CHAPTER II

Interactions Between Chemotherapy and Immunity

G. A. T. Targett

A. Introduction

It is perhaps not surprising that few planned studies on the interactions between chemotherapy of malaria and the immune status of infected individuals or animals have been carried out. Most antimalarial drugs have been developed in an empirical way, tested against acute-stage infection. Levels of specific resistance at the time of treatment, immunodepression as a result of infection or increased resistance to challenge as a result of chemotherapy have either been irrelevant or just not considered.

The past few years have seen major advances in our understanding of both immunological response to malarial infection and modes of action of antimalarial compounds. The details of these are given in other chapters of this book but, increasingly, it is being recognised that these two methods of control directed against the parasite can and do interact in both positive and negative ways, producing sometimes minor, sometimes profound, changes in levels of infection. Here I shall be considering (a) the effectiveness of drugs in relation to the immune status of the host; (b) malaria-linked immunopathogenic or immunopathological syndromes; (c) the immunodepressive effects of antimalarials; (d) the induction of immunity by chemotherapy; and (e) immunopotentiation and chemotherapy.

The modes of action of the commonly used antimalarials, so far as these are known, are discussed in detail elsewhere in the book (Part II, Chaps. 1–5, 9–15). The immune responses are also reviewed by Mitchell (Chap. 4) but it is perhaps useful to begin by indicating briefly those aspects of the immune response in malaria that have, or might have, a particular relevance where chemotherapy is concerned.

B. Immune Responses in Malaria

I. Innate Resistance

Those mechanisms that have been elucidated in any detail at all relate only to the blood stages of infection. Virtually nothing is known about natural resistance as it affects sporozoites and exoerythrocytic development in the liver although the high, if not absolute, degree of species specificity of Plasmodium species indicates a genetic basis to susceptibility. Of the various innate determinants affecting either invasion of red cells or development within the erythrocyte (see review by Targett 1981 a), few can be linked with responses to chemotherapy. The intraerythrocytic
factors suppress but rarely totally inhibit development of the parasite. Thus in individuals heterozygous (or indeed, homozygous) for haemoglobin S, development of *P. falciparum* is relatively normal under conditions of high oxygen tension, but greatly impaired at the lower oxygen tensions that might occur in the deeper circulation (PASVOL et al. 1978). ATP levels in red blood cells vary and low levels are thought to confer some resistance to *P. falciparum* (in black Americans), as a consequence, reducing the severity of the disease. Such individuals respond better to chemotherapy than those with normal ATP levels (POWELL et al. 1972), and the relatively lower levels of *P. falciparum* parasitaemias in Africans may be one reason why chloroquine resistance has appeared so much more slowly there than in Southeast Asia and South America (HALL and CANFIELD 1972).

II. Acquired Immunity

It is important first to appreciate in broad terms the influence of acquired immune responses on the pattern of human disease. Where the disease is highly endemic, very young children are protected to a large extent, partly as a result of non-immunological factors (TARGETT 1982), and partly through maternally derived immunity. There follows a period of several years during which repeated infection produces high parasitaemias and correspondingly high rates of mortality (in *P. falciparum* infections) and morbidity. A lessening of the clinical aspects of the disease precedes the gradual acquisition of an antiparasitic immunity. Adults show strong immunity that keeps parasite levels very low, but this is maintained only if sporozoite challenge continues. In areas where transmission is irregular, an effective immunity may never be attained, the whole population rather than the children alone remaining susceptible to clinical malaria or, at best, semi-immune. This pattern is broadly true for both falciparum and vivax malaria. Development of immunity in simian, rodent and avian malaria infections used as laboratory models is, as we shall see later, usually different from that of the human disease. Commonly the hosts develop either a strong, acquired immune response following a single infection, or a fulminant infection which, untreated, is invariably fatal.

An important feature of the human disease is that resistance depends on continuous challenge and on the continued presence of parasites in the body. It is not a sterile immunity. *P. falciparum* infections die out within a year if there is no further exposure. *P. vivax* infections under similar circumstances last about 3 years because of the presence of dormant stages within the liver (KROTOSKI et al. 1980, and see Chap. 1). The waning of resistance is shown by the susceptibility to re-exposure in both cases and the development of relapse infections of *P. vivax*.

A point of obvious relevance to the present discussion is the stage or stages of the parasite life-cycle against which the immune responses are primarily directed.

Immune responses to sporozoites have not been clearly established. NARDIN et al. (1979) have recently demonstrated the presence of antisporozoite antibodies in individuals from a *P. falciparum* hyperendemic area. Since they occurred mainly in immune adults, it was suggested that they might effect a sterilising immunity.

Evidence of functional immune responses directed against exoerythrocytic stages of mammalian malaria parasites is also difficult to find. There is much to suggest that this phase of the life cycle is, in fact, unaffected by the immune re-