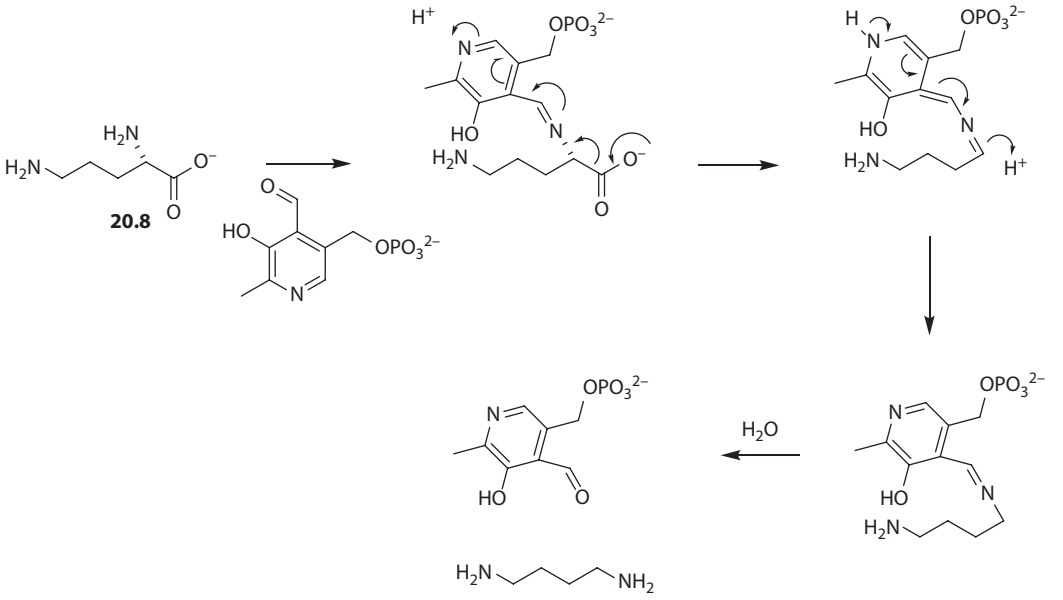

SCHEME 20.1 Decarboxylation of ornithine (**20.8**) by ornithine decarboxylase in which pyridoxal phosphate is a coenzyme.

found in South America, to life-threatening infections (visceral leishmaniasis). Visceral leishmaniasis can be fatal if untreated. Approximately 12 million humans are infected with leishmaniasis, and it is estimated that 59,000 die each year. The parasites nourish in the macrophages. The life cycle is illustrated in Figure 20.3.

Until an oral active drug became available, treatment of leishmaniasis was based on amphotericin B (Figure 20.4, **20.11**), pentamidine, or antimony-containing drugs like sodium stibogluconate and meglumine antimonate. Liposomal formulations of amphotericin B have increased the efficiency of the drug. Application of a drug in vesicles as liposomes will target the drug against cells performing phagocytosis like the macrophages. Since the macrophages host the parasites, some selectivity in activity is obtained. The main mechanism of action of amphotericin B is based on the amphiphilic nature of the molecule consisting of a lipophilic heptaene region and a hydrophilic polyol region. The polyene region complexes with steroids in the parasite membrane. The hydrophilic polyol region forms an ion channel permeable to small ions (Figure 20.4). Some selectivity is obtained because the drug has higher affinity for the double bonds of ergosterol dominating in the cell membrane of the parasites than for cholesterol in the membrane of mammalian cell.

Serendipitously, it was discovered that the cancer drug miltefosine (**20.12**) is an orally active drug against visceral leishmaniasis. The exact mechanism of action is still not understood, but it is assumed that accumulation in the cell membrane is important for the effect. The missing ester group in the molecule compared to phospholipids (e.g., see lysophosphatidylcholine **20.13**) causes resistance against metabolizing enzymes. In addition, miltefosine inhibits the formation of phosphatidylcholine which may predispose the cells for apoptosis (Figure 20.5).

20.4 MALARIA

Malaria is a leading cause of morbidity and mortality in the tropical world; some 300–500 million of the world population are infected with malaria parasites, presenting 120 million clinical cases each year. Among more than 100 species of *Plasmodium* parasites, only five can