Role of the Squirrel Monkey in Parasitic Disease Research

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Introduction

Squirrel monkeys are New World monkeys from South America whose taxonomy is as follows:

Order:	Primates
Suborder:	Anthropoidea
Family:	Cebidae
Subfamily:	Saimirinae
Genus:	*Saimiri*

Much controversy exists regarding the species of the squirrel monkey. Napier and Napier (Whitney 1995) divide the squirrel monkeys into two species: *Saimiri sciureus* and *Saimiri osterdii;* the former is used in biomedical research. Hershkovitz prefers to use two groups of *Saimiri* based on facial characteristics and other factors, which include "Roman" and "Gothic" types. He suggests four species in all: *boliviensis*, *sciureus*, *oerstedi*, and *ustus* (Whitney 1995). Thorington classifies the *Saimiri* into two species, *sciureus* and *madeirae,* with four subspecies of *S. sciureus*: *sciureus*, *boliviensis, crassiquiarensis*, and *oerstedii* (Thorington 1985). Squirrel monkeys have been karyotyped by their acrocentric chromosomes. Peruvian squirrel monkeys have 10 acrocentric chromosomes, Colombian types have 12, and Guyanan types have 14. The Costa Rican and Panamanian match the Peruvian karyotype of 10, and the Bolivian match the Colombian (Whitney 1995).

This article is not intended to be a taxonomic review; however, it is important for readers to understand the complexity of the situation. Much of the research literature refers to the squirrel monkey only as *S. sciureus.* Other studies refer to them as Bolivian, Peruvian, or Guyanan phenotypes or refer to them by their karyotype. It is difficult or impossible at times to identify exactly what type of squirrel monkey was used in a study or whether the designations match the described karyotyopes of the animals.

The squirrel monkey is critical to many studies involving human parasitic diseases. This article provides a review of the literature related to how this South American primate has been used in parasitic disease research.

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Squirrel Monkeys in Parasitic Disease Research Other Than Malaria

Squirrel monkeys have been used in a variety of parasitic disease research projects, some of which have involved the natural infections of squirrel monkeys. For example, one report discusses an acute disseminated toxoplasmosis infection in a group of squirrel monkeys that caused an apparent 100% morbidity and a 30% mortality in a captive born colony (Cunningham et al. 1992). Because of the similarity of the disease in the monkeys to the disease in immunocompromised humans, it was suggested that the squirrel monkey would be a good model for studying toxoplasmosis.

Another report indicates that about half of the squirrel monkeys in one colony were serologically positive for *Encephalitozoan cuniculi*, suggesting that the squirrel monkey is easily infected with this parasite (Shadduck and Baskin 1989). Studies of a naturally occurring trichomonad, *Tritrichomonas mobilensis,* define the parasite, the location of the parasite in the host, and the pathogenic properties of the parasite (Culberson et al. 1986; Demes et al. 1989; Scimeca et al. 1989).

Filiaral parasites are frequently encountered in New World primates (Eberhard and Lowrie 1987; Esslinger 1982; Petit et al. 1985). The squirrel monkey has also been experimentally infected with filiariae in the genus *Dipetalonema.* That study promoted a better understanding of the biology of the parasite, including development of the parasite in the vertebrate host, the prepatent period, the vector, and the pathological response of the host to the parasite (Travi et al. 1985).

Trypanosomes are also naturally found in squirrel monkeys. In one study, 67.9% of the animals were positive for trypanosomes (Ziccardi and Lourenco-de-Oliveira 1997); in other reports, the incidence was slightly less. In these articles, *Trypanosoma rangeli* and *Trypanosoma cruzi* were the two parasites reported (D'Alessandro et al. 1986; Sullivan et al. 1993). *T. cruzi* is of public health interest both in the laboratory situation, where an employee may be accidentally exposed, or in the wild, where the animal may serve as a reservoir for infection. Congenital transmission of *T. cruzi* is a well-known phenomenon in humans and has been reported in two cases in New World primates including the squirrel monkey (Eberhard and D'Alessandro 1982).

Babesia microti is a blood parasite that has been found in humans in the northeastern United States and has occurred in both splenectomized and spleen-intact individuals. This

parasite has been used experimentally to infect several types of monkeys, including squirrel monkeys. In one study, the infection in the squirrel monkey resulted in a moderate to high parasitemia for 5 to 7 wk with a recovery or marked depression of parasites at 15 to 20 wk (Moore and Kuntz 1981). In a second study, *Babesia* was accidentally transmitted to a squirrel monkey along with a malaria parasite from a rhesus monkey that had been previously infected with the *Babesia* but did not have a patent parasitemia at the time. In that study, *Babesia* was uniformly virulent and resulted in the death of the animals (Chin et al. 1983). At the time of this writing, research is being conducted with a virulent form of *B. microti* in the squirrel monkey to test the efficacy of certain types of drugs to treat the infection (M. Eberhard, Centers for Disease Control and Prevention [CDC[1]], Chamblee, Georgia, personal communication, 1998).

The squirrel monkey has also been identified as a nonhuman primate host for *Leishmania donovani*. Squirrel monkeys develop a suitable infection with a protracted course, which makes them a superior model in studies such as immunization, mechanisms of immunity to visceral leishmaniasis, enhancement of the suppressive activity of antileishmanial drugs, and the like (Chapman and Hanson 1981).

Parasitologically, the squirrel monkey is considered to be a satisfactory host for general studies on host-parasite relationships for a variety of schistosomes. In one study, eight different schistosomes infected squirrel monkeys with different levels of success and very little pathology. The schistosomes studied included the following species: *bovis*, *intercalatum*, *mattheei*, *mansoni* (Puerto Rico and South Africa), *rodhaini* (Uganda), *rodhaini* (Kenya), and *douthitti* (Kuntz et al. 1979).

Squirrel Monkeys Used in Malaria Research

The most prevalent use of squirrel monkeys in parasitic disease research is with malaria parasites. Parasite biology, infectivity of vectors, transmission studies, and vaccine studies have all used squirrel monkeys. Following is a summary of the types of malarial parasites and studies that have been done with squirrel monkeys.

Nonhuman Primate Malaria Research

Nonhuman primate malarias are better adapted to development in monkeys than the human malaria parasites. They have been largely ignored since the adaptation of human malarias to nonhuman primate hosts. However, the predictability of the parasitological response following both sporozoite and trophozoite challenge suggests that immunological and efficacy studies with these nonhuman parasites may be useful in initial studies of conserved antigens (Collins et al. 1994).

Plasmodium brasilianum and *Plasmodium simium* are the two malaria parasites found in New World monkeys. *P. simium* is naturally found in howler monkeys and spider monkeys in Brazil. This parasite has been studied because of its biological similarity to the human parasite *Plasmodium vivax*. *Plasmodium simian* has been transmitted to squirrel monkeys, and from these infections, *Anopheles* mosquitoes have been infected (Collins et al. 1987a).

P. brasilianum has been used for a number of biological and physiological studies. It naturally infects monkeys of the family Cebidae from Central and South America and is biologically similar to the human parasite *Plasmodium malariae*. This parasite has caused infection by blood stage parasite and by sporozoite inoculation of the parasite into squirrel monkeys that have been previously infected with various malaria parasites. Mosquito infection was readily obtained from these infections (Collins et al. 1985).

A chloroquine-resistant strain of *P. brasilianum* was isolated from a naturally infected squirrel monkey. This parasite is of interest because recommended dosages of chloroquine failed to clear the parasite in splenectomized animals (Collins et al. 1990a).

P. brasilianium has also been important in immunological studies. Because of the similarity of *P. malariae* and *P. brasilianum*, studies have been conducted to test the cross-reactivity of monoclonal antibodies between the two parasites. It was shown that monoclonal antibodies to the sporozoites of *P. malariae* abolished the infectivity of *P. brasilianum* sporozoites when they were given by injection into squirrel monkeys (Cochrane et al. 1985). Additional studies involve the production of antibodies to the circumsporozoite protein in squirrel monkeys infected with blood stages of *P. brasilianum* (Cochrane and Maracic 1991), viral transformation of squirrel monkey B cells to induce the generation of a *P. brasilianum*-specific monoclonal antibody (Chizzolini et al. 1991), and studies involving descriptions of parasitized erythrocyte membrane antigens (Sulzer et al. 1995).

Many of the Old World monkey malaria parasites are of interest as experimental models because they also have biological similarities to certain human parasites. Because of easier housing and handling of the smaller primates, New World monkeys have been used in many studies to learn whether they will be infected with these parasites. Different species of primate malaria from Old World monkeys have been studied in the squirrel monkey. *Plasmodium inui* is a quartan malaria parasite from macaques. In one study, splenectomized squirrel monkeys from either Guyana or Bolivia were infected with both blood stage parasites or sporozoites. One animal from this study was used to infect *Anopheles* mosquitoes (Chin et al. 1983). In a later study, *P. inui* was highly infective for Bolivian squirrel monkeys, but mosquito infection from the parasitized animals did not occur (Collins et al. 1988a).

[1]Abbreviations used in this paper: AMRU, Army Medical Research Unit; CDC, Centers for Disease Control and Prevention; EE, exoerythrocytic.

Plasmodium fragile is a malaria parasite found naturally in *Macaca radiata* from India and *Macaca sinica* monkeys from Sri Lanka. This parasite is of interest because its characteristics are similar to those of *Plasmodium falciparum*. Such characteristics include deep circulation schizogony and sequestration, high virulence, no marked enlargement of host cell, no Shuffner's stippling, heavy pigmentation, small schizonts, and lack of true relapses (Collins et al. 1975). The parasite has been successfully transmitted to splenectomized squirrel monkeys by both blood stage and sporozoite transmission. The blood stage transmission was the most successful. Infection of mosquitoes was attempted but did not occur (Collins et al. 1990b).

P. fragile has also been used in squirrel monkeys for vaccine trials and cross-protection trials. In one study, Peruvian squirrel monkeys were vaccinated with the apical membrane antigen-1 (AMA-1). There was a marked difference in parasitemias between the control group and the vaccinated group. Later infection of these animals with trophozoites of *P. falciparum* resulted in no detectable parasitemia in the vaccinated animals, showing some degree of protection against a heterologous challenge (Collins et al. 1994).

Plasmodium knowlesi is a nonhuman malaria parasite that is also infectious to humans (Chin et al. 1968). This parasite has infected squirrel monkeys that have been previously used in human malaria vaccine trials. In addition, exoerythrocytic (EE[1]) bodies have been demonstrated in large numbers in liver sections from infected squirrel monkeys. EE stages are difficult to obtain in adequate numbers for assessment of the immune response against this stage. These abundant EE stage parasites are very useful for serological studies and vaccine assessment (Collins et al. 1978; Sullivan et al. 1996).

Two strains of *Plasmodium cynomolgi* have been used to infect Bolivian squirrel monkeys by inoculation of sporozoites. The animals became parasitemic, but the prepatent periods extended out to 3 mo (W. E. Collins, CDC, Chamblee, Georgia, personal communication, 1998).

Human Malaria Research

The four species of human malaria parasites include *Plasmodium ovale*, *malariae*, *vivax,* and *falciparum* (Coatney et al. 1971). All four species have been used to infect squirrel monkeys.

P. ovale is a human parasite that is very similar to *P. vivax*. The asexual cycle of *P. ovale* requires 48 hr (Coatney et al. 1971). *P. ovale* has been transmitted to squirrel monkeys with the subsequent production of EE bodies in the liver, but no patent blood stage parasitemia was detectable. EE stage parasites were successfully cultured in primary cultures of hepatocytes from squirrel monkeys (Millet et al. 1994).

Attempts have been made to adapt *P. malariae* to the squirrel monkey. *P. malariae* is the cause of quartan malaria in humans. The asexual cycle of the parasite requires 72 hr (Coatney et al. 1971). Serial passage of blood stage parasites into squirrel monkeys results in a slow but steady rise in parasitemia. Infection of mosquitoes from the infected animals has not occurred. Splenectomized Bolivian squirrel monkeys may be useful in the maintenance of *P. malariae*, and peak counts may be high enough to produce antigens for serological and immunological studies (Collins et al. 1989b).

The two human malaria parasites that demand the most attention in the literature are *P. vivax* and *P. falciparum. P. vivax* is a tertian malaria with worldwide distribution (Coatney et al. 1971). It has, with some variability, been used to infect squirrel monkeys. One report indicated that *P. vivax* was maintained in unaltered squirrel monkeys for many passages (Young et al. 1971). Blood stages of *P. vivax* from Mauritania also infected Bolivian squirrel monkeys (Collins et al. 1998).

Sporozoites from the Chesson strain of *P. vivax* were shown to have a relatively high rate of transmission in squirrel monkeys, but the maximum parasitemias during the first 50 days were too low to consider this model a good one for testing sporozoite vaccines. To validate a good challenge for testing vaccine efficacy, the control animals must develop a readily detectable parasitemia in a predictable time (Collins et al. 1987b).

The Salvador I strain of *P. vivax* has significant potential for the testing and development of antisporozoite vaccines. Parasitemias after inoculation with sporozoites are dose related and predictable (Collins et al. 1988b). In one study of this strain of parasite, three phenotypically distinct squirrel monkeys (Peruvian, Guyanan, and Bolivian) were used. All three phenotypes were susceptible to infection. The Bolivian phenotype animals attained a higher density infection than the other two phenotypes (Campbell et al. 1983).

Additional studies have been done using the Papua New Guinean strains of *P. vivax*, Army Medical Research Unit (AMRU[1])-1 and AMRU-2, in Guyanan squirrel monkeys. The results of this study indicate that Guyanan squirrel monkeys could be infected with the AMRU-2 strain but were refractory to the AMRU-1 strain (Cooper 1995).

A polymorphic strain of *P. vivax*, Thai 561, has also been used to infect Bolivian squirrel monkeys. These monkeys are poor producers of infective gametocytes, so mosquitoes are not infected from the monkeys. However, the Bolivian squirrel monkey is a useful model for sporozoite transmission studies because it is easily infected with the *P. vivax* Thai 561 sporozoites (Collins et al. 1992a).

A primaquine-tolerant strain of *P. vivax* from Brazil has also been studied in squirrel monkeys. Squirrel monkeys were infected with sporozoites and developed a long-lasting parasitemia. Mosquitoes were subsequently infected from the monkeys (Nayar et al. 1997).

Along with the quest for a consistent challenge strain of *P. vivax* is the quest for a vaccine to prevent infection. Several of these studies have been done with recombinant circumsporozoite proteins (Collins et al. 1989a; Procell et al. 1991) and irradiated sporozoites (Collins et al. 1992b). Each of these vaccines has resulted in partial protection but none has completely prevented patent parasitemia.

Other research has focused on the demonstration of EE bodies in liver biopsies of experimentally infected squirrel monkeys, making them possible candidates for EE body investigations (Rossan and Baerg 1975). The ultrastructure of parasitized squirrel monkey erythrocytes has also been studied and has revealed caveolae-vesicle complexes in the cytoplasm of the erythrocytes and knob-like structures on the surface. One study investigated the anatomical distribution of developing trophozoites and schizonts in infected squirrel monkeys, revealing the maturing parasites' predilection for the spleen (Fremount and Rossan 1990). Primary cultures of squirrel monkey hepatocytes have been used to test the inhibitory activity of *P. vivax* sporozoites induced by the plasma of squirrel monkeys that have been immunized with various *P. vivax* vaccines (Millet et al. 1991a, 1992).

P. falciparum is a malignant tertian malaria parasite with a worldwide distribution but concentration in the tropics and subtropics. It is considered to be the newest of the human malarias and the least efficient as a parasite because its malignant nature tends to eliminate its host (Coatney et al. 1971). It is believed to be the causative agent of the most severe form of malaria.

Many publications specifically deal with the search for a readily available nonhuman primate model for studying *P. falciparum*. The owl monkey, *Aotus* sp., has been the primate model for experimental infection because of its susceptibility to the human malarias. The scarcity of these animals has pushed investigators to look for other hosts such as the squirrel monkey. Several strains of *P. falciparum* have been adapted to the squirrel monkey. One report states that blood stage parasites from the culture-adapted Geneve/SGE-1 strain of *P. falciparum* infected Bolivian squirrel monkeys with predictable rates (Fajfar-Whetstone et al. 1987).

The Indochina I/CDC strain of *P. falciparum* has also been adapted to the Bolivian squirrel monkeys. Campbell and colleagues (1986) characterized the squirrel monkeys phenotypically and reported by country of origin. The Bolivian squirrel monkey was characterized as large, with a yellow coat and black cap. Squirrel monkeys from Peru were captured from the vicinity of Iquitos; they were distinguished from those from Guyana by the arch over the eyes. All three types of squirrel monkeys were infected with blood stage parasites. No mosquitoes were infected from the parasitemic monkeys.

The Haitian I strain of *P. falciparum* has been successfully maintained in culture. Cultured parasites have been used to infect Peruvian and Guyanan squirrel monkeys. The blood stage parasites from the infected animals have been replaced successfully into culture (Campbell et al. 1980).

Other strains of *P. falciparum* that have been used to infect squirrel monkeys include the Uganda Palo Alto (FUP-1) strain and the Panama II strain (Gysin and Fandeur 1983; Gysin et al. 1980; Young et al. 1975). One extensive study of different strains of parasites characterized 15 strains of *P. falciparum* both phenotypically and genotypically. The course of infection in squirrel monkeys of each of these 15 strains was also followed to determine patterns of infection (Fandeur et al. 1996).

Additional in vivo studies using *P. falciparum* and the squirrel monkey include vaccine trials using a variety of vaccines. Three basic types of antimalarial vaccines are being developed: blood stage, sporozoite, and transmission-blocking (Collins 1992). These basic types of vaccines have included many variations, such as vaccines against attenuated parasites (Fandeur et al. 1992), surface antigens (Perrin et al. 1985), purified exoantigens and protein fractions (Caspers et al. 1991; Dubois et al. 1984; James et al. 1985; Jendoubi et al. 1985: Jouin et al. 1987; Perrin et al. 1984b), soluble antigens (Perrin et al. 1984a), and recombinant vaccines (Etlinger et al. 1991; Pye et al. 1991). These studies have resulted in varying degrees of success. Immune responses and passive immunity trials have also been studied extensively (Fandeur and Chalvet 1998; Fandeur et al. 1984; Gysin 1992; Gysin et al. 1982a; Groux et al. 1990; Gysin et al. 1982b; Michel et al. 1983; Roussilhon et al. 1988).

Other types of studies conducted with squirrel monkeys include in vitro studies such as genetic stability of strains propagated in squirrel monkeys (Fanderu and Mercereau-Puijalon 1991), karyotyping of *P. falciparum* propagated in squirrel monkeys (Hinterberg et al. 1995), and culturing studies using primary squirrel monkey hepatocytes (Millet et al. 1991a). Ultrastructural studies on the parasite and on *P. falciparum*-infected erythrocytes have also been conducted (Fandeur et al. 1993, 1995; Hommel et al. 1982; Lanners et al. 1991).

Finally, pathological changes in the squirrel monkey after infection with *P. falciparum* have been studied and have provided insight into the pathophysiological changes that occur in humans infected with the parasite. These types of studies include experimental cerebral malaria using *P. falciparum* and squirrel monkeys (Gysin et al. 1992), parasite sequestration studies and studies on cytoadherence (David et al. 1983), and histopathological studies describing pathological changes in the kidneys and other organs from animals infected with *P. falciparum* (Aikawa et al. 1988; Whiteley et al. 1987).

Squirrel monkeys have played an important role in past studies involving parasitic diseases of humans. They should continue to play an important role in future studies as the search for vaccines and drug therapies against parasitic diseases progresses.

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