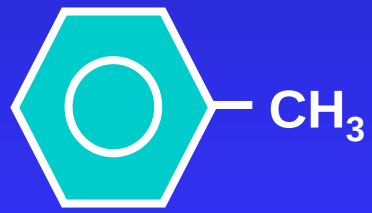
Environment and Gene Interactions Cancer Module

- Introduction
- Basics of Toxicology (The Science of Poisons)
- DNA and the origins of Cancer
- Defining Cancer Risk
- Tobacco and Alcohol
- Sunlight and Skin Cancer
- Diet and Nutrition
- Hormones and Cancer
- Viruses and Cancer

The Dose Makes the Poison

- all chemicals are toxic
- toxicity can be modified radically with minor chemical modifications

Benzene
Carcinogenic

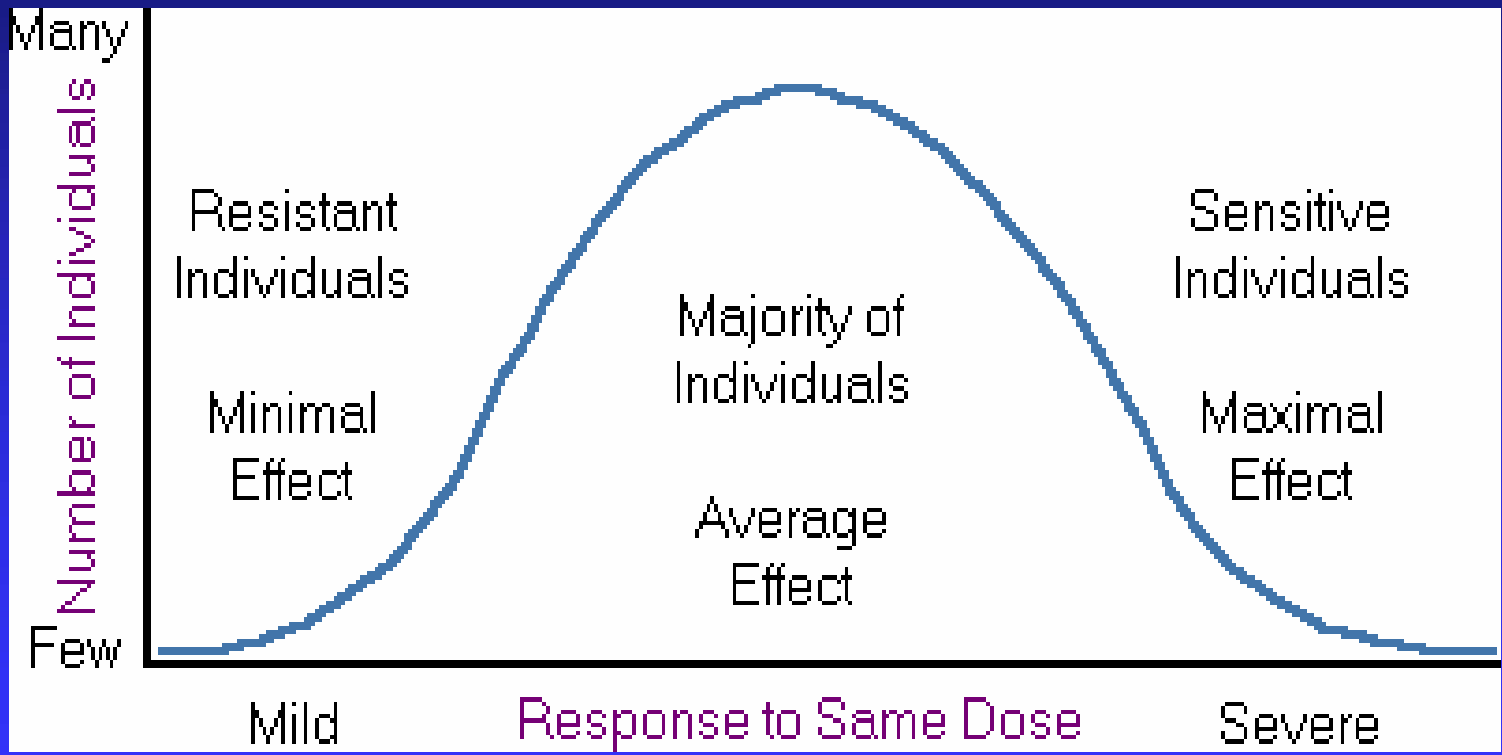


Toluene
Non-Carcinogenic

Definitions

- **Potency** is inversely related to the amount of a chemical that causes toxicity
- **Risk** is proportional to the amount of a chemical to which one is **likely** to be exposed, and the **duration** of the exposure
- **Potency** is just one factor in **risk**

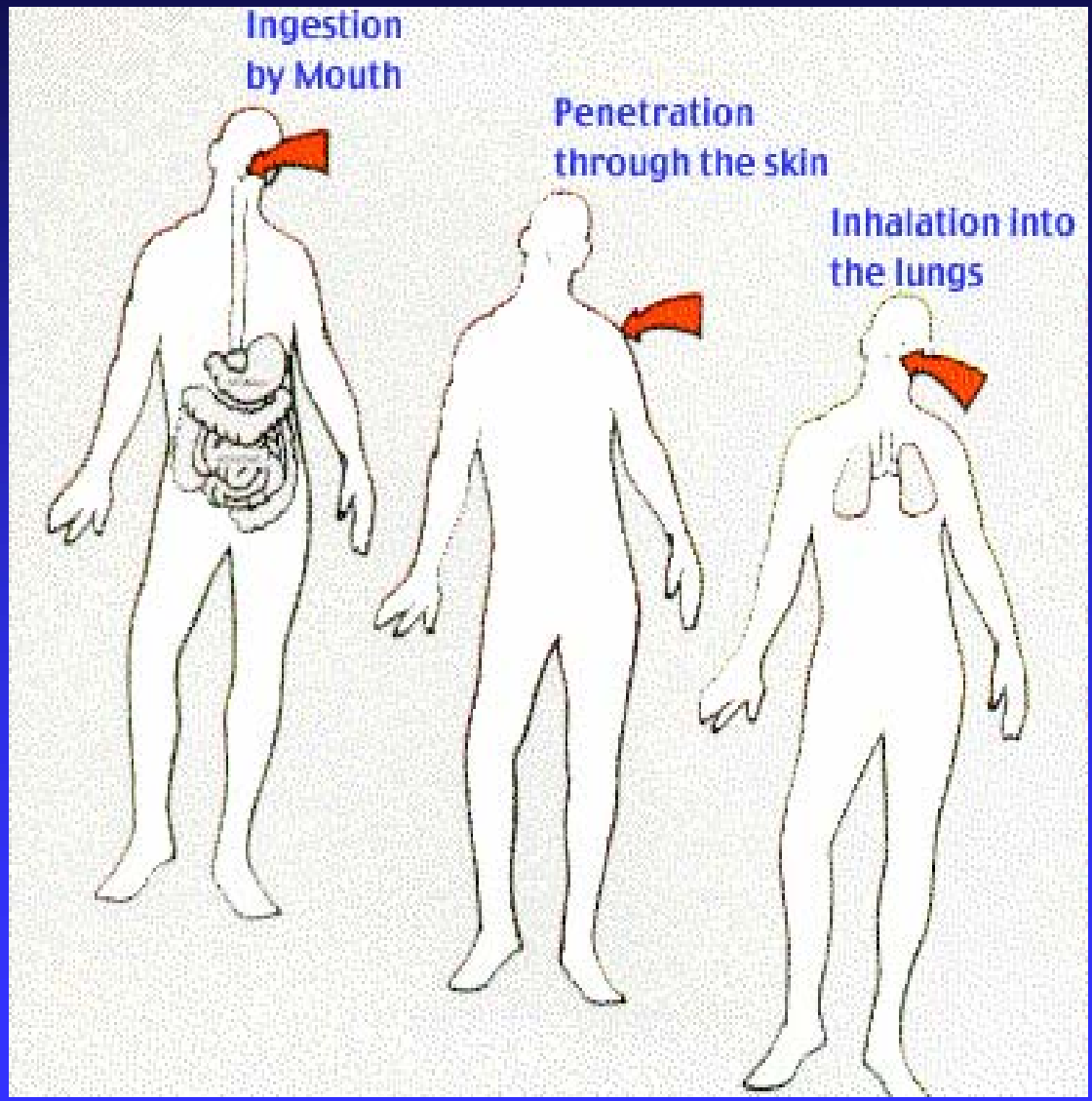
Dose-Response Relationship



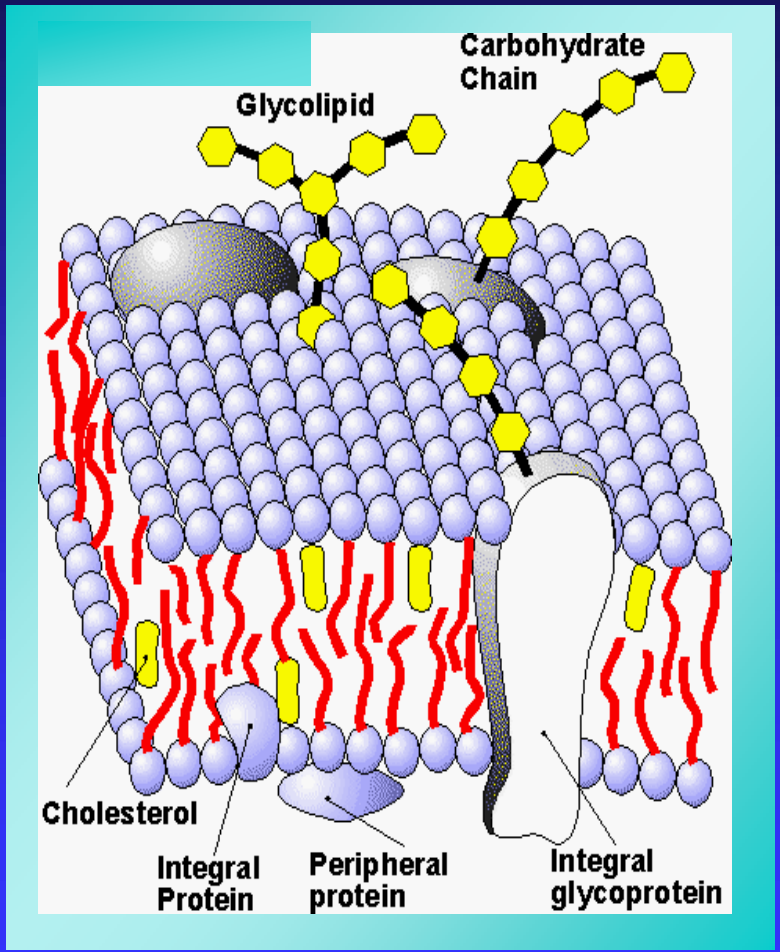
Dose versus Time

- A low dose for a long time may be more hazardous than a higher dose for a shorter time
  - Factors:
    - Mechanism of action
    - Accumulation
    - Reactivity

Routes of Toxin Exposure

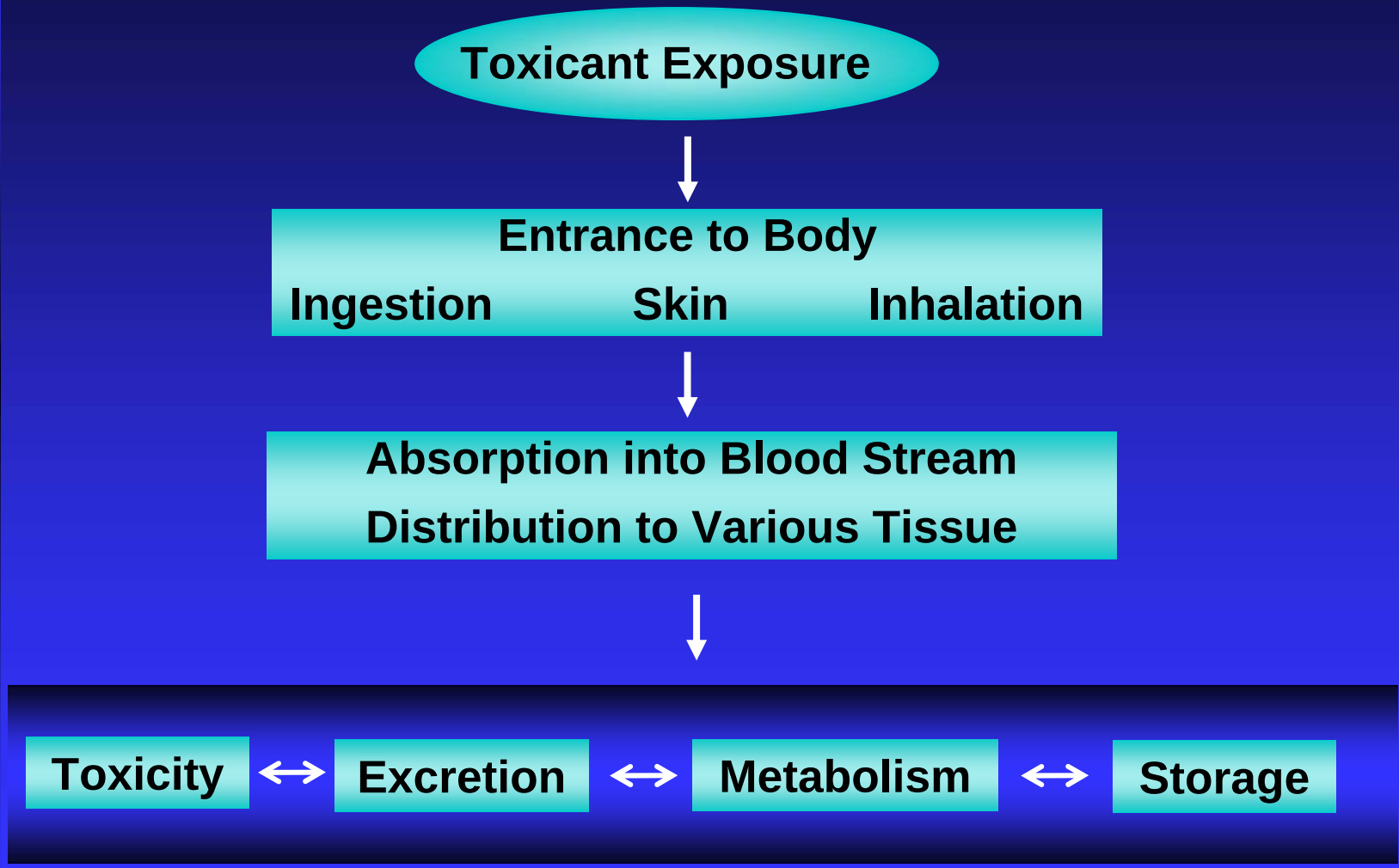


Cell Membrane



- Lipid barrier
  - Fat soluble substances penetrate better
- Dynamic
- Can itself be a target

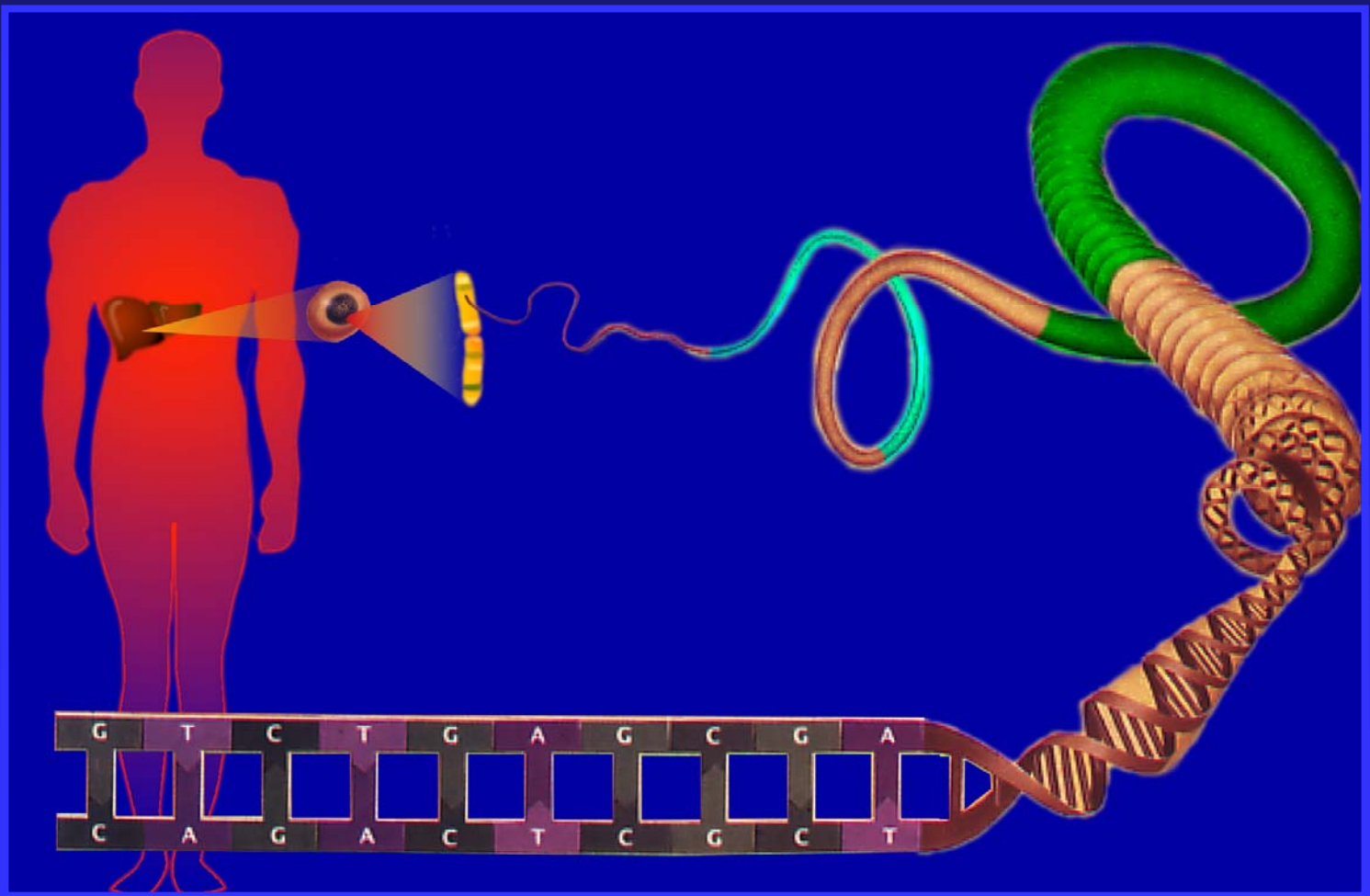
Entry and Fate of Toxicants



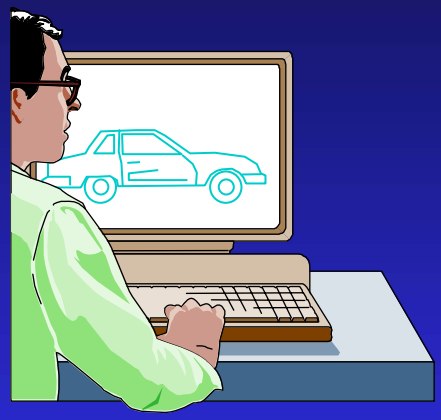
Computers Use a Binary (Two-Digit) Language

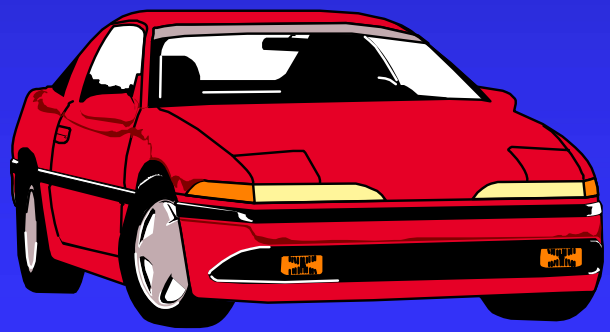
Cells Use a Four Letter Language- the “Genetic Code”

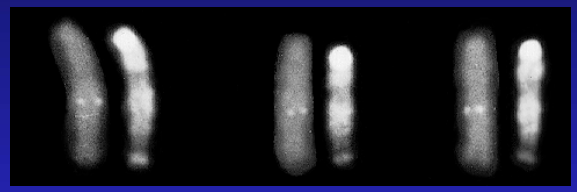
Long Strands of DNA Make up Our Chromosomes, the Functional Units of Chromosomes are Genes



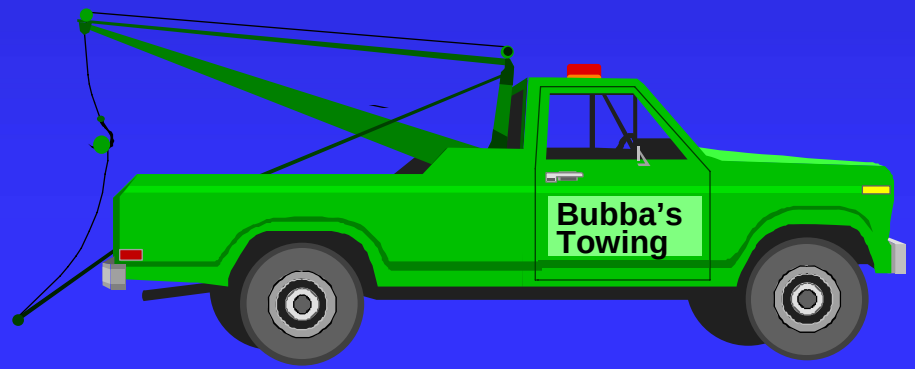
Our Genes Are the Blueprints for Making a Person





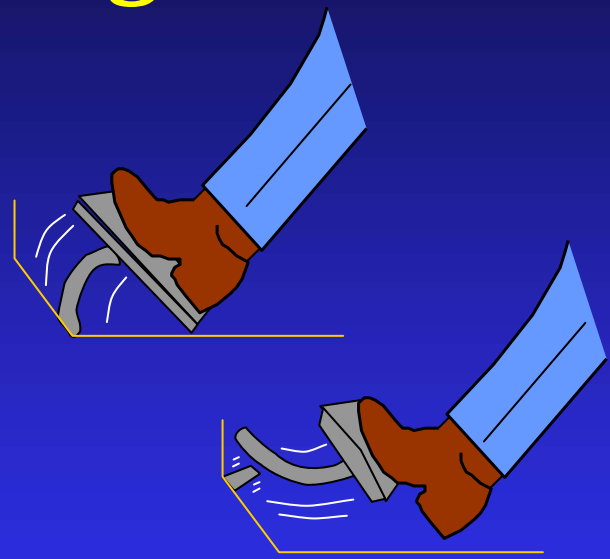


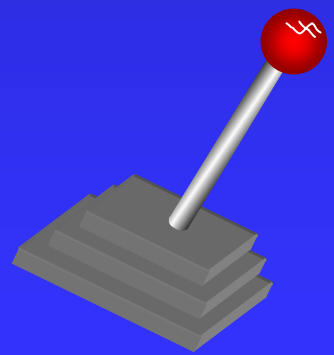
Damage to Blueprints Leads to a Faulty Car



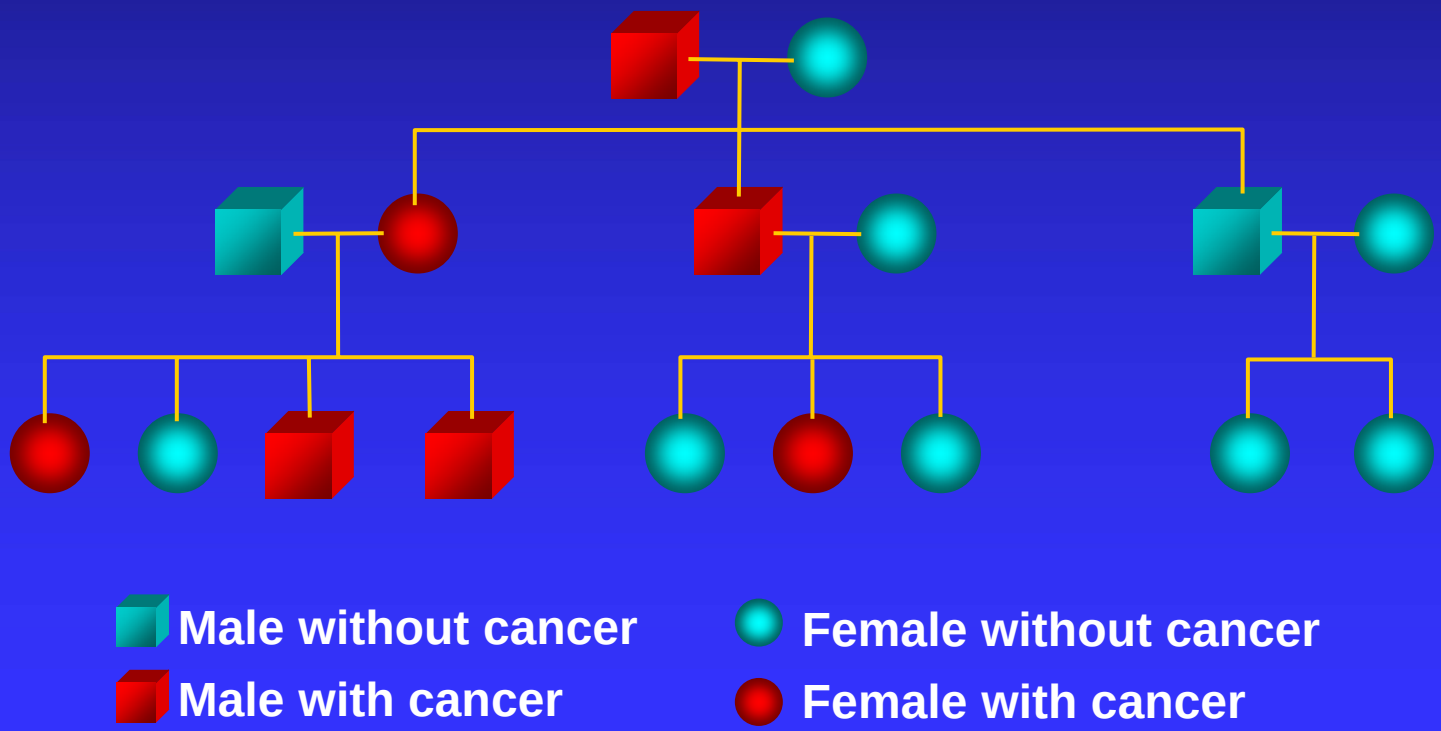
Three Main Classes of Genes are Important in Carcinogenesis

- Oncogenes: speed up cell growth
  - (like a car's accelerator)
- Tumor Suppressors: slow down cell growth
  - (like a car's brakes)
- Modifiers of Carcinogenesis: alter the effects of carcinogen exposure
  - (like a car's transmission)

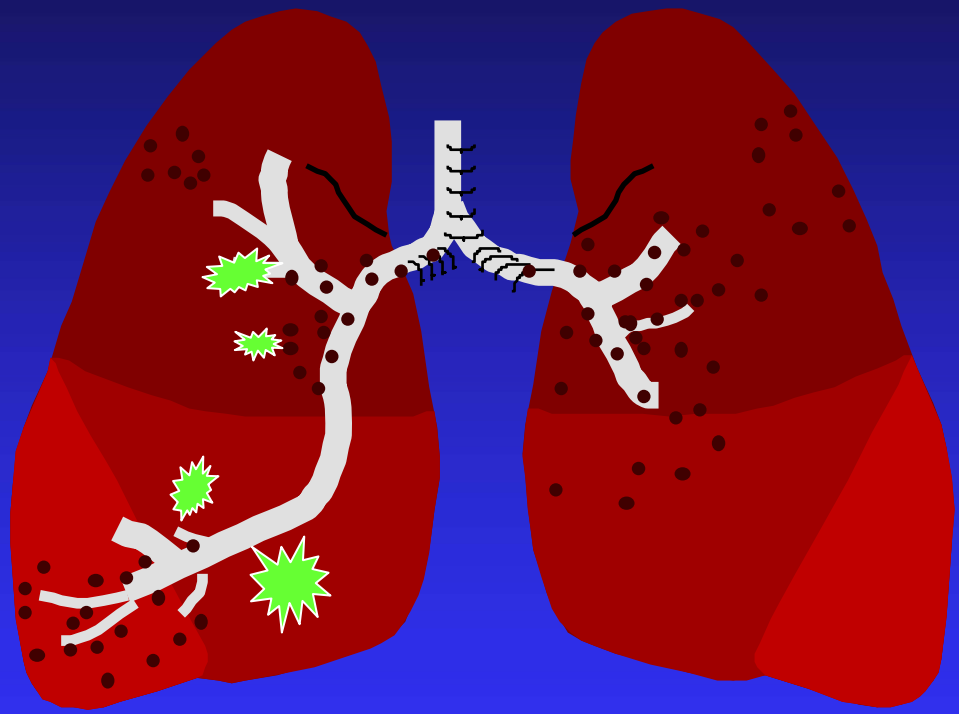




Alterations in Tumor Suppressor Genes, Due to Carcinogen Exposure or Heredity, Can Increase Your Likelihood of Getting Cancer



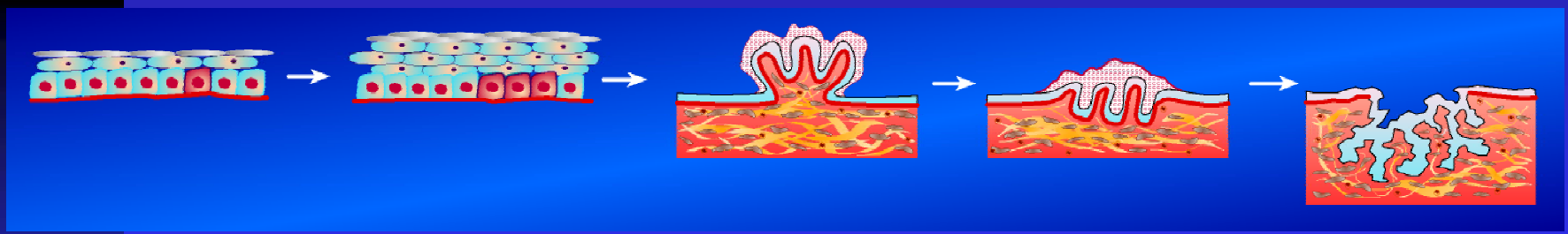
An Inactive Tumor Suppressor Gene Fails to Put the Brakes on Growth



Lung cancer often results from damage to the p53 tumor suppressor gene

Cancer is a Multi-step Process & Genetic Changes Can Occur at Various Stages of Tumorigenesis

Initiation **Promotion** **Progression**



Genetically altered cell → **Hyperplasia (cell division)** → **Dysplasia (pre-malignant lesion)** → **Carcinoma *in situ*** → **Invasive carcinoma**


Hepatitis, Sunlight
Known
Unknown
Environmental Exposure
Individual Susceptibility
Known
BRCA1,2
Unknown

Definition of “Risk”

- The chance of injury, damage or loss; dangerous chance; hazard
- To expose to hazard, as to “risk” one’s life

Absolute Risk

The rate of occurrence or death from cancer within the general population.

Relative Risk

The occurrence or death from cancer among those with a risk factor(s) relative to those without the risk factor(s).

Attributable Risk

Amount of disease within a population that could be prevented by alteration of risk factors.

Risk Factors

Inherited characteristics or exposure to substances, that create or increase the potential of developing cancer

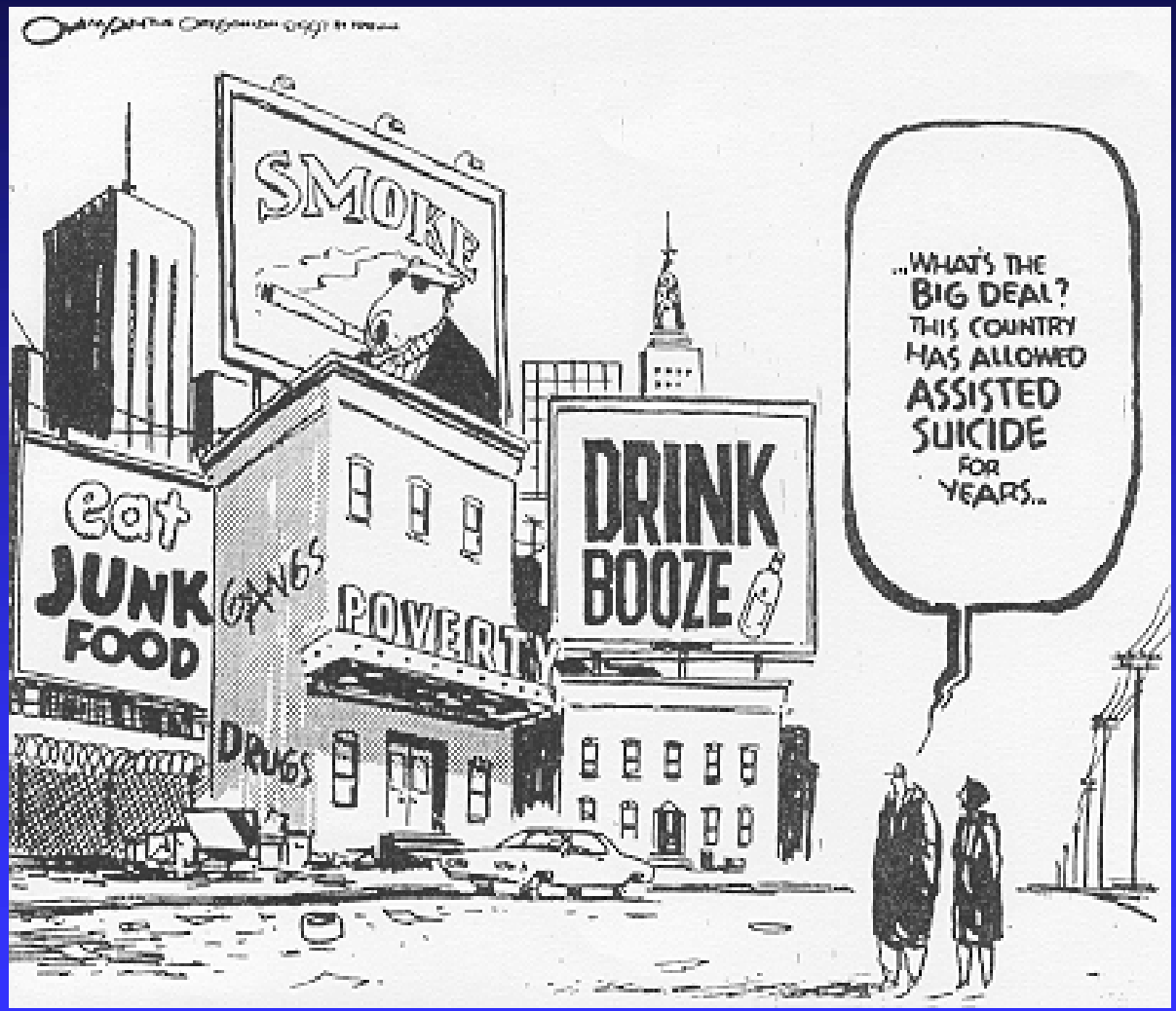
Traditional Epidemiology

One-in-a-Million Risk of Dying from Accidents

Activity

- 3 hrs in coal mine
- Traveling 6 minutes by canoe
- Traveling 10 miles by bicycle
- Traveling 300 miles by car
- Flying 1,000 miles by jet

Source: J NCI Res, 1991


SMOKE
Eat
JUNK
FOOD
GANGS
POVERTY
DRINK
BOOZE
DRUGS
...WHAT'S THE
BIG DEAL?
THIS COUNTRY
HAS ALLOWED
ASSISTED
SUICIDE
FOR
YEARS..

One-in-a-Million Risk of Dying from Cancer

Activity

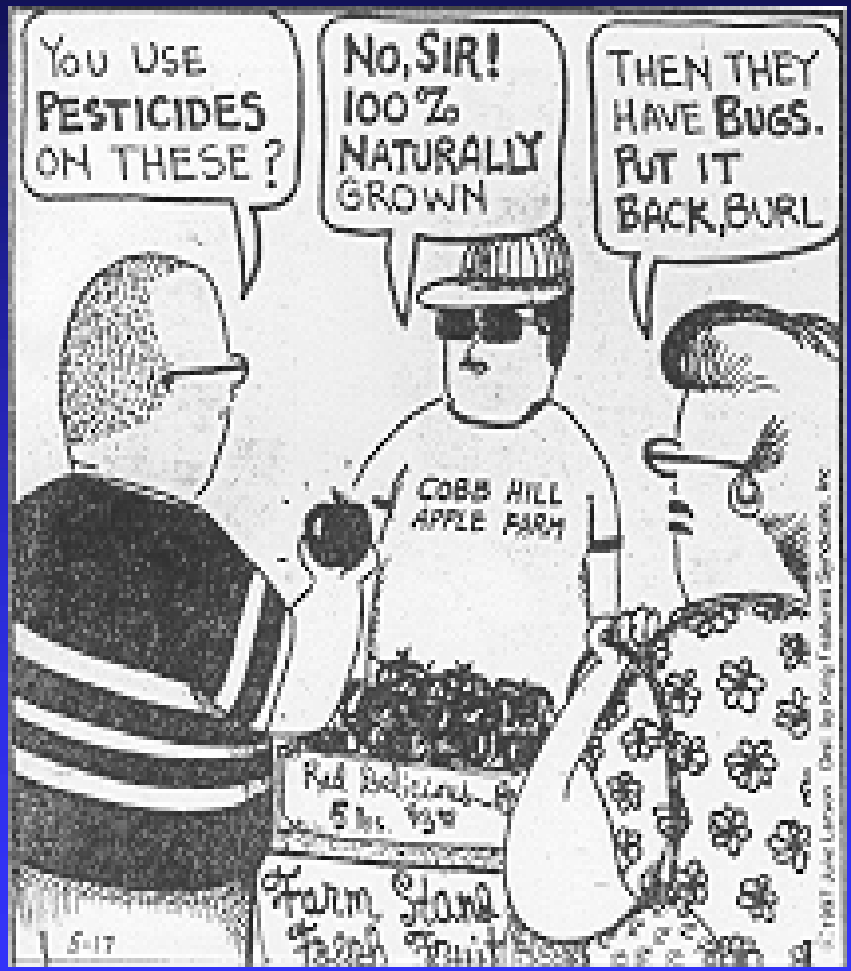
- Smoking 1.4 cigarettes
- Flying 6,000 miles by jet
- Living in Denver for 2 months
- Living in stone or /brick building for 2 months
- 1 chest x-ray in good hospital
- Living with cigarette smoker for 2 months
- Drinking Miami drinking water for 1 year
- Drinking 30 - 12 oz cans of diet soda
- Living 5 years at site boundary of a typical nuclear power plant
- Drinking 1,000 24 oz soft drinks from plastic bottles
- Living 20 years near polyvinyl chloride plant
- Living 150 years within 5 miles of a nuclear power plant
- Eating 100 charcoal broiled steaks

Source: J NCI Res, 1991

Perception of Risk

League of Women Voters	College Students	Business Club Members	Actual Rank/Risk
Nuclear power	Nuclear power	Handguns	Smoking
Motor vehicles	Handguns	Motorcycles	Alcohol
Handguns	Smoking	Motor vehicles	Motor vehicles
Smoking	Pesticides	Smoking	Handguns
Motorcycles	Motor vehicles	Alcohol	Electric power

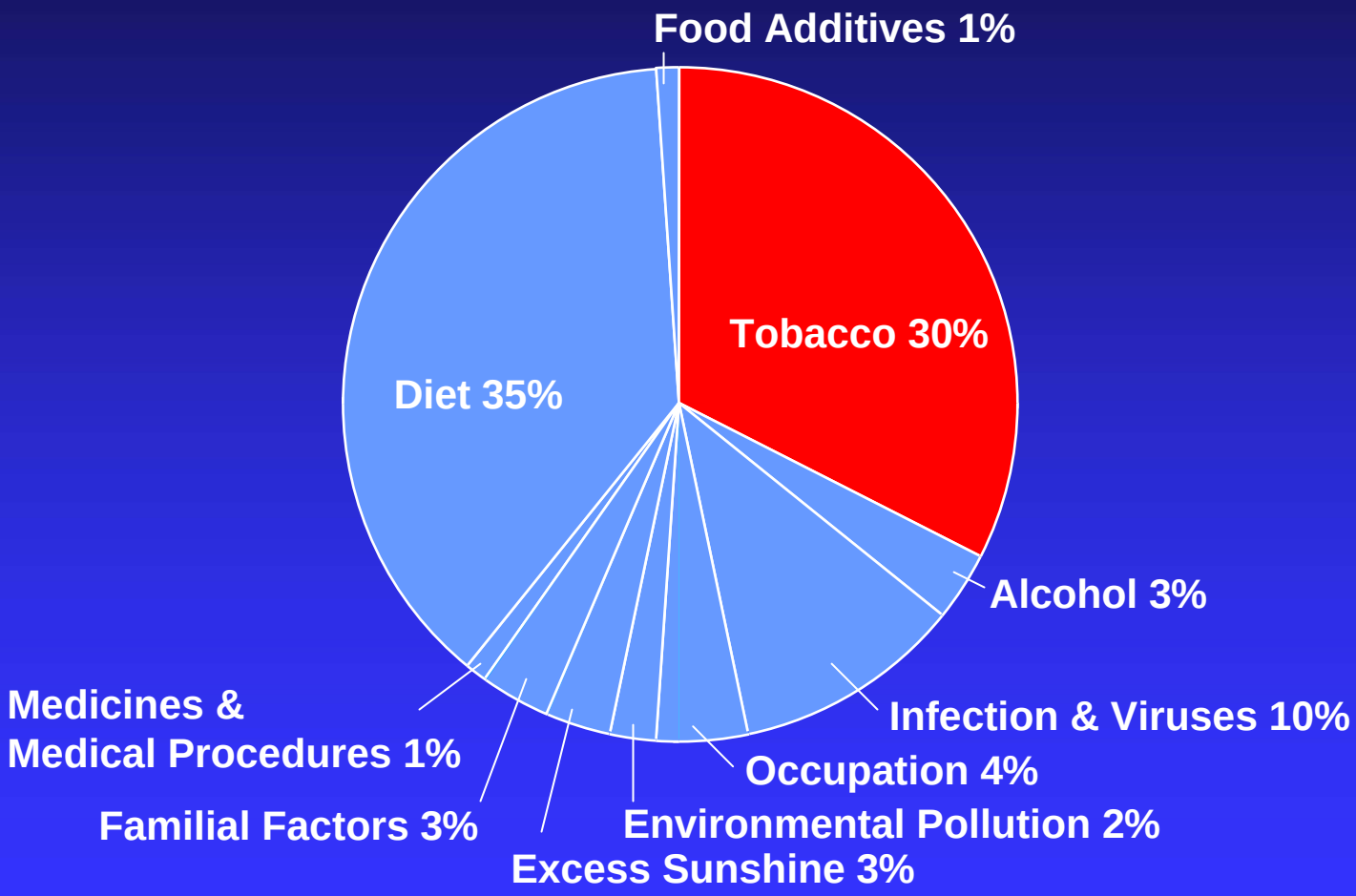
Source: Upton, AC


YOU USE PESTICIDES ON THESE?
NO, SIR! 100% NATURALLY GROWN
THEN THEY HAVE BUGS. PUT IT BACK, BURL
COBB HILL APPLE FARM
Farm Stand
Fresh Fruit

. . . but remember no cause is efficient without a predisposition of the body itself. Otherwise, external causes which affect one, would affect all . . .

Galen, 200 A.D.

Cancer Risk Factors

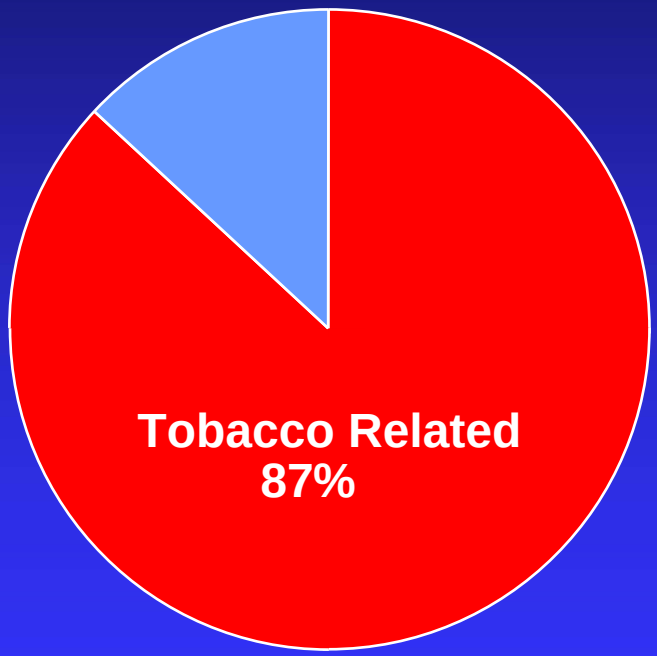


Tobacco in Any Form Kills

Cancer Risks Associated with Specific Tobacco Products

- Pipe and Cigar Smoking (alkaline smoke)
  - Mouth
  - Esophagus
  - Larynx
- Chewing Tobacco and Snuff
  - Mouth (leukoplakia)
  - Larynx
- Cigarettes (acidic smoke)
  - Lung
  - Esophagus
  - Larynx
  - Pharynx
  - Bladder
  - Kidney
  - Pancreas
  - Cervix

Lung Cancer

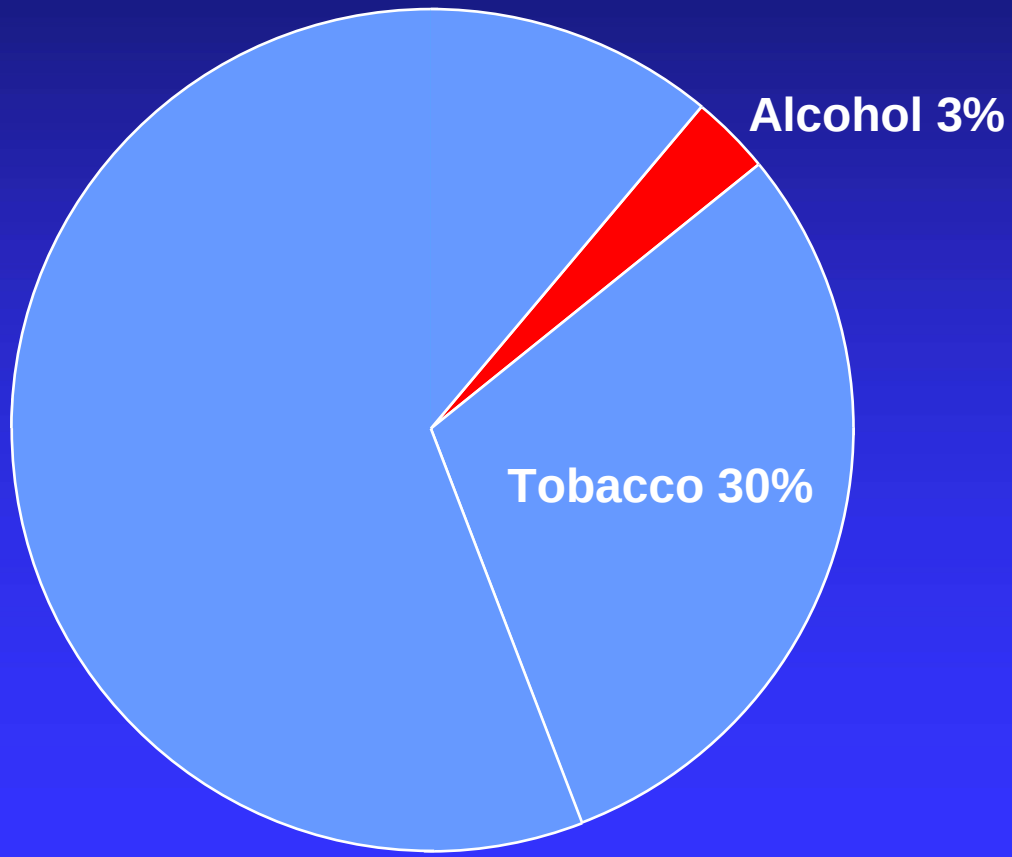


- More pack-years increases risk
- Passive smoking increases risk
- Low tar/nicotine cigarettes don’t decrease risk
- Quitting lowers risk

Passive Smoking Leads to Increased Risk of Lung Cancer

- Spouses of smokers have an approximately 30% increased risk of lung cancer

Cancer Risk Factors



Cancer Sites Linked to Alcohol

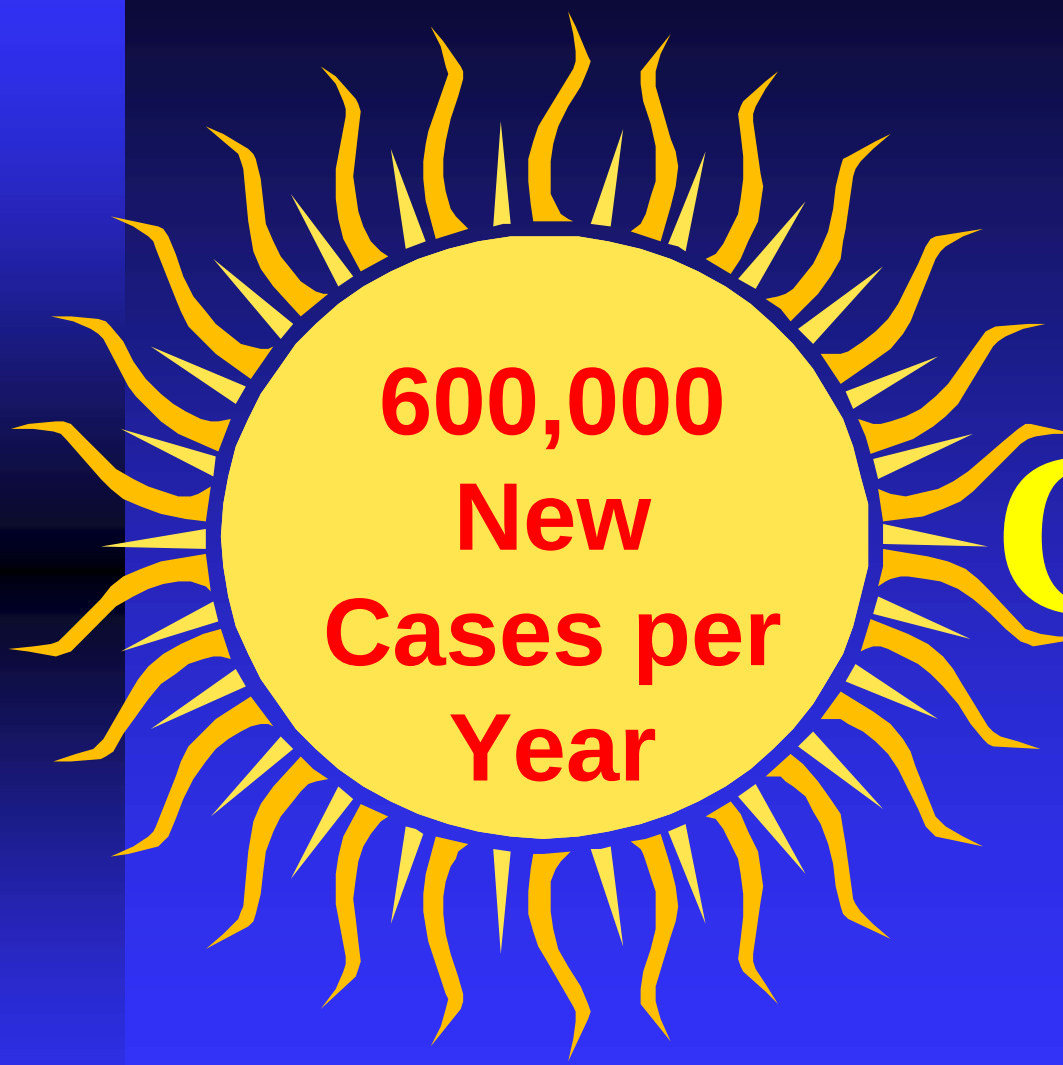
- Mouth
- Esophagus
- Larynx
- Pharynx
- Liver

Risk

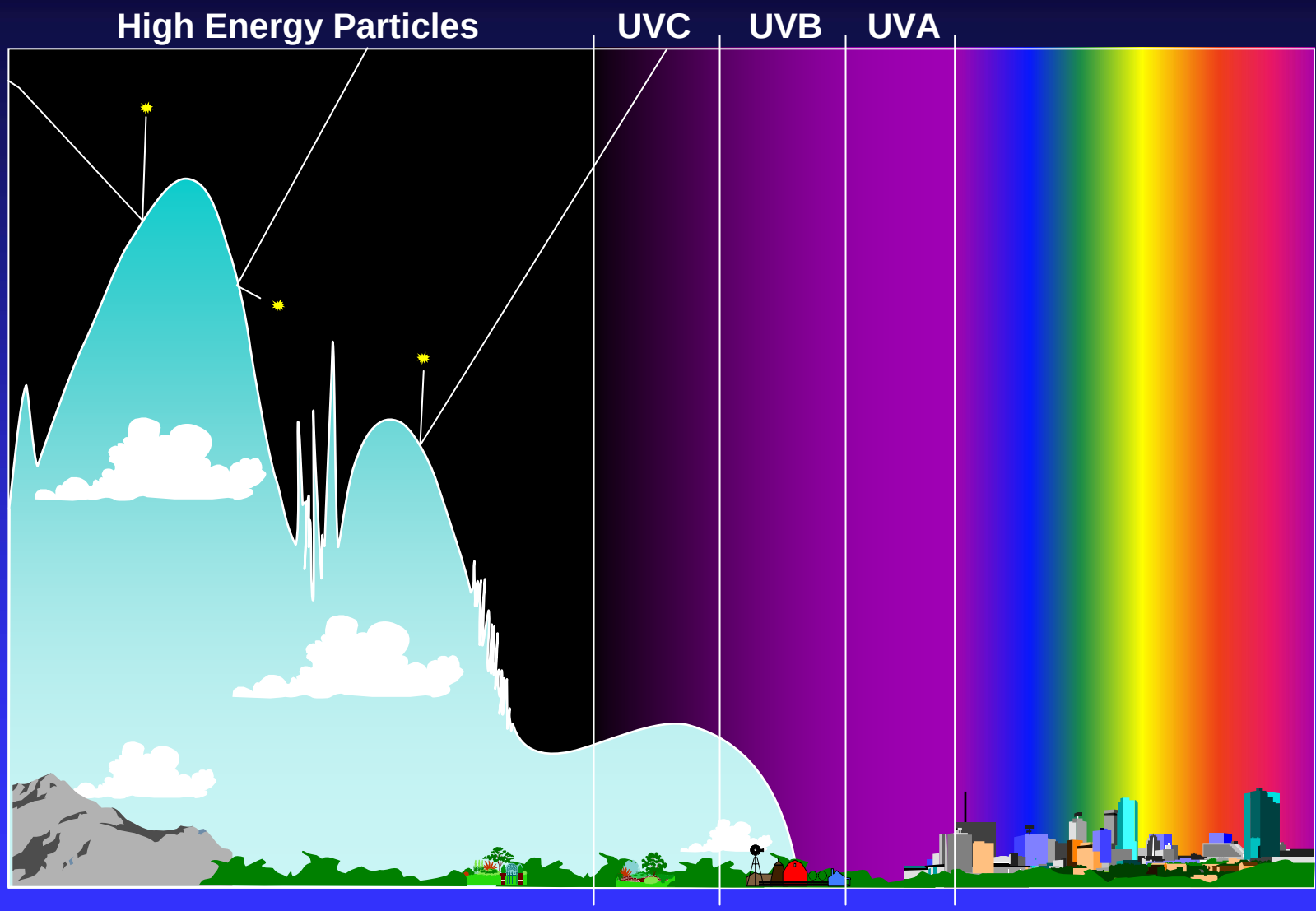
+

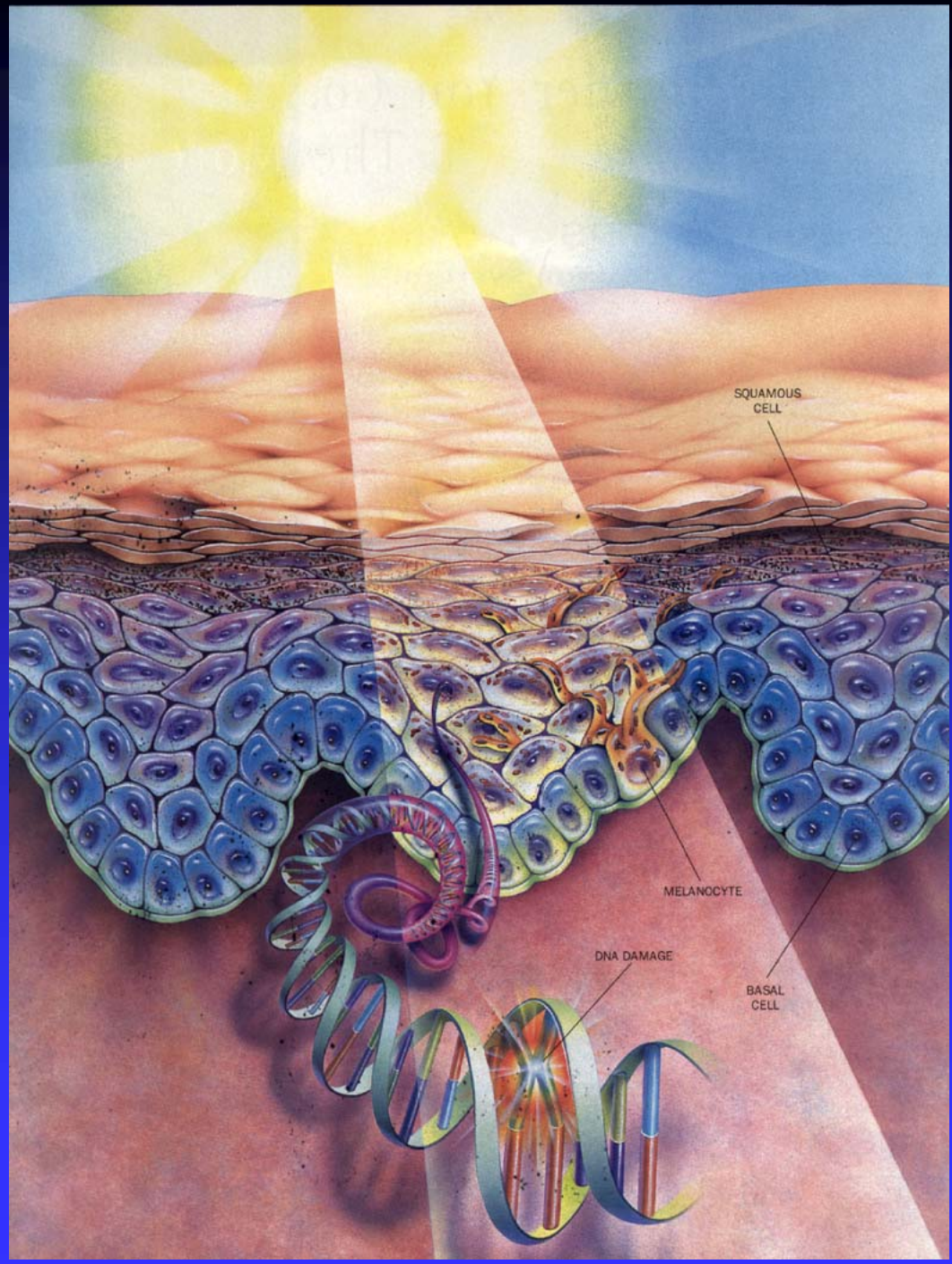
=

Esophagus
Mouth
Pharynx
Larynx



Skin Cancer


High Energy Particles
UVC
UVB
UVA


SQUAMOUS CELL
MELANOCYTE
DNA DAMAGE
BASAL CELL

Nonmelanoma

- Basal cell carcinoma
- Squamous cell carcinoma

Nonmelanoma

- Most Common
- 90% caused by overexposure to excessive radiation
- 95% curable when found and treated early

Melanoma

- Life threatening
- Spreads rapidly
- Linked to moles
- Incidence rapidly increasing

Skin Self-Exam

Look for:

- Moles
- Birthmarks
- Blemishes
- New marks
- Sores

Note changes in:

- Color
- Shape
- Size

Use Sunscreen of SPF 15 or Greater

Factors Contributing to Cancer Risk in the United States

- Diet: ~35%
- Tobacco: ~30%
- Occupational and Pollution: ~5%
- Infection: ~10%
- Other: ~20%
  - Genetic susceptibility
  - Sunlight / radiation
  - Alcohol
  - Long-term exposure to some drugs

Diet and the Cancer Process

Initiation

Harmful: Dietary carcinogens; reactive oxygen species --> DNA damage

Protective: Bioactive compounds in fruits and vegetables

Promotion

Harmful: Diet-related promoters--fat, total energy intake, obesity

Protective: Bioactive compounds in fruits and vegetables

Progression

Harmful : ?---fat, total energy intake, obesity

Protective: Bioactive compounds in fruits and vegetables

Cancer Promoter: Dietary Fat

- Cancers most associated with high fat intake: prostate, colon, breast
- Mechanism of Action:
  - increase bile acid production
  - increase steroid hormone production
  - suppress immune function
  - promote obesity

  Note: Saturated (animal) fat appears to be most harmful; monounsaturated (olive oil) least harmful.

Cancer Promoter: Obesity

- Cancers most associated with obesity: colon, breast, prostate, cervix, ovary
- Mechanism of Action:
  - increased levels of steroid hormones (estrogens), growth factors (IGF-1)
  - increased oxidative stress

Cancer Protectors in the Diet

- Foods associated with decreased cancer risk
  - Fruits and vegetables
  - Whole grain products
  - Beans, legumes, seeds
- Cancers most associated with protective effects of plant foods: lung, head and neck, colon, breast, bladder, prostate

What is an Antioxidant?

Microconstituents of the diet that protect DNA, proteins and cell membranes against oxidative damage, including that induced by carcinogens.

What is a Phytoestrogen?

Microconstituents of the diet (generally plant-derived compounds) with weak estrogenic properties, and thus the ability to interfere with the activity of endogenous estrogens.

Potentially Protective Nutrients in Fruits and Vegetables

Nutrient	Proposed Mechanism
Carotenoids (β-carotene)	antioxidant
Vitamin C	antioxidant
Vitamin E	antioxidant
Folic acid	prevents DNA hypomethylation
Selenium	antioxidant

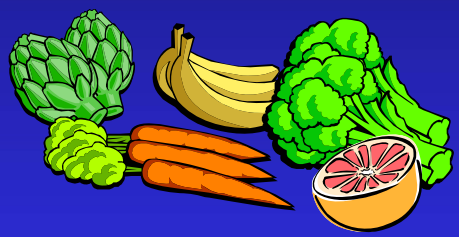
Other Potentially Protective Phyto (plant) Compounds

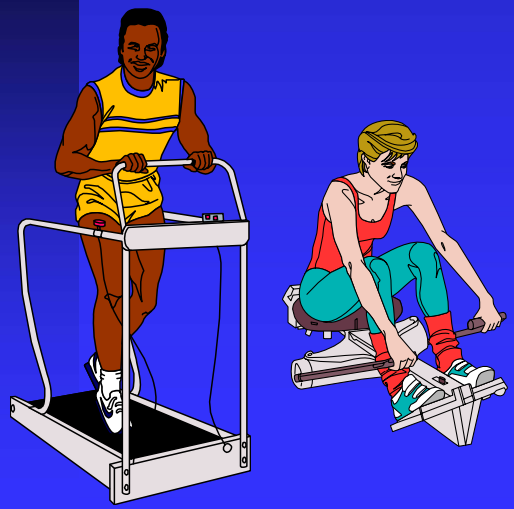
Compound	Source	Proposed Mechanism
Isoflavones (genistein)	soy	phytoestrogen; antioxidant
Flavonoids	variety	phytoestrogen; antioxidant
Alliums	onion; garlic	alter carcinogen metabolism
Polyphenols	tea	antioxidant
Coumarins	citrus	alter carcinogen metabolism
Lignans	grains	phytoestrogen
Isothiocyantaes	crucifers	alter carcinogen metabolism
Dietary fiber	grains	bind carcinogens; alters bile acid, hormone metabolism

Other Diet-Cancer Issues

- **Food contaminants**: no convincing evidence that chemical residues sometimes present in food and drink (fertilizer, pesticide, herbicide, hormones) increases cancer risk
- **Food additives:** no convincing evidence that any food additive (preservative, emulsifier, dye, flavoring) increases cancer risk (possible concern: nitrites)
- **Supplements vs. Foods:** evidence thus far from clinical trials suggest supplementation with high doses of isolated nutrients is probably unnecessary and possibly unhelpful for cancer prevention. The balance of multiple nutrients from a diet containing a variety of fruits, vegetables and grains may be very important

1999 American Institute for Cancer Research Dietary Recommendations



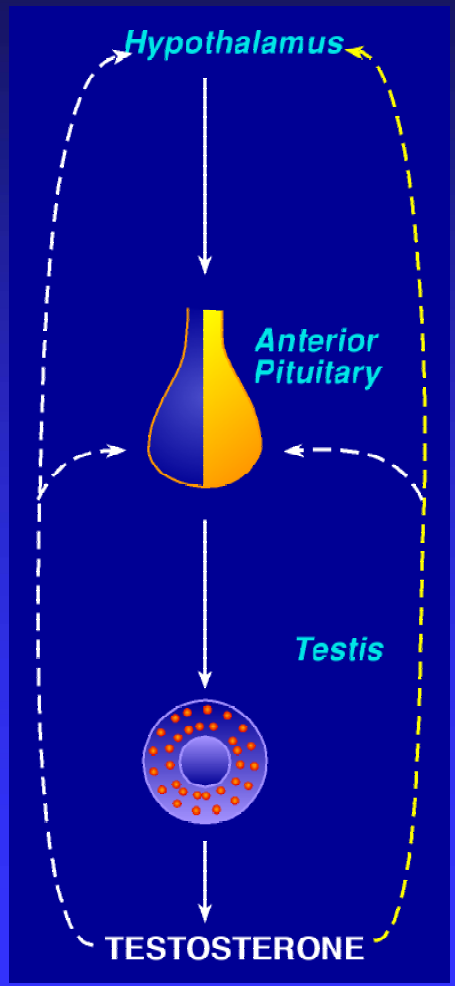


1. Choose diets rich in plant-based foods including a variety of fruits and vegetables, reduce processed, starchy foods.
2. Avoid being overweight or underweight.
3. If occupational activity is low or moderate, take a brisk walk (or similar exercise) every day and also exercise vigorously at least one hour per week.

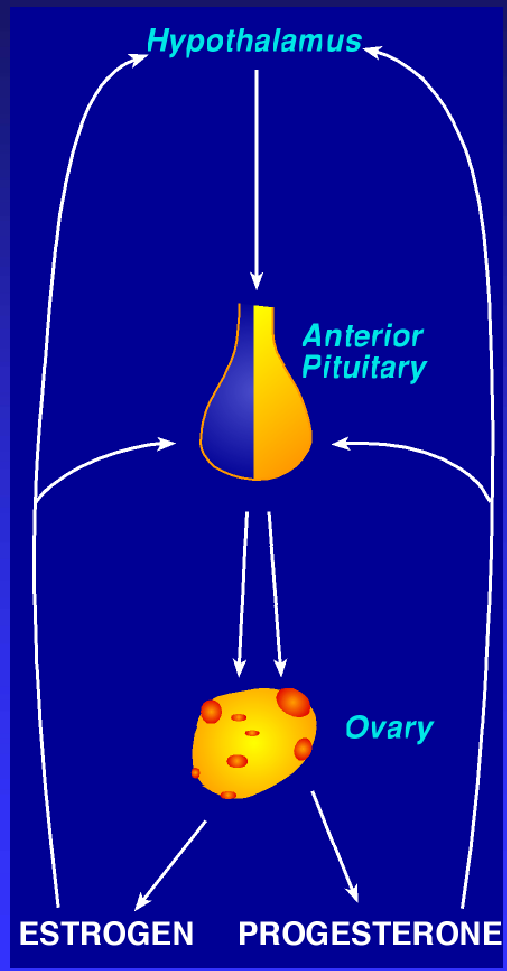
1999 American Institute for Cancer Research Dietary Recommendations *(continued)*

4. Eat 7 or more servings/day of cereals, pulses, roots or tubers, and limit consumption of refined sugar.
5. If consumed at all, limit alcoholic drinks to no more than than two drinks/ day for men and one for women.
6. Limit intake of red meat to less than 3 ounces; when possible, choose fish or poultry in place of red meat
7. Limit consumption of fatty foods, particularly those of animal origin. Choose modest amounts of appropriate vegetable oils, particularly olive oil.

The Endocrine System

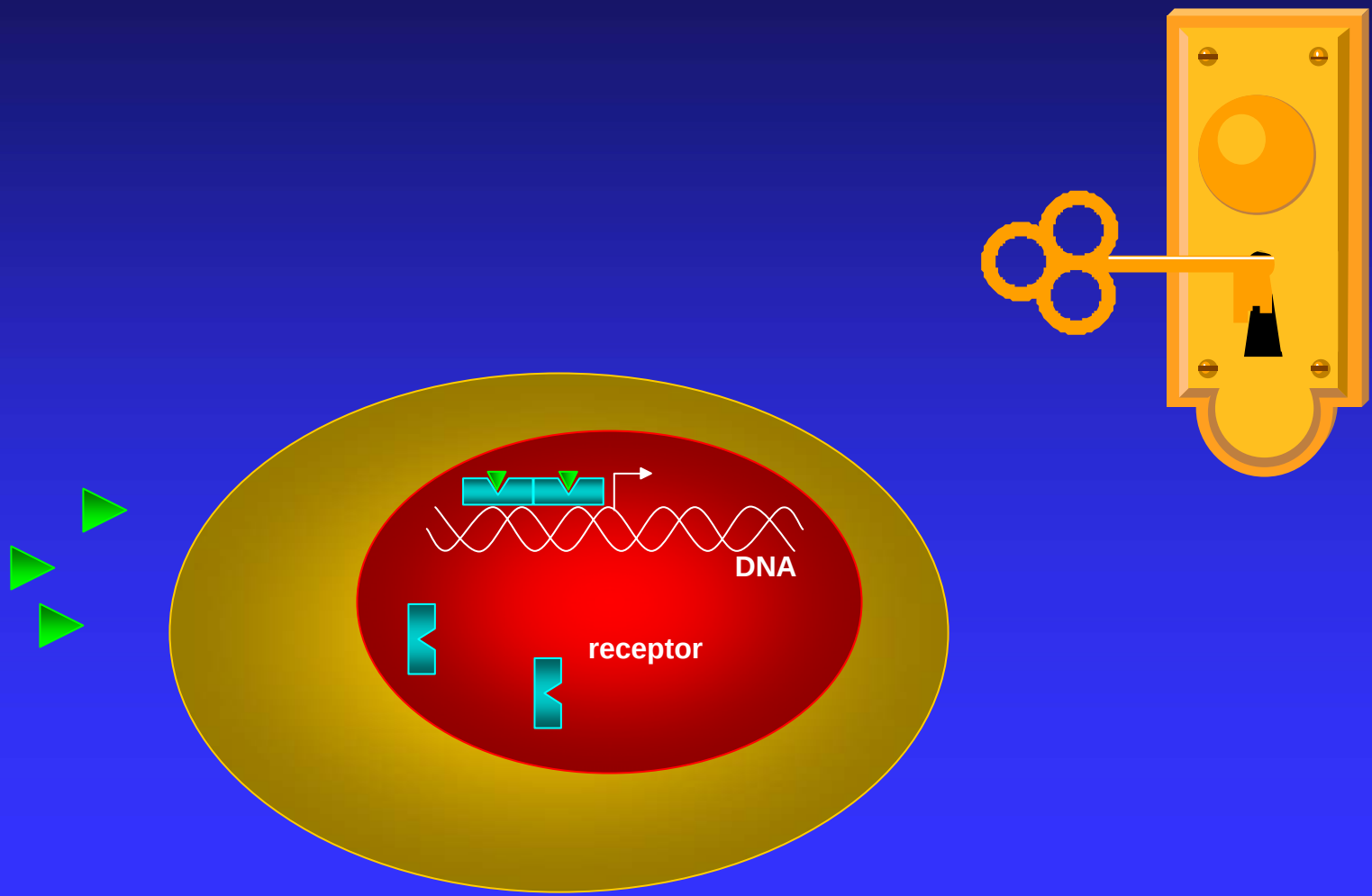


(Hormones)



(Hormones)

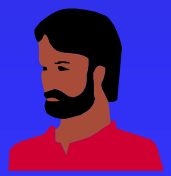
Hormones Bind to Specific Receptors like a Key Fits a Lock



Steroid Hormones Play an Important Role in Many Biological Processes

Bone Density

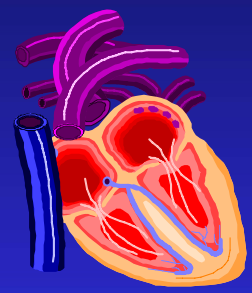
Muscular tone & development



Puberty

Testosterone

Estrogen
Progesterone



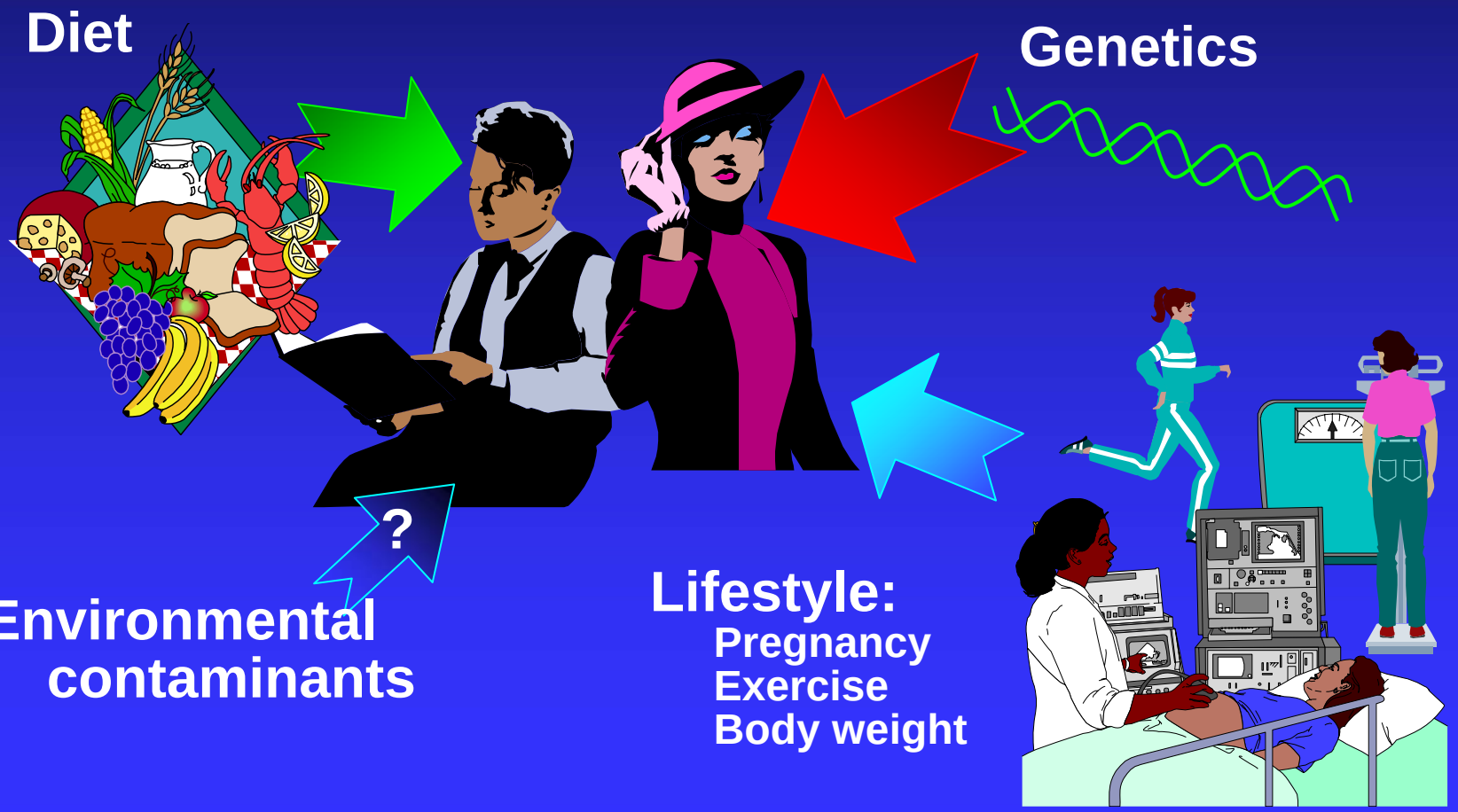
Cardiovascular Function & Lipid Metabolism

Fertility
Menstruation
Pregnancy
Lactation

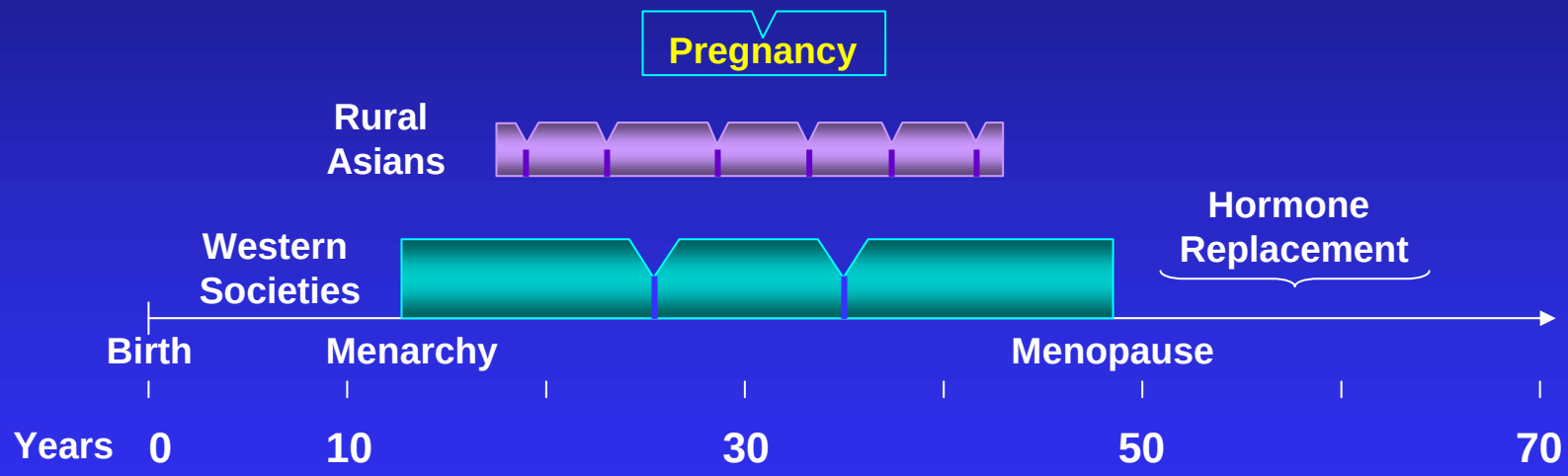
Common Tumors Occurring In Hormonally Regulated Tissues:

- Prostate
- Breast
- Uterus

A Variety of Factors Impact Risk of Hormonally Dependent Cancers



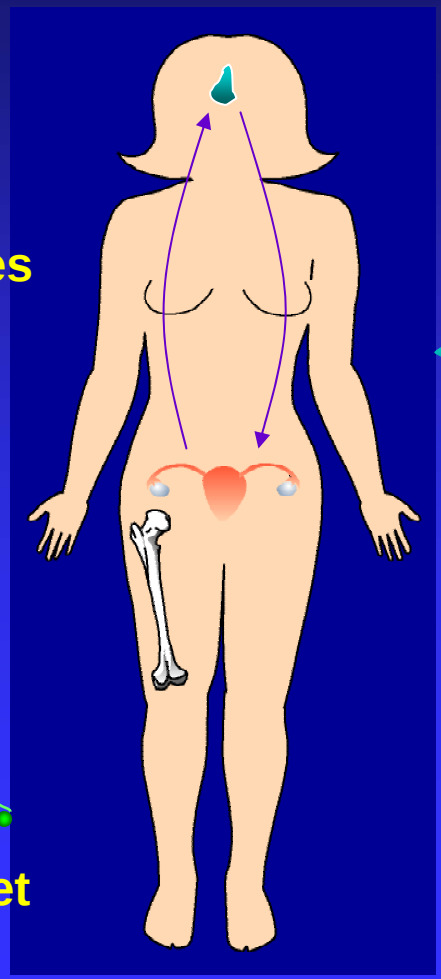
Evidence Suggests that Lifetime Risk of Breast & Endometrial Cancer is Proportional to Total Estrogen Exposure

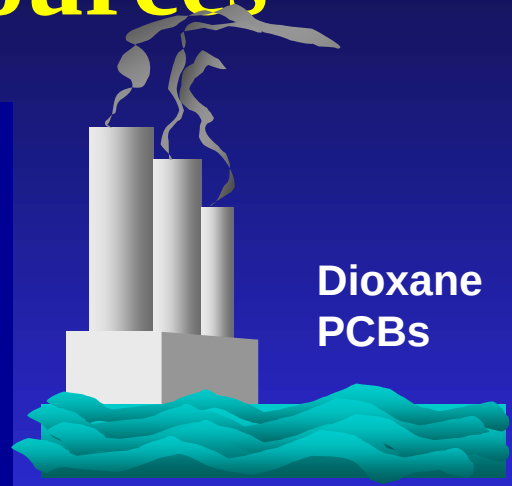


Hormonal Exposure From Internal & External Sources

DDT
Kepone

Pesticides





Dioxane
PCBs

Industrial Processes
& Products

Some
Medicines

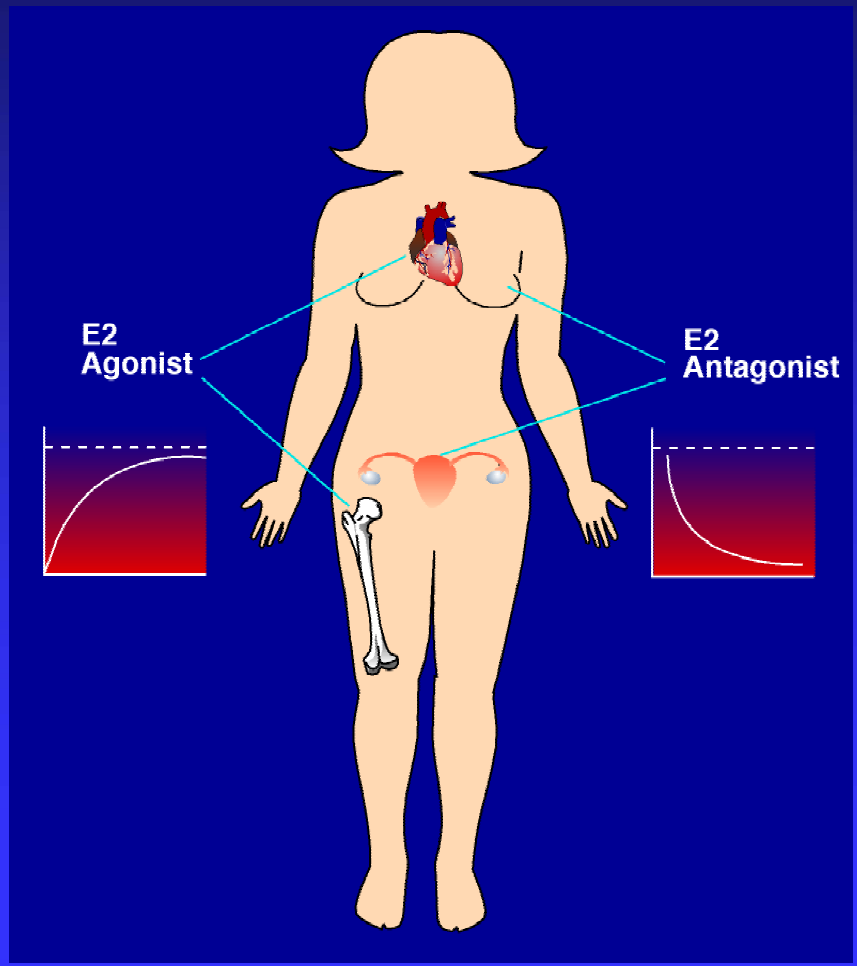
Hormone
replacement
BCPs

Diet

Soy

Bisphenol
(Plastics)

Medicines Can Act Like Hormones or Can Inhibit Hormonal Action



Compound	Use
Tamoxifen	Breast Cancer
Raloxifene	Osteoporosis
Hormone Replacement Therapy	Hot flash Cardiovascular Osteoporosis

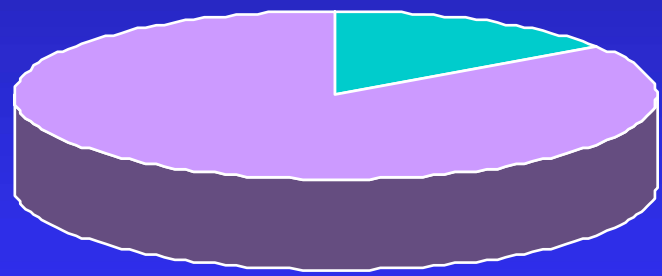
Q: Can You Catch Cancer as a Result of a Viral Infection?

Yes or No

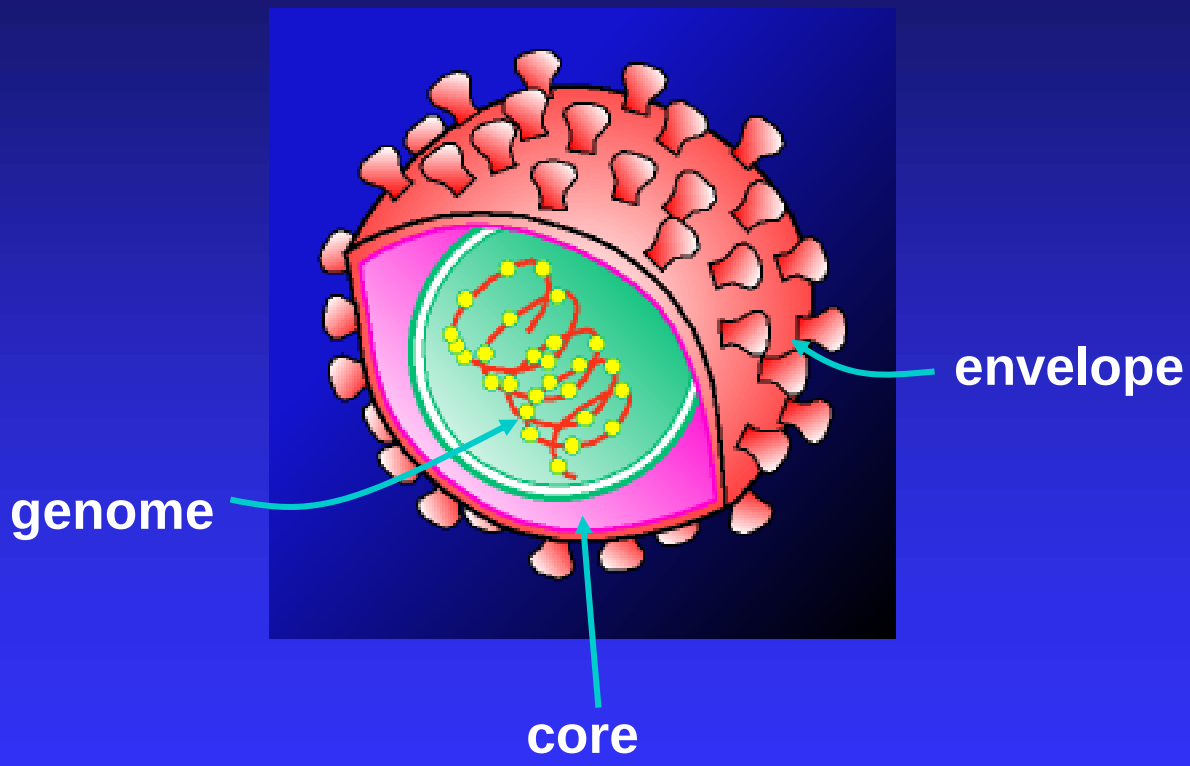
Viruses and Human Cancer

- Viruses are now believed to be an important risk factor for cancer in humans.

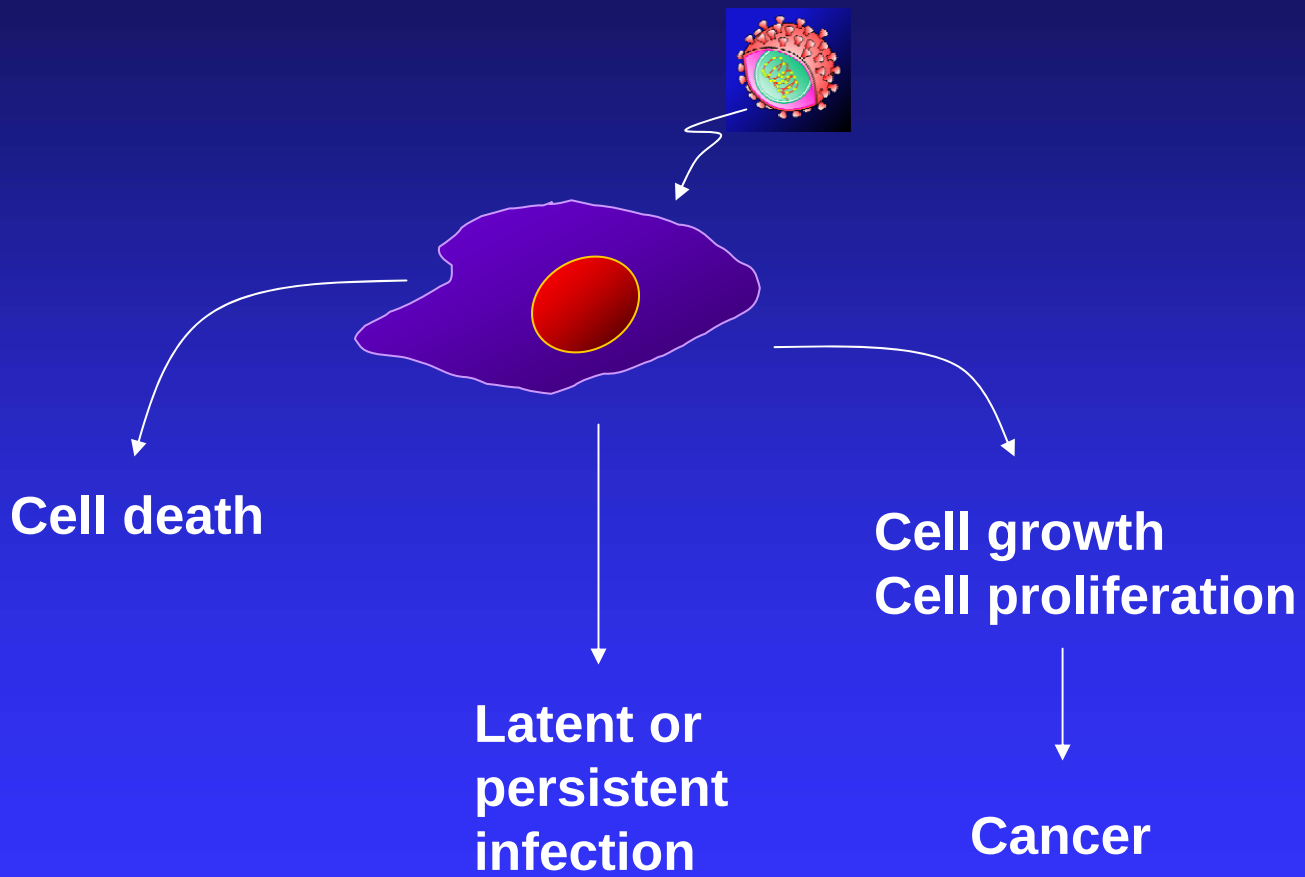
~ 10% - 15% of human cancer can be linked to virus infections



Virus Particle



Fates of Virus-Infected Cells

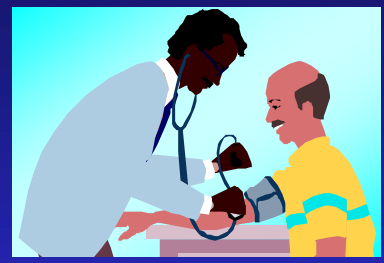


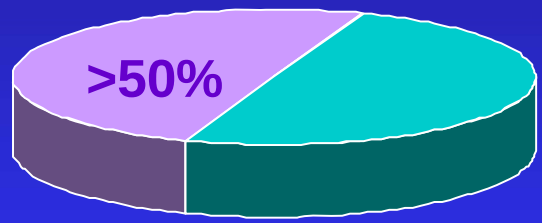
Different Viruses have Different Effects

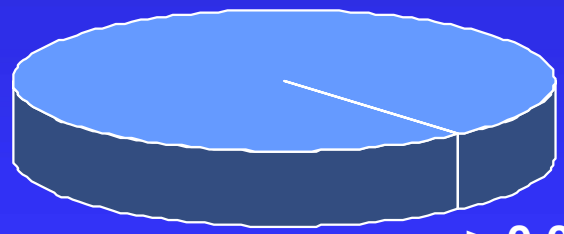
- **Human Viruses With Oncogenic Potential**
  - Human Papilloma Viruses (HPV)
  - Hepatitis B Virus (HBV)
  - Human Herpes Virus 8
  - Epstein-Bar Viruses
  - Human T-lymphotropic Viruses (HTLV)
  - Human immunodeficiency Viruses (HIV)
- **Common Characteristics**
  - Cause persistent infection
  - Can directly or indirectly promote carcinogenesis
  - Can inactivate tumor suppressors
  - DNA or RNA viruses with a DNA phase in lifecycle

- **Viruses That Do Not Participate in Cancer Development**
  - Influenza viruses
  - Common cold viruses
  - Polio
  - Chicken pox
  - Measles
  - Mumps
  - Rubella
  - Yellow fever
- **Common Characteristics**
  - Cause acute infection
  - Do not promote carcinogenesis
  - Usually cause cell death
  - Mostly RNA viruses

- More than 50% of cases physicians encounter daily involve viral infections
- Fortunately, only a very small % of people infected with specific types of viruses develop cancer
- Because this % is so low, cofactors, such as the genetic make-up of the host, environmental factors, and/or secondary viral infections are suspected to be needed for cancer to develop

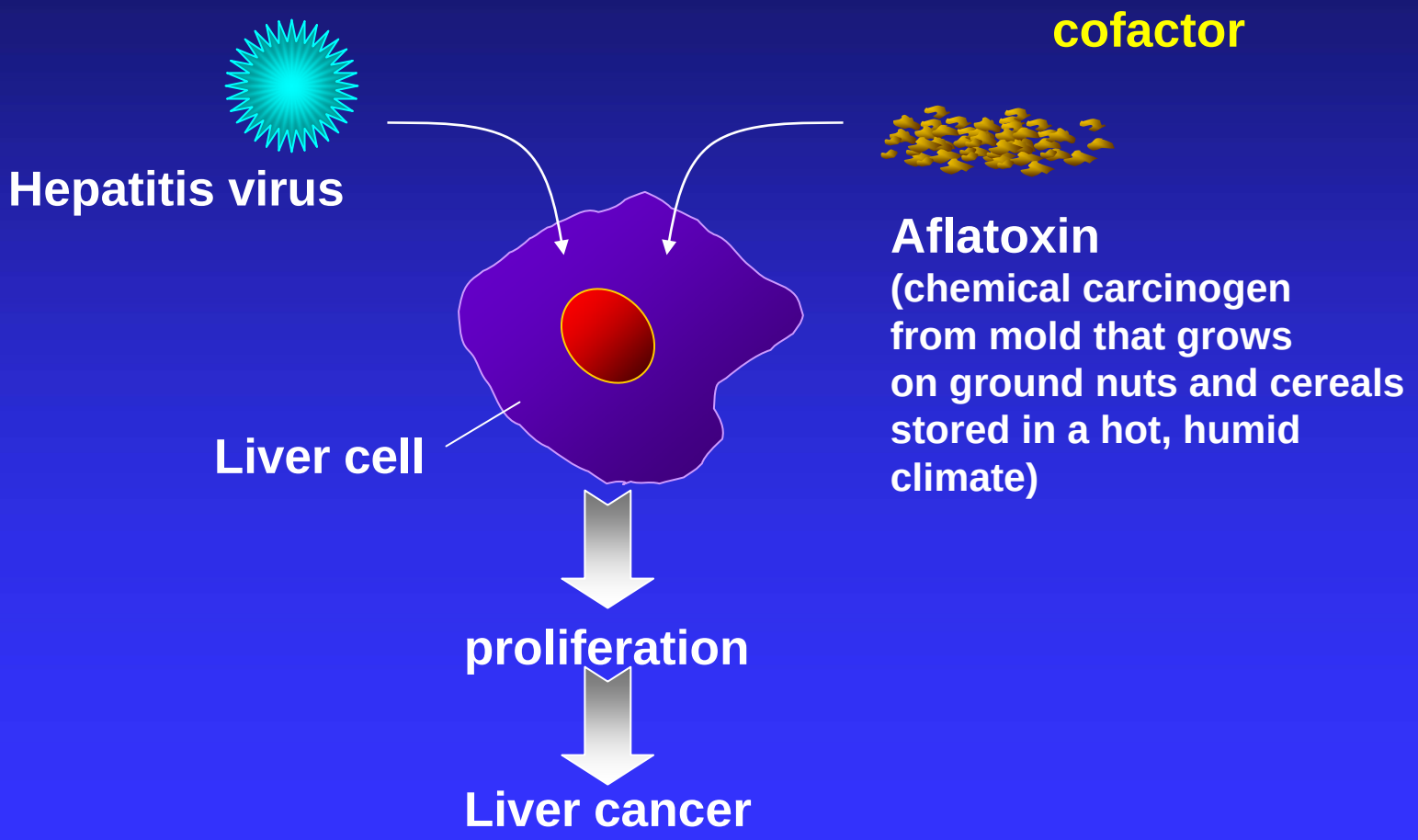






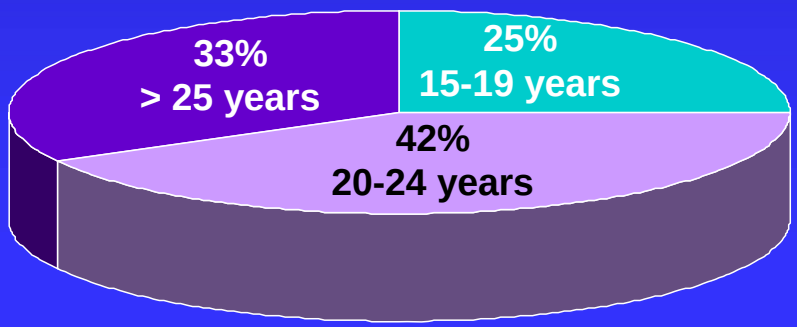
> 0.01%

Virus Interaction with Environmental Factors



Estimated Annual New Cases of Viral Sexually Transmitted Diseases in U.S.

Distribution



Important Points to Remember:

- About 15% of cancer is linked to viral infections
- Only a very small % of viral infections will lead to cancer
- Cancer itself is not contagious
- Virus is contagious but viral infection is preventable
- Cancer associated with viruses therefore can be prevented

What Can be Done?

- Chances of contracting a sexually transmitted virus can be reduced by practicing safe sex
- It is possible to prevent cancers associated with viruses by reducing exposure to environmental carcinogens
- Some viral infections can be prevented by immunization, this practice should also lower the worldwide cancer burden

One Change Can Change Your Life

Stop Smoking

Quitting smoking lowers risk by 30%

Improve Diet

Improving diet lowers risk by 30%

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