

JUNE, 2013
1.7.2020

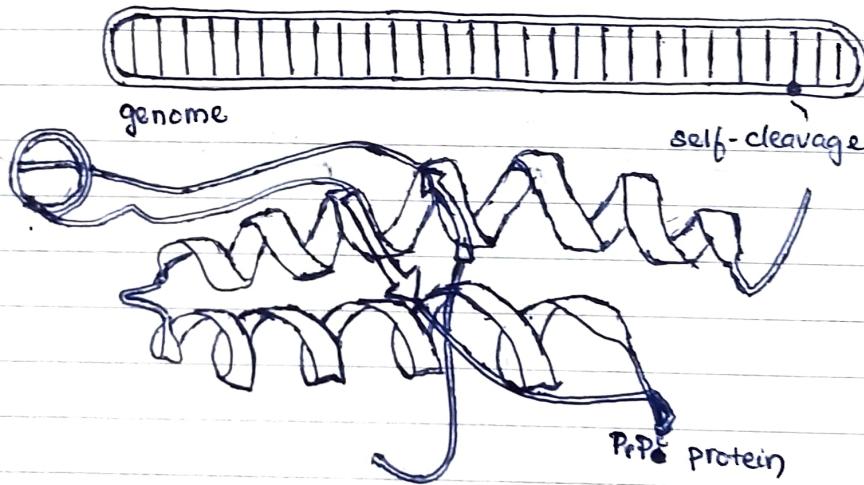
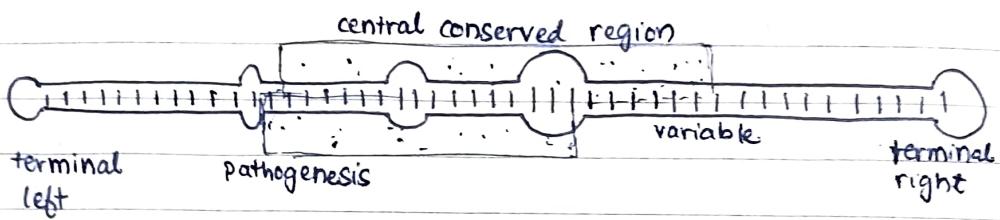
MONDAY WEEK 25 17

UNUSUAL INFECTIOUS AGENTS

A FUNDAMENTAL QUESTION

what is the minimum genome size needed to sustain an infectious agent?

Could an infectious agent ^(Smith) exist without any genome?



viroids
Satellites?
prions

NOTES

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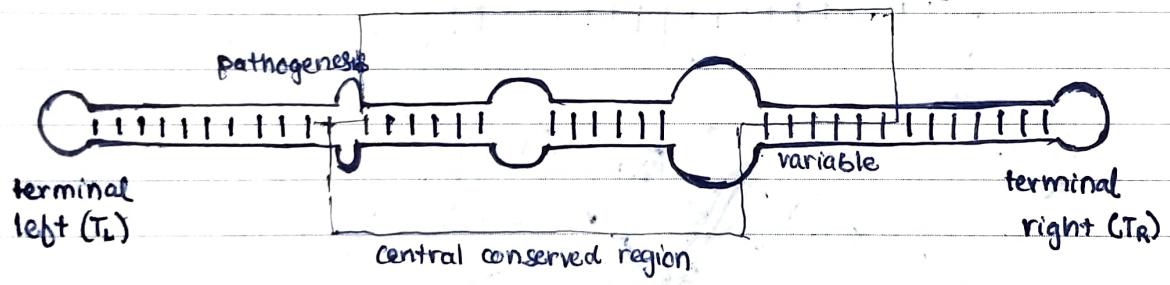
VIROIDS

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- Circular ssRNA
- no protein coding regions
- no protective coat, yet migrate from host to host (no receptors required)
- replicate when introduced into plants.
- families pospiviroidae (replicate in nucleus) and avsunviroidae (replicate in chloroplasts)



- not technically circular, but if you denatured it, it would be circular

pospiviroidi: potato spindle viroid

avsunviroidi: avocado sunblotch viroid.

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VIROIDS

- Circular ssRNAs, 246 - 401 nt nucleotides
 - RNA displays extensive internal base-pairing, appears as 50 nm rod in EM.
 - Some are ribozymes
 - activity essential for replication
 - distinction from the virus lifestyle
 - viruses are parasites of host's translation machinery
 - viroids are parasites of host's transcription machinery
- & translation machinery

ribozyme is an RNA that has enzymatic activity.
 in fact it cleaves itself.
 its another remnant of the RNA world where
 RNAs had enzymatic activity.

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POTATO SPINDLE TUBER VIROID (PSTVd)* DISCOVERED 1967

- prototype for smallest known nucleic acid-based agents of infectious disease
- 359 nucleotides
- some benign, others cause economically important diseases of crop plants.

healthy | mild | intermediate | RG-1
* production of potato seed stocks.

SOME OF PROF. RACANIELLO'S FAVORITE VIROIDS

- cadang-cadang coconut viroid
 - CCCVd causes lethal disease of coconut palms.
 - pina colada drinkers are sad.
- hop latent viroid
 - HLVd: no symptoms in the hop plant
 - beer lovers are relieved.
- apple scar skin viroid
 - ASSVd: mild symptoms; apples look bad, taste good.
 - picky consumers don't buy these apples.

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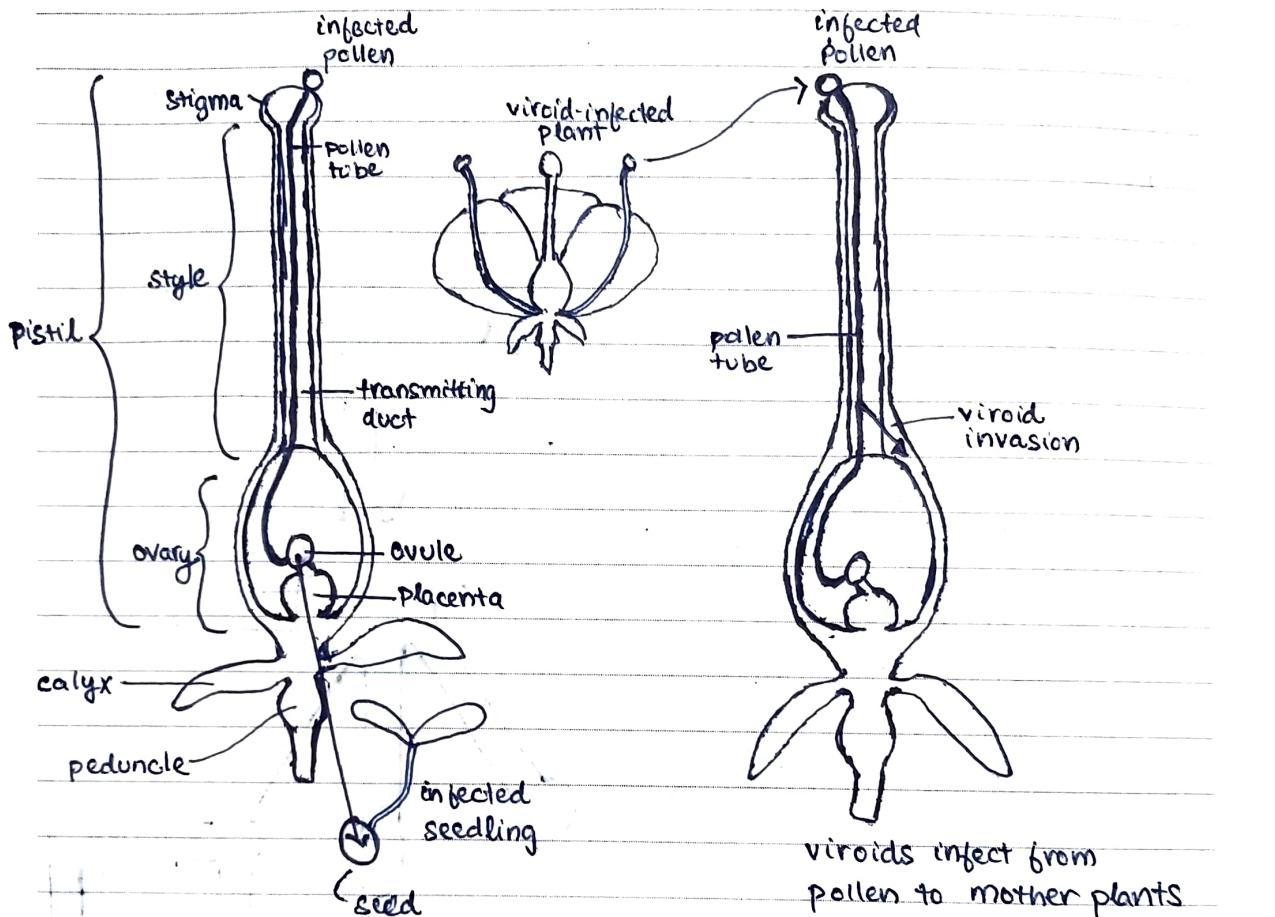
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VERTICAL AND HORIZONTAL TRANSMISSION OF VIROIDS IN PLANTS VIA POLLEN



VERTICAL TRANSMISSION
(POLLEN TRANSMISSION)

HORIZONTAL TRANSMISSION

NOTES

{ Spread by bees
spread by farm equipment brushing against
mechanically

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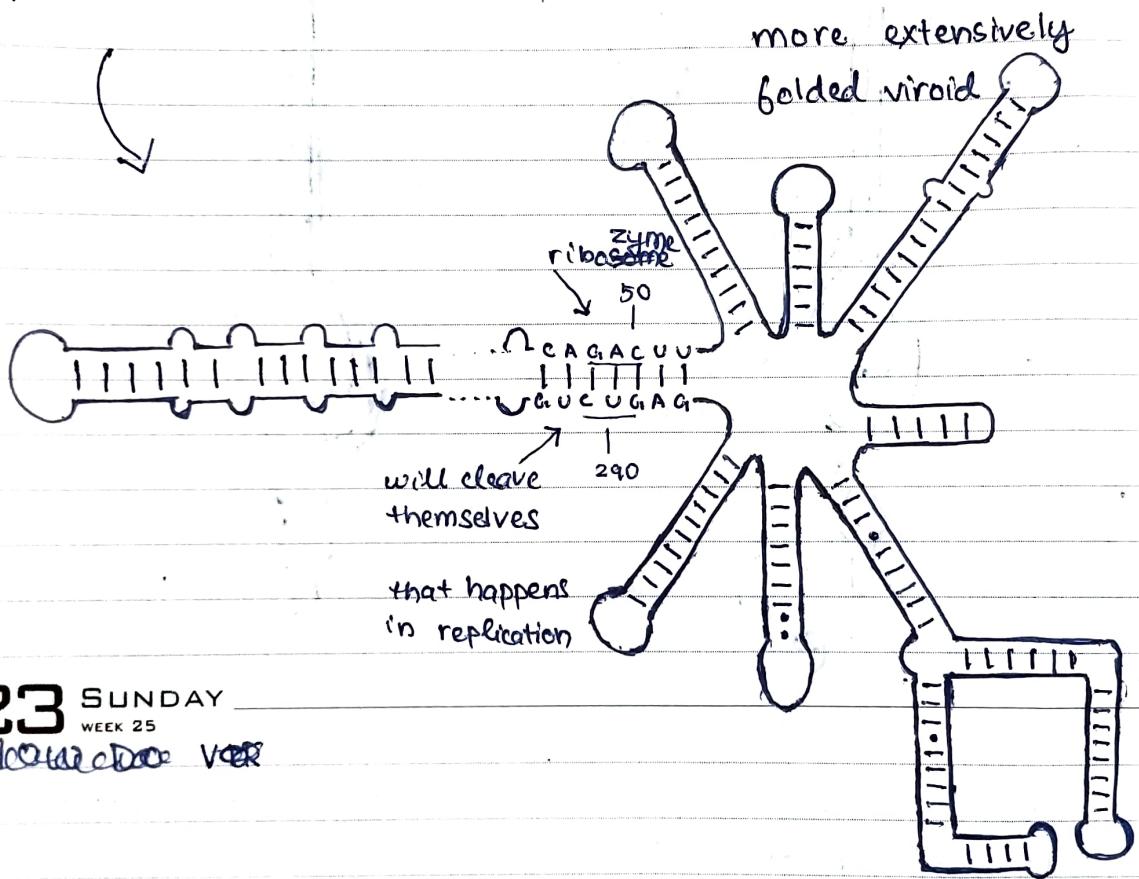
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FUNCTIONAL REGIONS OF VIROID RNA

PSTVd - popsviroidae
potato spindle tuber viroid

PLMVd - avsunviroidae
peach latent mosaic viroid



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~~Wednesday~~ VEE

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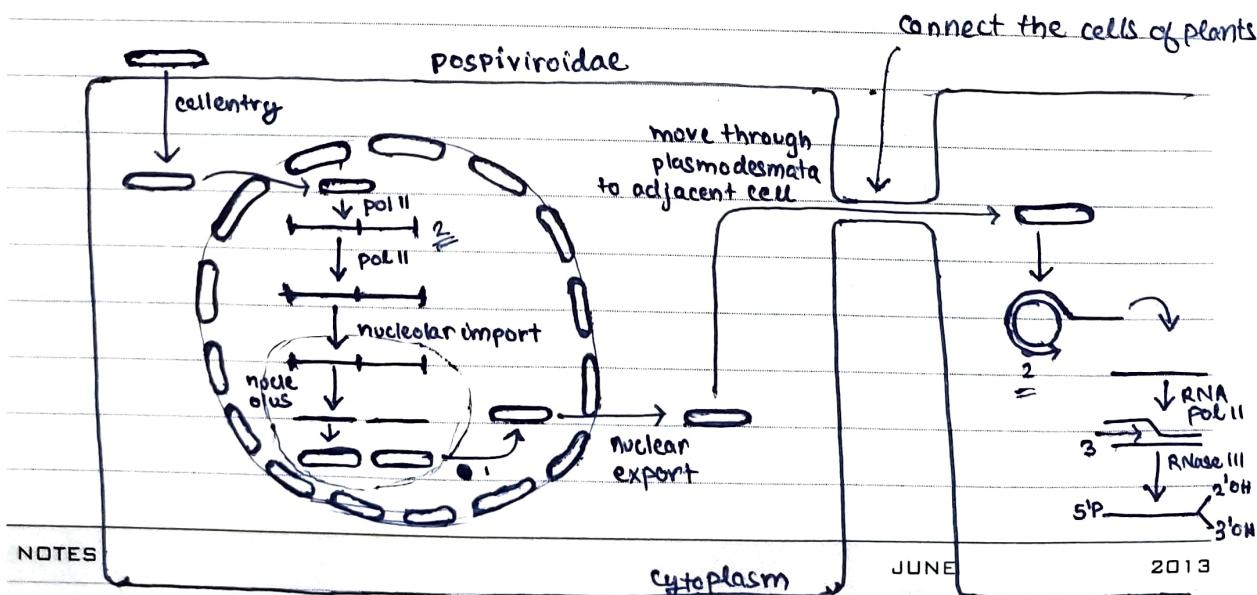
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HOW DO VIROIDS REPLICATE

- Concatamers of viroid RNA produced by host RNA polymerase II
- one group of viroids forms 'hammerhead ribozyme'
 - a ribozyme: autocatalytic, self cleaving RNA
 - ability of RNA to catalyze a reaction in the absence of protein discovered 1981.
 - used to cleave multimeric structures produced during replication.
- other viroids cleaved by host nuclear enzymes.



1 nuclear export

2 rolling circle replication (concatamer) 2 RNAA

3 strand displacement to form the other strand

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* similar for avsunviroidea (hammerhead ribozyme)

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ORIGIN OF VIROIDS

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- originated in the 20th century by chance transfer from wild plants used in breeding modern crops
- worldwide use of genetically identical plant breeding lines (monoculture)
- mechanical transmission by contaminated farm machinery, equipment, hands, plant to plant

HOW DO VIROIDS CAUSE DISEASE

- small 21-24 nt RNAs (siRNAs) derived from viroid RNAs in plants may guide RNA silencing of host genes and induce disease.
- symptom development correlates with production of small RNAs.
- many siRNAs map to pathogenicity-modulating domain of viroid.

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WEDNESDAY

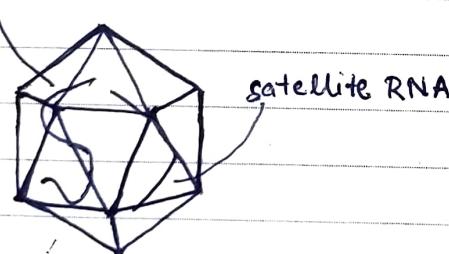
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SATELLITES

- ssRNA, DNA, cRNA genomes } diverse collection
- depend on helper virus for propagation
(helper-dependent)
- lack genes required for replication
- Satellite viruses: encode structural proteins that encapsidate the genome (form distinct particles)
- Satellite RNAs: packaged by helper virus proteins, also rely on helper for replication. may or many not encode protein.

helper RNA



helper virus
capsid.

word "satellite"
is falling out of
favor

better to call them
satellite viruses?

ex- AAV

adeno associated virus.

NOTES

cRNA : circular RNA

can't replicate without

Adeno virus.

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good for gene therapy.

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SATELLITES

- in plants, satellites cause distinct disease symptoms not seen with the helper virus alone.
(necrosis, chlorosis).
- Satellites are not defective viruses derived from the helper. genomes have no homology with helper.

SATELLITE VIRUSES

HELPER / SATELLITE	NUCLEIC ACID	PARTICLE NM	GENOME NT	CAPSID PROTEIN KDA	HOST
VIRUS					
• adenovirus or herpes virus / AAV	ssDNA	20-24	4700	87, 73, 62	vertebrate
• chronic bee paralysis virus / CBPV satellite	ssRNA	17	1100	15	animal
• tobacco necrosis virus / TNV satellite	ssRNA	17	1239	22	plant.

↑
1.2 kb
genome

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they are not just in plants

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HEPATITIS DELTA VIRUS

(not called satellite)

- properties of viroid and satellite
- helper virus is hepatitis B virus dont know why
- increases severity of HBV liver disease

HDV GLOBAL DISTRIBUTION

- 18 million people HDV infected;
5% of 350 million carriers of HBV
- declining in europe, asia-pacific region highly prevalent.

↑
used to be high in europe

you can't have HDV without HBV.

HDV can infect, but can't replicate without HBV.

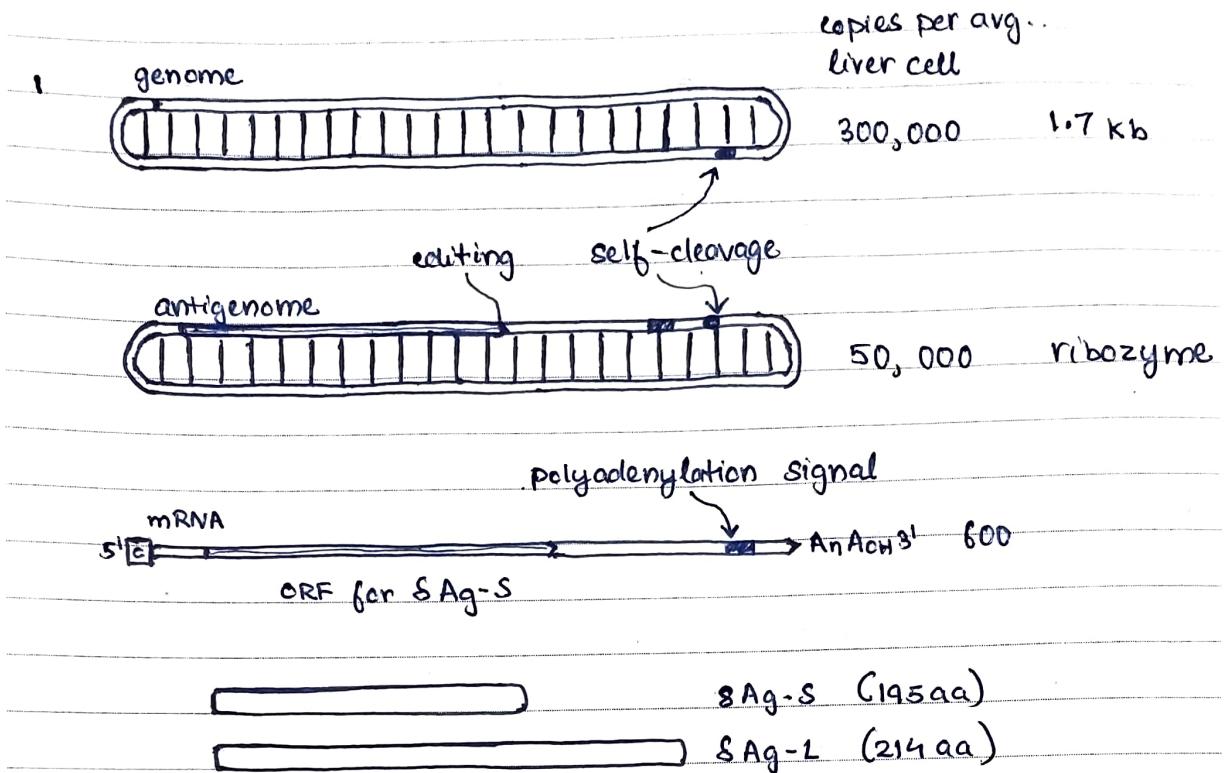
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HDV GENOME



I extensively base-paired. (Circle of RNA)
if you denature it, becomes single-stranded.

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antigenome is for replication
mRNA is made from the genome.

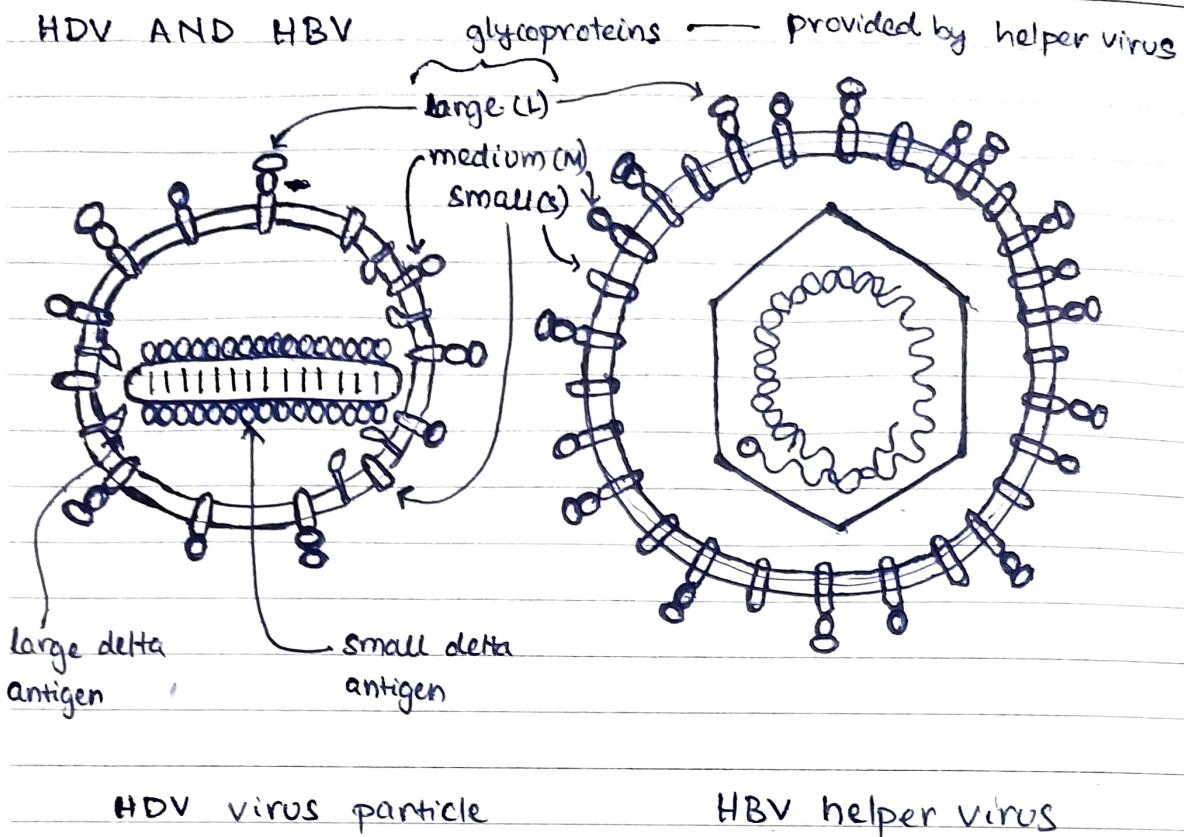
JUNE	2013						δAg - delta antigen (small, large)	NOTES
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□ 1



HDV genome is copied by host RNA polymerase II
Very much like viroids.

particles are taken up' by the same receptors
as HBV

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HEPATITIS DELTA-LIKE VIRUSES IN BIRDS AND SNAKES

- delta antigens divergent from human protein.
- no HBV-like viruses in birds or snakes examined.
- another enveloped virus might serve as helper.
- in vitro, HCV, VSV, dengue virus, WNV can be helpers for HDV.

not seen in the wild

in human population, hepatitis delta virus diverges into 3 genomes, much like HIV diversified, but much less extent.

HDV-like (Antigens) from snakes & birds.

we call these delta-like viruses because, we don't know if they cause hepatitis in the host, and we don't know what the helper is.

there are no HBV-like viruses in birds or snakes that harbour these sequences. maybe another envelope virus serves as helper.

HCV - hepatitis C virus

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03

VIROPHAGES

- derived from bacteriophage (phagein = to eat (greek)), means 'virus eater'.
- circular dsDNA viruses, icosahedral
- replicate only in cells infected with a giant virus.
- interfere with helper virus replication.
- another category of helper dependent virus not called satellite, just recently discovered.

sputnik
~~satellite~~

acanthamoeba polyphaga mimivirus

mavirus

cafeteria roenbergensis virus

OLV

large DNA viruses

sputnik 2

lentille virus

VSLV 1-4

phycodna- or mimiviruses?

NOTEBOOK

mimiviruses?

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VIROPHAGES

- mavirus - virophage of giant virus of *Cafeteria roenbergensis*, a marine phagotropic flagellate.
- organic lake virophage of phycodnaviruses that infect algae.
- gene exchangers? impact on ocean ecology?

it is suggested that virophage reduces the mortality of host alga from the phycodnavirus that infects them.

remember- i saw about the algae under antarctic ice that shrimp like to eat!

ARE VIROPHAGES SATELLITES?

like many autonomous viruses, they depend on transcriptional machinery, except in their case it is from another virus, not a host cell.

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05

PRIONS: INFECTIOUS PROTEINS, NO NUCLEIC ACID

- prions in the news

- BSE, mad cow disease, CJD, scrapie, Kuru, chronic wasting disease of deer and elk.

- 1997 nobel prize in medicine - Stanley prusiner.

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

- encephalopathy - disease of the brain.

- fatal neurodegenerative disorders of mammals.

- thousands of humans diagnosed each year, 1% arise ~~not~~ by infection.

- by 2002, 120 humans had contracted creutzfeld-jacob disease, from consumption of meat from animals with BSE.

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TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

- bovine spongiform encephalopathy (BSE)
("mad cow disease")
- Chronic wasting disease (CWD)
(deer, elk, moose)
- exotic ungulate encephalopathy (EUE)
(nyala and greater kudu)
- feline spongiform encephalopathy (FSE)
(domestic and great cats)
- scrapie in sheep and goats
- transmissible mink encephalopathy (TME)

07 SUNDAY
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TSE DISEASES OF HUMANS

cooking doesn't kill it.

- cruetzfeldt-jakob disease (CJD)
- fatal familial insomnia (FFI)
- gerstmann - sträussler syndrome (GSS)

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NOTES

• Kuru

• variant CJD disease

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SPONGIFORM

- infected brain has sponge-like holes throughout.
- severe psychomotor dysfunction.
- each disease has a characteristic symptomatology and pathology.
- symptoms depend on which part of the brain is damaged.

SCRAPIE

- first TSE recognized
- infected sheep rub on fences.
- motor disturbances, uncontrollable trembling (tremblant du mouton), paralysis, weight loss, death 4-6 weeks.
- recognized as disease of European sheep for over 250 years.
- endemic in some countries: UK v. of sheep / yr.

NOTES

we feed sheep to cows for protein,
from sheep brain.

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TSEs

- animal and human TSEs exhibit the same histochemical abnormalities.
- defect in plasma membrane formation.
- vacuolation of neurons, astrocytes, oligodendrocytes.
- loss of neurons in gray matter of brain.
- spongiform appearance.
- accumulation of glial fibrillary acidic protein in clumps.
- amyloidosis in brain, fibrils of misfolded prion protein.

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TSE PATHOGENESIS

- agent detected by injection of organ homogenates into susceptible species
- cerebellar ataxia, dementia, death after many months or years.
- agent first accumulates in lymphoreticular and secretory organs, then spreads to the CNS.
- in CNS, pathology includes astrocytosis, vacuolization (spongiform), loss of neurons.
- no inflammatory, antibody, or cellular response.
- undetectable before symptoms develop
- untreatable; no way to alleviate symptoms
- invariably fatal.

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PRIONS

- 1967 griffith suggested that TSE agents were protein.
- 1981 prusiner identified infectious protein complexes in scrapie brain, purified protein, transmitted to animals.
- called the agent a prion (proteinaceous and infectious particle).
- encoded by prnp gene, essential for pathogenesis of TSEs.

CURRENT VIEW OF PRIONS

- pathogenic prion is conformational isoform of a normal host protein, PrP^c.
- PrP^c is predominantly found on the outer surface of neurons, GPI anchor.
- the abnormal conformer, when introduced into the organism, causes conversion of normal PrP^c into the pathogenic conformation (PrP^{Sc} for scrapie).

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PrP^c : prion protein cellular

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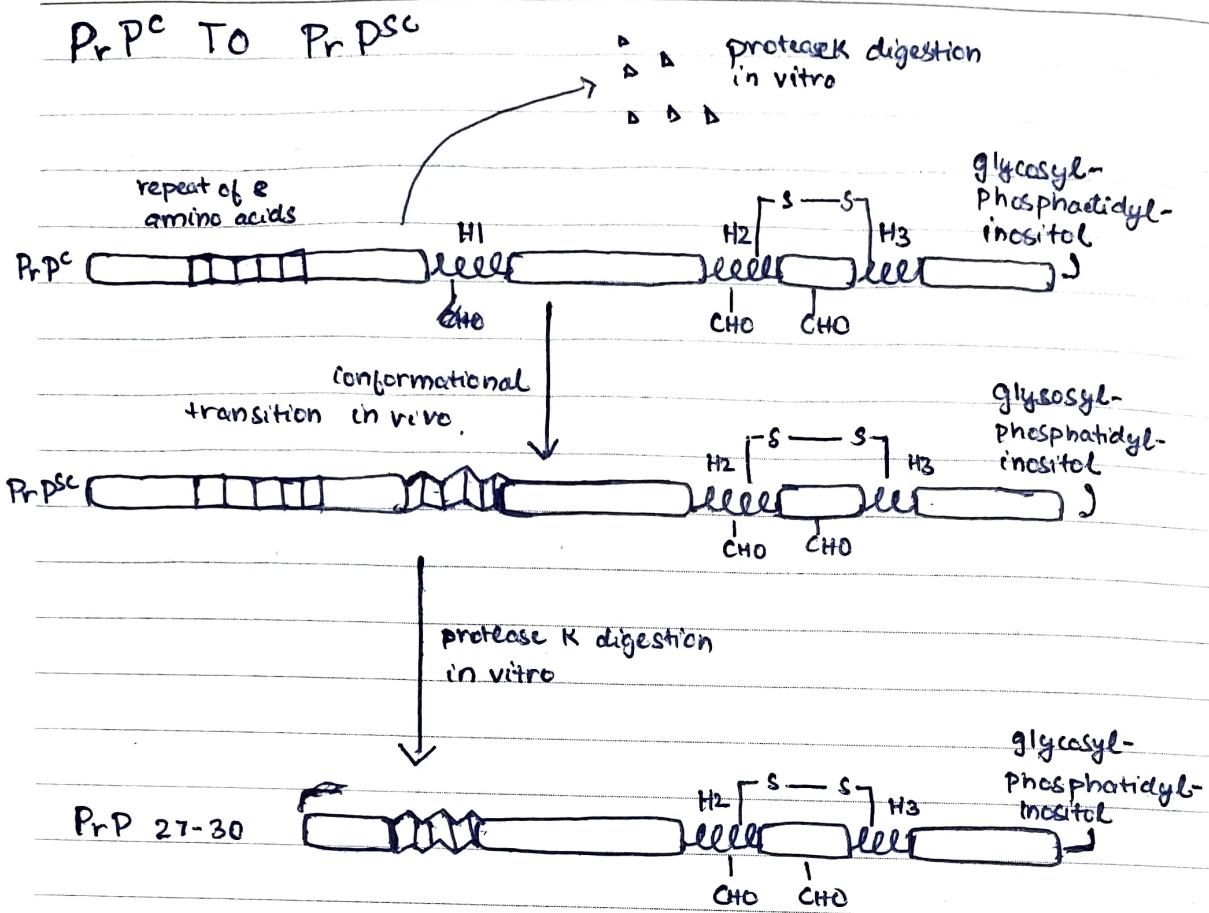
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PRION HYPOTHESIS

- mice lacking both copies of prnp are resistant to infection.
- PrP^{SC} can be introduced ('infection') or produced by rare mutations in prnp .
- PrP^{SC} accumulates in CNS, leading to symptoms.

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THE TYPES OF SPONGIFORM ENCEPHALOPATHIES

- infectious or transmissible spongiform encephalopathy
- familial (Genetic) spongiform encephalopathy.
- sporadic spongiform encephalopathy.
- all three diseases can be transmitted experimentally to animals by inoculation or ingestion of infected tissue.

HUMAN TSE

- infectious or transmissible
- Kuru

14 SUNDAY • Iatrogenic spread by transplantation of infected corneas, hormones, transfusion from patients with CJD.

- BSE: feeding infected animals to cattle.
- variant CJD: (new human disease)
eating BSE beef.

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HUMAN TSE

- Kuru: fatal encephalopathy found in fore people of new guinea.
- 30 year incubation period.
- found by carleton gajdusek to spread among women and children through ritual cannibalism of brains of deceased relatives.
- when cannibalism ceased, so did kuru.

SPORADIC CJD

G-12000?

- affects 1-2 / 1 million humans worldwide, 50-70 years of age; 65% of TSE.
- disease appears with no warning or epidemiological indications.
- patients have normal prnp genes.
- can be transmitted to others leading to CJD.

NOTES

Kuru may have been established in new guinea by eating brain of person with sporadic CJD.

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FAMILIAL SPONGIFORM ENCEPHALOPATHY

- an inherited disease
- autosomal dominant mutation in prnp gene.
- organs, corneas, blood products from afflicted with sporadic CJD can be infectious, transmit CJD to others.

CJD deaths, US, 1979 - 2017: 180 - 510.

FORCED CANNIBALISM SPREADS BSE

epidemic spread of bovine spongiform encephalopathy (BSE, mad cow disease) among British cattle was a form of cannibalism.

- resulted from the practice of feeding processed animal byproducts (including sheep with scrapie) to cattle as protein supplements
- in the 1970s method of preparing MBM changed, allowed scrapie proteins to survive and pass into cows.

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• Strong evidence that consumption of BSE-infected beef transmits bovine TSE to humans

VARIANT CJD (new disease): eating BSE beef.

MBM - meat and bone meal

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1-2 MILLION CATTLE WERE INFECTED WITH PRIONS
INCUBATION TIME 5yr, SLAUGHTERED 2-3yr.

CASES OF BOVINE SPONGIFORM ENCEPHALOPATHY

1988: 1000, 1992: 37000, 2007: 1000

CASE OF VARIANT CREUTZFELD-JAKOB DISEASE

1995: 7000, 2000: 25000, 2008: 2000.

PRIONS IN FOOD SUPPLY

- new cases of BSE in cattle still occur.
- most are likely to be sporadic.
- efforts are aimed at protecting the food supply, but in US and Canada <2% of slaughtered cattle are tested.
- diagnostic tests have been developed.
- screening for drugs that block accumulation of prions in cultured cells.

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PRION SPECIES BARRIER

- inoculation of diseased brain material into same species reproduces disease.
- inoculation into different species is inefficient
- sequences of PrP^{Sc} in inoculum and PrP^{C} in host should be isologous.
- barrier to interspecies transmission is in the sequence of PrP protein.
- bovine PrP^{Sc} has a broad host range, infects many meat eating mammals including humans.
- clearly some prions overcome the influence of primary sequence on host range.
- this is why BSE is a concern.

CHRONIC WASTING DISEASE - TSE OF DEER, ELK, MOOSE

- in standing herds up to 90% of mule deer and 60% of elk are positive,

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NOTES

- incidence of in wild cervids as high as 15%.

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WEEK 29

19

GRASS PLANTS, BIND, RETAIN, TAKE UP, AND TRANSPORT INFECTIOUS PRIONS.

cervid PrP^{SC} → mouse no disease

cervid PrP^{SC} → transgenic disease.
for cervid
prnp : mouse

cervid PrP^{SC} → transgenic for no disease
human prnp:
mouse

deer PrP^{SC} $\xrightarrow{^{14}C}$ cows disease

could CWD prions transmit to cattle grazing in contaminated pastures?

NOTES

JULY 2013						
S	M	T	W	T	F	S
1	2	3	4	5	6	
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

20 SATURDAY
WEEK 29

1.7.2020
30
JULY, 2013

HUNTERS -BEWARE! (CWD)

- do not shoot, handle, or consume any animal that is acting abnormally or appears to be sick.
- wear latex or rubber gloves when field dressing deer or elk.
- bone out meat. dont saw through bone, avoid cutting through brain or spinal cord.
- minimize handling of brain and spinal tissues.
- wash hands and instruments thoroughly after field dressing.
- dont eat brain, spinal cord, eyes , spleen, tonsils , lymph nodes.

21 SUNDAY

WEEK 29

don't eat meat from animal that tests positive.

JULY 2013							NOTES
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