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Latent Infections with *Plasmodium ovale* Malaria

MAX J. MILLER, M.D., Ph.D., DAVID M. MARCUS, M.D., F.R.C.P.[C]
and DOUGLAS G. CAMERON, M.D., F.R.C.P.[C], *Montreal*

ABSTRACT

Two cases of *Plasmodium ovale* malaria acquired in West Africa appeared as primary delayed attacks after one year's continuous residence in Canada. Both patients took full prophylactic doses of chloroquine before, during, and for several weeks after exposure. The inadequacy of the 4-amino-quinolines for protection against latent benign tertian malaria is noted, and the use of primaquine is recommended. Paroxysms occurred in the evening and were accompanied by severe muscle pain, features considered typical of *ovale* malaria. One patient showed electrocardiographic changes and clinical signs of cardiac malfunction; these disappeared following specific treatment for malaria. In this age of accelerated travel and international movements of people it is important that physicians in temperate regions be aware of the exotic infections of the tropics, as well as of the need for protective measures for travellers to areas where these diseases are endemic.

SOMMAIRE

Deux cas de malaria dus au *Plasmodium ovale*, contractés en Afrique occidentale, se sont manifestés comme une infection primaire retardée, après une année de séjour au Canada. Les deux malades avaient pris les doses prophylactiques recommandées, avant, pendant et pendant plusieurs semaines après le contact avec les anophèles. On a noté l'insuffisance d'action protectrice des 4-amino-quinolines contre la fièvre tierce bénigne et latent et on a recommandé l'emploi de primaquine. Les accès survenaient le soir et s'accompagnaient de vives douleurs musculaires, symptôme que l'on considère comme typique de la malaria à *Plasmodium ovale*. Un des malades présentait des modifications de tracé de l'ECG et des signes cliniques d'un dysfonctionnement cardiaque. Ces signes ont disparu après application du traitement spécifique anti-malarien. En notre ère de voyages ultra-rapides et de vastes déplacements internationaux, il importe que les médecins pratiquant dans des régions tempérées soient au courant des infections exotiques en provenance des régions tropicales, ainsi que des mesures protectrices à prendre à l'égard des voyageurs se rendant dans des pays où ces maladies sont endémiques.

INCREASED international travel must inevitably result in the more frequent appearance in temperate regions of the so-called exotic infections of the tropics. Two cases of *Plasmodium ovale* malaria which occurred recently in Montreal as delayed primary attacks bear witness of this. *P. ovale* malaria is not as well known as the more common benign tertian species, *P. vivax*. For this reason and because information on the latent phase of *P. ovale* infections is meagre, these cases are reported here in some detail.

From the Department of Medicine, Montreal General Hospital, and the Institute of Parasitology, McGill University, Macdonald College P.O., Que.

The two patients, while members of an "Operations Crossroads Africa" party, spent approximately two months of the summer of 1963 in Guinea, West Africa. They arrived in Conakry on June 25 and the following day travelled inland some 150 miles to Mamou, where they remained until their departure on August 24. On the return trip they spent one week in Dakar, Senegal, arriving back in Canada on September 1, 1963.

Both patients had taken weekly prophylactic doses of chloroquine phosphate (300 mg. base weekly) regularly for four weeks before leaving Canada. While in Africa they each took 75 mg. daily (525 mg. base weekly) of the same drug. Upon her return to Canada one patient (B.J.M.) continued the chemoprophylaxis for a further six weeks. She took 75 mg. daily for two weeks and then two 150-mg. doses weekly for an additional four weeks. The second patient (J.T.C.) continued to take 75 mg. daily for three weeks after his return. While in Africa they slept under mosquito nets but admitted to finding an occasional mosquito inside the net. Until the appearance of the attacks described here neither patient recalled symptoms of illness suggestive of classical malaria. B.J.M., however, developed infectious hepatitis four days after reaching Canada and J.T.C. has had recurring bouts of diarrhea and dysentery of gradually decreasing severity since his return.

CLINICAL DATA

CASE 1.—B.J.M., a 21-year-old female college student, noted that towards the end of June 1964 she experienced fatigue and continuously felt "tired and draggy". She did not improve and on July 4 in the evening developed generalized muscle pains which were particularly marked in the legs, the small of the back, between the shoulder blades, and the back of the neck. While she felt better the following morning (July 5), towards evening the muscle pains returned with headache characterized by a feeling of pressure at the base of the skull; she then developed a shaking chill (rigor) which after some time gave way to a hot and feverish period. After several hours the temperature dropped abruptly, with copious perspiration. The entire episode (paroxysm) lasted from 5 p.m. until 11.00 p.m. She slept well and there was no recurrence the following day. On July 7, the paroxysm recurred in the evening with rigor, fever and sweating,

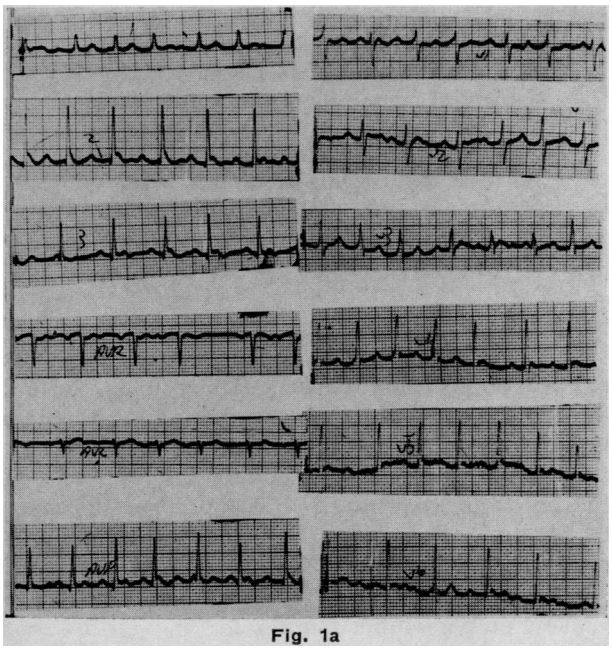


Fig. 1a

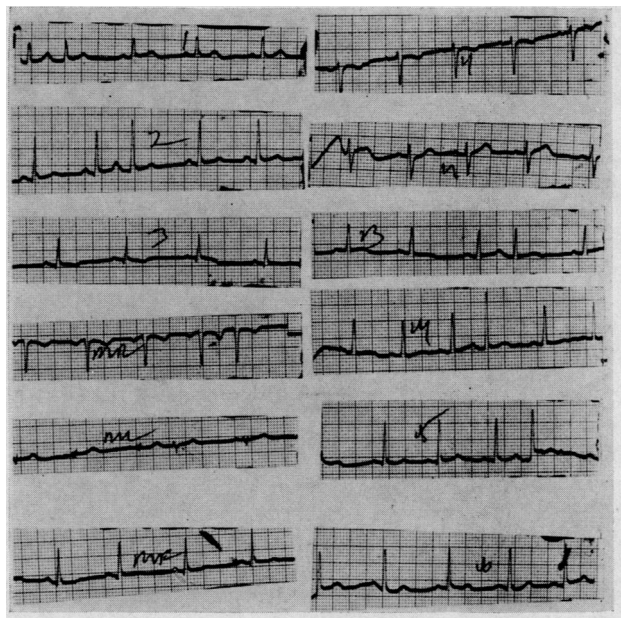


Fig. 1b

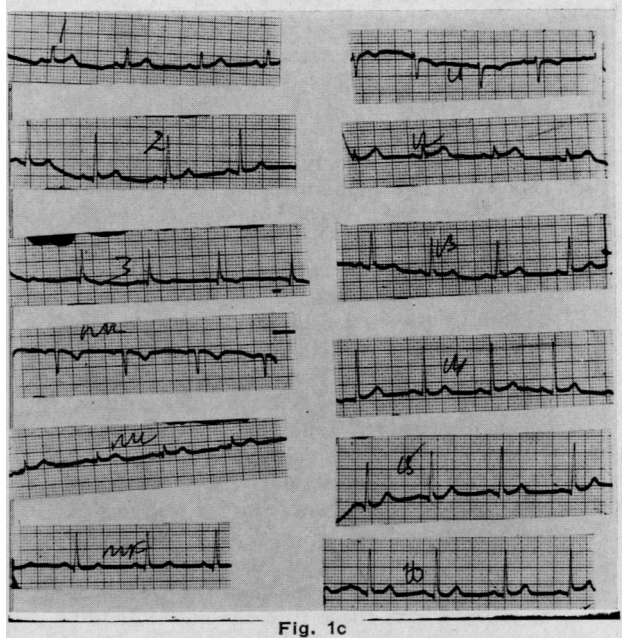


Fig. 1c

Fig. 1.—Electrocardiographic tracings in a patient with *P. ovale* malaria infection. (a) Pre-treatment tracing on July 12, taken during a paroxysm, showing sinus tachycardia (ventricular rate between 80 and 110/min.) with multiple premature atrial contractions some of which are blocked. (b) Pre-treatment tracing on July 13, showing normal ventricular rate (70/min.) but frequent premature atrial beats. (c) Post-treatment tracing of July 17, with no abnormalities.

in that order. The temperature reached 105° F., and there was nausea and vomiting. Thereafter the paroxysms returned regularly every second day, that is, on July 9, 11 and 13; the last paroxysm coincided with the start of specific chemotherapy.

Pertinent physical findings included a moderate pallor and a palpable, non-tender spleen. The liver was neither enlarged nor tender. During the initial period of hospitalization and before specific therapy was started, the patient showed rapid heart rate with intermittent gross cardiac irregularity, particularly marked during fever periods; on the basis of electro-

cardiographic (ECG) findings this was diagnosed as sinus tachycardia with multiple premature atrial contractions some of which were blocked (Fig. 1a, b and c). There was also a short, soft apical systolic murmur and at this time a diagnosis of bacterial endocarditis was considered.

Clinical pathology.—Laboratory findings of interest were confined to the blood. Blood smears showed the presence of malaria parasites which could be identified specifically as *P. ovale*. The hemoglobin value was 11.6 g. % on July 13, the day of the final paroxysm. For the next seven days the hemoglobin level continued to drop, reaching a low of 9.5 g. % on July 20. It then started to recover, and when the patient was discharged on July 29 the hemoglobin level had risen to 11.6 g. %. The white blood cell count (WBC) on July 13 was 6550/c.mm.; the differential count showed 59% polymorphonuclear leukocytes, 29% lymphocytes and 12% monocytes. Serum proteins on July 13 showed a total of 6.5 g./100 ml., with an albumin of 3.1 g. and globulin 3.4 g.

Treatment.—Chloroquine phosphate (Aralen) was administered. On July 13 the patient received 600 mg. base stat by mouth; six hours later 300 mg. base was given and this dosage was repeated daily on each of the next two days. On July 13 the patient was also started on primaquine and received 15 mg. of this drug daily for 14 consecutive days. The response to treatment was excellent.

CASE 2.—J.T.C. was a 25-year-old male college instructor. On July 7, following a strenuous game of handball, he developed unusual fatigue and for the next three days lacked the energy for even minimal effort. On the evening of July 10, he developed severe muscular pains in the legs, back and neck, and his head "felt as if it was bursting". This was followed by a shaking chill, then high fever and, finally, copious sweating—"soaked four T-shirts". This paroxysm was repeated on the evenings of July 11, 12 and 13, the one on the 13th being most severe and accompanied by nausea and vomiting. There was no paroxysm on July 14 but it recurred on July 15 and thereafter with great regularity every second day, that is, July 17, 19 and 21 (Fig. 2). Specific therapy was started on July 21.

Physical findings with the exception of a non-tender palpable spleen were essentially negative.

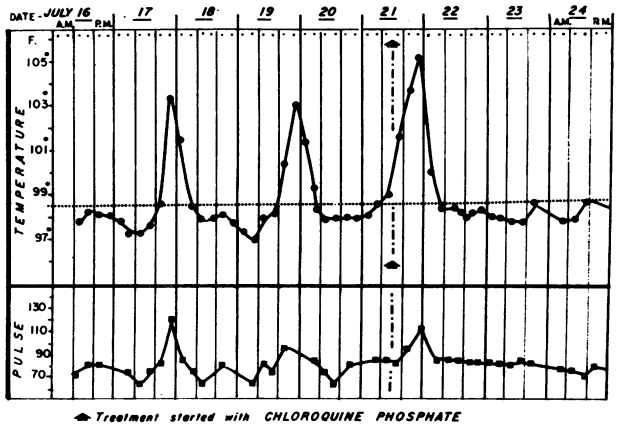


Fig. 2.—Temperature chart of patient J.T.C. (Case 2) infected with *P. ovale* malaria.

Clinical pathology.—The blood was positive for *P. ovale* parasites. The hemoglobin value on admission (July 17) was 15.0 g. %, and on July 22, 14.0 g. %. White blood cell counts on July 17 showed a total of 7800/c.mm., with 58% neutrophils, 36% lymphocytes, 1% monocytes and 5% eosinophils. The serum proteins were within normal limits.

Treatment.—Treatment was started on July 21. Chloroquine phosphate was given, 600 mg. base stat, 300 mg. in six hours, and 300 mg. on each of the next two days. Primaquine was also administered in daily doses of 15 mg. for 14 consecutive days. The clinical response to treatment was excellent, and a careful search of the blood on July 23 showed only a rare degenerate parasite.

DISCUSSION

Clinically, both of the foregoing cases were good examples of classical benign tertian malaria characterized by regularly recurring intermittent bouts of fever with a typical sequence of chills, marked fever and abrupt defervescence with drenching sweats. In both cases the paroxysms started in the late afternoon, and according to other workers[1-3] this is characteristic of *P. ovale* infections in contrast to those caused by *P. vivax*, in which paroxysms usually start before or at midday.

Our patients showed premonitory stages which were marked by severe lassitude and a feeling of great fatigue, lasting four days in one case and 10 days in the other. Of the symptoms ushering in the paroxysms in our cases pressure-type headaches and severe muscular pains were the most striking. The former is characteristic of all species of malaria, while severe muscle pain, particularly in the lumbar region, is considered to be most characteristic of *P. ovale* infection.[1,3] Before the establishment of the typical tertian fever pattern our patients showed a daily fever rise for two and five days, respectively. This is not unusual in primary attacks in which, for a variable but usually short period of time, there is an initial irregular or quotidian (daily) fever cycle. This may be confusing to the clinician but emphasizes the fact that any fever in a patient with a history of travel in endemic malaria areas should arouse the suspicion of malaria. Hale and Halpenny[4] reported that cases of atypical malaria fever in Canadians returning from abroad were initially diagnosed as pneumonia, acute tonsillitis, infectious mononucleosis, and infectious hepatitis. It is of interest to note that in one of our patients (Case 1) the fever associated with signs of cardiac malfunction suggested a diagnosis of bacterial endocarditis.

The abnormal heart signs found in Case 1 present an interesting problem. While one cannot be certain, there does appear to be a causal relationship between the malarial infection and the occurrence of signs indicative of heart malfunction. Following effective treatment and the disappearance of the parasites, heart sounds and ECG tracings returned to normal. Repeated later

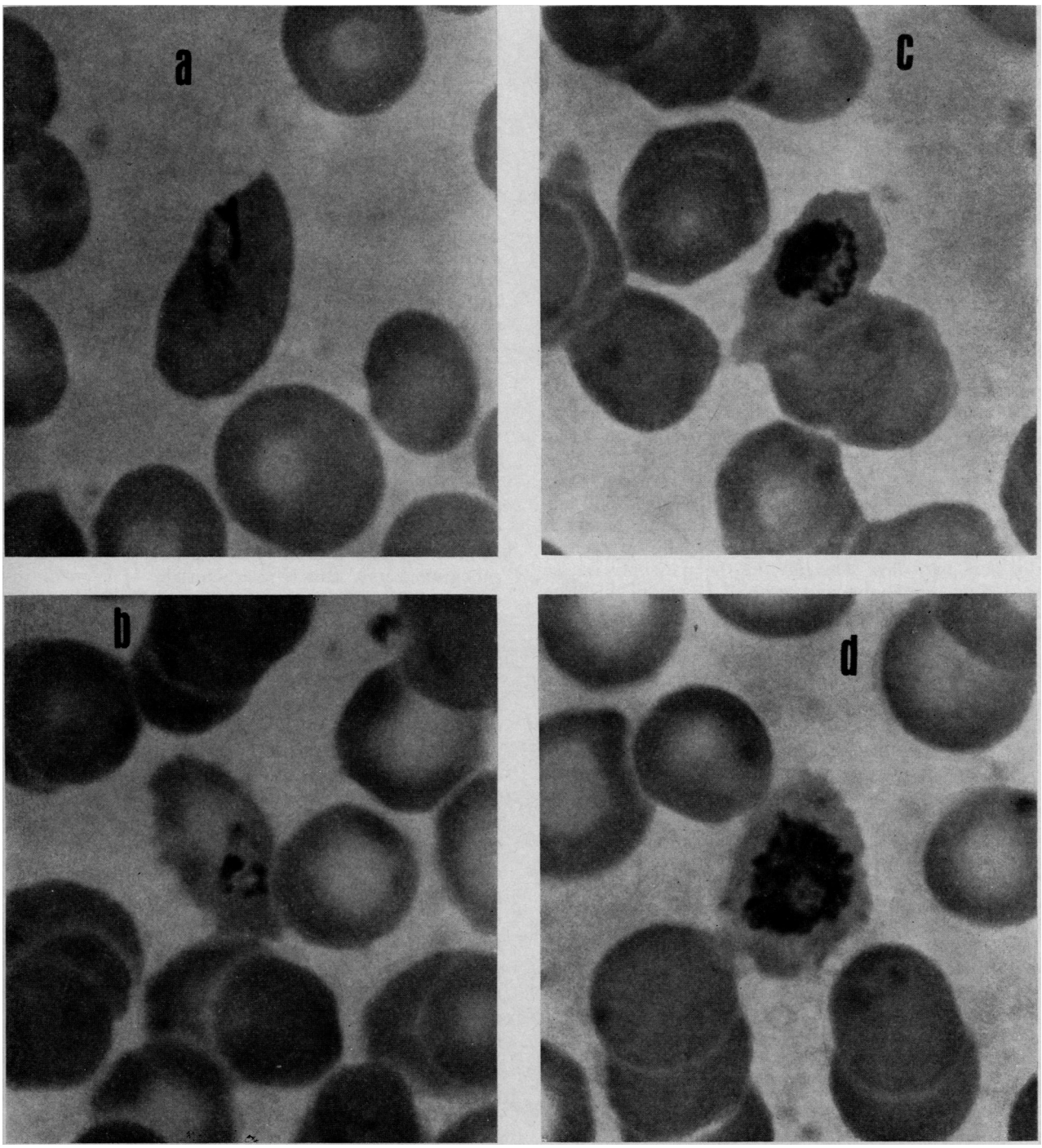
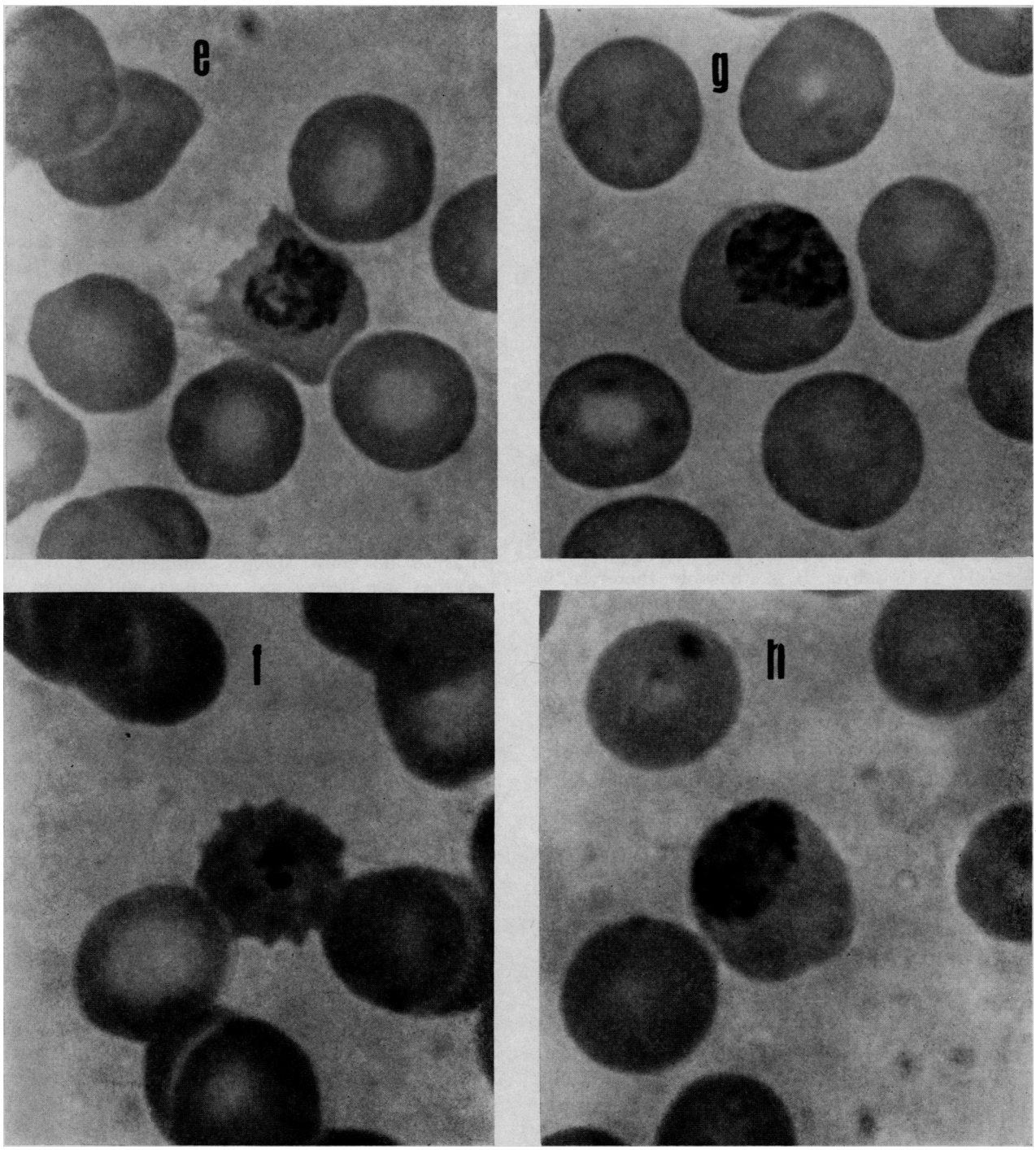


Fig. 3.—*P. ovale* malaria parasites. (a) Ring-stage in oval erythrocyte with faint stippling (Schüffner's granules). (b) Ring-stage in oval erythrocyte with crenated edges. (c) Late trophozoite in oval cell with irregular margins. (d and e) Two-nucleated schizonts in cells with distorted outlines showing slight enlargement and decolourization.

examinations have never shown tachycardia, arrhythmias, or murmur. To our knowledge, infections with benign tertian species of malaria have not heretofore been associated with cardiac malfunction. It may be that the signs of abnormal heart function in our patient were an unusual expression of the toxic reaction in malaria.

Although *P. ovale* is considered by some observers to be of minor clinical importance, the paroxysms in our cases were accompanied by severe myalgia, headache, nausea and vomiting, with temperatures reaching 105° F. Paroxysms of marked severity were also reported by Garnham *et al.*,[5] and it would appear that *P. ovale* infection may be potentially as clinically severe as that caused by *P. vivax*.

Delayed primary attacks and relapses are well known in *P. vivax* malaria and have been studied extensively in military personnel returning from theatres of war in the South Pacific and Korea.[4, 6, 7] Information in this regard on *P. ovale* is sparse, but there is accumulating evidence that it too may



(f) Ring-stage in cell with crenated margins. (g) Late trophozoite in non-distorted cell showing slight enlargement but no decolourization. The parasite is relatively small and compact. (h) Two-nucleated schizont in cell showing slight enlargement and decolourization. The parasite is dense and compact and the large nuclei can be readily seen.

persist as a latent infection for extended periods of time.[1] Trager and Most[8] reported two patients who developed primary attacks some two and four years, respectively, after exposure to infection. Our two patients developed delayed primary attacks approximately one year after exposure. Garnham *et al.*,[5] from a study of two patients, each of whom relapsed twice following the primary attack, concluded that relapses in this species occur at intervals of approximately 100 days. On the other hand, according to Jeffery, Young and Wilcox,[9] the Donaldson strain was isolated during the third relapse from an infection acquired four years earlier.

At present, inadequate information is available to establish a latency pattern for *P. ovale*. It is of interest to note, however, that both of our patients developed delayed primary attacks about one year after exposure. It may be a coincidence that the latency period in these two cases was identical; on the other hand, it could mean that a latency period of one year is an intrinsic feature of the

life cycle of this strain of *P. ovale* malaria. The fact that the delayed attacks occurred during the summer months, as is usual with temperate zone strains of *P. vivax*,[7] cannot be considered a factor in our cases, in which we are dealing with strains from equatorial Africa.

The discovery of an exo-erythrocytic cycle in the liver parenchyma cells of the human host for malaria[10] provided a mechanism to explain the phenomenon of latency. It is postulated that persisting exo-erythrocytic parasites in the liver of the host initiate delayed primary attacks and relapses. Evidence exists of the persistence of an exo-erythrocytic cycle in *P. ovale*.[11] The antimalarials in general use for clinical cure or prophylaxis are ineffective against the exo-erythrocytic stages of malaria.* The 8-amino quinoline compounds, on the other hand, do act on the exo-erythrocytic stages. Primaquine is the least toxic agent of this group and has been demonstrated to be effective in eliminating or greatly reducing the risk of latency in *P. vivax* infections.[12, 13] The exo-erythrocytic stages of *P. ovale* are probably equally responsive to this drug. It is advisable, therefore, to administer a full course of primaquine to all travellers leaving regions of active malaria transmission. The histories of our two patients clearly demonstrate that meticulous adherence to an antimalarial chemoprophylactic regimen with the 4-amino quinolines (chloroquine, amodiaquine, etc.) while exposed to malaria neither prevents parasitic invasion nor obviates the danger of delayed clinical attacks of *P. ovale* malaria.

A survey of reported cases of *P. ovale* infection shows that this species is relatively common in West Africa. The studies of Bray[14, 15] indicate that *P. ovale* not only is common in this region but probably replaces *P. vivax* as the prevailing species causing benign tertian malaria: a benign tertian malaria infection in a patient returning from West Africa is most likely to be caused by *P. ovale*.

P. ovale infections are frequently misdiagnosed as *P. vivax* malaria. Clinically they are very similar, and specific diagnosis depends upon identifying the parasites in blood smears. It is appropriate, therefore, to discuss briefly the criteria for identification of *P. ovale* parasites. Probably the single most useful specific character is the distorted outline of erythrocytes parasitized by *P. ovale*.† The oval distortion responsible for the specific designation, *P. ovale*, when seen, is of great diagnostic assistance. The percentage of cells which show oval distortion is variable, but generally a careful search will reveal their presence. In our material moderate numbers of oval host erythrocytes were seen (Fig. 3a, b, c). Of more frequent occurrence is an irregular distortion of the parasitized red blood cell. Those with older parasites assume bizarre outlines (Fig. 3d, e), while cells with ring-stage parasites often show a generalized crenation (Fig. 3f). In our two cases the percentage of parasitized cells showing distortion was 84% and 70%, respectively. *P. vivax* parasites characteristically do not cause a distortion of the host erythrocyte.

Stippling of the infected cells occurs in both *P. vivax* and *P. ovale* infections, but its presence depends on the staining procedure. The more advanced parasite stages cause enlargement and decolourization of the invaded red blood cell. In primary *P. ovale* infections these changes are not notable (Fig. 3g, h), in contrast to the marked enlargement and decolourization which occurs with *P. vivax* infections. While ring-stage parasites of the two species cannot be differentiated, the older parasites do show specific differences. *P. ovale* parasites are dense and compact and occupy a small volume in the host red blood cell (Fig. 3c, g, h). Furthermore, the nuclei in *P. ovale* are relatively large, being about twice the size of those seen in *P. vivax* (Fig. 3h). Finally, if mature schizonts are present in the blood the number of nuclei present will help to differentiate the two species. *P. ovale* schizonts usually show eight nuclei or less,* while those of *P. vivax* show more than 12.

It is again emphasized that the two patients discussed in this report returned from their visit to the tropics not only with malaria but in one case with infectious hepatitis and in the other with chronic diarrhea. These young people and others like them, visiting undeveloped areas in the tropics, find themselves placed in strange and often primitive environments where they are exposed to a broad spectrum of infectious agents. It behooves those responsible for their health on these sojourns to assure that all possible prophylactic measures have been taken to prevent those diseases which are preventable and to provide adequate advice and instruction on how best to minimize the possibility of acquiring others.

Case J.T.C. is presented through the courtesy of Dr. D. Reilly.

ADDENDUM

After submission of this paper it was learned through a personal communication from Dr. L. J. Bruce-Chwatt of the World Health Organization, Geneva, that 10 cases of *P. ovale* malaria were recently diagnosed in Moscow, U.S.S.R., and one case in Sydney, Australia. All infections were acquired in West Africa and are presumed to be delayed primary attacks or relapses.

*This is not strictly accurate, as both the diguanides (Paludrine) and pyrimethamine (Daraprim) are active against the exo-erythrocytic stages. Unfortunately, resistance to these drugs has been developed by some strains of all species of malaria of man.

†This is not the case when thin smears are prepared in regions of high atmospheric relative humidity such as are found in the wet tropics. It has been shown that the degree of distortion is positively correlated with the rapidity of drying of the thin smear.[15]

*In relapse cases of *P. ovale* the schizonts may have up to 16 nuclei. Also the degree of enlargement and decolourization of infected cells is greater and may approach that seen in *P. vivax*.

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Smallpox Control in Canada

E. W. R. BEST, M.D., D.P.H.* and J. W. DAVIES, M.B., B.S., D.P.H.,†
Ottawa, Ont.

ABSTRACT

During the period 1961 to 1963 there were 10 separate importations of smallpox cases by aircraft into England and Wales, Germany, Sweden, Poland and Canada. A feature of the resulting outbreaks was the number of cases and deaths of physicians and other health personnel. With the increasing volume of international air traffic there is a risk of importing incubating cases of smallpox into Canada, as occurred in 1962. Millions of Canadians have been protected against smallpox. Some complications of smallpox vaccination have occurred in Canada; such complications can be minimized by proper attention to contraindications to vaccination. The Food and Drug Directorate, Department of National Health and Welfare, has circularized all physicians in Canada to request their co-operation in reporting adverse reactions to drugs. This includes serious, unusual or unsuspected reactions to immunizing agents (vaccines, toxoids and antitoxins). The latter information will be shared with the Epidemiology Division, Department of National Health and Welfare, and the provincial epidemiologist and manufacturer concerned. The importance of maintaining the smallpox immunity of physicians, nurses and other hospital and health personnel in Canada is emphasized.

SOMMAIRE

Durant la période de 1961 à 1963, on a enregistré 10 cas où la variole a été "importée" par avion, en Angleterre et au pays de Galles, en Allemagne, en Suède, en Pologne et au Canada. Une caractéristique de l'épidémie qui en a résulté a été le nombre de cas et de morts parmi les médecins et les autres membres du personnel médical. A mesure qu'augmente le nombre de passagers transportés par avion, existe le risque de laisser entrer au Canada des cas de variole en incubation, comme ce fut le cas en 1962. Des millions de canadiens ont été vaccinés contre la variole. Si la vaccination antivariolique peut entraîner certaines complications, le nombre de celles-ci peut être minimisé en respectant les précautions à prendre et le contre-indications de la vaccination. L'Administration des Aliments et des Drogues, Ministère de la Santé Nationale et du Bien-Etre Social, a fait circuler à tous les médecins du Canada la demande de lui faire rapport de toutes réactions défavorables au drogues. Ceci comprend les réactions graves, rares et non suspectes survenues après administration de tout agent d'immunization, y compris les vaccins, les toxoïdes et les antitoxins. Cette information sera rapportée à la Division d'Epidémiology, Ministère de la Santé Nationale et du Bien-Etre Social, ainsi qu'à l'épidémiologiste de la province et au fabricant intéressé. On souligne dans l'article l'importance de maintenir une immunité valable contre la variole parmi les médecins, les infirmières et tous les membres du personnel médical du pays.

THIS communication presents information on the world-wide incidence of smallpox, morbidity and mortality trends in Canada, control procedures, adverse reactions to smallpox vaccination and conclusions. Recent outbreaks of smallpox in Europe and the importation of a case into Canada in 1962 have prompted re-examination of the problem. Dixon's[1] recent book on smallpox and the first report of the W.H.O. Expert Committee on Smallpox,[2] published in 1964, have been valuable sources of information.

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*Chief, Epidemiology Division, Department of National Health and Welfare, Ottawa.
†Medical Consultant, Epidemiology Division, Department of National Health and Welfare, Ottawa.