Chapter 17

Vehicles for Oral Immunization

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1. ORAL DELIVERY OF ANTIGENS

1.1. Introduction

New approaches to vaccine development have become possible since a common mucosal defense system was recognized whereby an antigen interacting with localized lymphoid tissue could stimulate IgA precursor cells that may then migrate to other mucosal surfaces (Craig and Cebra, 1971). Several oral vaccines have been shown to induce IgA responses at mucosal sites distal from that of the immunization, suggesting the feasibility of developing oral vaccines for protection against pathogens that gain entry through other mucosal routes (Table I). Mucosal surfaces represent the largest like-tissue type in vertebrates, providing an important anatomical, mechanical, and chemical barrier to the diverse environmental antigens of microbial and food origin, including pathogenic microorganisms, that are encountered daily. It is not surprising then that it is the most common portal of entry of ubiquitous viral, bacterial, and parasitic infectious agents. Oral immunization, by stimulating the gut-associated lymphoid tissue (GALT), presents a promising approach for protecting many secretory surfaces against a variety of infectious diseases. Not only are more lymphocytes found in the gut than in any organ in the body, but IgA is produced in twice the quantity of IgG, and more IgA is poured into the bowel each day than the combined IgG synthesized and released into the blood.

An enteric mucosal IgA response is probably best stimulated by locally administered antigen. Immature B cells that are precommitted to synthesis of IgA are especially numerous in gut-associated lymphoreticular tissue (Gearhart and Cebra, 1979) and are efficiently exposed to luminal antigens by a specialized mucosal antigen sampling mecha-
nism (Owen, 1977; Owen et al., 1986). By contrast, parenteral immunization is usually inefficient at evoking mucosal secretory IgA (sIgA) responses, and may actually suppress them (Pierce and Koster, 1980). It has been shown that mucosal lymphoid tissue differs from that of the systemic immune system in its lack of an age-associated decline in primary immune responsiveness (Szewczuk and Wade, 1983; Chen and Quinnan, 1989b). If the secretory antibody failed as the body's "first line of defense," the lack of serum antibody might allow pathogenesis. Thus, it would be advantageous to develop a system with a sequence of immunizations that would induce both a strong secretory antibody response as well as efficient humoral and cellular immune responses.

Immunizing via the oral route to stimulate the mucosal immune system offers several advantages over parenteral vaccination: (1) Ease and economics of preparation. Oral vaccines need not be highly purified, which would greatly simplify preparation. Larger amounts of material would probably be needed because of higher doses, but this could be offset by the less stringent requirements for manufacturing an oral formulation. In addition, preliminary studies indicate that some oral formulations may be lyophilized, thus reducing the need for refrigerated storage. (2) Ease and economics of dosing. These are probably the greater advantages. Oral formulations promote better patient compliance. The need to train in parenteral dosing is eliminated. Oral dosing enables home administration and facilitates mass vaccination. Intranasal immunization, although shown to be more efficient than oral immunization in several systems, has less acceptance by patients. In addition, appropriate inhalation delivery requires a critical level of cooperation and coordination not usually possible in young children. (3) Safety. Side effects (such as fever, diarrhea, flulike symptoms, malaise, erythema, and edema) associated with parenteral vaccines may be reduced or absent. For example, bacterial lipopolysaccharide contaminants are far less reactogenic by the oral route. These are important considerations, especially when vaccinating the chronically ill, children, and the elderly. (4) Efficacy. Effective stimulation of the mucosal immune system may improve vaccines that offer incomplete protection by parenteral immunization. Efficacy could also be improved in the elderly, since mucosal-associated lymphoid tissue appears not to undergo age-associated dysfunction. In addition, oral immunity may not be affected by maternal antibodies.

In addition, oral immunization may be more effective in controlling the spread of disease, facilitating eradication of diseases that persist through asymptomatic colonization of mucosal surfaces. An additional advantage is the potential of administering greater volumes of vaccine antigens used in combination vaccine strategies.

Several important barriers, however, must be overcome in order to efficiently immunize by the oral route: the obvious practical difficulties of avoiding degradation by the low pH and proteases in the GI tract, the short exposure to immune induction sites resulting from normal GI transit, and the very limited permeability that large molecules have through the GI tract. In addition, various tolerance mechanisms must be overcome in order to effectively immunize via the oral route. In that the gut is in constant contact with a large amount and variety of proteinaceous material, effective regulation mechanisms have been developed. Thus, mucosal immunosuppressant mechanisms have evolved to minimize the immune response to fed antigens (Genco et al., 1983). Prior mucosal contact of antigen may not only suppress the induction of serum antibody, it may also reduce the subsequent absorption of antigen. This is a function of intestinal antibodies and is known as immune