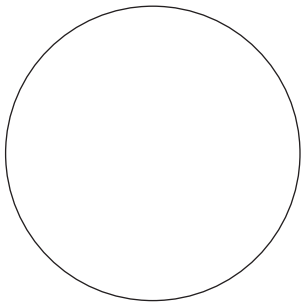
1: VIRUS MORPHOLOGY and ANATOMY

RODS ("Helices")

ICOSAHEDRONS (includes spheres)

COMPLEX shapes

CROSS SECTION



POSSIBLE PARTS of an ICOSAHEDRAL virus

All viruses have the first two. The others are options that might be present. There are also lots of variations within each option!

1) _____ (shell made of protein)

2) _____ (genetic material with instructions)

3) _____ (made of lipid [cell] membrane)

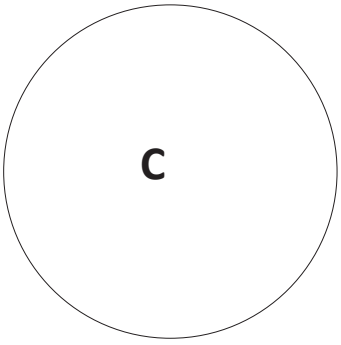
4) _____ (needed for making messenger RNA)

5) _____ (a bit of extra protein under envelope)

6) _____ (for attaching to cell)

WHAT IS PROTEIN?

A long chain of amino acids is called a polypeptide.



The basic unit of protein is the amino acid. It is made of atoms, but the shortcut is to draw a circle.

The polypeptide folds up to become a structural protein.

WHAT is DNA/RNA made of?

- ☐ Adenine
- ☐ Thymine
- ☐ Uracil
- ☐ Cytosine
- ☐ Guanine

The sides are made of ribose and phosphate.
The rungs are made of nucleid acid bases.
DNA: Adenine, Thymine, Cytosine, Guanine
RNA: Adenine, Uracil, Cytosine, Guanine

2(a): VIRUS SIZE

At this scale, how big would we have to draw these things?

a red blood cell = _____

a skin cell = _____

a paramecium = _____

this dot • = _____

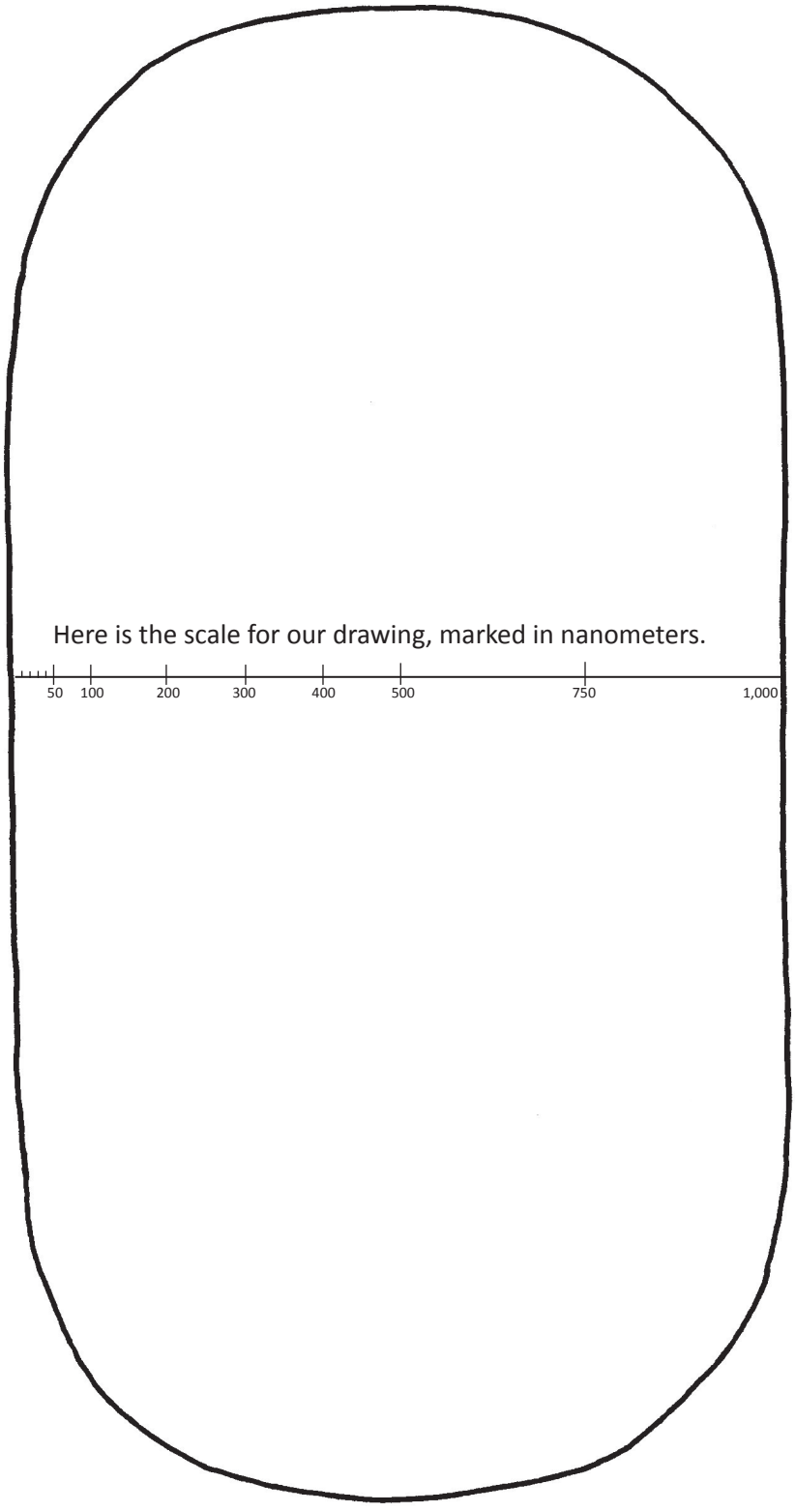
What would be too small to draw?

_____, _____

We might be able to draw DNA as a very thin line:

There are _____ millimeters (mm) in a meter (m).
There are _____ microns (μ) in a millimeter (mm).
There are _____ nanometers (nm) in a micron (μ).

This long, oval shape represent a bacillus bacterium.

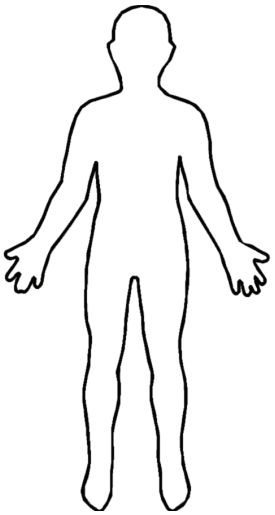


2(b): VIRUS PREVALENCE

("how much of it there is")

VIRUSES ARE UBIQUITOUS (They are everywhere!)

Viruses outnumber all other forms of life. We haven't found any place on the planet that doesn't have viruses. Even water from frozen lakes under Antarctica has viruses! As far as we know, there isn't a plant, animal, fungus or bacteria that doesn't have a virus to infect it. Even large viruses can be infected with smaller viruses!



Almost everyone is infected with this "harmless" virus: _____ It has been passed from parent to child for so many generations that we can use it to figure out where people migrated.

95% of all humans are infected with up to a dozen species of: _____
Some species infect us as soon as we are born. Others are acquired during childhood.

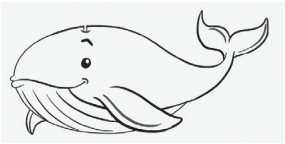
Each part of our body (skin, mouth, intestines, feet, etc.) has _____ of viral species in it.
For every one human cell, we have _____ bacteria that live around the cell.
For every bacteria, there are _____ virions (virus particles). Virions outnumber our cells _____.

When we eat fruits and vegetables, we ingest _____ virus particles (virions).
(These are mostly viruses that attack the insects that like to eat these plants.)

Human feces have _____ virions in them. (mostly plant or insect viruses)

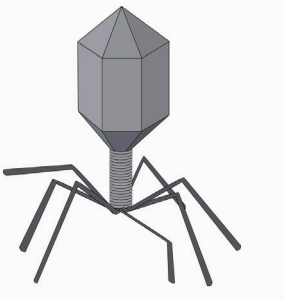
Everytime we take a breath, we probably inhale _____ of virions.

The bacteria in your body are called your _____. The viruses in your body are called your _____.



Whale feces have _____ virions, mostly Calici viruses, which are in the same viral family as the ones that cause "cruise ship disease" (diarrhea and vomiting).

Whale breath has been sampled, also, and contains an amazing number of viruses.



Bacteriophages are viruses that attack bacteria, including blue-green bacteria that float in the ocean. These blue-green bacteria (or "phytoplankton") act like plants, using light for photosynthesis.

There are about _____
bacteriophages in the ocean. A teaspoon of ocean water contains _____ virions.

If all these phages were end to end, how long would the line be? _____

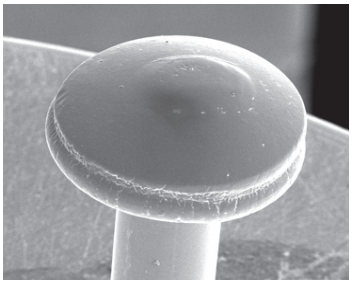
If you collected all the phages on the planet, and weighed them, they would out-weigh all the _____ on the planet by _____ times!

Examples of "good" viruses:

1) A virus that infects _____ which live in _____ can allow both of them to live at extreme temperatures. (studied in Yellowstone Park)
2) A virus that infects _____ can restore normal function to injured gut bacteria.
3) Viruses that infect _____ produce stripes, making them more valuable.
4) Bacteriophages that infect diseases-causing bacteria in _____ can be used as a treatment for that disease.
5) A virus that lives in _____ stops them from producing nitrogen-fixing nodules when there is enough nitrogen in the soil, preventing the plant from wasting its energy.
6) Parasitic _____ carry a virus that gets injected into the _____ that their larvae will feed on, increasing the survival rate of the larvae.

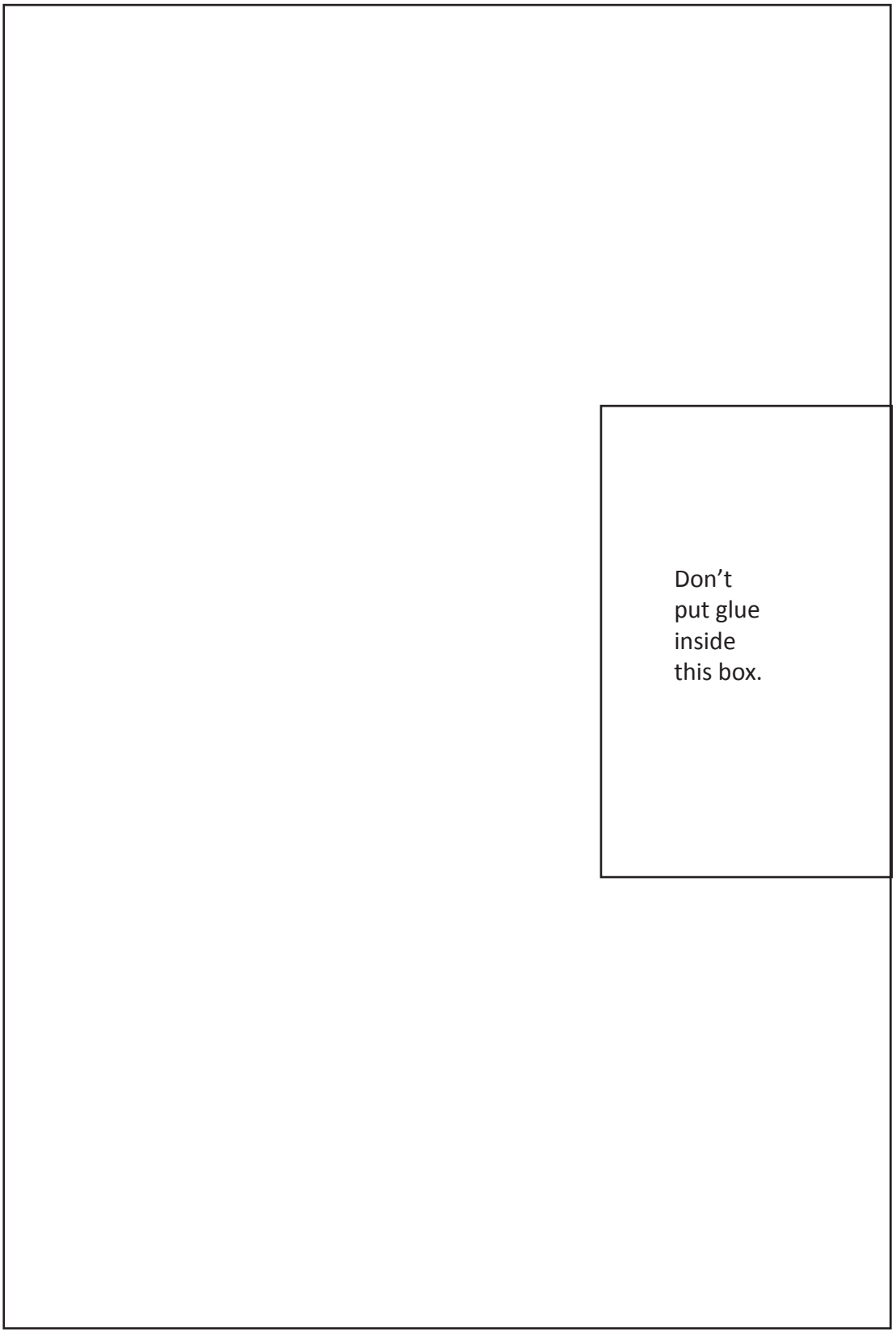
How many virions would fit onto the head of a pin?

_____



3: HISTORY OF VIROLOGY

This timeline presents some of the major events in the history of virology.



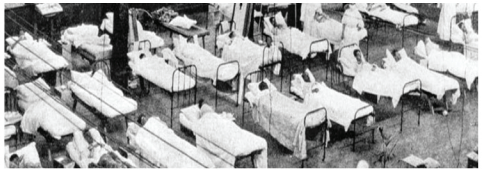
TIMELINE of VIROLOGY

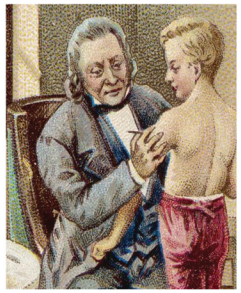
"Variolation" was done for several centuries before Jenner's famous vaccination experiment. It was practiced in Asia and Africa. Scabs or pus were collected from someone who had a light case of smallpox, and these were dried and then blown in the nose (or scratched into the skin) of people who had not yet caught it.

Lady M. in Turkish costume

Lady Montagu, the wife of the British ambassador to the Ottomans brought this technology to England in 1717. The practice soon spread to Europe and became very popular.

1918 Flu pandemic



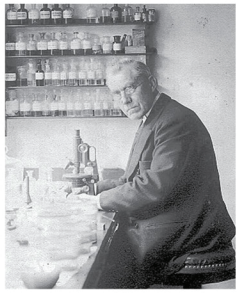


uses **cowpox** to "vaccinate" a small boy against smallpox. (He discovered this by talking to a milkmaid.)

"vacca" = cow

gives a rabies vaccine to a boy who was bitten by a rabid dog. Pasteur had already vaccinated sheep against anthrax bacteria.

observes that even after straining with the Chamberland filter, the water from his plants still contain an infectous agent.



works with what later turns out to be TMV, and coins the word "virus" for this newly discovered infectous agent.

Vaccinia virus grown in a culture dish.

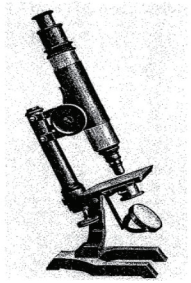
Coins the word "bacteriophage" and begins using phages to treat bacterial diseases of animal and humans. Took this tech to other countries.

1500 1600 1700 1796 1885 1892 1898 1913 1917 -- 1919

1884 1906 1914

Smallpox was called "variola." If it didn't kill you, if left you scarred for life. Variolation spared many people.

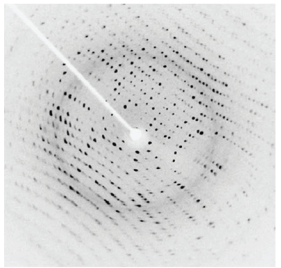
The microscope was being developed all during the 1700s and 1800s. This allowed the discovery of bacteria.



This device allowed scientists to strain out anything larger than 100 nm. (.1 micron) They knew that bacteria were much larger than that, so anything that got through the filter could not be a bacteria.

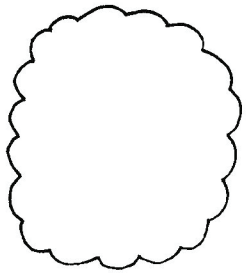
Ross Harrison discovers how to grow animal tissues in lymph solution.

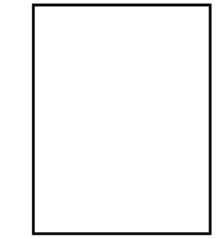
This is the first time scientists can work with tissues **"in vitro."** (vitro = glass)

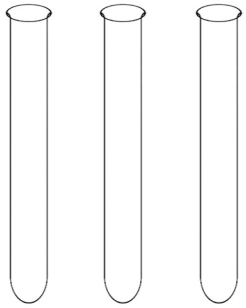


X-ray diffraction patterns allow scientists to figure out structure of crystals.

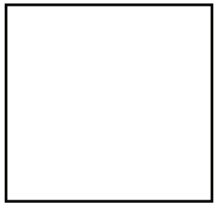
1933: Influenza grown in eggs.

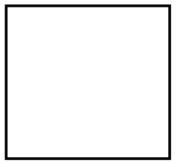




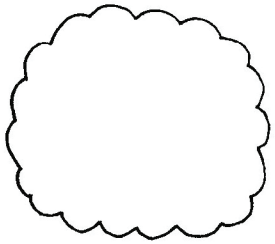


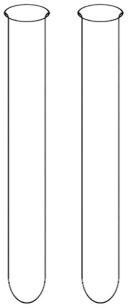
First micrograph of TMV using an electron microscope.





Wendell Stanley crystalizes TMV and uses X-ray diffraction to show that it is a rod made of protein.

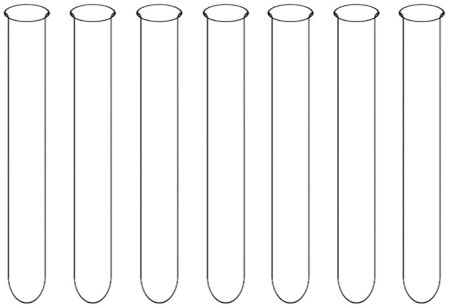


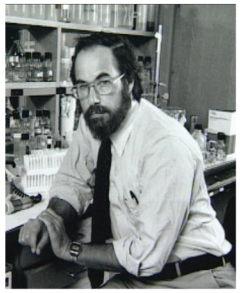


GLOBAL IMMUNIZATION EFFORTS

develops a vaccine for the dreaded polio virus.

(After that, he builds the Salk Institute for virology in San Diego.)





discovers "**reverse transcriptase**" along with Howard Temin.

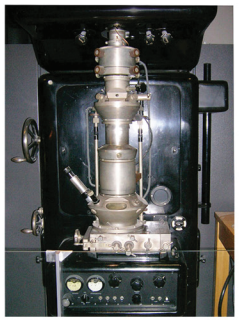
In 1971 he develops the **Baltimore classification** system, which is based on viral genome.

Scientists figure out that insects can carry viral diseases from plant to plant, acting as "vectors."

1922 1932 1933 1934 1935 1938 1940 1949 1952 1953 1954 1962 1963 1964 1966 1970

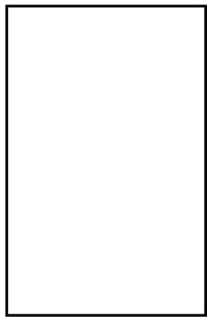
Chemists discover the chemicals that DNA is made of:
1) ribose sugar
2) phosphate
3) nucleic acids

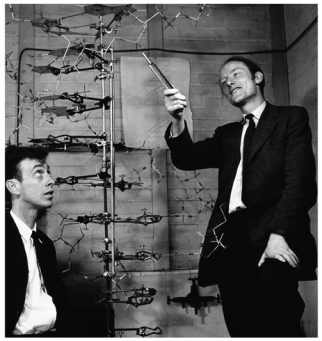
They have no clue as to what it looks like and don't even know it is in the nucleus. They do guess that it might have something to do with heredity.

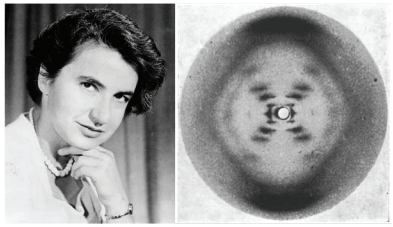


Invented by Ernst Ruska and Max Knoll.

Hemagglutination test discovered. (Some viruses will stick to red blood cells and make them clump.



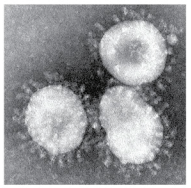




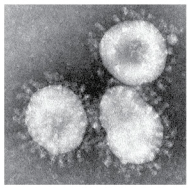
becomes available for Herpes infections

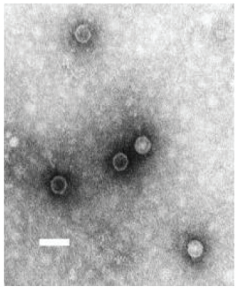
becomes available to treat Influenza infections

2002 SARS coronavirus in Asia



2014 MERS coronavirus in Middle East



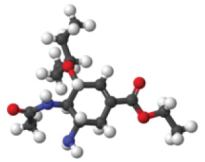


is created in a lab.
Then a phage was made.

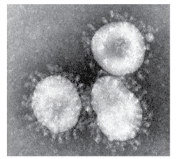
You can't do this with bacteria because they are living things.
Viruses are not alive.

Thousands of viruses are being catalogued, and their genomes sequenced.

New antiviral medicines are designed using computerized models of the structure of the virus.



2019 Covid-19 global pandemic

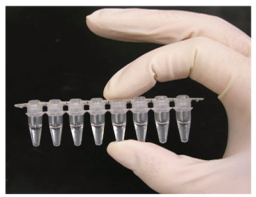


Complete structure of adenovirus revealed.

1971 1972 1976 1977 1983 1985 1992 1997 2002 2008 2010 2013 2019

Thermus aquaticus

Discovery of **"Taq polymerase"** inside bacteria that live at extreme temperatures in places like geysers and thermal vents.



Invented by Kary Mullins

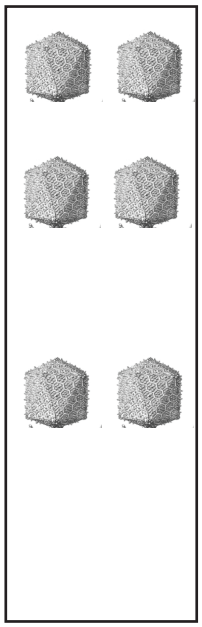
Polymerase
Chain
Reaction

2017: Nobel prize goes to inventors of Cryogenic Electron Microscopy (Cryo-EM), where samples are quickly frozen before being viewed. The detailed images this produces are stunning, and extremely helpful to virology researchers.

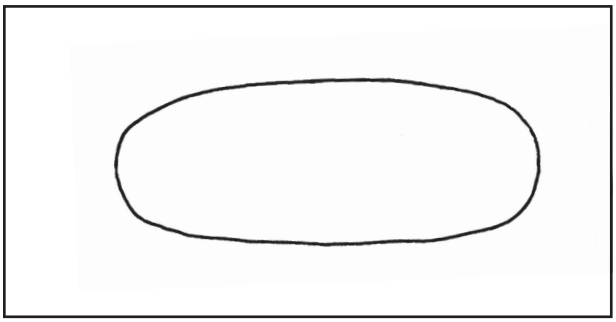
4(a): BACTERIOPHAGES

T4 is perhaps the most studied of all pages.

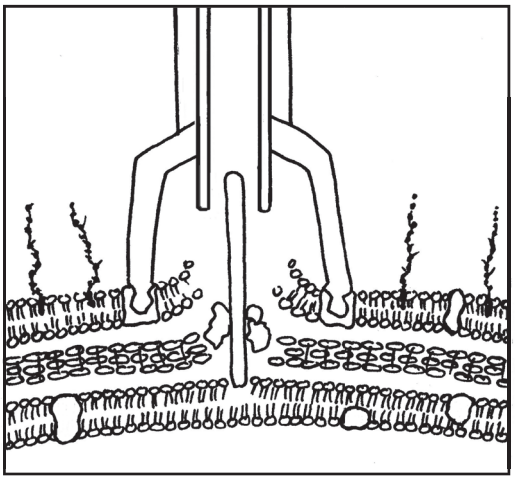
OTHER PHAGE MORPHOLOGIES



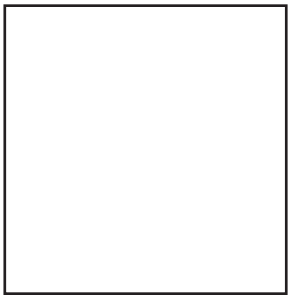
T4 attacks *Escherichia coli (E. coli)* bacteria



(1) flagellum **(2)** Bacterial "nucleoid" made of DNA
(3) cell envelope made of membrane and wall
(4) cytoskeleton framework that gives shape to the cell
(5) ribosomes **(6)** enzymes (little task "robots")
(7) includsions (viral production sites)



(1) Baseplate **(2)** DNA **(3)** protein "needle"
(4) peptidoglycan (sugars held together by proteins)
(5) lysozymes to digest the peptidoglycan layer
(6) outer membrane **(7)** inner membrane

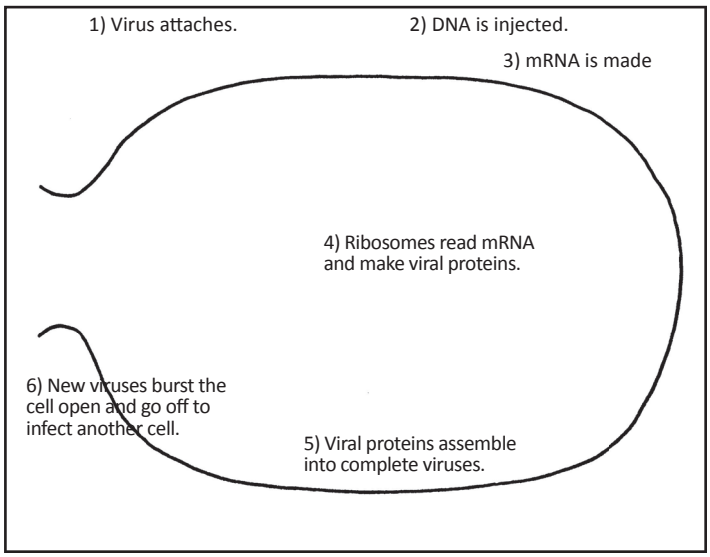


The tail sheath contracts and injects the DNA into E. coli

Phages have two life cycle options: **lytic** or **lysogenic.**

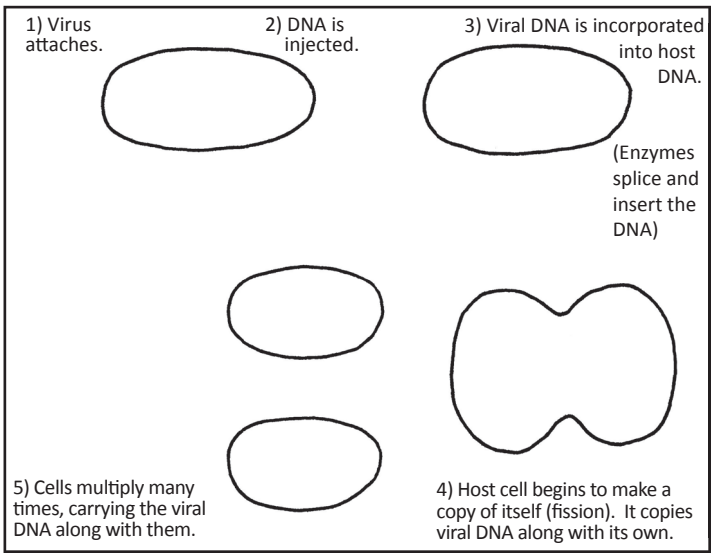
LYTIC (causes bacteria to burst)

The virus replicates quickly (30 minutes) and then causes the cell to burst, releasing 100-150 new viruses. New viruses infect more cells.



LYSOGENIC (hides in bacteria's DNA)

The viral DNA is incorporated into the bacteria's DNA, so when the bacteria reproduces by fission, the viral DNA is also copied.

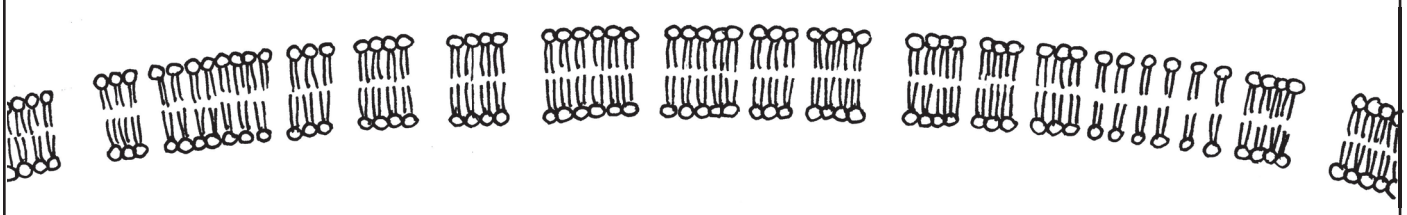


5(a): HOW VIRUSES ENTER CELLS

There are three steps to the entry process. All viruses do (1) and (2). Viruses with envelopes must also do (3).
1) Attach 2) Release genome into cells 3) Merge viral envelope with cell membrane

1 The surface of all cells is covered with a "forest" of receptors. Some are used to identify the cell, some are used for attachment to other cells, some take in nutrients, and some are there to send or receive chemical messages.

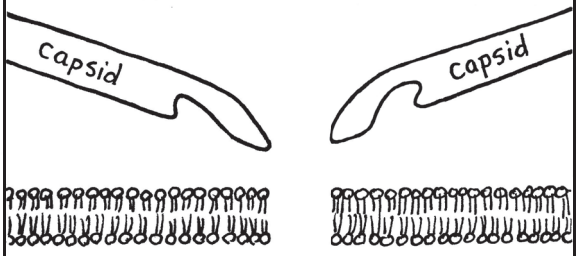
Each virus has a unique glycoprotein structure on its surface that happens to match the shape of a cell receptor.



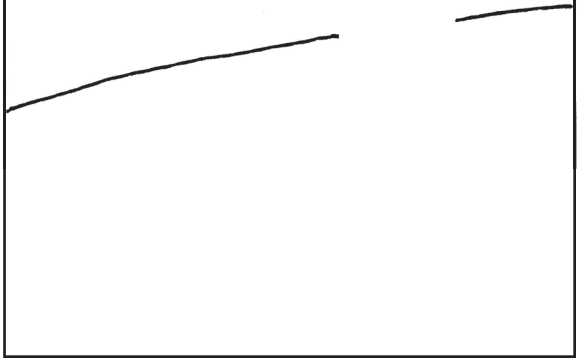
1) _____: a tiny sugar found on the end of many long chains, especially on respiratory system cells
2) _____: an enzyme that tells blood vessels to relax, found in lungs, heart, blood vessels, intestines
3) _____ aka _____: used to connect to other cells, found mostly in epithelial cells (skin, lungs, intestines)
4) _____: a receptor found on T cells to communicate with macrophages (both are white blood cells)
5) _____: Coxsackie-Adenovirus Receptor is necessary for proper formation of the heart, and attaches cells to cells

2 The virus must release its genome.
(Exception: Reoviruses)

1) A pore can open in the capsid. (EX: polio)



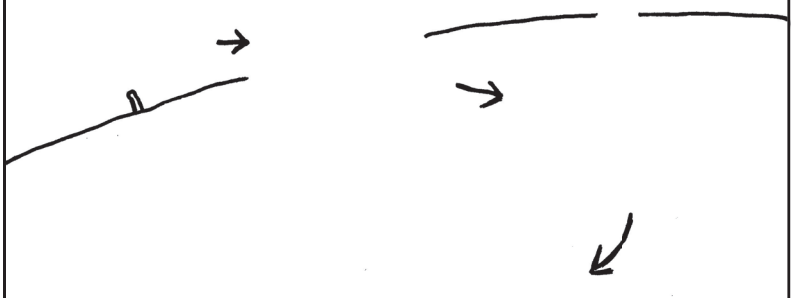
2) The capsid must fall apart or at least become very leaky (EX: adenovirus)



3 The viral envelope uses a "fusion protein" to merge with the host cell membrane.

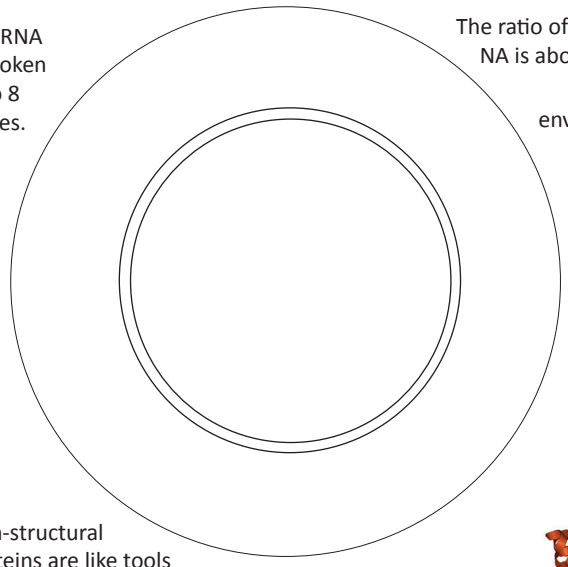
1) Fusion occurs at the surface. (EX: HIV and measles)

2) Fusion occurs after the virus is brought inside the cell.
(EX: Influenza)

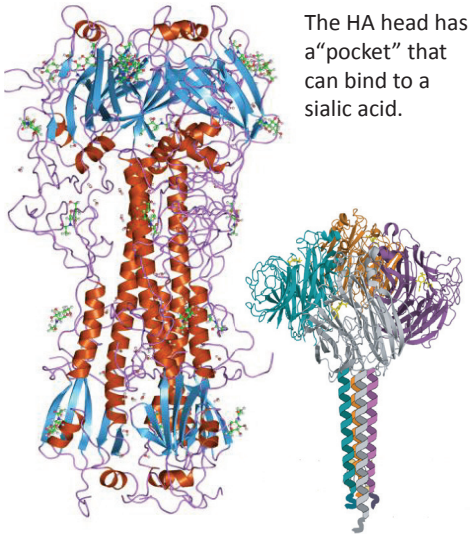


5(b): HOW INFLUENZA ENTERS CELLS

Influenza A is one of the most studied viruses of all time. Its binding site, sialic acid, was the first virus receptor to be discovered (1985). Its genome and its glycoprotein structures have been completely mapped.



"Spikes" are a type of glycoprotein. (Glyco = _____)

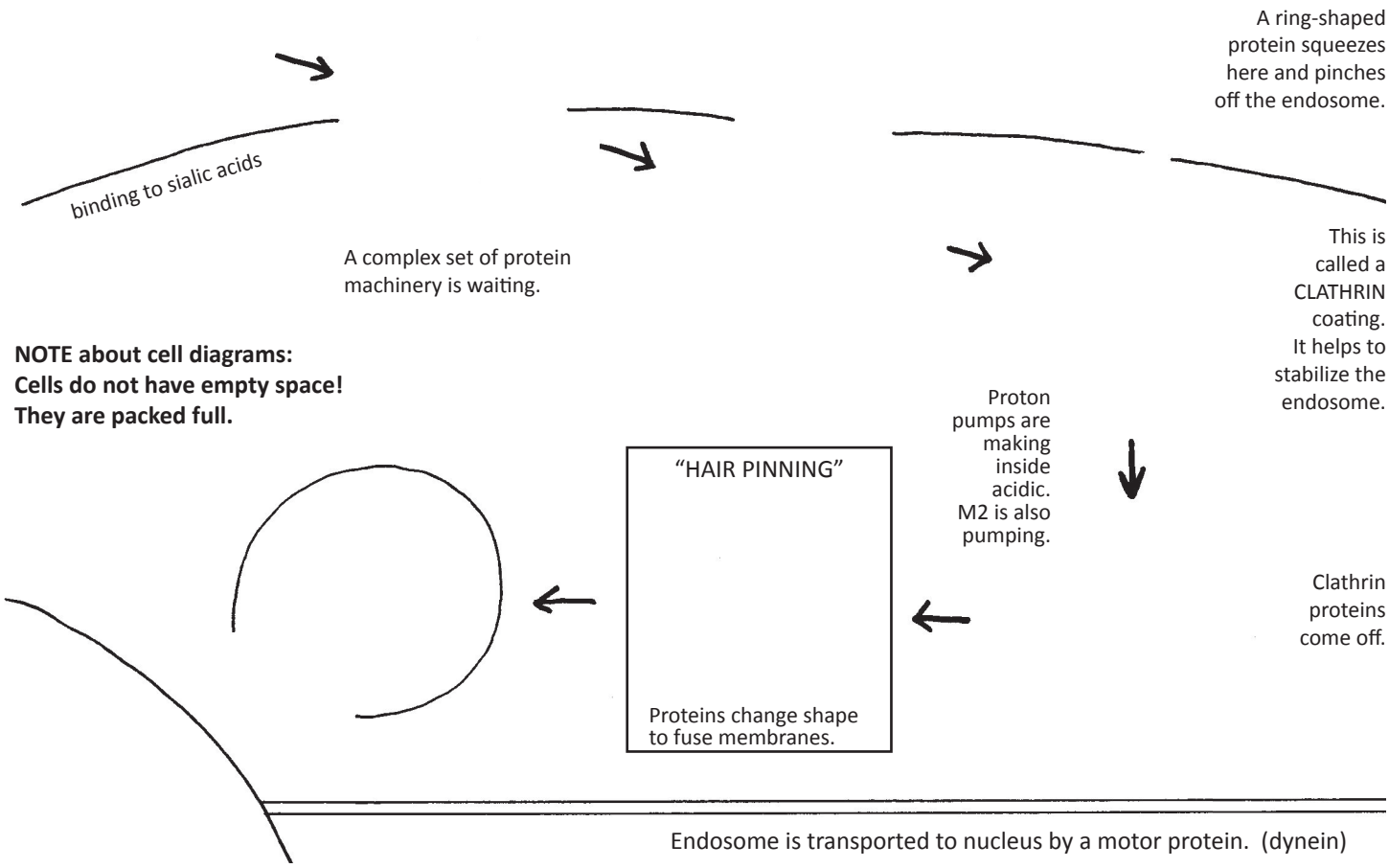


_____ Neuraminidase is a "snipping enzyme" that cuts off (cleaves) sialic acid molecules. **(This enzyme will be needed to exit cell.)**

_____ Hemagglutinin (heme= blood, agglutinate= clump)

Influenzas are named according to the structure of their HAs and NAs. As the virus replicates (billions upon billions of times) small changes occur. The first variations that were mapped were called H1 and N1. (This corresponds to the flu pandemic of 1918.) As more variations were found, they were named by number (H2, H3, H4, etc.).

HOW THE INFLUENZA VIRUS IS TAKEN INTO CELLS



NOTE about cell diagrams:
Cells do not have empty space!
They are packed full.

6: INSIDE A CELL

What does a cell look like from a virus's viewpoint?

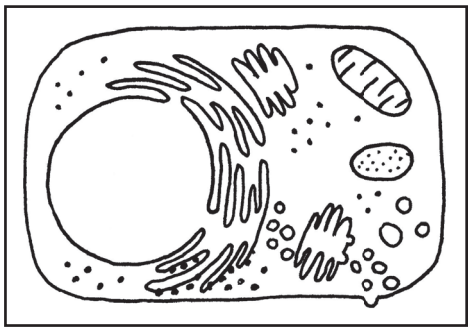
What materials and tools are available?

Where are the best locations to work?

Are there any dangers?

Will the cell's neighbors find out that I'm here?

CELL "MAP" showing organelles



DNA library

copy machines

Mitochondria: power plant making ATP

Lysosome: recycling (BEWARE!)

Vesicles and endosomes are like bags and boxes

Endoplasmic Reticulum: makes lipid membrane

Ribosome: protein factory

Golgi bodies: processing and shipping

RAW MATERIALS

Most structures in our environment are made from metal, glass, plastics, and plant fibers. Cells have 4 basic materials that all their stuff is made of.

0)

1)

2)

3)

4)

INSTRUCTIONS

TOOLS/"TASK ROBOTS" (need energy)

They are usually made of protein but can have one of the other ingredients mixed in. Tools/robots can only operate on ONE type of molecule.

scissors staplers folders

editors (spell checkers) fixers pumps

vehicles shredders

keys

copiers

clips

STRUCTURES

Not all cellular structures are similar to the structures in our own environment but a surprising number are.

cables

string

hooks flags anchors

mailboxes letters labels

LIPID

walls bags tubes

The energy to run these tools comes from the cell's "rechargeable batteries."

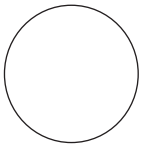
Energy is released when the third phosphate is popped off. Energy is needed to put it back on.

7(a): INSIDE A CAPSID

All viruses have a genome, which can be either DNA or RNA.
Many viruses also have one or more protein "tools"inside the capsid (tools it will need immediately after entry).

POLIO

RNA(+)

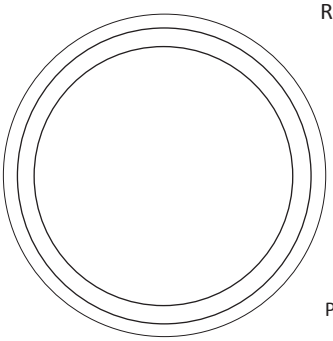


flat attachment proteins

PolyA tail

HIV-1

RNA(+)



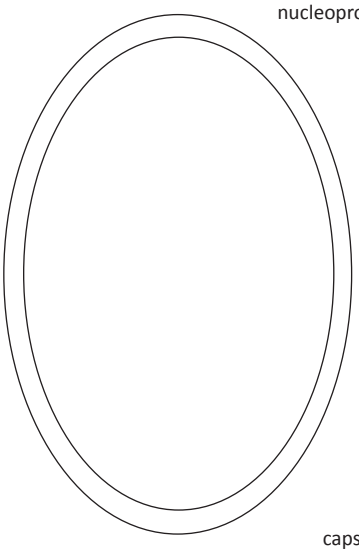
Protease

Integrase

Reverse Transcriptase
(for turning RNA into DNA)

SMALLPOX

DNA nucleoproteins



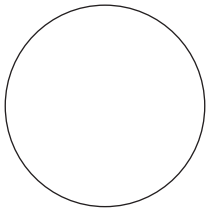
capsid

over 100 enzyme tools!

lateral bodies (function unknown)

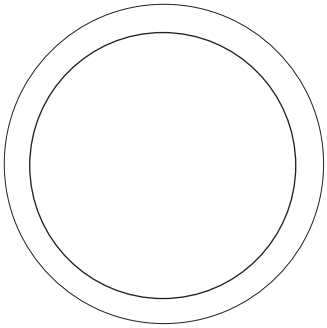
envelope with attachment "tubules"

PAPILLOMA



DNA wound around protein spools

CORONA

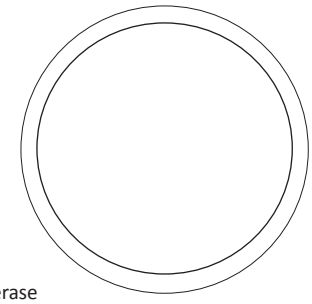


Huge genome - 30,000 bp
RNA(+) is wrapped around nucleoproteins

INFLUENZA

NEP

RNA polymerase



RNA(--) wrapped around nucleoproteins

Viruses do not have:

1) _____

2) _____

3) _____

Virologists draw viral genomes as a straight line when they want to show where information is located.
Each segment represents the instructions for one thing, sort of like a chapter in a book.

Both RNA and DNA are directional.
One end is called 5-prime and the other is 3-prime.

As a general rule, the genome is read and used in this direction.

how to make viral structures

when to use tools

how to make tools

NOTE: Viruses don't have spell checkers or editors.

UTR = untranslated region *(not read by ribosomes)*

7(b): CLASSIFYING VIRUSES

THE VIRUS'S STRATEGY WILL DEPEND ON WHAT TYPE OF GENOME IT HAS.

KEY: ds = double-stranded (+) = "positive sense" RNA that is ready to be read by ribosomes
ss = single-stranded (-) = "negative sense" RNA that is "backwards" [So a (+) copy will need to be made.]

1) _____	Herpes family Papilloma (warts) Pox family Adenovirus Polyoma
2) _____	<u>Animals</u> Parvo Circo Anello <u>Plants</u> Gemini Nanoviruses Microvisuses
3) _____	Reoviruses (Ex: Rotavirus-- "the stomach flu")
4) _____	Calici Corona Flavi (yellow fever) "Picorna" family: polio, rhino Coxsackie B
5) _____	Arena Rabies Ebola Influenzas Measles Mumps
6) _____	HIV (AIDS) cancer-causing viruses, esp. leukemias
7) _____	Hep B fish viruses feline leukemia

THIS CHART REPRESENTS THE "BALTIMORE CLASSIFICATION SYSTEM" invented by David Baltimore.

David Baltimore won a Nobel Prize in 1975 for discovering _____.

Recently (and quite surprisingly) RT has been found in the human genome. It allows sections of the genome to be moved to a new location, and also seems to be used in restoring the length of chromosomes as they shrink over time

8(a): HERPES SIMPLEX-- A DNA VIRUS

Herpes simplex viruses (HSV) include: HSV-1, HSV-2, Varicella zoster (chickenpox), Epstein-Barr virus, and cytomegalovirus (HCMV).

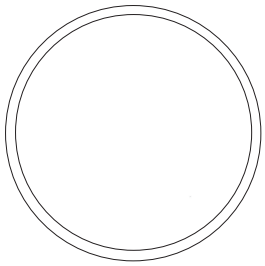
DNA genomes have 120,000 to 240,000 base pairs.

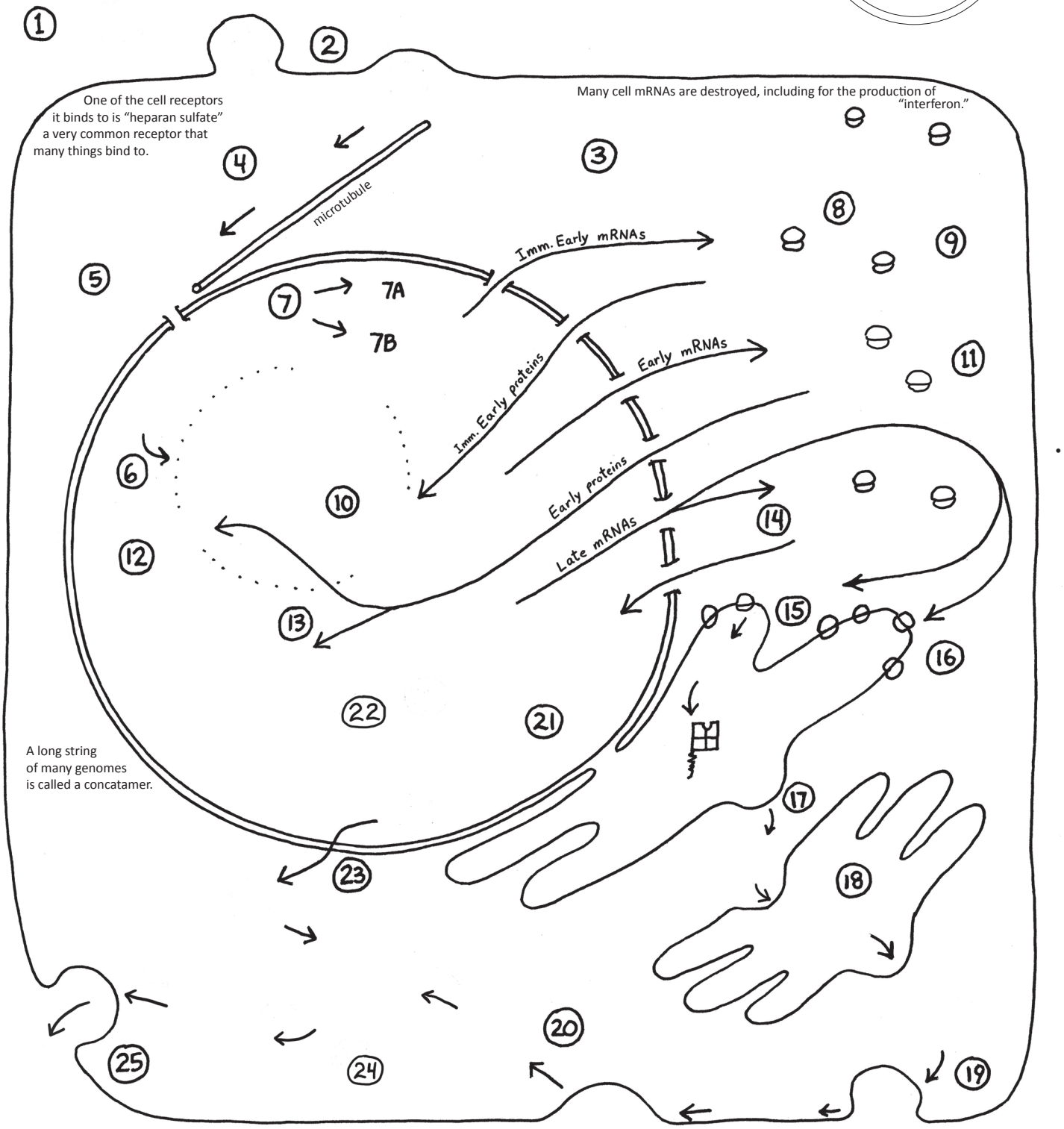
- ☐ capsid
- ☐ glycoproteins
- ☐ tegument proteins
- ☐ DNA
- mRNA:

HERPES VIRION (150-200 nm)

Some tegument proteins will help capsid get through membranes.

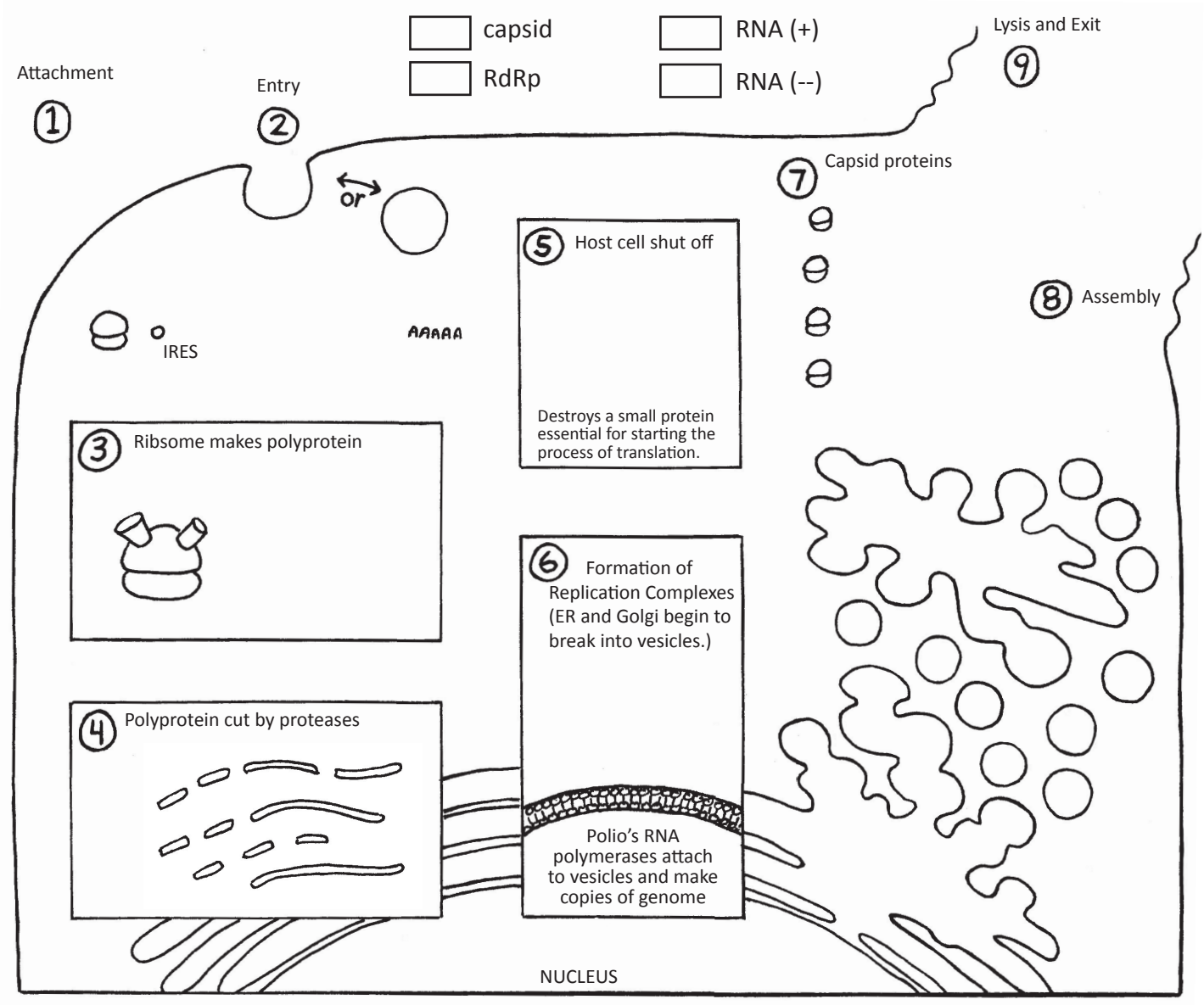
Has several types of spikes.





8(b): POLIO-- AN RNA VIRUS

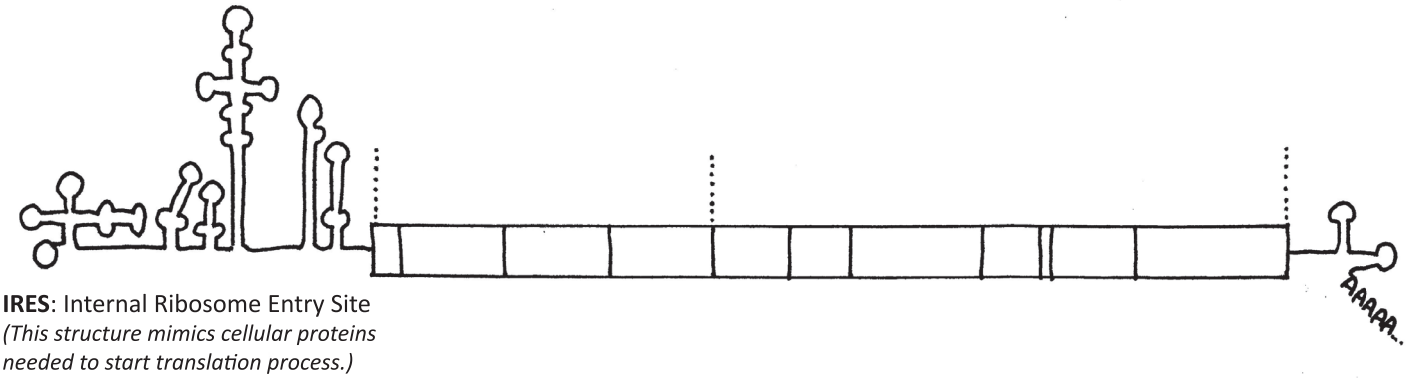
Poliovirus is a positive sense RNA virus and is a member of the Picorna family of viruses. Its genome contains about 7,500 base pairs, and its replication process takes place entirely in the cytoplasm (cytosol).



This cell would be an epithelial (surface) cell in the intestines.
After infecting many intestinal cells, the viruses will go into the blood and then make their way to nerve cells, especially motor neurons in the spine.

NOTE: It takes two rounds of copying to get a (+) sense strand for the capsids.

This is how virologists draw the polio genome. They like to show the IRES, but also like to use a line to show genes.



IRES: Internal Ribosome Entry Site
(This structure mimics cellular proteins needed to start translation process.)

9: THE BODY FIGHTS BACK

This lesson is not a complete overview of the immune system. We'll focus on the fight against viruses, although much of this information would apply to other pathogens as well. The body has several layers of defense. Most viruses are kept out because of physical barriers, but if some get past those, we have two more levels of defense: the **innate** (non-specific) immune system, and the **adaptive** (specific) system.

1) PHYSICAL BARRIERS

These work so well that under normal circumstances we go about our lives oblivious to the vast number of viruses in our environment.

2) ROAMING "EATERS" (phagocytes)

If viruses get past our physical barriers, they are met by roaming immune cells that eat all foreign substances they find.

3) SENSORS that detect viruses

TLR-3 Found on the outside of phagocytes, and inside their endosomes.

EXAMPLES:

RIG-1 **MDA-5**

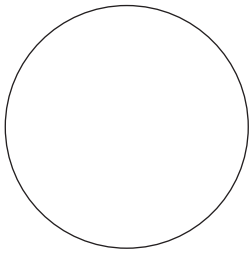
Found in the cytoplamsm of all cells. They detect viral RNA (usually dsRNA).

4) INTERFERON

The sensors trigger the production of interferon, a chemical message that causes the production of many anti-viral proteins, and also alerts other cells to the presence of the virus.

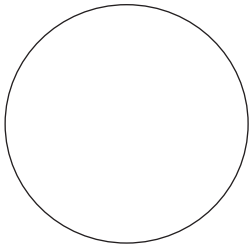
5) NATURAL KILLER CELLS

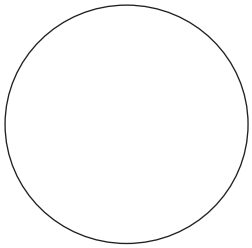
NK cells are a type of white blood cell called a lymphocyte.



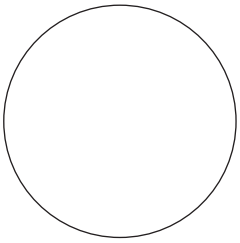
6) KILLER T CELLS

Killer T cells must get permission from helper T cells.

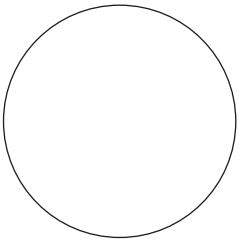




7) B CELLS and their ANTIBODIES



Macrophages present viral proteins to T helper cells.

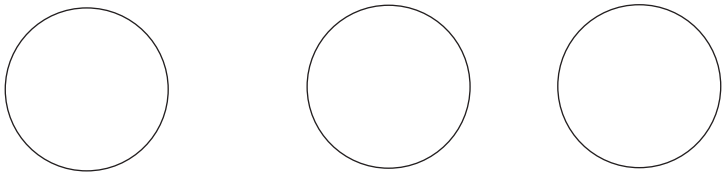


T helper finds B cell with matching antibody.

The B cell starts making many antibodies, which stick to the virus.

10: VACCINES and ANTI-VIRALS

VACCINE: The goal is to imitate an infection by giving the macrophages viral antigens (either parts or whole) so they can present them to T cells who then tell B cells to make antibodies against them. Some B's will be memory cells.



Vaccines can be prepared in 4 ways:

1) _____

The genome has mutated so the virus can't cause illness. Virus retains some ability to replicate.

EX: _____

_____

2) _____

The virus has been treated with chemicals to "kill" it, but the T cells still recognize the proteins.

EX: _____

_____

3) _____

Only small parts of the virus are used, such as a piece of the spike, or one capsid protein.

EX: _____

_____

4) _____

Cloning techniques are used to make yeast cells produce either empty capsids, spikes, or strands of RNA.

EX: _____

_____

ANTI-VIRALS: The goal is to block or break a viral structure without harming any host cells. This is tricky! Here are three of the most successful strategies so far (though resistance is already a problem).

Strategy #1: Nucleoside analogue

Try to stop the replication of viral DNA or RNA by giving the virus a supply of fake rungs that do not have a ribose sugar.

Ex: Acyclovir is a guanosine (G) mimic (for herpes)

Other examples:
1) AZT (for HIV) mimics "T."
2) Remdesivir (for Ebola) mimics "A."

Strategy #2: Block action of NA (Influenza)

Block the snipping action of neuraminidase so influenza viruses can't bud out of cell.

Ex: Tamiflu and Relenza

Strategy #3: Stop fusion (HIV)

The HIV drug Fuzeon is a protein that binds to HIV's fusion mechanism.

Can't prevent attachment, but prevents fusion.

Strategy that used to work: Block Influenza's M2 ion channel

Influenza viruses are now resistant to Amantadine, so it is no longer used.