Editorial

That malaria parasites consume their host erythrocyte, transforming most of its contents into parasite cytoplasm and a residual dark pigment, was obvious to the earliest observers (1) soon after discovery of the parasite by Laveran in 1880. Just how the parasites do this, and the exact nature of the pigment, are only now becoming clear. The paper by Gluzman et al. (2) in this issue of *The Journal* serves to draw together much previous work and to provide a cohesive picture of the digestion of hemoglobin, a process whereby the malaria parasite obtains the bulk of its nutrients.

Our understanding of what happens within the malaria-infected red blood cell began with the electron micrographs of Rudzinska and Trager (3), showing clearly that the parasite ingests red cell cytoplasm into food vacuoles. Within the food vacuole the hemoglobin could be seen to be digested, with the concomitant formation of hemozoin, the characteristic pigment of malaria. This process, first described for the bird malaria *Plasmodium lophurae,* was soon found to occur in all species of malaria parasites (4), including the most important human parasite, *P. falciparum* (5). Biochemical work by a number of investigators then showed that the food vacuoles were acidic and probably not very different from the typical lysosomal vesicles of other eukaryotic cells. At the same time it was found for a number of species of malaria parasites that the infected erythrocytes had a variety of proteolytic activities not present in the uninfected cells. But the exact location and function of these proteases were uncertain.

Goldberg and his colleagues (2) approached the problem by first isolating, from cultures of *P. falciparum,* the digestive vacuoles. They then looked at the proteolytic enzymes in these vacuoles. They have found and characterized two aspartic hemoglobinases (I and II). Both attack native hemoglobin in the hinge region, opening up the molecule for further degradation. Aspartic hemoglobinase I appears to be the more important. Also present is a cysteine protease, previously found in extracts and recently cloned by Rosenthal and Nelson (6). This enzyme cannot act on native hemoglobin but rapidly digests the denatured molecule and the globin portion. This enzyme works synergistically with the aspartic hemoglobinases. In keeping with this fact, two specific inhibitors, one for the aspartic hemoglobinase I and the other for the cysteine protease, show marked synergism in their antimalarial effect on *P. falciparum* in culture.

This work also ties in with recent work on hemozoin and the possible relationship of heme to the antimalarial effect of chloroquine. There has been much controversy as to whether the malarial pigment is actually heme or something more than heme. Evidently, it is a polymerized form of heme produced by a specific enzyme of the parasite, a heme polymerase. This enzyme is inhibited by chloroquine (7), resulting in the accumulation of free heme in the food vacuoles. This in turn inactivates the cysteine protease, which is very sensitive to heme, thereby interfering with the parasite's digestion of hemoglobin. Years ago, in examining stained slides of malaria parasites that had been exposed in vitro to therapeutic levels of chloroquine, I remarked that the large brown bolus in each parasite made them look as if they had indigestion. This seems indeed to be the case. In view of the now widespread resistance of *P. falciparum* to chloroquine, it is to be hoped that suitable compounds will be developed that will give the parasites indigestion by acting directly on their proteases. Several active compounds of this type are already available but none as yet with a sufficiently selective action and low toxicity to the host. Further work on characterization of the enzymes should facilitate development of much needed effective new antimalarials.

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J. Clin. Invest.

0021-9738/94/04/1353/01 $2.00
Volume 93, April 1994, 1353