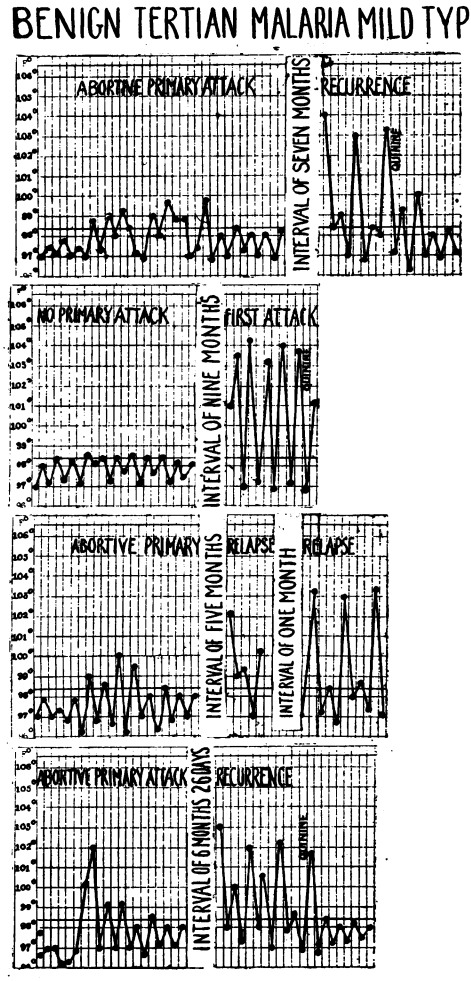


FIG. 6.

symptom of any kind at the period when the primary attack should occur. The first type is called an abortive case, the second a latent case, but the difference is only one of degree and the subsequent course of both types is the same, namely that there is a long period of complete freedom from fever and parasites and then, at a period corresponding with the period of "recurrence" in the severe type, there is a sudden sharp attack. This observation is a repetition in the laboratory of what

happens in countries like Holland and England where (because only one or two lightly-infected mosquitoes are responsible for each indigenous case) most of these cases are abortive or latent in the primary attack and are only detected at the period of recurrence in the following spring. Another observation showing the influence of dosage is that in benign tertian malaria the condition of latency can always be produced by a few prophylactic doses of atebrin which kills most, but not all, sporozoites injected by a mosquito. Thus persons who take three tablets of atebrin (each containing 0·1 grm.) on the day before they are bitten by mosquitoes infected with *P. vivax* and the same dose on the day of being bitten and for five following days remain quite free from the risk of a malarial attack within the usual incubation period of the disease but usually have an attack at the period of recurrence about eight months later. Yet another is the fact that in persons who are naturally resistant to infection with the benign tertian parasite one can often break down the resistance and give the person an attack by repeating the dose. An example is illustrated in fig. 7.

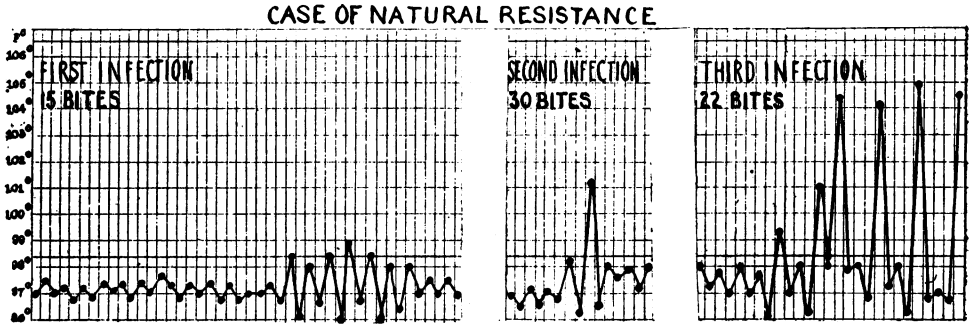


FIG. 7.

The first infection was by the bites of 15 mosquitoes but there was only a very slight reaction characteristic of a latent infection. The second infection was by the bites of 30 mosquitoes but only a mild abortive attack developed. A third infection by the bites of 22 mosquitoes produced a frank attack which, however, showed a tertian instead of a quotidian periodicity and tended to die out spontaneously after eight peaks of fever.

### (3) *The "Recurrence" in Benign Tertian Malaria*

The recurrence in benign tertian malaria is a striking event and why and how it happens is still a mystery. It has never been observed in any other kind of malaria than that due to *P. vivax*. In induced malaria it occurs only in cases inoculated in the natural way by the bites of mosquitoes, never in cases induced by the inoculation of malarial blood. Like the first frank attack in latent infections it occurs at a definite period after the primary infection and the time of its onset is not in any way dependent on season or climate or changes in atmospheric humidity or any other environmental factor which has been thought from time to time to provoke the onset of a relapse. Observations with regard to it have upset several views and opinions, particularly about the value of some antimalarial drugs for radically preventing the effects of an infection and for preventing relapses. The phenomenon of recurrence has also upset published views on the influence of season and climate on the incidence of relapses. An interesting example was mentioned by Professor Blacklock in a recent discussion on the Ceylon epidemic. During the War he and other workers in Liverpool made the important observation that, with any system of anti-relapse treatment, much better results were obtained on cases treated during the summer than on cases treated during the spring. It was suggested that the higher summer temperature was the cause. However, in all

probability, the true reason was that the soldiers treated had contracted their benign tertian malaria in Macedonia during the autumn of 1916 and 1917 and that in the spring of the following years they were due for their recurrences against which no system of anti-relapse treatment is effective. The consequence was that an anti-relapse treatment given in the spring was effective in only about 4% of cases while the same treatment given in the summer (by which time most of the men had had their recurrence and the recrudescences which follow it) was effective in 60%.

Lastly, the phenomenon of recurrence and the allied phenomenon of latency serve to explain some epidemic waves of benign tertian malaria which cannot be

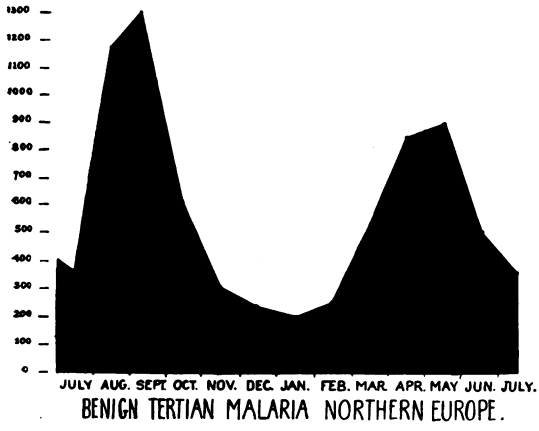


FIG. 8.

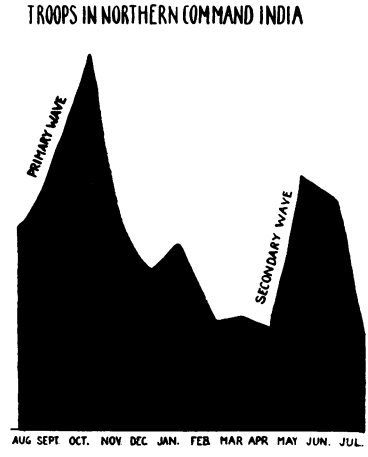


FIG. 9.

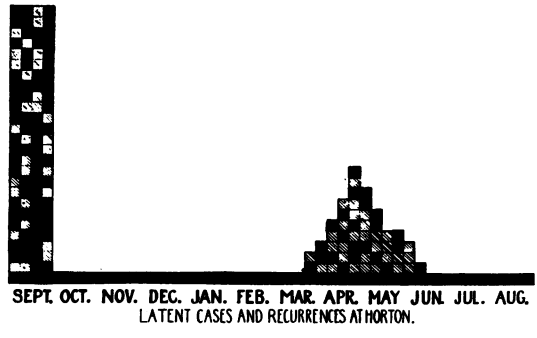


FIG. 10.

correlated with the incidence of anopheles mosquitoes. Fig. 8 shows the annual epidemic curve of benign tertian malaria in Northern Europe and fig. 9 the curve of admissions to hospital for malaria among troops in Northern India.

There is a major summer-autumn wave and a minor spring wave. For a long time the explanation of the spring wave in Northern Europe was a puzzle to epidemiologists. It begins in March before the first brood of anopheles has hatched out and it ends in June just when these insects are beginning to become prevalent. The explanation is that the wave is due to recurrences + first attacks in latent infections as can be seen from fig. 10 which shows results obtained at Horton.

(4) *The Different Sequence of Relapses in Benign Tertian and Malignant Tertian Malaria*

The usual sequence of relapses in benign tertian malaria as observed in 107 cases at Horton is shown in fig. 11. A is the period of freedom from fever and parasites which follows cessation of the treatment which brought about recovery from the primary attack. B is the period of about two months' duration during which one or more recrudescences of fever and parasites are very likely to occur. C is the much longer period (usually between six and ten months) during which it seems as if the

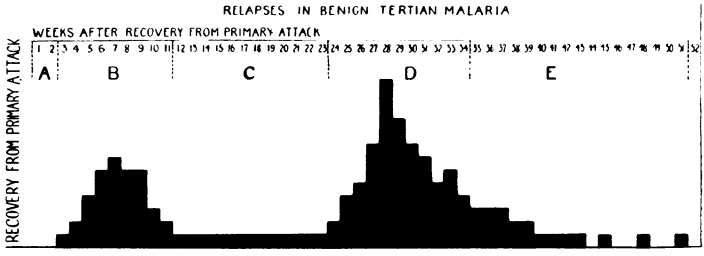


FIG. 11.

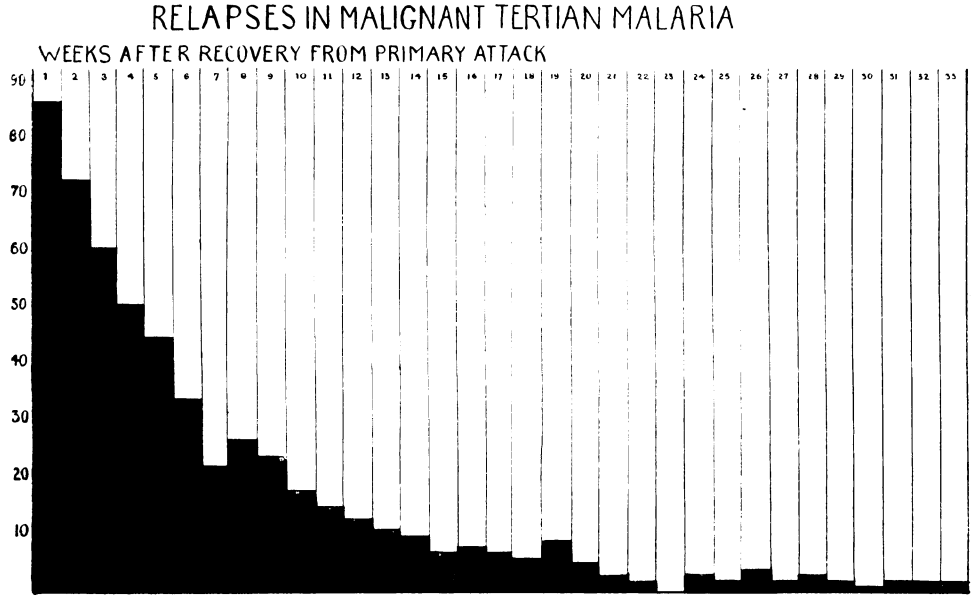


FIG. 12.

infection had been completely overcome. D is the period when the probability of a "recurrence" of fever parasites is about twice as great as at any earlier period. E is the period during which recrudescences often follow the recurrence.

The usual sequence of relapses in malignant tertian malaria as observed in 87 cases at Horton is shown in fig. 12. It will be seen that in the malignant tertian disease the only relapses are "recrudescences" occurring at short intervals after

recovery from the primary attack. There is no "recurrence" and the total duration of febrile manifestations seldom exceeds six months and is usually less. This difference from benign tertian malaria is very remarkable and is of much importance clinically and epidemiologically.

(5) *Note on the Application of Some of the Above Observations to a Study of the Clinical and Parasitological Features of the Recent Malaria Epidemic in Ceylon*

The recent epidemic in Ceylon, as in other countries in which *P. vivax* as well as *P. falciparum* is prevalent, manifested itself in two waves. The major wave began in October and the secondary wave began in the following April. From what was said in Note 3 above it will be evident that if *P. vivax* played a considerable role in the primary wave it was inevitable that a secondary wave due to recurrences and first attacks in latent infections would occur in the following spring. It was very probable, too, that if the recurrences happened to coincide with a prevalence of the insect vector they would give rise to new infections because of all types of relapse the "recurrence" is the best infector of anopheles. Thus, unless Ceylon is a country in which the phenomenon of recurrence in benign tertian malaria does not occur, the onset of the secondary wave can be explained satisfactorily on these grounds. At the same time an explanation based on the inevitability of recurrences and first attacks in latent infections does not rule out the view that some cases in the secondary wave (particularly in areas which did not suffer during the primary wave) arose in the manner described by Dr. Briercliffe on page 32 and in *Appendix 3* of his official report.

The primary wave is a more difficult problem. First there is the question whether it was initiated by an outburst of relapses or whether it started with an increase of primary cases. Available evidence on this question is partly clinical, partly parasitological. On the clinical side I have received from Ceylon, through the good offices of Dr. Briercliffe, 180 temperature charts of cases admitted to hospital between October and December 1934. Of these charts 63, which were kindly sent by Dr. Somasundram, Visiting Physician to the Civil Hospital, Kandy, are of the earliest cases which occurred during the epidemic. They are of cases admitted to hospital between the first week of October and the second week of November. They comprise cases in which only *P. vivax* was found and cases in which the infection was a mixture of *P. vivax* and *P. falciparum*. The charts of 16 cases due to *P. vivax* are reproduced in fig. 13. Clearly they are primary cases with one or more febrile paroxysms every day and it is interesting to see that some of them resemble the charts of cases of our Madagascar strain of *P. vivax* illustrated in fig. 1.

Charts of some cases of mixed infection with *P. vivax* and *P. falciparum* are reproduced in fig. 14. They, too, show the type of fever which is characteristic of a primary attack. Thirdly, in fig. 15 I have reproduced six charts which probably represent recrudescences or relapses. These six are all that I could find among the charts of cases admitted before the second week of November. Later I received from Dr. Seneviratne, Medical Registrar, General Hospital, Colombo, a second collection of temperature charts of some of the earliest cases which occurred during the epidemic. Most were of cases admitted to the civil hospitals at Kurunegala and Kegalle between September 26 and October 6, 1934. They included cases in infants and young children and appeared on the whole to represent a less severe clinical type than was exemplified in the first collection received.

On the parasitological side the chief evidence available is that provided in the parasitological study of cases made during the epidemic by Dr. Wijerama, Pathologist to the General Hospital, Colombo. He studied more than 3,000 positive blood-films collected between October 1, 1934, and March 31, 1935, and described

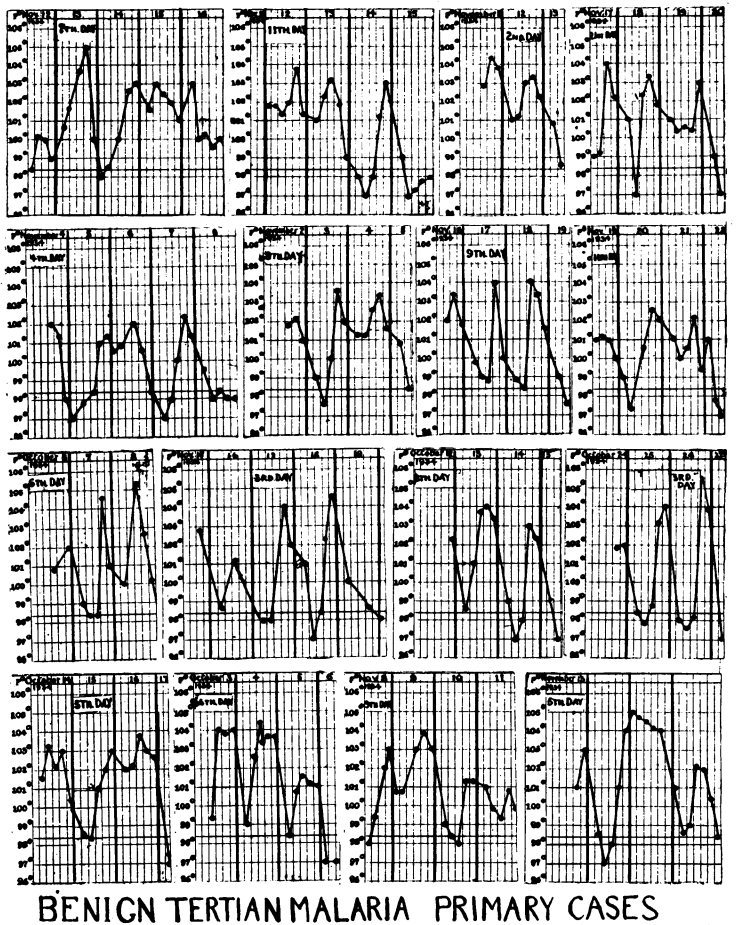
ONSET OF CEYLON EPIDEMIC
BENIGN TERTIAN MALARIA PRIMARY CASES

FIG. 13.

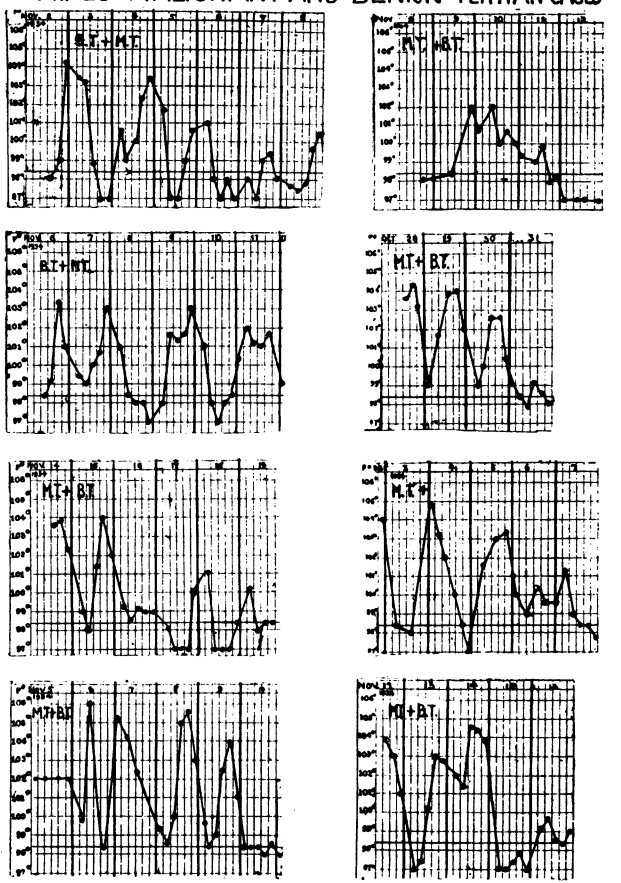
CEYLON EPIDEMIC.
MIXED MALIGNANT AND BENIGN TERTIAN CASES

FIG. 14.

the results in detail in a paper published in the *Journal of the Ceylon Branch of the British Medical Association.* An important item of evidence relative to the question whether the epidemic started with an outbreak of relapses or with an increase of primary cases is that in films from 230 cases admitted to hospital between October 1 and November 11, no gametocytes at all were found. The first occasion on which gametocytes were found was in two of 70 cases admitted during the week ending November 18. Thereafter they were found in increasing numbers of cases to the end of March. This failure to find gametocytes during the first six weeks of the epidemic is strong evidence for the view that most cases during that period were primary attacks. Another important item of parasitological information comes from

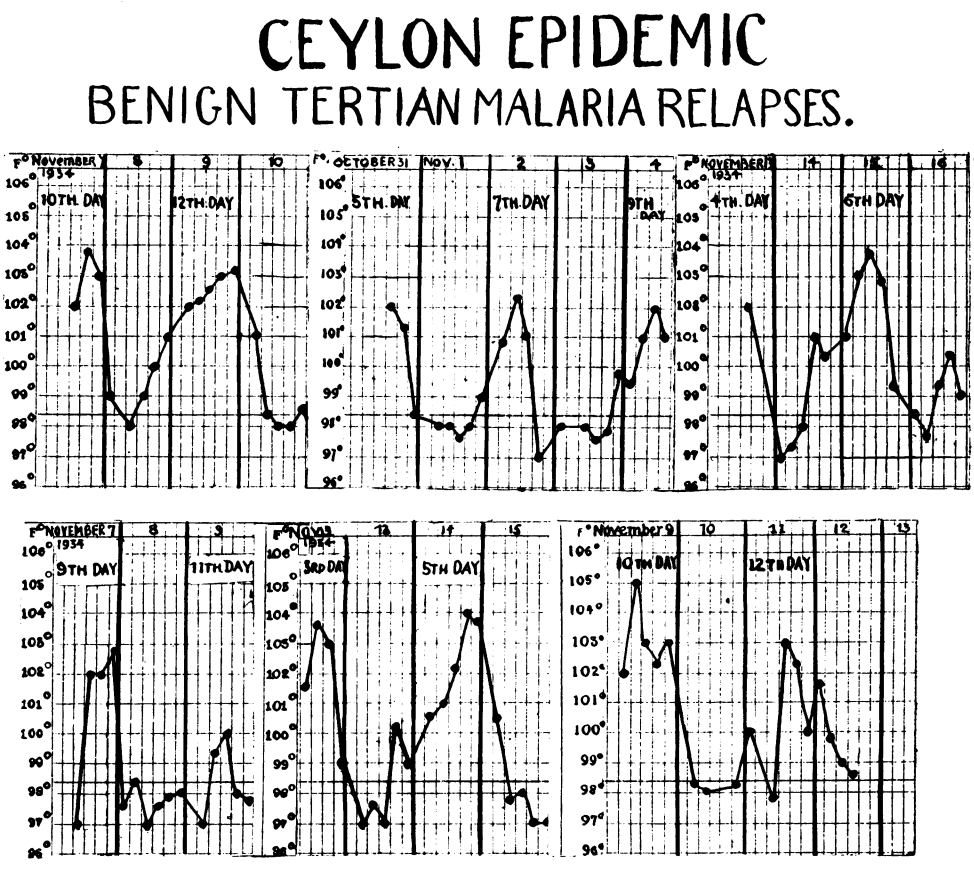


FIG. 15.

Dr. P. B. Fernando, Visiting Physician of the General Hospital, Colombo, who in his account of the study of 647 cases, reports that a noteworthy feature was the uncommonly heavy parasitic infections met with. He writes that his previous experience had been that in order to find parasites in a thin film careful search of a number of microscope fields was necessary but that in the recent epidemic the results of examination were quite different. Heavy parasitic infections were found in most cases and in some there were infections with as many as from 15 to 80 parasites per field. This argues in favour of primary attacks rather than of relapses and accords with what was said in the earlier part of this paper about the cause of the severity of primary attacks in cases infected with our Madagascar strain.

On a consideration of both the clinical and the parasitological evidence summarized above, it seems to me that in all probability the first event in the epidemic was an increase of primary cases rather than an outburst of relapses and that the increase of primary cases began in some areas as early as the last week of September or the first week of October. I may add that inspection of the temperature charts of cases admitted to Hospital at Kurunegala and Kegalle during those weeks leaves one with the impression that the cases which occurred at the beginning of the epidemic were of a milder clinical type than were the cases which occurred later when the epidemic was at the height of its activity.

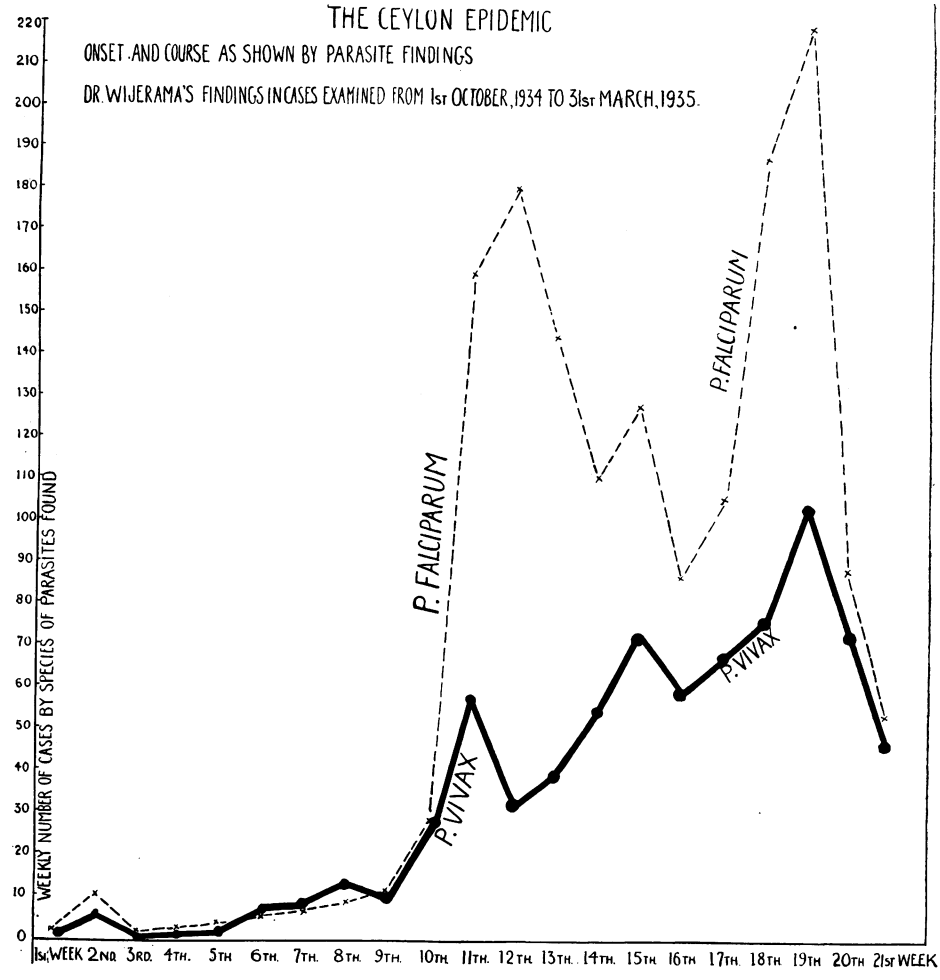


FIG. 16.

A second important question is whether the epidemic began suddenly in an explosive manner or whether it began gradually with a steady increase of cases week by week. I think that on this question the best available evidence is provided by the results of Dr. Wijerama's laboratory survey of parasites in blood-films, because these are the only results which enable the onset and progress of benign tertian and malignant tertian malaria to be examined separately. For this reason I have reproduced Dr. Wijerama's results in fig. 16. The curve starts with cases admitted

during the week ending October 7 when one film positive for *P. vivax* and one for *P. falciparum* were recorded. In the next week there were five infections with *P. vivax*, ten with *P. falciparum*, and one mixed. During the next eight weeks infections with *P. vivax* and *P. falciparum* were about equal, both types showing a gradually rising prevalence. In the ninth and tenth weeks, both types rose sharply and a week or two later malignant tertian malaria evidently became severely epidemic. Thereafter there was a striking difference between the two curves. The curve of cases due to *P. vivax* rose more slowly than that of cases due to *P. falciparum* and did not attain its maximum until the nineteenth week.

The curve of positive blood-films shown on this chart agrees with the curve of clinical cases given in the paper by Dr. Fernando and if we accept it as exemplifying what happened in most parts of "the epidemic area" it seems as if we must decide that the epidemic began gradually rather than suddenly and that it did not become explosive in character until it had been increasing steadily for six weeks or more. It is noteworthy in this connexion that Dr. Briercliffe on page 32 of his official report says that in all districts the peak was reached in from five to eight weeks from the start of the epidemic and that according to Dr. Wijerama's records the first high peak of *P. falciparum* occurred about three weeks after gametocytes were first found in blood-films. A further point in favour of a gradual increase might be that during the first six weeks of the epidemic the mortality at all ages was low and that when deaths did begin to occur the first rise in mortality was among infants and young children and that later there was a rise among adults. This would be consistent with the view that the endemic strains gradually attained their maximum vigour and activity in the manner which was described in Note 1 as having happened to our Madagascar strain of *P. vivax*.

The conclusion which seems to emerge from this analysis of the constitution of the primary wave is that its onset and progress were not very different from the onset and progress of epidemics which have occurred under similar conditions in other parts of the world where the bulk of the population at risk possessed little or no natural or acquired immunity to the disease. Among several examples which might be quoted, Dr. Wenyon has reminded me that an epidemic in the town of Nemi near Rome, which we visited together a few years ago, was perhaps as instructive as any. Nemi is one of the so-called "castle towns" in the Alban Hills. It is situated on Lake Nemi, at no great distance from endemic foci of malaria in the Agro Romano but ordinarily, except for imported cases, it is quite free from the disease and anopheles are very rare. In 1928 and 1929 the level of Lake Nemi was lowered about 14 metres in a search for the sunken barges of Caligula. This work created numerous suitable breeding places of anopheles which became very abundant. The result was that in 1929 there was a serious epidemic in which 616 persons out of a population of about 1,000 were affected. This epidemic, like the epidemic in Ceylon, showed that in an area where there are few gametocyte carriers and almost no anopheles, an invasion by great numbers of these insects can give rise to a serious epidemic provided that the population at risk possesses no immunity to the disease. It is equally true that areas in which there are plenty of anopheles but no gametocyte carriers may almost immediately suffer from an epidemic when a number of gametocyte-carrying cases are imported. This is what happened in England and various countries in Europe after the War. In both conditions, for reasons which I mentioned in the discussion on the Ceylon epidemic at a previous meeting of this Society, lack of immunity in the population at risk is almost certainly an essential factor.

In concluding this paper I should like to make it clear that although what I have said seems to show that the mode of onset of the epidemic was different from that suggested by Colonel Gill in a previous discussion,[1] I am not myself

[1] *Proceedings*, 1936, **29**, 537, and references below.

committed to one view rather than to the other. Colonel Gill, in the discussion referred to, advanced strong reasons for the view that the onset of the epidemic was sudden and explosive, the prime cause being an outburst of relapses. What I have done is to advance reasons for the view that the onset was gradual, that it consisted of an increase of primary cases rather than relapses, and that it did not become explosive until it had been increasing steadily for six weeks or more. I have stressed this view in order that workers may be in a position to study the problem from both aspects before arriving at a final conclusion with regard to it.

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*Discussion.*—Sir RICKARD CHRISTOPHERS: Of the various points dealt with by the authors of the paper, that relating to the effects of "dose" of infection is one of the most important. The severity of the malaria often contracted by those on shooting or other expeditions into the jungle is well known. This has sometimes been thought to indicate infection with some particularly virulent strain of parasite, or even some very virulent form of parasite derived from monkeys or other jungle animals. From experience of the conditions under which such infections are acquired it is much more probable that the severity of the case has been brought about by massive inoculation of sporozoites. In the laboratory it certainly appears that in bird-malaria infections may be "worked up" by choosing heavy gametocyte carriers for infecting the mosquitoes, just as has been described in human malaria by the authors of the paper at Horton. Recently, in order to obtain uniformity in series of infected birds used in carrying out certain drug tests, it was thought that it might be a good thing for each bird to be bitten by a single mosquito known to have sporozoites in the glands. The plan, however, did not work, owing to the number of negative cases following such a procedure, even though in every case it was certain that the bird had been fed on and that the mosquito feeding had sporozoites. A number of these birds, however, developed infection eventually, say by the tenth or twelfth day instead of on the sixth day. It seemed probable that here minimal dosage had delayed the appearance of infection.

In regard to the causation of epidemics, the final and fully satisfactory answer can only be arrived at when the actual conditions have been worked out in the field. An interesting account has been given by Covell and Baily of the regional epidemic observed by them in Sind.[1] This is almost the only epidemic of the kind which has been studied on the spot at its commencement, and with what may be called modern methods of malaria investigation. Colonel James and his colleagues have rather stressed the point that the Ceylon epidemic developed gradually and not suddenly. "Gradually" is perhaps not a good word to apply to what is known of the usual onset in this kind of epidemic. At the same time it is undesirable to exaggerate the suddenness or to introduce unnecessarily any mysterious element that is not really there. Covell and Baily in the first week of the Sind epidemic found only a very low sporozoite rate and also a very low percentage of gametocyte carriers. Yet by the sixth week it was estimated that everyone in the area was infected. Allowing four weeks for the time necessary for one complete infective cycle (gametocyte to gametocyte), this gives at most two cycles by which such a result had been brought about. The authors,

[1] *Records Mal. Survey of India*, 1932, **3**, 279.

however, point out, in explanation of this seemingly remarkable result, that if it is assumed that under optimal conditions for infection each crescent-bearer in four weeks gives rise to ten, then even 1 : 200 crescent bearers at the beginning of the epidemic is sufficient to give 5% crescent bearers in the fifth week and 50% by the ninth week, these being about the rates actually encountered. In fact Covell and Baily's view is that, given optimum conditions and a step-like geometrical increase of the order noted, the length of the time during which optimum conditions exist is all-important and determinative. Thus if we suppose that in normal years time allows only for three geometrically increasing cycles, merely an ordinary fever season results. Increase in the period of optimal conditions (humidity, temperature, &c.), antedating by four weeks the normal, might well, by allowing for a further cycle with its magnified effect, make this an epidemic year.

Sir JOHN MEGAW said that the only question that he wished to ask Colonel James was why he showed such timidity in avoiding the use of the term " virulence ? " In connection with parasites of all kinds the word virulence was ordinarily used to express the power of the parasites to damage the hosts, and when Colonel James succeeded in breeding a race of parasites which were capable of causing very serious disease, he (the speaker) saw no reason why their increased capacity for damage should not be referred to as heightened virulence.

Dr. L. FABIAN HIRST said that the only epidemic of malaria on record in Colombo previous to 1934, when the great Ceylon epidemic reached the outskirts of the city, had occurred during 1903-4 in a northern suburb. It was severe, but was strictly localized to the neighbourhood of certain quarries containing pools of water in which the carrier insect bred abundantly. The outbreak responded promptly to anti-larval measures. Mr. H. F. Carter had seen the original drawings by the late Dr. Marshall Philip, and there was no doubt that the species of mosquito concerned was correctly identified as *culicifacies* over thirty years ago. This small epidemic appeared to have had features in common with the vast one of 1934-35 likewise spread by *culicifacies*, mostly bred in pools of water in the drying beds of rivers and streams. Normally this anopheline was not found in the Colombo district or in the south-west wet zone of Ceylon.

Group-Captain H. E. WHITTINGHAM, said that experiences in the Great War had proved that there was a type of malaria that was recurrent, and tended to resist all treatment. It was difficult, however, to impress the younger generation with this fact, for there was a tendency to assign to newer anti-malarial drugs, such as atebrin and plasmoquin, the power to cure malaria in a few days or weeks. It had almost seemed that another war would be needed to dispel this erroneous conception, but Colonel James had succeeded in doing so quite peaceably by the aid of experiments at Horton and observations on the recent Ceylon epidemic.

Could Colonel James explain the tertian periodicity of benign tertian malaria? Many, if not most, sufferers from malaria were probably bitten by infective mosquitos on several occasions, yet after a few days continued fever tertian periodicity would manifest itself.

COLONEL JAMES (in reply) said that the method of infection by the intravenous inoculation of sporozoites (the approximate number injected in each case being known) was now being used at Horton for studying quantitatively the effect of the " dose " of infection. One finding was that a malarial attack within the usual incubation period could be caused by a much smaller number of sporozoites of *P. falciparum* than of *P. vivax*. He agreed with Sir Rickard Christophers that to speak of the onset of the Ceylon epidemic as having been " gradual " might be misleading unless it were mentioned that the word was being used to mean only " proceeding step by step " without reference to speed. In reply to Sir John Megaw's question, he thought that " virulence " implied the possession or elaboration of a poisonous or venomous active principle (" toxin "). If so, it was not a good word to apply to the malaria parasite in which, so far as he knew, no " toxin " had been found. In reply to Group-Captain Whittingham, he agreed that in primary attacks of benign tertian malaria the change from quotidian to tertian fever was difficult to explain when several groups of parasites in different stages of development were present in the peripheral blood day after day. He supposed that the difficulty would remain until it was known precisely by what pathological process the febrile paroxysms of malaria were caused.