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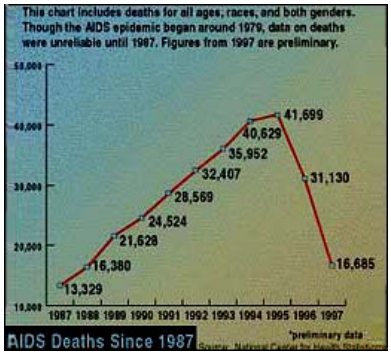
lecture #:	date:	professor:
31	Wednesday, April 4th	Dr. Desbarats
32	Wednesday, April 11th	Dr. Desbarats

announcements:

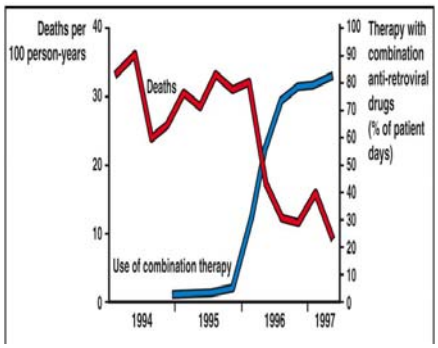
- Good luck on finals

LAST LECTURE REVIEW AND CONTINUATION: HIV & AIDS

- The most important thing about a virus affecting your immune system is that is impacts your T-cells.
  - *We will discuss this more when we talk about vaccines.*
  - However, **this is what HIV does.**
- For a long time after AIDS was described in the late 1970s, there were no mechanisms in place to treat it.
  - Viruses are extremely hard to treat because they affect your own cells, unlike bacteria, which can be treated extracellularly. Therefore, it is hard to prevent a virus from functioning while maintaining self-cell function.



- Today, after much research, **antivirals** were developed. These are administered to patients via **triple therapy** or HAART [another name for triple therapy]. This treatment consists of two drugs. The first is called a **chain terminator**, which stop the retrovirus from replicating by terminating the chain during RNA replication. The next drug is a **protease inhibitor** which prevents the formation of gp 120, which is what the virus uses to bind to C4 cells to enter. The drug therefore **prevents replication and infection.**
  - This drug is fairly effective. *Note the graph to the right. Can you tell when the drug was introduced?*
  - However, the development of the drugs began an interesting **new social phenomenon**. People became less afraid of contracting AIDS, became more promiscuous and actually increased the occurrence of AIDS incidence.
  - ***This proves that biochemical policies and social conduct must work symbiotically to medicate people.***



- In the past thirty years many new infectious diseases have developed and then been discovered [*see chart to the right*]. This leads to the need for much more research.
  - New diseases, like HIV, are not unique and are continuously evolving sometimes according to an immune system treatment.
    - e.g. selecting for a specific MHC receptor that seems to be common in the general population and new diseases are thus emerging.

TABLE 17-5 EMERGING PATHOGENS RECOGNIZED SINCE 1973

Year	Pathogen	Disease
1973	Rotavirus	Major cause of infantile diarrhea globally
1974	Hepatitis C	Non-A, non-B hepatitis commonly transmitted via transfusions
1976	*Cryptosporidium parvum*	Acute chronic diarrhea
1977	Ebola virus	Ebola haemorrhagic fever
	Legionella pneumophilia	Legionnaires' disease
	Hantavirus	Haemorrhagic fever with renal syndrome
	Campylobacter jejuni	Enteric diseases distributed globally
1980	Human T-lymphotrophic virus I (HTLV-1)	T-cell lymphoma
1981	Toxin-producing strains of *Staphylococcus aureus*	Toxic shock syndrome
1982	*Escherichia coli* 0157:H7	Haemorrhagic colitis
	HTLV-II	Hairy cell leukemia
	Borrelia burgdorferi	Lyme disease
1983	HIV	AIDS
	Helicobacter pylori	Peptic ulcers
1988	Hepatitis E	Enteric non-A, non-B hepatitis
1990	Guanarito virus	Venezuelan haemorrhagic fever
1991	*Encephalitozzon hellem*	Conjunctivitis, disseminated disease
1992	*Vibrio cholenae* 0139	New strain of epidemic cholera
	Bartonella henselae	Cat scratch disease
1994	Sabia virus	Brazilian haemorrhagic fever
1995	Human herpes virus-8	Associated with Kaposi sarcoma in AIDS patients
1996	TSE causing agent	New variant of Creutzfeldt-Jakob disease (mad cow disease)
1997	Influenza A subtype H5N1	Avian influenza
1999	Influenza A subtype H9N2	New strain of human influenza
	Nipah virus	Encephalitis

- ***Take-Home Message:*** *initially, there were no treatments for AIDS. However, now we have made much progress, including antiviral drugs. This involves the administration of both a chain terminator [to prevent replication] and a protease inhibitor [to prevent infection of other cells]. Although this drug does not prevent acquiring AIDS, it helps keep it under control. In addition, social conduct must be accounted for even with the introduction of treatment.*

CANCER

OVERVIEW:

- Cancer is a huge problem and incidence is increasing. It is estimated that in the Canadian population, one in three people will get cancer. What's worse is that it is predicted in 2010 that these statistics will rise to affecting one in two people.
    - Therefore, we need to focus on new therapies because the methods we have now are not compensatory. These methods consist of poisoning your body so the cancer dies. However, it kills off a lot of normal cells and tissues at the same time.

- ***What is cancer?*** The uncontrolled proliferation of cells. They are trying to be immortal but in reality kills the rest of the body.
- ***What is the number one cause of cancer death?***
    - It is not normally the primary tumor, but the metastases caused elsewhere in the body via spreading of cancer cells.
    - Unless the tumor is in the brain or another primary critical area, normally it can be operated on and be removed.
    - However, the tumor can shed cells that move to other areas in the body and spread the cancer. These individual cells need to be found and killed to prevent death.

- ***Take-Home Message:*** *Cancer is the uncontrolled proliferation of cells. Although it is thought of as the formation of a primary tumor, this is not usually what causes the problems. It is the metastases caused by the shedding of tumor cells that is the large problem.*

THE CAUSES OF CANCER:

- ***What causes cancer?***
    - **1.** Viruses
    - **2.** Mutations
        - Caused by mutagens, chemicals and radiation altering the structure of the DNA
            - Radiation can include sunlight or chemical incidences like Chernobyl.

- Cancer is caused if the virus changes the way the cell grows or if the mutation changes the control over cell proliferation.
    - Each cell has an apoptosis pathway that will cause cell suicide if mutations increase to a specific point. In cancer cells though, these protective pathways have been disabled.

VIRUSES:

- *See the chart to the right* for viruses that can cause cancer. Not all viruses can cause cancer, but they do act as triggers, especially when combined with other factors [e.g. mutagens].
    - **Papillomavirus**, which causes warts. However, warts are localized and the body can attack it.
        - This virus can also cause cervical cancer in women. This is a particularly bad disease, because they are very easily metastasized and can kill the person.
    - **Hepatitis B**
        - Is endemic in large areas of Asia
        - Implicated in liver cancer
    - **Epstein Barr**
        - This is the virus that gives you mononucleosis.
        - It is also implicated in B-cell lymphoma, but it is not understood why

        - It is important to note that if you obtain this disease in temperate areas, the incidence of cancer is much lower than in tropical areas. This proves that other factors have an influence on this development.
    - **RNA viruses,** e.g. Kaposi's Sarcoma, herpes
        - These are often the viruses that give rise to cancer in HIV patients.
- We don't need to memorize this but the important point is that certain viruses can cause cancer by disrupting cell growth.

Mutations:

- Mutations causing cancer can be either **inherited** or **acquired** and are the cause of a variety of cancers. e.g. breast cancer, or prostate cancer
    - Whether acquired or inherited is caused due to either
        - **Over-expression of a gene causing cell growth**
        - **Suppression of a gene preventing proliferation**

- ***Take-Home Message:*** *cancer can be caused either via viruses or mutations to the DNA. Viruses usually change the way the cell grows and mutations usually affect genes in charge of control of the cell cycle and cell proliferation.*

THE IMMUNE SYSTEM AND CANCER:

- These are the changes that the immune system is able to recognize. ***It is important to note that the immune system is critical in preventing cancer.***
    - We saw that during immuno-suppression, cancer occurs at a much higher prevalence.
        - This is seen in both AIDS & transplant patients.
        - The process by which the immune system travels the body to search is called **immune surveillance**. This system is constantly watching to prevent changes in cells that can lead to cancer.

- The **T-cells and natural killer cells** [NK Cells] are the most important cells to be surveilled by this system.
    - *Remember that* T-cells can pick up viruses. Killer cells then talk to T-lymphocytes (CD8 cells), which are the most important for production of virally induced cancers.
        - This is why AIDS and transplant patients get such weird cancers (i.e. not breast, prostate, etc.). However, they do develop rare cancers (i.e. Kaposi's Sarcoma, B-cell lymphoma, etc.) at a higher rate. This is because the **virally-induced immunity is suppressed.** Cancers that one would consider "normal" cancers are due to malfunctioning of the NK cells.

- *Remember that* **T-cells** recognize antigens via MHC and if you have a mutation in self-protein, sometimes T-cells can pick that up and prevent any outcome caused by it being used. Certainly though, they prevent viruses from harming you.

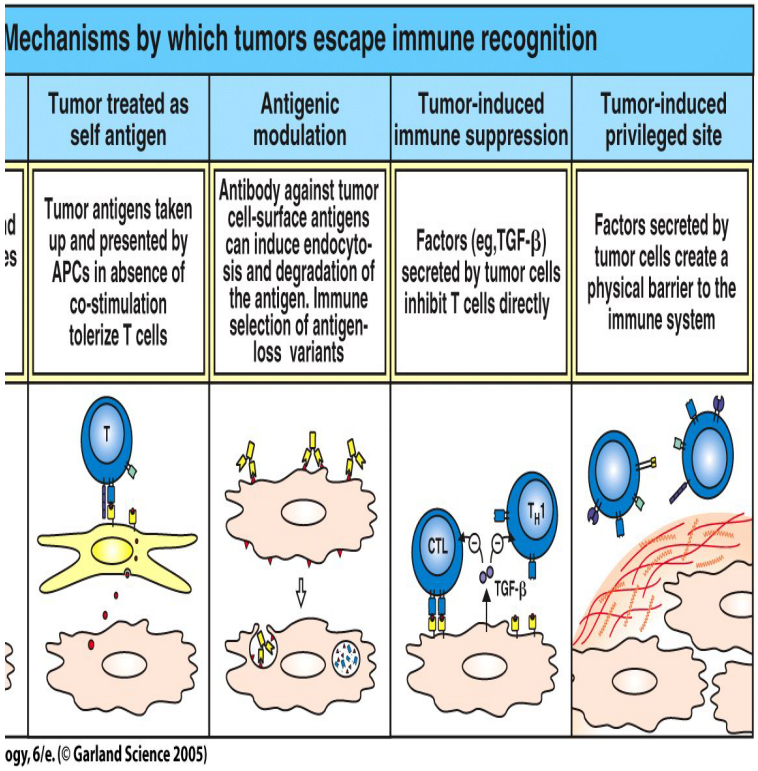
- The **NK cells** function via a different mechanism.
    - Sometimes to escape T-cell immunity, the tumor stops making MHC 1, which is interesting because all nucleated cells should express this. Normal healthy tissue will express MHC I while tumor cells will not.
    - This is where NK cells enter. They move through the body to ensure that all cells present MHC I receptors. If the cell does present them, then the NK cell moves on. If it does not, the NK cell destroys it.

- This works through **receptor binding**. However, the **default is to kill**. If the binding occurs the signal is turned off. If there is no binding, the NK cell destroys it, as the signal remains on.
- This is useful because if you have any form of MHC, the cell is not killed, so if you are presenting a mutated protein, the T-cells take care of it. But if you do not have MHC I, the NK cell takes care of it.

- ***Take-Home Message:*** *immune surveillance is constantly occurring in your body. This consists of the T-cells and NK Cells patrolling your body, noting abnormalities. T-cells recognize antigens via MHC molecules and can prevent viruses from harming you. NK cells are crucial when tumor cells have ceased to produce MHC molecules [a mechanisms of escape]. If the NK cell does not bind to a specific molecule on the cell surface, it will kill the cell. Therefore, with both T-cells and NK cells, viruses that may cause cancer and tumors should both be killed.*

BUT CANCER STILL HAPPENS: MECHANISMS OF ESCAPE:

- However, **we still get cancer** although the B-cells, T-cell, and NK cells work together to prevent it. This is because tumor cells proliferate and although the immune system may be able to kill one cell, it may not be able to kill all cells. ***Every cycle of growth, the tumor cell gets better at escaping the immune system due to the proliferation of cells.***
  - ***How does the cell do this?***
    - Tumors that are not caused by viruses have little for the cell to recognize. The cancer cells do not have ligands for TOLL-like receptors or pathogen associated molecular patterns. They also do not have signal two (the co-stimulatory signal) for full activation of the T-cell.
      - *Remember that our body has developed a two signal system to fully activate T-cells. This requires signals via the antigens and a co-stimulatory signal.*
        - This mechanism developed to prevent autoimmune disease, although this is a case where the protective mechanism is working against you because the tumor looks like normal cells.



    - In addition, tumors are able to produce factors, such as **interleukins**, that suppress your immune system. This causes the tumor to act as a giant regulatory T-cell to turn off your immune system.
  - ***Therefore, not only are you not fighting the tumor, but the tumor is causing immunosuppression, meaning that there may be many other problems before the tumor is detected.***

- ***How do you find the tumor?***
    - Often it is a solid mass of cells that is encapsulated. The encapsulation is found by the secretion of collagen from the tumor cells themselves. This makes it easier to find and remove the tumor. However, this created a barrier to the T-cells to attack it.

- ***Take-Home Message:*** *Therefore, the tumor has numerous ways of allowing it to escape detection by protective mechanisms of the body. Since the tumor cells are normal cells, they have no co-stimulatory signal and no antigen presented on their surface. Therefore, to the cell, they are not recognized as foreign. In addition, tumors have the ability to produce IL-2, which suppresses the immune system, making it easier for the tumor to grow. The primary tumor is usually encapsulated by collagen causing localization and protection from T-cells.*

THERAPEUTICS:

- Although the tumor has ways to invade the immune system, the body can still detect it. In terms of therapeutic developments, this can be exploited: we can determine what mechanisms the body has and enhance them artificially to help the immune system fight the disease. This is called **immunotherapy.**
    - The US is currently working on **biological response modifiers,** which enhance natural biological response to fight the cancer.

- You can target almost any aspect of the immune system to enhance the fight for cancer.
    - To the right we can see a chart that lists some of the possible areas that have been tried. Most of these ways are just being tested and are not available to most cancer patients.

- One of the new mechanisms available involves **targeting new antigens** presented by tumor cells, such as PSA [prostate specific antigen], which is increased in prostate cancer. We can take these antigens in the lab and create antibodies to them. These antibodies are then attached to toxic/radioactive substances. These antibodies would then move through the cell and attach themselves to tumor cells, even if the cells have metastasized. The toxic attachment then acts as a killer for the tumor cell.
    - *However, for most types of cancer, we do not know what antigens they express, so this mechanism is useless.*

- Another mechanism has been seen with **melanoma**: Although it is cancer of the skin, it can metastasize very easily to the lung. This is usually what kills people.
    - In this case, we do not know what the T-cells are attacking, but we do know they are attacking the cells. For example, if you remove one of the tumors, you can dissociate the mass into individual cells and can detect immune cells located there.
        - Therefore, the immune system is trying, but it is either too suppressed or too confused to work successfully.
    - In the lab, you can take these **T-cells and give them growth factor to enhance growth.** They then inject them back into the patient with an injection of IL-2, so the T-cells continue to proliferate.
        - It is hoped that these enhances T-cells will then be more powerful, enough to kill the tumor.
    - This method is relatively successful, but very expensive because it must work on an individual basis.
    - ***By using this mechanism, we do not ever have to know what the T-cell is binding too.***

    - In this case, it was eventually determined that the T-cell was binding to a component of melanin. Therefore, although the T-cells killed the tumor, they triggered an autoimmune reaction against the skin, causing discoloration. This discoloration indicates that the treatment is working.

- ***When you receive immunosuppressants for a transplant, the T-cells are downregulated, but the NK cells are not affected. This means that virally-induced cancers will be more common, but NK affected disease will remain under control.***
    - For example, fungal infections are huge problems in these cases.

- ***Take-Home Message:*** *Almost any aspect of the immune system can be targeted for therapeutic abilities. These methods include the creation of toxic/radioactive antibodies against an antigen emitted during cancer or the creation of enhanced T-cells. However, as with any treatment, we must be careful to recognize that the cancer is proliferation of normal cells, and make treatments that do not create susceptibility in the human body itself.*

VACCINATIONS

HISTORY:

- Vaccinations are huge developments and have rid many diseases that used to plague the world.
- There is evidence as early as 3000BC of people attempting to manipulate the immune system to prevent disease. However, in these cases, most people thought it was magic
    - e.g. if you expose yourself to the powdered essence of small pox, you can prevent catching it
    - Although this was thought to be magic, we now know the mechanisms behind the immune system and it helps with safety of these prevention mechanisms.
        - e.g. if powdered small pox contained too much live virus, you would catch the disease and most likely die.

- The second huge breakthrough was **virulation**. This involved putting the virus directly on the skin and stabbing the area with a needle, which causes a small amount to enter the immune system. This entrance can formulate an immune response.
    - The same problem arises with safety. The quality of the virus used can alter the outcome of infection with it.

- ***Take-Home Message:*** *The two largest discoveries on the road to vaccinations were the development of the fact that giving some of the virus would cause immunity and the development of virulation, which was placing the virus on the skin and allowing it to enter the immune system. In both cases, if too much of the live virus is given, or the strain is impure, safety problems arise.*

- The invention of vaccination in the modern world has been attributed to **Edward Jenner**.
    - He was the first to apply scientific methods to develop a modern vaccine.
- Later, Pasteur further developed these techniques to create vaccines.
- ***What did Jenner do?***
    - He noticed that women who were milking cows did not ever get small pox. However, they got a similar disease, cow pox, which was not dangerous.
    - Jenner reasoned that it was possible that obtaining cow pox prevented you from getting small pox.
    - He did experiments, through taking pustulent material from a cow that was sick and injecting it into a child. Upon the next small pox outbreak, this child did not get it. This was so awesome that he tried it on many more people.
    - Now we know that cow pox and small pox share some of the same antigens. Since cow pox forms antibodies, but does not kill you, memory cells are created. These cells can later be used to stack the small pox virus upon entry into your body.

- Through Jenner's developments, we have eradicated small pox, diphtheria, measles and polio.
    - **Polio** causes paralysis and is transmitted through water. If this occurs in the lungs or diaphragm, you cannot breathe and you die. Upon the spreading of the vaccine, polio essentially disappeared [at least from the Western world].
    - **Measles** were previously thought of as benign. However, it can leave many people deaf or blind or mentally retarded. When the vaccine was introduced, incidence dropped, but at some points there are small outbreaks. This is mainly due to parents who became afraid of vaccinating their children, which causes a loss of immunity and a small epidemic.
        - This has been a common occurrence with the development of many vaccines.

- ***Take-Home Message:*** *the development of the vaccine is attributed to Edward Jenner, who noticed similarities between cow pox and small pox. The development of these vaccines helped eradicate small pox, diphtheria, measles, and polio from most of the world.*
- *There was also a scare with these vaccinations. Many people that they were dangerous and thus they did not vaccinate their child. This caused for the disease to "stick around" longer.*
- *In 2000, there was a rumour going on saying that vaccination will cause mental retardation. Thus, people stopped vaccinating themselves and the diseases were more predominant. So the immune system is not the only thing that will determine if vaccination works. It is also dependant on the social factors.*

- As a child you are vaccinated several times, with the same shot [i.e. booster shots] because your T-cell immunity is very weak in your first year of time and you body does not make many memory cells. Since this causes you to be vulnerable to the disease later in life, the vaccinations boost the memory response every time.

IMPORTANT POINTS ABOUT VACCINES:

- The largest problem is **safety**: if they cause the disease, you cannot give it to people. Some vaccines today, such as for cholera and TB, are only fifty percent effective, so we are still trying to do better.
- The vaccines should **last** for an extended period of time. People cannot get revaccinated very often and if the immunity decreases in this time, it will no longer protect you.
- We want a **balanced** response: antibodies and T-Cells [Th2 and Th1]. Even a virus, if you do not have antibodies, will attempt to find a cell to infect. If you have antibodies already, the virus can be neutralized before it finds this cell. If the virus does manage to infect a cell, only the T-Cells can fight this. *Therefore, we need both B-Cell and T-Cell responses.*
- You need to make sure that the vaccine is not too **expensive.**
- Does it have to be **refrigerated**? Because people in third world countries may not have the availability for this.

- The **main immunological consideration** is that your vaccine needs to **contain an antigen that resembles or comes from the pathogen** you want immunity to.
- In addition, you need an **adjuvant.** This is something that gives your immune system a **danger** signal. Since we know that an antigen is not enough to illicit the response we want, we need ligands that will bind to receptors, such as TOLL-like receptors and other receptors that recognize pathogen-associated molecular patterns.

- ***Take-Home Message:*** *vaccines can be dangerous. Therefore, many precautions need to be taken by pharmaceutical industries to create the safest vaccine possible. These factors must include safety of the antigen being used [so it does not cause the disease], the time the memory cells will last, the formation of a balanced response of both B-Cells and T-Cells, cost, and storage. However, the main consideration is that if*

the antigen is from the bacteria/virus itself or the protein create resembles the antigen. In addition, there is the need of an extra ligand to bind to receptors that recognize pathogen-associated molecular patterns [e.g. TOLL-like receptors].

WAYS TO MAKE VACCINES:

- ***The simplest way to make a vaccine:***
  - **1.** Take whatever you want to protect against, destroy it, and inject it into an animal.
    - This consists of killing or inactivating the bacteria. If you want immunity against only the toxin, you can inactivate this and add it to a mixture of bacteria.
  - **2.** This elicits a response and you will make memory cells.
  - **3.** When you are exposed to the virus, these memory cells will prevent you from getting sick.

  - ***However, there is a problem with this vaccine.***
    - It only gives you immunity for a little while because your **memory cells do not last forever.** They need to be restimulated.
    - When you have a natural infection, a small part of this virus lives in your lymph node for years. This small amount is enough to keep memory cells alive, but not cause the disease.
      - Since we did not use a live virus here, there is nothing for the lymph nodes to keep. Therefore, we need **booster shots.**

- ***However, there is a way to counteract this:***
  - We can use a **live, attenuated vaccine.**
    - *Now, with the advent of biochemistry, we can **purify proteins** from the bacterium and inject them.*
  - Here, we take a virus and grow it in the lab until it becomes less virulent. Then we inject it.
  - This gives a more natural type of immunity and it **lasts longer.**
  - Finally, this vaccine will illicit the exact right type of immunity to protect you.
    - For example, since polio was passed through water, the first polio vaccine was given as an oral substance in a liquid suspension.
      - Therefore, the vaccine would take the same course as the actual virus and cause stronger immunity in places where it is necessary. It will start by affecting our gut cells and we would have an IgA and IgG response. It will give a more appropriate immunity.

  - ***So why aren't all of our vaccines like this?***
    - In our society today, there are many immuno-suppressed people (HIV and transplantation). If these people receive even an attenuate live virus, they will most likely contract the disease and possibly may die.
    - Even more dangerous is the fact that if you get vaccinated and have contact with an immuno-suppressed person, you can pass the virus to the person. **This is dangerous!**
    - *These viruses are not given to people who are immuno-suppressed or people who live with people who are immuno-suppressed. This is a huge drawback to this type of vaccination.*

- There is also an **experimental way** of making vaccines that is still not yet used on a large scale. However, this is what we hope will make vaccines against HIV.
  - This involves making an attenuated virus via **genetic engineering.** You can remove the virulent factor selectively and you can use your genetically engineered virus as a vaccine.

- ***Take-Home Message:*** *All of the vaccines currently used fall into one of the categories we have just discussed: toxoids, killed bacteria/inactivated viruses, or attenuated viruses. Killed and inactivated vaccines are effective, but require booster shots because the memory cells produced do not last forever. Attenuated viruses have both pros and cons. The pros involve the fact that they illicit more natural and longer lasting immunity with a more appropriate immune response. However, these vaccines are dangerous to the immuno-suppressed person, so must be used carefully. Hopefully genetically engineered viruses will be helpful in the future.*

- Prof. Desbarats recommends for everyone to do the questions at the end of every lecture for proper preparation for the final. She is willing to help you, as is the TA, so if you have a problem, make sure to e-mail them. **The question answers will be posted on WebCT. Also, if there is demand, the TA will set-up a tutorial, so e-mail her**
- Online there is also a clicker evaluation. Do it.
- There is also a course evaluation, one for the course itself and one for Prof. Desbarats herself. They are really helpful, so do it.

CONTINUATION OF VACCINES

- *Remember the* **Types of Vaccines:**
  - **Inactivated**
  - **Toxoid**
  - **Live Attenuated**
  - **Purified Proteins [Subunit Vaccines]:**
    - Instead of killing the whole bug and mixing it with adjuvant, you can synthetically produce or purify protein from the bug and mix it with adjuvant. It is safer and easier to be mass produced. However, you do not have the entire antigen from the microbe so it is not as efficient.
  - **DNA**:
    - *This is only experimental as of now, but has great promise for the future.*

THE LACK OF VACCINES…

- Although we have eradicated many diseases, there are some diseases for which effective vaccines are not yet available. *See the chart to the right.* ***Why is this so?***
  - The market for these vaccines is poor, so pharmaceutical companies do not have a financial interest it. The diseases do not seem to plague the Western world to create enough demand. Diseases like this are funded by private donors, such as Bill Gates.

Some diseases for which effective vaccines are not yet available

Disease	Estimated annual mortality	Estimated annual incidence
Malaria*	1,124,000	300–500 million
Schistosomiasis	15,000	no numbers available
Worm infestation	12,000	no numbers available
Tuberculosis	1,644,000	~8 million
Diarrheal disease	2,001,000	~4,100 million
Respiratory disease	3,947,000	~362 million
HIV/AIDS	2,866,000	~2 million

- **TB:** has a vaccine, but does not work very well.
- **Viral diseases, such as colds:** too many strains to create a functional vaccine
- **Influenza:** there is no problem in making a vaccine for one strain of the flu. However, as we saw, there is antigenic drift and antigenic drift, which causes the virus to subtly change. By the time we know what the most common strain is for the year, there would not be any time to create a vaccine. Therefore, companies predict the strain that will be active for the winter and create a vaccine for this [*this occurs every year*]. The only problem is if the company guesses wrong, the vaccine will be useless for everyone that was vaccinated.
- **HIV:** tons of money has been put into this, but there are no promising developments yet. The problem with HIV is that **vaccines rely on having very good memory T-cell responses** [CD4 cells to increase B-cell antibodies and NK cell function]**.** *Since HIV affects T-cells, specifically CD4 helper cells, vaccines that activate CD4 T-cells could actually make the disease* ***worse***.
  - When the virus enters the cell, it attacks CD4 cells. If you had a vaccine, you have proliferated many CD4 cells already. This only **increases the reservoir of cells that HIV can infect.**

        - *By activating CD4 cells that recognize the HIV virus, the virus will infect these cells preferentially and efficiently.*
        - Upon second contact with the virus, it is even easier to infect and spread.
    - The entire strategy for this virus needs to be rethought so it **does not activate T-Cells, but still mounts an anti-viral killer response.**
        - ***This is where the DNA vaccination enters.***
            - Usually we inject a protein with an adjuvant. Now, we can inject a piece of **DNA that codes for an adjuvant and the HIV antigen**. The DNA is inserted into a plasmid and expanded in bacteria. The copied DNA is injected with a special needle that also gives you an **electric shock**. The shock permeablizes the cell membranes and allows the DNA to enter the muscle cells where it moves to the nucleus. The DNA will not incorporate into the cell DNA, but it will reproduce and transcribe independently. The muscle cells then express the protein for a couple of weeks.
            - In addition, one could add additional coding sequences. For example, for IL-2. When we inject the DNA, eventually we will have the HIV antigen expressed on the muscle cell. The muscle cell also expresses MHC I. With the IL-2, it is everything a CTL cell, a **CD8 cell,** needs to become an **anti-viral killer cell.**
                - *This bypasses the need to have a CD4 response, because the muscle can make its own IL-2 now.*
            - By adding ligands for co-stimulatory factors or TOLL-like receptors, you can turn muscle cells into very good stimulatory cells for an anti-viral response.
            - The plasmids last only for a couple of weeks, but this is long enough for your killer cells to become activated and become memory cells.
                - They will kill off the muscle cells that contained the virus, but this is not dangerous at all.
        - ***This is only an experimental strategy, but has lots of promise.***

- The other field where vaccines may show promise is **cancer.**
    - When a tumor is removed during surgery, you can find immune cells that can be stimulated from outside the body and re-inserted into the cells.
    - **From the remainder of the tumor, you can create a vaccine:**
        - 1. Kill the tumor cells.
        - 2. Mix them with adjuvant [ligands for TOLL-like receptors].
        - 3. Reinject both into the individual.
        - 4. The body will form a **boosted** immune response.
            - *It may be able to attack not only remnants of the original tumor, but any metastasized cells.*
    - This is an individual vaccine, since it is based on tumor self-cells.
    - This may cause **autoimmune diseases**, since there are **self-**cells involved.
        - However, if you have cancer, it may be worth the risk.
        - However, tailoring may be able to be done in the future.

LECTURE ELEVEN: NEUROIMMUNOLOGY
Interactions Between the Immune and Nervous Systems

- The **autonomic system** controls many involuntary actions in your body. This is includes many immune functions.
    - This can happen because immune tissues are innervated by the **sympathetic** nervous system. These tissues include lymph nodes, the spleen, bone marrows, etc.

    - Efferent nerves move from the brain to the organs.
    - Afferent nerves move from the organs to the brain.

- On a molecular level, immune cells [e.g. B-cells, T-cells, neutrophils macrophages, etc], express receptors for many neural products.
    - e.g. **neurotransmitters, neuropeptides, and neurohormone receptors**
    - *Although you do not have to memorize it, see the chart to the right for more information.*

Neurotransmitter receptors are found on immune cells:

- Norepinephrine (=noradrenaline)
- Serotonin
- Dopamine
- Acetylcholine

Neuropeptides receptors are found on immune cells:

(the immune system can sense when you're in pain, and pain is very immunosuppressive!)

- Enkephalins
- Substance P
- Vasoactive intestinal peptide
- Neuropeptide Y

Neurohormone receptors are found on immune cells:

- corticotrophin-releasing factor
- growth hormone
- adrenocorticotropin hormone
- prolactin

- In addition, your neurons and other cells in **your brain have the ability to recognize cytokines that are produced by the immune system**, particularly IL-1 and TNF.

- ***What happens when your brain recognizes cytokines?***
    - You get a **fever** from binding of molecules to receptors in the hypothalamus that controls the set-point of temperature regulation. This resets the "internal thermostat."
        - This is due to the fact that higher temperatures allow immune cells to proliferate faster, and inhibit bacteria proliferation.
    - Fatigue
    - Increased sleep and lethargy
    - Sleep disturbances
    - Lowered pain threshold
    - Cognitive impairment [especially concentration and memory]
    - Anorexia
    - Mood disorders [asocial behaviors, withdrawal, anhedonia, depression, etc]

    - ***These are the general feelings of sickness behaviour.***
        - They are adaptive responses that permit survival [for the individual and the group], i.e. they are evolutionarily advantageous, following exposure to a variety of microorganisms.
        - In addition, they have a social benefit. If you feel like crap, you are less likely to go out and therefore, expose less people to catching what you have.

CNS effects of cytokines	Non-specific symptoms of sickness
• General malaise	• Feeling sick
• Decreased activity	• Loss of energy or fatigue
• Decreased social investigation	• Loss of interest in usual activities
• Decreased food and water intake, weight loss	• Poor appetite and significant weight loss
• Sleep changes	• Sleep changes
• Fever	• Fever

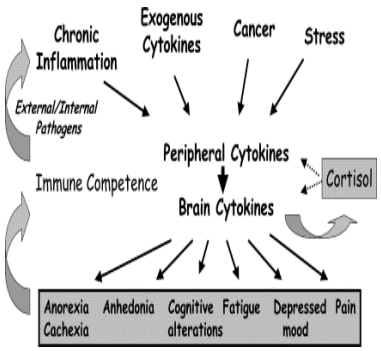
- ***What if your brain makes pro-inflammatory cytokines inappropriately?***
    - This can occur during autoimmune disorders, or other **chronic cytokine production.**
    - Possible **depression.**

    - The clinical definition of depression is the following:
        - "Must have at least 5 of the following every day [or nearly every day] for at least 2 weeks"
            - Depressed mood
            - Anhendoia
            - Weight loss or gain
            - Changes in sleep pattern
            - Restlessness or lethargy

- Fatigue or loss of energy
- Feelings of worthlessness or guilt
- Diminished ability to think or concentrate
- Suicidal thoughts

- **People with cancer or chronically inflammatory disorders have chronically activated immune systems**.
  - The activation of the immune system may be one of the causes for the feelings of these individuals.
  - *There is a growing suspicion that **proinflammatory cytokines are involved in development of feelings of despair, depression and hopelessness** that occur in many cancer patients.*
    - Now, maybe we can use these patients for possible research.

- In a normal individual, these responses **must be turned off** to avoid chronic activation and the problems associated with that.
  - **1.** When the pathogen leaves, the body should automatically shut off the response.
  - **2.** Make **glucocorticoids**, i.e. **cortisol**
    - Initiated via the brain and production of cytokines and carried out through the hypothalamus-pituitary axis [HPA].
    - You can inject synthetic glucocorticoids to turn off the immune system for autoimmune patients.
  - ***This negative feedback loop is crucial to the function of the immune system in the body.***
    - *However, if you have too much of anything, your body stops responding via desensitization. So what happens in chronic situations? Let's look at stress.*



STRESS

- The main source of chronic glucocorticoids in your body is **stress.**
  - ***Chronic stress**, both physical and mental, causes persistent activation of the HPA axis with chronic glucocorticoid secretion.*
    - It is a very good adaptive response for a while, but eventually this causes **immunosuppression**, which can leads to infections and even cancer.
    - This also desensitizes the brain-immune feedback loop, which causes the **inability to decrease cytokine production when appropriate.**
      - This leads to uncontrolled inflammation [autoimmune disease] and depression.
      - This is due to the fact that the T-cells, from the overabundance of glucocorticoids, will **remove receptors** from the surface of their cells.
        - *If you get a massive infection, there is nothing to stop the cytokine production. So, you go from not enough to way too much, since there is no control over the feedback loop.*
          - This can lead to many immunological problems.
  - Research is currently being done on this and two groups of people are being analyzed for this:
    - Special forces in the military
    - Medical Students during their licensing exams

- ***Is stress always bad for your immune system?***

- **Acute stress** causes activation of **the fight-or-flight response**, which releases adrenal catecholamines
- **The catecholaminergic stress response can provide the immune system with a needed boost to deal with an immediate threat. It activates both innate and adaptive immunity. The catecholamies can circulate:**
  - Locally through nerve terminals [at the site of injury]
  - Systemically by circulating hormone

- **Treating Alzheimer's Disease:**
  - New treatments exploit the immune system to combat the disease.
  - Alzheimer's is the most common neurodegenerative disease.
  - *The main symptom* is **progressive dementia:**
    - Loss of memory
    - Cognitive decline
    - Impairment of judgement, abstract thinking, and ability to learn
    - Changes in personality
  - *Becoming more and more common, but mostly affects the elderly.*
  - Histopathology of Alzheimer's is characterized by the **accumulation of protein aggregates** in the brain:
    - Intracellular: neurofibrillary tangles consisting mostly of Tau, a microtubule-associated protein
    - Extracellular: deposition of **amyloid plaques**
      - Amyloid-beta is generated from its precursor, **amyloid precursor protein**, through consecutive cleavages by secretases.
      - The resulting small oligomers are thought to be **neurotoxic**
      - Eventually insoluble Amyloid-β is deposited in amyloid plaques
    - ***These lead to progressive cortical neuron loss and cortical atrophy.***

  - ***Immunizing Alzheimer's disease patients with Abeta in adjuvant will lead to clearance of plaques and clinical improvement.***
    - So what if we could get the immune system to recognize and make antibodies against the plaques? Then macrophages would just enter and phagocytose the opsonized plaques and we should be fine.
    - So researchers did this: they injected plaque material and adjuvant into a mouse. This made the mice better and decreased many symptoms.
      - They then did this with people. Although it worked in many people, in some it stimulated an immune response.
        - If this was a Th1 response, it would kill off parts of the cell, this is bad! If it was a Th2 response, antibodies would be created to bind to the plaque material, which is good.
  - ***This is a very good new way to exploit the immune system and use natural functions of the body to target neurodegenerative disease.***

PRACTICE PROBLEM FROM LAST YEAR

- You transplanted a mouse of MHC-B with a thymus of MHC-A and remove the mouse's own thymus. Immediately after the thymus transplant, you irradiate the mouse, which kills all the mouse's immune cells [including T cell, B cells, dendritic cells, and macrophages]. The mouse's thymic epithelial cells are not killed by the irradiation. You then give the mouse new bone marrow stem cells [these do not contain mature T-cells] to prevent it from dying of the irradiation. The bone marrow stem cells come from an MHC AxB

mouse [that means that all the bone marrow cells have both MHC A and MHC B]. The bone marrow stem cells will reconstitute the mouse's immune system with new MHC AxB cells.

- **Process of Thought:** After transplantation, the mouse's thymus will be MHC A. After irradiation, the mouse's immune system is complete wiped out, meaning that all proliferating cells die with radiation and all of the immune cells in your system, when they are activated start proliferating. After irradiation, you **have to give the mouse a bone-marrow transplant** [or it will die without RBCs]. This produces AxB bone-marrow [since this is what the bone-marrow donor had].
    - ***Now, the thymus is MHC A, but the thymus epithelium does not change, so it is still A [not AxB]. But all bone-marrow derived is AxB.***
        - *Remember thymic selection:*
            - The thymic epithelium is where **positive** selection occurs.
            - The bone-marrow derived compartment is where **negative** selection occurs.
                - *If you don't reconstitute the bone-marrow, it will come from the normal MHC of the mouse.*

- **Will the T-cells be restricted by MHC A or MHC B?** This is positive selection, so it will be mediated by A in the thymus, so all T-cells will be restricted by A.
- **Will the T-cells be tolerized by MHC A or MHC B?** This is negative selection, so it will be tolerated to both A and B from the bone-marrow derived compartments