first vaccines were similar to early pneumococcal vaccines, based on polysaccharides which were incapable of provoking a memory B-cell response. Because of the failure of these polysaccharide vaccines, protein conjugate *H. influenzae* vaccines were introduced, and have proved to be much more effective. Vaccines conjugated with at least four different carrier proteins have been developed: PRP-T, Hb-OC, PRP-OMP, and PRP-D. Of these, PRP-T seems to be the one which is most immunogenic and has become the most widely used vaccine. PRP-D is no longer used in children because of poor immunogencity. *H. influenzae* type B (Hib) vaccines may be administered separately or in combination with other vaccines.

Carriage of type B *H. influenzae* is reduced in vaccinated individuals, and this reduction in carriage provides a degree of herd immunity, as nonvaccinated children have a lower risk of coming into contact with the organism if they are exposed mainly to vaccinated persons.

On an epidemiological basis, since the introduction of conjugate Hib vaccines in developing countries, the incidence of serious infections due to type B *H. influenzae* has declined sharply. Overall, results of randomized trials demonstrate an 80% reduction in invasive disease caused by the pathogen. As noted above, this effect has been confirmed by epidemiologic surveillance which demonstrates the virtual elimination of invasive disease from type B *H. influenzae* in many parts of the USA. The vaccine is quite safe and is associated only with minor adverse effects.

Infections due to Nontypable *H. influenzae*

In adults, most serious infections are caused by nontypable *H. influenzae*, and vaccinations against these pathogens have proved to be much more difficult. At present, although there are several candidate vaccines in preclinical trials, none has shown significant promise, and the reality of an effective vaccine for nontypable infections remains in the future.

See also: **Pneumonia**: Overview and Epidemiology; Community Acquired Pneumonia, Bacterial and Other Common Pathogens. **Upper Respiratory Tract Infection**.

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Viral

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Abstract

Vaccines are preparations of weakened or killed viruses or viral subunits that trigger specific protective immunity. Vaccination is the single most effective tool for preventing communicable disease, highlighted by the achievements of the smallpox and poliomyelitis eradication programs and the rise in infections for which no effective vaccine is available: human immunodeficiency virus, malaria, worms, and tuberculosis. World Health Organization initiatives target acute respiratory diseases in infancy and early childhood with novel immunization approaches.

Effective vaccines are needed urgently for viral respiratory diseases, but progress has been disappointingly slow. Vaccine candidates often show reduced efficacy in infancy, in partially immune adults, the immunocompromised, and the elderly. However, several promising vaccines are in clinical trial, and it is likely that vaccines against respiratory syncytial virus and parainfluenza will be licensed within the next 5–10 years. Mucosally delivered influenza vaccine is now available, and novel adjuvants offer the prospect of better immunogenicity. Ideally, multivalent mucosal vaccines will be developed that provide protection against a spectrum of respiratory infections in specific target age groups.

History

The ability to grow viruses in eggs and tissue culture has allowed the development of most of the live and killed viral vaccines in current use. Killed whole virus

influenza vaccine was introduced in 1936, and vaccines against measles, mumps, and rubella came soon after World War II. These contributed substantially to the virtual eradication of these diseases from many industrialized countries. However, optimism was tempered by the trials of formalin-inactivated respiratory syncytial virus (RSV) and measles vaccines which lead to enhanced disease, with atypical measles rash or enhanced pneumonia, bronchiolitis, or bronchitis. This experience slowed progress and led to a more cautious approach in vaccine development.

Recent history is also characterized by withdrawal of apparently effective vaccines because of unacceptable side effects (e.g., vaccines for rotavirus and Lyme disease). Oral live attenuated adenovirus vaccination had been used in US army recruits since the 1970s, eliminating the frequent epidemics at trainee camps. But in 1996, the manufacturer of this vaccine ceased production and outbreaks of adenoviral respiratory illness re-emerged in military settings. Developing a new vaccine for adenovirus infection is a very expensive exercise.

The Burden of Disease

Viruses transmitted by the respiratory, gastrointestinal, and genital routes result in virtually all infections that propagate without the assistance of biting insects. Respiratory viruses are remarkably successful, causing very substantial morbidity and mortality in all parts of the world. About 200 serologically distinct viruses occupy this one ecological niche, but the most problematic pathogen changes with age: RSV, human metapneumovirus (hMPV), and parainfluenza are common in infancy, whereas rhinovirus and influenza predominate in older or elderly persons. The seasonality of many of these pathogens makes if difficult to plan efficient and economic health care for affected patients.

Each year, influenza A causes 13 000–20 000 excess deaths in the UK. Approximately 90% of these deaths are in persons aged 65 years or older. Influenza deaths have increased substantially in the last two decades, in large part because of an aging and increasingly dense population. Rhinoviruses and coronaviruses cause most common colds, but relatively little direct mortality. Although sometimes considered a minor nuisance, they may infect the lower respiratory tract and cause exacerbations of chronic bronchitis and asthma.

The effects of viral diseases during infancy are exacerbated by conditions such as prematurity, cardiac, or pulmonary diseases. RSV is the major cause of infantile hospitalization and infects about 65% of children in the first year of life, and parainfluenza accounts for approximately 20% of respiratory hospitalizations in children. Interestingly, parainfluenza virus 3 (PIV-3) peaks in late spring or summer, whereas peaks of PIV-1 and PIV-2 occur at one- or two-yearly intervals in the late autumn or early winter. Adenovirus causes 8–15% of all respiratory diseases in children younger than 5 years old. The emergence of new respiratory pathogens (e.g., severe acute respiratory syndrome (SARS) and avian influenza) to which we have little resistance, is a particular threat to human health and prosperity.

Challenges and Opportunities in Respiratory Viral Vaccination

A global alliance in the area of respiratory vaccination has been supported by a $750 million donation from the Bill and Melinda Gates Foundation, but there are difficulties in developing vaccines that will work in target populations. In neonates, the presence of maternal antibodies and the nonmature immune system are major challenges and in the elderly immune responses tend to be relatively weak and ineffective. The rapid rate of viral mutation and the presence of different strains each year, together with the fact that infection with one strain offers no substantial immunity to another, provide the key challenges to the advancement of vaccine technology.

An additional specific issue with emerging pathogens is the difficulty of predicting the viral strain and responding rapidly once it has been identified. For pandemic influenza, very large quantities of vaccine would be required in a short time to make significant impact in the face of a spreading epidemic that could kill a significant proportion of the world's population in 4–6 months, the time required for vaccine production. Novel technology may assist in accelerating vaccine production. For example, cell culture could be more suitable than embryonated chicken eggs. However, the safety of growing large bulk stocks of lethal viruses for purification or inactivation is an additional concern.

A major hurdle for RSV vaccine development is the possible enhancement of disease during subsequent natural infection. Formalin-inactivated RSV (FI-RSV) vaccines were tried in normal children in the 1960s, but vaccinees were not protected. Moreover, those that became naturally infected suffered an increased rate of hospitalization due to pneumonia, bronchiolitis, rhinitis, or bronchitis. This enhancement was clearly caused by an overexuberant immune response, but the exact reasons for the effect are still unclear. The full elucidation of mechanisms involved in vaccine-enhanced disease is crucial to the development of future RSV vaccines.

Ideal Vaccines

Any new vaccine must be completely safe. According to the 'precautionary principle', any possibility of side effects (even theoretical) can call a halt to development, or cause the vaccine to be withdrawn. This is especially true of vaccines for children, and for the prevention of so-called trivial diseases. The costs of developing a single candidate vaccine are growing at about 12% per year and now approach $1 billion; novel technologies and concepts are not expected to reduce the price significantly. On average, it now takes 15 years to make a new vaccine (Figure 1).

Ideally, vaccines should confer long-lived protection after a single dose and should be easy to manufacture on a large scale. The final product should resist extremes of temperature and be convenient to store and use. They should also be available as combinations (to reduce the number of injections needed) and be effective by local (needle-free) administration. The licensing of vaccines should be global so as to bypass the need for costly local approval processes.

Uses in Respiratory Medicine

The most widely used and effective vaccines against respiratory viral infections are the inactivated purified subunit influenza vaccines. These are made from hemagglutinin and neuraminidase proteins, produced from the currently circulating influenza strains. The composition of these vaccines is decided each year according to the exact strains likely to cause winter influenza, determined the previous spring by expert international committees. The influenza isolates most likely to spread globally are selected, expanded by culture in embronated eggs and tested by limited immunogenicity study in human volunteers. The different vaccine preparations are not tested for efficacy in preventing influenza infection or symptoms. These vaccines are based on the assumption that induction of antibody is necessary and sufficient to protect against influenza.

These normal vaccines have no efficacy against other strains of influenza, and are ineffective against emerging or mutant strains. A particular problem is that cross-species transmission of avian influenza (e.g., H5N1 or the 1918 Spanish influenza strains) is

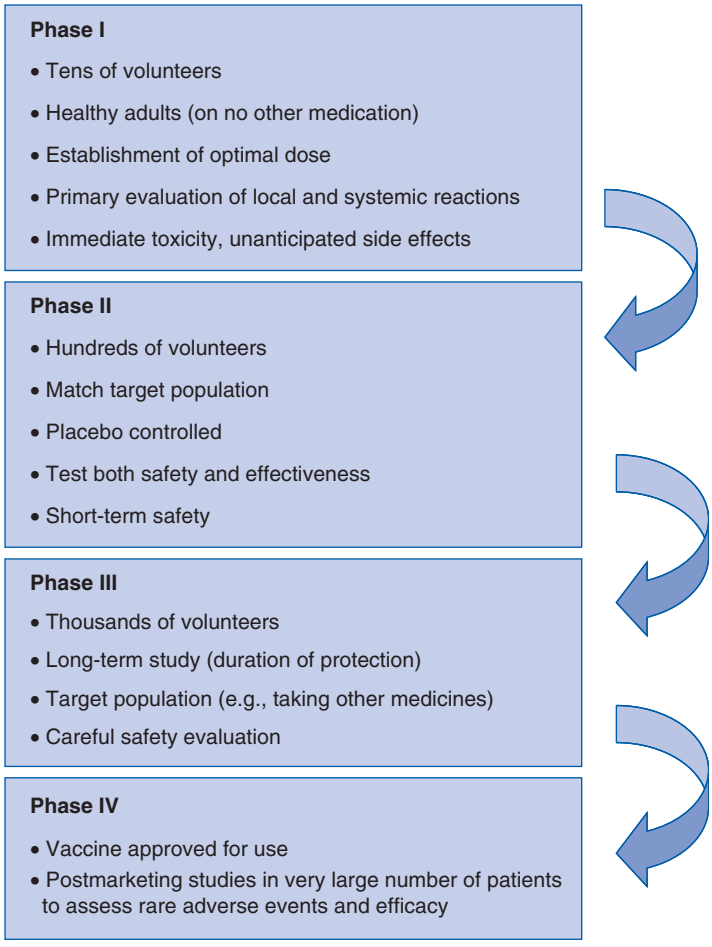

Figure 1 Procedure of clinical testing of a potential vaccine.

not prevented by these vaccines. An important priority is therefore to develop new methods of vaccination that extend the specificity of vaccines, giving at least some protection against newly emerging strains of influenza.

Inactivated vaccines have been in use for more than 60 years, but tend to be associated with local side effects (**Table 1**). Live attenuated vaccines offer significant advantages, particularly when applied mucosally. They can be highly immunogenic, inducing good serum antibody levels, mucosal immunoglobulin A (IgA), and T cell responses. Cold-adapted live influenza vaccines have been widely evaluated in the US and Japan since 1975. Development continues, and a recent live attenuated, cold-adapted influenza virus vaccine was found to be 93% effective against influenza A (H3N2) in healthy children. For example, FluMist (MedImmune) is available for intranasal use in healthy persons aged 5–49 years. Paradoxically, it seems that protection can be seen in the absence of serum antibody under some circumstances, challenging the view that antibody is essential for protection.

Attenuated cold-passaged RSV vaccines *(cpts*RSV 248 and *cpts*RSV 530) have entered clinical trial. However, some insufficient attenuations lead to otitis media. The more attenuated *cpts*RSV 248/404 appears to be safe, infectious, and immunogenic in seronegative children, only causing upper respiratory tract congestion in some young infants. Currently, methods of achieving full attenuation without the possibility of reversion to virulence are being tested, including deletion or insertion of entire genes. It is not clear whether genetically modified live viruses will be acceptable to the regulatory authorities and the public. Purified RSV glycoproteins have also been tested as vaccine candidates, and shown to induce neutralizing antibodies. They are effective in cotton rats and do not appear to enhance pulmonary pathology. Clinical trials have been performed with the F protein (PFP-1), purified by immunoaffinity chromatography from RSV-infected cell lysates. This was tested in seropositive children, inducing an eightfold increase in serum-neutralizing antibodies and a reduced risk of subsequent infection. Further studies in seronegative infants showed that multiple immunizations were

Table 1 Summary of common methods of vaccine preparation

Active immunization	*Explanation*	*Advantages*	*Disadvantages*
Whole virus	Inactivated using physical or chemical means to destroy the integrity of viral particles Heterologous virus to induce milder/cross-protective disease	No residual pathogenicity No chance of reversion to wild-type infectious virus	Poor inducers of cellular immunity No long-lasting immunity Batch testing required to ensure no residual virus Expensive Examples of enhanced disease
Live attenuated (mutated) virus	Can be random or specifically site directed resulting in subclinical disease	Mimics natural infection, most efficacious induction of immunity Long-lasting immunity Less expensive to manufacture	Residual pathogenicity Possibility of reversion to wild-type virus Requires cold storage
Antigenic fragments or peptides	Purified antigen from the virus, usually present on surface of virus to which immune response is directed	Safer, as not whole virus	Industrial-scale production can be difficult and thus expensive (purification, stabilization)
DNA	Using plasmid vectors encoding protein of choice	Safe, simple Easily manufactured on a large scale Well defined, characterized, and controlled	Not very immunogenic, require large volumes to induce responses in humans
Genes cloned into living viral vector	Viruses can be engineered to introduce new genetic sequences from viral target	Directly infects target cells of the immune system Highly immunogenic	Prior immunity to carrier virus in target population can reduce immunogenicity Limits to size of insert without compromising replication of carrier virus

required to achieve high antibody titers. A more highly purified preparation (PFP-2) has been tested in children suffering from bronchopulmonary dysplasia and shown to be safe. It is not yet clear if it is effective.

Formalin-inactivated parainfluenza vaccine is also nonprotective against infection. Live-attenuated PIV-3 and cold-adapted PIV-3 vaccine candidates are undergoing testing. For example, cp45 has been shown to be genetically stable, safe, and appropriately attenuated and immunogenic, even in infants as young as 1 month of age. Vaccines that are genetic hybrids of bovine PIV-3 with human coat proteins are being tested. A vaccine for parainfluenza has reached phase II in clinical trials, tested in 2 month old infants for safety, tolerability, infectivity, and immunogenicity.

Emerging Respiratory Viruses

Human metapneumovirus Human metapneumovirus (hMPV) was discovered in 2001, but has been ubiquitous for at least 50 years and in all parts of the globe. It is now known to be the second most important cause of respiratory tract infections in young children. Clinical symptoms are similar to those of RSV and co-infection is sometimes seen, possibly leading to more severe disease. RSV and hMPV belong to the same family of viruses (Paramyxoviridae), and a vaccine effective against both viruses would be highly desirable. Genetic hybrids of bovine PIV-3 expressing the fusion protein of hMPV are protective, immunogenic, and attenuated in African green monkeys, and warrant further evaluation in humans.

Severe acute respiratory syndrome Severe acute respiratory syndrome (SARS) spread alarmingly in Southeast Asia in 2002–03. It was rapidly discovered that a coronavirus (SARS-CoV) was the cause, probably from wild-caught animals (e.g., via civet cats). The high mortality rate and potential for rapid spread gave great urgency to conventional (Table 2) and DNA vaccine initiatives (Table 3). A range of animal models has been used for testing, as no single model seems ideal. One particular concern is the possibility of enhancing disease (in a manner similar to that seen with formalin-inactivated RSV and feline peritonitis due to a coronavirus infection of cats), an effect already seen in murine models of SARS. Since SARS has now disappeared, it now seems unlikely that the opportunity will arise to test vaccine efficacy.

Avian influenza A viruses A more worrying problem is the emergence of avian influenza A viruses (IAVs). These have spread from wild aquatic birds to domestic poultry, and cause sporadic infections in

Table 2 Viral-vectored vaccines against SARS

Viral vector	*Encoded antigen*	*Animal model*	*Route of immunization*	*Antibody response*	*T-cell response*	*Challenge?*	*Protective immunity*
Adenovirus (Ad5)	S,M,N	Macaques	Intramuscular	✓ (S)	✓ (N)	No	
MVA	S	BALB/c mice	Intramuscular and intranasal	✓	×	Yes	Reduced viral titers
Attenuated parainfluenza virus (BHPIV-3)	S	African green monkeys	Intranasal, intratracheal	✓	×	Yes	

S, spike protein; N, nucleocapsid; M, membrane protein of SARS-CoV; MVA, modified vaccinia Ankara.

Table 3 DNA vaccines against SARS

Encoded antigen	*Animal model*	*Route of immunization/ delivery method*	*Antibody response*	*T-cell response*	*Challenge?*	*Protective immunity*
S	BALB/c mice	Intramuscular	✓	✓	Yes	Reduced viral titer
N	C57BL/6 mice	Gene gun delivery	✓	✓	Yes, with rVV-N	Reduced viral titer
N	C3H/He mice	Intramuscular	✓	✓–CTL	No	
N	BALB/c mice	Intramuscular	✓–Dominant IgG2a	✓–CTL	No	
M and N	SCID-PBL/hu mice	Intramuscular	×	✓–CTL induction and T-cell proliferation	No	

S, spike protein; N, nucleocapsid; M, membrane protein of SARS-CoV; rVV-N, recombinant vaccinia virus expressing N protein of SARS-CoV; CTL, cytotoxic T lymphocytes.

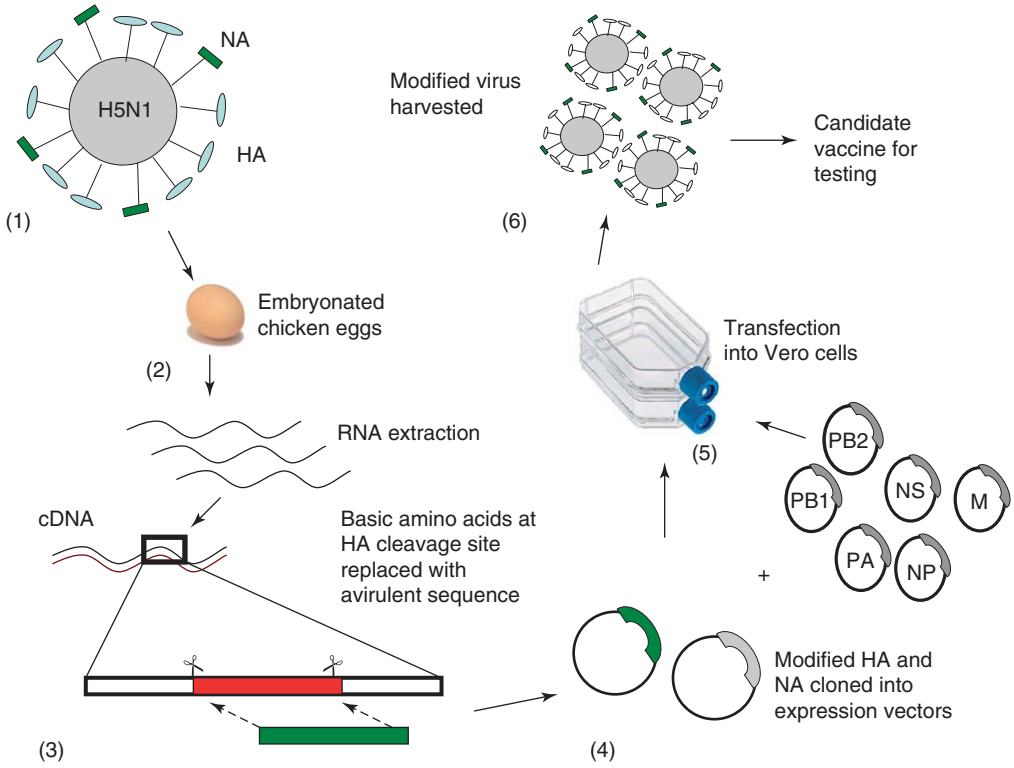

Figure 2 Molecular approach to production of influenza vaccine as discussed by Webby RJ *et al.* (1) H5N1 virus passaged in 10-day-old embryonated chicken eggs. (2) Total RNA is extracted and used to create a cDNA copy for polymerase chain reaction (PCR). (3) PCR used to amplify HA and NA genes using primers designed to modify specific sites in the sequence known to be associated with avirulent virus. (4) PCR products cloned into mammalian expression vector. (5) These plasmids and the six other plasmids expressing the remaining genes are transfected into Vero cells to reform the avirulent virus. (6) After 72 h of culture, cell supernatants are harvested and the virus extracted for testing. H, HA, hemaglutinin; N, NA, neuraminidase; NP, nucleoprotein; M, matrix protein; NS, non-structural protein; PB1, PB2, PA, RNA polymerase proteins.

humans. Initial reports came from Asia where H5N1 IAV was found to cause disease in chickens, big wild animals, and pet cats. Among 129 confirmed cases of H5N1 IAV infected humans, 60 were fatal by the time of writing (October 2005). Infections have been reported in the Netherlands (H7N7), the USA (H7N2), Hong Kong (H9N2), Canada (H7N3), and Egypt (H10N7), leading to fever, cough, and/or conjunctivitis progressing to respiratory failure and death in some infected persons. A major problem will be the ability to identify the correct subtype, scale up production, test vaccine stocks, and send out supplies of vaccine in time to have a significant impact on worldwide spread (Figure 2).

Vaccines for the Twenty-First Century

Genetically Engineered Vaccines (Recombinant DNA Technology)

As previously described, it is now possible to genetically engineer not only DNA virus vectors, but to create novel RNA viruses by reverse genetics. It is therefore feasible to coexpress cytokines or chemokines from the host to cause selective enhancement of certain types of immunity that may be protective and non-pathogenic, reducing reactivity of a vaccine and lessening the chances of disease augmentation. Mutations in spontaneous attenuated mutants can be identified and engineered, and intelligent knockout live vectors created. In the long term, it may be possible to understand the reasons why some pathogens evade immune recognition and persist. Once this is understood, vaccines that are able to modify immune responses to clear persistent infections may become feasible.

'Naked DNA' Vaccines

Injection of DNA that encodes viral antigens that confer protective immunity is able, under some conditions, to trigger protective immune responses (Figure 3). This surprising effect seems to be due to DNA uptake by antigen-presenting cells, and subsequent protein expression. Typically, the response includes cytotoxic T cells and in some cases good antibody responses. DNA has the advantage of stability and safety, but needs to be given in large quantities to achieve immunogenicity. There is

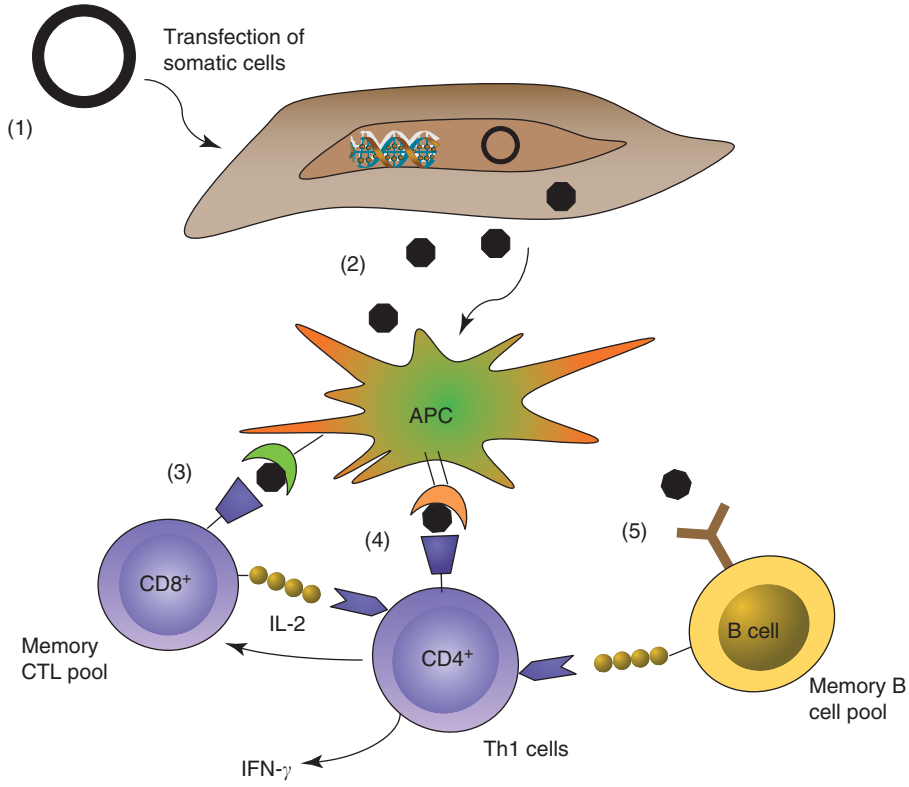

Figure 3 How DNA vaccination works. (1) DNA vaccine administered intramuscularly by injection or gene gun targets myocytes or keratinocytes. Once inside the target cell, the specified antigen is expressed using DNA replication material present. (2) APCs can be directly transfected with the plasmid, or the target cell acts as the APC directly. However, the majority of evidence exists for the secretion of antigen and phagocytosis/endocytosis by APCs for presentation via either the major histocompatibility complex (MHC) class I or class II pathways. (3) Presentation via MHC class I induces $CD8^+$ T cells to differentiate into effector and memory T cells, with the capacity to kill virus-infected cells. (4) Presentation via MHC class II induces $CD4^+$ T-cell activation. In turn, these cells, known as helper T (Th1) cells, function to promote B-cell antibody production and survival via CD40L–CD40 stimulation. This same interaction and interleukin (IL-2) secretion acts to help $CD8^+$ T-cell functions. $CD4^+$ T-cells also secrete a multitude of cytokines (e.g., interferon gamma, IFN-γ) with consequent immunoregulatory effects. (5) A humoral response is also elicited following antigen encounter, which can lead to a pool of memory B cells as well as neutralizing antibody production.

currently much interest in finding ways to make lower quantities of DNA immunogenic with adjuvants, and to deliver DNA vaccines using gene guns or by mucosal administration.

See also: **Antiviral Agents**. **Human Immunodeficiency Virus**. **Pneumonia**: Viral. **Viruses of the Lung**.

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VASCULAR DISEASE

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Abstract

Pulmonary arterial hypertension is defined as a mean pulmonary artery pressure above 25 or 30 mmHg with exercise. Pulmonary arterial hypertension may be idiopathic, familial, or associated with conditions such as congenital heart disease, liver disease and connective tissue disease. Pulmonary artery hypertension may also occur after ingestion of appetite suppressant drugs and toxic oils.

The histological sequential changes are smooth muscle hypertrophy of the arterial wall, intimal proliferation, *in situ* thrombosis, small vessel occlusion, and the formation of plexiform lesions. The cross-sectional area of the pulmonary vascular bed is diminished severely by small vessel obliteration. The progressive and sustained elevation in pulmonary vascular resistance leads to right heart insufficiency. After the onset of symptoms, the clinical course is unremitting with progressive right heart failure until death. Until the last decade, conventional therapy was limited to digoxin, diuretics, calcium channel blockers, and warfarin anticoagulation. Median survival was 3.5 years. However, therapies now include prostacyclin and analogs delivered intravenously, subcutaneously or by inhalation, endothelin receptor blockers (bosentan), phosphodiesterase type 5 inhibitors (sildenafil), and continuous inhalation of nitric oxide gas. Pulmonary veno-occlusive disease is a form of pulmonary arterial hypertension associated with significant venous involvement. It is usually idiopathic but may be associated with malignant disease or treatment, congenital heart disease, and autoimmune disease. Pulmonary veno-occlusive disease is difficult to treat and pulmonary edema may be exacerbated by vasodilators. Early lung transplantation is the current treatment.

Pulmonary arteriovenous malformations are characterized by abnormally large communications between the pulmonary arterial and venous systems. The physiological consequences are secondary to hypoxemia caused by the right to left shunt of desaturated pulmonary arterial blood into the pulmonary vein without traversing the pulmonary vascular alveolar interface.

The etiology of pulmonary arteriovenous malformations may be idiopathic, or associated with hereditary hemorrhagic telangiectasia syndrome (Osler–Rendu–Weber syndrome), in patients with liver disease associated with portal hypertension. Pulmonary arteriovenous malformations complicate the course of patients with complex congenital heart disease who receive palliation with a superior cavopulmonary anastomosis. Treatment is by coil embolization of large malformations.

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is defined as a mean pulmonary artery pressure above 25 mmHg or 30 mmHg with exercise. PAH may be idiopathic, familial, or associated with other conditions such as congenital heart disease, liver disease, and connective tissue disease. It may also occur after ingestion of appetite suppressant drugs and toxic oils.

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The early descriptions of pulmonary hypertensive disorders were histological. In 1891, E von Romberg described histological features of 'pulmonary sclerosis'. In 1901, Dr A Ayerza described a syndrome of chronic cyanosis, dyspnea and polycythemia associated with pulmonary artery sclerosis. The etiology of the disease was obscure and obscured further by attributing it to syphilis. Brenner, in 1935, observed the disease to be a manifestation of right heart failure secondary to pulmonary disease. The introduction of cardiac catheterization allowed not only direct measurement of pulmonary pressures but also investigation of the functional state of the pulmonary vascular bed. In the late 1940s and 1950s hypoxic vasoconstriction