A LONGITUDINAL SURVEY OF NATURAL MALARIA INFECTION
IN A GROUP OF WEST AFRICAN ADULTS

by

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The amount of information on the course of the malaria infection in infants and children in holo-endemic areas of Africa has increased considerably during the past few years. On the other hand, our knowledge of the epidemiology of malaria in the African adult is still limited and thus the picture of the natural history of malaria in tropical Africa is far from complete. Problems such as the duration of the natural infection in the subject that has achieved a substantial degree of immunity, the clinical aspects of the relapse or re-infection, the frequency of asymptomatic infection, the pattern and quantitative characteristics of patent parasitaemia, the infectivity of sub-patent gametocyte carriers to Anopheles have not been sufficiently investigated. Febrile response to infection constitutes the most important screening device for case detection in malaria eradication programmes. The validity of this symptom in tropical Africa has been challenged by a number of workers and the problem is still open. The need for a proper assessment of this is considerable, as there is no other reasonably simple procedure and the difficulty of mass blood surveys is only too obvious. In the

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1 This investigation was carried out at the Federal Malaria Service, Lagos-Yaba, Nigeria, while the author was serving the Federal Government of Nigeria as a member of the United Kingdom Overseas Medical Service.

Some findings given in this paper were briefly reported to the WHO Technical Meeting on Malaria in Africa (Brazzaville, 1959) and to the WHO Scientific Group on Malaria Research (Geneva, 1959) but the full account of the investigation is given now for the first time.
traditional malaria surveys the data obtained from the examination of children were accepted as good yardsticks of the epidemiological situation; however, in malaria eradication the case detection covers the whole community in which, after all, at least two-thirds are adults.

Any long-term planning of malaria eradication programmes in Africa depends on the adequate knowledge of the epidemiology of the disease in highly endemic areas where the operational difficulties of our task are greater than anywhere. A longitudinal study of the natural malaria infection in a group of African adults from Nigeria was carried out in the attempt to provide some additional data.

In contradistinction to a traditional single, random sample, malariometric survey, longitudinal investigations of a population have not been much used generally, and rarely in Africa. The work of Earle et al. (1939) showed the value of longitudinal study in Puerto Rico; Russell, Sweet & Menon (1939) and Viswanathan (1945) used this technique in India; Pampena & Casini (1940) - in Sardinia; Hill, Cambournac & Simões (1943) - in Portugal; Rice & Watson (1943) - in the United States of America; Gilroy & Scott (1958) - in Assam. A review of some of this work in relation to malaria eradication was made by Yekutiel (1960) and by Covell (1960).

The earliest reports on results of a malaria survey carried out in Africa by repetitive monthly, or more frequent, examination of the same sample of the child population are those of Macdonald (1926) in Freetown and of Barber & Olinger (1931) in Lagos; Thomson (1934) used a somewhat similar technique in Nyasaland; Wilson (1936) and Mackay (1935, 1938) in Tanganyika; Walton (1948) in Sierra Leone; Garnham (1949) in Kenya and Bruce-Chwatt (1952) in Nigeria.

The recent studies by Miller (1958), McGregor (1960) and Bray (1962) provide excellent examples of longitudinal surveys, which give us a much clearer picture of the dynamics of the host/parasite relationship in holo-endemic areas of tropical Africa.

1. The environmental setting

The investigation reported here was carried out during the period April 1956 to April 1958 at the Psychiatric Hospital of the Federal Ministry of Health, situated at Yaba, a suburb of Lagos, the capital of Nigeria.
The Federal Territory of Lagos which includes the capital of the Federation of Nigeria is situated on the island of Lagos and extends over a large portion of the mainland. It covers an area of nearly 30 sq.miles with an estimated population of 312,000 in mid-1956 (approaching the figure of 400,000 in 1961). It is a large, fast-growing, very congested, cosmopolitan, urban area, with a sub-urban periphery that still had in 1956-1958 many of the characteristics of rural communities.

The Lagos Federal Territory lies within the Swamp Forest zone (Buchanan & Pugh, 1955) of the coast of south-western Nigeria where malaria is prevalent and can be epidemiologically classified as holo-endemic, though the more recent name of stable malaria (Macdonald, 1957) describes better some of its main attributes. It is characterized by a transmission season which always exceeds eight months and is usually perennial; by small seasonal variations of malarious indices which are especially high in young age-groups; by a high specific morbidity and mortality of infants and children; absence of epidemics and a mild clinical picture in the generally unprotected indigenous adult, rural population.

Although the antimalarial measures carried out in the urban area by the Lagos Town Council have been efficient and decreased the amount of malaria in the city to a fraction of what it was 20 years ago, the epidemiological picture of this disease seen in the semi-rural areas at the periphery of Lagos has changed but little since 1952 when it was described as intermediate between hyperendemic and holo-endemic, according to the classification adopted at the Kampala Conference (WHO, 1951). The spleen rate in the 2-10 age-group varied between 55 and 70%, while the parasite rate varied between 70 and 80%. Spleen rates in adults were as a rule below 10% and the parasite rate varied between 15 and 26% (Bruce-Chwatt, 1951).

Details of the local epidemiology of malaria transmitted mainly through A. gambiae gambiae and A. gambiae melas were described before (Bruce-Chwatt, 1952) and need not be repeated here. Suffice it to say that during the period 1955-1956 the mean inoculation rate per person per day, estimated from entomological data gathered by the Federal Malaria Service (1955-1957), oscillated between 0.01 during the dry season (November-March) and 0.25 during the rainy season (April-October).
In 1955 the calculation of the actual malaria inoculation rate from the infant parasite rate according to Macdonald (1950) gave the daily figure of 0.0032; the relevant figure calculated for 1957 was 0.0025. The large discrepancy between the inoculation rate calculated from entomological data and from the infant parasite rate has been found previously in West and East Africa and was commented on by Macdonald (1950), by Davidson & Draper (1953) and by Bruce-Chwatt (1956, 1961).

In view of the importance of the subject of malaria morbidity dealt with in this paper, and because of the scarcity of relevant data, it will be of interest to outline briefly, as a background to the local epidemiology of malaria, the estimated amount of sickness due to this infection so prevalent in Nigeria.

The collection of reliable medico-statistical data from an African territory the size of Nigeria (372,674 square miles or 964,853 square kilometres) with a population estimated in 1956 at 33.4 million, and in 1961 at over 40 million, of whom 90% live in rural areas, is understandably difficult.

This is certainly true with regard to morbidity and mortality figures attributed to malaria. Main "Returns of Diseases and Deaths" refer only to native administration hospitals, while the attendance figures for rural dispensaries are generally not shown in the consolidated annual reports. It is true that the morbidity statistics based on dispensary figures might be misleading since the clinical diagnosis made by auxiliary medical staff is of limited value. On the other hand, the dispensaries are over 10 times more numerous than the hospitals, more evenly distributed, more accessible to the rural population and their over-all attendance figures are at least twice the total number of patients seen in all hospitals in Nigeria. Thus, the hospital data represent not a cross-section of the population seeking medical aid, but refer to a selected sample.

Actually, when it comes to the diagnosis of malaria in West Africa, even the hospital figures, based on medical evidence, are of limited value. There is little doubt that the diagnosis of malaria in tropical Africa is subject, as often as not, to individual interpretation of clinical symptoms by the medical practitioner and, more often than not, without the blood examination. To complicate the issue, a positive blood slide from an African patient does not necessarily clinch the diagnosis.
Sub-clinical parasitaemia may be found in the majority of children in rural areas of Nigeria and in about 15-20% of adults. Thus, the data on malaria morbidity and mortality quoted from annual medical reports must be critically assessed even though they give the only information available for the whole country.

In spite of these cautionary remarks, the recorded data on malaria morbidity amongst the African population of Nigeria are of considerable interest because of their remarkable proportional constancy.

Table 1 shows malaria morbidity data recorded from hospitals in Nigeria and quoted in the official "Annual Returns of Diseases and Deaths" during the period 1949-1954. (Nigeria Annual Medical Reports, 1949-1954.) Consolidated figures for the period 1944-1948 are also shown for comparison; records for each year of the latter period are not included as they were quoted previously elsewhere (Bruce-Chwatt, 1951).

This table contains also the relevant data for 1955 and 1956 from the Federal Territory of Lagos. It is a matter for regret that consolidated returns for the whole of Nigeria are not available since 1954 when the medical services became regionalized.

**Table 1. Malaria Morbidity Recorded in the Annual Returns of Diseases and Deaths from Hospitals in Nigeria (1948-1954) or in the Federal Territory of Lagos (1955-1956)**

<table>
<thead>
<tr>
<th>Year</th>
<th>In-patients</th>
<th>Out-patients</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Malaria %</td>
<td>Number</td>
</tr>
<tr>
<td>1944-1948</td>
<td>572 175</td>
<td>40 293 7.0</td>
<td>5 082 091</td>
</tr>
<tr>
<td>1948-1949</td>
<td>136 928</td>
<td>9 928 7.2</td>
<td>1 232 822</td>
</tr>
<tr>
<td>1949-1950</td>
<td>141 766</td>
<td>12 869 9.1</td>
<td>1 380 223</td>
</tr>
<tr>
<td>1950-1951</td>
<td>143 280</td>
<td>10 730 7.5</td>
<td>1 261 598</td>
</tr>
<tr>
<td>1951-1952</td>
<td>138 516</td>
<td>10 667 7.7</td>
<td>1 054 400</td>
</tr>
<tr>
<td>1952-1953</td>
<td>174 199</td>
<td>12 758 7.3</td>
<td>1 363 424</td>
</tr>
<tr>
<td>1953-1954</td>
<td>170 679</td>
<td>11 418 6.7</td>
<td>1 476 101</td>
</tr>
<tr>
<td>1955</td>
<td>12 757</td>
<td>792 6.2</td>
<td>281 641</td>
</tr>
<tr>
<td>1956</td>
<td>9 874</td>
<td>574 5.8</td>
<td>276 656</td>
</tr>
</tbody>
</table>
Figures quoted in Table 1 which show a slow decreasing trend of the incidence of malaria in in-patients and little change in the incidence of malaria diagnosed in out-patients can be usefully compared with the records showing the part apparently played by malaria in mortality statistics in Nigeria (Table 2).

**TABLE 2. MALARIA MORTALITY AMONG IN-PATIENTS IN HOSPITALS IN NIGERIA (1944-1954) AND IN THE FEDERAL TERRITORY OF LAGOS (1954-1956)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Total deaths</th>
<th>Deaths from malaria</th>
<th>Proportional percentage of deaths due to malaria</th>
<th>Malaria case fatality rate (per 1000 patients)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1944-1948</td>
<td>23 734</td>
<td>808</td>
<td>3.4</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>1948-1949</td>
<td>5 708</td>
<td>264</td>
<td>4.6</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>1949-1950</td>
<td>5 057</td>
<td>297</td>
<td>5.9</td>
<td>1.9</td>
<td>Records for the whole of Nigeria</td>
</tr>
<tr>
<td>1950-1951</td>
<td>5 997</td>
<td>239</td>
<td>4.0</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>1951-1952</td>
<td>5 640</td>
<td>257</td>
<td>4.6</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>1952-1953</td>
<td>6 223</td>
<td>347</td>
<td>5.6</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>1953-1954</td>
<td>6 520</td>
<td>303</td>
<td>4.6</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>1955</td>
<td>871</td>
<td>53</td>
<td>6.1</td>
<td>1.9</td>
<td>Federal Territory of Lagos (all races)</td>
</tr>
<tr>
<td>1956</td>
<td>900</td>
<td>53</td>
<td>5.9</td>
<td>1.9</td>
<td></td>
</tr>
</tbody>
</table>

The value of Table 2 is limited since it refers to a highly selected sample, is based mainly on clinical diagnosis and is not age-specific. An attempt to assess in 1950 the malaria mortality for the total population exposed to risk gave a figure of 1.4 per 1000.

The age-specific malaria mortality of the African population in and around Lagos was estimated as follows: up to one year of age - 12.5 per 1000; 1-4 years - 7 per 1000; 5-10 years - 1 per 1000; adolescents and adults - 0.3 per 1000.

Compared with similar estimates from other parts of tropical Africa, the figures quoted from the Lagos area of Nigeria were lower for infants and toddlers. It is probable that the Nigerian figures, if available from the vast rural territory, would be higher by about one-third to one-half (Bruce-Chwatt, 1952).
It is hoped that more recent data covering the past 10 years and gathered from records of the whole Federation of Nigeria and for other countries and territories of tropical Africa will be available before long.

2. Materials and methods

After obtaining the necessary permission from the Government, from the appropriate medical authorities and from the patients themselves or their relations, 68 African adult inmates of the Yaba Psychiatric Hospital were selected for the longitudinal survey after a preliminary medical screening which assessed the possibility of following up the individual patients for a prolonged period, without upsetting unduly their psychiatric treatment.

The original group was composed of 36 males and 32 females; their mean age was $36.8 \pm 1.4$ (S.E.), with a range between 26 and 57.

The investigation commenced in April-May 1956 and consisted of examining the whole group at least once a week. The presence of any clinical symptoms and the results of examination of blood slides for malaria parasites were duly recorded. Blood examinations were carried out using the combined thick and thin film stained with Giemsa.

For the routine examination of the thick film the 95x oil immersion objective was used but most of the slides were also scanned for the presence of gametocytes of *P. falciparum* using the dry 40x objective, the whole area of the thick blood film having been lightly smeared with immersion oil to obtain a better definition. (This method, introduced by Sinton in India some 40 years ago, and advocated by Wilson (1936) is of considerable value and deserves to be more widely used.) Whenever necessary the thin film was examined for the confirmation of some parasite species (*P. ovale*).

At least 200 thick film fields with not less than 10 leucocytes per field (corresponding roughly to 0.2-0.25 mm$^3$ of blood) were examined before the blood slide was recorded as negative. All positive slides were further examined until additional 100 thick film fields were covered. Parasite counts were made from the determination of the parasite leucocyte ratio and expressed as number of parasites per mm$^3$. The leucocyte "standard count" was established on a series of counts,
of 10 adults daily, for one week. In some cases when the leucocytes appeared to be either unusually few or numerous, separate counts were made in the relevant subject. The Parasite Density Index (of positive slides) was calculated as described elsewhere (Bruce-Chwatt, 1958). Oral temperatures were taken at first only in those subjects who obviously had fever; in the later stage of the investigation a more regular taking of temperature in all subjects was instituted and provided a fairly satisfactory series of data.

The whole group of inmates was examined at the beginning of the survey for the presence of splenomegaly and for the sickle cell trait. A number of other investigations, the purpose of which was to assess the relationship of malaria parasitaemia to physical stresses were also carried out in some selected patients and will be referred to in a separate section. No patient in the investigated group received any antimalaria drugs during the whole period of observation.

Of the initial group composed of 68 subjects, 18 were lost to the investigation: two by being released, four by death, and 11 because of irregularity of their follow-up. At the end of the first year of the investigation it was decided to discover the response of a few volunteers to a challenge by physical or other stresses. This was done on eight patients, and as the results of this investigation were disappointing, the patients were re-incorporated into the remainder of the original survey group.

Beginning in June 1957, an attempt at induced infection was made, and during every week of the following months, two or three patients of the original series were selected for an investigation which will be described in the subsequent section of this report. The 22 patients undergoing induced infection (group B) were not re-integrated into the original survey group A which gradually decreased in number from 50 to 24 (four patients having left the group) towards the end of the second year. In order to keep up the weekly survey of a reasonably large group of adult Africans, an additional group C of 32 patients was added at the beginning of the second year, integrated with the original group A. Of this additional group of 32 patients, 24 were followed up with regularity until April 1958, when the investigation was completed (Table 3).

<table>
<thead>
<tr>
<th>Date</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C (additional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 1956</td>
<td>68 (36 males,</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>32 females)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>May 1957</td>
<td>50</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>June 1957</td>
<td></td>
<td></td>
<td>32 (20 males,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12 females)</td>
</tr>
<tr>
<td>December 1957</td>
<td>26</td>
<td>22</td>
<td>28</td>
</tr>
<tr>
<td>April 1958</td>
<td>24 (14 males,</td>
<td>16 (12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 females)</td>
<td>males,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 females)</td>
<td></td>
</tr>
<tr>
<td>Duration of</td>
<td>2 years</td>
<td>1 year</td>
<td>1 year</td>
</tr>
<tr>
<td>follow-up</td>
<td>(1956-58)</td>
<td>(1956-57)</td>
<td>(1957-58)</td>
</tr>
</tbody>
</table>

In the final recording, the number of subjects followed up with adequate regularity was 24 (group A) for two years, 22 of group B for about one year and 24 of group C for one year.

3. Results of the investigation

The results of the survey obtained during the follow-up for two years of group A, and for one year's survey (excluding induced infection) of group B and of group C are so similar that there is no need to show them separately. The three groups were therefore combined and the total figure of 4926 examinations refers to this number of person/day-weeks observed in a group of 24 subjects followed up for two years and to 46 subjects followed up for one year.

The results of the investigation shown in Table 4 are assessed in terms of "weeks", although it is perfectly obvious that this does not mean that a finding on any one day would represent the picture throughout the week. Daily examinations of the whole group were not practicable for the duration of the investigation and it is assumed that once-weekly examination represents an approximate picture, even though we know that the changes from one day to another might be considerable.
Splenoemgaly

The palpation of the spleen in the African adult presents considerable difficulty because of the generally well-developed musculature of the abdominal wall and the added difficulty of obtaining a relaxation of the abdomen even in the recumbent position. It is therefore not surprising that only two men out of 28 and three women out of 22 of the group A showed any degree of the enlargement of the spleen during the first year of the investigation. The over-all spleen rate was 7% for men and 13.6% for women or 10% for both sexes of the group. The enlarged spleen remained virtually unchanged during the first year in the five subjects. Another woman showed a transient enlargement of the spleen lasting for three weeks. In three cases (one man and two women) the spleen was of Hackett’s size 2, and in two cases (one man and one woman) of Hackett’s size 1.

All the palpable spleens were round, hard, generally palpable with some difficulty and with hardly any changes from week to week. In view of the fact that the results of the spleen palpation were of limited value, this investigation was not pursued beyond the end of the first year.
<table>
<thead>
<tr>
<th>4-week period</th>
<th>Months and year</th>
<th>Numbers examined each week</th>
<th>Mean crude P.R. over 4 weeks</th>
<th>Range of parasite rate</th>
<th>P. falciparum trophozoites. Mean % over 4 weeks</th>
<th>P. falciparum gametocytes. Mean % over 4 weeks</th>
<th>P. malariae. Mean % over 4 weeks</th>
<th>P. ovale. Mean % over 4 weeks</th>
<th>Parasite Density Index. Mean over 4 weeks</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>May-June 1956</td>
<td>50,50,50,50</td>
<td>27/200</td>
<td>13.5</td>
<td>12.0-16.0</td>
<td>9.6</td>
<td>4.0</td>
<td>4.5</td>
<td>0</td>
<td>1.27</td>
</tr>
<tr>
<td>2</td>
<td>June 1956</td>
<td>50,50,50,50</td>
<td>40/199</td>
<td>20.1</td>
<td>18.0-20.4</td>
<td>19.0</td>
<td>2.1</td>
<td>3.0</td>
<td>0</td>
<td>1.47</td>
</tr>
<tr>
<td>3</td>
<td>July 1956</td>
<td>50,50,50,50</td>
<td>35/200</td>
<td>17.5</td>
<td>14.0-22.0</td>
<td>16.5</td>
<td>2.0</td>
<td>1.1</td>
<td>0</td>
<td>1.37</td>
</tr>
<tr>
<td>4</td>
<td>July-August 1956</td>
<td>48,48,49,49</td>
<td>38/194</td>
<td>19.6</td>
<td>16.3-23.5</td>
<td>19.5</td>
<td>1.5</td>
<td>1.4</td>
<td>0</td>
<td>1.56</td>
</tr>
<tr>
<td>5</td>
<td>August-September 1956</td>
<td>50,50,50,48</td>
<td>42/198</td>
<td>21.2</td>
<td>16.0-22.9</td>
<td>20.0</td>
<td>1.5</td>
<td>1.5</td>
<td>0</td>
<td>1.55</td>
</tr>
<tr>
<td>6</td>
<td>September-October 1956</td>
<td>49,49,49,49</td>
<td>30/194</td>
<td>15.5</td>
<td>14.6-16.3</td>
<td>15.5</td>
<td>3.6</td>
<td>0.6</td>
<td>0</td>
<td>1.23</td>
</tr>
<tr>
<td>7</td>
<td>October-November 1956</td>
<td>49,49,49,50</td>
<td>21/194</td>
<td>10.7</td>
<td>10.0-12.2</td>
<td>10.6</td>
<td>0.6</td>
<td>1.48</td>
<td>0</td>
<td>1.48</td>
</tr>
<tr>
<td>8</td>
<td>November-December 1956</td>
<td>49,50,48,47</td>
<td>18/194</td>
<td>9.3</td>
<td>8.0-12.7</td>
<td>9.3</td>
<td>0.6</td>
<td>1.8</td>
<td>0</td>
<td>1.43</td>
</tr>
<tr>
<td>9</td>
<td>December-January 1957</td>
<td>46,46,47,48</td>
<td>27/187</td>
<td>14.4</td>
<td>14.0-17.1</td>
<td>14.5</td>
<td>1.1</td>
<td>2.2</td>
<td>0</td>
<td>1.41</td>
</tr>
<tr>
<td>10</td>
<td>January-February 1957</td>
<td>48,48,46,49</td>
<td>27/191</td>
<td>14.1</td>
<td>14.0-16.7</td>
<td>13.0</td>
<td>2.1</td>
<td>1.0</td>
<td>0</td>
<td>1.36</td>
</tr>
<tr>
<td>11</td>
<td>February-March 1957</td>
<td>46,47,48,49</td>
<td>25/190</td>
<td>13.2</td>
<td>14.6-15.2</td>
<td>12.6</td>
<td>1.1</td>
<td>2.2</td>
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<td>1.29</td>
</tr>
<tr>
<td>12</td>
<td>March-April 1957</td>
<td>48,50,50,49</td>
<td>33/197</td>
<td>16.8</td>
<td>12.3-20.4</td>
<td>16.2</td>
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<td>1.5</td>
<td>0</td>
<td>1.25</td>
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<td>13</td>
<td>April-May 1957</td>
<td>48,48,49,48</td>
<td>30/193</td>
<td>15.6</td>
<td>14.3-16.6</td>
<td>14.5</td>
<td>2.1</td>
<td>2.6</td>
<td>0</td>
<td>1.27</td>
</tr>
<tr>
<td>14</td>
<td>May 1957</td>
<td>46,47,47,45</td>
<td>24/189</td>
<td>12.7</td>
<td>11.2-14.0</td>
<td>12.2</td>
<td>1.5</td>
<td>1.6</td>
<td>0.5</td>
<td>1.31</td>
</tr>
<tr>
<td>15</td>
<td>June 1957</td>
<td>45,44,44,42</td>
<td>19/175</td>
<td>10.9</td>
<td>9.5-11.4</td>
<td>10.2</td>
<td>1.7</td>
<td>1.7</td>
<td>0</td>
<td>1.33</td>
</tr>
<tr>
<td>16</td>
<td>July 1957</td>
<td>54,53,53,54</td>
<td>25/214</td>
<td>11.7</td>
<td>9.4-14.8</td>
<td>10.2</td>
<td>2.3</td>
<td>1.4</td>
<td>0</td>
<td>1.38</td>
</tr>
<tr>
<td>17</td>
<td>July-August 1957</td>
<td>54,51,52,51</td>
<td>38/208</td>
<td>18.3</td>
<td>15.4-20.4</td>
<td>15.5</td>
<td>2.4</td>
<td>1.2</td>
<td>0.3</td>
<td>1.83</td>
</tr>
<tr>
<td>18</td>
<td>August-September 1957</td>
<td>49,49,48,49</td>
<td>30/195</td>
<td>15.4</td>
<td>14.3-16.4</td>
<td>14.3</td>
<td>3.1</td>
<td>1.6</td>
<td>0</td>
<td>1.79</td>
</tr>
<tr>
<td>19</td>
<td>September-October 1957</td>
<td>48,48,47,48</td>
<td>27/191</td>
<td>14.1</td>
<td>10.4-20.8</td>
<td>12.0</td>
<td>2.6</td>
<td>1.6</td>
<td>0</td>
<td>1.90</td>
</tr>
<tr>
<td>20</td>
<td>October-November 1957</td>
<td>49,48,47,49</td>
<td>28/193</td>
<td>14.5</td>
<td>12.2-17.1</td>
<td>12.8</td>
<td>2.6</td>
<td>2.6</td>
<td>0.3</td>
<td>1.79</td>
</tr>
<tr>
<td>21</td>
<td>November-December 1957</td>
<td>48,47,48,48</td>
<td>28/191</td>
<td>12.6</td>
<td>10.4-14.5</td>
<td>11.0</td>
<td>1.6</td>
<td>1.0</td>
<td>0.6</td>
<td>1.69</td>
</tr>
<tr>
<td>22</td>
<td>December-January 1958</td>
<td>47,47,46,47</td>
<td>22/187</td>
<td>11.8</td>
<td>8.6-14.8</td>
<td>10.2</td>
<td>1.1</td>
<td>1.1</td>
<td>0.6</td>
<td>1.91</td>
</tr>
<tr>
<td>23</td>
<td>January-February 1958</td>
<td>47,48,47,47</td>
<td>27/189</td>
<td>14.3</td>
<td>12.3-17.1</td>
<td>12.2</td>
<td>1.1</td>
<td>1.6</td>
<td>1.1</td>
<td>1.60</td>
</tr>
<tr>
<td>24</td>
<td>February-March 1958</td>
<td>46,47,47,48</td>
<td>24/188</td>
<td>12.8</td>
<td>10.4-15.3</td>
<td>11.2</td>
<td>2.1</td>
<td>1.5</td>
<td>1.0</td>
<td>1.76</td>
</tr>
<tr>
<td>25</td>
<td>March-April 1958</td>
<td>48,48,47,48</td>
<td>26/191</td>
<td>13.6</td>
<td>12.3-14.5</td>
<td>12.6</td>
<td>2.1</td>
<td>1.5</td>
<td>1.0</td>
<td>1.83</td>
</tr>
<tr>
<td>26</td>
<td>April 1958</td>
<td>46,42,43</td>
<td>16/131</td>
<td>12.3</td>
<td>9.5-15.3</td>
<td>12.3</td>
<td>0.7</td>
<td>0.8</td>
<td>0</td>
<td>1.44</td>
</tr>
</tbody>
</table>

* Over-all mean and S.E.

|               |                |                           |                             |        | 4.92 ± 1.5 (mean of differences) | 13.8                                         | 1.9                                          | 1.7                                          | 0.17                          | 1.52    |
|               |                |                           |                             |        | ±0.65                           | ±0.42                                        | ±0.19                                         | ±0.18                                         | ±0.07                         |

**Note:** P.R. stands for parasite rate.
Parasitaemia

A total of about 5600 slides would have been expected had the steady decrease of the original numbers not taken place. The total number of slides collected was 4926, or about 13.5% less. On the other hand, this figure exceeds the expected figure of 4860 weekly examinations of the final number of inmates quoted in Table 3. This is due to some subjects being examined twice a week and to the fact that blood slides of inmates seen during the early months of the survey and not followed up to the end were included. Table 4 gives in a consolidated form the most important information obtained during the total period from May 1956 to April 1958 as far as the weekly "cross-section" examination of the described group is concerned.

In order to visualize the seasonal variation of malarial indices without the need for quoting an over-long table of 103 weekly results, it was decided to group them into 26 sequences, each of which covers four consecutive weeks.

Detailed presentation of results of this study requires a preliminary discussion of some terms used below.

For the designation of the proportion of findings of malaria parasites discovered in a selected sample of the population examined repeatedly over a stated period the use of the time-honoured term "parasite rate" is unsatisfactory and might be misleading. "Parasite rate" is used conventionally to describe the "point prevalence" of the infection or the proportion of the number of positive cases found at a given time in a population. On the other hand, the frequency of infections in existence during a defined period should be referred to as "period prevalence", while the frequency of new illnesses (or infections) developing during a defined period should be termed "incidence" (Puffer, 1950; Swaroop, 1960).

In highly endemic malarious areas it is practically impossible to distinguish between an existing infection and a new one arising over the period. Thus, it would be impracticable to separate the concept of "period prevalence" from that of "incidence".

It seems that the time has come not only for a greater emphasis on the need for longitudinal surveys in field studies of the natural history of malaria, but also for a more precise terminology involved. Thus, there should be a clear distinction between the "parasite rate" of cross-section surveys and the "parasite rate" of observations repeated for an extended period of time.
We propose to use the well-known term "parasite rate" (meaning usually "parasite point prevalence rate") with reference to cross-section results of the investigation. The term "parasite incidence rate" will be reserved for the results of the longitudinal survey, over the period of the investigation. The adjective "crude" occasionally found in this paper in conjunction with "parasite rate" stresses that the relevant index of infection comprises all species of plasmodia found.

The mean "parasite prevalence rate" shown in Table 4 for every four weeks instead of four separate weekly results, was used simply for convenience. The results of the cross-section survey of the group obtained from week to week were so similar that this "telescoping" of four weekly examinations was justifiable.

The over-all numerical distribution of the three species of malaria parasites found during the survey is shown in Table 5.

### TABLE 5. OVER-ALL RESULTS OF BLOOD EXAMINATIONS CARRIED OUT IN 1956-1957

<table>
<thead>
<tr>
<th>Species of parasite</th>
<th>No. of positive findings</th>
<th>Per cent. of total examined (4926) slides</th>
<th>Per cent. of 723 positive slides</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. falciparum</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trophozoites</td>
<td>680</td>
<td>13.8</td>
<td>94.4</td>
</tr>
<tr>
<td>gametocytes</td>
<td>97 (20)</td>
<td>1.97</td>
<td>13.4</td>
</tr>
<tr>
<td>all forms</td>
<td>700</td>
<td>14.3</td>
<td>97.4</td>
</tr>
<tr>
<td><em>P. malariae</em></td>
<td>84 (17)</td>
<td>1.7</td>
<td>11.7</td>
</tr>
<tr>
<td><em>P. ovale</em></td>
<td>9 (4)</td>
<td>0.18</td>
<td>1.2</td>
</tr>
<tr>
<td>Undetermined</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed infections</td>
<td>70</td>
<td>1.4</td>
<td>9.6</td>
</tr>
</tbody>
</table>

Note: Numbers of *P. falciparum* gametocytes found without trophozoites of this species are shown in brackets. Frequency of *P. malariae* and *P. ovale* found without any other parasite species is also shown in brackets in a corresponding column.

Of the 723 positive slides 680 (94%) were found with trophozoites of *P. falciparum* (in 12 cases the trophozoites were unidentifiable and might have been *P. malariae*). In each case the parasite count was made and the arithmetic mean of all parasite counts of *P. falciparum* was 385 per mm$^3$. The frequency distribution of the array of 680
parasite counts of *P. falciparum* showed that 68% of slides had less than 100 parasites per mm$^3$; a geometric mean of the array was computed and found to be 155 parasites per mm$^3$. The parasite density index calculated from the frequency distribution of 680 parasite counts grouped according to 10 arbitrary classes (Bruce-Chwatt, 1958) was 1.53 (Table 6).

**Table 6. Frequency distribution of 680 slides according to the count of trophozoites of *P. falciparum* per mm$^3$.**

<table>
<thead>
<tr>
<th>Class</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.00</td>
<td>&lt;200</td>
<td>&lt;400</td>
<td>&lt;800</td>
<td>&lt;1,600</td>
<td>&lt;3,200</td>
<td>&lt;6,400</td>
<td>&lt;12,800</td>
<td>&lt;25,600</td>
<td>&gt;25,601</td>
</tr>
<tr>
<td>Frequency</td>
<td>459</td>
<td>131</td>
<td>70</td>
<td>12</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Per cent.</td>
<td>67.5</td>
<td>19.2</td>
<td>10.4</td>
<td>2.0</td>
<td>0.5</td>
<td>0.2</td>
<td>0</td>
<td>0.1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Gametocytes of *P. falciparum* were found 96 times in 4926 examined slides (1.97%); 13.4% of all positive slides contained gametocytes of *P. falciparum*. In three-quarters of all findings these gametocytes had the usual crescent-shaped appearance, but in approximately one-quarter of the relevant slides some gametocytes of *P. falciparum* had the "rounded up" form described previously by several authors and especially by Field (1948). These forms might be occasionally confused with gametocytes of *P. malariae* and the "pink tongue" sign described by Wilcox (1960) was found to be a most useful distinguishing sign, providing that the parasite was not too distorted in the thick film.

The count of *P. falciparum* gametocytes in each slide showed that out of the total of 97 findings *P. falciparum* gametocytes were scanty in 88 slides with counts below 60 per mm$^3$: in six slides the numbers of gametocytes were between 70 and 100 per mm$^3$. Only in three slides were the gametocyte counts 120, 180 and 380 per mm$^3$. The over-all arithmetic mean of gametocytes of *P. falciparum* was 39 per mm$^3$. 
The frequency of *P. malariae* was 82 in 4926 slides (1.67%) or 11.3% of all positive slides. The arithmetic mean of the density of *P. malariae* infections was 86 per mm$^3$, but 80% of the slides positive for *P. malariae* had counts below 60 parasites per mm$^3$. The highest single count of quartan parasites was 460 per mm$^3$.

There was little evidence of any constant relationship of the parasite rate (whether crude or specific) with the season of the year. The relatively high *P. falciparum* parasite rate of periods 2-5 (corresponding with the rainy season of 1956) was not repeated in 1957, though the two annual rainfalls were not greatly different. On the other hand, the parasite density index in 1957 was higher than in 1956. The *P. falciparum* gametocyte rate showed occasionally (periods 6 and 7) an apparent association with the *P. falciparum* trophozoite rate of the previous two weeks, but this association was far from regular.

The parasite rate decreased from about 10% during the first six months of the investigation to about 13% during the last six months (November 1957 to April 1958). The cause of this decrease is unknown, but certainly not due to any specific antimalaria treatment.

The *sickle* cell trait was found in 13 out of the 70 inmates seen (18.6%). There was no obvious relationship between the presence of the sickle cell trait and the incidence of density of parasitaemia, gametocyte output, frequency of clinical symptoms or distribution of parasite species. Microfilariae were found in five patients during the period of the survey; in three subjects they were identified as *A. perstans* and in two subjects as *M. loa-loa*. One patient with the latter infection had ocular symptoms and complained of "Calabar swellings".

Although the over-all parasite rate of female patients was slightly higher (17.6%) than that of males (13.7%) the difference was not significant. There was no evidence that any other results of this survey were related to the sex ratio of the inmates examined during the stated period. There were no pregnancies in female patients during the investigation.

As mentioned before, the relationship between the body temperature and the presence of parasites in the blood was investigated with a satisfactory degree of regularity in 32 subjects for one year. The findings of the 1658 temperature "takes", classified into groups according to four temperature ranges, are shown in Table 7.
TABLE 7. ORAL TEMPERATURES IN 1658 "TAKES" IN 32 ADULT AFRICAN SUBJECTS INVESTIGATED ONCE WEEKLY OVER THE PERIOD APRIL 1957 - MARCH 1958

<table>
<thead>
<tr>
<th>Temperature range</th>
<th>No. of observations</th>
<th>Malaria parasites in a sample of observations of each group</th>
</tr>
</thead>
<tbody>
<tr>
<td>°Fahrenheit</td>
<td>°Centigrade</td>
<td></td>
</tr>
<tr>
<td>97-97.9</td>
<td>36.1-36.6</td>
<td>10 0.6%</td>
</tr>
<tr>
<td>98-98.9</td>
<td>36.7-37.1</td>
<td>912 55.0%</td>
</tr>
<tr>
<td>99-99.9</td>
<td>37.2-37.7</td>
<td>631 38.1%</td>
</tr>
<tr>
<td>100 and over</td>
<td>37.8 and over</td>
<td>105 6.3%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1 658 100.0%</td>
</tr>
</tbody>
</table>

*Note: Malaria parasites present at the time of taking the blood slide

4. Longitudinal survey

Out of the total of 24 inmates observed for two years and 46 observed for one year, only two of the first group and three of the second group showed an absence of malaria parasites in the blood throughout the period of the survey. Thus, the "parasite incidence" of the first group examined repeatedly once a week for two years, was found to be 91.5%, while the respective rate of the second group was found to be 93.5%. The summary result of this investigation is shown in Table 8, and the results of the longitudinal survey are presented separately for the group A followed up for two years and for the remaining 46 inmates observed for one year.

TABLE 8. SUMMARY OF RESULTS OF THE LONGITUDINAL MALARIA SURVEY OF TWO GROUPS OF AFRICAN INMATES OF THE PSYCHIATRIC HOSPITAL AT YABA-LAGOS

<table>
<thead>
<tr>
<th>Group and No. investigated</th>
<th>Duration of observation</th>
<th>Parasites found in:</th>
<th>P. falciparum trophozoites</th>
<th>P. falciparum gametocytes</th>
<th>P. malariae</th>
<th>P. ovale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>2 years</td>
<td>22 (91.5%)</td>
<td>21 (87.5%)</td>
<td>12 (50%)</td>
<td>5 (20.8%)</td>
<td>2 (8.3%)</td>
</tr>
<tr>
<td>24 inmates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B+C</td>
<td>1 year</td>
<td>43 (93.5%)</td>
<td>42 (91.5%)</td>
<td>13 (28.3%)</td>
<td>8 (17.4%)</td>
<td>3 (6.7%)</td>
</tr>
<tr>
<td>46 inmates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Similarly to the cross-section results shown in Table 4, the scrutiny of records of the longitudinal survey showed no evidence of any pronounced seasonal or other pattern of the frequency of positive parasite findings. It was possible, however, to discern two main groups of serial observations. In one group composed of 15 inmates, the trophozoites of *P. falciparum* appeared in irregular single, double or at most triple "bursts" over the whole period of observation. As a rule, the parasites were scanty, not exceeding 200 mm$^3$, but sporadically reaching the counts of 600-800 parasites per mm$^3$.

In a smaller group of five inmates, there was evidence of more continuous "waves" of parasitaemia lasting week after week for periods of between one-and-a-half months to four months. The number of such "waves" was 1-4 depending on their length.

Of the total number of 12 such "waves", eight occurred during the period May to September and four during the "dry season". The parasite counts in such waves were usually of the order of 100-200 per mm$^3$ although higher counts, of the order of 1600-3200 per mm$^3$ were more frequently seen either at the beginning or at the end of the "wave".

In two inmates, no pattern was discernible, single "bursts" of parasitaemia being preceded or followed by irregular short "waves" of parasitaemia.

The difference between the two types of the trend of parasitaemia is shown diagramatically in Figure 1. It is of interest that these two patterns, followed or not by "bursts" of crescents, have also been observed by Earle and his colleagues (1939) and are mentioned in Earle's (1962) recent discussion of his original results.

As a result of the longitudinal survey, it was found that the number of subjects that produced gametocytes of *P. falciparum* at any time during the investigation in the group A of 24 examined during the period of two years was 12 (50%); in the groups B and C examined for a year, it was 13 out of 46 (28.3%).
Out of the total of 25 subjects in the two groups who showed gametocytes of *P. falciparum* in the course of the longitudinal survey, two types of gametocytæmia could be noted. In 18 subjects gametocytes were seen only once, twice or at most three times, at irregular long intervals and always (with the exception of one) with a low gametocyte count not exceeding 60 per mm$^3$. In seven subjects there were definite "waves" of gametocyte production lasting for periods of three to 10 weeks in succession (Fig. 1). In most of these cases the gametocyte count was also of the order 20-80 per mm$^3$, although occasional counts of over 100 per mm$^3$ were seen more often than in the previously mentioned group. In five subjects the gametocyte production seems to have been preceded by a wave of asexual parasitaemia recorded one to two weeks previously. The mean (arithmetic) gametocyte count in this group was 48 per mm$^3$.

The "parasite-incidence rate" of *P. malariae* (usually associated with *P. falciparum*) was 20.8% in group A and 17.4% in the combined group B and C. *P. malariae* appeared in those found infected with this parasite species either sporadically or more often in short "waves" of two to six weeks' duration. There was one case, however, which showed a continuous parasitaemia in two long "waves" of 29 and 20 weeks' duration, over two years.

The mean parasite count of *P. malariae* was 60 per mm$^3$, but the one subject with the persistent *P. malariae* parasitaemia showed peaks of parasite counts reaching figures of 220-360 per mm$^3$. In the low level counts of *P. malariae* infections, the only developmental forms were mainly trophozoites and schizonts, while in the higher counts seen in the one case mentioned above, numerous gametocytes of *P. malariae* were also present. There was no association of clinical symptoms with high counts of *P. malariae* parasites.

There were two subjects in group A and three subjects in group B who, during the course of observation, showed an infection with *P. ovale*. Only one subject showed this infection present over three consecutive weeks; the parasite count varied between 80 and 240 per mm$^3$. In the remaining four subjects, *P. ovale* was seen only once or twice, and often when the subject was re-examined on the following day *P. ovale* could not be found again. No clinical symptoms could be associated with the presence of this parasite.
From the record cards of the 70 inmates, totalling 94 complete annual observations (24 for two years and 46 for one year), 84 annual cards free of errors or any but occasional absences were selected for the comparison of the relationship between the "parasite prevalence rate" obtained at a single cross-section examination of the group and the "parasite incidence rate" resulting from repeated weekly examination for periods between one month and one year. The results of this investigation shown in Table 9 and Figure 2 are of interest as they show the cumulative effect on "parasite incidence" of the frequency of examinations.

**TABLE 9. PARASITE INCIDENCE RATE OBTAINED FROM A SAMPLE OF 84 MAN/YEAR OBSERVATIONS OF AFRICAN ADULTS EXAMINED EITHER ONCE OR REPEATEDLY ONCE A WEEK FOR PERIODS BETWEEN ONE MONTH AND ONE YEAR**

<table>
<thead>
<tr>
<th></th>
<th>Mean single cross-section examination</th>
<th>Once-weekly examinations for a period of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 month (4)</td>
</tr>
<tr>
<td>Positive/Examined</td>
<td>12/84</td>
<td>26/84</td>
</tr>
<tr>
<td>Parasite rate (all species)</td>
<td>14.3±1.2</td>
<td>-</td>
</tr>
<tr>
<td>Parasite incidence rate (all species)</td>
<td>-</td>
<td>31.0</td>
</tr>
</tbody>
</table>

5. **Induced malaria infection**

Experimentally induced infections were carried out on 22 subjects removed from the original group A during 1957. The parasitized blood was obtained from naturally infected African children in the neighbouring villages. These children were being investigated for the purpose of chemotherapeutic field trials and suitable individuals infected with *P. falciparum* were selected during the preliminary screening procedure. The children's blood was obtained from the cubital vein, mixed in a 10-ml syringe with 0.1 ml of heparin, transferred into a sterile vial in the refrigerator for not more than 24 hours and given intravenously to selected inmates with their full consent and after explaining the purpose of this action to them or to their next of kin.
TWO MAIN TYPES OF RESULTS OF LONGITUDINAL MALARIA SURVEYS OBSERVED IN 24 ADULT AFRICAN INMATES OF THE PSYCHIATRIC HOSPITAL AT YABA-LAGOS DURING A 2-YEAR FOLLOW-UP. APPEARANCE OF P. FALCIPARUM TROPHOZOITES AND GAMETOCYTES AT WEEKLY BLOOD EXAMINATIONS.

Note: A rectangle denotes a positive finding of P. falciparum infection; the parasite count is shown by the height of the rectangle; gametocytes are shown as black rectangles. When the count of trophozoites and gametocytes is the same the rectangle is divided into two halves.
Longitudinal survey of malaria infection in African adults.

Value of the Parasite Prevalence Rate (single examination) compared with the values of Parasite Incidence Rates when the once weekly examinations are repeated for periods from one month (4 examinations) to one year (32 examinations).
The parasite count of 16 samples of infected blood varied between 6000 and 24,000 parasites per mm$^3$ with a mean of 11,600 parasites per mm$^3$. The amount of parasites administered to the patients varied between 42 million and 120 million with a mean of 83.7 million parasites.

The group of 22 patients was selected for this investigation from the original group A after one year of observation and called group B. In most cases the infections during the previous week were carried out when the recipients showed no parasites in the peripheral blood, but occasionally scanty parasites were present. The subjects were followed up for at least eight weeks after the superinfection, but 16 patients were seen weekly for six months until April 1958.

Subjects that were given the induced infection were followed with more attention and blood slides were generally taken twice a week, or in some cases more often. The parasite counts were done as usual in relation to the white blood cell count, but the number of thick film fields covered exceeded the routine 200 fields and often amounted to 400 when the parasites were scanty. Thus, the individual parasite counts could be assessed at the low level of five to fifteen parasites per mm$^3$.

The results of this investigation were of interest. Out of 22 infected adult Africans, four remained constantly negative for two months. Two were not seen with regularity and are excluded from the assessment of results. The 16 others have shown the presence of a more or less evident parasite wave following the induced infection, and the results of their blood examination are presented in Table 10.

The results show that induced infection with what might conceivably have been a heterologous strain of *P. falciparum* is not impossible. We might perhaps exclude the cases numbered 22, 38, 42, 51, and 78 in which parasitaemia due to a previous infection might have been either coincidental with the investigation or provoked by the injection of foreign protein. The resulting 11 induced infections out of 20 attempted show an interesting feature. In the whole group the parasite rate went up from 20% at the beginning of the experimental induction of malaria to reach the high figure of 75% during the second week. At the same time, the mean positive parasite count of *P. falciparum* increased progressively from the average of 30 per mm$^3$ to 1300-1700 during the first week, to 1600 during the second week and fell to 200 and to 100 during the following two weeks. There was no renewed high parasitaemia during the subsequent months of the observation.
TABLE 10. RESULTS OF INDUCED INFECTION IN 16 AFRICAN ADULTS GIVEN ON THE DAY D AN INTRAVENOUS INJECTION OF BLOOD HEAVILY PARASITIZED WITH *P. FALCIPARUM*

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Dose of parasites in millions</th>
<th>Blood examination on days following the infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D + 3/4</td>
<td>D + 7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D + 12/14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D + 21/26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D + 6 wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D + 8 wks</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>F80</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>F15</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>F20</td>
</tr>
<tr>
<td>15</td>
<td>68</td>
<td>F200</td>
</tr>
<tr>
<td>21</td>
<td>72</td>
<td>F80</td>
</tr>
<tr>
<td>22</td>
<td>80</td>
<td>Q80/Q120</td>
</tr>
<tr>
<td>23</td>
<td>64</td>
<td>F80</td>
</tr>
<tr>
<td>24</td>
<td>90</td>
<td>P80</td>
</tr>
<tr>
<td>30</td>
<td>72</td>
<td>F420</td>
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<td>56</td>
<td>120</td>
<td>F45</td>
</tr>
<tr>
<td>78</td>
<td>58</td>
<td>F400/Q120</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parasite rate of group</th>
<th>4/20</th>
<th>8/20</th>
<th>12/20</th>
<th>14/19</th>
<th>10/19</th>
<th>6/19</th>
<th>6/19</th>
<th>6/19</th>
<th>8/20</th>
</tr>
</thead>
<tbody>
<tr>
<td>of group</td>
<td>20%</td>
<td>40%</td>
<td>75%</td>
<td>60%</td>
<td>60%</td>
<td>30%</td>
<td>30%</td>
<td>30%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Note: Parasite rate of group includes the four subjects that remained negative throughout two months of the follow-up. It excludes the subjects which were not seen on some days and are marked by the sign (-). The asterisks refer to subjects who showed symptoms that might have been due to clinical malaria.

F - *P. falciparum*.  Fe - gametocytes of *P. falciparum*.  Q - *P. malariae*.  Ov - *P. ovale*.  Figures refer to parasite counts per mm³.
Clinical symptoms coincidental with parasitaemia were absent, with the exception of three cases (marked with an asterisk) in which headache, fever over 100°F and muscular pains were recorded. These symptoms disappeared within two to three days without any specific treatment.

6. Clinical symptoms seen in the course of the longitudinal survey

An investigation of clinical symptoms suggestive of overt malaria was made either before or after the taking of each blood slide, but in addition to that the nursing staff of the psychiatric hospital reported any complaints occurring throughout the week. Symptoms such as fever, headache, chills, various "pains", general ill-feeling, were recorded. In view of the once-weekly examinations and the generally mild symptoms, it is likely that a number of minor complaints were missed if they occurred between two examinations.

Out of the 24 subjects of group A followed up for two years, 13 presented at some of the weekly examinations symptoms that could be ascribed to overt malaria as they coincided with the presence of malaria parasites in the blood.

In the combined 46 subjects of groups B and C, followed up for one year, 22 subjects presented at one time or another possible clinical symptoms of malaria ("attacks") coincidental with the presence of parasitaemia. The results are shown in Table 11.

<table>
<thead>
<tr>
<th>TABLE 11. FREQUENCY OF CLINICAL SYMPTOMS SUGGESTIVE OF OVERT CLINICAL MALARIA AND COINCIDENTAL WITH THE PRESENCE OF PARASITES IN TWO GROUPS OF AFRICAN ADULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period of follow-up</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>2 years</td>
</tr>
<tr>
<td>Numbers of subjects in the group</td>
</tr>
<tr>
<td>Subjects having symptoms</td>
</tr>
<tr>
<td>One &quot;attack&quot;</td>
</tr>
<tr>
<td>Two &quot;attacks&quot;</td>
</tr>
<tr>
<td>Three &quot;attacks&quot;</td>
</tr>
<tr>
<td>Total number of &quot;attacks&quot;</td>
</tr>
<tr>
<td>&quot;Attacks&quot; per man/year</td>
</tr>
</tbody>
</table>
All these "attacks" were of a mild nature with the temperature between $99^\circ$ and $103^\circ$F. In spite of the fact that no specific antimalaria treatment was instituted, they lasted on the average for 2.6 days with a maximum of five days. In three cases the illness was due to other causes, such as pleurisy, chickenpox and dysentery for which the patients were duly treated.

Of the total number of 20 cases of group A with clinical symptoms of malaria, 10 cases had at that time \textit{P. falciparum} counts below 800 per mm$^3$, six cases had a parasitaemia between 800 and 3200 parasites per mm$^3$ and four cases had between 3200 and 12 800 parasites per mm$^3$ of blood.

7. **Infectivity of adult carriers of \textit{P. falciparum} gametocytes to \textit{A. gambiae}**

Infection of \textit{A. gambiae} on patients showing the presence of gametocytes of \textit{P. falciparum} was attempted on 11 subjects (once on 10 subjects and twice on one). About 30 females of insectary reared \textit{A. gambiae gambiae} from the Lagos colony maintained by the Federal Malaria Service were fed on the selected patients who, at the time of feeding, showed a gametocyte count between 20 and 180 per mm$^3$. After the infective feed, the batches of mosquitoes were maintained in cages at the temperature of 84-90$^\circ$F and humidity of about 80% for 13-15 days. They were fed every two days during that time on guinea-pigs. A few specimens were dissected on the sixth to eighth day after the infective feeding for the detection of oöcysts, but preferably the mosquitoes were kept until the infection of the salivary glands.

Out of 380 female \textit{A. gambiae} used for this investigation, only 120 survived for two weeks after the first feed on man. All those that died during that period were dissected for oöcysts; those that survived for two weeks were dissected for sporozoites.

Sporozoites were found only in two \textit{A. gambiae} of one batch of 18 fed on a carrier with 80 gametocytes of \textit{P. falciparum} per mm$^3$. One of the females of this batch dissected on the eighth day after the infection showed four pigmented oöcysts in the midgut.
In another batch of 21 *A. gambiae* fed on two occasions on a carrier with 20 gametocytes of *P. falciparum* per mm$^3$, two females, dissected on the seventh and eighth day, showed the presence of six oöcysts and four oöcysts respectively. Unfortunately, none of the remaining females survived for two weeks and were not dissected for sporozoites.

The remaining nine batches of *A. gambiae* were not found to be infected, but the high mortality and some other features of this investigation prevent us from drawing any definite conclusions as to the degree of infectivity of adult African carriers of *P. falciparum* gametocytes ingested by the local vectors of malaria.

8. **Provocation of parasitaemia**

Some attempts at inducing parasitaemia by the use of physical stress in high temperature were carried out in eight adult African volunteers who were known to have been infected before but had negative blood slides at the time of this attempt. These preliminary investigations were unsuccessful and were soon given up.

A subcutaneous injection of 1 ml of adrenalin (1:1000) was given to one patient, and two others were given 0.25 ml of adrenalin (1:1000) in a very slow intravenous injection. Blood slides were taken 30 minutes and one hour after the administration of the drug and, although the numbers of leucocytes showed an average increase by 25% to 40% (this increase was mainly due to high counts of large mononuclear cells), there was no obvious change in parasitaemia following the injection. No further attempts of this kind were made.

Subsequently, an investigation of the influence of some rather special physical stresses on the appearance of malaria parasites in the peripheral blood of semi-immune adult Africans was carried out in conjunction with the electro-convulsive treatment of the mental disease in a group of African patients of the psychiatric hospital at Yaba.

In June 1957 a considerable number of patients at the hospital underwent electro-convulsive therapy (ECT) and some subjects belonging to this group were followed up by us. In view of the fact that ECT produces a severe physical shock due to the tonic and clonic muscular contractions following the application of the electric
current through the brain, it was thought that the assessment of the influence of this stress on the parasitaemia of adult Africans would be of interest. Blood slides were taken as follows: (a) immediately before the ECT; (b) within 5-15 minutes after the patient lost consciousness; (c) 24 hours later when the patient recovered from the effects of the treatment. Thirty-six patients were investigated (20 men and 16 women) and in 15 of them (10 men and 5 women) the investigation was repeated twice or three times. The results (Table 12) showed that there was very little difference between the parasite rate or parasite count in blood slides collected before the ECT or after it. Some differences noted in three subjects were within the variations that occurred without ECT and are not significant.

| TABLE 12. PARASITAEMIA IN MENTAL PATIENTS UNDERGOING ELECTRO-CONVULSIVE THERAPY |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| | No. of patients and frequency of investigation | No. of subjects with parasites in the blood | Before the ECT | After the ECT |
|-------------------------------------------------|-------------------------------------------------|-----------------|-----------------|
| Patients investigated following one ECT session | 21 (x 1=21) | 3 (14.3%) | 4 (19.1%) |
| Patients investigated at two ECT sessions | 11 (x 2=22) | 3 (13.7%) | 2 (9.1%) |
| Patients investigated at three ECT sessions | 4 (x 3=12) | 2 (16.7%) | 2 (16.7%) |

9. Discussion

9.1 Results of the cross-section survey

The crude parasite rate

Could the results of a single examination at any one week of the investigated group of African inmates of the Lagos asylum be compared with a cross-section malariometrical survey of the random sample of the adult indigenous population from southern Nigeria or any other part of West Africa? How does the average crude parasite rate (point prevalence rate) of 14.7% found in the course of 103 once-weekly
examinations of a not intentionally selected group of African adults compare with results obtained during ordinary malarialmetrical surveys of Nigeria, other parts of West Africa or some other equally highly endemic areas of tropical Africa?

Attention should be drawn here to the fact that any comparison of results of malaria surveys carried out in several countries of tropical Africa throughout the past 20-30 years calls for much caution. The difficulty of interpretation of the results is particularly obvious with regard to some older records such as those quoted by Thomson (1924a), Knowles & Senior-White (1930), tabulated by Gordon & Davey (1932) and by Brumpt (1949). Data reported in the past annual reports from the former colonial territories in tropical Africa vary unaccountably from year to year (Granville Edge, 1937, 1950). Some bewildering inconsistencies in the early reports on the amount and distribution of malaria in Tanganyika were quoted and commented on by Clyde (1962). While a few older surveys lump together all age-groups of the investigated population, most of the others including the recent ones, are limited to the child population, the malarialmetric indices of which give the easiest assessment of the epidemiological situation. This explains why the information on the parasite rates of the adult population in tropical Africa is meagre, inconsistent and scattered.

Only some exceptionally well-documented reports give a detailed account of the conditions of the survey and of the technique used. Thus, figures quoted from some surveys carried out in the same locality at a few years' interval may show considerable differences even without the interference of any intensive malaria control measures. ¹

¹ The distribution of malaria in tropical Africa was outlined 12 years ago by Cambournac (1950) in his comprehensive report to the WHO Malaria Conference in Equatorial Africa. The general conclusions incorporated in the published report of this conference (World Health Organization, 1951) are probably still valid but some aspects of the situation have changed. An enormous amount of information has been collected in Africa during the recent years and little of it has been published. It seems that there is now an urgent need for a review and consolidation of available records which will increase our knowledge of the geographical distribution of species of malaria parasites and of our understanding of collective immunity in Africa.
The development of African tropics brings about rapid urbanization of rural areas, general improvement of environmental conditions, greater availability of health services, increased, though often haphazard administration of antimalarial drugs - all these factors tend to diminish the amount of malaria. On the other hand, the vastly increased means of communications are responsible for population movements between different parts of Africa and for constant or seasonal influx of large numbers of people harbouring new strains of parasites or having a degree of immunity different from that of the indigenous local populations.

There are also some more pedestrian factors influencing the reported results of malaria surveys and the validity of any comparisons. The time of the survey and the origin, source, size and age-composition of the investigated sample have an obvious, though often neglected, bearing on the parasite rate and on the parasite species composition.

The influence of the technique of the blood examination on the resulting "parasite rate" is well known to all those who had to work in African tropics with no technical assistance, or worse still, when this assistance was either unreliable or erratic. This applies particularly to imperfectly stained blood slides which are either difficult to confirm or too time-consuming to re-check since parasites are scanty.

It is obvious that the "parasite rate" reported depends on many variables connected with the technique of examination and that the error is bound to be much greater when the parasite count in a large proportion of slides is low.¹ In one

¹ The discussion of probability of finding malaria parasites in examining a small proportion of a small sample of blood obtained from an unknown number of infected subjects belonging to the selected sample of the human population would require a deployment of statistical methods. It seems that the situation represents a statistical series known as Poisson distribution. It refers to the probability of occurrence of a relatively rare event; if a sufficiently large number of independent cases are taken to obtain a number of occurrences, then the likelihood of this event can be estimated. In the case of blood examination for malaria parasites it seems that the expected number of occurrences is not constant from trial to trial and a modification of the Poisson distribution would be necessary taking into account the expected mean and its variance. Some aspects of the Poisson distribution applied to biological research were discussed by Fisher in his "Statistical methods for research workers".
of his "enumerative studies on malarial fever" Ross pointed out, over half a century ago, that the error of the blood examination depends not so much on the magnitude of the measured sample as on the number of parasites actually counted in the thick film (Ross & Thomson, 1910). According to Field (1948) the threshold at which parasites are first demonstrable by microscopic examination is probably about 10 per mm$^3$ with good technique and the examination of at least 100 thick film fields.

One tends to forget that most of the early records of surveys in Africa were based on the examination of thin films only. The adoption of the thick film as a routine method took place only gradually during the 1930s but this technique was not used with the same degree of efficiency in many African countries. The time spent on the examination of a slide influences the subsequent records to a surprising degree. This point was well stressed by Covell, Russell & Swellengrebel (1953). Knowles & Senior-White (1930) quoted Vaillant's findings that a single examination revealed only one-third of all positive films. In Africa, Schwetz (1938a) reported from the Congo that the examination of a single slide gives an adult parasite rate of 20%, while the examination of three slides taken from the same individual and at the same time increases the previous figure to 40-50%. More recently, Colbourne (1950), examining a group of 100 infants in Ghana, showed that the parasite rate increased from 52% to 61% when, instead of 100 fields of the thick film, 400 fields were examined. This difference would have been much greater in older age-groups. The difficulties of collecting reliable information and of generalizing the findings in one locality by referring them to a larger area were discussed and plaintively stressed by Schwetz (1944); his comments are applicable to most of tropical Africa.

Bearing all this in mind, the comparison of results obtained in the course of surveys in Africa should preferably be limited only to recent and fully documented investigations.

While our cross-section survey in the sample of adult Africans gave a parasite rate of 14.7%, a much higher parasite rate of 48.6%, based on the examination of 2139 adult visitors to the health offices in Lagos, was recorded some 30 years ago by Barber & Olinger (1931). Such a high single examination-parasite rate in adults
could not be confirmed in the coastal area of Nigeria by any subsequent investigator and it is likely that Barber & Olinger (1931) examined a selected sample of the population. Moreover, it must be remembered that during the years 1926-1930 most of the present suburbs of Lagos were a purely rural area. Nevertheless, in some rural areas of southern Nigeria the parasite rates of the adult population may be considerably higher than those mentioned previously.

In the course of single reconnaissance malaria surveys carried out during the period 1942-1950 in rural areas of southern Nigeria, the mean parasite rate found in 5240 adult Africans was 22% with a range between 11% and 28% (Bruce-Chwatt, 1951). Other reports gave figures varying more or less widely around the above mean. In Ilaro, situated in south-western Nigeria, the adult parasite rate found in 1949-1953 was 15.4% in 1849 subjects (Bruce-Chwatt et al., 1954); Draper (1953) who carried out a special survey in a small rural area of south-western Nigeria near the Dahomey border, reported an adult parasite rate of 16%; Archibald (1956) quoted for an area of south-western Nigeria an adult parasite rate of 26.4%, while Walters (1958) gives for the village of Ilobi in south-western Nigeria a figure of 29.3% in 615 adults. In a recent survey carried out on young adults at Ibadan, Cobban (1960) found a "cross-section" parasite rate of 6.4% in 576 films examined.

Parasite rates of 47.7 were recorded on a single examination of a sample of adults in south-eastern Nigeria by Bruce-Chwatt (1957); a relevant figure of 32.3 was reported in an adult African population of 692 in a group of villages of the Enugu-Ezike area in south-eastern Nigeria by Gibson (1958); a figure of 17.3% was recorded in the Niger Delta by Service & Gibson (1960) on a slightly smaller group of adults.

In northern Nigeria, the mean parasite rate in subjects over 15 years was given by Archibald (1956) as 27.4%. In the area of the Western Sokoto Pilot Project the adult parasite rate found during the pre-control surveys varied between 17.5 and 33.0% (Bruce-Chwatt & Archibald, 1958).

It might be of interest to compare the adult parasite rates found in Nigeria with those found in other parts of West Africa.
In Accra (Ghana) the adult parasite rate was 24-29% (Colbourne & Edington, 1954) or 20% (Colbourne, 1955); in one rural area of southern Ghana the relevant parasite rate was 13% (Colbourne, Edington & Hughes, 1950); in another area of Ghana, near Ho, a high parasite rate of 45.0% was recorded in 3553 adult subjects (WHO, 1962); in an area of Ashanti (Bonfa) this figure was 24%, while in northern Ghana the adult parasite rate was as high as 51% (Colbourne & Wright, 1955). A close figure of 47% based on the examination of 1700 blood slides taken from an African over 15 years of age was recorded in 1961 in the Bolgatanga area of North Ghana by a WHO team.

In Sierra Leone, the most complete investigations have been carried out around Freetown and the adult parasite rate of 10.3% reported by Turner & Walton (1946); a later paper by Walton (1949) quotes the 1944 parasite rate of adults as 15%, but indicates also the twice as high parasite rate of pregnant women. In Gambia, the parasite rate of 310 adults examined by Macgregor & Smith (1952) was 27.4%. In the Portuguese Guinea, the mean adult parasite rate was 43% as quoted by Cambournac (1950).

In Liberia, Barber, Rice & Brown (1932) found an exceedingly high adult parasite rate of 78.9% which could not be confirmed by any subsequent workers. Young & Johnson (1949) examined the population in many parts of Liberia and quote in their excellent report an over-all figure of 21.3% in 5943 Africans over 15 years of age. Ten years later a mean adult parasite rate of 21% was quoted by Miller (1958) and a relevant figure of 35.7% in 3133 adults examined in 1958 before the institution of a pilot project was recorded from Kpaim in northern Liberia by Guttuso (1962). The latter investigator quoted also a not too different adult parasite rate of 29% from the neighboring territory of Guinea. On the other hand, the relevant data available for Cameroun show considerable differences. Thus, in the southern, densely forested part of former French Cameroun, the parasite rate of 7.5% was reported by Languillon et al. (1956); in the early stage of the WHO pilot project in South Cameroun the parasite rate of adults averaged 8.0% (Livadas et al., 1958), but this figure decreased to 1.9% three years after the commencement of the pilot project (Chastang, 1959); a figure of 38% was recorded in the former British South Cameroun by Gibson (1958). In the former French North Cameroun situated in the Sudan savannah zone the parasite rate in adults was 32.6% (Cambique, 1950) in one area and 12% in another (Cavelie & Mouchet, 1961).
The results of early surveys in the former territories of French West Africa show many unaccountable differences. Léger & Nogue (1923) in one of the earliest surveys in Senegal recorded a parasite rate in adults of 47%. The most valuable data for this large area of the African continent were reported recently by Escudie & Hamon (1961) who analysed the records covering over 85,000 subjects of all ages. The figures referring to nearly 34,000 Africans over 14 years of age have been extracted from this comprehensive paper and tabulated below:

<table>
<thead>
<tr>
<th>Territory of Former French West Africa</th>
<th>Number of adults investigated</th>
<th>Slides positive for malaria parasites</th>
<th>Parasite rate (all species)</th>
<th>Range %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Côte d'Ivoire</td>
<td>10,516</td>
<td>2457</td>
<td>23.4</td>
<td>2.0-58.0</td>
</tr>
<tr>
<td>Chad</td>
<td>2,979</td>
<td>225</td>
<td>7.6</td>
<td>1.8-24.0</td>
</tr>
<tr>
<td>Guinea</td>
<td>4,031</td>
<td>551</td>
<td>12.7</td>
<td>2.3-42.0</td>
</tr>
<tr>
<td>Haute Volta</td>
<td>3,757</td>
<td>2,326</td>
<td>28.1</td>
<td>4.9-49.6</td>
</tr>
<tr>
<td>Niger</td>
<td>1,130</td>
<td>28</td>
<td>2.5</td>
<td>0.2-9.5</td>
</tr>
<tr>
<td>Senegal</td>
<td>3,738</td>
<td>319</td>
<td>8.4</td>
<td>5.8-17.0</td>
</tr>
<tr>
<td>Sudan</td>
<td>2,985</td>
<td>271</td>
<td>9.1</td>
<td>2.1-17.0</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>33,706</strong></td>
<td><strong>6,137</strong></td>
<td><strong>18.2</strong></td>
<td></td>
</tr>
</tbody>
</table>

Some other records based on large samples of populations are of interest. Thus, Duren (1938) quotes the over-all adult parasite rate as 23% based on 6159 adults examined over the whole of the former Belgian Congo. Schwetz (1933, 1934, 1938a)

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1 A series of new surveys covering a number of previously missed areas of West and Central Africa was carried out in 1960-1961 by the French and preliminary results were summarized by Escudie (1962). Details of this report which covers only the young age-groups need not be quoted here except for findings of species of parasites other than *P. falciparum*.
confirmed this mean figure, but pointed out that the range of findings is wide and that, using the thick film in many parts of that country, parasite rates in adult Africans may reach at a single examination the 40-50% level. The same observation was made by Jadin, Fain & Rupp (1952) in Ruanda-Urundi where the adult parasite rate was found to be 41% in 6444 subjects. In the Katanga area before the introduction of large-scale spraying by Vincke the adult parasite rate was 34.4% (Cambournac, 1950). In Zanzibar, McCarthy (1941) reported the figure of 12.7% in a sample of adults.

A considerable amount of relevant data from East and South Africa was quoted in a review by Wilson, Garnham & Swellengrebel (1950): surveys carried out in Kenya gave mean adult parasite rates of 36%; in Zanzibar and Pemba the relevant figure was 11%; in East Transvaal and North Natal - 34%; and in Tanganyika - 22%.1 In Uganda Garnham and the Wilsons (1948) recorded an adult parasite rate of 25-28%.

An impressive collection of malarialmetrical data was obtained in the course of the Pare-Taveta Malaria Scheme in East Africa (East Africa High Commission, 1960). The adult parasite rate recorded in the preparatory stage of this project gave an average figure of 24% in areas with moderately high transmission, and about 29% in areas with a higher level of transmission.

According to Smith & Draper (1958) and Draper (1960a), the mean adult parasite rate in the Taveta forest where the intensity of malaria is greater was 30-33%. Adult parasite rates obtained from other areas of Tanganyika by Clyde (1962) are very similar, however, as they vary between 27 and 34%.

In Southern Rhodesia the relevant parasite rate before the commencement of spraying operations was around 18% (WHO Regional Office for Africa, 1960) though in some areas it was lower.

In a southern area of Mozambique, Cambournac (1950) reported the adult parasite rate of 13.5% and a rate of 18.0% was recorded by Sueiro (1956). In Madagascar a recent report quoted the respective rate of 4.9% in adults compared with an average

1 The figure of 45% obtained by Wilson (1936a) in Gombero was based on repeated examinations of the same group and is not strictly comparable with the others.
of 13.3% in unprotected children (Lumaret, 1961, personal communication). Recently a number of surveys were carried out by a WHO team in some areas of West and Central Africa south of the equator. The following adult parasite rates were recorded by Maffi (1960, 1961): in Spanish Guinea - 40%; in Gabon - 42%; in the Central African Republic - 26%, and in the Congo (Brazzaville) - 8.6%. In South West Africa De Meillon (1951) reported that between 36% and 42% of adults are infected with malaria.

The relationship of the parasite rate to the seasonal wave of transmission is not very obvious in our investigation. It is true that during the period June to September 1956, when the transmission of malaria was intense, the weekly parasite rates were somewhat higher than during the remaining 20 months, but this difference is not striking.

The present study showed no obvious relationship of the crude parasite rate to the season of the year, and this is not very surprising. The transmission of malaria in southern Nigeria is virtually perennial, and any seasonal waves of increased endemicity would not greatly affect the malarialometric indices of the adult population. That this may be different in other parts of Nigeria with different climatic conditions, has been shown by Archibald (1956) and Bruce-Chwatt & Archibald (1958) in northern Nigeria where the adult parasite rates during the dry and rainy seasons were 17.5% during the period of minimum transmission and 33.0% at the end of the period of maximum transmission.

The importance of this was even better brought out by the East African Malaria Institute (East Africa High Commission, 1960) during the pre-control surveys in connexion with the Pare-Taveta Malaria Scheme; the adult parasite rates in the investigated area showed a range of variation from 11% to 51%. The same observation was well brought out in Swaziland by Mastbaum (1957).

The fact that striking differences in the parasite rates of adult African populations living within a comparatively small area, but where the local variations of climate and topography are pronounced, was well pointed out by Wilson (1958) quoting the results of a malaria survey in three separate populations living close to the Victoria Lake in Uganda. The parasite rates in adults were 18%, 20% and 42% respectively; no better example could be given to indicate the amount of caution necessary for the interpretation of results of single malarialometric surveys in Africa.
It will obviously be impossible to quote in this paper all the published or unpublished but available records of adult parasite rates in tropical Africa, but it appears that the figure of 14.7% obtained for the cross-section parasite rate of the group of adult African mental patients investigated in Lagos during the period 1956-1958 is not grossly different from the results of other surveys carried out in highly endemic areas.

It should, perhaps, be pointed out that this parasite rate was found in a sample of African population of a mean age of 37 years with about one-third of individuals over 45 years of age. Many authors quoted previously (Léger & Nogue, 1923; Walters, 1958; Smith & Draper, 1958; Young & Johnson, 1949; Wilson, 1936b; Macgregor & Smith, 1952; Colbourne, 1955; Wilson, Garnham & Swellengrebel, 1950; Wilson, 1958; Draper & Pringle, 1962) showed that in holo-endemic areas the parasite rate of young adults (15-30 years) is usually higher than that of a corresponding group composed of middle-aged (31-45) or older individuals. The difference between the first and the two latter groups may be of the order of one-third to one-half.

This observation is particularly striking in the survey of the Ilobi village of south-western Nigeria carried out by Walters (1958) who recorded the parasite rates of 53% in the 15-19 years age-group; 30.8% in the 20-29 years age-group; 27.3% in the 30-39 years age-group and 20% in people of 40 years and over. Considering this fact it seems that in any thorough malarialometric survey of adults in highly endemic areas a more detailed age-grouping by 10-year intervals up to the age of 50 may be indicated.

The parasite species distribution

According to numerous surveys made in tropical Africa over the past quarter of a century, and schematizing greatly the general conclusions, one might state that *P. falciparum* is a dominant species of malaria parasite in all age-groups, though the intensity of infection, which is very high in children, decreases greatly in adults. *P. malariae* irregularly distributed constitutes between one-tenth to one-half of all infections in children and its frequency falls so much in adolescents and adults that in the latter group it rarely exceeds 5% of all infections. *P. vivax* has an uneven distribution: it is very rare in West Africa but not uncommon in the equatorial parts
of East Africa where it may constitute between one-tenth to one quarter of all positive
findings; to the north of the 15° North and to the south of the
15° South, its frequency increases still more and, even within these
two limits as in some areas of Ethiopia, it may become at times a dominant parasite
with a relatively even distribution in all age-groups.

*P. ovale* is quite common all over West Africa and can be found in up to 10%
of all positive findings in children but is only exceptionally reported from adults;
this parasite is, however, much less common in East and Central Africa and becomes
exceptional outside the tropics of Cancer and Capricorn.

The distribution of species of parasites found in our cross-section survey
showed that among the investigated population 14.3% were infected with *P. falciparum*,
1.7% with *P. malariae* and 0.2% with *P. ovale*. Thus, *P. falciparum* constituted over
97% of positive slides, *P. malariae* alone or, more commonly, in association with
*P. falciparum* was found in nearly 12% of all positive slides. The presence of
*P. ovale* in 1.2% of all positive slides was not unexpected in this part of West Africa.

This pattern of distribution of the main species of malaria parasites in adults
is quite typical of tropical Africa generally and of West Africa in particular,
although the actual proportions of *P. malariae* and *P. ovale* vary considerably in
relation to the age of the examined subject and to the area concerned (World Health
Organization, 1951).

The pattern of distribution of *P. malariae* in the adult population of tropical
Africa shows a number of exceptions. Thus, in Nigeria and Ghana *P. malariae* rarely
exceeds 5.0% in examined adults but higher figures approaching 10.0% or more were
reported by Charles & Archibald (1955), by Bruce-Chwatt (1957) from some areas;
a WHO team recorded recently that *P. malariae* was found in the Bolgatanga area of
Ghana in 11.3% of adults (Van der Kaay, personal communication). This confirms the
statement of Escudie & Hamon (1961) and of Escudie (1962) who found *P. malariae*

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1 The collection and assessment of data on the species infection rate and gametocyte
rate from many published and unpublished reports is at times very difficult because
a number of authors quote the percentages in relation either to the numbers of sub-
jects examined or to the numbers of positive slides but without explaining the method
of calculation. The importance of proper and full reporting cannot be over-emphasized
and the adherence to established standards such as those given by Covell, Russell
& Swellemegrebel (1953) or by the forthcoming new edition of this monograph should be
the duty of every author.
particularly frequent in the Sahel savannah zones of Central and West Africa (Mauritania, Niger, Mali) especially during the dry season. Gordon & Davey (1932) described a high frequency of *P. malariae* in Freetown not only in children but also in young adults with a quartan parasite rate of about 10%. Turner & Walton (1946) believe that an epidemic of *P. malariae* occurred on the coast of Sierra Leone during the period 1920-1940. Gordon & Davey (1932) quote a number of older French surveys from Senegal, Niger and Guinea with *P. malariae* rates between 25 and 55% of all infections, but according to Léger & Nogue (1923) the rate of quartan malaria in adults in Senegal averaged 9%. Young & Johnson (1949) found in adults a parasite rate of 14% in Liberia, but a lower figure of 2.0% was found in Northern Liberia by Guttuso (WHO Regional Office for Africa, 1960). Cambournac (1950) quoted in his report the following frequency of *P. malariae* in adults: 7.0-9.0% in Uganda; 8.0% in Tanganyika; 10.0% in Kenya. On the other hand, Garnham (1949) found the quartan parasite only in 2.0% of adults in Kenya, while in the Taveta-Pare scheme of East Africa, Smith & Draper (1958) recorded that *P. malariae* is seen in 3.0% of adult Africans. A close figure of 4.0% was reported from the Usambara area of Tanganyika by Davidson & Draper (1953).

Duren (1936) in his general review of malaria surveys in the former Belgian Congo comes to the conclusion that *P. malariae* averages in adult Congolese a parasite rate of 12.5, but that this rate increases to 24% in areas at altitudes between 1000 and 1500 m (3000-4500 feet). In Angola, Cambournac et al. (1955) found an over-all low rate of *P. malariae* between 0 and 2.7%. Garnham (1949) in Kenya found *P. malariae* in 2.0% of adults; Schuffner et al. (1932) recorded in Transvaal and Natal a low figure of 0.5%.

According to Saugrain (1959) and to Maffi (1960, 1961) *P. malariae* is rare in some of the former territories of French Equatorial Africa (Gabon, Central African Republic, Congo-Brazzaville) where the over-all rate in all age-groups was less than 2% with the exception of one area (Azande) where the quartan malaria was more common and reached the rate of 12.8%. The extraordinary irregularity that can be sometimes seen in the distribution of *P. malariae* could be best illustrated by quoting a recent finding of Jelliffe & Jelliffe (personal communication) who recorded in the Karamojong area of Uganda 92.0% of quartan infections in children while in the neighbouring district the rates for *P. malariae* were low or even nil.
It seems that the generally low frequency of reported findings of *P. malariae* in the adult population of tropical Africa is often due to the difficulty of finding this parasite in scanty infections. Even if *P. malariae* is present in about 10-20% of all positive slides, its count in tropical Africa is approximately between one-fifth to one-half of that of *P. falciparum* (Young & Johnson, 1949). This decreases greatly the chance of spotting and identifying *P. malariae* on a single examination, especially when its younger forms predominate. Multiple infections with *P. falciparum* and *P. malariae* are common and may be present in up to one-third of all positive slides, but the more numerous falciparum parasites overshadow the quartan infections.

Consequently, it appears that the true frequency of quartan infections in African adults cannot be properly assessed on single malarialmetric surveys. This point will be discussed further in another section of this paper. On the other hand, this in no way invalidates the current opinion that a degree of high immunity is achieved with regard to *P. malariae* sooner than to *P. falciparum* and that this is evidenced by the relatively low prevalence of quartan infections in the older age-groups in areas of holo-endemic malaria in Africa.

The relative increase of the over-all frequency of *P. malariae* from 12% to 25% in the Taveta-Fare area of Tanganyika during the first two years of the central scheme is of significance as it indicates the greater persistence of this species when the amount of *P. falciparum* infections decreases (East Africa High Commission, 1960).

... *P. ovale* shows an interesting distribution in tropical Africa and already 30 years ago Barber & Olinger (1931) in their report from Lagos mentioned that "about a dozen infections with benign tertian parasites all or most of which seemed to be 'ovale'". Most of the pre-1948 records will be found in Brumpt (1949) and in Boyd (1949). Since then, *P. ovale* was reported in several parts of Nigeria by Bruce-Chwatt (1951), by Bruce-Chwatt et al. (1954), by Archibald (1956), by Bruce-Chwatt & Archibald (1958) and by Gibson (1958). Colbourne & Wright (1955) and Charles (1960) reported this parasite from Ghana; Walton (1946) from Sierra Leone; Young & Johnson (1949), Cattuso (1962) and Bray (1957) from Liberia; McGregor & Smith (1952) from Gambia; Masseguin & Palinacci (1955) from the Upper Volta;
Languillon (1957) from the Cameroun; Lacan & Peel (1958) from several territories of the former French Equatorial Africa; Blair (1938) from Rhodesia. *P. ovale* is very uncommonly found in the territories of former French Equatorial Africa, but in a small zone of the Congo (Brazzaville) along the Congo river it was present in higher numbers and formed about 1.5% of slides (Maffi, 1960, 1961).

In East Africa *P. ovale* exists together with *P. vivax* (Wilson, 1936; Smith & Draper, 1958). Garnham (1962) outlined briefly the distribution of *P. ovale* in Africa, and a review of the present situation is now being prepared by WHO on the basis of available data.

Most of these reports refer to children; the presence of *P. ovale* in adults is exceptionally recorded and the results of our investigation confirm that this parasite may be found in one to six adult West Africans out of 1000 examined. As usual, *P. ovale* is very fleeting and often it cannot be seen again on the next day after the first appearance (Lacan, 1962). It is likely that the 3.3% of "*P. vivax*" reported from the Upper Volta, Ivory Coast and Guinea by Jonchère & Pfister (1951) are in reality *P. ovale* infections; the same is possibly true with regard to 3.8% of "*P. vivax*" found by Cambournac & Gandara (1955) in S. Tomé and Principe, two small islands off the coast of West Africa.

It is probable that most, if not all, records of *P. vivax* in the indigenous population of West Africa are *P. ovale* not recognized as such. Thus, the interpretation of malarialiological findings in a series of older documents (such as the "Medical and Sanitary Reports from British Colonies, Protectorates and Dependencies") and in some published papers must be cautious.

The parasite density

The degree of parasitaemia of adult Africans investigated by us was expressed by the parasite density index of 1.5 which corresponds to the mean (geometric) figure of 100-200 parasites per mm$^3$ of blood and is quite typical of the malaria endemicity found in tropical Africa by many investigators (Léger & Nogue, 1923; Barber & Olinger, 1931; Schwetz, 1933; Schwetz, 1934; Wilson, 1936; Schwetz, 1938; Wilson, 1939; Schwetz, 1944; Young & Johnson, 1949; Walton, 1949; Garnham, 1949; Wilson, Garnham & Swellengrebel, 1950; McGregor & Smith, 1952; Davidson & Draper, 1953; Colbourne & Wright, 1955b; Davidson, 1955; Miller, 1958; Smith & Draper, 1958).
It should be noted that, using the same method of calculation as ours, Colbourne & Wright (1955b) obtained for African adults the parasite density index of 1.35 in South Ghana and 1.5 in North Ghana respectively. In Tanganyika, Mackay (1935) and later Wilson (1936b) found the mean (arithmetic) parasite density of 190-202 per mm$^3$ in the whole adult group and little difference between this figure in young adults (16 to 30 years) or those between 31 and over 50 years of age. Garnham et al. (1958) found that the mean count in the adult group in Uganda was 400 parasites per mm$^3$.

However, in Liberia, Miller's (1958) mean daily parasite count of adults was only 56 parasites per mm$^3$ or three to four times less. The reason for this discrepancy is not clear, but may be due to a different technique of counting and recording.

The much reduced parasite density of all species of malaria parasites of African adults in comparison with the young age-groups is one of the main characteristics of an immune community (Wilson, Garnham & Swellengrebel, 1950; Macdonald, 1951, 1956, 1957). This index assesses the trend of collective immunity much better than the parasite rate which in adults may vary greatly, depending on the thoroughness of blood examination, since parasites are generally very scanty. The results of our investigation showed very little seasonal variation of the parasite density index, and this was expected. Wide variations in parasite counts are found in highly endemic areas in children; in areas of pronounced seasonal transmission where populations have little immunity the parasite density index of adults may be two to four times higher during the transmission season as it was shown by Wilson (1939) in Tanganyika and by Mastbaum (1957) in Swaziland.

The parasite density indices quoted here refer to all species of malaria parasites but mainly to *P. falciparum*. The proportion of other species is generally so low that the results are not greatly altered by their numbers. It is obvious that the separate counts of *P. malariae* and *P. ovale* are not practicable because of the virtual impossibility of identification of very young trophozoites in a thick film. Young & Johnson (1949) attempted to obtain some proportional counts of the three species in adults in Liberia and their results expressed as geometric means were as follows: *P. falciparum* - 125 parasites per mm$^3$; *P. malariae* - 59 parasites per mm$^3$; *P. ovale* (*P. vivax*) - 34 parasites per mm$^3$. 
Gametocytes of *P. falciparum*: rate, density, infectivity

The gametocyte rate of *P. falciparum* averaged 2% in our examined sample of the adult population and 13% in all positive slides. These figures are also typical of the West African malaria when assessed on the basis of a single survey. Other authors found the *P. falciparum* gametocyte rate of examined adults varying between 1 and 5%. Lower or higher rates were quoted by several authors: thus Schwetz (1933) says that "les gametocytes deviennent d'une rareté extraordinaire chez des adultes" while Muirhead-Thomson (1954) recorded 6.0% in a coastal village of Ghana; Barber & Olinger (1931) found 7.0% in Lagos; Duren (1936) quotes 7.0 to 12.0% in several surveys of the former Belgian Congo; Colbourne & Wright (1955) found 15% in a village of North Ghana and a figure of 10.5% was found recently in Bolgatanga (North Ghana) by a WHO team; from Swaziland, Mastbaum (1957) reports gametocyte rates up to 15%. Wilson (1936) in a holo-endemic area of East Africa found seasonal variations from 0.5% to 5.4% in adults.

The *P. falciparum* gametocyte density averaging (arithmetic mean) 39 per mm$^3$ in our sample of adults is also quite typical of the epidemiological picture of African malaria in areas with a high transmission. Nearly all surveys carried out in these areas produced the same results showing that the *falciparum* gametocyte count in the adult African is less than 100 per mm$^3$ (Colbourne & Wright, 1955; Davidson & Draper, 1953; Davidson, 1955). Some particularly well-documented reports such as Young & Johnson's (1949) quote the arithmetic mean of 25 per mm$^3$; Barber & Olinger (1931), having examined 1039 positive slides taken from adult Africans in Lagos found no one slide with over 80 crescents per mm$^3$ while Lacan (1958) in a thorough survey carried out in the territories of the former French Equatorial Africa found the mean density of gametocytes to be 14 per mm$^3$ in subjects over 12 years of age.

The prevalence of gametocytes at various stages of *P. falciparum* infections has been extensively studied and the subject was admirably reviewed by Covell (1960). It has been stated already by Ross & Thomson (1910) that varying proportions of asexual forms of *P. falciparum* constantly generate crescents which appear in the blood after 8-10 days; the normal elimination of crescents from the organism is constantly being compensated so that their persistence is due to the replenishment of the stock from fresh broods.
Working with East African and West African strains of *P. falciparum* for malaria induction in non-immune patients, Shute & Maryon (1954) noted that gametocytes were not seen in thick films for at least eight days after invasion of the blood by asexual parasites in detectable numbers and that these early forms required several days for maturation. They concluded that gametocytes evolve from asexual parasites circulating in the blood during remissions between attacks and that the maximum longevity of individual crescents is about two months. A fairly general concensus of opinion is that the production of gametocytes is related to the appearance in the blood of the asexual parasites but not necessarily to the clinical symptoms. The decrease of the parasite density in the immune populations has therefore a direct effect on the gametocyte rate and gametocyte density. It seems that as the mean number of crescents is roughly proportional to the mean number of parasites in the blood, the crescents will be detectable in approximately the same proportion of the population. Macdonald (1957) stressed with vigour the influence of acquired immunity on the restriction of the gametocyte output and thus on the community aspects of transmission of malaria; the restriction of gametocyte output may occur very early, before the curb of the production of asexual parasites becomes evident.

The importance of this from the point of view of malaria eradication is considerable. It is possible, however, that the survival of *P. falciparum* in some conditions is assured by a process whereby the incidence of crescents falls relatively slowly in comparison with the rapid fall of the parasite rate. More epidemiological studies of this problem are needed and one of the important aspects of it is the infectivity to *Anopheles* of *P. falciparum* gametocytes in symptomatic and asymptomatic infections.

A certain threshold gametocyte density must be present in the blood-meal for the *Anopheles* to become infected. It is agreed that only a limited number of adult gametocyte carriers are a source of infection because few of them normally carry sufficient numbers of gametocytes to allow ingestion of both male and female sexual forms of *Plasmodia* by the mosquito at a single blood-meal.

An excellent review of the previous studies on the infectivity of gametocytes to *Anopheles* will be found in Covell (1960) and only some findings pertaining to investigations in tropical Africa will be mentioned here.
The pioneer studies of Darling (1910) in the Panama Canal Zone showed that the limit of infectivity of crescents of *P. falciparum* (to *A. albimanus*) can be as low as 12 per mm$^3$ of blood. Green (1929) found in Malaya that the infectivity threshold of *P. falciparum* is 42 gametocytes per mm$^3$. In South Africa, Swellengrebel et al. (1931) estimated that blood with gametocyte counts of only 1:5000 leucocytes (about two per mm$^3$ of blood) is infective, while Barber, Rice & Brown (1932) found that Liberian adults with approximately 50 crescents per mm$^3$ will infect 20% of *A. gambiae* feeding once only. Robertson (1945) recorded in West Africa infections of *A. gambiae* on subjects having less than three crescents per 1000 leucocytes; in one batch of 13 *A. gambiae* one specimen became infected when the crescent density was 0.7 per 1000 leucocytes, or about five per mm$^3$ of blood. Young and his colleagues (1948) and later Muirhead-Thomson & Mercier (1952) confirmed that the threshold of infective density of *P. falciparum* can be as low as one crescent per mm$^3$. Walton (1949) concluded that blood-meals containing as few as 12-20 gametocytes per mm$^3$ can normally be responsible for infecting a large population of *A. gambiae* in Sierra Leone. Draper (1953) in Nigeria, found a positive correlation between the probability of *A. gambiae* becoming infected and the gametocyte density of the human host, the rate of infection varying from 5% with densities less than 100 per mm$^3$ of blood to 50% with those above this figure. Muirhead-Thomson (1954), working in Ghana, found that one-quarter of the 24 batches of *A. gambiae* were infected after feeding on subjects whose crescent counts were less than 1:1000 of white blood cells and two mosquitos became infected on carriers with a crescent density less than one per mm$^3$. Out of 28 Ghanaian adults, two proved infective in this series of investigations, but in a later study (Muirhead-Thomson, 1957), 347 Africans of all ages were tested in this manner, the results indicating that under hyperendemic conditions adults and adolescents may form as much as 30% of the total reservoir of malarial infection in the human population.

It is regrettable that our own investigation brought no new facts even though it showed that two asymptomatic adults out of 10 were capable of infecting *A. gambiae*. However, a recent study of Bray & Burgess (1962) in Liberia provided additional and valuable information. The Liberian study was carried out on 44 children and 25 adults.
The most interesting result of this study was the high proportion (77%) of gland and gut infections of mosquitoes fed on African adults with less than 100 gametocytes per mm$^3$ of blood. In 7 out of 11 cases infections were obtained from donors with less than 20 gametocytes per mm$^3$ and in three cases an infection of mosquitoes was obtained although no gametocytes were seen in some blood films. The authors concluded that highly endemic malaria in West Africa may be maintained by carriers with less than 100 gametocytes per mm$^3$.

Adults living under holo-endemic conditions were previously considered of little importance as a source of malaria infection. It seems now that this belief has been seriously challenged and that adolescents and adults - the "cryptic infectors" in Muirhead-Thomson's description - may form, under highly endemic conditions, a more important reservoir than had usually been believed. This conclusion suggests that the blood film alone is not a reliable guide to the assessment of the reservoir of malaria infection of an indigenous community in tropical Africa. Moreover, it reopens the discussion on a problem on which the WHO Expert Committee on Malaria (1959) expressed the opinion that although mosquitoes may be infected by carriers with low gametocytaemias, the number of oocysts which develop is small and the percentage of Anopheles infected negligible so that they infect only a small proportion of the persons they bite.

Much more experimental and field work on this important aspect of epidemiology of malaria in Africa is urgently needed. At the present time the only way to assess the potential danger of asymptomatic carriers to the community is by test feeding of Anopheles and establishing the index of resulting infections. Perhaps one of the more important points to solve is the infectivity of carriers of relatively "old" gametocytes of P. falciparum which are so common in the consolidation phase when the transmission has been interrupted.

With regard to P. malariae and persisting scanty infections with it, the general consensus of opinion is that they are of little importance because of the low counts of these parasites and the notorious difficulty of infecting Anopheles even under optimal conditions. This is probably true but it is also worth mentioning that in Liberia, Muirhead-Thomson (1957) was able to infect A. gambiae with quartan malaria fairly easily, the oocysts being half grown by the eighth day as compared with the
usual figure of 11 days or more. Bray (1959) in the course of his work on pre-erythrocytic stages of *P. malariae* infected *A. gambiae* with ease and transmitted the infection to chimpanzees. His comments on the apparent lack of correlation between the low number of gametocytes and infection of mosquitos are of considerable interest.

7.2 **Induced malaria infection in adult Africans**

Our attempts at transmission of malaria to African adults by intravenous injection of heavily parasitized blood showed that a continuous wave of parasitaemia followed the apparent induction of infection in 55% of cases. The explanation of this result is not easy but the fact of its reliability was recently confirmed by Bray (1962) who carried out a series of sporozoite-induced infections in 40 African adults using *A. gambiae*, infected with local or other Liberian strains of *P. falciparum*. The results of this interesting work showed that in 16 subjects no parasites were found in the blood, in 14 subjects there was a low parasitaemia without clinical symptoms, but in the remaining 10 subjects the consequent parasitaemia appearing during the third week after the infective bite was accompanied by clinical symptoms. The similarity of results obtained in Nigeria and Liberia with induction of malaria in African adults either by blood transmission or through sporozoites is indeed striking. It is almost certain that we are not dealing here with reinfections but with superinfections. The fact that the possibility of superinfection must be considered in spite of the high degree of immunity of the investigated subjects is of the greatest interest. The problem of superinfection has been lucidly exposed by Sinton (1939) on the basis of his work with simian malaria. Sinton concluded that when a host with a degree of immunity is superinfected with a homologous strain of a parasite the response is a slight rise in the number of parasites, but seldom any clinical manifestations. The results of superinfection with a heterologous strain are different even if the degree of immunity already achieved by the host is high.

There is general agreement that within each species of malaria parasites there are races or strains distinctive by their infectivity to the vertebrate and invertebrate host, antigenic properties and response to drugs (James & Ciucu, 1938; Covell & Nicol, 1951; Shute, 1951). The absence of cross-immunity between the Madagascar and Sardinian strain of *P. falciparum* was demonstrated in induced malaria by James, Nicol & Shute (1972).
Taliaferro (1949) pointed out that some strains of malaria parasites do not protect against other strains of the same species and that heterologous immunities in *P. falciparum* may be less strong than for other species of malaria parasites, probably because of the variable amount of antigen absorbed.

The results of our work and that of Bray (1962) would corroborate the views of Macdonald (1957) that stimulation of immunity in falciparum malaria is relatively slow and that repeated superinfections with different strains of *P. falciparum* are a common occurrence; this would explain a number of epidemiological happenings. It is surprising, however, that apparent superinfection should be so easy in African adults who, having been exposed to malaria since childhood could presumably have a considerable "multi-strain" resistance to infection with *P. falciparum*. It seems that until we have the immunological means of distinguishing between two strains of the same species of *Plasmodium* the explanation of such happenings and their follow-up will be difficult.

The general problem of strains of human plasmodia was lucidly assessed by Shute & Maryon (1954) on the basis of the authors' exceptional experience with induced malaria. Geographical strains of *P. falciparum* showed wide variations, not only in their amenability to drugs, but also in their infectivity to one particular vector as also in their gametocyte output. The authors pointed out that, while physiological and immunological differences in geographical strains can be confirmed on circumstantial evidence, it is most difficult at the present time to prove them beyond any doubt. This difficulty is particularly great with regard to the "locality strains" within the same geographical area. The moot question - how does any such strain retain its identity? - is of fundamental importance. In the absence of any definite knowledge of cross-fertilization between gametocytes of various strains, the answer can be given only by a long series of passages from man to mosquito to man carried out in conditions which preclude an accidental reinfection of the subject. A vast area of immunological investigations seems to be opening here and it is hoped that new techniques such as the use of fluorescent antibody may clear up a number of points that remain obscure.
9.3 Results of the longitudinal survey

It was stressed previously that the assessment of the amount of malaria on the basis of the usual single cross-section survey has a "built in" wide margin of error. This is partly due to the shortcomings, viz. systematic and accidental errors of our traditional technique which does not easily reveal the presence of malaria parasites in the blood if they are scanty, as is the general case in the adult population in highly endemic areas of Africa.

Naturally, a prolonged examination of each single slide or a routine examination of several slides taken on one day from the same individual would increase the parasite prevalence rate of a sample of the adult African population.

The difference between the "parasite rate" determined on a single survey and the frequency of parasitaemia recorded cumulatively after repeated examinations of the same subjects is even more impressive. This is well shown in our results which emphasize the fact that the true incidence of malaria infection of indigenous adults in a holo-endemic area of Africa is very much higher than generally assumed. In fact, one could say that there is little if any difference between the parasite incidence of adults and that of children. The parasite incidence rate of 91.5-93.5% in two groups of adults followed up for one to two years suggests that the true infection rate is probably close to 100% and indicates that complete immunity with consequent permanent freedom from parasitaemia is never achieved in the adult African. Whenever an attempt at a repetitive examination of adults was made in tropical Africa the results were remarkably similar.

Barber & Olinger (1931) observed that in one group of 51 adults examined four times once a month the parasite rate was raised from 43.1 to 92.2%. One part of Wilson's (1936) well-known survey of Gombero (Tanganyika) was carried out by examinations of a sample of the population every two months; it was found that only 12 adults out of 246 examined at random over 15 months had no parasites in the blood on six or more occasions. This would give an approximate parasite incidence of 91.5%. 
Charles & Archibald (1955) carried out a brief, repetitive random survey of the population of a small village in south-western Nigeria and found that the cumulative adult parasite rate was 36.3% instead of the 15% seen on a single survey of 330 subjects.

Miller (1958) reported from Liberia that 19 out of his 20 young adults examined every second day for a year showed the presence of malaria parasites one or more times. This would give a parasite incidence rate of 95%. Cobban (1960) found that a single examination of a sample of 250 young adults in western Nigeria gave a parasite rate of 6.8%, but out of nine adults examined once weekly for half a year, six (77.7%) had malaria parasites at one time or another.

The cumulative frequency of parasitaemia showed in the course of longitudinal survey is much higher than indicated by the conventional "parasite rate" but does not give the idea of the type of immune response of the adult African in a highly endemic area.

The effect of acquired immunity is very pronounced and clearly indicated by the parasite density which in adults amounts to about 1/10-1/60 of that seen in children at the peak of their infection (Putnam, 1931; Wilson, 1936; Young & Johnson, 1949; Bruce-Chwatt, 1951; Colbourne & Wright, 1955; Davidson & Draper, 1953; Smith & Draper, 1958, and others).

The parasite density index of the investigated sample of the population remained remarkably steady over the whole period and kept within the range of 1.25-1.91 which corresponds to 100-200 parasites per \( \text{mm}^3 \). There were, however, "waves" of higher counts in a few subjects and in five of them counts of the order of 1600-3200 parasites per \( \text{mm}^3 \) were seen. The parasite density of our group of adults was about three times higher than the "mean daily parasite count" of 56 parasites per \( \text{mm}^3 \) recorded by Miller (1958). In a recent investigation carried out also in Liberia, Bray (1962) stated that over half of the population shows parasitaemia below 100 per \( \text{mm}^3 \) and that in adults such low parasitaemias are prevalent.
There was little evidence of any significant seasonal variation in the parasite incidence or parasite density of our sample except perhaps for the period of July-September 1956. Our results are less indicative of the influence of the transmission season than those of Wilson (1936) and of Miller (1958). In comparison with the Liberian investigation the age composition of our group was different, the Lagos sample of the population being considerably older; this might have had a bearing on the final data.

An important finding concerns *P. malariae*: this parasite, present on the average in 1.7% of all slides taken during the period of the investigation, was found in about 20% of adults followed up for one to two years. The ratio of frequency of *P. malariae* to *P. falciparum* in cross-section surveys was approximately 1:8 but in the longitudinal survey this ratio increased to about 1:5. These results are close to those (1:9 and 1:5) obtained by Miller (1958) who found that although *P. malariae* was seen in 2% of all slides it was found over the year in 50% of the examined adults. It seems that the true incidence of *P. malariae* in African adults in many areas is generally under-estimated and that any carefully conducted longitudinal survey would correct the traditional notions and show that the rarity of this species is only relative. One half of Wilson's (1936) six adults examined during six months showed quartan malaria at one time or another, while in Cobban's (1960) small series of eight adults examined once a week for 30 weeks, the incidence of *P. malariae* was 25%.

While the frequency of gametocytes of *P. falciparum* was found to be at the usual mean level of about 2% at any weekly survey with variations between 0.6% and 4.5%, the longitudinal survey showed that 36% of all adults produced "crescents" at one time or another. This figure is lower than the comparative figure of 80% obtained by Miller (1958) and the difference is most probably due to our group being older.

The mean density of gametocytes in our selected sub-group was 48 per mm$^3$ or slightly higher than 39 per mm$^3$ seen in the total sample. This figure is remarkably close to the mean figure of 46 per mm$^3$ found by Barber, Rice & Brown (1932) who examined their adult crescent carrier "John of Tom's Camp" daily for a week and found that he had an extraordinarily steady gametocyte output. Young & Johnson (1949) in Liberia found a mean parasite count of 23 per mm$^3$ and Miller's (1958) mean gametocyte count is probably of the same order.
The fact that over one-third of all adults in our group and four-fifths of adults in Miller's (1958) group keep up a more or less steady production of gametocytes may be of considerable importance for the maintenance of transmission.

Schuffner (1938)\(^1\) drew attention to the variations in the prevalence of gametocytes of \textit{P. falciparum} in endemic conditions and Macdonald (1951) stressed that these studies have not been adequately followed up and extended. It is now well established that in highly endemic areas there is a very marked age distribution of the prevalence and density of gametocytaemia. The bulk of the gametocyte reservoir is in the young age-groups while only a small proportion of the community output of gametocytes is found in adults. Macdonald (1951) drew attention to the fact that although gametocytaemia of adults is of low numerical order, the variations of its rate are sufficient to show that under the stress of increased transmission the braking effect of immunity on the gametocyte production would be markedly weakened.

We were able to confirm Miller's (1958) finding that in a number of cases an increased gametocytaemia was preceded by a wave of asexual parasitaemia recorded one or at most, two weeks before. Our results showed that this occurred in at least 10\% of the subjects, though it might have conceivably happened more often without being detected by a once- or twice-weekly examination of the blood. On the other hand, we noted the presence of a previous clinical episode only once and our findings differ here from those of Millor (1958). Altogether we were struck by the apparently disorderly appearance and disappearance of gametocytes in the blood of our subjects. The two main types of parasitaemia shown in Fig. 2 represent only the classifiable happenings and suggest one a persisting low-level infection and the other a super-infection; it is only in the second case that the connexion of a gametocyte "burst" with a new infection is recognizable.

\(^1\) This admirable paper ("Two subjects relating to the epidemiology of malaria") was first published in Dutch in 1919 and then translated into English by Swellengrebel at Sinton's request and published in the Journal of the Malaria Institute of India. It is one of malariological classics and should be read in its entirety by all interested in epidemiology of malaria.
As it was pointed out by Covell (1960) many observers have noted a relationship between the invasion of the peripheral blood by asexual parasites and the subsequent appearance of sexual forms. On the other hand, gametocytæmia may exist in the absence of clinical attacks, if the degree of tolerance possessed by the patient is sufficient to suppress symptoms which would otherwise have accompanied the invasion of the blood by asexual parasites. In short, the presence of gametocytes in the peripheral blood at any particular stage of a malarial infection after the achievement of a degree of immunity is largely unpredictable.

The study of the governing mechanism of the reservoir of infection in relation to the amount of transmission led Macdonald (1951, 1957) to formulating a fascinating hypothesis of immunobiological cybernetics in endemic malaria, much of which is now being confirmed.

The present study, together with Miller's (1958) work tends to show that the incidence of low-level gametocytæmia in supposedly immune adults is not inconsiderable. As they comprise two-thirds of the community their contribution to the reservoir of the infection may be unexpectedly large. A tentative estimate based on the proportion of adult gametocyte carriers and the mean density of the parasites in the blood suggests that the potential contribution of the adult group amounts in West Africa to about 1/50-1/100 of the total gametocyte output of the community. Naturally the problem of infectivity of these gametocytes to the vector is of cardinal importance and some recent important investigations mentioned previously showed that mosquitos may be infected at *P. falciparum* densities considerably lower than has formerly been supposed. The finding of such "cryptic gametocyte carriers" undermines the value of Schuffner's (1938) distinction between non-infective and infective crescent carriers and lowers the estimated threshold for the level of the reservoir of infection capable of maintaining transmission.

Generally speaking, it is felt that although individually adult subjects with low gametocyte counts do not substantially contribute to the reservoir of infection. Nevertheless, in any community where the density of the vector is high, this may slow down the trend of interruption of transmission or maintain it at a low level for a considerable time. In malaria eradication programmes, this would call for a wider use of gametocytocidal and sporontocidal drugs.
9.4 Malaria morbidity in tropical Africa

The discussion of the value of fever for detection of cases of malaria and the relationship of clinical symptoms to the infection with *P. falciparum* in holo-endemic areas of Africa is of particular interest when one considers the available data on the malaria morbidity in the indigenous populations.

In the early section of this paper it was shown that the available records can give only some imperfect idea of the proportional malaria morbidity and mortality in a selected portion of the population that attended hospitals in Nigeria during the period 1944-1956. The shortcomings of these records were stressed and it was pointed out that they probably underestimate the effects of the disease in the vast rural areas.

It might be of interest to compare the Nigerian records with those of other parts of tropical Africa to better assess the general picture. Once again, however, the hospital records are the only source of information which must be interpreted with caution.

The incidence of malaria among hospital patients in all former British tropical African territories was tentatively assessed by Granville Edge (1937) who quoted for 1935 the over-all rate of 10.2% of all in-patients and 28.2% of all out-patient attendances. Naturally, these hospital figures referring to the situation of 25 years ago give little information on the real incidence of the disease in the exposed population and (in Granville Edge's own words) "provide but a shadowy picture".

In order to assess the possible differences between various African territories records given in "Medical and Sanitary Reports" from the former British colonies, protectorates and dependencies for the years 1942-1945, summarized and annotated by Granville Edge (1950), were extracted and are shown in Table 13.
TABLE 13. PROPORTIONAL MALARIA MORBIDITY IN THE INDIGENOUS POPULATIONS ATTENDING HOSPITALS IN SOME WEST AFRICAN AND EAST AFRICAN COUNTRIES OR TERRITORIES DURING THE PERIOD 1942-1945
(Re-calculated from the data given by Granville Edge, 1950)

<table>
<thead>
<tr>
<th>Country and estimated population</th>
<th>In-patients</th>
<th>Out-patients</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Malaria</td>
<td>%</td>
</tr>
<tr>
<td>Nigeria (10 million)</td>
<td>386 101</td>
<td>28 457</td>
<td>7.4</td>
</tr>
<tr>
<td>Ghana (3.2 million)</td>
<td>63 999</td>
<td>5 820</td>
<td>9.1</td>
</tr>
<tr>
<td>Sierra Leone (1.9 million)</td>
<td>28 984</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>8 546</td>
<td>600</td>
<td>7.0</td>
</tr>
<tr>
<td>Gambia (0.2 million)</td>
<td>3 375</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kenya (3.1 million)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Uganda (3.7 million)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tanganyika (5.1 million)</td>
<td>64 973</td>
<td>10 778</td>
<td>16.6</td>
</tr>
<tr>
<td>Zanzibar (0.25 million)</td>
<td>11 638</td>
<td>993</td>
<td>8.5</td>
</tr>
<tr>
<td>Nyasaland (1.6 million)</td>
<td>23 369</td>
<td>2 311</td>
<td>9.9</td>
</tr>
<tr>
<td>Northern Rhodesia (1.4 million)</td>
<td>61 323</td>
<td>6 777</td>
<td>11.0</td>
</tr>
</tbody>
</table>

*Note: Estimated populations quoted after Halley (1938) for 1935-1936; the figures are given here only for comparison and were very greatly increased as a result of subsequent censuses carried out in most of these countries. The revised edition of Halley's book (1937) given the following figures based either on a census (C) or on an estimate (E): Nigeria (E 1952-1953) - 31 million; Ghana (E 1953) - 4.5 million; Sierra Leone (E 1947) - 1.9 million; Gambia (E 1953) - 0.3 million; Kenya (C 1948) - 5.3 million; Uganda (E 1953) - 5.3 million; Tanganyika (E 1953) - 7.9 million; Zanzibar (C 1948) - 0.26 million; Nyasaland (E 1953) - 2.5 million; N. Rhodesia (E 1953) - 2 million.
This table, with all its lacunae and imperfections shows much similarity to the Nigerian records shown in Table 1 and indicates that in the past malaria was diagnosed in about 8% of hospitals in West Africa and 12% in East Africa. In out-patients the difference between the frequency of diagnosis of malaria in West and East Africa was much less pronounced and in both vast areas of the African continent the mean figure was about 10%.

The above data indicate only a trend of events and as such are of some interest. The need for more reliable and recent information of malaria morbidity and mortality in all age-groups of the indigenous population of tropical Africa is very great and it is hoped that they will be available before long.

9.5 Symptomatology and duration of malaria infection in tropical Africa

The importance of asymptomatic parasitaemia as a factor in the transmission of malaria in Africa was studied already at the beginning of this century by Koch, by Stephens & Christopher, and later by many authors quoted by Covell (1960).

It is generally agreed that among the indigenous populations of highly malarious countries asymptomatic or pauci-symptomatic parasitaemia is at times more common than the presence of parasites accompanied by symptoms, the proportion varying widely according to the degree of tolerance possessed by the community and the species of parasite involved. The density of parasitaemia and of gametocytaemia is, however, lower in the asymptomatic than in the symptomatic individuals.

In the group of mental patients investigated by us the febrile response associated with the presence of parasitaemia was slight; over one-half of the total group had a temperature below 98.9°F (37.2°C) although 11% of them had malaria parasites in the blood. Nearly 40% of our group had a temperature which might be regarded as sub-febrile in temperate countries and yet the frequency of parasitaemia in this group was almost the same as in the previously mentioned, namely 12%. On the other hand, parasitaemia was three times more frequent (35%) in those who had pyrexia over 100°F (37.8°C).
This finding confirms the results of many previous investigations in West Africa though only few of them referred to adults. The "pyrogenic limit" of asexual forms of *P. falciparum* set by Ross at some 600-1500 parasites per mm$^3$ varies considerably according to the immune status of the subject; this was stated by Ross & Thomson (1910) who pointed out that in two cases followed up by them as many as 1200-1600 parasites per mm$^3$ were found, as an average during four to six non-febrile days. Field (1948) showed that the fever threshold varies between 50 parasites per mm$^3$ in non-immunes to many thousands per mm$^3$ in those with high tolerance. All those who worked in West Africa are well acquainted with the situation when three-quarters of schoolchildren are found infected with malaria parasites and at least one-quarter with heavy parasitaemia between 3000 and 20 000 per mm$^3$ (Jonchère & Pfister, 1951).

Magill (1923) in Accra (Ghana) found 14% of children with temperatures of 100°F (38°C) and over when the parasite rate was 19%, while Macdonald (1926) in Freetown recorded one-third of children with pyrexia when the parasite rate was 41%, and over one-half of children sub-febrile, though their parasite rate was 72%.

Léger & Nogue (1923) carried out a parasitological and clinical study of malaria infection in Senegal and concluded that the 47% of African adults who are "parasite carriers" show few if any symptoms of infection. The relevant passage is as follows: "pour les fébriles ayant dépassé la vingtième année ce n’est qu’une douzaine de fois en 4 ans ... que nous pûmes porter de façon certaine le diagnostic d’accès palustre et vérifier la présence d’hématozoaires dans le sang." These authors estimate, nevertheless, that the majority of adult Africans have, over the year, an average of one or two attacks of malaria, usually brief and mild.

Wilson (1936) attempted to assess the relationship between pyrexia and malaria in Tanganyika but his results were inconclusive because of the "absence of a standard normal temperature for Africans and little likelihood that any information will be obtained by this method". Wilson (1939) and Schwetz (1944) emphasized the virtual absence of pyrexia in adults living in highly endemic areas of Africa, although clinical symptoms were much more common in incompletely immune adults from less endemic areas. Garnham (1949) in his study of malaria in Kenya reported the mild symptoms of parasitaemia in Luo children, of whom all were infected but only 40% showed febrile reaction.
Colbourne (1955) who investigated the relationship between malaria infection and body temperature in schoolchildren and in a group of adults in Accra (Ghana) found that the mean oral temperature in the 14-17 age-group was 99.0°F (37.7°C) and that of the adult group - 98.3°F (36.8°C). His results indicated the lack of obvious association between the body temperature and presence of parasites in children.

Oral temperatures of a large sample of "normal" adolescents and adults were recorded in the course of the Taveta-Pare Scheme in Tanganyika and showed that in the 15-19 age-group only over one-half had a temperature below 98.9°F (37.1°C); 36% had a temperature within the 99°-99.9°F (37.2°-37.7°C) range and 6% had a temperature of over 100°F (37.8°C). In the adult group some 70% had a temperature below 98.9°F (37.1°C); 28% had the temperature within the 99°-99.9°F (37.2°-37.7°C) range and 1% had the temperature over 100°F (37.8°C) (East African Institute, 1960). Cobban (1960) showed that pyrexia over 100°F (37.8°C) gave a significantly higher association with parasitaemia (66%) than the temperature below this figure (17.5% of positives). It appeared from this investigation that the temperature above 100°F (37.8°C) in the African adult may serve as an indication of a febrile reaction due to malaria as judged from a single blood film. Naturally, it does not follow that the presence of parasites in the blood is unlikely if the temperature of the subject is normal. As Cobban (1960) mentions "fever and parasitaemia may occur at one time and both might be absent at another".

The consideration of the proportion between the number of symptomatic and asymptomatic episodes of malaria infection is of special importance, since the symptom of "fever" is used for sampling in active and passive surveillance procedures.

Yekutiel (1960) and Covell (1960) summarized in their papers a number of findings in various parts of the world and mention will be made here only to some points particularly relevant to our present work.

The longitudinal study carried out by Earle et al. (1939) on children in a highly endemic area of Puerto Rico showed that the proportion of total person/days with parasitaemia to person/days with parasitaemia accompanied by clinical symptoms was approximately 9:1.
In our series the total number of "attacks" in 94 man/years was 44 giving an average of about one attack of malaria over two years. The proportion of days of asymptomatic to symptomatic malaria calculated in 723 episodes with positive slides was 16:1. This is a higher figure than that obtained by Miller (1958) in Liberia who in the course of a more frequent follow up of 20 African adults for one year found that the proportion of days of asymptomatic to symptomatic parasitaemia was 12:1. Of 20 adults 16 had one or more attacks of clinical malaria due to *P. falciparum* during the year; there were 32 malarial attacks in all, or approximately 1.5 per subject per year; each attack lasted an average of 6.5 days per person per year.

It is of interest that Colbourne (1955c) quoted a report from Ghana according to which in a group of 248 adolescents and adults each individual suffered about one attack of malaria every one to two years. Cobban (1960) who followed up for one year a group of young adults in Ibadan (Nigeria) estimated the frequency of pyrexial malaria episodes at approximately 0.1 per person per annum. This is over 10 times less than the frequency of 1.5 per person per annum recorded by Miller (1958) in Liberia.

With regard to the frequency and duration of these febrile episodes the differences between our results and those of Miller (1958) are also considerable; this is probably due to the different age composition of the two investigated groups and also to the greater frequency of observations possible in the conditions of the work carried out in Liberia.

Febrile episodes not associated with parasitaemia and observed as frequently (and often much more so) in adult Africans, were given by some authors a rather unfortunate name of "pseudo-malaria". It seems that this term presumes too much and one wonders if the unpopular but perfectly honest old term of PUO\(^1\) ("pyrexia of unknown origin") should not be re-introduced; this is particularly pertinent today when we know that a number of viral infections (e.g. Zika virus, Bwamba fever, etc.) are responsible for many obscure clinical illnesses accompanied or not by a fleeting, low-density parasitaemia.

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\(^1\) This term in a modified version has now apparently received a blessing of the Post Graduate Medical School, London, where at a clinico-pathological conference a "Case of Pyrexia of very uncertain Origin" was recently presented and discussed. (*Brit. Med. J.* 1962, 2, 1384)
In our series of observations the duration of untreated febrile episodes linked with the presence of malaria parasites in the blood was in the range 1-5 days with an average of 2.6 days, as compared with 4.2 days recorded by Miller (1958) in young Liberian adults. Cobban (1960) found that a number of pyrexial attacks subsided spontaneously in 24 hours but did not estimate their mean duration in his small sample.

Colbourne (1955b) reported from Ghana that the duration of a malaria attack in schoolchildren averaged 4.5 days and presumed that this period was shorter in adolescents. The latter author stresses rightly that any averaging of such figures is an arbitrary concept since even within an African community individuals react differently to malaria. It has often been said that the concept of "fever" is generally vague and depends on cultural background or on educational level. The relevance of this to the methods of case detection by auxiliary medical personnel or voluntary collaborators is obvious.\(^1\)

The discussion on symptomatology of malaria infection in tropical Africa cannot be separated from the consideration of the normal duration of malaria in Africans removed from the environment where the transmission is at a high level.

Reporting on the implications of the results of antimalaria projects in East Africa, Pringle, Draper & Clyde (1960) believe that three to four years' freedom from re-infection is sufficient to lower immunity in the Bantu to the level at which malaria infection is followed by a clinical episode. The authors also stress that in the case of renewed transmission, infants and adults are relatively insensitive indicators.

It might be pertinent to recall here that Walton (1949) reported from Freetown (Sierra Leone) an increased proportion of clinical symptoms of malaria in Africans after the institution of control measures and attributed it to the loss of immunity. On the other hand, Bruce-Chwatt et al. (1954) have not observed any increased sickness of the indigenous population of Ilaro in south-west Nigeria when a substantial degree of malaria transmission was resumed after three years of protection by residual spraying. The same observations were made by Bray (1962) who stated that two years' protection during the pilot project in Kpain (Liberia) did not seem to have much influence on the response to experimentally induced infection in subjects from that area.

\(^1\) In Southern Rhodesia slides for case detection are taken from individuals who answer in the affirmative the question: "Have you been sick since the last monthly visit?". There is no word for "fever" in the local language (Charles, pers. comm.)
Colbourne (1955a) attempted to find some data on malaria morbidity of African students returning to Ghana after several years' stay in the United Kingdom and concluded on the basis of a small sample, that they are more susceptible to malaria, but even then the disease is not severe. Some of the students showed a transient parasitaemia without symptoms suggesting that the immunity is largely retained.

Pringle (1962) carried out recently an important investigation based on 1600 cases in the Gonja area of South Pare with the aim of assessing the value of detection methods based on the examination of fever cases. Comparing the number of cases of malaria found using this criterion with the results of a mass blood survey Pringle considers that only 26% of all the parasite carriers would be discovered by active case detection.

This is a surprisingly high figure considering the findings in West Africa referred to above, but it should be stressed that Pringle's data were collected in an area of the former Taveta-Pare malaria control scheme which achieved a striking decrease of transmission, even though its complete interruption was not obtained. Two interesting observations were made recently by Mastbaum (1962) and by Goeckel (personal communication). The first concerns an area of Southern Rhodesia where transmission has been interrupted for at least two years and where a localized outbreak of malaria occurred through the introduction from an uncontrolled neighbouring territory. It was found that in this area among the Africans found with malaria parasites in the blood 70% had a history of fever while only 30% were asymptomatic.

The second refers to the situation in the Cameroun where after a successful pilot project which resulted in the interruption of transmission for three years an outbreak of malaria followed in 1961-1962 the temporary cessation of spraying. During this outbreak it was noted that about three-quarters of patients with positive slides were febrile and had a number of other typical symptoms of acute malaria, only exceptionally recorded before in the mission hospital which they attended.

These observations suggest that in a large proportion of the population the acquired immunity decreased sufficiently low during the non-transmission period to influence the symptomatology of what might be considered as reinfection.
There are still many gaps in our knowledge of this subject and intensive studies of it are difficult, especially in areas where transmission persists. Earle (1962) points out that in trying to determine the stage of infection, early or late, attention to two longitudinal observations were helpful: (a) the degree of parasitaemia, and (b) its constancy. Isolated low parasite counts - no treatment having been given - are most likely infections that occurred many months since the infective mosquito bite which gave rise to them. On the other hand, presence of parasite counts in the range of 5000 to 10 000 or more, per mm$^3$, especially if fever is present, indicates a new infection.

There is no need to stress the importance of better knowledge of the duration of survival of malaria parasites in man in numbers sufficient to infect mosquitoes and start a chain of secondary cases of introduced malaria focus. The subject has been reviewed by Covell (1960) who stated that the bulk of available evidence suggests that in the great majority of cases P. falciparum lasts for about a year, P. vivax for two years, while P. malariae may last considerably longer, perhaps for an indefinite period (Shute, 1960).

Ciucu et al. (1955) estimated that P. falciparum infections may persist for 27 months, P. vivax exceptionally for eight years and P. malariae for 10 years.

There are several reports on the long duration of induced infections with P. falciparum and in some cases parasitaemia was observed for as long as 480 or 503 days. An infective feed of Anopheles was obtained with low density of gametocytes after 320 and 410 days (Eyles & Young, 1951; Jeffery & Eyles, 1954). The duration of infection depends not only on the species of the parasite but also on the strain and perhaps even more on the immune status of the subject. Data obtained in experimental conditions of induced malaria in non-immunes cannot be interpreted as expected happenings in nature. Results of some eradication programmes indicate that the majority of P. vivax infections may die out already in the second year. On the other hand, it has been found that some P. falciparum infections persist longer than one or even two years.
The problem of longevity of naturally acquired malaria was recently discussed by Earle (1962) on the basis of his pioneering work in Panama some 25 years ago (Earle, Perez, del Rio & Arzola, 1939). The reassessment of the original data led to the conclusion that infections with *P. falciparum* might still be patent some 30 months after the original infection and possibly longer. It is of particular interest that these long-drawn-out, discrete infections were found mainly in Negroes.

The problem of "quiescent malaria parasites" in Africans residing in the United Kingdom was discussed by Shute (1960) and Walters (1960). The latter author described the presence of *P. falciparum* in a pregnant Nigerian young woman who resided in England for 19 months before the infection was discovered rather accidentally during a routine differential blood count in a hospital.

Sirivorasarn (1958) investigated in London 252 students from West Africa who have resided in England between six months and three years and found three of them carriers of scanty *P. falciparum*.

The importance of such cases for blood transfusion is self-evident in countries where the numbers of visitors from tropical Africa is great, and fuller investigation of this problem is being stimulated by WHO in the United Kingdom and in South Africa. In the latter country an investigation on the duration of the natural infection with *P. falciparum* in adult African mine-workers transferred to malaria-free conditions has been set up recently, and the preliminary results indicate that the parasite rate in the group decreased from 10% to about 6.5% after 1-1/2 years and then fell to nil after a period of approximately two years. The numbers in the investigated group are still too small to warrant any conclusions, however (WHO, 1962).

The relationship of relapses of latent *P. falciparum* infections to environmental conditions or other stimuli is of evident interest. The negative results of our attempts to influence the trend of parasitaemia through the use of various physical and other stresses were not entirely unexpected. The failure of adrenaline injection to make any significant difference to the parasite came as a mild surprise, since one might have expected that the contraction of the spleen and subsequent expulsion into the circulation of temporarily stored erythrocytes would increase the number of parasitized cells in the blood (Hughes & Shrivastava, 1930).
The failure of the electro-convulsion therapy to make any difference in the parasitaemia of a substantial sample of the investigated psychiatric patients confirmed the impression that the immune status of adult Africans is not easily upset by such coarse stimuli. This was recently confirmed by Bray & Voller (1962) in Liberia, who found that traumatic events such as surgical interference, TAB inoculation, artificial pyrexia or blood loss do not automatically cause rise in parasitaemia and clinical episodes.

This difficulty of eliciting a parasite response in adult West Africans already infected with malaria is in contrast to the often described "relapses" of malaria in non-immunes due to the influence of various sympathicotrophic drugs, pyretotherapy, physical traumata, et al., noted in profusion by Muhlen (1942). The influence of these various factors on relapses of malaria in German wounded soldiers was observed by Wozenig (1947). Little work on this aspect of relapsing malaria in African races was done, but Russell (personal communication) investigated some 20 years ago a Negro family in the United States of America for one year. During that time the mother had two attacks and the father one attack; there was a low-level asymptomatic parasitaemia for several weeks, followed, after a physical stress and cold, by a sudden increase of parasites and pronounced clinical symptoms.

This is in striking contrast to our own observations and those of Bray (1962) in West Africa and it appears that any apparent host-parasite equilibrium seen in subjects with a high degree of acquired immunity is much less influenced by non-specific physical stresses.

In concluding, one might say that in areas with a high degree of transmission the presence of "fever" alone is an unreliable guide to the presumed diagnosis of malaria infection. Parasitaemia without pyrexia (whether perceptible to the subject himself or to an investigator armed with a thermometer) is very common in the indigenous adult population of tropical Africa; nevertheless the chance of finding malaria parasites in the blood of subjects with fever over 100°F is probably twice to four times greater than in non-febrile individuals. This alone indicates that malaria attacks may occur in a supposedly immune population.
The duration of natural *P. falciparum* infections in Africans is not well known and more extended observations are necessary before any conclusions can be drawn.

It is important to know if new infections can be identified or an estimate made of time since infection took place. In the absence of the probable date of infection, adequate epidemiological investigation cannot be made to determine the source of infection or the factors which led to a breakdown in eradication procedures. Of equal importance is knowledge of the length of time untreated infections may last of sufficient intensity to be identified by the usual examination of the blood. There is some evidence that the course of infection with this parasite shows a relatively long period of gradually decreasing parasitaemia followed by irregular intermittent parasitaemia. With regard to the quartan infections, it is possible that, in an endemic area where the disease is acquired very early in life in a high proportion of the population, the infection remains discrete or asymptomatic for most of the normal life of the individual.

9.6 Some problems of host-parasite relationship in highly endemic areas of West Africa

It is not intended to discuss here the numerous aspects of the natural history of malaria in indigenous communities living permanently under highly endemic conditions. This fascinating problem has now a very large bibliography (Christophers, 1924; Schuffner et al., 1932; Sinton, 1937, 1939; Hackett, 1941; Pampana, 1944; Boyd, 1959; Taliaferro, 1949; Wilson, Garnham & Swellengrebel, 1950; Sergent, 1956, 1959; Macdonald, 1951, 1957, and others). Some specific aspects of the natural course of malaria infection in tropical Africa were dealt with more recently by Bruce-Chwatt (1956, 1961), by Wilson (1958), Colbourne (1959), McGregor et al. (1956), McGregor (1960), Macdonald (1951, 1956, 1961), by Gilles (1961) and by Boye (1962). Attention should also be drawn to the three conferences on malaria in tropical Africa organized during the past decade by the World Health Organization (WHO, 1951, 1956 and 1962).

The general consensus of opinion concerning the natural history of malaria in tropical Africa is that when in attempting to outline the type of endemicity present in a community one should take into account both the collective response of the population and the circumstances of malaria transmission. There is much greater
variation of the type of the group immunity to malaria on the eastern side of the African continent than in the west. Epidemic malaria may be found in Africans wherever the transmission season is very brief either because of the altitude or arid climate.

When it comes to endemic malaria its degree depends largely on the duration of the transmission season. Wherever this period is relatively short, endemic malaria is more or less seasonal with a pronounced wave at the end of the rains. It would be a mistake, however, to estimate the type of endemic malaria solely on the basis of climatological data. There are in central equatorial Africa large areas with a short rainy season which have all the characteristics of relatively stable malaria because of the maintenance of a sufficient amount of transmission over most of the year by the same or an alternative vector.

The most characteristic type of endemcity in tropical Africa especially in the west, is represented by holo-endemic malaria (WHO, 1951); it depends on a very high rate of transmission and in these areas the resulting collective immunity of the population is very pronounced.

The causes of such differences in endemcity are due mainly, but not only to, variations of climate and topography: human ecology plays here an equally important part and factors such as type of housing, distance from vector breeding areas, occupation, animal husbandry, should not be forgotten. The question of genetic factors in the sense often stressed by Schuffner (1938) has not been sufficiently investigated but it is conceivable that some biological selection acting over the course of many centuries produced its effect.

The course of natural infection with malaria in West Africa is now better understood and McGregor (1960) classified it into five successive stages starting from birth. Bruce-Chwatt (1956) suggested that there may be yet another stage - a pre-natal one due to the passage of maternal protective substances to the foetus with a consequent proliferation of the foetal spleen which in African new-born is relatively half as heavy as in non-African babies.¹

¹ This hypothesis has not been proved but the isolation of specific protective fractions of gamma-globulin present in immune Africans should be able to produce some experimental evidence in suitable animals.
It is agreed that in infants the initial infection occurs usually during the first three to six months, but the clinical symptoms are often surprisingly mild. This protective mechanism is still not fully elucidated, but the work in Gambia during the period 1955-1960 kept pointing out that the high level of gamma-globullnaemia in West Africans was related to their immune status and relative protection from malaria. The recent discovery by Gilles & McGregor (1960) and by Cohen, McGregor & Carrington (1961) that the mechanism of acquired malaria immunity is partly dependent on the presence in the blood of protective antibodies associated with 7S gamma-globulin goes a long way towards the explanation of many problems. It also confirms spectacularly the hitherto circumstantial evidence of the displacental transmission of humoral antibodies from the immune mother (Bruce-Chwatt, 1961). Confirmation of the pronounced antiparasitic effect of West African adult and cord blood gamma-globulin has now been reported by Edozien, Gilles & Udeozo (1962). Moreover, the reality of the transfer of maternal immunity to the new-born was provided by Bray & Voller (1962) using the fluorescent antibody technique.¹

Although the first malaria infections may not cause any severe clinical symptoms in a proportion of African infants, nevertheless these episodes are a hazard to health because of nutritional disturbances, subsequent anaemia, or concomitant diseases.

In the early childhood the severity of the infection is far greater and malaria is nearly always a direct danger to life. During the middle and late childhood the previous infections confer some immunity and the frequency and severity of clinical symptoms decreases, although in areas of relatively low-level transmission the gradual acquisition of immunity is delayed.

Finally, in the adolescent and adult living in holo-endemic areas, malaria infection achieves a considerable degree of stability, the primary feature of which is a regular and potent stimulation of immunity through the subsequent repeated infections

¹ Many problems concerning the present and future trends of immunological research in malaria were outlined and discussed at the "Symposium on the Immunity to Protozoa" (Garnham, 1961). The proceedings of this symposium organized by the British Society for Immunology in June 1961 are now in print.
In the adult population this is characterized by the apparent absence of enlarged spleens, low parasite rate with a predominance of *P. falciparum*, very low parasite density and, last but not least, rarity of clinical symptoms of malaria and their mildness if an overt attack of malaria occurs. Two aspects of such high degree of immunity are often quoted: the "antiparasitic effect" as a result of which parasitaemia is at a low level, and the "antitoxic effect" or quasi-suppression of clinical symptoms.\(^1\) Macdonald (1956) stressed the third effect - of far greater importance to the community - namely the restriction of gametocyte output, manifest first as a reduced gametocyte count and later as a reduced gametocyte rate.

In spite of Swellengrebel's (1950) insistence on the compensating aspects of such host-parasite relationship, it is questionable if an equilibrium eventually achieved by the African adult (at a high price for the community!) is so perfect that it amounts to commensalism. Wherever malaria eradication projects were carried out in African tropics and even if they did not achieve the interruption of transmission, the decrease of the morbidity of the population as a whole was striking. In Pare-Taveta the reduction of malaria transmission was accompanied by a substantial rise of mean haemoglobin levels in all age-groups (Draper, 1960).

The present investigation, while confirming all the fundamental conclusions of epidemiology of holo-endemic malaria as seen in West Africa, seems to have added two points. First of all it showed the complicated pattern of a prolonged, low-degree infection with *P. falciparum* which maintains the level of immunity already achieved by the immune African adult. It seems probable that nearly every individual carries malaria parasites for the greater part of the year and possibly every adult is nearly constantly in a state of parasitaemia which is frequently at the threshold of patenty.

\(^1\) In his Liberian study, Miller (1958) underlined the differences between the "antiparasitic" and "antitoxic" effects of immunity and stated that the first is more evident in the adult, while the second is commoner in children. This opinion could be accepted only if it meant that high parasitaemia in children is relatively less symptomatic than the low parasitaemia of adults; but the conclusion that the high degree of "antiparasitic resistance" of adults is achieved at the cost of a lower "detoxifying resistance" might be arguable.
The finding of high parasite incidence in immune adults may explain the conclusions of a previous investigation of spleen weights carried out in Nigeria by Bruce-Chwatt (1956). This biometric study showed that the virtual absence of enlarged spleens in adult Nigerians is a myth, due to physical difficulties of palpation of the moderately enlarged organ in adults and not to the fact that it has reverted to its "normal" size. The weight (and volume) of the spleen recorded in 2540 adult Nigerians during autopsies was 1-1/2 to 2 times greater than the "normal" spleen of Caucasians or American negroes. This means that the maintenance of the constantly high level of immunity in adult Africans is associated with a more or less permanent state of proliferation of the organ which constitutes the largest collection of lymphoid-macrophage tissue in the human body.

The present investigation seems to have provided evidence of the possibility of superinfections with (probably!) a heterologous strain of P. falciparum; possible consequences of this are a temporary spurt of gametocyte production and subsequent boosting of immunity, which in turn puts a brake on the gametocyte output.

It is likely that in spite of such more or less frequent happenings, the generally low gametocytaemia of the adult population is of little importance for the maintenance of transmission (Macdonald, 1956). Nevertheless, the problem of the adult population in highly endemic areas maintaining for some time a low level of transmission is of importance in malaria eradication especially in a later stage when the collective immunity of the population falls to a lower level. This point deserves greater attention; some facets of it could be investigated experimentally, others require an epidemiological approach. The problem of relationship of superinfection to the state of premunition is too vast and too involved to be discussed here, especially as it has important theoretical implications. Sergent (1959) states that premunition does not necessarily result in an absolute protection; "la résistance conferée ... peut être seulement partielle" and yet according to this author (Sergent, 1961) superinfection with the same species of the parasite is unlikely. Moshkovsky (1948), while admitting that premunition has very distinct aspects from true residual immunity, challenges the doctrine of their essential difference and believes that the possibility of reinfection and superinfection depends on the secondary immunological status of the organism of the vertebrate host in response to the first infection.
The problem of frequency measurement of "remittent and intermittent disease" has been recently discussed by Cobb (1962) who stressed the inadequacy of the "point prevalence" estimation and the value of assessing frequency distribution of persons according to the proportion of time spent in the disease episode. The method proposed by Cobb is not directly applicable to longitudinal malarialmetrical surveys, but the characteristics of malaria infection in a large proportion of the immune populations in Africa are so different from the simple phenomenon of absence or presence of a disease that new concepts for epidemiological study of pauci-symptomatic malaria should be developed.

There is increasing evidence that the normal single, cross-section malarialmetric survey gives about as much information of the natural history of malaria in tropical Africa as a few "frames" taken out at random from a reel of film. Seeing the isolated piece of such a film one can recognize the actors, situate the environment and judge the standard of photography, but it is impossible to get an idea of the story that the projected, moving film would tell. For the full understanding of the dynamics of malaria infection in Africa new epidemiological methods of investigation must be developed and longitudinal surveys are only one of them. Recent advances in the field of immunology such as the fluorescent antibody staining, gel precipitation, immuno-electrophoresis, haemagglutination tests and others, offer a wide variety of new laboratory techniques suitable for this purpose. The challenge of this new field of research is great and its success will bring us closer to the aim of malaria eradication in Africa.
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