In this issue of the Journal, Gaur et al.\(^1\) report a case of human babesiosis from India. The asplenic patient sustained a 70% parasitemia, demonstrated clear signs of a hemolytic disease, became hypotensive after admission, and suffered a terminal cardiac arrest. Babesia sp. was identified from blood smears and by 18S ribosomal DNA (rDNA) sequencing. This is the second well-documented case of babesiosis from India; Marathe et al.\(^2\) previously provided a detailed case report, with photomicrographs of blood smears that established the diagnosis. That patient was a normosplenic 51-year-old man who presented with fever, palpable spleen, scleral icterus, and hemoglobinuria. Malaria was suspected, but “antimalarial drugs” had no effect. Once babesiosis was suspected, a standard course of clindamycin and quinine was followed by a rapid recovery.

The piroplasms (Hematozoa: Piromplasmida), comprising the genera Babesia, Theileria (including Cyttauxzoon), Anthemosoma, and Echinocnozoon, are typically maintained by ticks and vertebrate hosts. It is likely that there are more than 100 valid Babesia spp. and perhaps a third as many Theileria spp. The piroplasms were initially thought to be very host specific, to the point that finding one in a different kind of animal prompted the description of a new species. Asa Chandler’s widely used introductory parasitology textbook\(^3\) had the pithy statement “they are found in all kinds of mammals except man.” The concept of host specificity of the Babesia was eroded when unequivocal evidence of human infection was first reported in 1957. Since then, two major epidemiologic patterns have been recognized: stable endemic risk due to Babesia microti in the northeastern and upper midwestern United States (incidence in highly endemic communities about 100 per 100,000 people/year), and sporadic global cases due to diverse Babesia spp., mainly those of ruminants. The diversity of piroplasms causing human babesiosis is increasingly recognized. Recently, an HIV-infected Zimbabwe resident suffering fever, anemia, and weight loss was found to be infected by Anthemosoma gamharni, a piroplasm of rodents\(^4\); despite the fact that the name of the causative agent is Anthemosoma, there is no need to apply a new name to the disease, which was typical of human babesiosis. To date, there has been no report of human infection by Theileria spp. or Echinocnozoon. Gamharn and Bray\(^5\) failed to infect splenectomized chimpanzees by feeding T. parva-infected ticks on them, suggesting that Theileria spp. are unlikely to be found to infect humans.

Within the last two decades, Babesia spp. have been increasingly identified and reported from tropical, low- to middle-income countries, with classical morphologic and modern molecular confirmations. The question that remains to be answered is whether Babesia has been infecting people in tropical sites all along. Routine use of polymerase chain reaction (PCR), amplicon sequencing, and phylogenetic analysis has greatly promoted identifying etiologic agents, and our awareness of babesiosis as a potential rule-out diagnosis has likely increased.

It is not that tropical medicine workers have historically ignored the possibility of human babesiosis when searching for the etiology of fevers. Laveran and Mesnil\(^6\) named the agent of dum-dum fever Piroplasma donovani, after studying spleen impression smears from a cachectic Calcutta soldier sent to them by Donovan. They found piroform bodies within red blood cells, and indeed they looked tantalizingly like piroplasms (Figure 1). They wrote: “Les Piroplasmes occupaient deja une place importante en pathologie veterinaire. C’est la premiere fois qu’on signale une maladie humaine produite par un Piroplasme bien caracterise.” Ronald Ross,\(^7\) studying the same series of slides from Donovan as well as some sent to him by Leishman from a Madras case, opined that the parasites in such smears were artificially superimposed on red blood cells, and noted the almost universal presence of a small rod of nuclear material perpendicular to a larger typical nucleus. He thus rejected the presence of a piroplasm, suggested the genus Leishmania, and reclassified the parasite as Leishmania donovani. An outbreak of “pyroplasmosis” in 1,800 of 2,500 residents of a village in Uttar Pradesh in India, notable for remittent fever that was not responsive to quinine, was reported in 1902.\(^8\) However, the illustrations of the causative parasites are more suggestive of Plasmodium vivax, and thus these cases do not comprise human babesiosis. Hayashi in 1906\(^9\) reported finding ring-shaped bodies in red blood cells at the eschars and within the viscera of tsutsugamushidisease patients and named “Theileria tsutsugamushi” as the cause. The rickettsial etiology of scrub typhus was suspected by 1918, and the agent named in the early 1930s. Similarities with redwater (bovine babesiosis) led Wright\(^10\) to report the involvement of a piroplasm in the development of blackwater fever, but the infecting organisms were later identified as plasmodia. It may be that many examples of erroneous incrimination of a piroplasm as an etiologic agent for a human disease inhibited future such considerations, leading to statements such as Chandler’s.

Although “piroplasm” implies pear-shaped, early babesial trophozoites generally assume a ring form. Given the morphologic similarity of piroplasm ring forms with those of Plasmodium spp., the prevailing hypothesis is that tropical babesiosis has been occurring all along, but with diagnoses missed, and the disease ascribed to malaria parasites. Distinguishing between Babesia spp. and Plasmodium spp. by microscopy can be difficult.

The eminent malariologist P.C.C. Gamharn wrote in his authoritative monograph on the malaria parasites\(^11\) that seven validly described Plasmodium spp. (from dogs, otters, 
ruminants, porcupines, and even a snake) were in fact piro-
plasms, and that, when he had been asked to review slides
of purported new plasmodia from animals, they usually
turned out to be piroplasms. Indeed, the band-like and
rosette forms shown by Gaur et al.1 are very suggestive of
*P. malariae*
Garnham12 stated that the presence of these vacuoles were as useful as
the absence of hemozoin in differentiating piroplasms from
plasmodia. Dying babesia have prominent vacuoles ("crisis
forms") and seem to be commonly represented in blood
smears from animals or patients with heavy infections. The
typical "Maltese cross" form (division into four merozoites) is
seen only with piroplasms and establishes the diagnosis, but
may not always be present in a blood smear.

The tropical population at risk is far greater than when
babesiosis was first recognized as a zoonosis, and the global
cohort of susceptible people has increased. There are 38 mil-
lion people living with HIV/AIDS, and HIV is a known risk
factor for *B. microti* babesiosis.14 Cancer patients are living
longer; 60% of chronic myeloid leukemia patients in India are
taking Glivec or imatinib.15 Rituximab, a known risk factor for
treatment-resistant *B. microti* babesiosis,16 was placed on
the WHO Model List of Essential Medicines in 2015. With
increased life expectancy, there are more older individuals in
the tropics. Babesiosis was first described by Smith and
Kilborne in their classic investigations of Texas cattle fever as
having age-related pathology, and that fact remains today.17
More susceptible people should imply more cases, even if
transmission (ecologic) conditions have remained constant.

Garnham, who had reviewed slides and gave his opinion
on the identity of the infecting parasites for four of the first
eight known cases of human babesiosis,12 provides a quote
that is still relevant today: "Man, particularly agricultural work-
ers and people who spend much time in rural areas, undoubt-
edly comes into contact with Babesia-infected ticks quite fre-
quently. Three species of piroplasms have been the cause of
the three cases reported from human beings. Few places in
the world are free of piroplasms; their presence presents a
hazard to numerous people who are splenectomized and an
unknown number whose splenic function is de

Although ticks are said to be obligately required for transmis-
sion, *B. microti* is readily transmitted by blood and is the
most common protozoal transmission risk associated with
blood products in the United States.19 Humans exposed to
animal blood may be at risk of acquiring infection without tick
exposure. Nonetheless, it is unlikely that human babesiosis
will be reported from sites where ticks are not common.

The vast majority of sporadic human babesiosis cases
were initially detected by routine blood smear, with malaria
the presumptive diagnosis. Modern molecular methods
powerfully complement classical microscopy, additional
analyses being stimulated by inconsistencies in clinical details and increased awareness of healthcare providers. Case reports such as that of Gaur et al. serve to educate clinicians and laboratorians in sites where human babesiosis has historically not been included in a differential diagnosis.

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