antibody in resistance to infection, particularly in protection of the upper respiratory tract. Polymeric IgA has been shown to be specifically transported into the nasal secretions of mice, and to protect against nasal challenge. Protection can be abrogated by intranasal administration of antiserum against IgA but not IgM or IgG (38). Limited studies have demonstrated significant mucosal responses to influenza virus infection in humans, with development of both HA-specific IgA and IgG in nasal secretions. Nasal HA-specific IgG is predominantly IgG1, and correlates well with serum levels, suggesting that nasal IgG originates by passive diffusion from the systemic compartment (39). Nasal HA-specific IgA is predominantly polymeric and mostly IgA_1, suggesting local synthesis. These studies in human have also suggested that the protective immunity induced by influenza virus infection can be mediated by mucosal HA-specific IgA (33,40). However, studies in IgA knockout mice (41) have shown that mucosal immunity is not required for vaccine-mediated protection, and persons with selective IgA deficiency do not appear to be at increased risk for influenza infection.

Cellular Immunity

Influenza infection generates robust cellular immune responses in mice, including both $CD8^+$ cytoxic T lymphocytes and $CD4^+$ helper T cells. Influenza-specific, $CD8^+$ HLA class I–restricted cytotoxic T cells lyse influenza infected cells by a variety of mechanisms, and may recognize peptide epitopes from the HA, NA, or internal proteins such as M, NP, or PB2 (42). Therefore, cytotoxic T lymphocytes (CTLs) may be subtype-specific, or in the case of those which recognize internal proteins, may be broadly cross-reactive, for example, lysing cells infected with influenza A but not influenza B virus (43–45). In mouse models, $CD8^+$ cytotoxic T cells play an important role in limiting viral replication. However, to be effective in mediating protection in these models, they must be able to migrate to the infected respiratory epithelium quickly enough, and in large enough numbers to be able to suppress the virus before it gets out of control. In one sense, this can be seen as a race between the virus and the CTL response. $CD4^+$ helper T cells are class II restricted, and may recognize peptides from either envelope or internal proteins. Their main function is to provide help for B cell production of antibody, and to secrete a wide array of proinflammatory cytokines. In addition, class II–restricted cells may exhibit cytotoxic activity similar to that shown by class I–restricted cells (44).

Adoptive transfer experiments have shown that virus-specific T lymphocytes, including both HA-specific and cross-reactive T cells, can mediate recovery from influenza virus infection in animal models. The significance of T cells directed against internal viral proteins in protection against severe disease in humans is unclear, as the internal virus proteins were shared between viruses causing the pandemics of 1957 and 1968, and the viruses in circulation immediately prior to these pandemics. However, the presence of virus-specific prechallenge class I–restricted CTLs has been shown to correlate with reductions in the duration and level of virus replication in adults with low levels of serum HA and NA antibody who were experimentally challenged with influenza A virus (46). Lymphocyte responses may play a role in ameliorating the severity of disease and speeding recovery following infection, as suggested by the finding of more severe influenza in individuals with severe defects in cell-mediated immunity (7). In addition, during pandemics, adults who may have cross-reactive T cells from previous infections appear to have some protection compared with children who have not previously had influenza, despite the fact that neither group would be expected to have antibody to the pandemic virus (47).

INFLUENZA VACCINES CURRENTLY LICENSED IN THE UNITED STATES

Inactivated Influenza Vaccines

Inactivated influenza virus vaccines were first licensed in the United States in 1943. Early vaccines consisted of formalin-inactivated whole virions grown in embryonated chicken eggs demonstrated ~70% protective efficacy in healthy adults (48). Since then, although there have been several important advances in the techniques for producing vaccine, the basic vaccine strategy has remained the same. The development of the zonal gradient centrifuge allowed more efficient production and more highly purified vaccines in which reactogenic contaminants had been removed (49). Treatment of the whole virus to create split vaccines, or subunit vaccines has resulted in a vaccine with fewer adverse reactions. The efficiency of vaccine production has also been improved through the use of reassortant strains which contain the HA and NA genes from currently circulating influenza viruses, and the remaining genes from a master strain adapted to grow in high yield from hens' eggs (50). The vaccine is currently formulated to contain at least 15 μg of each HA antigen as assessed by single radial immunodiffusion (SRID) (51), although higher-dose vaccines are being contemplated (see below).

Safety

Influenza vaccine is generally very well tolerated in adults. A randomized, double-blind, prospective study in over 800 healthy working adults (52) documented rates of arm soreness of 64% in vaccine recipients compared with 24% in recipients of placebo. The majority (67%) of those experiencing arm soreness after vaccination rated this symptom as mild, and only 3% rated arm soreness as severe. Rates of mild local soreness following inactivated influenza vaccine in the range of 60% to 80% have been documented in other, similar studies (53–55). Local side effects are slightly more common in women than in men (52). Among elderly persons living in the community, injection site soreness was reported more frequently in recipients of trivalent inactivated vaccine (TIV) compared with placebo recipients (20% vs. 5%, respectively) (52,56). Clinical protocols have been proposed to administer TIV to persons who are at high risk for severe or complicated influenza, who also have a history of immediate hypersensitivity to eggs, if the benefit of immunization is judged to outweigh the risk (57,58).

Guillan-Barré syndrome (GBS), an acute inflammatory demyelinating polyneuropathy, has been associated with a variety of infectious agents, particularly *Campylobacter jejuni*, and occasionally develops after influenza vaccination (59). An increased risk of GBS was observed after receipt of swine influenza vaccine in 1976 (60). In subsequent years, surveillance for influenza vaccine-associated cases did not detect an obvious association, but a small risk of GBS was noted in 1992 and 1993 surveillance that would result in about one additional case of GBS per million persons vaccinated against influenza (61). The most recent studies suggest a statistically significant but very slight increased relative risk of GBS within seven weeks of influenza vaccination (62). For patients who have a history of