

Source: [KBiologyMasterIndex](#)

1 | Overview of Human Diseases

A lecture by the Legendary Dr. Paul Hauser. Slides are here

#flo #disorganized

Disease is an abnormal condition that causes impairment in/loss of function of an organism (a.k.a. decreased fitness) that is not due to immediate external injury.

- What causes human disease?
 - Infectious agents
 - Deficiency disorders
 - Heritable factors
 - Physiological disorders (immunodeficiency, autoimmune disorders, allergies, etc.)

1.1 | Congenital vs. Acquired disease

Congenital diseases => diseases present at birth due to DNA abnormalities / pregnancy pathological issues

Acquired diseases => diseases that begin during lifetime, including...

- Microorganism invasion => “infectious diseases”
- Autoimmune reaction
- Nutrient deficiency
- Mechanical wear
- Ingestion of noxious chemicals

Infectious diseases actually smaller on the causes of death in the US

- Heart disease => wear + deficiency
- Cancer => heritable + DNA
- Unintentional injuries => not a disease
- Chronic respiratory disease => wear
- Stroke => not a disease
- Alzheimer disease => wear
- Diabetes => autoimmune, nutrient, wear
- Influenza <= **here, finally, an infectious disease.**

1.2 | Disease causing agents

- **Protozoan** => single-celled eukaryotes
- **Fungal** => single/multi-celled eukaryotes
- **Bacteria** => single-celled prokaryotes
- **Viral** => acellular parasitic infectious agent
- **Helminths** => multicellular worms
- **Prions** => acellular misfolded proteins
- **Viroids** => infectious nucleic acids w/o protein coat to make virus

1.3 | **Pathogenicity + Virulence**

Pathogenicity => relative capacity to cause disease

- Non-pathogenic agents => no disease
- Primary pathogens => yes disease
- Opportunistic pathogens => yes disease only when it can, for instance, in immunocompromised individuals

Virulence => numerical measures for pathogenicity

- Measured experimentally with LD50 + ED50
-

1.4 | **Overview of various diseases**

This video

1.4.1 | **Protozoan**

- **Protozoan factors** => direction pathogenesis leading to tissue damage
- **Host-mediated factors** => immune evasion + escape mechanisms + immunosuppression

Adaptable!!

1.4.2 | **Fungal**

- **Fungal factors** => many shapes and very adaptable, could produce specialized enzymes to take root in body
- **Host-mediated factors** => cause immunocompromise, acquired through inhalation, etc.

1.4.3 | **Bacteria**

- **Bacterial-induced toxicity** => produces toxins + has hard capsule cell
- **Host-mediated factors** => may develop host resistance, could compete for resources, and could be grown intracellularly



Figure 1: Screen Shot 2020-10-12 at 3.08.53 PM.png

1.5 | Bacteria causing diseases

Biofilm formation

- Communities of bacteria could work together by adhering and exchanging information
- Bacteria could perform quorum sensing => exchange of information with each other + recognize various members of their group

1.5.1 | Fighting bacterial infections

Antibiotics => drugs with selective toxicity for specific bacterial types

Act by...

- Disrupting membrane + cell wall integrity
- Selectively target + impair bacterial ribosomes
- Block bacterial DNA replication/transcription
- Inhibit bacterial metabolism

1.6 | Viruses causing diseases

Viruses: acellular macromolecular assemblies

- Contain protein coat called capsid
- DNA or RNA, but not both
- Are obligate parasites that could only replicate within host
- Assembled and mature viral particles => virions, which contain...
 - Capsid
 - Genetic material

- Occasionally outside lipid layer

=> Viruses exist on the nanometre scale, but they are difference in share and size

1.6.1 | **Structure of viruses**

- **All contain**
 - Capsid => structural protein coat
 - Genome => RNA/DNA; but not both
- **Some contain**
 - Membraneous-enclosed capsid => envelope
 - Externally-facisg host-cell fusion proteins => spikes
 - Viral genome replication enzymes => prlymerases
 - Other proteins for fun => enzymes, motor proteins, transcription factors, host-cell interacting proteins, etc.

1.6.2 | **Two types of virus**

- **Prokaryotic-infecting viruses**
 - Variety of shapes
 - Complex and prolate shapes
 - Has, sometimes complex shapes! a la this image
- **Eukarotic-infecting viruses**
 - Much more “boring” in terms of shape
 - Icosahedral/sphercial outside
 - Enveloped constructions => envelope protein layer outside, spherical inside
 - Helical/Cylindrical/Bullet shapes, too!
 - Often single patterns assemble together to create symmetric shape that creates the whole of the virus

1.6.3 | **Viral Life Cycle**

1. Attachment => protein contact between virus and host
2. Viral entry/Uncoating => shedding the protein layer
3. Biosynthesis => make baby viruses
 1. Genome Replication: transcribe DNA/RNA
 2. Genome Expression: read DNA/RNA to make proteins
4. Viral genome integration => retrovirus only
5. Assembly => put it all togethr
6. Viral Exit => mature virons leave

Viral Entry *Option 1: Direct Injection/insertion*

- Insert genome through the bi-layer
- Leave the rest behind
- Tada!

Option 2: Endocytosis

- Trick the host cell into introducing the virus as food
- Endocytosis!
- Bam

Option 3: Fusion

- Virus fuse with cell membrane
- Shed the protein coat once in
- Shazam!

All of these involve attachment first, which usually takes two steps.

This process causes the organism-specific response to viruses:

1. Attachment: adhere roughly to random sugar proteins
2. Binding: roll over slowly, and bind to the entry receptor it needs

Uncoating

- Virus triggers *early endosome*
 - Causes pH dependent protein denaturation
 - Causing the capsid to fall apart
 - Triggering *late endosome* => releasing genome

Viral Replication Key questions:

- **How are viral mRNAs produced from the viral genome?** => virus will hijack the ribosomes in the host cells. So, it is more important to ask how the mRNAs are produced to tell ribosomes what to do
- **What serves as the template for viral genome replication** => replication will need a polymerase; but the source and mechanism is dependent on viral genome structure/composition



Figure 2: Screen Shot 2020-10-12 at 11.04.53 PM.png

DNA Viruses

How are viral mRNAs produced from the viral genome?

- Viral DNA enters, through RNA polymerase II in the host cell, mRNA is produced
- mRNAs then read by ribosomes, and there we go

What serves as the templates for viral genome replication?

- Viral DNA serves as template for host cell DNA polymerase
- Viral genome copied repeatedly
- Virus, then, **will be replicated within the nucleus** due to it needing the polymerase to copy DNA

Except! Poxviridae carry their own polymerase, so they replicate in the cytoplasm.



Figure 3: Screen Shot 2020-10-12 at 11.09.46 PM.png

RNA Viruses

How are viral mRNAs produced from the viral genome?

- +Strand: reproducible RNA => could be directly translated by the ribosomes
- -Strand RNA: useless template RNA (less easy to be detected)
 - Need to be processed by RDRP (RNA-dependent RNA Polymerase)
 - Once entered the cell, RDRP goes to work copying -Strand RNA to +Strand RNA
- double-stranded RNA viron => (+, a.k.a. sense)
 - +-stranded RNA => same idea as above
 - strand RNA => virus comes with RDRP that convert -ssRNA to +ssRNA. Then, same idea as above.

What serves as the templates for viral genome replication?

- RNA viruses does not need host-cell polymerase to copy RNA
- They come with polymerase that...
 - with dsRNA; takes +ssRNA and makes -ssRNA; combining the two to produce dsRNA
 - with +ssRNA, takes +ssRNA and makes temporary -ssRNA which makes more +ssRNA
 - with -ssRNA, takes -ssRNA, and makes temporary +ssRNA, which makes -ssRNA



Figure 4: Screen Shot 2020-10-12 at 11.14.30 PM.png

Packaging Does not require ATP. Just sealed in.

Viral Exits Lysis

Replicate so much that the membrane bursts.

Budding

Trigger...

- Trigger exocytosis
- Meanwhile, send virus's own spikes to the membrane
- On exit by exocytosis, steal a part of the newly-spikey membrane with it to serve as new casing

1.6.4 | Retroviruses

Viruses that have the ability to intergrate into the chromosomes of the host cell

To make this happen, the virus needs...

- **Reverse Transcriptase**
 - Transcribe RNA to double-stranded RNA
 - Take double-stranded RNA to turn into DNA
- **Integrase**
 - Force insert the DNA into the genome of the host cell

And because of the fact that viral DNA is now in cellular DNA, these viruses' DNAs are hard to get rid of.

And this is why we can't cure HIV.

Virus, in this case, spread through cell duplication

- Proviral region on the DNA, every time the ribosome comes across it, makes a new viron
- These components are then assembled, sent, etc. as usual
- Because of the fact that the ribosome needs to, well, come across the bit of DNA for this to work, the virions are made slowly by "trickling out."



Figure 5: Screen Shot 2020-10-12 at 11.22.35 PM.png

Preventing Retroviruses

- Prevent Fusion gp120, gp41, CCR5
- Prevent reverse transcription RT
- Prevent intergrease IN
- Prevent viron maturation PR

1.6.5 | Viral Genome vs Mutation Rate

Viral genome size vs. mutation rate



Figure 6: Screen Shot 2020-10-12 at 11.24.39 PM.png

- RNA viruses could mutate more because it does not have checks
- More complex+largest viruses harder to mutate

Genetic drift — viruses mutate due to polymerase error

Genetic shift — viruses recombine without mutating by crossing-over mechanism or genome segment reassortment. Think! the flu

1.7 | Why are viruses bad

Damage host cells/tissues by...

- Reducing gene expression capacity
- Depleting cellular resources
- Causing cell lysis (to explode)
- Promoting tumorigenesis — cancer
- Creating damaging immunological response

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2.1 | Making Proteins, a guide

Genetic Code => “nucleotide code” found in the DNA that helps make protein. There are two parts of this: translation and transcription.

- The process of **Transcription** involves taking the DNA, separating it, and copying its corresponding pairs to RNA
- The process of **Translation** involves taking the RNA and making proteins.

Occasionally, the RNA is what we want to end up with, so then obviously we no longer need the process of Translation.

2.1.1 | **Transcription => converting DNA to mRNA**

- Done by RNA Polymerase Enzyme
- Rip apart hydrogen bonds using DNase enzyme
- Read one side (“template strand”, a.k.a. noncoding strand) of the double helix, recognizing each nucleotide
- Pluck the correct corresponding nucleotide out of the nucleus
 - G->C
 - C->G
 - A->U
 - T->A
- Prokaryotes lack membrane-bound nucleus (or any organelle)

Definition 1 · **Gene** information that successfully encodes a functional protein or a functional catalytic RNA

RNAs could also be catalysts!

- “Promoter”’s denotes beginning of a gene. “Terminator”’s denotes the end of gene.

Starting Transcription * Series of utility “factors” proteins begin to assemble to call the attention of RNA polymerase. (How + when does this happen? #ASK) * RNA polymerase binds to the Sigma Subunit => form a holoenzyme to unwind DNA * Sigma subunit informs the enzyme where to find a promoter (beginning of binding) * “Enhancer” gene sequences help bind with activator proteins to help attract RNA polymerase II

Promoters

- Polymerase Enzyme starts at a promoter (typically found upstream of the 5' start site) and ends at a terminator
 - Box of TATTA highlights transcription rate and the start site
 - TFIIA cofactor in RNA recognizes TATTA box, TFIIB recognizes C/CG/CG/CGCCC upstream
- Stronger promoters/enhancers => “enhance” “more.” i.e. tumor viruses strengthen promoters for cell growth

Terminators

- Found in the end of the template sequence
- Two types in prokaryotes
 - Rho-independent terminators — roll back onto itself, causing the RNA to terminate and mRNA to be released
 - Rho-dependent terminators — activate cofactor named rho + unwind the transcribed RNA-DNA hybrid
- In Eukaryotes

- Pol I genes — transcription stopped through termination factor by unwinding the transcribed RNA-DNA hybrid
- Pol II genes — don't stop until the end, but a polymerase has a "cleavage" mechanism that clips the end out using a poly(A) tail consensus sequence

2.1.2 | **Before we continue, two words**

- *Non-coding sequence*: metadata for DNA for the processors
- *Coding sequence*: DNA content for amino-acid production

2.1.3 | **mRNA processing => splicing mRNA**

Pre-process the mRNA.

Prokaryotes does not do this! Prokaryotes' coding sequence always makes a full protein, so we just start at promoter and end at terminator and make a protein!

In Eukaryotic DNA...

Between Promoter and Terminator, **Exon** and **Intron** alternate. Exon is coding, whereas Intron is non-coding and works as metadata.

After reading the intron, they are spliced out during mRNA processing => done by the "spliceosome". The mRNA, after splicing, is "capped and tailed" to mark pre-processing completion, at which point they leave the nucleus + go to the ribosome.

- Begin by assembling helper proteins at intron-exon borders => "splicing factors"
- Other helping factor proteins come together and form the "spliceosome" to do the splicing
- Spliceosome splices by bringing exon ends together
- After it's done, the spliceosome disintegrates

2.1.4 | **Translation => RNA-directed polypeptide synthesis**

Mature mRNA sent to ribosome. mRNA must travel to the cytoplasm in the Eukaryotes to catch the RNA, whereas in prokaryotes they don't have to go anywhere.

Ribosomes has two units: 50S unit + 30S unit => they come together whenever a mRNA needs it. Each contained specialized rRNA + tRNA to catalyze attachment of and carry amino acids + adapt the incoming mRNA respectively.

Note! The beginning of mRNA is not translated. There a portion on the 5' end of the mRNA (starts with AGGAGG) — about 170 nucleotides in humans, and shorter in bacteria — that's called UTR (untranslated region.) This region helps ribosomes bind to it + stabilize the binds.

- 3 protein factors IF1, IF2, IF3 forms a complex for transcription by binding to a subunit on the ribosome
- Methionine-carrying tRNA binds to the start of the mRNA, which forms the initiation complex. This is typically removed after translation if not coded for (if M-A amino acid pair coded for, methionine removed; but if M-L pairs coded for, methionine not removed.)
- A-site: translates mRNA to tRNA — anti-codon pairs
- P-site: amino acid dumped from tRNA to the actual chain being built
- Spent tRNA ejected to the E-site, which is then recycled
- Catalyst tRNA combines with rRNA to catalyze amino acid peptide bond
- Each codon (group of 3 units in tRNA), matches a specific [\[KBhBIO101AminoAcids\]](#)

Smaller ribosome unit grabs, larger attaches + forms amino acid

After the amino acids are assembled, it's time for [\[KBe2020bio101refProteinFolding\]](#). See also [\[KBhBIO101Proteins\]](#).

=> Shaperones fold proteins, and if its finds proteins impossible to fold, it flags it using ubiquitin to send to the garbage

Eukarotic gene expression is regulated at many stages — prevents error

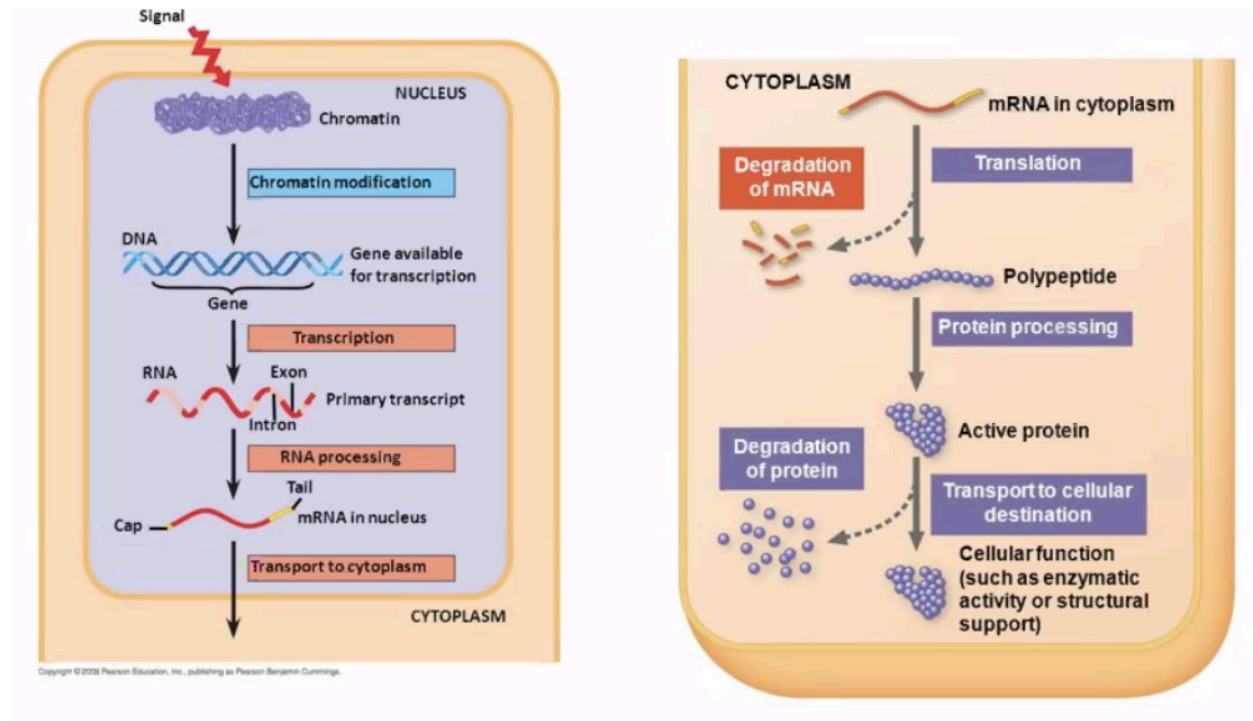


Figure 7: preprocessing.png

- Viral proteins are usually easy to assemble

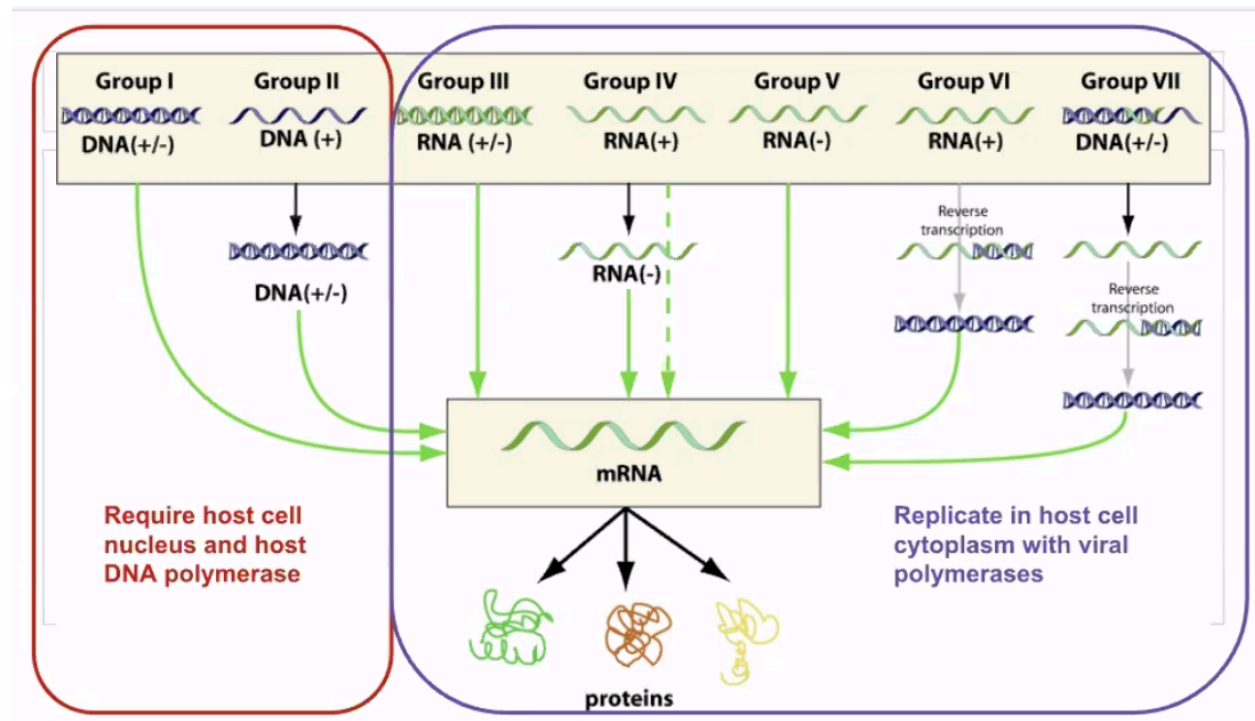


Figure 8: Screen Shot 2020-11-02 at 2.48.22 PM.png

Question: how are proteins made in the viral genome

- No viruses produce ribosomes
- Ribosomes become centrally important for the virus
- What serves as the template to make new virus copies

Viruses attempt to overwhelm the enzyme to entry.

- **DNA Polymerase** takes DNA and makes more DNA
 - Duplicates cell DNA
 - Could be hijacked during cell cycle to duplicate DNA viruses
 - DNA viruses may also carry their DNA Polymerase to not wait for the cell cycle
- **RNA Polymerase** takes DNA and makes mRNA
 - Have lower fidelity with an error about 1/100,000
 - Hence why safety mechanism needed

Capping and Tailing * 3' end => AAAAAA tail (using poly-adenine tailing enzyme) * 5' end => GGGGGG cap (using guanine-capping enzyme)

DNA viruses are “less complex”, in that as long as they are able to get into the nucleus, the rest would just be the body’s work automatically.