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Dr. SEREEN

DISEASE CAUSATION AND NATURAL HISTORY OF DISEASE

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Cause of Disease

- Cause defined as "anything producing an effect or a result". [Webster]
- Cause in medical textbooks discussed under headings like- "**etiology**", "**Pathogenesis**", "**Mechanisms**", "**Risk factors**".
- Important to physician because it guides their approach to three clinical tasks- **Prevention, Diagnosis & Treatment.**

Causal Relationships

A causal pathway may be direct or indirect

- In direct causation, A causes B without intermediate effects (very rare)
- In indirect causation, A causes B, but with intermediate effects

In human biology, intermediate steps are virtually always present in any causal process

Theories of Disease Causation

- Supernatural Theories: curse, evil force of the demon.

  Or the darkness

- Hippocratic Theory

  Hippocrates when he thought that human behavior and the environment affect their health status

- Miasma

  Explained contagious or infectious diseases

- Theory of Contagion

  How contagious disease transfer

- Germ Theory (cause shown via Henle-Koch postulates)

  Appeared after invention of microscope so we can see germ (microorganism) that caused disease

- Classic Epidemiologic Theory
- Multicausality and Webs of Causation (cause shown via Hill's criteria)

  Most advanced, after discovering the causes of chronic disease

Hippocratic Theory

Hippocrates promoted the concept that disease was the result of an imbalance among four vital "humors" within us:
Yellow Bile, Black Bile, Phlegm, Blood

Hippocrates believed that if one of the humors became excessive or deficient, health would deteriorate and symptoms would develop.

Hippocrates was a keen observer and tried to relate an individual's exposures (e.g., diet, exercise, occupation, and other behaviors) to subsequent health outcomes.

Henle-Koch Postulates (Germ Theory)

Even though there was a "germ" of truth in miasmatic theory, in that it focused attention on environmental causes of disease and partly explained social disparities in health (poor people being more likely to live near foul odors (dirty street/environment), the theory began to fall into disfavor as the germ theory gained acceptance.

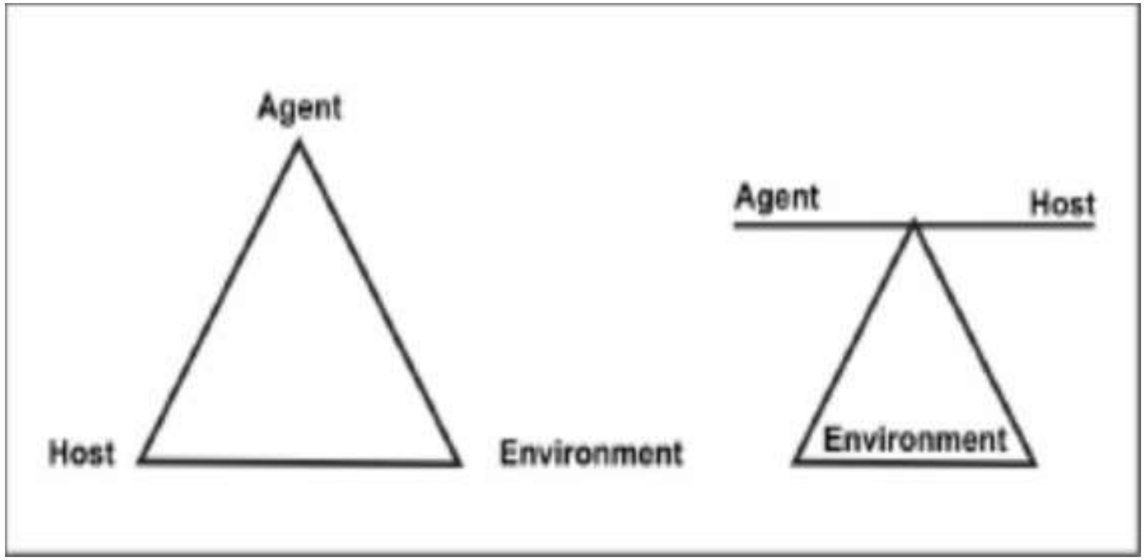
Louis Pasteur introduced the germ theory in 1878, that was developed later into Henle-Koch postulates:

- ✓ The agent is present in every case of the disease
- ✓ It does not occur in any other disease (one agent one disease)
- ✓ It can be isolated from a person who's infected and if exposed to healthy subjects will cause the related disease

Classic Epidemiologic Theory: Epidemiologic Triad

Disease is the result of forces within a dynamic system consisting of:

1. Agent of disease
2. Susceptible Host
3. External environment



Classic Epidemiologic Theory (Epidemiologic Triad)

- Agent, host, and environmental factors interrelate in a variety of complex ways to produce disease.
- Different diseases require different balances and interactions of these three components.
- Development of appropriate, practical, and effective public health measures to control or prevent disease usually requires assessment of all three components and their interactions.

Classic Epidemiologic Theory

Agent originally referred to an infectious microorganism or pathogen: a virus, bacterium, parasite, or other microbe.

- Generally, the agent must be present for disease to occur; however, presence of that agent alone is not always sufficient to cause disease.
- Not everyone who's exposed to any virus will get the disease and develop their clinical disease.
- A variety of factors influence whether exposure to an organism will result in disease, including the organism's **pathogenicity, infectivity, virulence,** and dose.

An Infectious Agent:

For an infectious agent:

Infectivity refers to the proportion of exposed persons who become infected.

Pathogenicity refers to the proportion of infected individuals who develop clinically apparent disease.

Virulence refers to the proportion of clinically apparent cases that are severe or fatal.

Classic Epidemiologic Theory

Agent: Over time (changed from older days to modern days), the concept of agent has been broadened to include chemical and physical causes of disease or injury.

- These include chemical (poison, smoke, alcohol) , as well as physical forces (such as repetitive mechanical forces associated with carpal tunnel syndrome, radiation), and nutritional (vitamin deficiency).

Classic Epidemiologic Theory

Host refers to the human who can get the disease.

- A variety of factors intrinsic to the host, sometimes called risk factors, can influence an individual's exposure, susceptibility, or response to a causative agent.

Not all people exposed to the same virus or the amount will get the same susceptibility of response

- Opportunities for exposure are often influenced by behaviors such as sexual practices, hygiene, smoking, physical exercise, dietary habits, and other personal choices as well as by age and sex.
- Susceptibility and response to an agent are influenced by factors such as genetic composition, nutritional and immunologic status, anatomic structure, presence of disease or medications, and psychological makeup.

Classic Epidemiologic Theory

Environment refers to extrinsic factors that affect the agent and the opportunity for exposure.

Environmental factors include

physical factors such as geology and climate,

biologic factors such as insects that transmit the agent,

socioeconomic factors such as crowding, sanitation, and the availability of health services.

Factors Associated with Increased Risk of Human Disease

HOST (Intrinsic)	**AGENTS**	**ENVIRONMENT** (Extrinsic)
Age	Biological (bacteria, etc.)	Temperature
Gender	Chemical (poison, alcohol, smoke)	Humidity
Ethnicity	Physical (auto, radiation, fire)	Altitude الارتفاع عن سطح البحر
Religion	Nutritional (lack, excess)	Crowding
Customs		Housing
Occupation		Neighborhood
Heredity		Water
Marital status		Milk
Family background		Food
Previous diseases		Radiation
		Air pollution
		Noise

Multicausal Theories

…… While the epidemiologic triad serves as a useful model for many diseases, it has proven inadequate for cardiovascular disease, cancer, and other diseases that appear to have multiple contributing causes without a single necessary one. Epidemiology triad became inadequate to explain many disease, so the multicausal theories appeared and became very useful in explaining these chronic disease

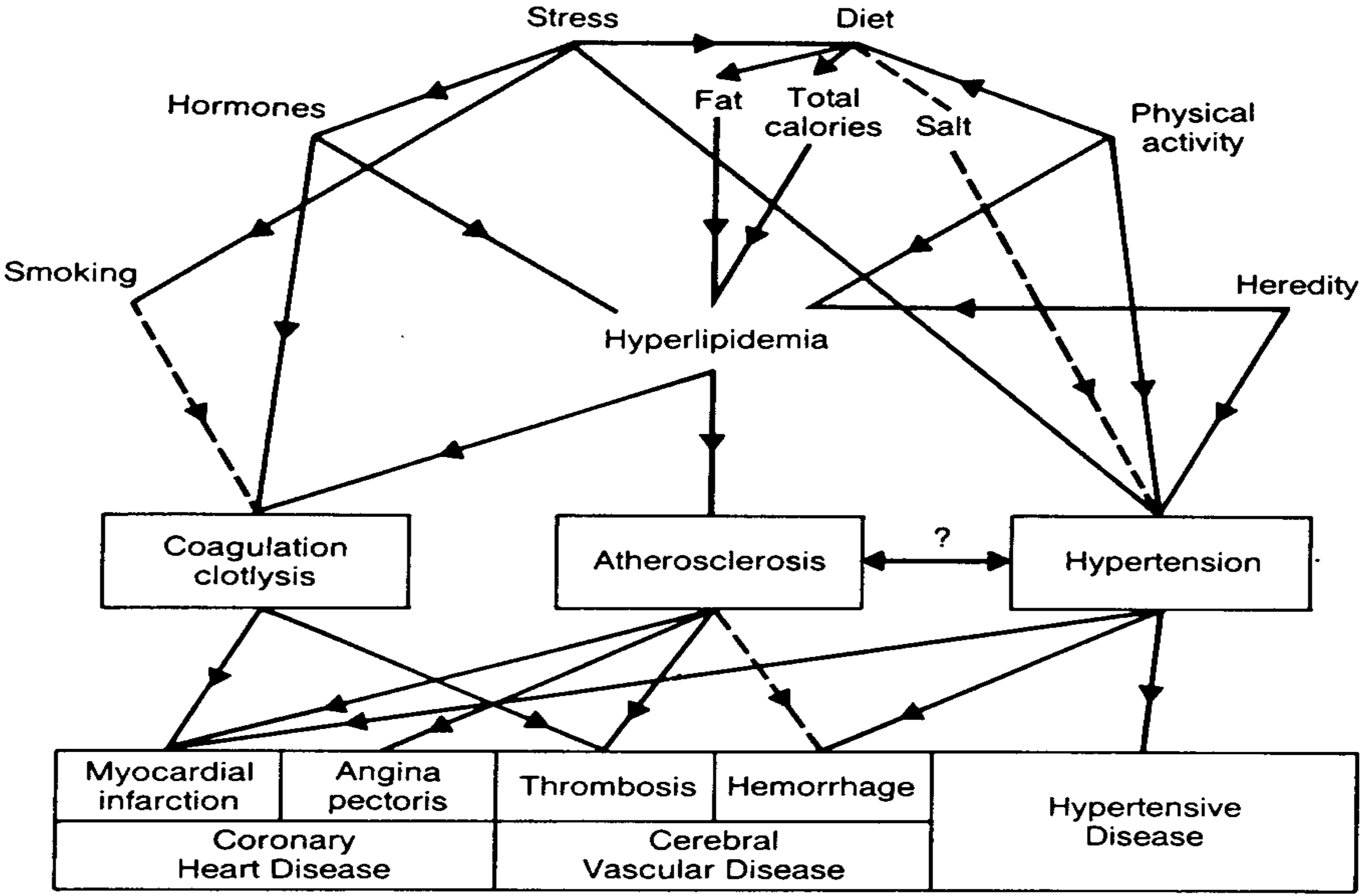
Several other models that attempt to account for the multifactorial nature of causation have been proposed.

Web of Causation (Multicausal theory) for Major Cardiovascular Diseases

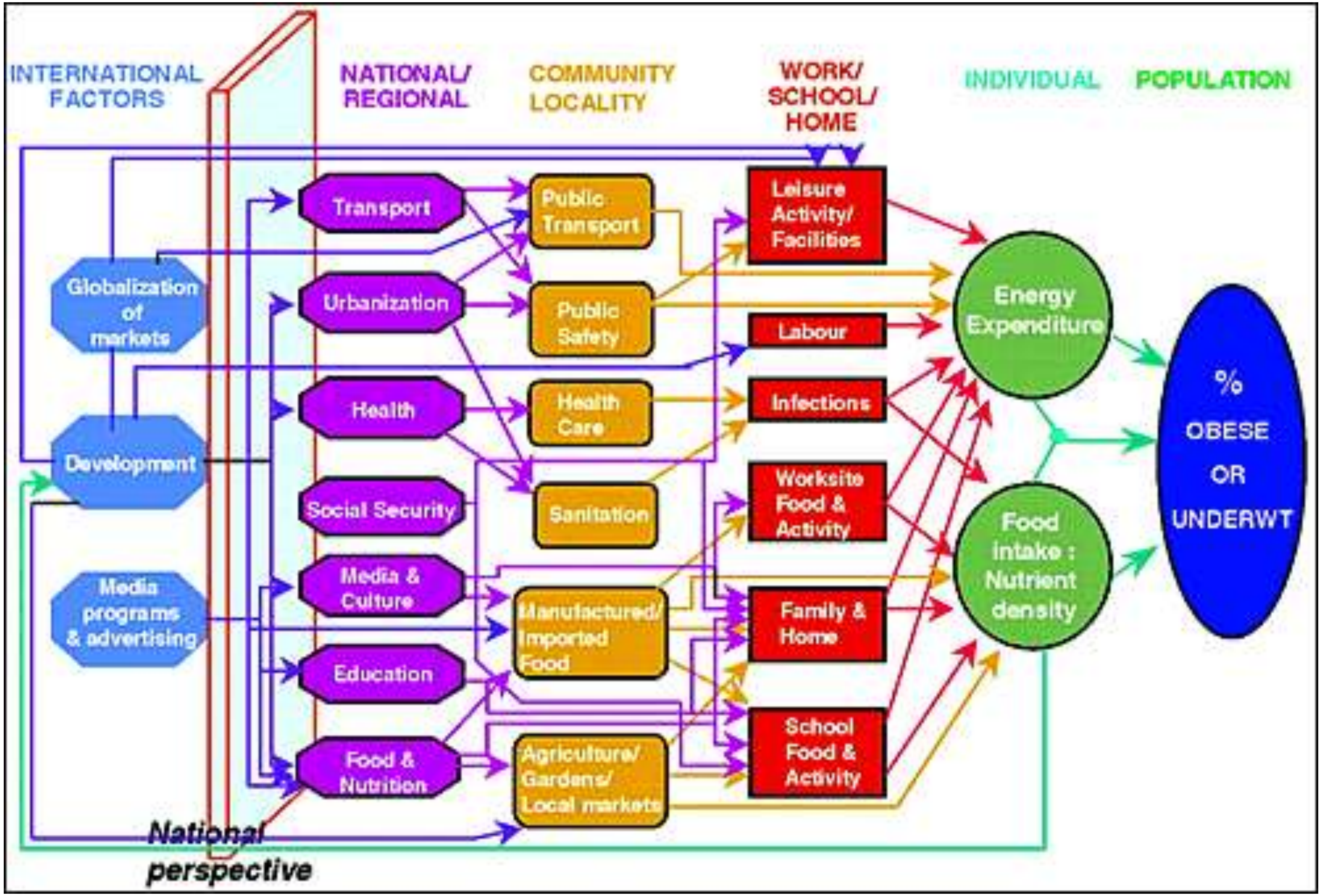
Risk factors

Back to 18:15

Causes



Multicausal theory for Obesity



Concept of Disease Occurrence ….Etiology of a disease

- ✓ The sum of all factors that contribute to the occurrence of a disease

- ✓ Agent factors +Host factors +Environmental factors = Etiology of a disease
- ✓ The factor which can be modified, interrupted or nullified is most important.

Ex: if a factor is a hereditary susceptibility, we can do nothing about it, but we can do a lot about behavior and lifestyle like smoking or diatary habits

Causal Relationships

- A causal pathway may be **direct or indirect**
- In **direct** causation, A causes B without intermediate effects (very rare)
- In **indirect** causation, A causes B, but with intermediate effects

In human biology, intermediate steps are virtually always present in any causal process

Factors for disease causation

can be classified into:

- **Sufficient factors**: one that inevitably produces disease (the presence of the factor always result in disease).

- **Necessary factors**: without which disease does not occur, but by itself, it is not sufficient to cause disease (the disease will not occur without the presence of the factor)

Types of Causal Relationships

Four types possible:

- Necessary & sufficient
- Necessary, but not sufficient
- Sufficient, but not Necessary
- Neither Sufficient nor Necessary

I. Necessary & Sufficient

- Without that factor, the disease never develops (factor is necessary)
- and in presence of that factor, the disease always develops (factor is sufficient).
- **Rare situation (it almost never exists).**

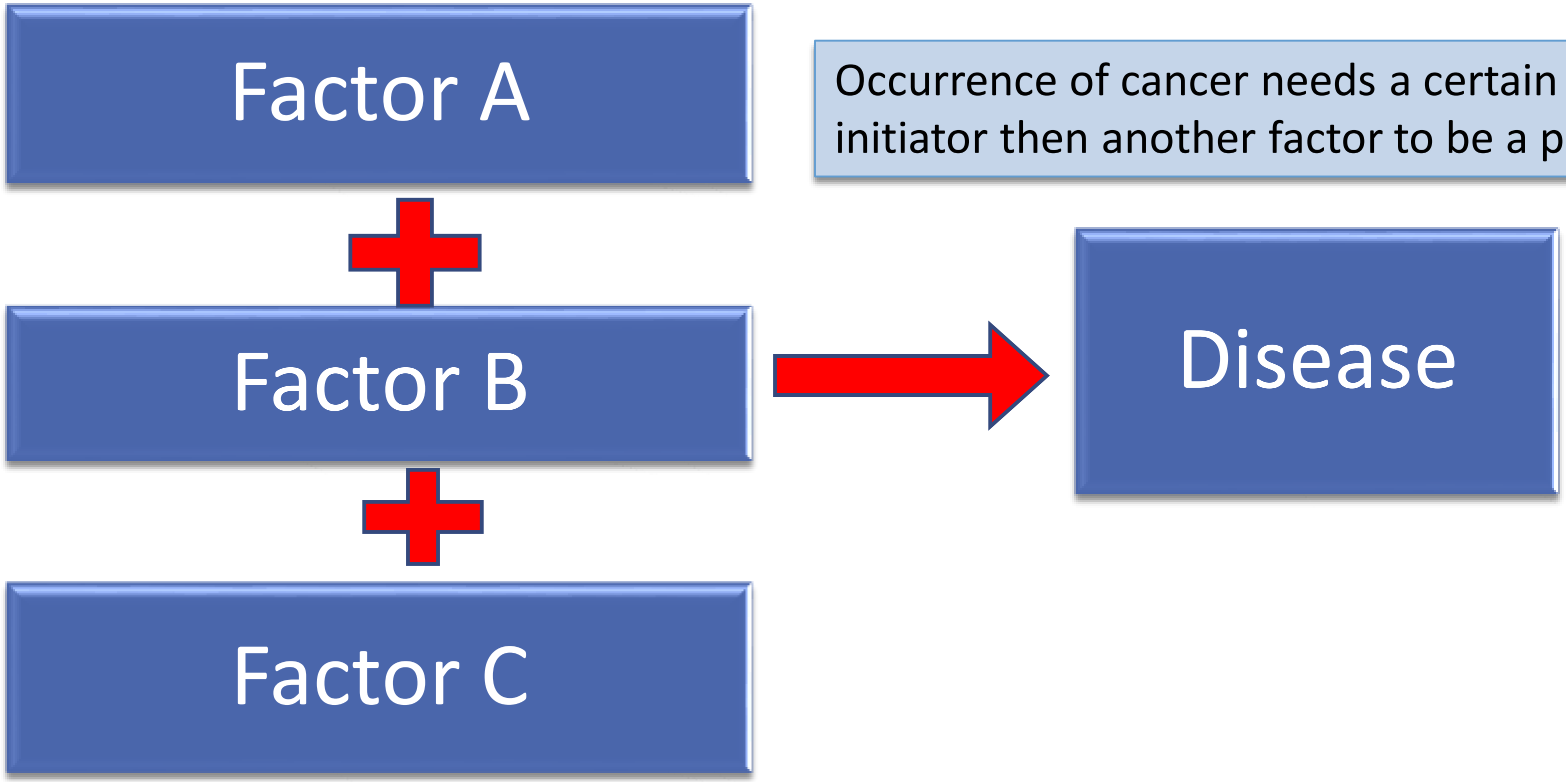
Factor A → Disease

Factor A, whenever it's there, by itself will result in occurrence of a disease.

II. Necessary, but not Sufficient

- Multiple factors are required, often in specific temporal (time) sequence (cancer, initiator then promoter). Infectious diseases also (Infection with HIV is necessary but not sufficient to cause AIDS).

Occurrence of cancer needs a certain factor to be an initiator then another factor to be a promoter.

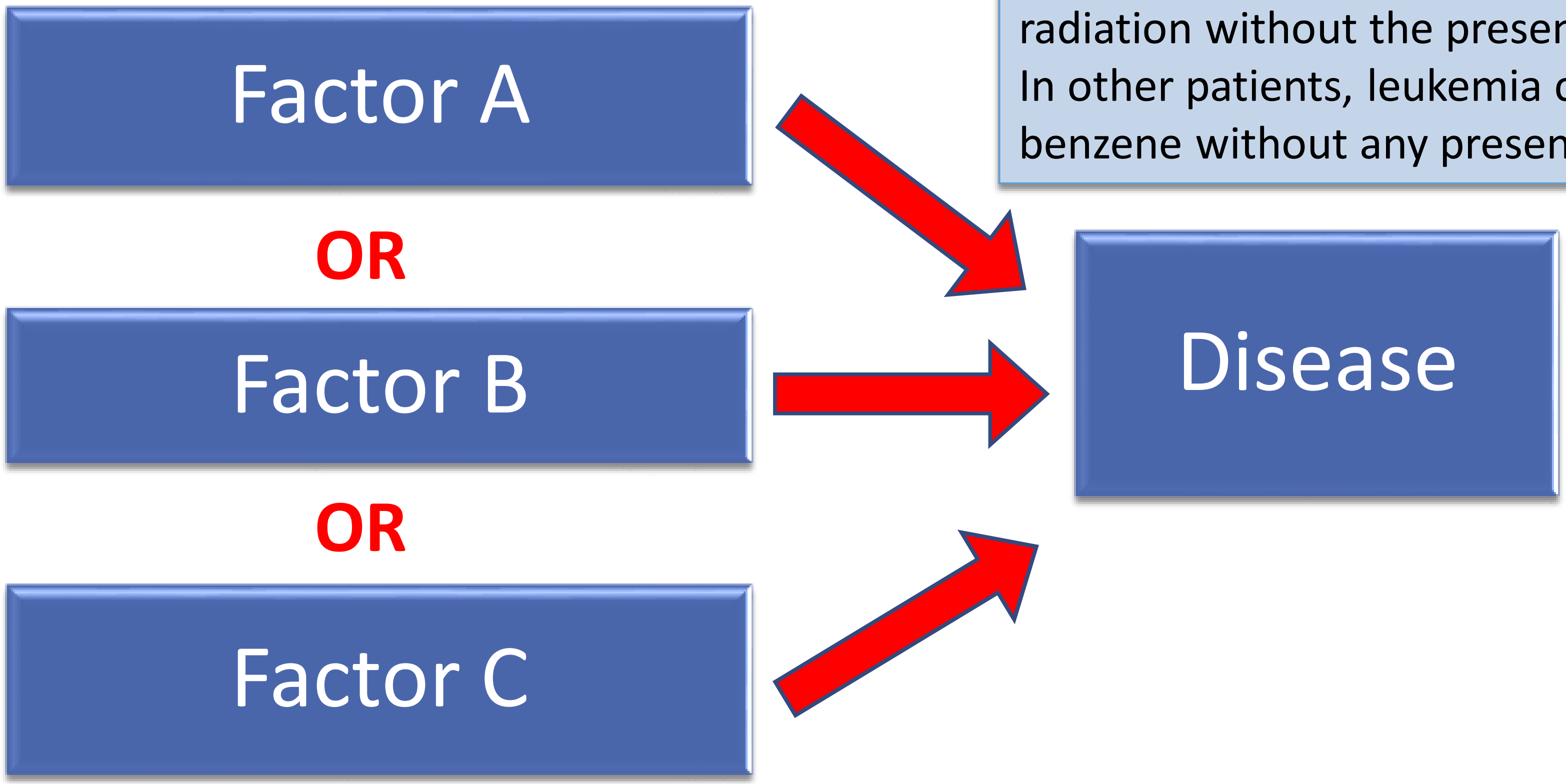


- Factor A should be there first, then joined by factor B and then joined by factor C, with temporal sequence.
- If C came first with out the existence of A this sequence will not be started.

III. Sufficient, but not Necessary

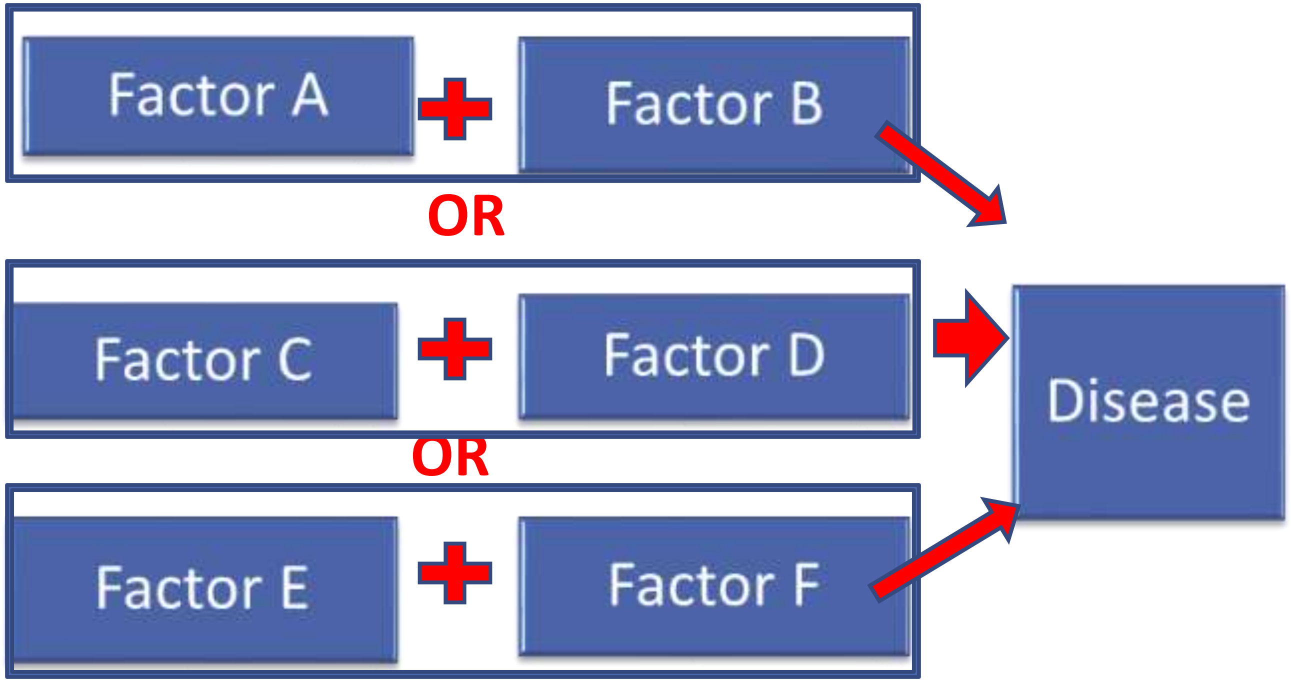
- Various factors independently can produce the disease **(Either radiation or benzene exposure can each produce leukemia without the presence of the other).**

In some patients, leukemia can be triggered by radiation without the presence of benzene at all. In other patients, leukemia could be triggered by benzene without any presence of radiation.



IV. Neither sufficient nor Necessary

- More complex model.
- Probably most accurately represents causal relationships that operate in most **chronic diseases**.



- ✓ Either of these combinations could lead to disease by the absence of others.
- ✓ The combination of factors can be different from one person to another for a disease to happen.
  → like the case about coronary heart disease or cardiovascular diseases: smoking plus hereditary factors could be the trigger for cardiovascular disease; in other people with cardiovascular disease they have never smoked in their life, even they are not obese, but they have other factors.

IV. Neither sufficient nor Necessary

- Public health action does not depend on the identification of every cause of a disease.
- Disease prevention can be accomplished by **blocking** any single factor from any combination of causes.
- For example, elimination of smoking would prevent lung cancer, although some lung cancer would still occur to people who never smoked but have the right combination of other risk factors.

NATURAL HISTORY OF DISEASE AND DYNAMICS OF DISEASE TRANSMISSION

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Natural History and Spectrum of Disease

Natural history of disease refers to the progression of a disease process in an individual over time, in the absence of treatment.

For example, untreated infection with HIV causes a spectrum of clinical problems beginning at the time of seroconversion (primary HIV) and terminating with AIDS and usually death. It is now recognized that it may take 10 years or more for AIDS to develop after seroconversion.

Natural History and Spectrum of Disease

Because the spectrum of disease can include asymptomatic and mild cases, the cases of illness diagnosed by clinicians in the community often represent only the **tip of the iceberg**.

→ This is only the portion of those who have the disease that have been presented to the health services or seeked health care, so we know them.

Many additional cases may be too early to diagnose or may never progress to the clinical stage. Unfortunately, persons with inapparent or undiagnosed infections may nonetheless be able to transmit infection to others.

- Note about the last point:
  This is very applicable to the case of COVID-19, the number of cases that is being reported every day in the news represents the percentage of those who have been tested for this day and proved to be positive, we only hear also about the number of deaths for this day, and the number of those who have been admitted to hospitals because they have symptoms and needed health care, we also know the number of those who need ICU (they are in intensive care) or needed to be on artificial respiration. → This is only the tip of the iceberg.
  • What is really troublesome? The too many cases in the community having the disease but without any symptoms, they have subclinical and we may never know them, they have infected so many people when they were carrying the disease.

Natural History and Spectrum of Disease

Such persons who are infectious but have subclinical disease are called **carriers**. Frequently, carriers are persons with incubating disease or inapparent infection. Persons with measles, hepatitis A, influenza and several other diseases become infectious a few days before the onset of symptoms.

Natural History and Spectrum of Disease

However **carriers** may also be persons who appear to have recovered from their clinical illness but remain infectious, such as chronic carriers of hepatitis B virus, or persons who never exhibited symptoms.

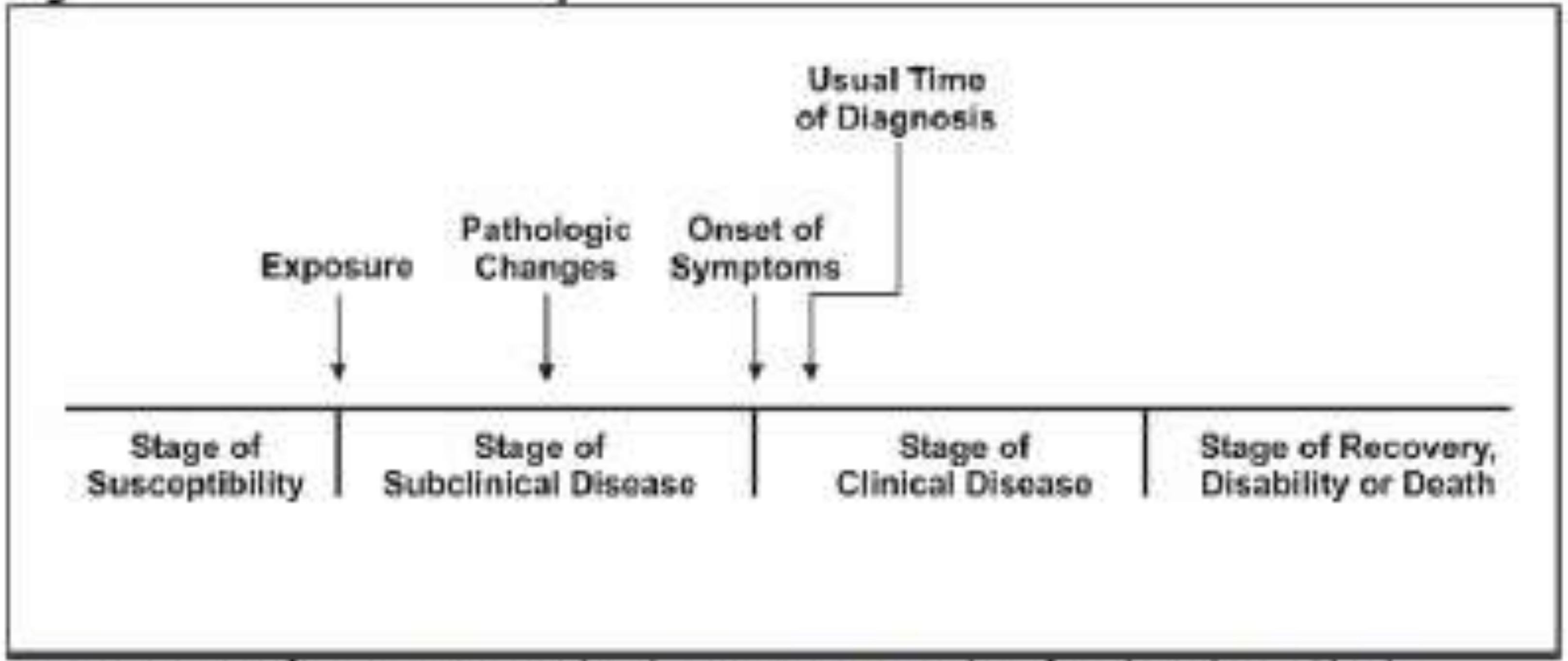
The challenge to public health workers is that these carriers, unaware that they are infected and infectious to others, are sometimes more likely to unintentionally spread infection than are people with obvious illness. These are the dangerous group in the population…..

During the current Covid-19 epidemic, you should perceive anybody as infectious …..literally, any body.

- ✓ Or you maybe infectious and you should protect others.

Natural History and Spectrum of Disease

Figure 1.18 Natural History of Disease Timeline



Source: Centers for Disease Control and Prevention. Principles of epidemiology, 2nd ed. Atlanta: U.S. Department of Health and Human Services;1992.

- The last figure shows the natural history of disease timeline;
  - It starts on the left of the figure with the **stage of a person who is susceptible**.
  - Following that there is **exposure**.
  - After exposure of a susceptible person for an infectious agent, **pathologic changes** start to happen. The stage of pathological changes is the **stage of subclinical disease** (there are no apparent signs or symptoms of disease in the person).
  - The next stage start with **onset of symptoms**, this indicates the start of the **clinical disease stage**. After a while of starting symptoms, it is the **usual time of diagnosis**.
  - Following the end of the clinical disease, there is the **stage of recovery or disability or death** in some of the severe debilitating diseases.

- About infectivity, the person is not only infective while having apparent symptoms that are clinically proven to be there, but people can be infectious even before clinical disease or any symptoms appears.
  → In the second part of the subclinical stage and pathological changes, the virus is in the body, it is multiplying and present in the secretions of the person respiratory tract or other secretions, the person is infectious even though the person does not feel ill or seem to be sick.

Unapparent Infection

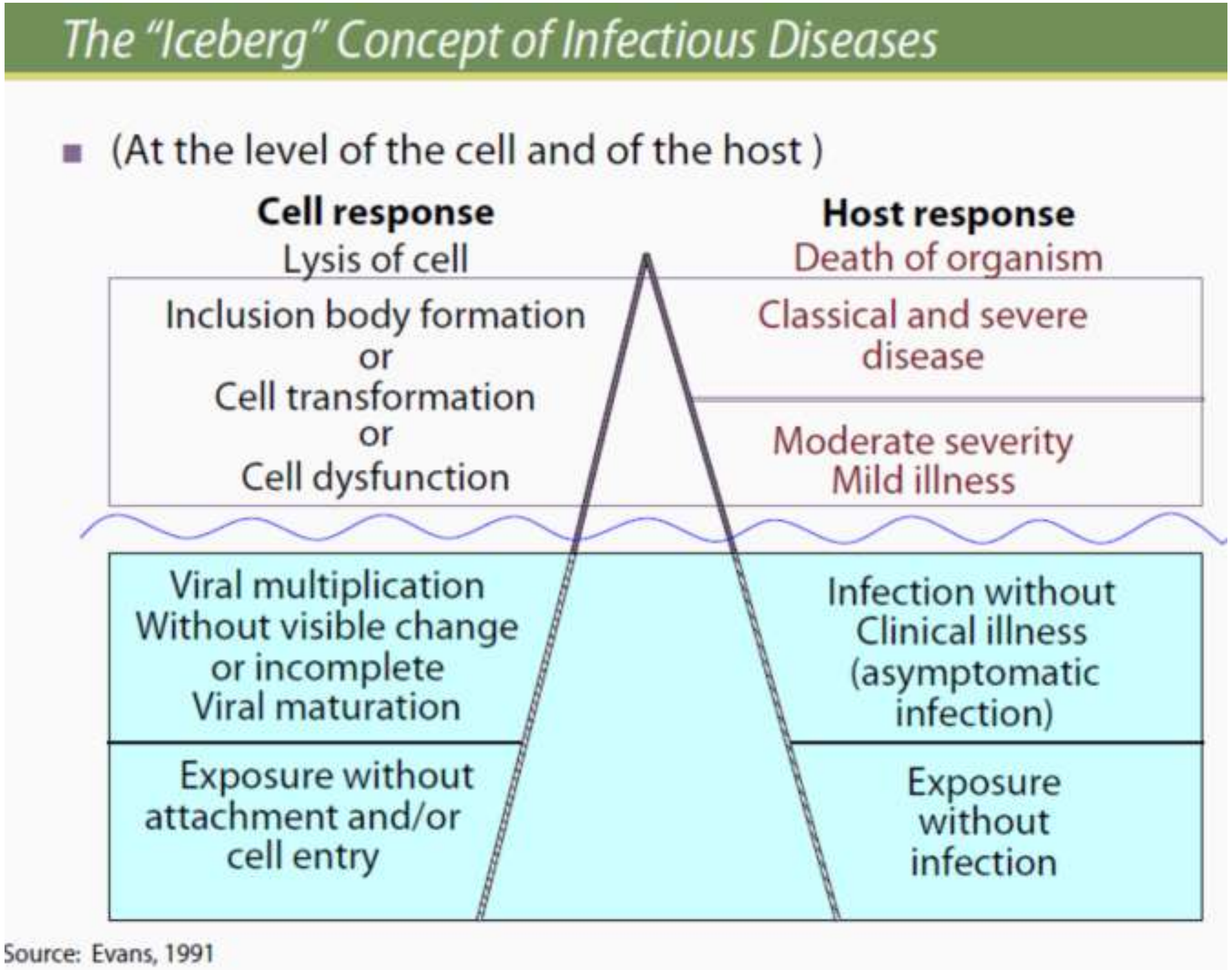
→ All these cases can be infectious to others without even knowing about it.

- **Preclinical disease**: in the early stage of disease progression, disease is not clinically detected but is destined to become clinical disease.
- **Subclinical disease**: disease is not detected but the host carries the organism or has antibody response.
- **Chronic carriers** are those who continue to harbor a pathogen such as hepatitis B virus or Salmonella Typhi, the causative agent of typhoid fever, for months or even years after their initial infection.

Unapparent Infection

One notorious carrier is Mary Mallon, or Typhoid Mary, who was an asymptomatic chronic carrier of Salmonella Typhi. As a cook in New York City and New Jersey in the early 1900s, she unintentionally infected dozens of people until she was placed in isolation on an island in the East River, where she died 23 years later.

Natural History and Spectrum of Disease



Up the sea level:

what presents to the health services, what we can see and have been diagnosed as cases are only the cases who start to have the clinical infection who start to seek health care or have apparent symptoms.

The sea level

Beneath the sea level:

we have more than five times the amount of those who have been diagnosed and counted as cases, most of them are having subclinical infection, they may never even develop the disease, but we have to be careful from them.

Distribution of Clinical Severity for Three Infections

(not drawn to scale)

Class A: unapparent infection frequent (Most of the cases)
Example: tubercle bacillus

0 Percentage of infections 100

Class B: clinical disease frequent; few deaths
Example: measles virus

0 Percentage of infections 100

Class C: infections usually fatal
Example: rabies virus

0 100

Notice these percentages in each class☺

Unapparent Mild Moderate Severe (nonfatal) Fatal

Table 1.7 Incubation Periods of Selected Exposures and Diseases

You can only have a look at this by yourself and try to compare the exposures (to a certain infectious agents, radiation and others), the clinical effect and the incubation or latency period (from minutes to years) for these diseases.

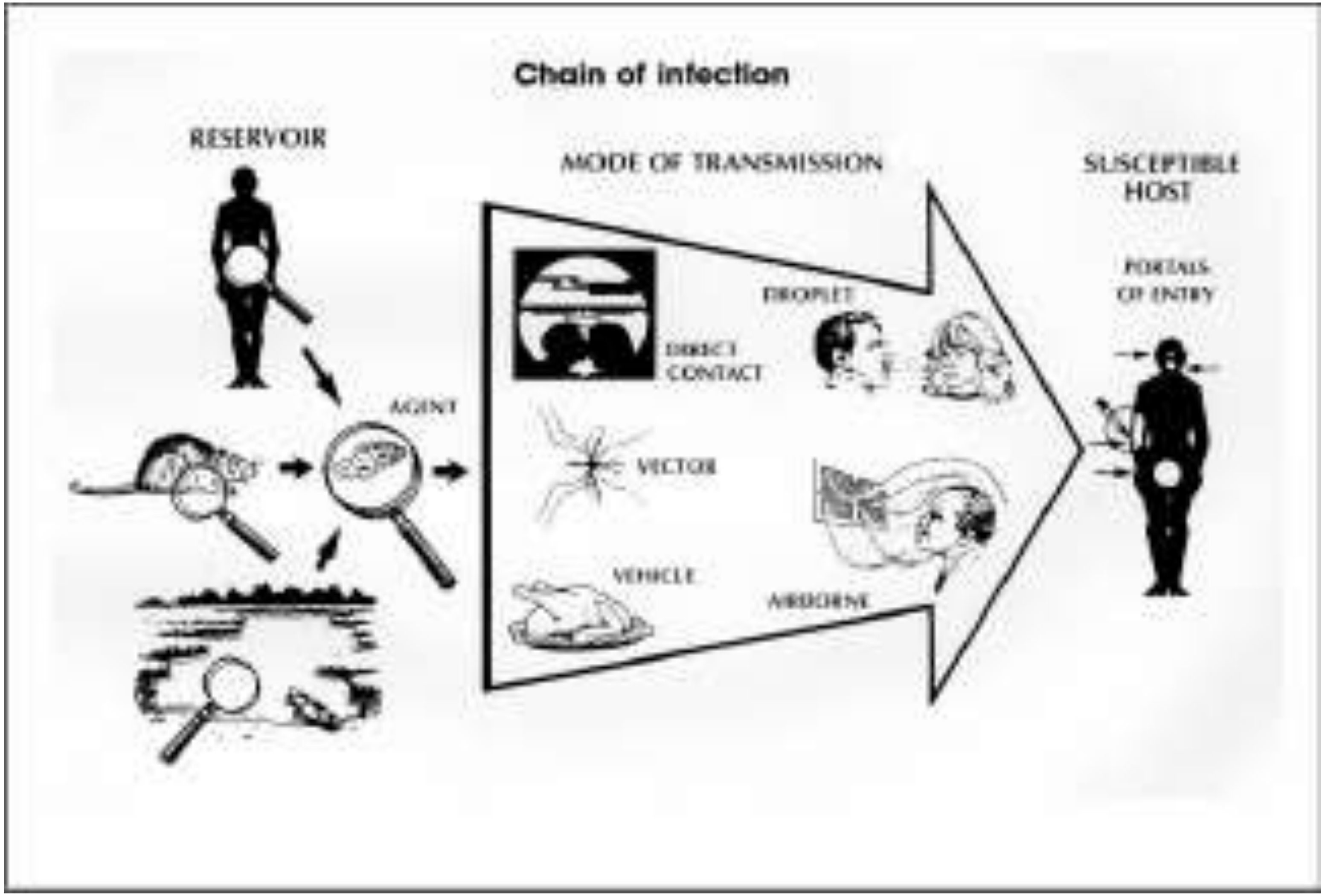
Exposure	Clinical Effect	Incubation/Latency Period
Saxitoxin and similar toxins from shellfish	Paralytic shellfish poisoning (tingling, numbness around lips and fingertips, giddiness, incoherent speech, respiratory paralysis, sometimes death)	few minutes-30 minutes
Organophosphorus ingestion	Nausea, vomiting, cramps, headache, nervousness, blurred vision, chest pain, confusion, twitching, convulsions	few minutes-few hours
Salmonella	Diarrhea, often with fever and cramps	usually 6–48 hours
SARS-associated corona virus	Severe Acute Respiratory Syndrome (SARS)	3–10 days, usually 4–6 days
Varicella-zoster virus	Chickenpox	10–21 days, usually 14–16 days
Treponema pallidum	Syphilis	10–90 days, usually 3 weeks
Hepatitis A virus	Hepatitis	14–50 days, average 4 weeks
Hepatitis B virus	Hepatitis	50–180 days, usually 2–3 months
Human immunodeficiency virus	AIDS	<1 to 15+ years
Atomic bomb radiation (Japan)	Leukemia	2–12 years
Radiation (Japan, Chernobyl)	Thyroid cancer	3–20+ years
Radium (watch dial painters)	Bone cancer	8–40 years

Chain of Infection

As described above, the traditional epidemiologic triad model holds that infectious diseases result from the interaction of agent, host, and environment.

More specifically, transmission occurs when the agent leaves its reservoir or host through a portal of exit, is conveyed by some mode of transmission, and enters through an appropriate portal of entry to infect a susceptible host. This sequence is sometimes called the chain of infection.

Chain of Infection



Reservoir

- The reservoir of an infectious agent is the habitat in which the agent normally lives, grows, and multiplies. Reservoirs include humans, animals, and the environment.
- The reservoir may or may not be the source from which an agent is transferred to a host.
- For example, the reservoir of Clostridium botulinum is soil, but the source of most botulism infections is improperly canned food containing C. botulinum spores.

Human Reservoir

Many common infectious diseases have human reservoirs. Diseases that are transmitted from person to person without intermediaries include the sexually transmitted diseases, measles, mumps, streptococcal infection, and many respiratory pathogens.

Because humans were the only reservoir for the smallpox virus, naturally occurring smallpox was eradicated after the last human case was identified and isolated.

Animal Reservoir

- Humans are also subject to diseases that have animal reservoirs. Many of these diseases are transmitted from animal to animal, with humans as incidental hosts.

  If humans come into contact with these animals.

- The term zoonosis refers to an infectious disease that is transmissible under natural conditions from vertebrate animals to humans. Long recognized zoonotic diseases include brucellosis (cows and pigs), anthrax (sheep), plague (rodents), trichinellosis/trichinosis (swine), and rabies (bats, raccoons, dogs, and other mammals).
- Many newly recognized infectious diseases in humans, including HIV/AIDS, Ebola infection and SARS, are thought to have emerged from animal hosts, although those hosts have not yet been identified.

  This is what happened also with COVID-19 where scientists are trying to understand where it came from, it could have come from bats or any other host, this is not clear yet!

Environmental Reservoir

- Plants, soil, and water in the environment are also reservoirs for some infectious agents.
- Many fungal agents, such as those that cause histoplasmosis, live and multiply in the soil.
- Outbreaks of Legionnaires disease are often traced to water supplies in cooling towers and evaporative condensers, which are the reservoirs for the causative organism Legionella pneumophila that causes severe pneumonia.

Portal of Exit

The second part of the chain of infection after the reservoir.

Portal of exit is the path by which a pathogen leaves its host. The portal of exit usually corresponds to the site where the pathogen is localized. For example, influenza viruses and Mycobacterium tuberculosis exit the respiratory tract, schistosomes through urine, cholera vibrios in feces, Sarcoptes scabiei in scabies skin lesions.

Some bloodborne (exist in the bloodstream) agents can exit by crossing the placenta from mother to fetus (rubella, syphilis, toxoplasmosis), while others exit through cuts or needles in the skin (hepatitis B) or blood-sucking arthropods (like mosquitoes in the transmitting malaria).

Modes of Transmission

An infectious agent may be transmitted from its natural reservoir to a susceptible host in different ways:

Direct transmission OR Indirect transmission

Direct transmission (person-to-person):

Direct contact: skin-to-skin contact, kissing (saliva), sexual contact, and soil.

Droplet spread: spray with relatively large, short-range aerosols produced by sneezing, coughing, or even talking (Polio, hepatitis B, HIV, influenza).

Modes of Transmission

Indirect transmission:

[1] Airborne: infectious agents are carried by dust or droplet nuclei suspended in air (very small, very light weight) (<5micons)(measles in a doctor's office).

⟶ A child comes with measles to see the doctor through sneezing and coughing measles can stay with droplet nuclei suspended in the air from this child in the doctor's office and can stay in the air for even hours. This child goes home, another child comes later and then can get the measles infection through inhaling these droplet nuclei suspended in the air that were still in the doctor's office.

[2] Vehicleborne (inanimate objects): food (Clostreniam Botulinum), water (Hepatitis A virus), biologic products (blood), and fomites (such as handkerchiefs, bedding, surgical scalpels, tooth brush, toys, cutting board).

⟶ If contaminated food was used on this cutting board and not cleaned, these are fomites.

[3] Vectorborne (mechanical or biologic) through small insects like: mosquitoes, fleas, and ticks may carry an infectious agent through purely mechanical means (on their legs or wings) or may support growth or changes in the agent (E. coli infection, coxsackievirus (hand-foot-mouth disease), lice, meningitis, rotavirus diarrhea)

- In the biologic way, mosquito has the infectious agent inside their body where it grows and multiplies.

Transmission of Agents from Mother to Child

All pathways of transmission that we have discussed earlier are considered horizontal transmission.

Vertical transmission (inter-generation) is the transmission of disease-causing agents from mother directly to baby

- Just before or just after birth
- Via placenta or breast milk

Horizontal transmission: all other transmissions

Diseases that can be transmitted from mother to baby include:

- HIV
- Hepatitis C

Portal of Entry

After knowing the reservoir of the disease, then the portal of exit, after that in the chain of infection we learned about the mode of transmission, then we need to know more about portal of entry.

- The portal of entry refers to the manner in which a pathogen enters a susceptible host.
- The portal of entry must provide access to tissues in which the pathogen can multiply or a toxin can act.
- Often, infectious agents use the same portal to enter a new host that they used to exit the source host.
- For example, influenza virus exits the respiratory tract of the source host and enters the respiratory tract of the new susceptible host.

Portal of Entry

- In contrast, many pathogens that cause gastroenteritis follow a so-called “fecal-oral” route because they exit the source host in feces, are carried on inadequately washed hands to a vehicle such as food, water, or utensil (equipment that we use for eating), and enter a new host through the mouth.
- Other portals of entry include the skin (hookworm which penetrates the skin), mucous membranes (syphilis), and blood (hepatitis B, human immunodeficiency virus (HIV)).

Susceptible Host

The final ring in the chain of infection.

- Susceptibility of a host depends on genetic factors, specific immunity, and nonspecific factors (skin, mucous membranes, gastric acidity, cilia in the respiratory tract, the cough reflex) that affect an individual's ability to resist infection or to limit pathogenicity.
  → Nonspecific factors they are the physical barriers against the organism.
- For example, persons with sickle cell trait seem are partially protected from a particular type of malaria. → This is an example of genetic factors.
- Specific immunity refers to protective antibodies that are directed against a specific agent. Such antibodies may develop in response to infection, vaccine, or toxoid.

Factors that may increase susceptibility to infection by disrupting host defenses include malnutrition, alcoholism, and disease or therapy that impairs the nonspecific immune response (chemotherapy).

Implications for public health

Why the chain of infection is important in epidemiology?

Knowledge of the portals of exit and entry and modes of transmission provides a basis for determining appropriate control measures (preventive measures). In general, control measures are usually directed against the **segment in the infection chain that is most susceptible to intervention:**

⟶ Any place in the chain that we can block or make a break, this can stop the infection sequence.

- Some interventions are directed at the mode of transmission (isolation of someone with infection, or counseling persons to avoid the specific type of contact associated with transmission)e.g. personal hygiene and social distancing to prevent Covid-19.

  ⟶ Also, by continuous hand washing and washing surfaces where droplets of the infection can be.

Implications for public health

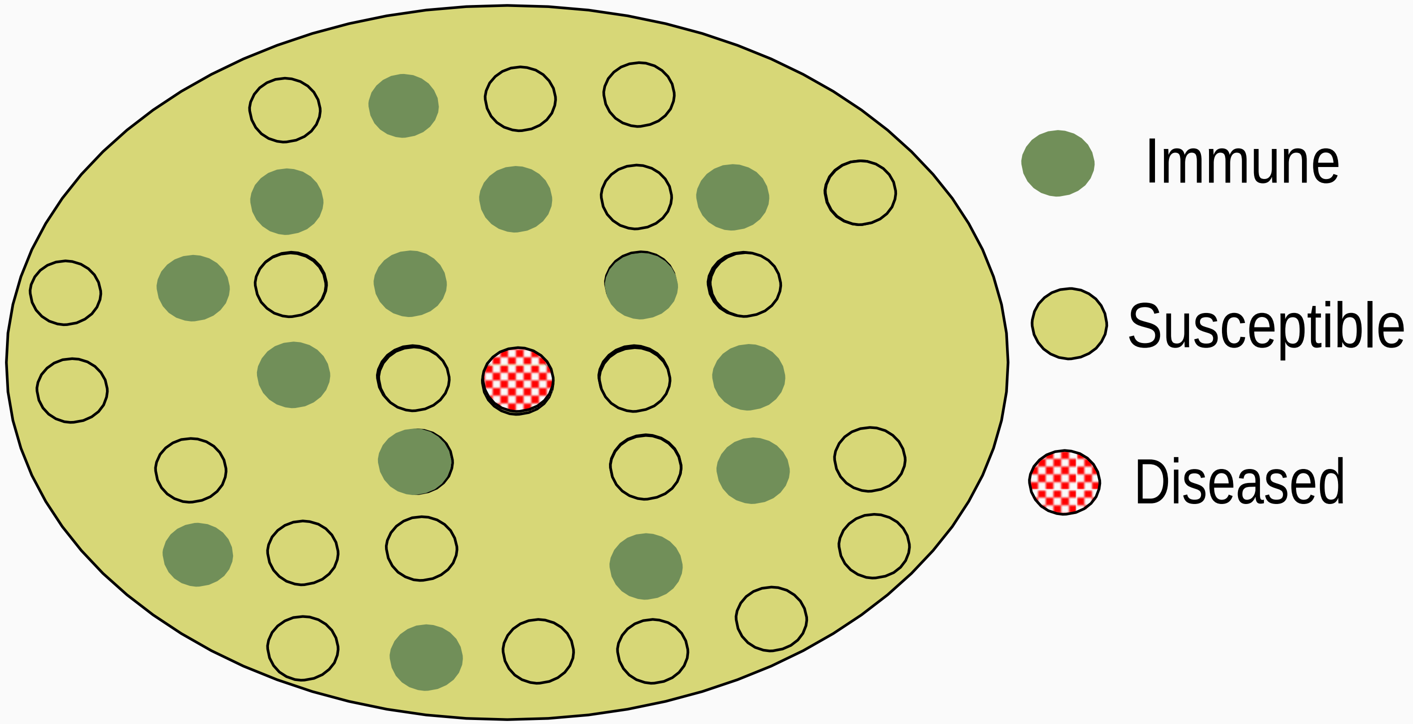
- Some strategies that protect portals of entry are simple and effective (bed nets for mosquitoes, mask, gloves, and face shield). As how with covid-19, advising every body to use personal protective equipment, if we use mask we block portal of entry and exit, and limit the possibility of transmission of the disease.
- Some interventions aim to increase a host's defenses (Vaccinations).
- Some interventions attempt to prevent a pathogen from encountering a susceptible host (The concept of herd immunity in childhood vaccines). When we vaccinate a larger proportion of children, the small proportion who aren't vaccinated yet, **most probably** will not get the disease because the majority of children have been vaccinated.

Wear a mask and stay safe ☺

Herd Immunity and Disease Transmission

- In a population, disease transmission may stop before all susceptible individuals are infected
- **Herd immunity** is the resistance of a group to attack from a disease to which a large portion of members are immune, thus lessening the likelihood of a patient with a disease coming into contact with a susceptible individual

The larger number of dots that are given mean that's the immune people will lead to lower probability that this person with a disease will come into contact with someone in the population who is susceptible.



يعني كل ما بزيد عدد الناس الي ماخدين المطعوم كل ما بقل التواصل مع الاشخاص الي معرضة للمرض و هيك بخف المرض

Requirements for Herd Immunity

- The disease agent is restricted to a single-host species within which transmission occurs (For example, smallpox in human; no reservoir in the environment).

- There is relatively direct transmission from one member of the host species to another (direct contact only).

- Infections must induce solid immunity (also from immunization).

Herd Immunity and Disease Control

The success of herd immunity in controlling the disease depends on the proportion of subjects with immunity in a population (Immunity can be from immunization or infection) → Natural or unnatural immunity.

So, when the population is immunized (e.g. ,vaccinated) at or above the herd immunity level (a level for the proportion of the population that should be immunized or have got the infection for the herd immunity to start working, critical immunization threshold level), the infectious disease will be more rare, will spread less and will be eliminated.

Herd immunity level differs for various diseases

- For example, it is estimated that **94%** of the population must be immune before measles can be controlled
- For mumps, it is around **90%,** and for polio is **80%**
- The more infectious the disease is, the higher the herd immunity level.

{وَمَا تَكُونُ فِي شَأْنٍ وَمَا تَتْلُو مِنْهُ مِن قُرْآنٍ وَلَا تَعْمَلُونَ مِنْ عَمَلٍ إِلَّا كُنَّا عَلَيْكُمْ شُهُودًا إِذْ تُفِيضُونَ فِيهِ ۚ وَمَا يَعْزُبُ عَن رَّبِّكَ مِن مِّثْقَالِ ذَرَّةٍ فِي الْأَرْضِ وَلَا فِي السَّمَاءِ وَلَا أَصْغَرَ مِن ذَٰلِكَ وَلَا أَكْبَرَ إِلَّا فِي كِتَابٍ مُّبِينٍ}

[سورة يونس: 61]

احنا عنا sea level

لكنّ الله لا يخفى عليه شيء في الأرض ولا في السماء