Status Report: Vaccines for Neurologic

This enticing concept is being applied to several conditions common in neurology. Here's a look at the mechanisms and likelihood of success.

Vaccines have probably prevented more diseases than any other medical or public health intervention except sanitation. The practice can be traced back to the ancient Chinese practice of variolation, a method of protection against smallpox by intranasal inoculation of a healthy person with a small quantity of scabs from an infected person. Edward Jenner established the scientific principle of immunization in 1796 by using cow pox as a related immunogen against smallpox and introduced smallpox vaccination for human use. The first vaccine intended for those people who were already infected (the vaccine for rabies) was tested by Louis Pasteur in human beings in 1881. Robert Koch, the German microbiologist who isolated *Mycobacterium* tuberculosis in 1882, attempted a therapeutic tuberculosis vaccine, but it was not until 1921 that the most widely known attenuated bacterial vaccine for protection against tuberculosis, bacille Calmette-Guerin, was introduced. This vaccine remains in use today.

Considerable advances have taken place in vaccination technology in the past 200 years, and vaccines are available for a large number of infections. Vaccination has had its impact on neurologic disorders as well. The most important developments in this respect were the introduction of the polio vaccines: the poliovirus vaccine and the oral polio vaccine in 1961. Currently, poliomyelitis is on the way to eradication.

The traditional use of vaccines has been mostly limited to the prevention of disease. The trend changed in the 1990s when several clinical trials were underway for treatment of active infections with viruses such as HIV-1 and the Herpes simplex virus. DNA vaccines, which are easy to produce and stable, were the most important development in this area in the last decade.

Apart from infectious diseases, therapeutic vaccines are in development for cancer, autoimmune disorders (*e.g.*, multiple sclerosis), and degenerative disorders (*e.g.*, Alzheimer's disease). Alzheimer's and stroke have important inflammatory and immune components and may be amenable to treatment by anti-inflammatory and immunotherapeutic approaches including vaccines.[1] Cancer vaccination involves attempts to activate immune responses against antigens to which the immune system has already been exposed. Vaccines are available in various forms and given by several routes of administration. Advances in genomics with sequencing of genomes of infectious organisms are providing opportunities for genetically engineered specific vaccines.

This article provides a brief overview of vaccines for neurologic disorders. Only active immunization is considered here. Active immunization should be distinguished from passive immunization, which results in immediate protection of short duration, and may be achieved by the administration of antibodies themselves in the form of antisera (of animal origin) or immunoglobulins (of human origin). Neurologic disorders where vaccines have either been used or are in development are shown in Table 1.

Disorders

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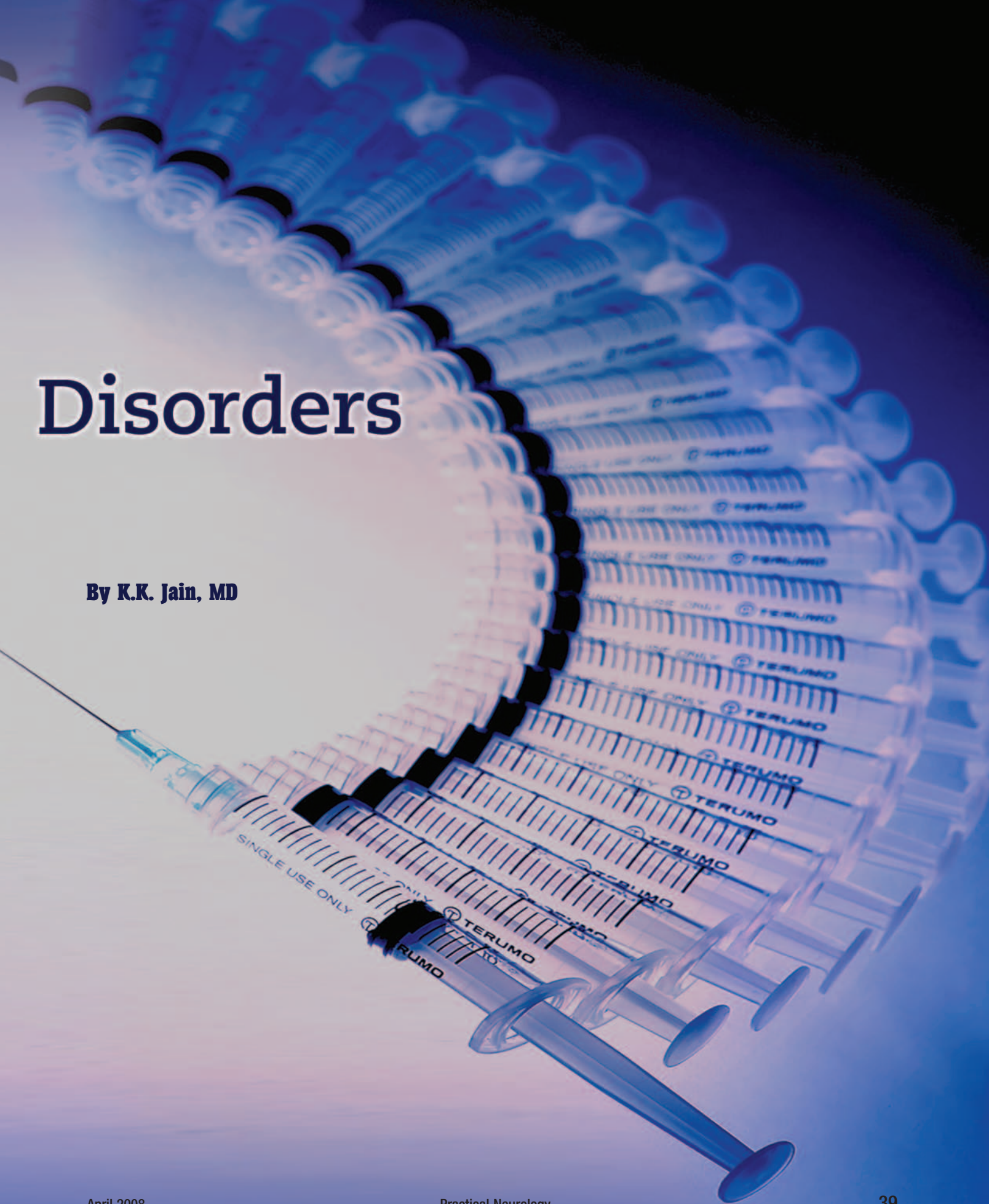

Table 1. Neurologic Disorders for Which Vaccines Are in Development or Use

Prevention of infections to the central nervous system:
- Encephalitis
  - Eastern equine encephalitis
  - Japanese encephalitis
  - Tick-borne encephalitis
  - Venezuelan equine encephalitis
  - Western equine encephalitis
- Lyme disease
  - Malaria
- Meningitis
  - Meningococcal meningitis
  - Lymphocytic choriomeningitis
  - Haemophilus influenzae
- Poliomyelitis
- Rabies
- Tetanus
- Herpes Zoster infections

Prevention of congenital and neonatal infection:
- Congenital rubella
- Congenital cytomegalovirus
- Congenital HIV-1 infections
- Neonatal meningitis

Treatment of infections that can affect the nervous system:
- HIV-1
- Herpes simplex
- Leprosy
- Tuberculosis

Treatment of noninfectious neurologic disorders:
- Alzheimer's disease
- Amyotrophic lateral sclerosis
- Cocaine addiction
- Glioblastoma multiforme
- Multiple sclerosis

Scientific Basis

The main aim of vaccination is the induction of an immune response designed to prevent infection or limit the effects of infection. Vaccination differs from natural or innate immune protection against infection in two ways. First, in pathogen-specific immune response induced by a vaccine, both the humoral (antibody-mediated) and cellular arms of the immune system are involved, whereas the phagocytes and cytokines participate in natural protection against infection. Second, the immune response induced by a vaccine is more durable (months to years) and takes place before exposure to the infection. Note that prophylactic vaccination should be postponed in patients suffering from acute infections. Live vaccines should not be given to patients on immunosuppressant therapy or systemic corticosteroids.

Vaccines have been used to attenuate damage after injury to the central nervous system and circumvent some of the impediments to recovery. Vaccines are under investigation to promote axonal regeneration and repair following traumatic injury and manipulate the immune response to reduce neural damage.[2] Two well-known approaches for vaccine construction are:

(1) The use of a related immunogen to achieve cross-reactive immunity against the more pathogenic organism (*e.g.*, the use of cowpox for smallpox immunization).

(2) The use of attenuated or weaker version of an organism by passage of an organism in culture or animals with selection of a weaker version (e.g., the Bacille Calmette-Guerin vaccine).

Bacterial vaccines were broadly of three types: (1) killed suspensions prepared from virulent organisms, (2) live preparations of strains selected for attenuation by manipulation of culture conditions, (3) and toxoids prepared by detoxification of crude bacterial toxins. Viral vaccines corresponded to the first two types of bacterial vaccines.

Newer developments include the use of peptide vaccines based on purified components of the pathogens and polysaccharide-protein conjugates. Many of the new developments in vaccination technology are based on tools of molecular biology and involve genetic engineering as shown in Table 2.

DNA vaccines. In a DNA vaccine, the antigen of interest is cloned into the bacterial plasmid that is engineered to augment the expression of inserted gene in the mammalian cells. After injection into a living animal, the plasmid enters the host cell and directs the synthesis of the antigen it encodes. In a naked DNA vaccine, the DNA has been freed of all the proteins in the usual DNA-protein complex. Naked DNA vaccines derived from plasmids could bypass the numerous problems associated with other vectors, such as immune response against the delivery vector. This has several advantages over immunization with exogenous recombinant proteins or microorganisms:

- Elimination of the threat of introducing a potentially virulent virus associated with "attenuated" vaccines.
- DNA can be stored in a dry, powdered form for years and still retain its activity.
- Low doses of a proper gene construct can induce protective immunization.
- A single application can lead to long-lasting immunity, eliminate the need for booster doses, and increase compliance.

Delivery systems and adjuvants for vaccines. An adjuvant, usually an aluminium salt, is used to increase the immune response to an antigen. Cytokines are now being evaluated as adjuvants for vaccines. Traditionally, most vaccinations have been administered by injection. An oral route of delivery was first used for the polio vaccine. Other methods of delivery for

Should Vaccines Be Administered During Pregnancy?

Live virus vaccines should not be administered during pregnancy because of the potential risk to the fetus. However, other immunizations are often avoided in pregnancy and the early post-partum period because of the mistaken belief that vaccines are harmful to the fetus or neonate. The protective effect of maternal antibody against many viral diseases has been recognized, and the use of maternal immunization has been considered as a means to augment this protection in the young infant. Advantages of maternal immunization include the following:

- Prevention of congenital neonatal infections.
- IgG antibodies cross the placenta wall during the third trimester so that immunization of the pregnant women protects the infants who remain highly susceptible to infections, but are the least responsive to vaccines given directly.

Disadvantages of maternal vaccination are:

- Potential inhibition of an infant's response to active immunization or natural infection.
- Liability issues with pharmaceutical companies and physicians.

Immunization of pregnant women with viral vaccines for poliovirus, influenza viruses, and rubella has been found to be safe for both the mother and the fetus. The efficacy of the rubella vaccine has not been proven, and it is used only during pregnancy with rubella titers.

vaccines are transmucosal, such as the intranasal and transdermal route shown by the use of a gene gun in the case of DNA vaccines.

Results and Effects

Vaccination is used for both prophylaxis and treatment of neurologic disorders, which includes mainly infections but also diseases (e.g., malignant brain tumors and multiple sclerosis).

Lyme disease vaccine. A Lyme disease vaccine that consists of recombinant Borrelia burgdorferi outer surface lipoprotein A, was approved by the Food and Drug Administration in 1998. In one clinical trial, the vaccine was 69 percent effective in preventing Lyme disease after exposure.[3] A similar vaccine, based on outer surface protein A, has completed a phase III clinical trial.

Companies are collaborating to develop a second generation combination vaccine composed of decorin-binding protein A and outer surface protein A. It is believed to be more efficacious in preventing infection by *Borrelia burgdorferi* and related species in mice than vaccination with either immunogen alone. The companies intend to use decorin-binding protein A for the development of European and improved American vaccines for the prevention of Lyme disease.

Because the vaccine is expensive and the risk of infection in a low-risk area is minimal, cost-effectiveness is a consideration. The Lyme disease vaccine is cost-effective only for individuals who live in areas where Lyme disease is endemic and who are frequently exposed to ticks.[4]

Herpes Zoster vaccine. In May 2006, the U.S. FDA approved the first Herpes Zoster vaccine, Zostavax, which is intended to reduce the risk of herpes zoster in persons 60 years of age and older. Zostavax markedly reduced morbidity from herpes zoster and postherpetic neuralgia among older adults in a randomized controlled trial.[5]

Cytomegalovirus vaccine. The manner in which cytomegalovirus stimulates the immune system is not known. It is a complex virus that encodes for hundreds of proteins, and the portions of the virus that are needed to make a protective immune response have not been determined adequately. The Towne strain of the virus has been used for years in vaccines and is safe, but it is overly attenuated. A hybrid virus has been produced by combining Towne and Toledo strains of cytomegalovirus and is the basis of a vaccine undergoing phase I clinical testing in subjects who are seropositive for cytomegalovirus.

If found to be safe, it will be used to cut the toll of congenital neurologic defects caused by the cytomegalovirus infection in utero. A canarypox vector-expressing cytomegalovirus phosphoprotein 65 has been shown to induce long-lasting cytotoxic T-cell responses in cytomegalovirus-seronegative subjects and is potentially useful in preventing the disease caused by cytomegalovirus.[6]

Meningococcal meningitis vaccine. Commonly available vaccines contain purified polysaccharide from *Neisseria meningitidis* groups A and C or groups A, C, Y, and W135. The United Kingdom's Medicine Control Agency has approved a conjugate vaccine against disease caused by the bacterium. It was initially used in the United Kingdom for vaccinating children 12 months of age and older, adolescents, and adults. Market approval in the United Kingdom was also granted to a group C meningococcal conjugate vaccine, MenC, that provides a longer and stronger immune response across a wider age range than nonconjugate vaccines. MenC has proved to be highly safe and effective, but there is some uncertainty about the duration of effectiveness of this vaccine, even though it is extended by booster doses.[7]

Menactra, a polysaccharide diphtheria toxoid conjugate vaccine for protection against meningococcal meningitis in adolescents and adults, was approved by the FDA in January 2005. It has completed clinical trials in 7,500 participants and has shown

Table 2. Genetically Engineered Vaccines

Approach	Basis	Example
Genetic engineering of an organism	Deletion or mutation of a gene encoding virulence of the organism.	Simian immunodeficiency virus vaccine using deletion of Nef gene
Vaccinia viral vector	Gene transfer to deliver the antigen-encoding gene to the host.	HIV-1 vaccine for AIDS
Alpha virus vector	Alpha viruses are RNA viruses, and replicons are engineered to replace the gene with by a sequence encoding the antigen.	Venezuelan equine encephalitis
Bacterial vectors	Bacteria are engineered to serve as vectors for delivering plasmid DNA into cells that the bacterium invades.	Attenuated vector versions of Listeria monocytogenes for lymphocytic choriomeningitis vaccine
Nucleic acid vaccines: DNA and RNA vaccines	Bacterial plasmids carrying genes encoding pathogen or tumor antigens.	Several infectious diseases; Cancer vaccines
Dendritic cell vaccines	Human dendritic cells pulsed with RNA-encoded tumor antigen	Cancer vaccines

an excellent safety and immunogenicity profile. It is a quadrivalent conjugate candidate for the prevention of meningococcal infection caused by four serogroups of meningococcal disease: A, C, Y, and W-135.

Conventional research approaches to protect against different strains of meningococcal B disease have failed. The completion of the genome sequence of *N. meningitidis* represents a major step forward in the molecular understanding of an important human pathogen, and this information is now being used in the search for new vaccine candidates.[8] Using information derived from the DNA sequence, investigators were able to identify novel surface proteins in *N. meningitidis*. These newly discovered proteins behave differently from those previously identified and are present across a wide range of strains. These proteins can stimulate an antibody response capable of killing the bacterium.

This property is known to correlate with vaccine efficacy in humans. Work is now underway to identify the most promising vaccine candidates while incorporating one or more of these surface-expressed proteins. This genomics-based approach enables the creation of a vaccine capable of protecting against the broad diversity of invasive strains of this virulent microorganism. In one study, five antigens were formulated with adjuvants suitable for human use, and this vaccine induced bactericidal antibodies in mice against 78 percent of a panel of 85 meningococcal strains representative of the global population diversity.[9] If these results can be confirmed in clinical trials, universal protection can be provided against meningococcal B disease.

Gene expression profiling by using microarrays gives a better understanding of what happens when bacteria interact with the host cells. Microarray technology is considered a valid approach for identifying new vaccine candidates and complements other genome mining strategies used for vaccine discovery.[10]

Japanese encephalitis vaccine. A live vaccine for Japanese encephalitis has been in use for many years and is effective in preventing this disease in children without any serious adverse effects. A single dose of the vaccine is highly efficacious in preventing Japanese encephalitis when administered only days or weeks before exposure to infection.[11] A new, cell-culture derived, purified, inactivated virus vaccine was found to be safe in phase II clinical trials and induced immune response lasting up to two years after vaccination.[12] Phase III trials of this vaccine are planned.

Tick-borne encephalitis vaccine. Immunization with the whole-killed virus vaccine is shown to protect mice against a subsequent challenge with a highly lethal dose of tick-borne encephalitis virus. This protection is mediated by antibodies to the surface protein of tick-borne encephalitis virus, glycoprotein E. Although this vaccine is highly effective, protection has been shown to be nonequivalent with complete neutralization of the challenge virus. An inactivated and parenteral vaccine is commercially available for immunization against tick-borne encephalitis. It was tested in an accelerated immunization schedule in soldiers deployed in a peace-keeping force in the Balkans where tick-borne encephalitis is endemic.[13] It was found to be

safe and effective and led to the recommendation that this method be used for travelers on short-term notice.

Neuroprotective vaccine in neurodegenerative disorders. Immunological approaches to neuroprotection are based on the concept that T-cells can play an important role without causing autoimmune disorders. This could be accomplished by vaccination with a universal weak T-cell-reactive antigen. T-cells that home to the damaged area in the brain may modulate local microglial response and protect against neurodegeneration.[14] This concept is supported by experimental studies, but there is no product in development based on it.

Alzheimer's disease vaccine. Proteolytic processing of the amyloid precursor protein generates amyloid beta peptide, which is thought to be causal for the pathology and subsequent cognitive decline in Alzheimer's disease. A pathogenic mutation at the beta-secretase cleavage site in the amyloid precursor protein leads to increased beta-secretase cleavage of the mutant substrate. Immunization with a 42 amino acid form of the beta-amyloid peptide (AB42), significantly reduced pre-existing amyloid plaque and inhibited further plaque formation in the brains of transgenic mouse model of AD.[15] In December 1999 a pharmaceutical company initiated phase I clinical studies with AN-1792 for the treatment of Alzheimer's disease. It appeared to halt the progress of AD and was found to be safe and well-tolerated in phase I safety trials. Further development was discontinued in phase II in 2002 because of complication of encephalitis in patients treated with AN-1792. Release of antigenic peptides derived from beta-amyloid processing may enhance T-cell inflammatory responses accounting for the meningoencephalitis following amyloid-beta peptide immunization.[16]

Further animal experimental work continues on immunization with nonamyloidogenic amyloid beta derivatives, which represents a potentially safer therapeutic approach toward reduction of amyloid burden in Alzheimer's than using toxic amyloid beta fibrils. In contrast to active amyloid beta peptide immunization, passive amyloid beta antibodies can be targeted to the periphery to clear systemic amyloid beta rather than brain amyloid beta.[17] Disturbance of equilibrium between central and peripheral amyloid beta should then result in efflux of amyloid beta out of the brain, and subsequent removal of plaques.[18]

Cognitive functions were tested in patients who received a prime and a booster immunization of aggregated amyloid beta42 over a one-year period in a placebo-controlled, randomized trial.[19] Patients who generated antibodies against amyloid beta had significantly slower rates of decline of cognitive functions as compared to patients without such antibodies, indicat-

ing that antibodies against amyloid beta42 plaques can slow cognitive decline in patients with Alzheimer's disease.

Gene vaccination has been used to generate an immune response to amyloid beta42 that produces antibody response but avoids an adverse cell-mediated immune effect.[20] In contrast to previous amyloid protein-based vaccines for Alzheimer's, this is an amyloid gene-based vaccine.

Amyotrophic lateral sclerosis. An experimental vaccine, based on bacterially purified recombinant SOD1 mutant protein as an immunogen, has been tested in a mouse model of amyotrophic lateral sclerosis and reduced the SOD1 mutant protein levels.[21] These results suggest that immunization strategies should be considered as potential approaches for delaying the onset as well as for treatment of familial amyotrophic lateral sclerosis caused by SOD1 mutations.

Central nervous system trauma. Current evidence suggests that the injured central nervous system can benefit from autoimmune manipulations. Regulation of the immune system is required for the adequate phagocytic activity and growth factor activity. Boosting of this autoimmune response by vaccination is a potential strategy for neuroprotection.

Multiple sclerosis vaccine. Immunomodulators are used for the treatment of multiple sclerosis. Vaccines for infectious diseases have been tested for immunomodulating effect in multiple sclerosis. In a single crossover, MRI-monitored trial with Bacille Calmette-Guerin vaccine in patients with relapsing-remitting multiple sclerosis, MRI lesions were significantly reduced.[22]

T-cell receptor peptide vaccination is a novel approach to treating multiple sclerosis. NeuroVax, a combination vaccine of three T-cell receptor peptides (BV5S2, BV6S5 and BV13S1) is in phase II clinical trials for multiple sclerosis.[23]

Cocaine addiction vaccine. Vaccination has been investigated for cocaine addiction due to the lack of an effective therapeutic agent. With this strategy, cocaine is treated as an invading pathogen. Active immunization against cocaine is achieved by linking stable cocaine-like conjugates with a foreign carrier protein to activate the immune system to produce anti-cocaine antibodies. Anti-cocaine antibodies bind to cocaine and prevent it from crossing the blood-brain barrier, slow entry into the brain and prevent psychoactive effects on the brain. In an open clinical trial, the conjugated cocaine vaccine was well tolerated and cocaine-specific antibodies persisted at least six months with decreased use of cocaine.[24]

Brain tumor vaccine. It has been shown that antibrain tumor immune responses can be generated using cytokine-modified vaccines. Recent advances in the understanding of antigen presentation, antigen recognition, and T-cell activation have revolved around dendritic cells that are the most potent "professional" antigen presenting cells in the body. A vaccine containing dendritic cells derived from bone marrow and pulsed with peptides derived from autologous tumors has been tested in patients with glioblastoma and was not associated with any serious adverse effects. Among the treated patients, those with low TGF-beta 2 expression may represent a subgroup of glioma patients who would be potential responders in future clinical investigations of dendritic cell-based vaccines.[25]

DCVax, a dendritic cell-based immunotherapy, is an active immunization tailored to a specific cancer type with either purified tumor-specific antigens or tumor cell extracts derived from patients at the time of resection. DCVax-Brain is in phase II clinical trials for glioblastoma multiforme.[26]

The effect of human monoclonal antibody CLN-IgG on malignant glioma has been evaluated in patients. CLN-IgG was prepared by fusing a human lymphoblastoid B-cell line with lymphocytes obtained from a patient with the cervical carcinoma. A phase II study concluded that specific immunotherapy with CLN-IgG is safe and effective in patients with malignant glioma.[27]

A phase I study has demonstrated the feasibility, safety, and bioactivity of an autologous peptide-pulsed dendritic cell vaccine for patients with malignant glioma.[28]

Adverse Effects

Administration of a vaccine by injection may be followed by local reaction, possibly with inflammation and lymphangitis. Fever, headache, and malaise may occur a few hours following vaccination and last for one to two days. Hypersensitivity reactions may occur, and anaphylaxis has rarely been reported. Further details of adverse effects of vaccines are listed in the product inserts of various preparations.

Neurologic adverse effects of vaccines used for infections affecting the nervous system are sometimes difficult to distinguish from the manifestations of the disease. The most significant neurologic complication of vaccination is acute disseminated encephalomyelitis, a syndrome characterized by rapid development of multifocal neurologic dysfunction. Neurologic sequelae of smallpox vaccination in the 1920s led to an awareness that such complications can follow other vaccines. Acute disseminated encephalomyelitis has been reported in association with several vaccines. These include the rabies vaccine and the Japanese encephalitis vaccine. According to a meta-analysis, there is no evidence that hepatitis B, varicella, tetanus, or Bacille Calmette-Guerin vaccines increase the risk of multiple sclerosis exacerbations.[29]

Rabies vaccine. The incidence of encephalitis with original Pasteur vaccine, prepared in rabbit brain, was estimated to be from 1 to 3,000 vaccinations to 1 to 35,000 vaccinations. Various other preparations involving neural tissues continue to be associated with encephalomyelitis. Introduction of non-

neural tissue vaccines, particularly human diploid cell vaccine, have markedly reduced, but not eliminated the neurologic complications.[30] Cases of encephalitis, radiculitis, and acute inflammatory demyelinating polyradiculoneuropathy have been reported following rabies vaccination containing neural elements.[31]

Antitetanus vaccine. Antitetanus vaccination is generally safe but adverse effects such as neuropathy may occur. History of such vaccination should be considered in the differential diagnosis of neuropathies. An elderly person was reported to develop tetraplegia due to polyneuropathy within a few hours following antitetanus vaccination.[32]

Japanese encephalitis vaccine. The Japanese encephalitis vaccine has been used for childhood immunization programs in Asia since the 1960s and is generally considered to be safe. Neurologic side effects reported in larger vaccine trials in Asia range from one to 2.3 per million vaccines. A few patients have been reported to develop severe encephalitis-like illness with MRI changes indicating acute disseminated encephalomyelitis. Similar findings have been reported in naturally occurring Japanese B encephalitis.

Tick-born encephalitis. According to a safety study in Switzerland, adverse neurologic reactions after tick-borne vaccination are rare and reversible.[33] Most frequently reported adverse reactions were headache, neuropathy, and meningeal irritation.

DNA vaccines. Even though the DNA is not injected with adjuvant, induction of antibodies to DNA is always a possibility and might depend on the sequences found in the injected plasmid. However, the results obtained to date have indicated that high levels of high affinity antibodies are not induced. In addition, it has been shown that plasmid DNA can be reinjected at later times to boost the immune response. This suggests that any immune response to the DNA that might occur is not able to block the effect of subsequent injections of DNA.

Miscellaneous neurologic complications. Various reported neurologic complications not listed above include autism following measles vaccine, Guillain-Barré syndrome following influenza vaccine, and seizures following pertussis vaccination.[34]

Several case reports of the onset or exacerbation of multiple sclerosis or other demyelinating conditions shortly after vaccination have suggested that vaccines may increase the risk of demyelinating diseases. A case-control study showed that vaccination against hepatitis B, influenza, tetanus, measles or rubella is not associated with an increased risk of multiple sclerosis or optic neuritis.[35]

A strong association was found between the inactivated intranasal influenza vaccine used in Switzerland and Bell palsy.[36] This vaccine was withdrawn from clinical use.

There is a suggestion that the inflammatory response of amyloid beta vaccination in AD is dose-related. A low dose of vaccine with a rather small peptide or low levels of antibodies would help to keep the inflammatory response as low as possible. **PN**

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