The study was aimed at analyzing immunological cross-reactivity between Leishmania major and Leishmania donovani and possible cross-protection between the two parasite species in the vervet monkey model of the disease. Nine vervet monkeys (Cercopithecus aethiops) from the institute animal colony were sued in the study. Five of the animals had been previously infected with L. donovani but had remained asymptomatic while the other four animals were naive and comprised the control group. Immunological responses to both L. major and L. donovani antigens in the five animals with prior exposure to L. donovani were examined before challenge. High antibody titers to the two antigens were demonstrated in an enzyme-linked immunosorbent assay, but the antibody titers to L. donovani were significantly higher than those to L. major (P < 0.005). Positive in vitro peripheral blood leucocyte (PBL) proliferation to L. major and L. donovani antigens was also demonstrated, but there was no significant difference in the response to the two antigens (P > 0.1). High and varying levels of interferon gamma (IFN-gamma) were secreted in PBL from the five vervet monkeys when stimulated with L. major antigen, but vervet monkey 1296 secreted marginal levels of IFN-gamma. When the animals were challenged intradermally with $1 \times 10^5$ virulent L. major promastigotes mixed with sandfly vector salivary gland lysate all four vervet monkeys in the control group developed nodules of varying sizes at the inoculation sites that eventually ulcerated. However, nodule formation and ulceration occurred at different times among these animals. The other five animals (animals with prior exposure to L. donovani) did not pick up the infection at all, but one animal from this group, vervet monkey 1296, developed a transient lesion that healed within 9 weeks, the same animal that had been shown to secrete low levels of IFN-gamma. The results demonstrate high cross-reactivity between L. donovani and L. major and that L. donovani protects against L. major infections. This finding is important for vaccine development studies against leishmaniasis.