INTRODUCTION

The first rabies vaccine was prepared by Pasteur over 100 years ago, and was used more or less successfully (1). Since then, rabies vaccines have been improved to the point where the recipient can be confident of surviving both the vaccination and exposure to rabies virus. This considerable achievement was made almost entirely by empirical means, that is by formulating various vaccines and testing their efficacy in appropriate animal models. It is therefore pertinent to ask the question as to what contribution modern immunology has to make to rabies prevention and prophylaxis. A partial answer is that a better understanding of the immune response to rabies virus and its antigenic components will allow us to formulate the next generation of rabies vaccines. Some improvements that could be made are:

(i) Economy. The current rabies vaccine recommended for use in humans is produced in human diploid cell culture and is therefore prohibitively expensive for use in most of the world. More relevant for veterinary medicine is the duration of immunity following vaccination. If this can be improved, significant reductions in the cost of rabies control programs will result.

(ii) Routes of administration. One of the aims of rabies control programs is to reduce the frequency of rabies virus in indigent species. In the case of wildlife, it is obviously not practical to vaccinate by conventional means; therefore, there has recently been a lot of interest in oral rabies vaccines which could be distributed in baits.
(iii) Safety. It is generally considered that the fewer components in a vaccine the less the risk of unwanted side reactions. This is one of the strongest arguments for the introduction of subunit vaccines, especially for human use.

Several other papers in this volume deal with specific approaches to improving rabies vaccines to meet the above objectives. My aim is to focus on some of the basic immunological principles that are important either for protection against rabies infection or in the development of subunit and/or recombinant vaccines. I will summarize some recent results on the characterization of rabies virus antigens which I believe may be particularly relevant to vaccine development, and I will also make an attempt to evaluate which immune effector mechanisms are important in protection against rabies.

IMMUNOGENICITY OF RABIES VIRUS ANTIGENS

The rabies virion consists of 5 structural proteins, including a single transmembrane glycoprotein which is assembled as a trimeric spike (2). This glycoprotein is responsible for the initial binding interaction during the infection of susceptible cells (3), and is also the only target for virus neutralizing antibody (2,4). For this reason much attention has been focused on its possible use in a subunit vaccine. This field has recently been reviewed by Wunner et al. (5), and can be summarized by saying that, if adequately presented, the purified rabies virus glycoprotein protects experimental animals against rabies as effectively as vaccines consisting of inactivated virus. In a comparative study, Dietzschold et al. (6) compared the neutralizing antibody responses induced by monomeric "soluble" glycoprotein (a form of the glycoprotein secreted by infected cells, and lacking the hydrophobic transmembrane amino acid sequence), aggregated glycoprotein (rosettes), and glycoprotein inserted into lipid membranes (liposomes). Their conclusion was that, although each of these forms of glycoprotein carried all the antigenic information needed for induction of virus-neutralizing antibody responses, immunogenicity (as measured by induction of virus-neutralizing antibody and protection against challenge) was directly dependent on the state of