**Microbial infection**
For many autoimmune diseases, there is compelling evidence that infection can trigger some forms of autoimmune disease via 2 possible mechanisms:

1) **Release from resting state**
During infection, circulating autoreactive T cells (in an anergized or suppressed state) are activated and start destroying tissue

2) **Molecular Mimicry**
Example is rheumatic fever - inflammation of heart following throat infection with *Streptococcus pyogenes*

During infection, antibodies are generated that are specific for cell Ag’s of *S. pyogenes* but also cross-reactive to epitopes expressed by epitopes present within heart, joints, and kidneys
Molecular Mimicry - resemblance between microbial antigen and host tissue antigen(s)

Figure 11-29 The Immune System, 2/e (© Garland Science 2005)
<table>
<thead>
<tr>
<th>Infection</th>
<th>HLA association</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A Streptococcus</td>
<td>Not known</td>
<td>Rheumatic fever (carditis, polyarthritis)</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>HLA-B27</td>
<td>Reiter's syndrome (arthritis)</td>
</tr>
<tr>
<td>Shigella flexneri, Salmonella typhimurium, Salmonella enteritidis, Yersinia enterocolitica, Campylobacter jejuni</td>
<td>HLA-B27</td>
<td>Reactive arthritis</td>
</tr>
<tr>
<td>Borrelia burgdorferi</td>
<td>HLA-DR2, DR4</td>
<td>Chronic arthritis in Lyme disease</td>
</tr>
<tr>
<td>Coxsackie A virus, Coxsackie B virus, echoviruses, rubella</td>
<td>HLA-DQ2, HLA-DQ8 DR4</td>
<td>Type 1 diabetes</td>
</tr>
</tbody>
</table>
Mimicry between self-peptide and pathogen peptide may result in generation of autoimmunity

First panel shows the same MHC molecule presenting both a pathogen peptide and a self-peptide that mimics it. The second panel shows naive T cell activated by the pathogen peptide. This activated CD4 Th1 cell can activate a macrophage presenting the self-peptide mimic, as shown in third panel – resulting in inflammatory reaction.
Induction of HLA class II expression on tissue cells facilitates autoimmunity. When tissues become inflamed, some cells are induced to increase the expression of MHC class I and class II molecules. These changes – which increase the number of different peptide Ags presented by a cell – can lead to interactions with clones of T cells that are potentially reactive. When IFN-γ is expressed, it induces MHC class II expression on cells that normally do not express these molecules. Although induced expression of MHC class II in the absence of co-stimulatory molecules is insufficient to activate naïve T cells, it elevates potential for autoimmune disease. For example, following infection DCs are able to pick up and present tissue-specific proteins from dead, apoptotic, or infected cells. Naïve autoimmune T cells could then be stimulated by a professional APC whereupon activated effector T cells are capable of entering infected tissue and directly attacking healthy cells making tissue-specific protein.
Animal models have benefited our understanding of how T cells contribute to autoimmune diseases.

EAE – experimental autoimmune encephalomyelitis – model for MS

Inject purified proteinase components from myelin sheath -> trigger disease i.e. destruction of myelin (can even use peptide derived from these proteins to trigger disease)

Can also adoptively transfer disease via injection of autoreactive T cells into MHC-matched mouse. T cells are autoreactive to myelin components.

![Diagram showing steps of EAE induction and disease mediation.](image)
Transgenic mouse model of virus-induced diabetes - elegantly tests molecular mimicry theory
Autoimmune diseases are usually initiated with a lymphocyte response directed to limited number of self-peptide antigens. However, as time goes by the number of self-antigens inducing T cell/B cell responses can increase - known as Epitope Spreading.

This can occur as a result of cryptic epitopes being revealed during the course of disease e.g. MS. This occurs because targeted tissue is gradually being destroyed resulting in the uptake, processing, and presentation of self-proteins the immune system is not normally sensitized.

Also - in SLE, T cells specific for self-peptide can stimulate B cells specific for DNA (T cells can not recognize nucleic acids)
Broadening of immune response in SLE. SLE patients have an ever broadening immune response against nucleoprotein Ags including histones and DNA. A single autoreactive CD4 clone (recognizing H1 peptide) can lead to diverse B cell response to nucleosome components. B cells at top bear Ag receptor specific for surface epitopes of nucleosome e.g. H1 and DNA. Internalization and processing leads to presentation of H1 peptides to autoreactive CD4 T cells which subsequently stimulate B cells to produce either anti-H1 or anti-DNA antibodies.
Broadening T cell response to nucleosome in SLE patients. H1-specific B cell (Ag receptor recognizes H1) has processed an intact nucleosome and is presenting a variety of nucleosome-derived peptide Ags on MHC class II molecules. This B cell can activate a T cell specific for any of these peptide Ags which will include those from internal histones H2, H3 and H4 (as well as H1).
VACCINATION

Smallpox - viral pathogen that has killed ~ 300 million People in the 20th century

Has been eradicated from human population through Vaccination

Numerous civilizations recognized that people that survived Smallpox were extremely resistant to re-infection

Thus, the process of “variolation” - whereby scabs were collected from smallpox patients, dried, and inhaled or rubbed into open lesion of skin
Records from Sung Dynasty (China) from 960-1280 indicate that variolation was practiced in some form to protect people from smallpox.

During Revolutionary War, George Washington was so concerned that the British would use smallpox as a weapon that he had entire Continental Army variolated.
Edward Jenner - British physician noticed that many cowmaids had perfect skin

More importantly, recognized that those cowmaids that had been exposed to cowpox were protected from smallpox

Therefore, he reasoned that cowpox infection elicited some form of protection against infection by smallpox

Thus, the field of vaccination was developed whereby dried scabs from cowpox lesions were used to vaccinate people and this resulted in protection from disease
REPORTS
OF A
SERIES OF INOCULATIONS
FOR THE
VARIOLE VACCINE,
OR
COW-POX;
WITH
REMARKS AND OBSERVATIONS ON THIS
DISEASE, CONSIDERED AS A SUBSTITUTE FOR
THE
SMALL-POX.

By WILLIAM WOODVILLE, M.D.
PHYSICIAN TO THE SMALL-POX AND INOCULATION HOSPITALS.

London:
PRINTED AND SOLD BY
James Phillips and Son,
GEORGE-YARD, LOMBARD-STREET.
1799.
Jenner’s strategy - unique in that the pathogenic smallpox virus (cowpox virus) had a natural safe counterpart that has shared antigenic determinants that elicit protective immunity to smallpox.

![Diagram showing the interaction between cowpox and smallpox viruses and the role of cowpox antibodies in binding and neutralizing the smallpox virus.]

*Figure 12-1 The Immune System, 2/e (© Garland Science 2005)*
Important considerations for vaccine development
1) Type of infection - extracellular (Ab) or intracellular (T cell)
2) Good protection at site of entry i.e. mucosal protection
3) Vaccine must be safe - and public convinced of safety
4) Limited to no serious side effects

Ex. Bordetella pertuss – bacterial pathogen, causes whopping cough

Turn of century, Bordetella killed ~ 0.5% of US children

Vaccine using whole cell (killed) developed in 1940’s – resulted in <0.002% death

Problems – some reports of brain damage/death as a result of vaccination (not confirmed in all medical communities and there was greater morbidity from whopping cough as compared to the vaccine)

However, public sentiment changed and it was generally considered that the whole cell vaccine was dangerous

Research focus turned to evaluate the natural immune response to the bacterium – Ab developed to toxin, hemagglutinin and surface associated Ag’s

New vaccine (currently in use) is acellular i.e. consists of purified toxin (inactivated) and other Ag’s
<table>
<thead>
<tr>
<th>Features of effective vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Safe</strong></td>
</tr>
<tr>
<td>Vaccine must not itself cause illness or death</td>
</tr>
<tr>
<td><strong>Protective</strong></td>
</tr>
<tr>
<td>Vaccine must protect against illness resulting from exposure to live pathogen</td>
</tr>
<tr>
<td><strong>Gives sustained protection</strong></td>
</tr>
<tr>
<td>Protection against illness must last for several years</td>
</tr>
<tr>
<td><strong>Induces neutralizing antibody</strong></td>
</tr>
<tr>
<td>Some pathogens (such as poliovirus) infect cells that cannot be replaced (e.g., neurons). Neutralizing antibody is essential to prevent infection of such cells</td>
</tr>
<tr>
<td><strong>Induces protective T cells</strong></td>
</tr>
<tr>
<td>Some pathogens, particularly intracellular, are more effectively dealt with by cell-mediated responses</td>
</tr>
<tr>
<td><strong>Practical considerations</strong></td>
</tr>
<tr>
<td>Low cost-per-dose</td>
</tr>
<tr>
<td>Biological stability</td>
</tr>
<tr>
<td>Ease of administration</td>
</tr>
<tr>
<td>Fewside-effects</td>
</tr>
</tbody>
</table>

Fig 14.23 © 2001 Garland Science
Methods for generating safe vaccines for virus:

1) Killed/inactivated virus - influenza, rabies, Salk polio vaccine
   • Requires viruses whose nucleic acid can be reliably inactivated;
   • Drawback is that large preparations of virus must be generated in order for vaccination

2) Live-attenuated viruses - more potent in eliciting protective immune response due to ability to replicate to certain extent. Examples include: Measles, mumps, polio (Sabin), and Yellow fever
   Attenuation can be achieved by passage virus through cells from nonhuman species
3) Subunit vaccines - identify key immunogenic targets on virus
Generally these are surface components e.g. allow virus to bind/enter host cell

Examples: Hepatitis B

BACTERIAL VACCINES

- limited number of vaccines using live-attenuated bacteria (ex. Bacille Calmette-Guerin (BCG) which is used in some countries - not USA - for protection Against tuberculosis)

- key feature of many bacterial pathogens is that disease is the result of toxins secreted by the pathogen ex. Diptheria and tetanus. Vaccines against these pathogens are directed towards the toxin e.g. diptheria and tetanus toxin.

- These toxin’s usually rendered inactive via formalin treatment

- combinatorial vaccines include several toxins e.g. DTP - Diptheria, Tetanus, & Pertussis
Bacterial vaccines can also target polysaccharide capsule - Ex. Pneumococcus, salmonellae, the meningococcus.

-under normal circumstances, capsule prevents C’ fixation therefore -Bacteria are protected from this component of the innate immune response

- Ab bound to capsule can fix C’ and lead to clearance.

- This type of subunit vaccine composed of purified capsular polysaccharide is effective in adults in that they can generate a T-independent Ab response.

- This type of vaccine is ineffective in children under 18 months of age in that they have not yet developed good T-independent responses

-To solve this problem, conjugate vaccines have been generated in which polysaccharide is conjugated to protein (ex. Tetanus toxin) which generates good T cell response to peptide -> also drives Ab production to polysaccharide via signaling to B cell with receptor specific for polysaccharide
Conjugate vaccines enhance Ab response via generated T cell help

Fig 9.4 © 2001 Garland Science
<table>
<thead>
<tr>
<th>Vaccine given</th>
<th>1 month</th>
<th>2 months</th>
<th>4 months</th>
<th>6 months</th>
<th>12 months</th>
<th>15 months</th>
<th>18 months</th>
<th>4–6 years</th>
<th>11–12 years</th>
<th>14–16 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria–tetanus–pertussis (DTP/DTaP)</td>
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<tr>
<td>Inactivated polio vaccine</td>
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<td>Measles/mumps/rubella (MMR)</td>
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<td>Pneumococcal conjugate</td>
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<td><em>Haemophilus B</em> conjugate (HiBC)</td>
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<td>Hepatitis B</td>
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<tr>
<td>Varicella (chickenpox virus)</td>
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Figure 12-3 The Immune System, 2/e (© Garland Science 2005)