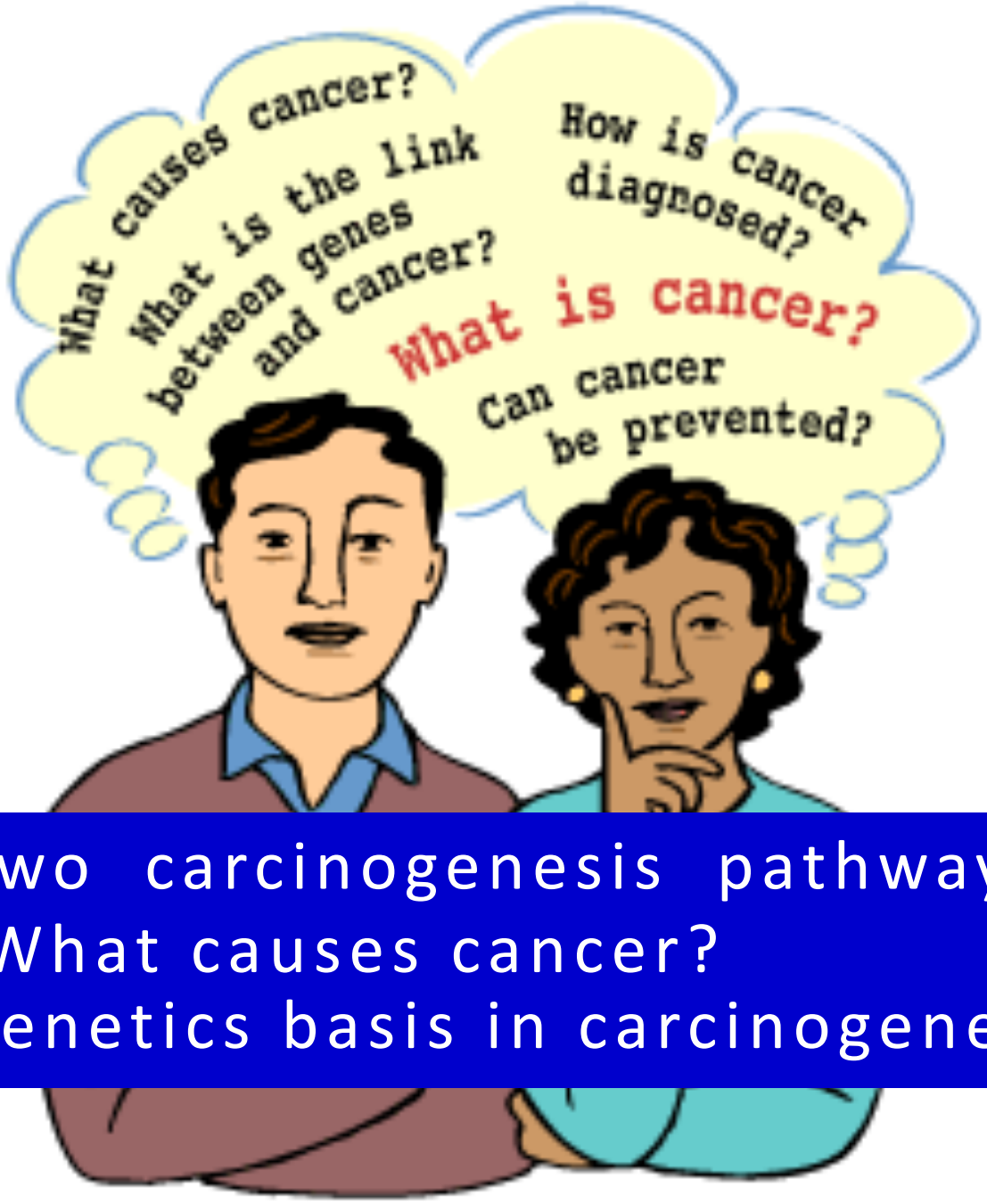
Genetics basis in carcinogenesis : Lec. 2

Chawalit Pairojkul, KKU, Jul 2025

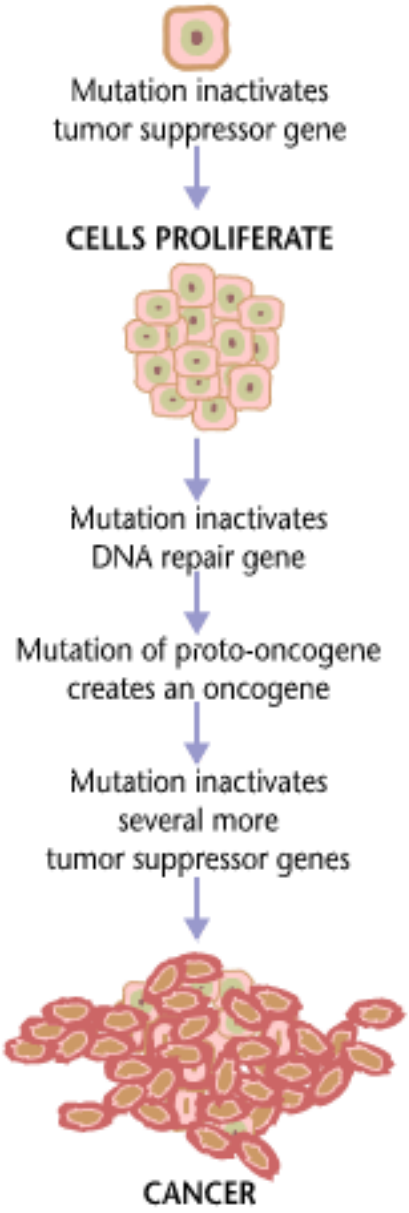
Neoplasm II : *Learning objectives*



2.1] Two carcinogenesis pathways
2.2] What causes cancer?
2.3] Genetics basis in carcinogenesis

Carcinogenesis
(*the creation of cancer),* is the process by which normal cells are transformed into cancer cells.

- Multifactorial diseases
- Multi-stage processes
- Take years to complete
- Multi-genes involvement

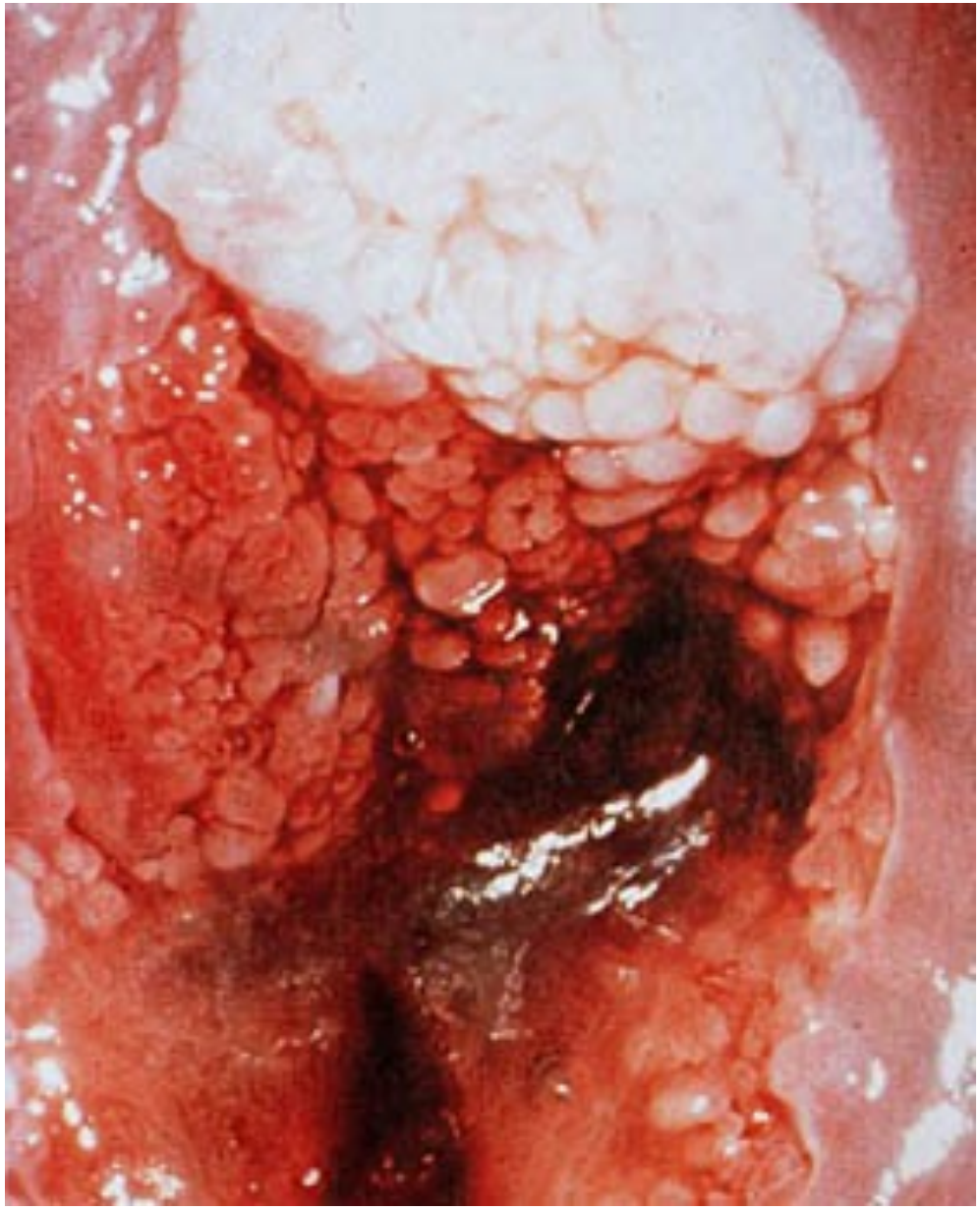


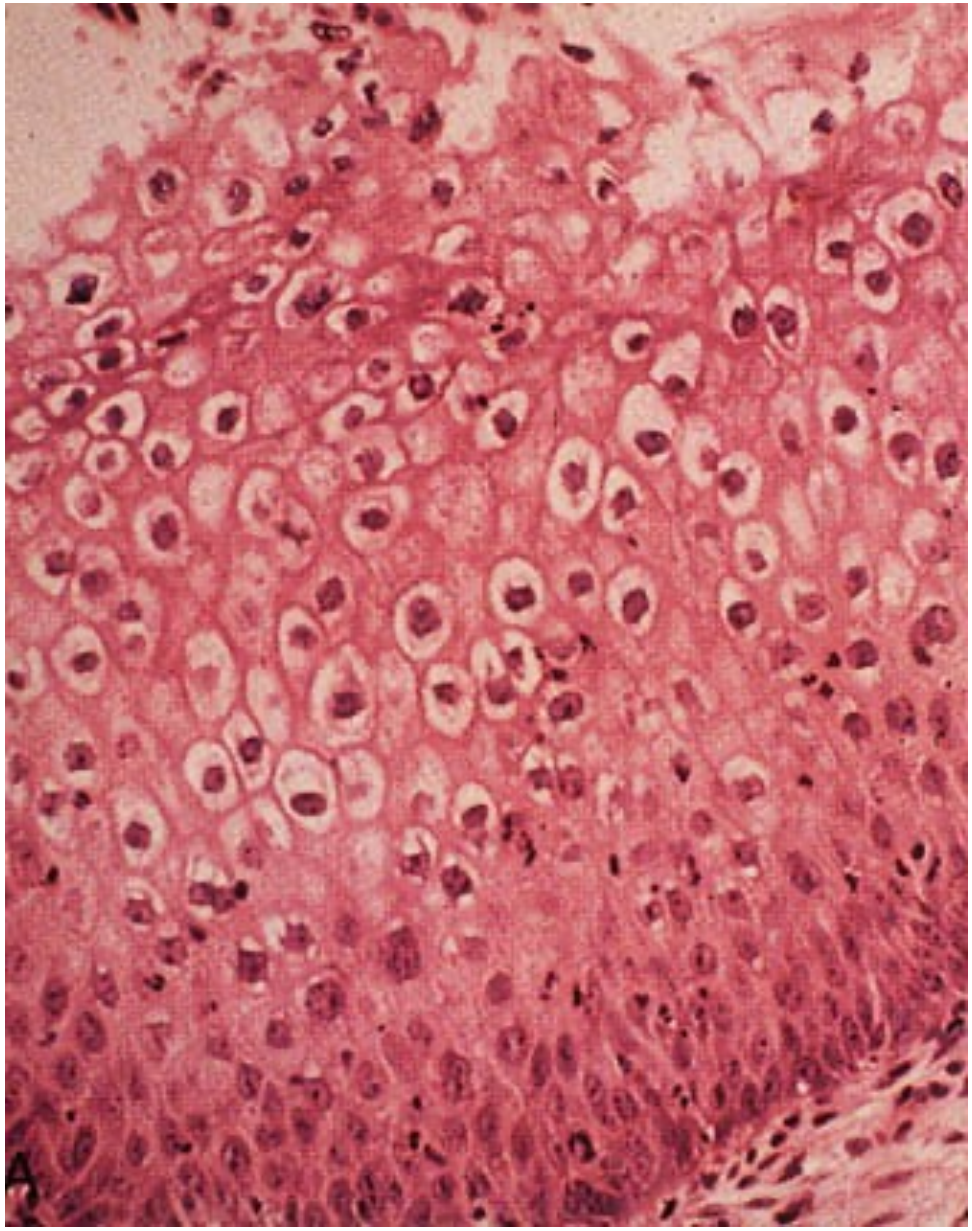
- There are two carcinogenesis pathways.

- **Hyperplasia – Dysplasia - Carcinoma Sequence**

- Adenoma [*dysplasia*] –Carcinoma Sequence

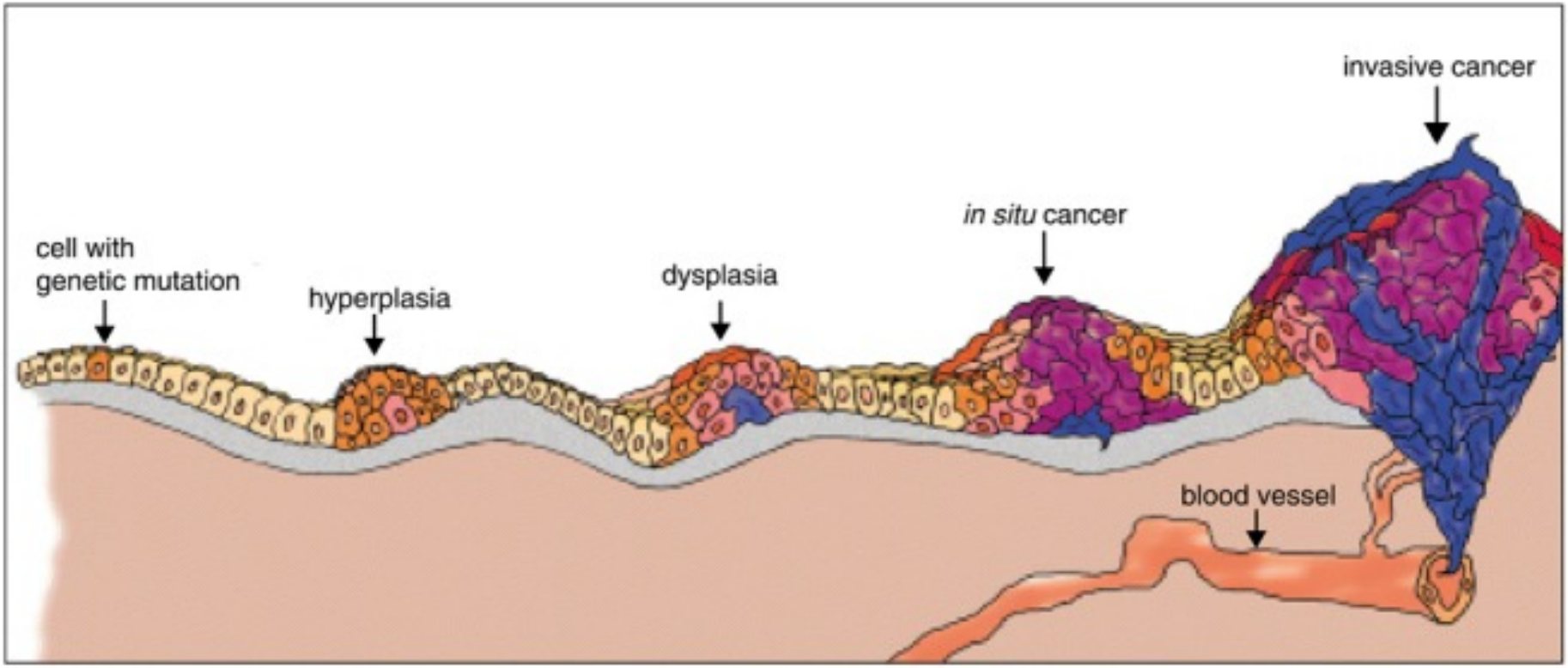
- **Hyperplasia – Dysplasia - Carcinoma Sequence**





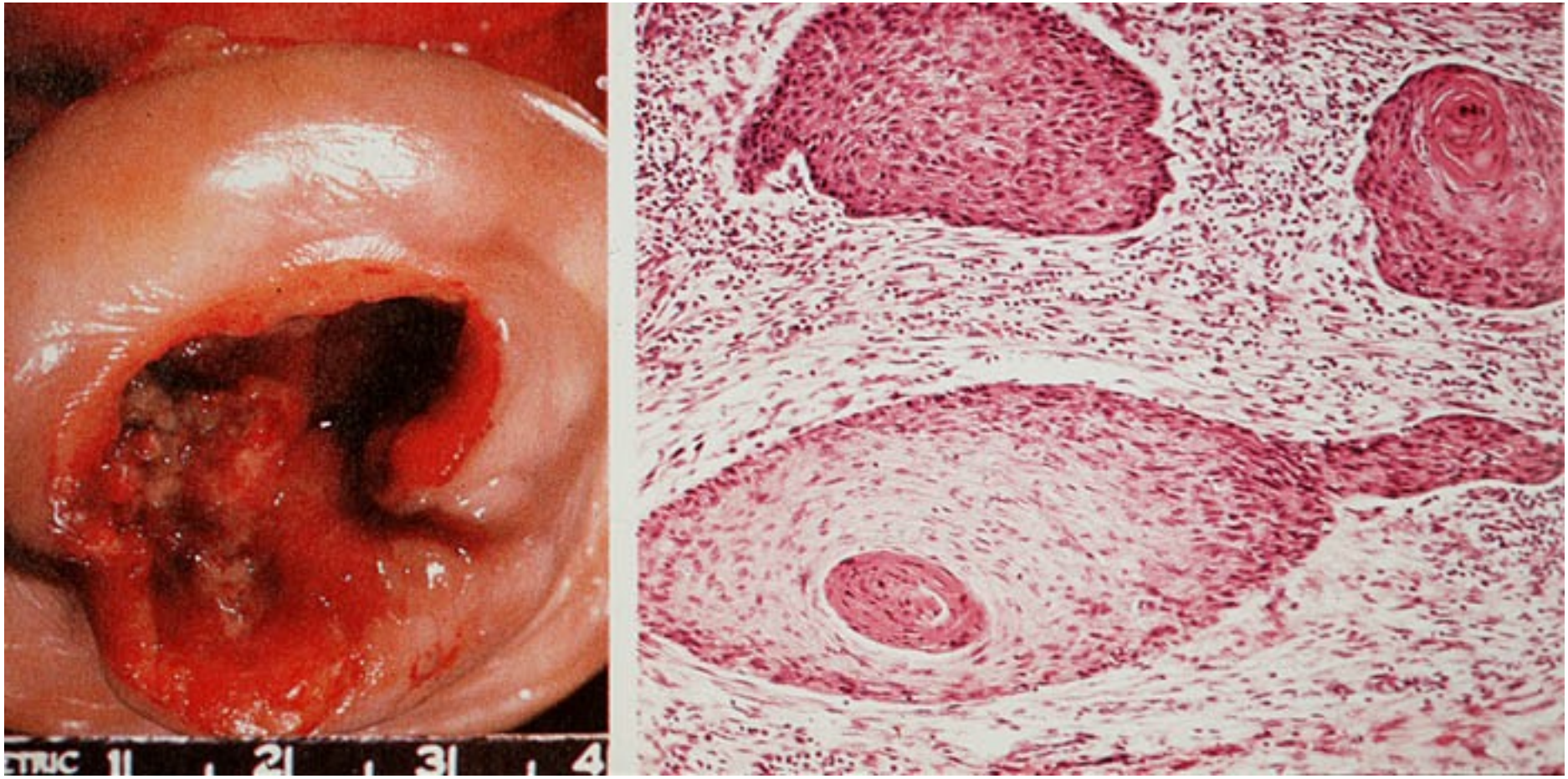
- Cervix with HPV lesion (cancer related : HPV type 16-18-31)

Hyperplasia – Dysplasia – Carcinoma Sequence



- CA in situ : carcinoma in place
- Invasive CA : carcinoma invading beyond basement membrane and can spreading *via* blood and lymphatic vessels

- Hyperplasia – Dysplasia - Carcinoma Sequence



- Squamous cell carcinoma of CERVIX [invasive SQC]

- **Hyperplasia – Dysplasia - Carcinoma Sequence**

Normal **Dysplasia / mild** **moderate** **severe**

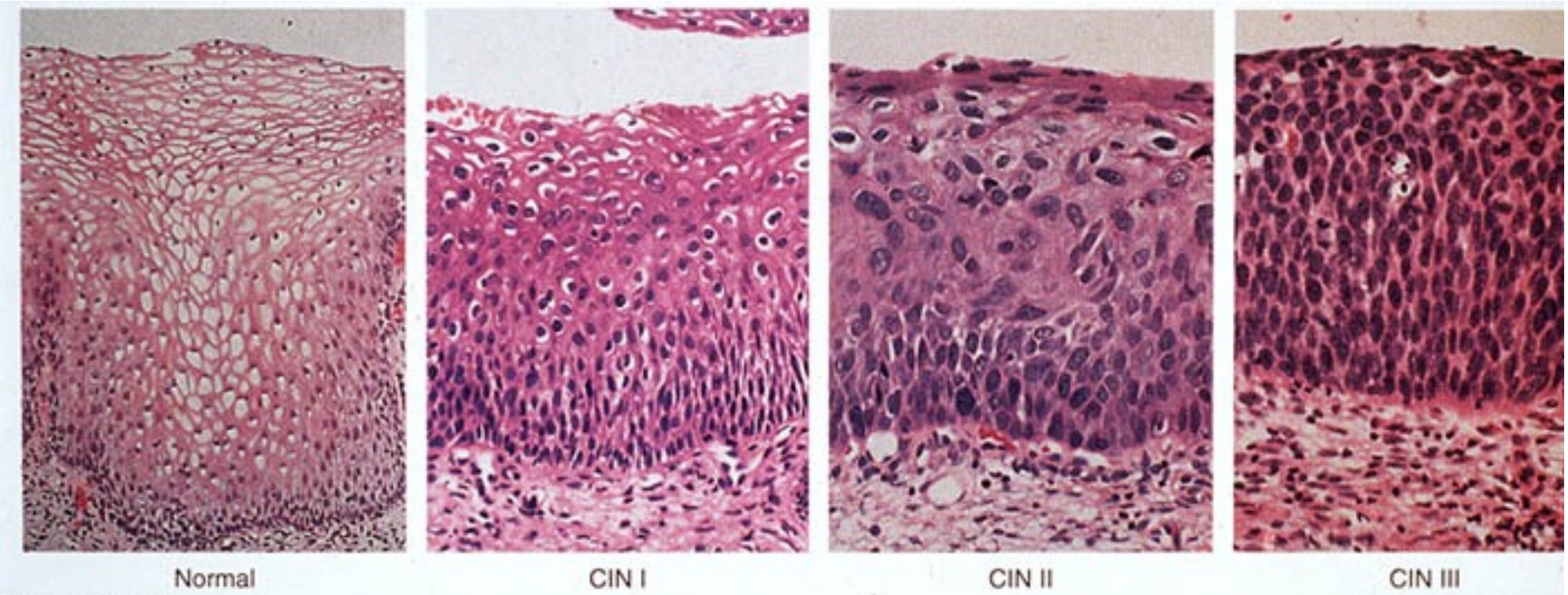


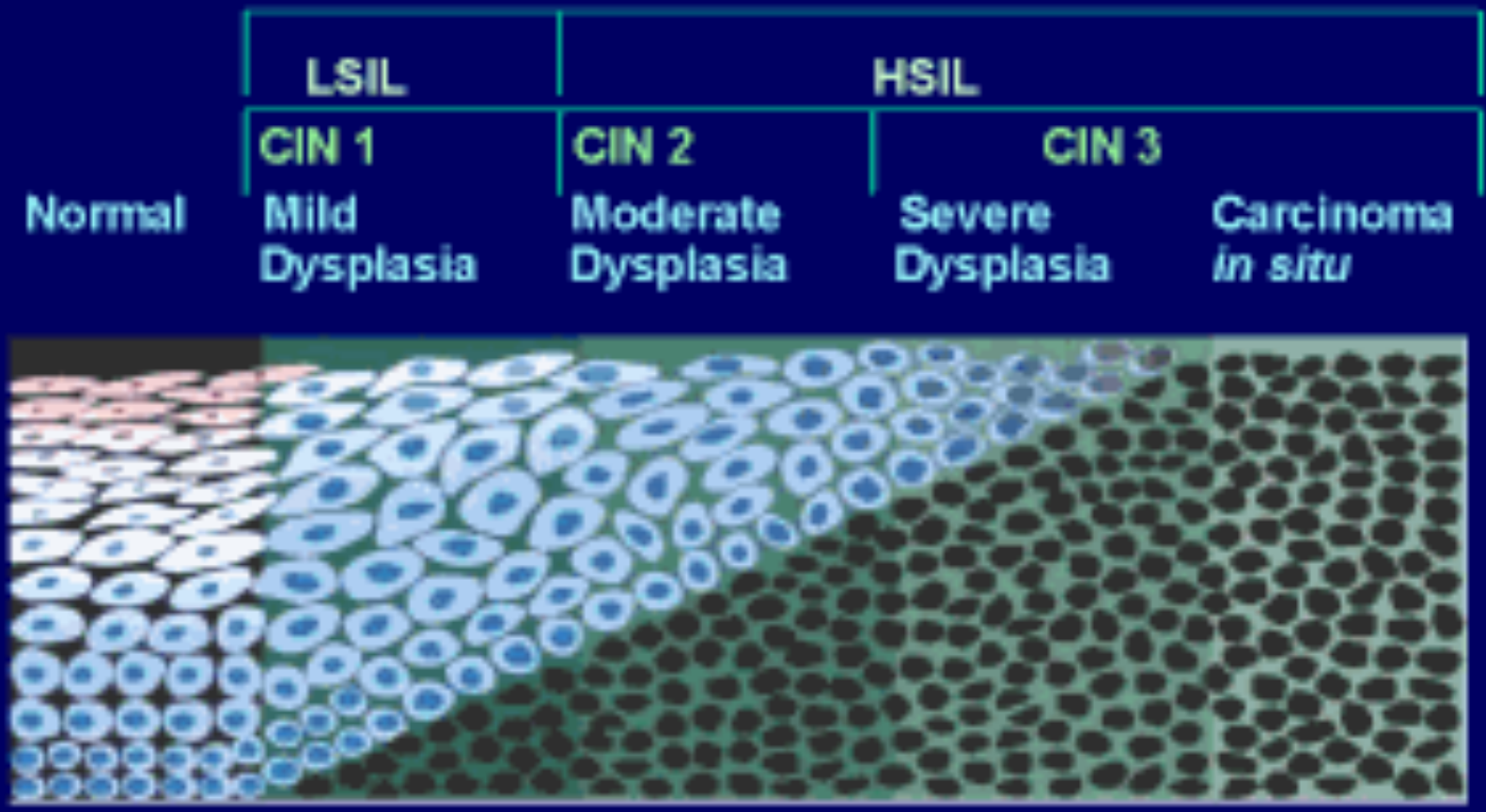
Figure 24–20

- **Cervical intraepithelial neoplasia (CIN)**

Spectrum of cervical intraepithelial neoplasia: normal squamous epithelium for comparison; CIN I with koilocytotic atypia; CIN II with progressive a
in all layers of the epithelium; CIN III, (carcinoma in situ) with diffuse atypia and loss of maturation.

- **Hyperplasia – Dysplasia - Carcinoma Sequence**

Precursor Lesions of Cervical Carcinoma



From Figure 6.13, Dehlay RM. The Art and Science of Cytopathology. CD-ROM. ASCP. 1999.
Wright TC, Kurman RJ, Ferenczy A: Precancerous Lesions of the Cervix. In Kurman RJ, ed: *Blaustein's Pathology of the Female Genital Tract*. 4th ed. New York: Springer-Verlag NY Inc, 1994.

LSIL = Low Grade Squamous Intraepithelial Lesion CIN = Cervical Intraepithelial Neoplasia
HSIL = High Grade Squamous Intraepithelial Lesion

- **Hyperplasia – Dysplasia - Carcinoma Sequence**

Natural History of CIN

	Regress	Persist	Progression to CIN 3	Invasion
CIN 1	57%	32%	11%	1%
CIN 2	43%	35%	22%	5%
CIN 3	32%	<56%		>12%

Table 7 (Modified) from Östör AG: Natural history of cervical intraepithelial neoplasia: A critical review Int. J Gynecol. Pathol. 12:186-92, 1993. (Literature Review)

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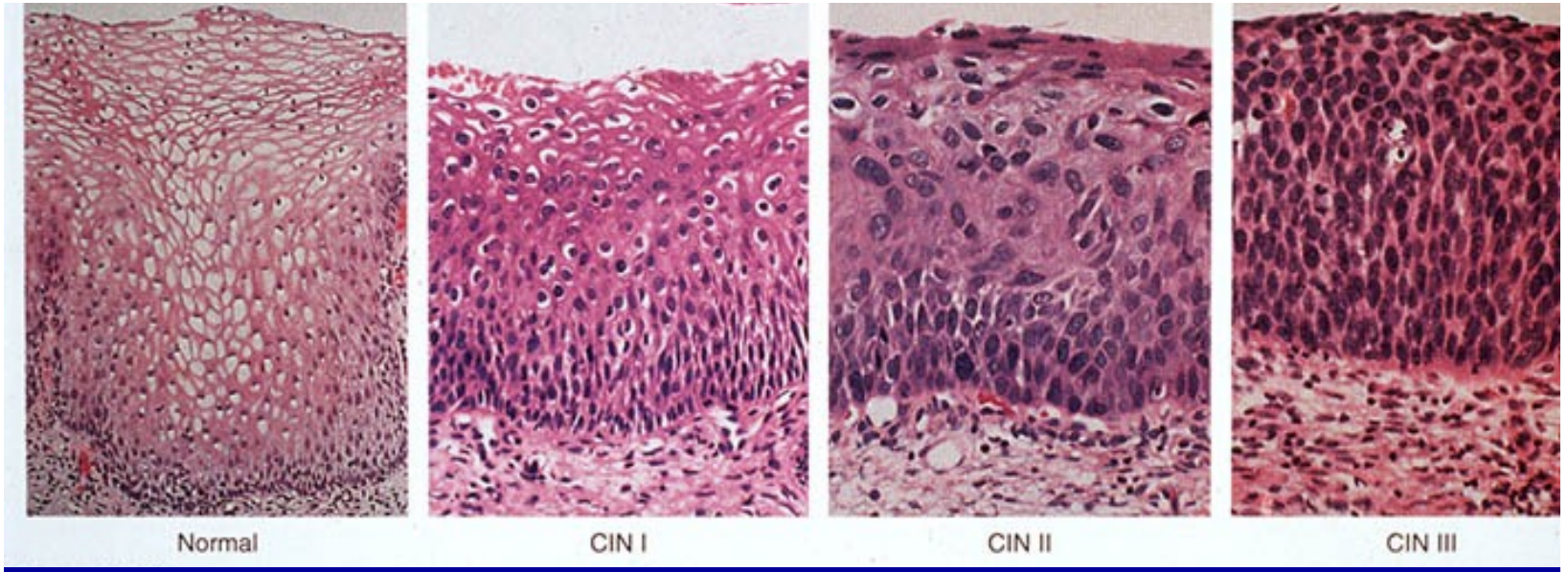
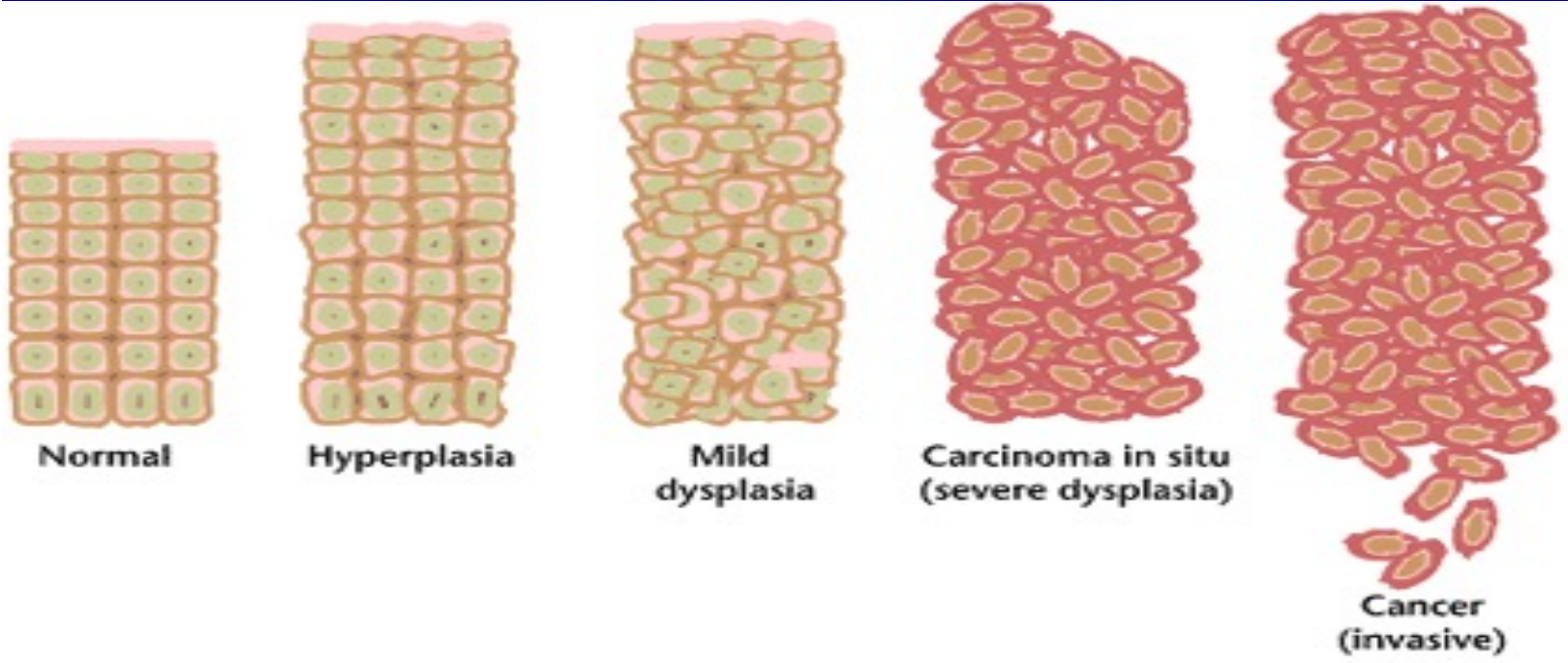
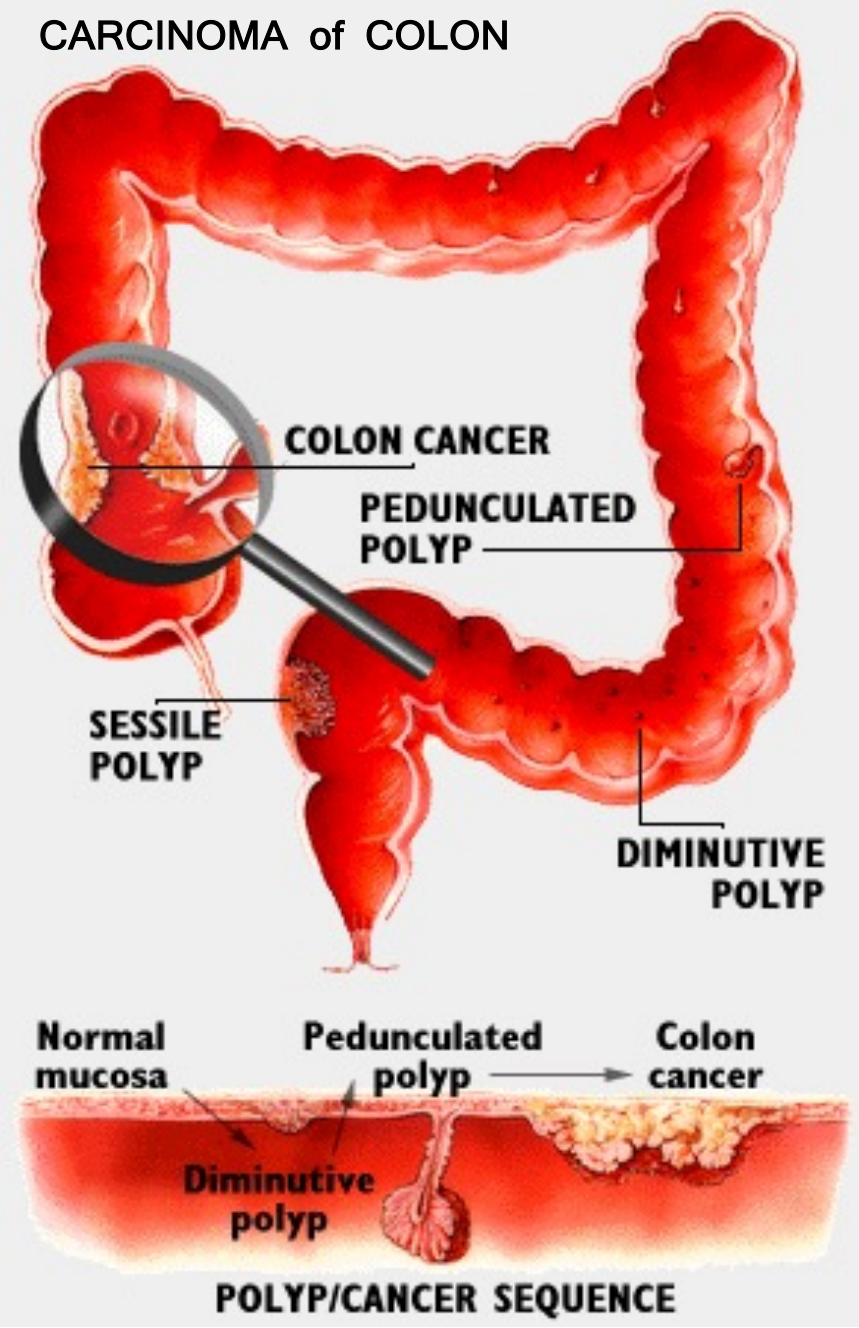
CIN / Cervical Intra -epithelial Neoplasia



Hyperplasia – Dysplasia - Carcinoma Sequence



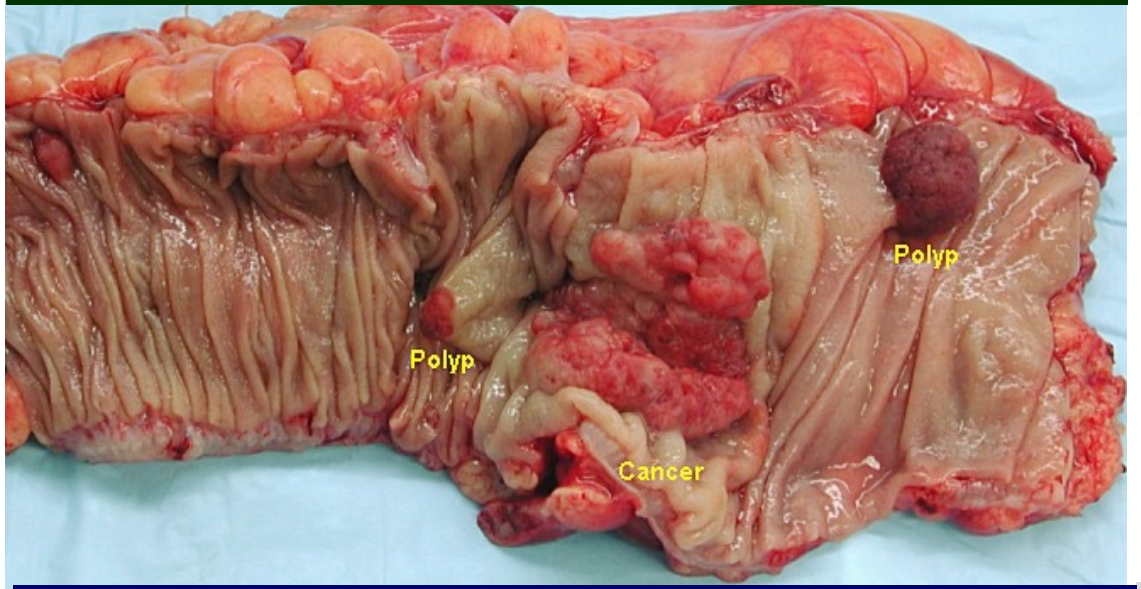
- Adenoma - Carcinoma Sequence



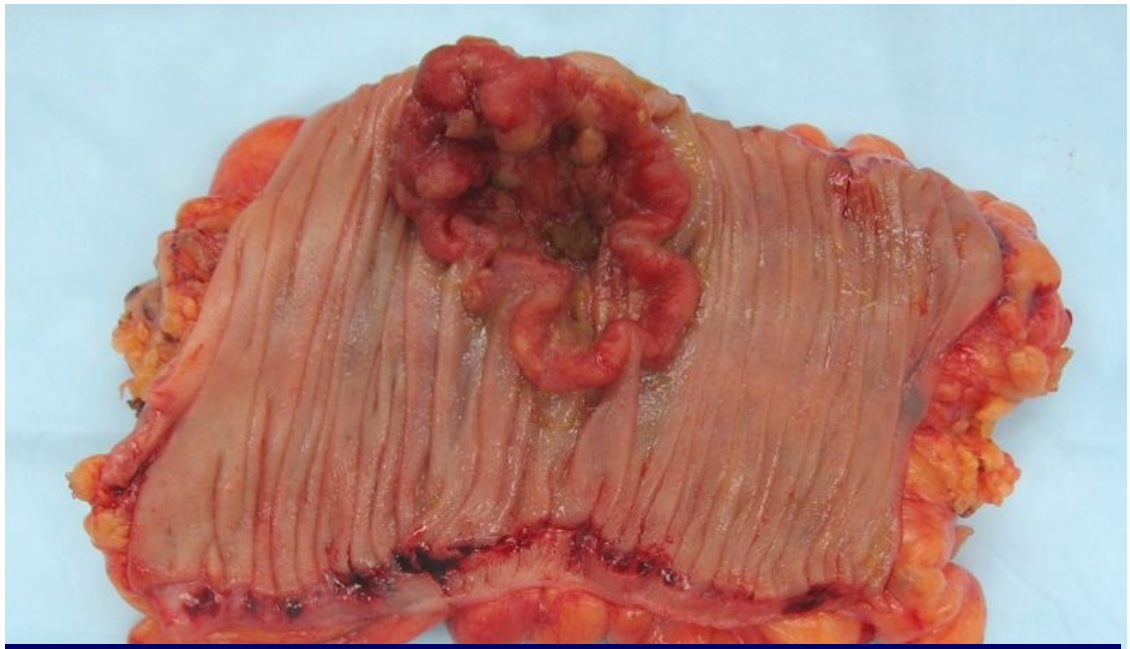
Adenoma - Carcinoma Sequence :

Malignant tumor arising from a prior benign tumor

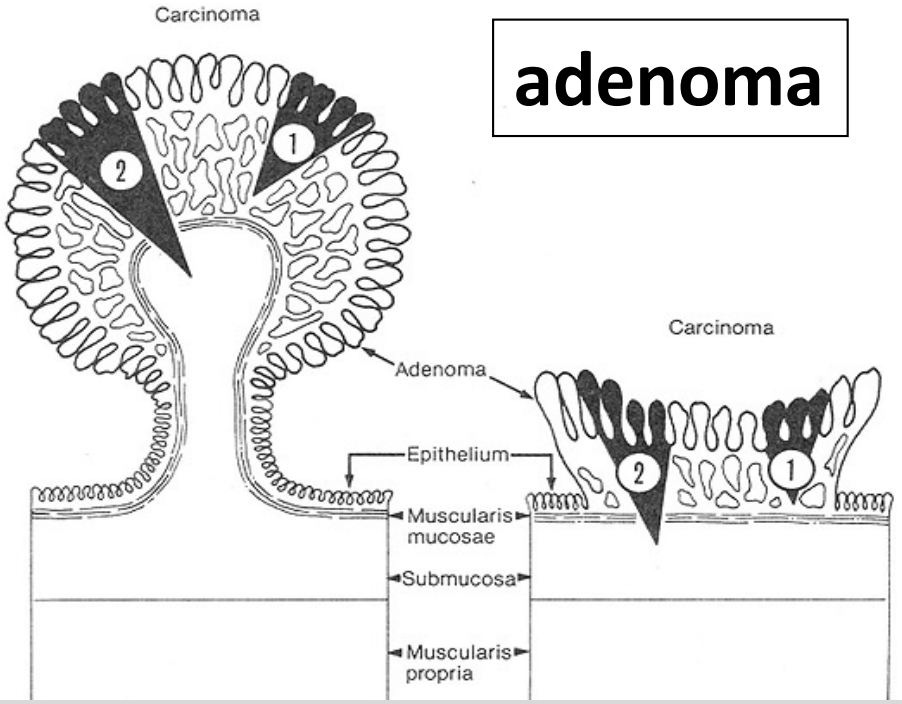
Adenoma - carcinoma sequence



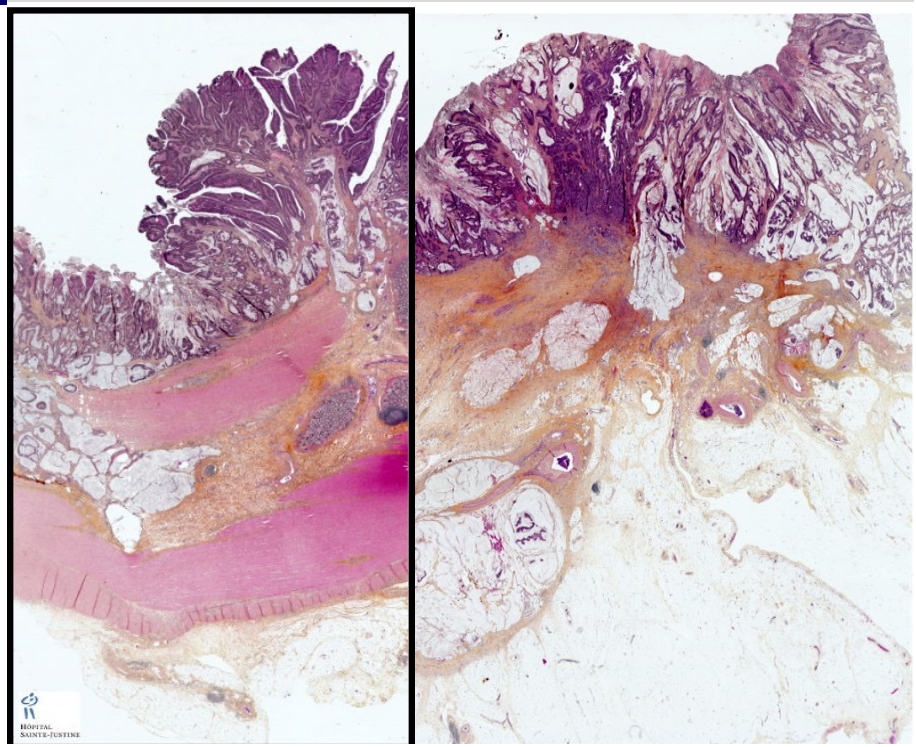
Adenocarcinoma from pedunculated polyps



Adenocarcinoma from sessile polyps



Pedunculated polyps Sessile polyps

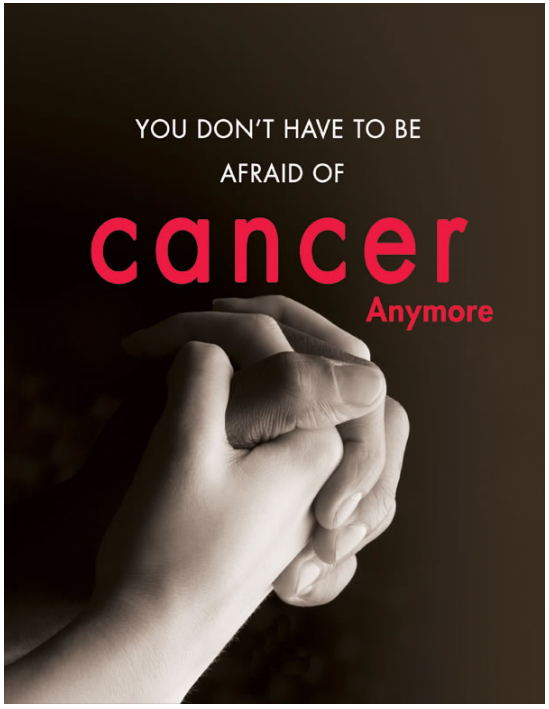


- Cancer prevention is detected precancerous lesions .

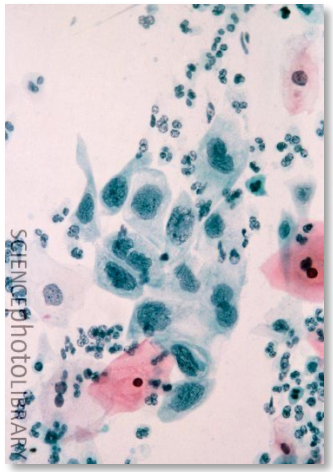
[PRECURSOR LESIONS IN CARCINOMA]

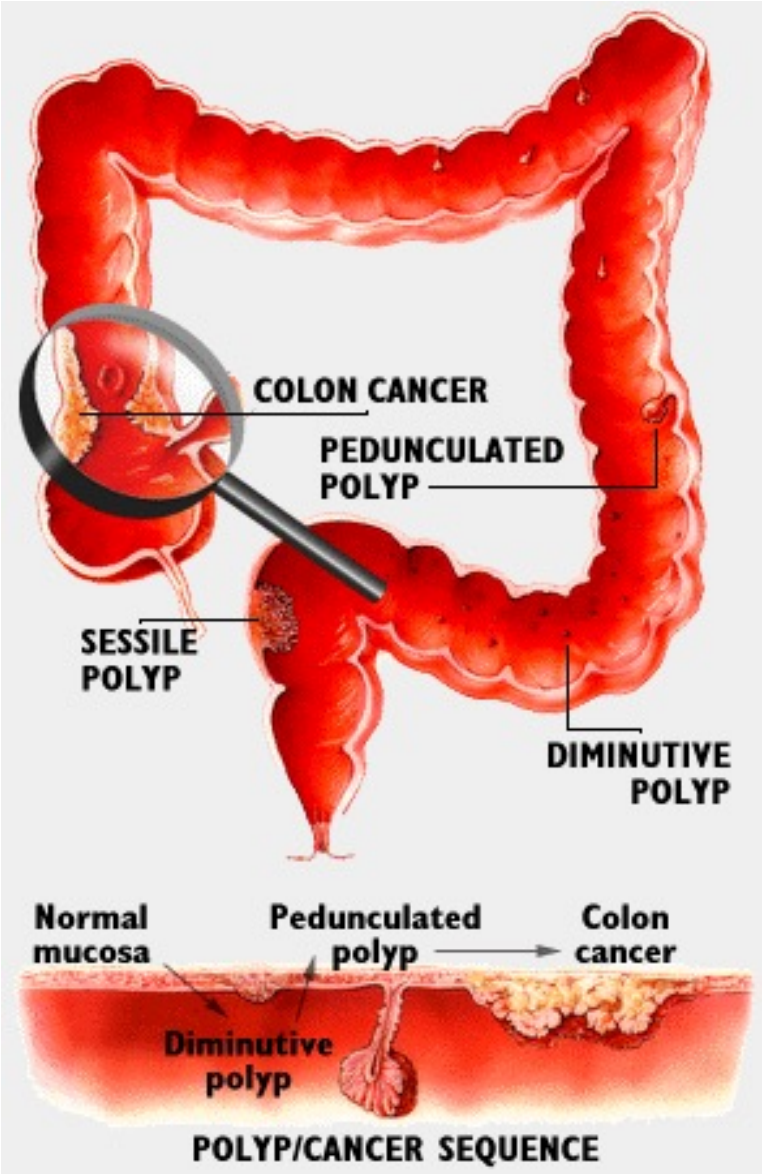
Hyperplasia – Dysplasia - Carcinoma Sequence

Adenoma - Carcinoma Sequence



There is a golden period for cancer detection.

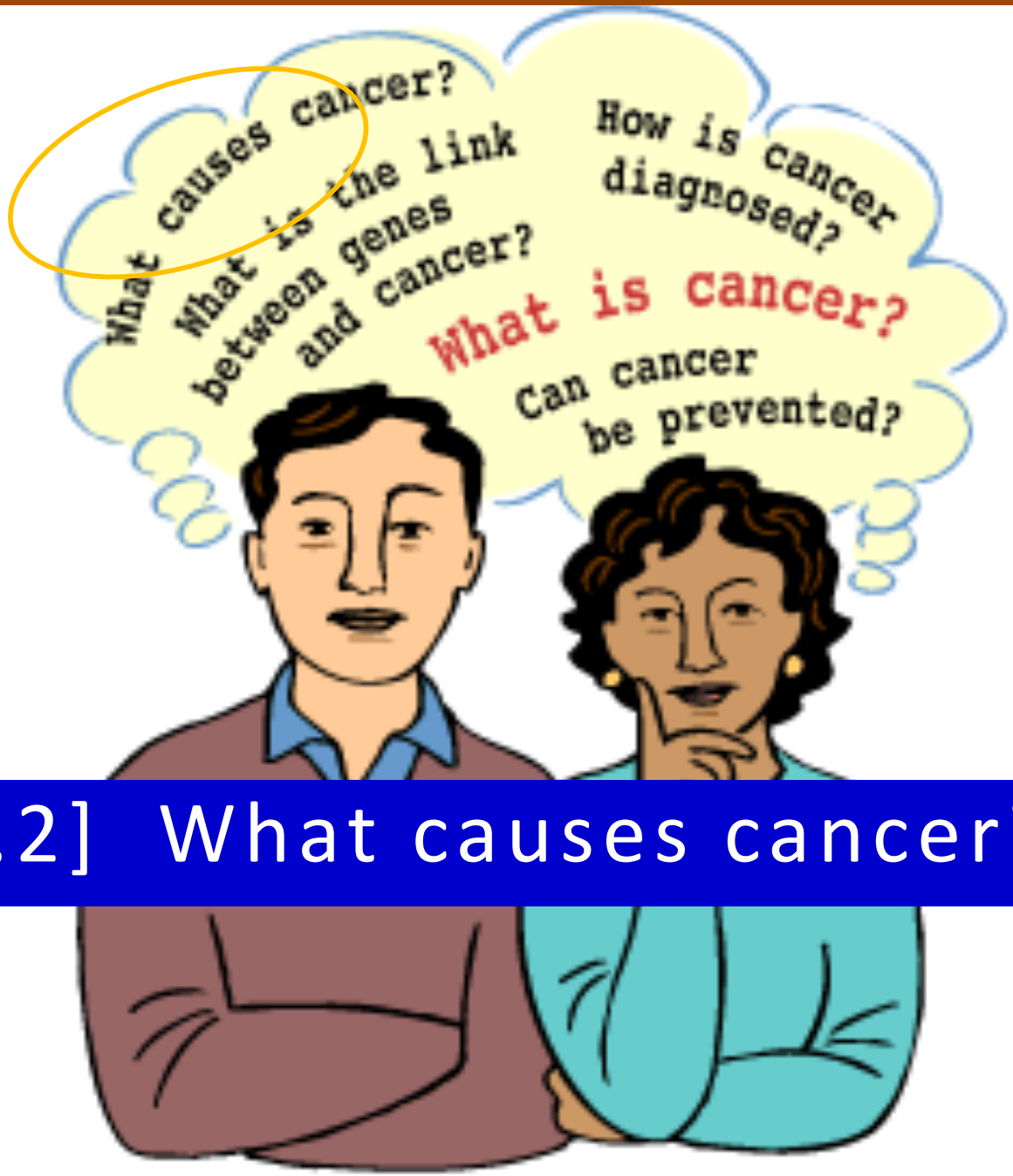




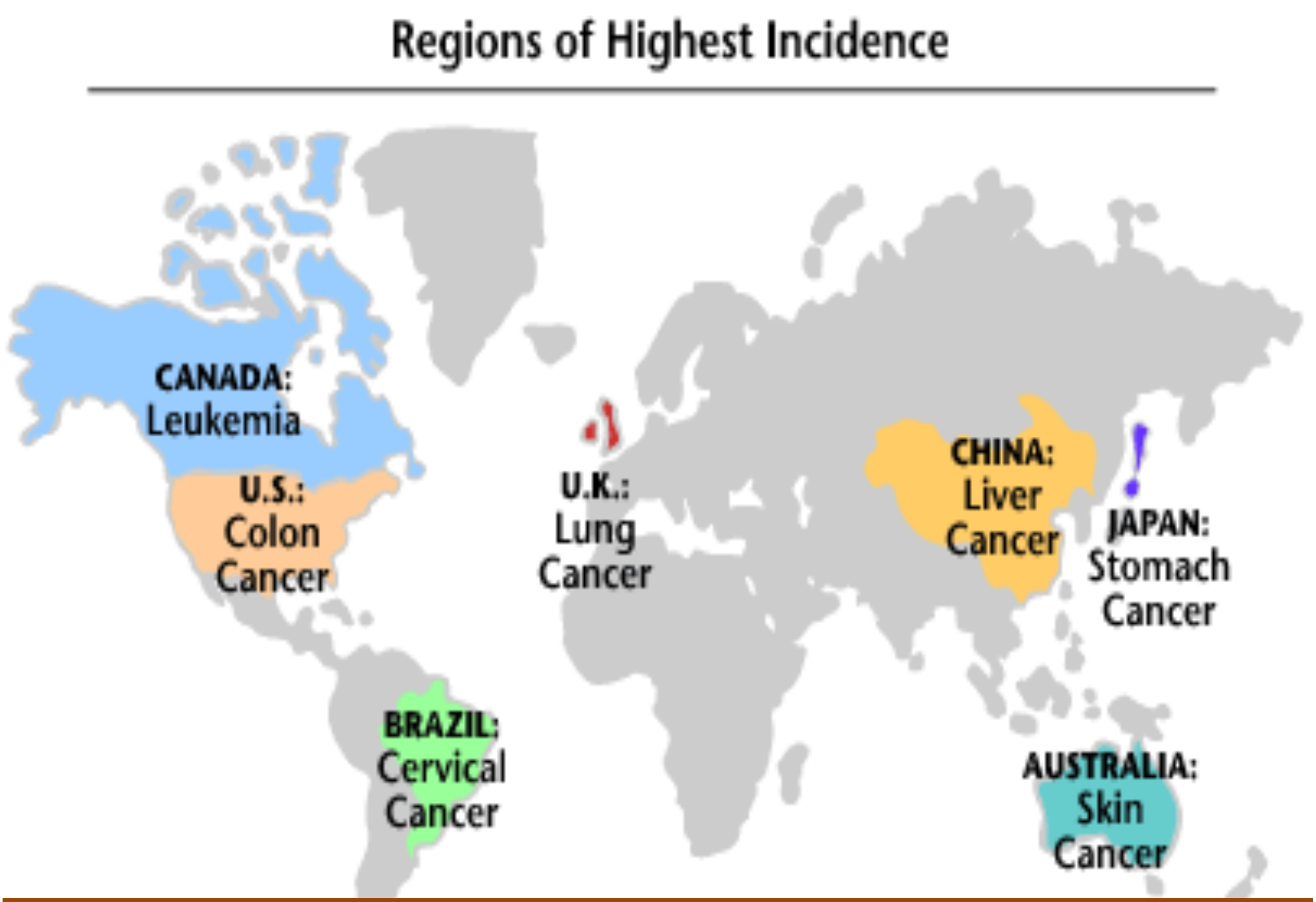
Cervix : detect dysplasia by Pap smear

Colon : detect adenoma by endoscope

Neoplasm II : *Learning objectives*



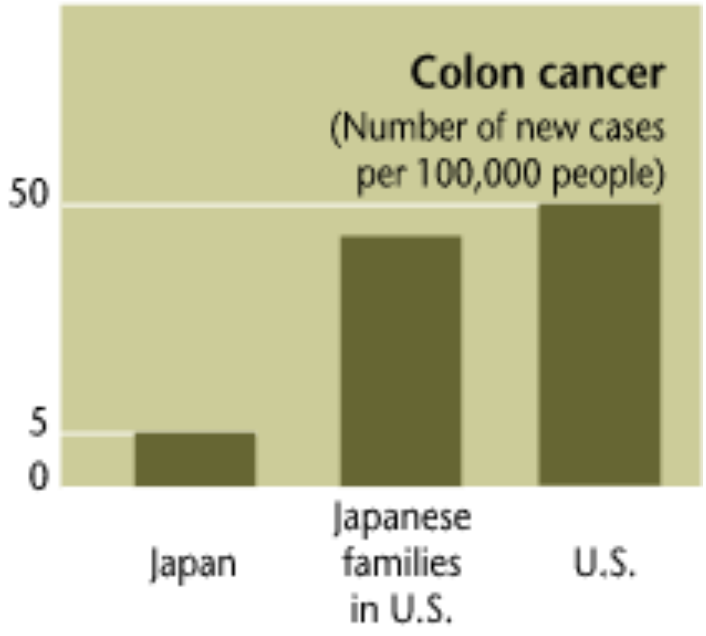
- 2.2] What causes cancer?

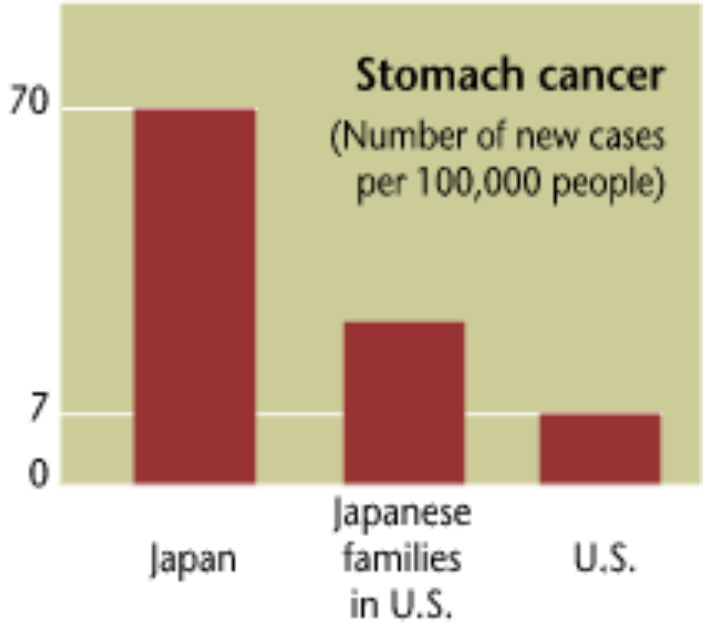


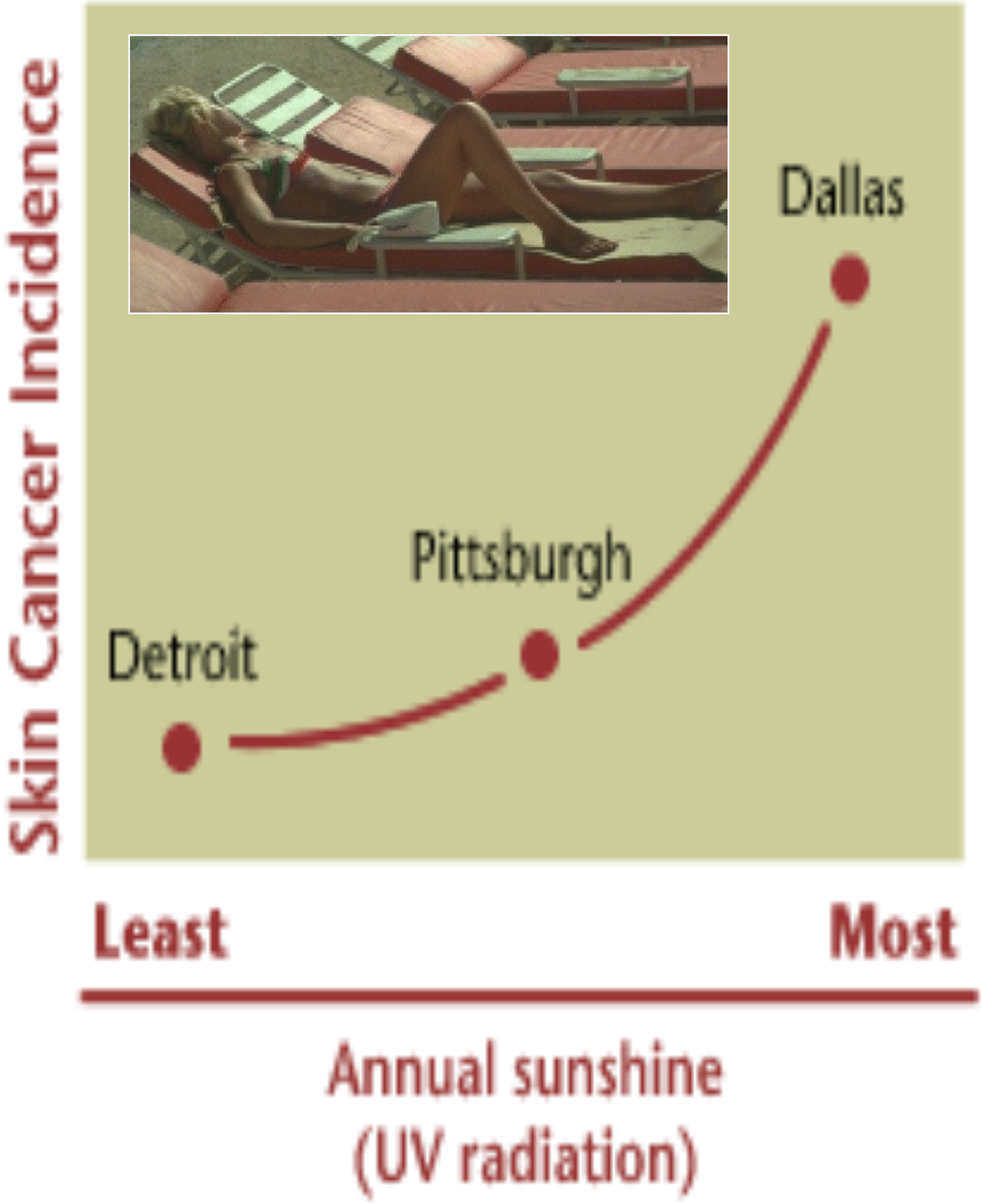
Geographical cancer incidence variation

Carcinogen : *Any substance that causes cancer.*

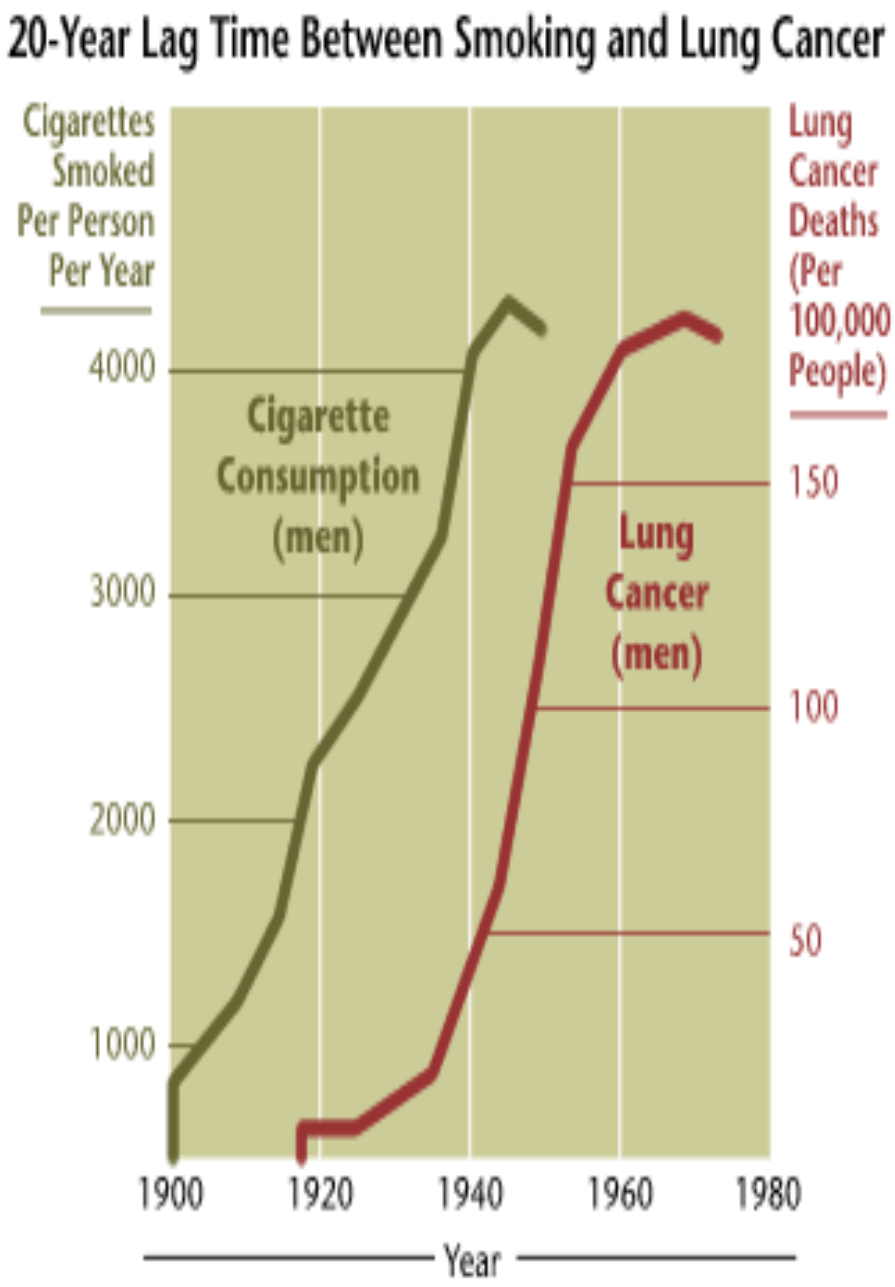
Cancer cause : hereditary or environmental factors





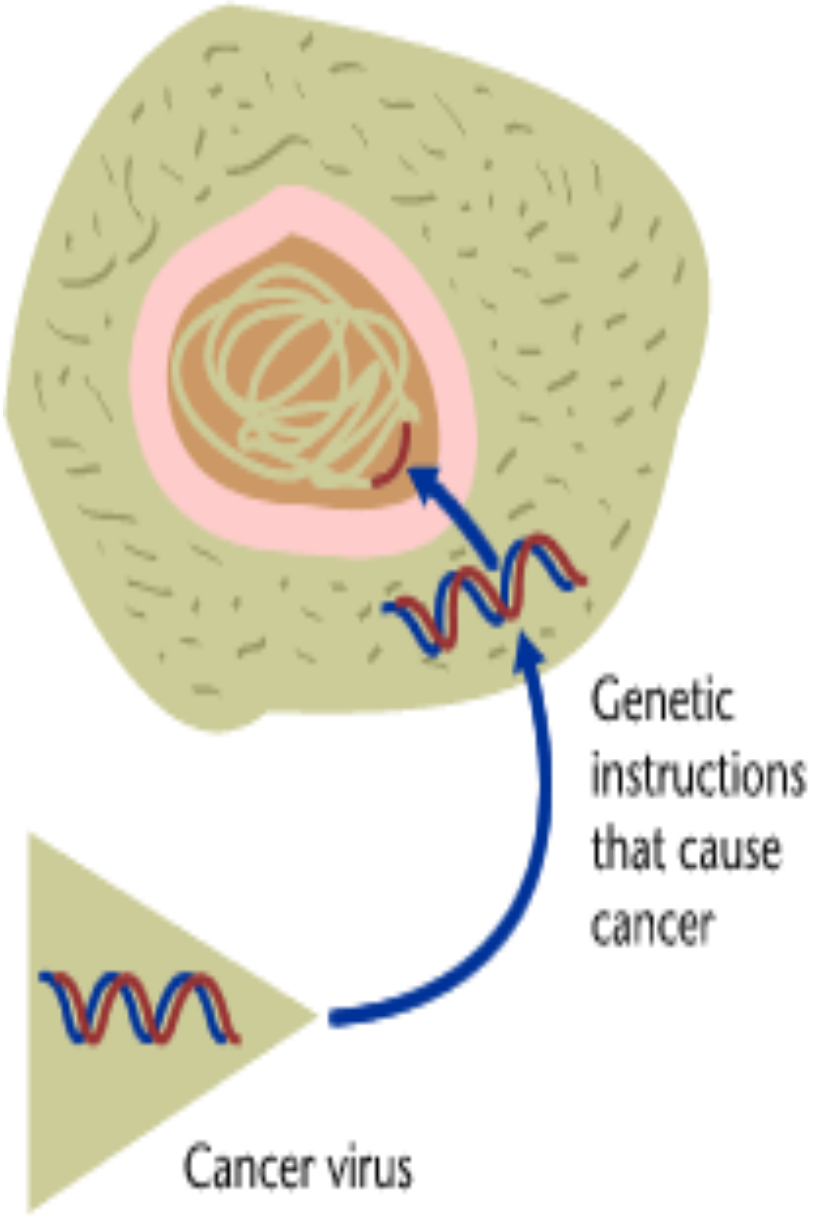


Epidemiology : *identified environmental risk factors*

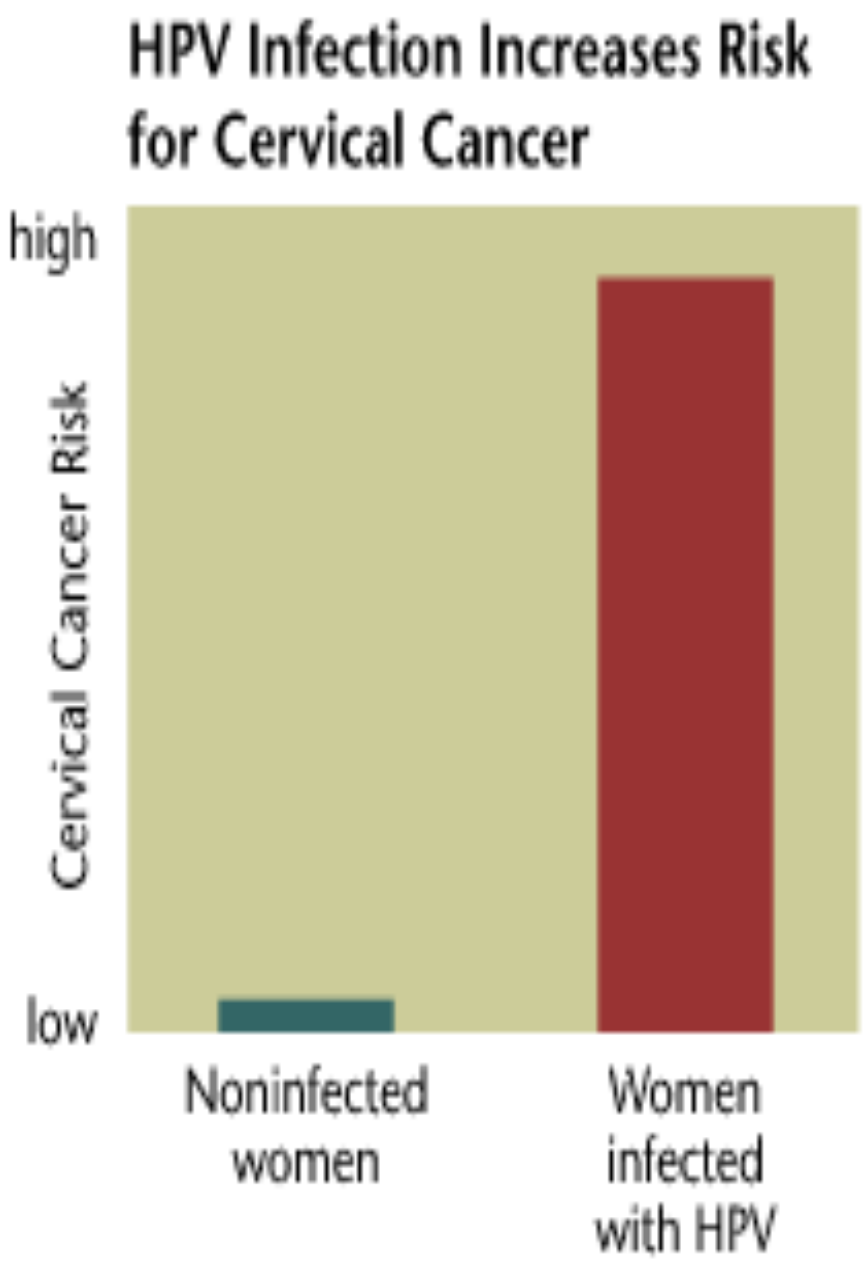


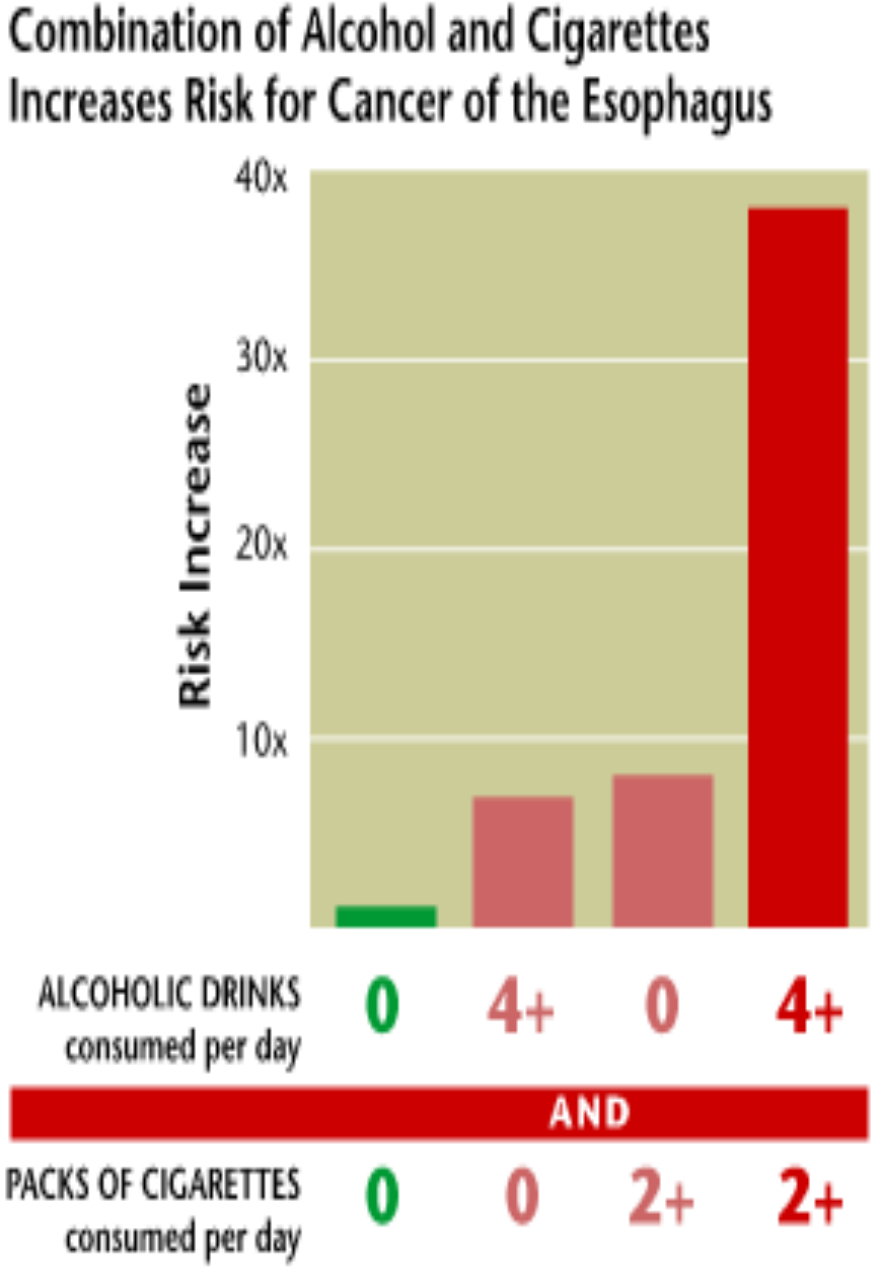
- 10 % of all cancers

Some Viruses Associated With Human Cancers	
VIRUS	**TYPE of CANCER**
Epstein-Barr virus	Burkitt's lymphoma
Human papillomavirus	Cervical cancer
Hepatitis B virus	Liver cancer
Human T-cell lymphotrophic virus	Adult T-cell leukemia
Kaposi's sarcoma-associated herpesvirus	Kaposi's sarcoma

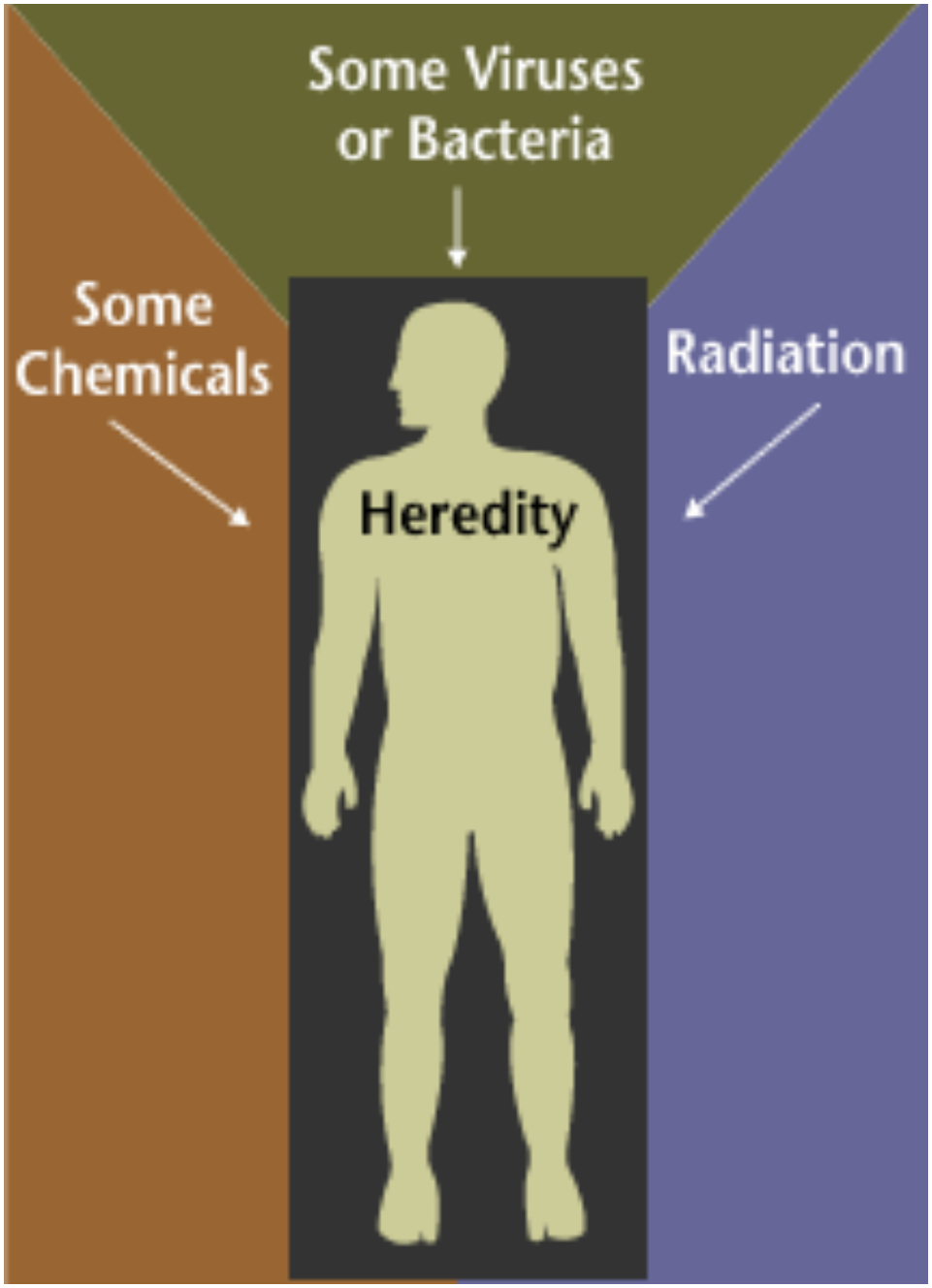


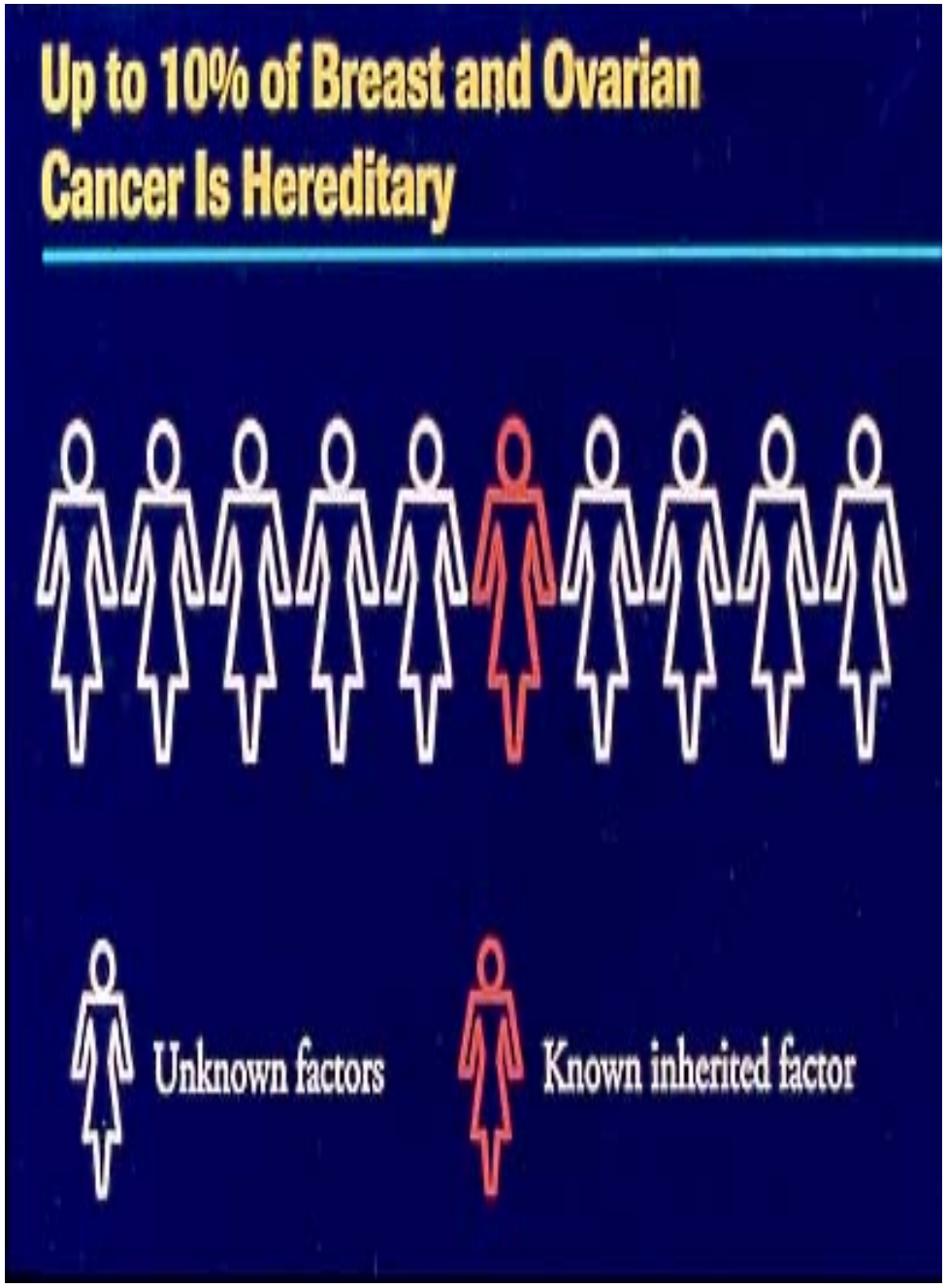
• Identified risk factors





- Cancer cause : hereditary or environmental factors



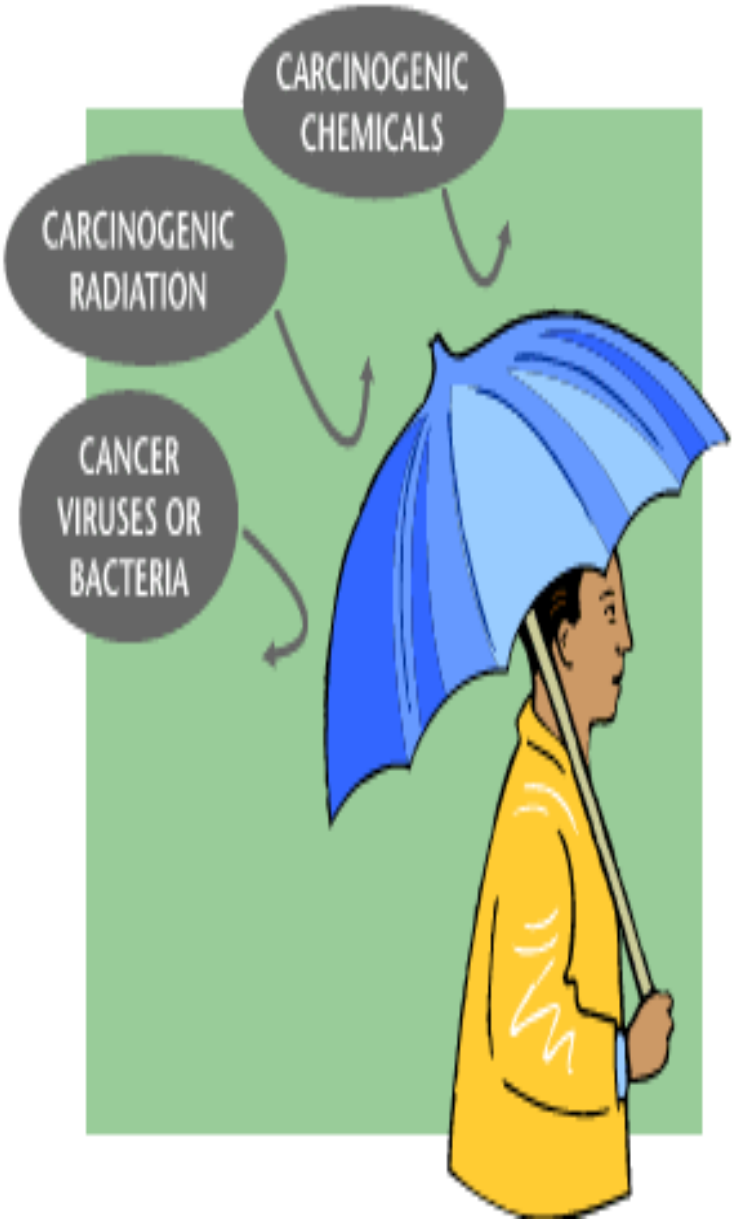


Cancer cause : Lifestyle factors are strongest risk factors

Lifestyle Factors	Percent
Diet	35%
Tobacco use *(mainly inhaled cigarette smoke)*	30%
Reproductive and sexual behavior	7%
Alcohol consumption	3%

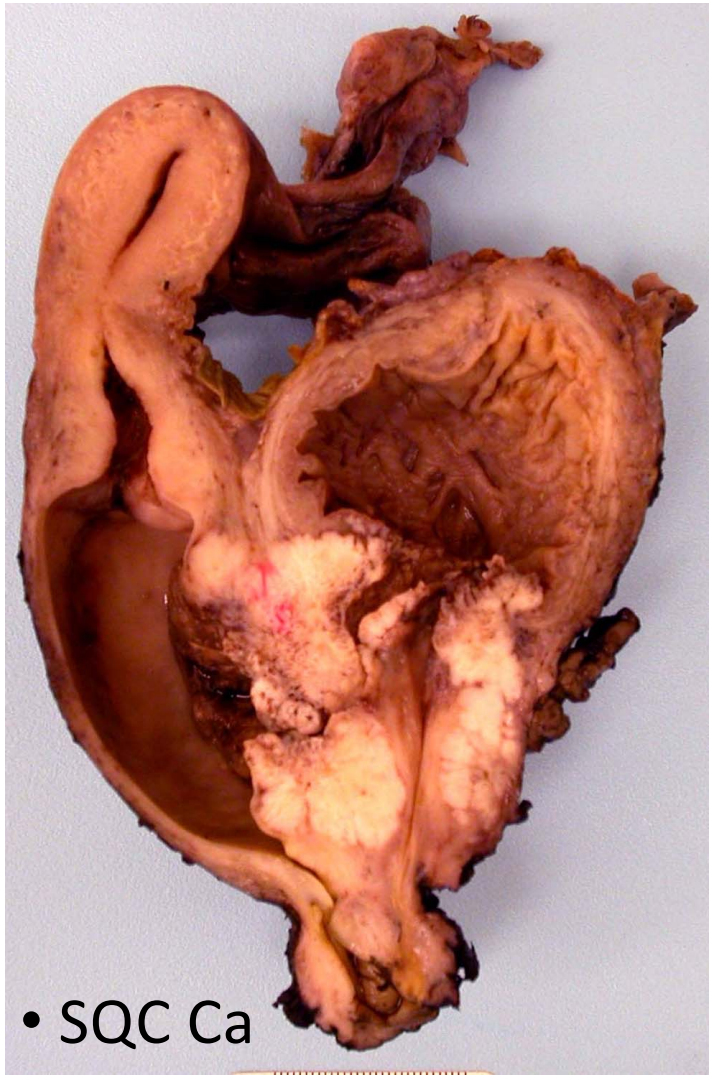
Other Factors	Percent
Infections	10%
Occupational exposures	4%
Geophysical factors *(including UV; ionizing radiation)*	3%
Pollution	2%
Iatrogenic *(drugs and medical procedures)*	1%
Food additives	< 1%
Industrial products	< 1%
Other	3%

- **Cancer is a preventable disease !!!**



2.3] Genetics basis in carcinogenesis

• Man speculation cause of cancer…



• SQC Ca

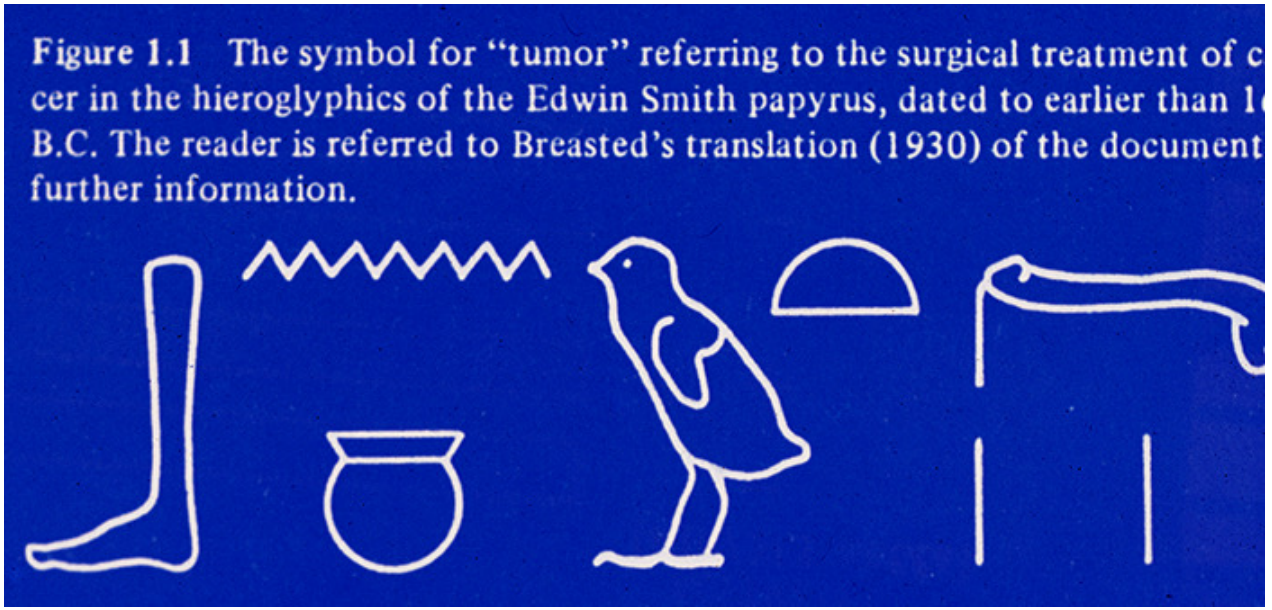
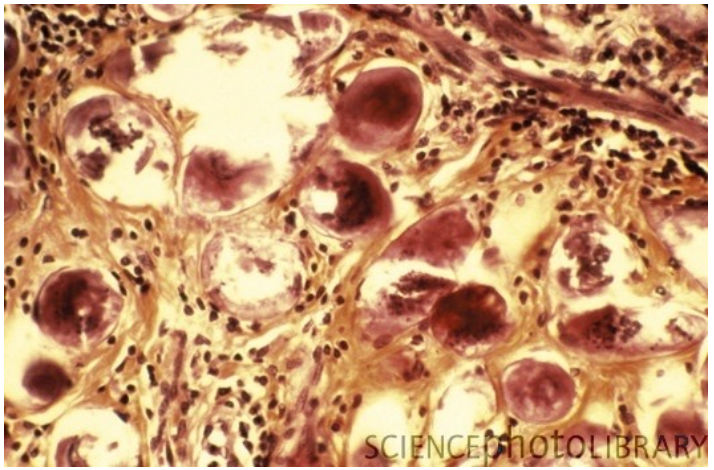


Figure 1.1 The symbol for "tumor" referring to the surgical treatment of c
cer in the hieroglyphics of the Edwin Smith papyrus, dated to earlier than 1
B.C. The reader is referred to Breasted's translation (1930) of the document
further information.

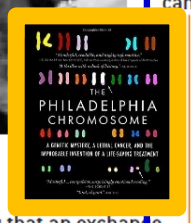


BRANCHING POINTS IN THE EVOLUTION OF CANCER THEORY

1914 Boveri suggests that aberrant chromosomes may cause cancer

1927 Hermann J. Muller observes that radiation mutates cells

1951 Muller proposes theory that multiple mutations turn a cell malignant



1960 Discovery that an exchange of DNA between chromosomes 9 and 22 leads to chronic myelogenous leukemia

1971 Alfred G. Knudson explains different rates of inherited and spontaneous retinal cancer with the hypothesis that two "hits," or damaging mutations, are needed to disable both alleles of the *RB* gene and that one mutation can be inherited

1974 Loeb argues that random mutations must accumulate much faster than is normal inside cells that become malignant

1990 Vogelstein and Eric R. Fearon publish a model of sequential gene mutations that lead to colon cancer

1986 Weinberg and colleagues isolate *RB*, the first tumor suppressor gene

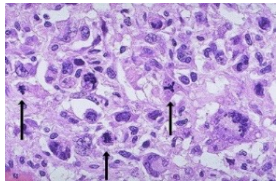
1997 Lengauer, Vogelstein and co-workers demonstrate dramatic increase in gain and loss of chromosomes in colon tumor cells and propose that chromosomal instability is a critical early event that leads to the mutation of oncogenes and tumor suppressor genes

2002 Reid identifies recurrent patterns of aneuploidy in human cervical and colon cancers

2003 The number of identified cancer genes, now well over 100, continues to grow rapidly

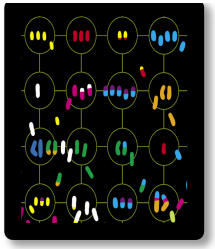
1999 Duesberg and collaborators publish detailed theory of how aneuploidy may be sufficient to cause cancer itself, even without mutations to any particular set of genes

1915 1920 1925 1930 1935 1940 1945 1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000

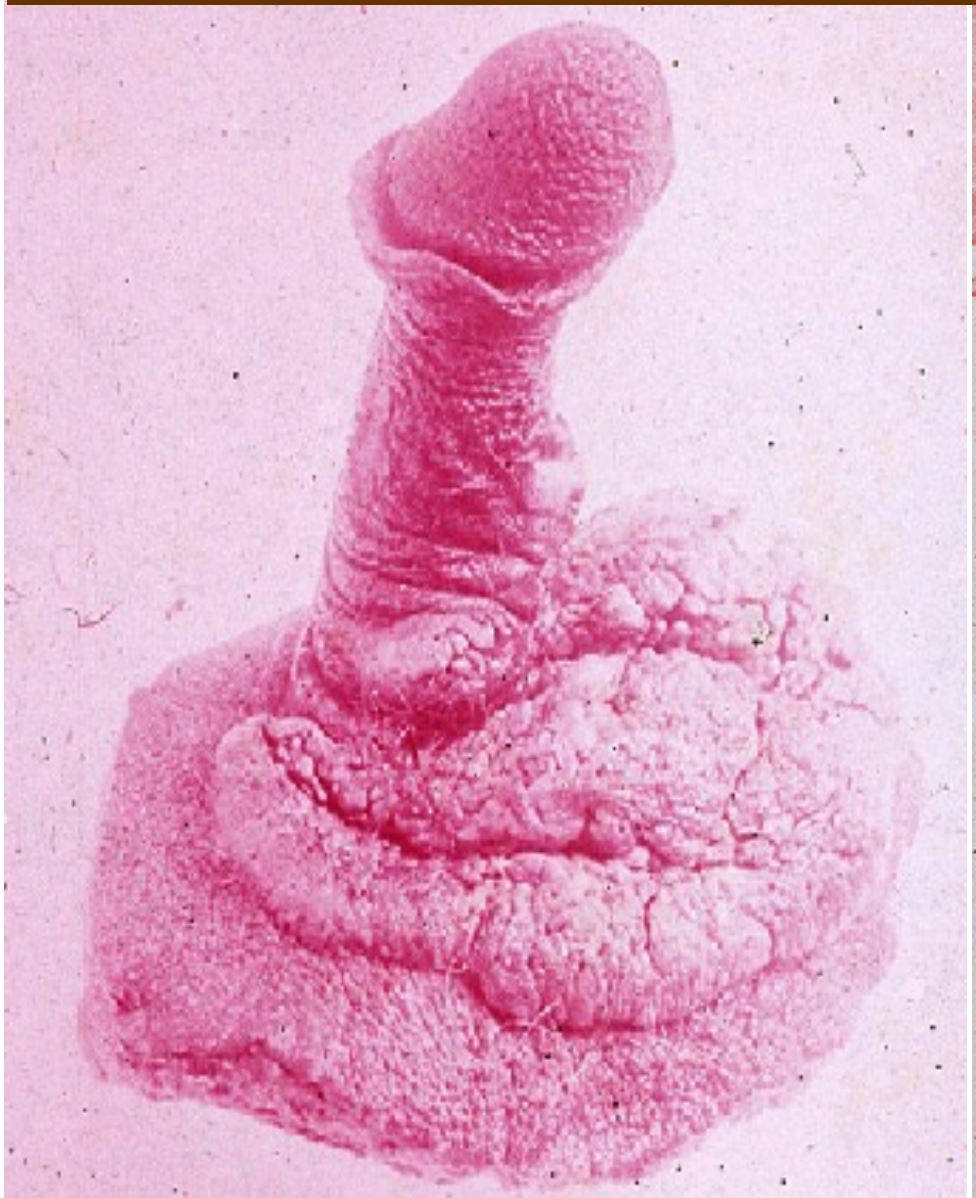


An important difference

It takes (at least) two to tango

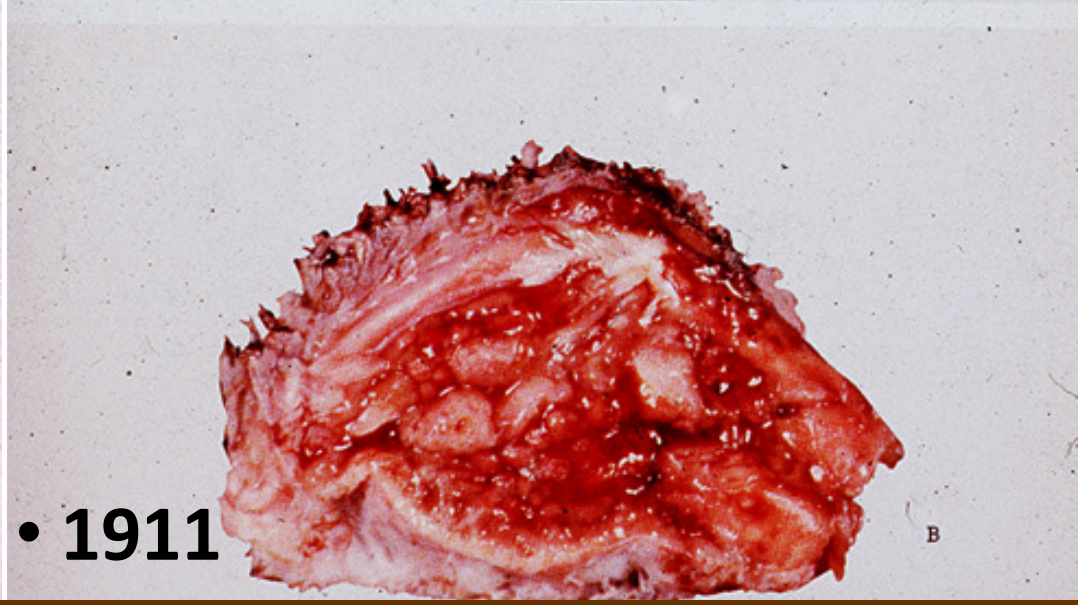


• Cancer etiology : chemical or viral infection ?



• 1775

Tar / skin cancer (Sir P. Pott)

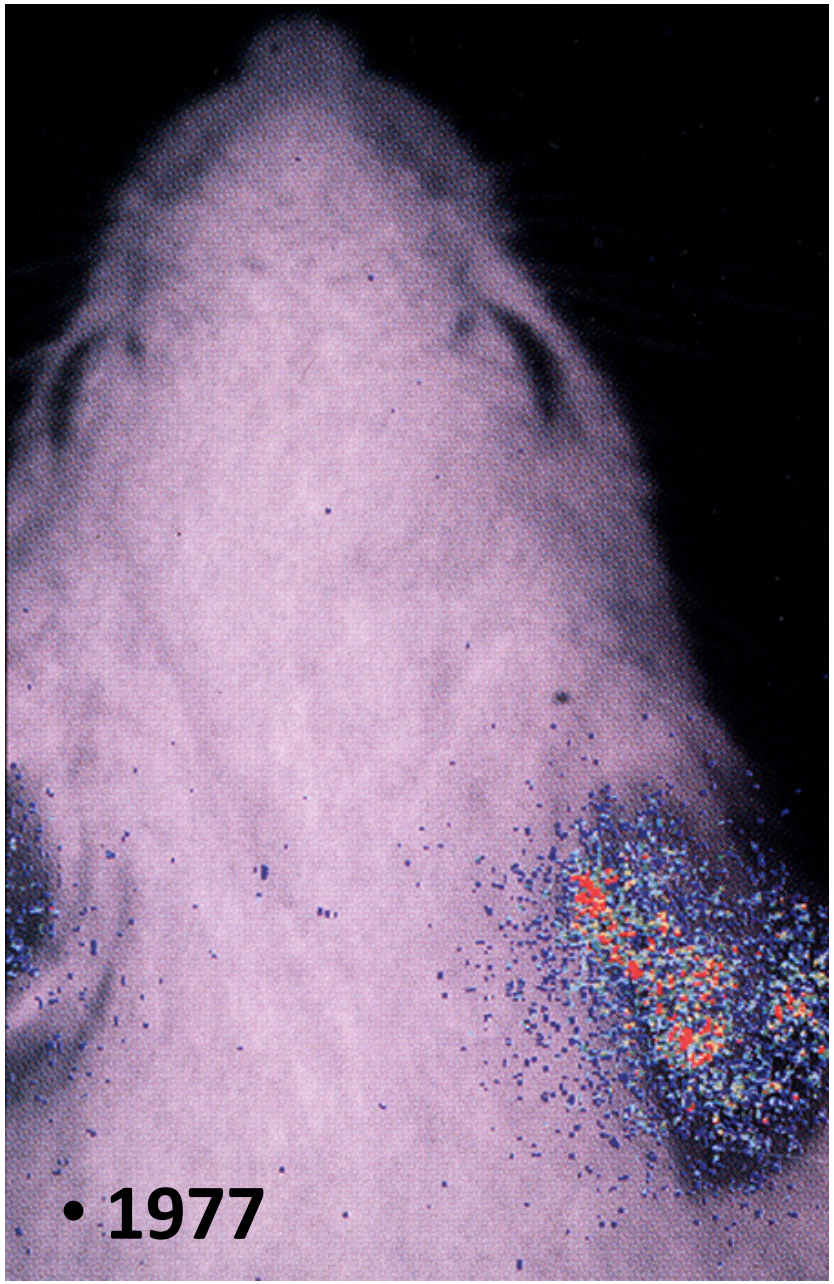


• 1911

Chick / Sarcoma (P. Rouse)

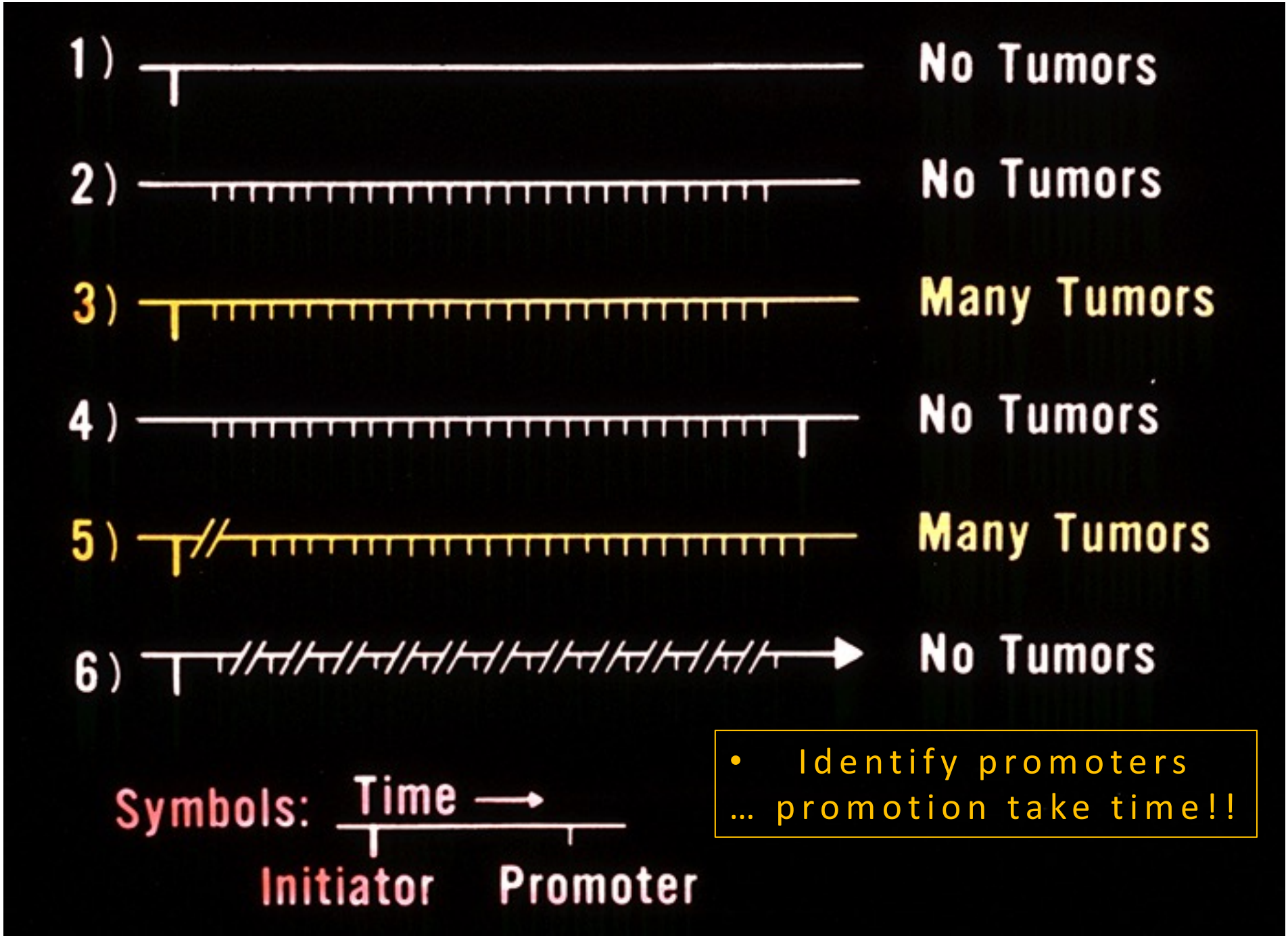
- First study of chemical caused cancer

Dr Katsusaburo Yamagiwa



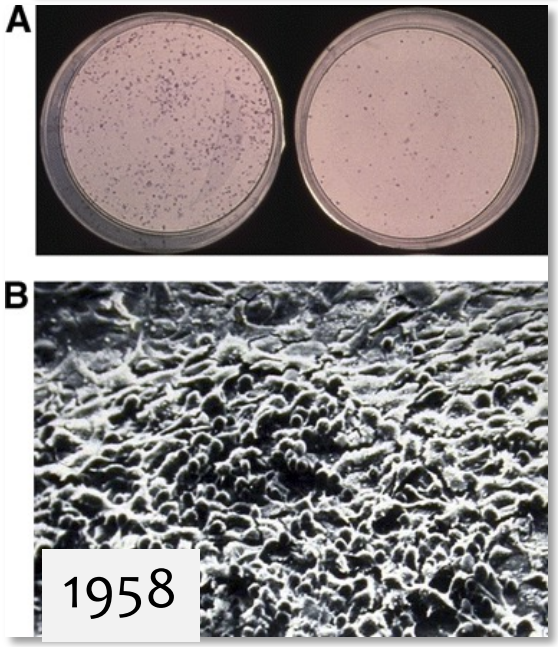
- 1977

- 1977-Two-stage carcinogenesis models / @ promoter



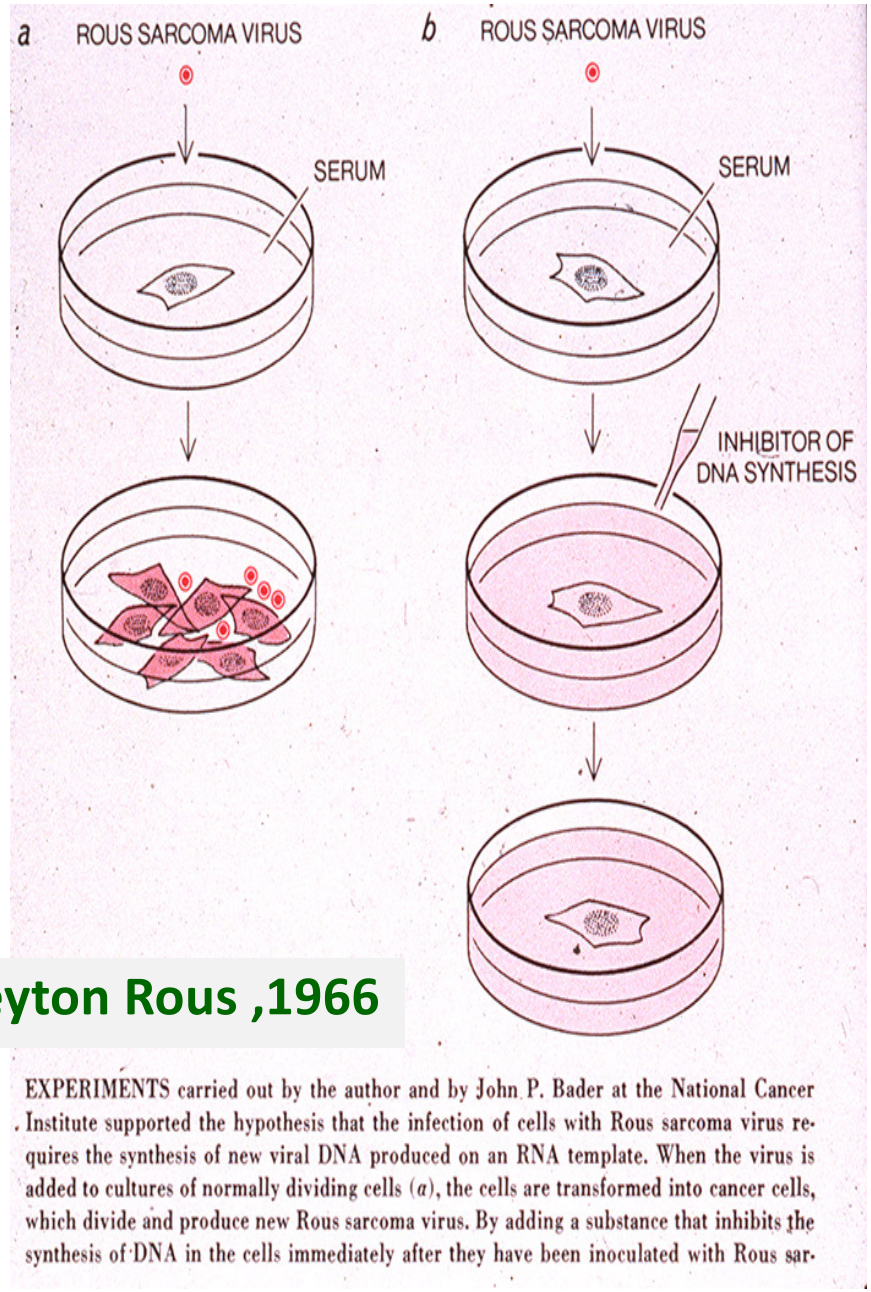

สมาคมอนุรักษ์อีสานไม้กินปลาดิบ

- *Cell transformation by RSV*



(A) The RSV focus assay of transformed cells in a chick embryo fibroblast monolayer as described by Temin and Rubin (1958) showing a 1:100 and 1:1000 dilution of the virus stock. Each stained dot represents a focus of transformed cells (B) .

- Cytoplasm or nucleus is the site of changes?



Peyton Rous ,1966

EXPERIMENTS carried out by the author and by John P. Bader at the National Cancer Institute supported the hypothesis that the infection of cells with Rous sarcoma virus requires the synthesis of new viral DNA produced on an RNA template. When the virus is added to cultures of normally dividing cells (*a*), the cells are transformed into cancer cells, which divide and produce new Rous sarcoma virus. By adding a substance that inhibits the synthesis of DNA in the cells immediately after they have been inoculated with Rous sar-

- **Carcinogenesis : targeting nucleus (genes)**

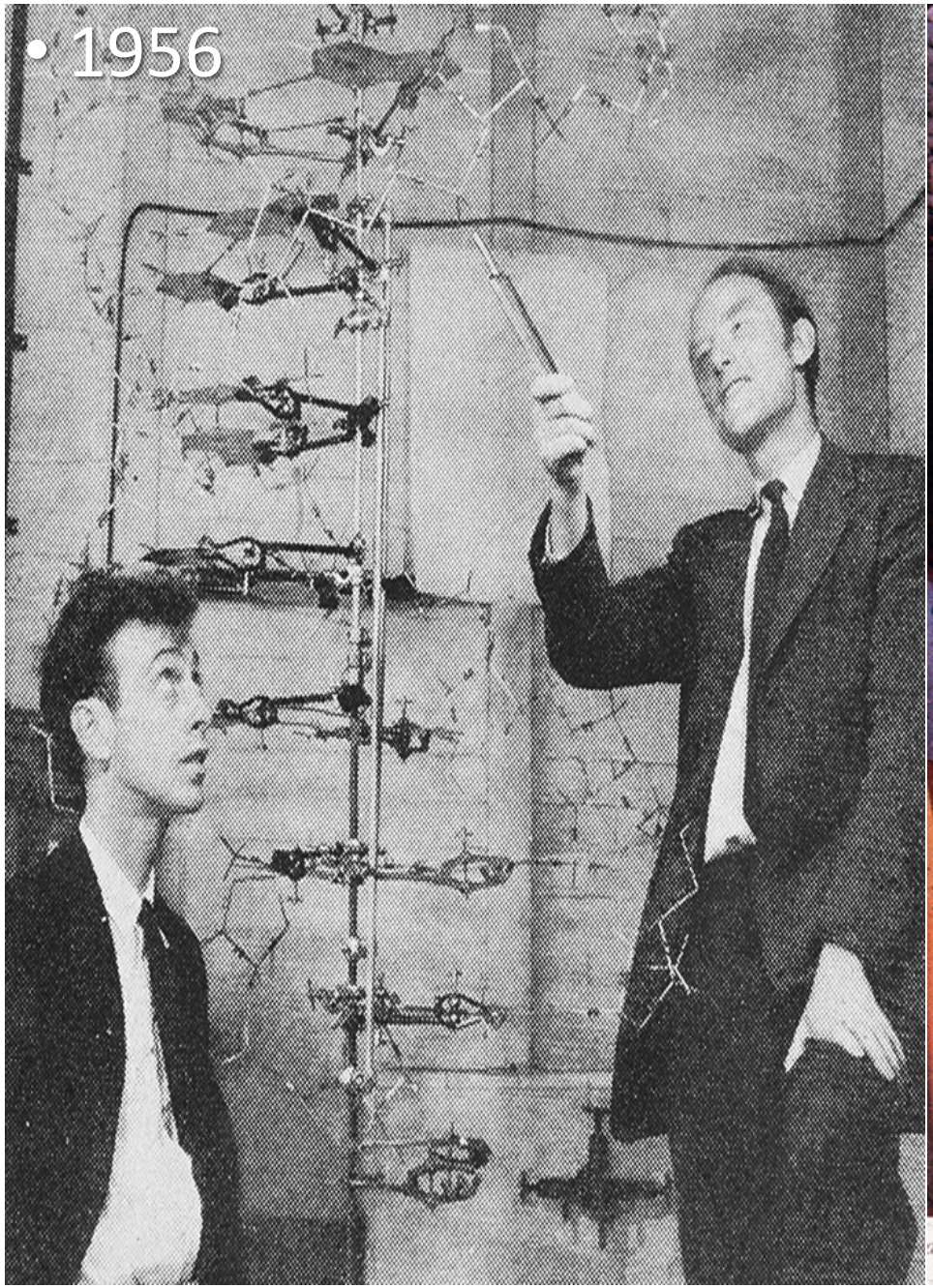
• (1910)Viruses and cancer : *From hens to eternity*

- A year later, Rous published another paper, which took this work a giant step further. He made cell-free filtrates from the tumour using various protocols, and found that they were sufficient to induce tumour growth.
- So, a biological agent in the cell-free filtrate could cause tumour development; this agent was subsequently shown to be a virus, and was named after its discoverer as Rous sarcoma virus (RSV).
- The importance of this finding was not fully appreciated for some time, and it was only in 1966, at the age of 77, that Rous was awarded the Nobel Prize for this research.

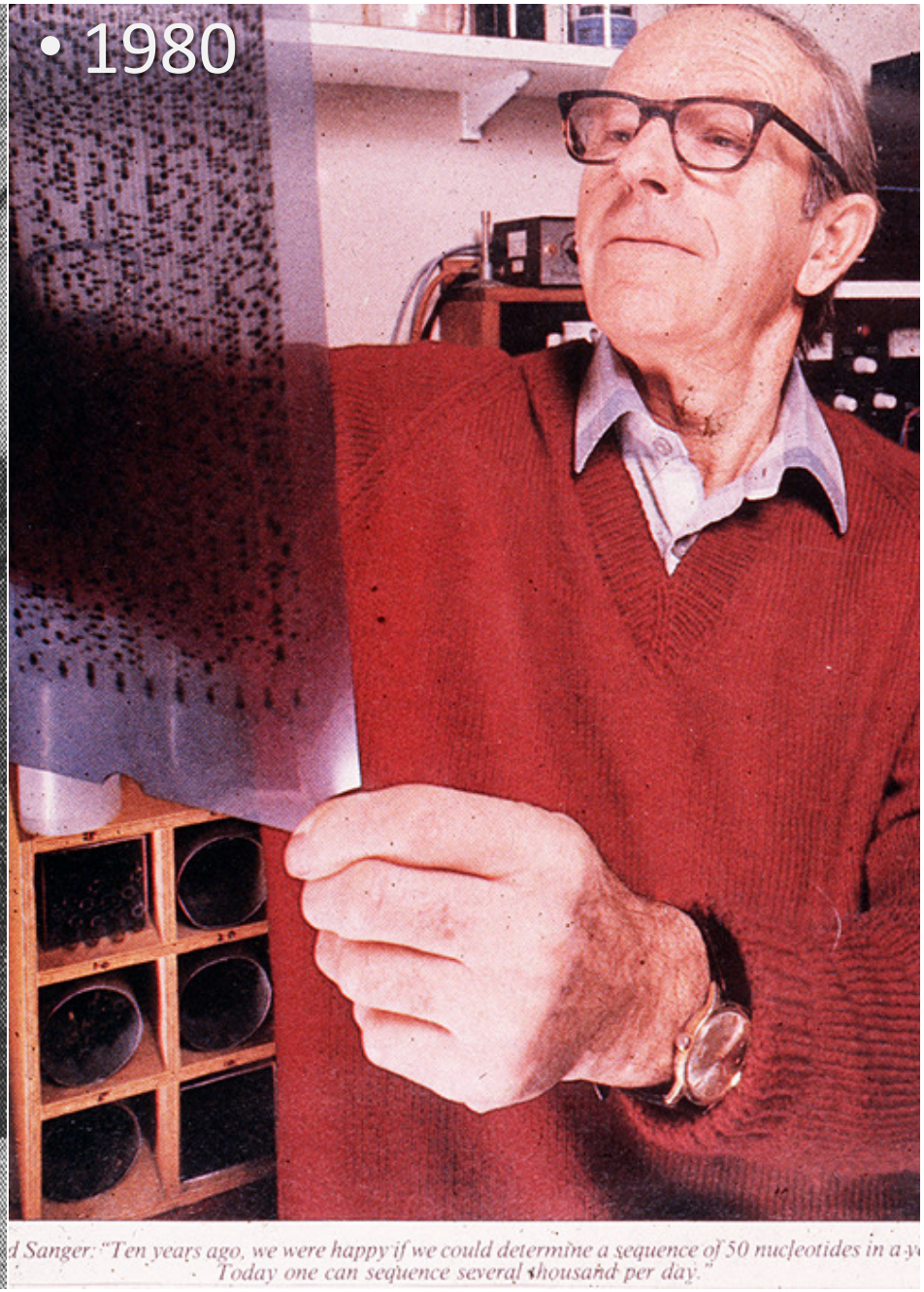
• Dr. Francis Peyton Rous (1879-1970), 1966 winner of the Nobel Prize for Medicine for his work viruses that cause cancer in humans. ca 1966

• From DNA to DNA sequencing

• 1956



• 1980



d Sanger: "Ten years ago, we were happy if we could determine a sequence of 50 nucleotides in a y
Today one can sequence several thousand per day."

• (1979) First human oncogene

- By the late 1970s, it was well known that retroviral oncogenes could rapidly transform cells, and that the viruses had acquired these genes fromthe genomes of the mammalian and avian cells that they infected .

An important difference

- **In 1982, not only was the concept of the cellular oncogene confirmed by the cloning of cellular *RAS, but the activating mutation* was also identified.**

- It was therefore proposed that mutations in the cellular homologues of these genes could transform cells in the absence of any viral involvement, and that this occurred in a substantial proportion of human cancers.

- Key discoveries by the Robert Weinberg and Geoffrey Cooper groups showed that such transformation could occur when the DNA of a chemically mutagenized transformed mouse cell was transferred.

HOW ONCOGENES CAUSE CANCER

In a normal cell *(above)*, a proto-oncogene plays a role in manufacturing proteins that regulate cell growth.

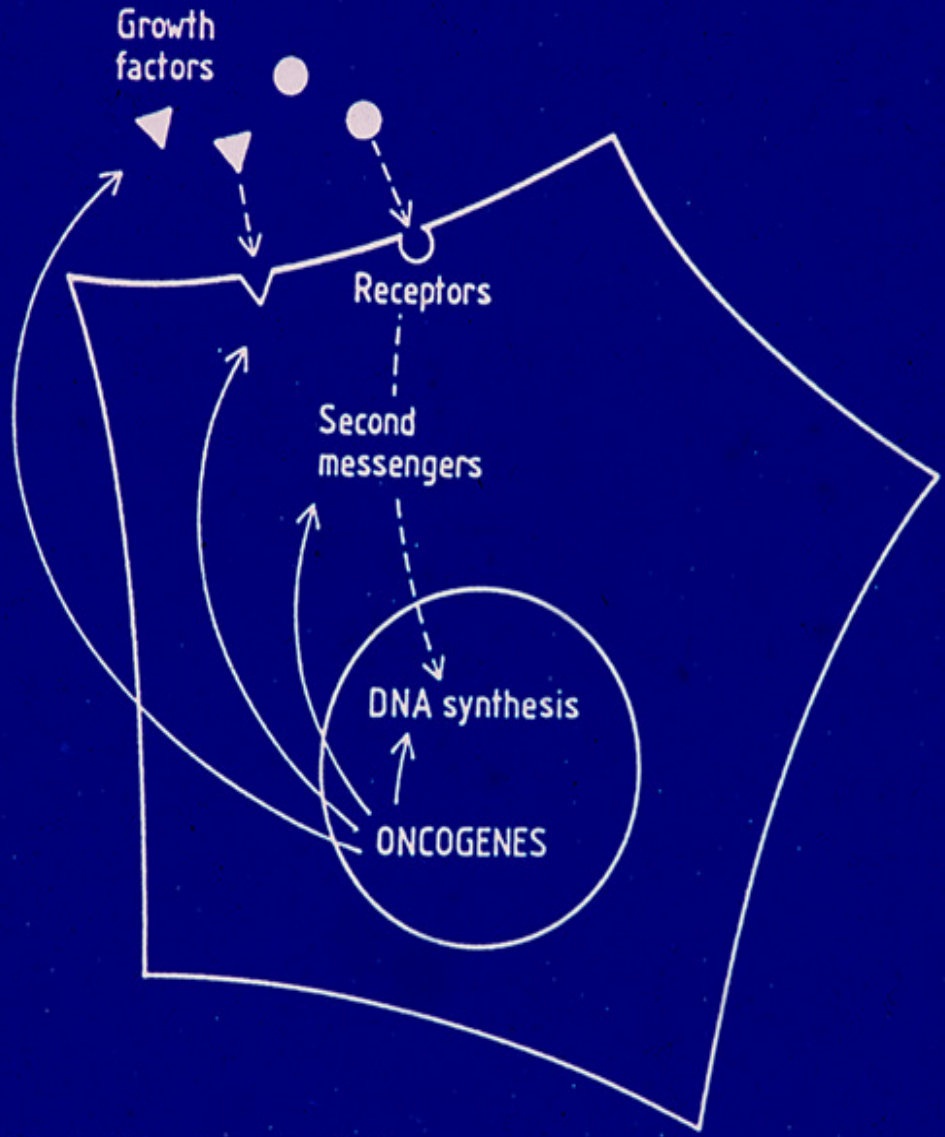
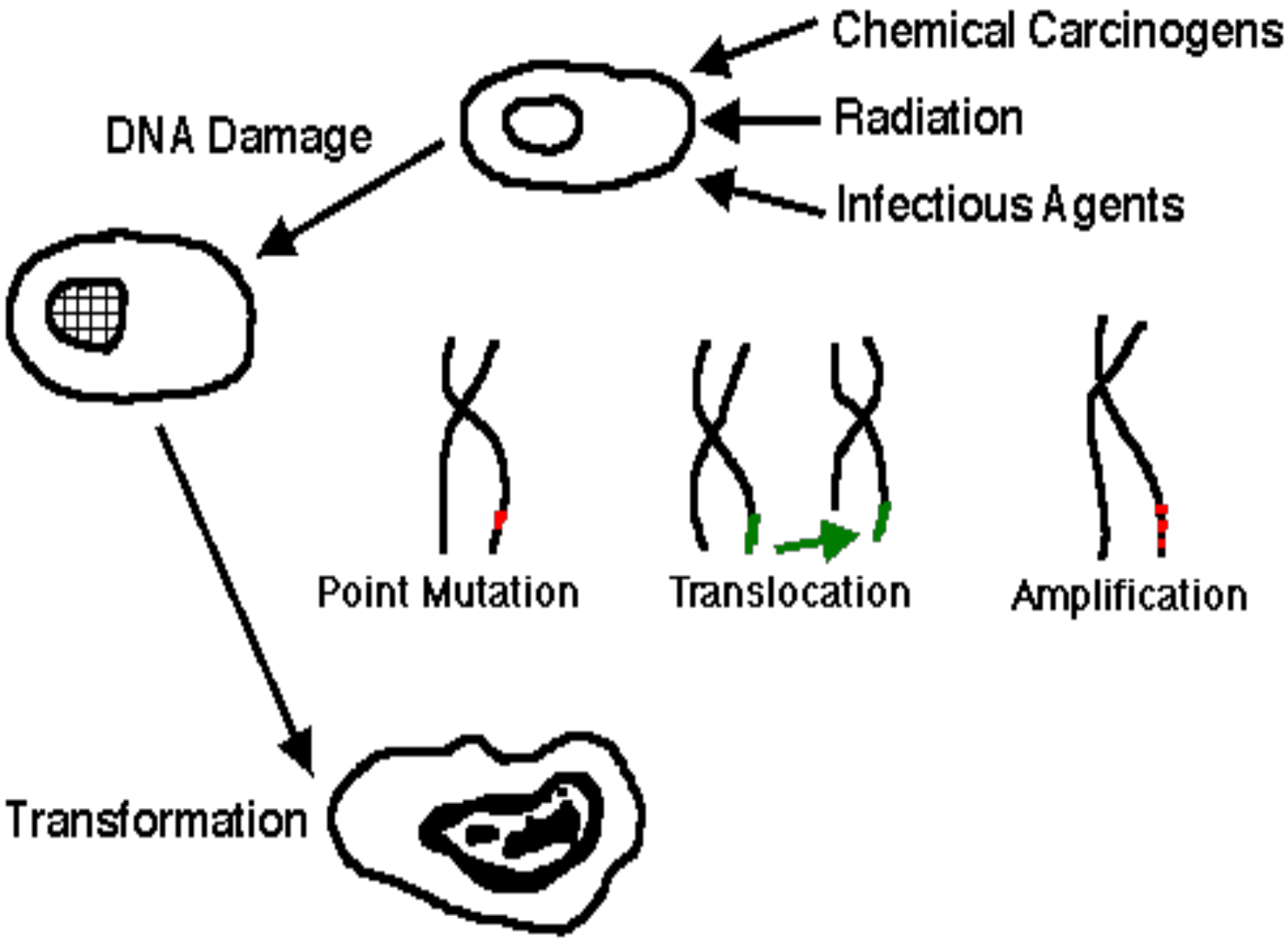


Fig 1—Ways by which different oncogene products may disrupt normal regulation of cell growth (after Wyke and Weiss, 1984).

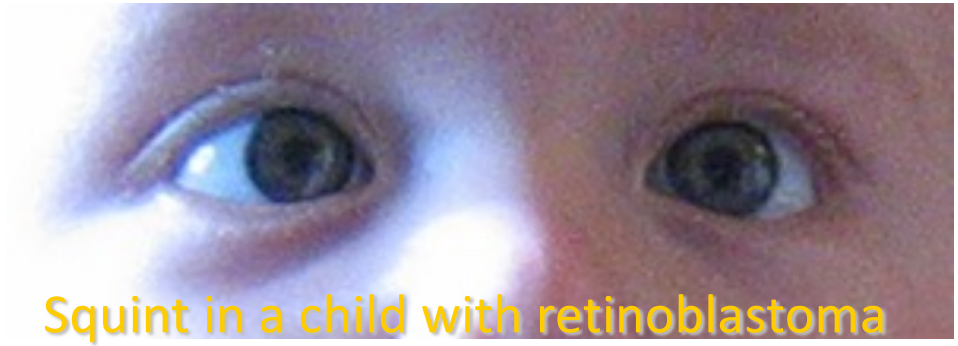
The following are the properties of some oncogene products: growth factor, *sis* (PDGF); growth factor receptor, *erb*-b (for EGF); phosphokinases (receptor kinases?), *src, fps/fes, abl, yes, ros, fms, mos, raf/mil;* GTPase (second messengers?), H, N, K-*ras;* nuclear proteins, *myc, fos, myb,* B-*lym.*

•Mechanism underline oncogenes in tumorigenesis



- Then , they found another types of genes in carcinogenesis !!

Leukocoria in a child with retinoblastoma

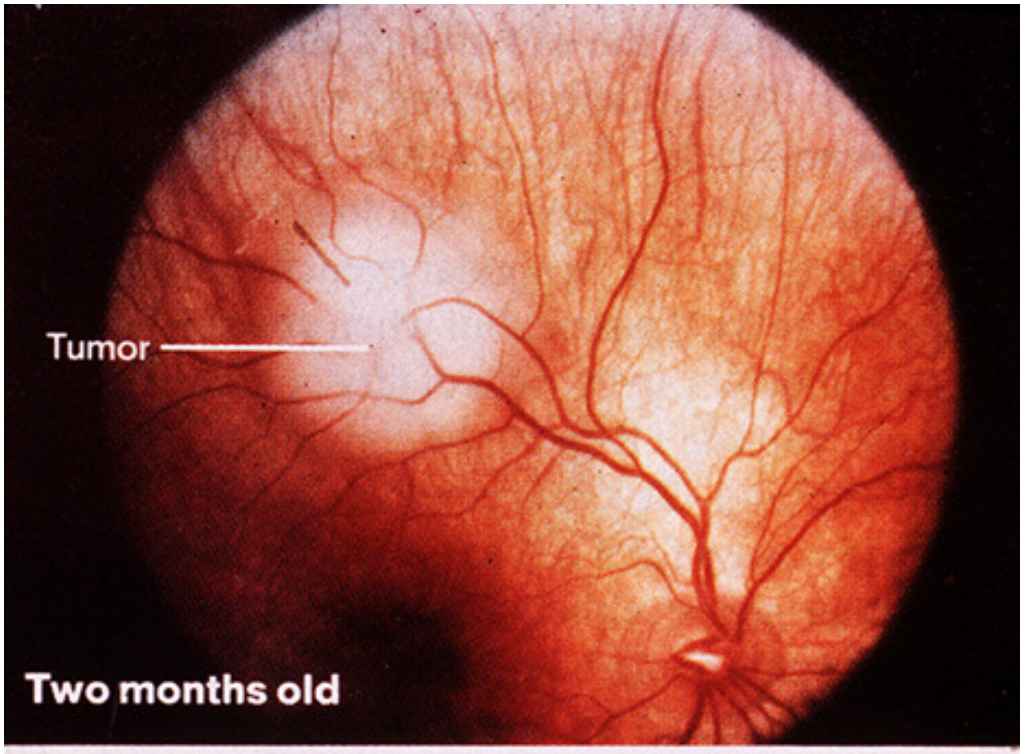


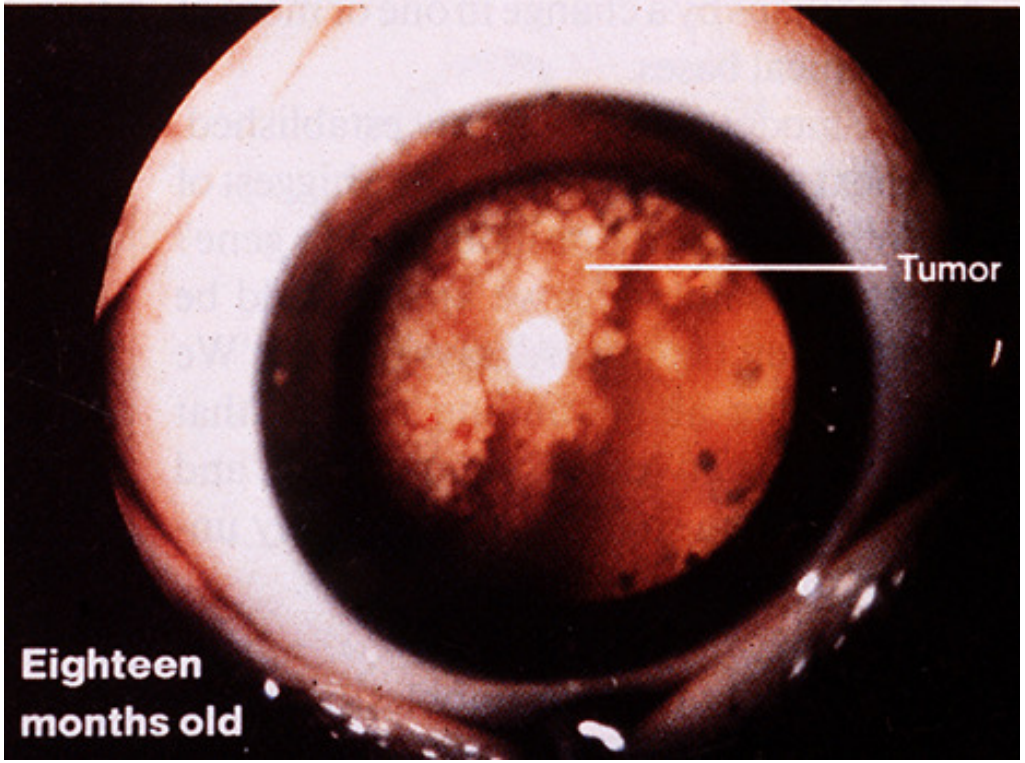
Squint in a child with retinoblastoma

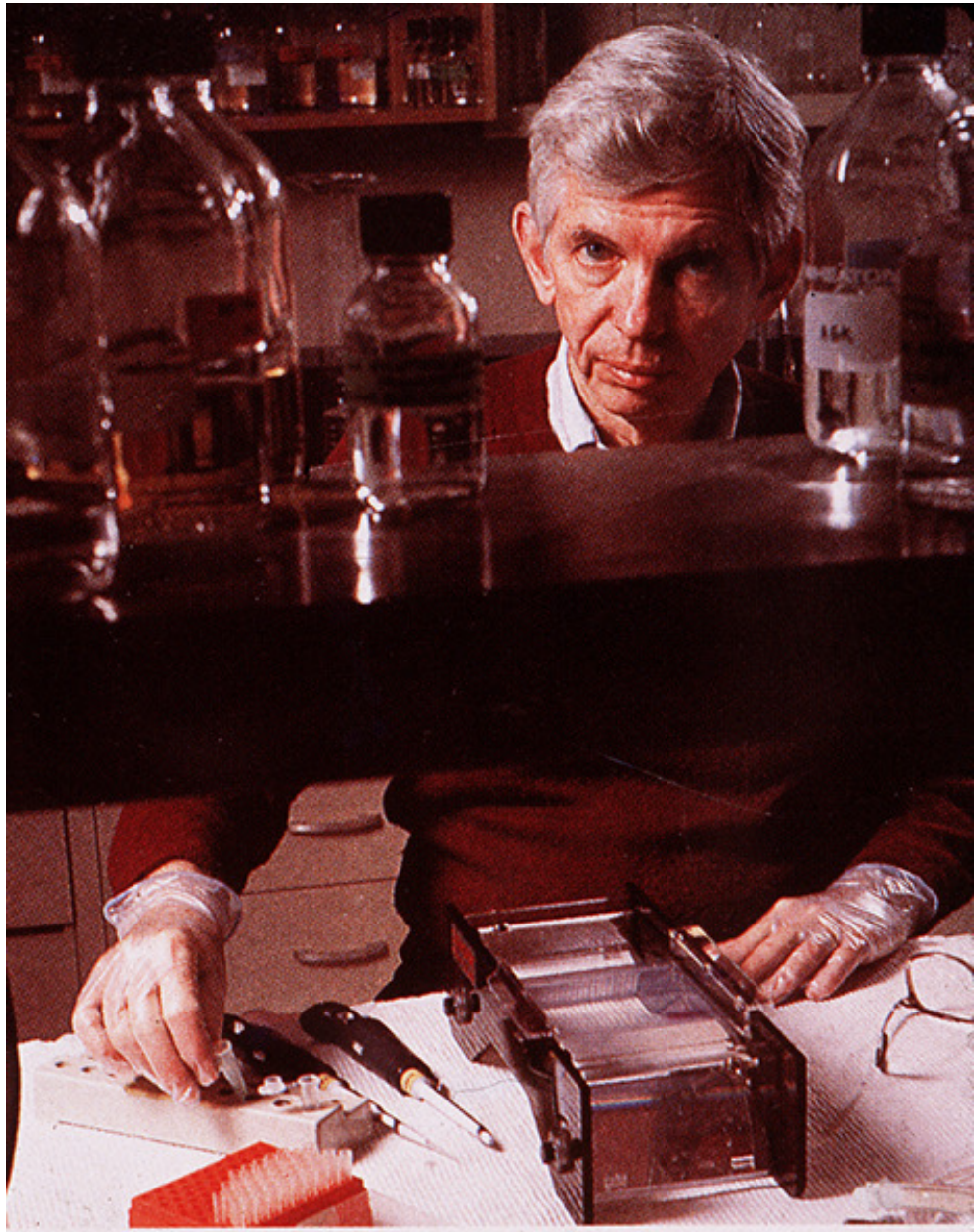
- **Retinoblastoma** (Rb) is a rapidly developing cancer that develops in the cells of retina, the light detecting tissue of the eye.

- In the developed world, Rb has one of the best cure rates of all childhood cancers (95 - 98%), with more than nine out of every ten sufferers surviving into adulthood.

- Heritable retinoblastoma

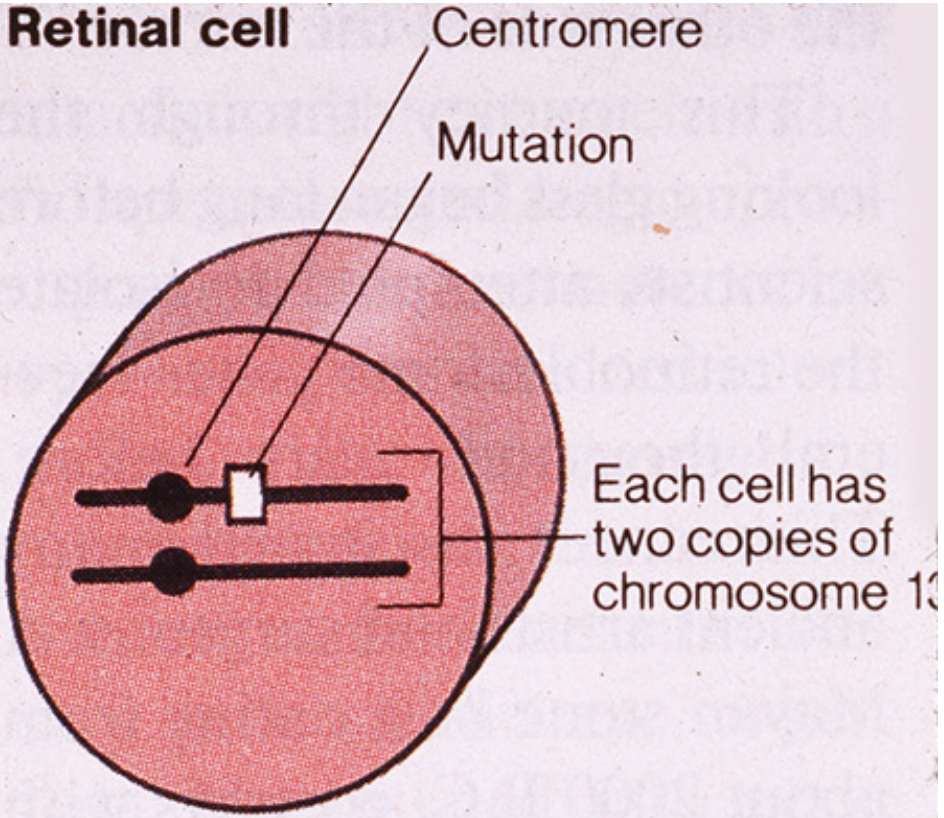






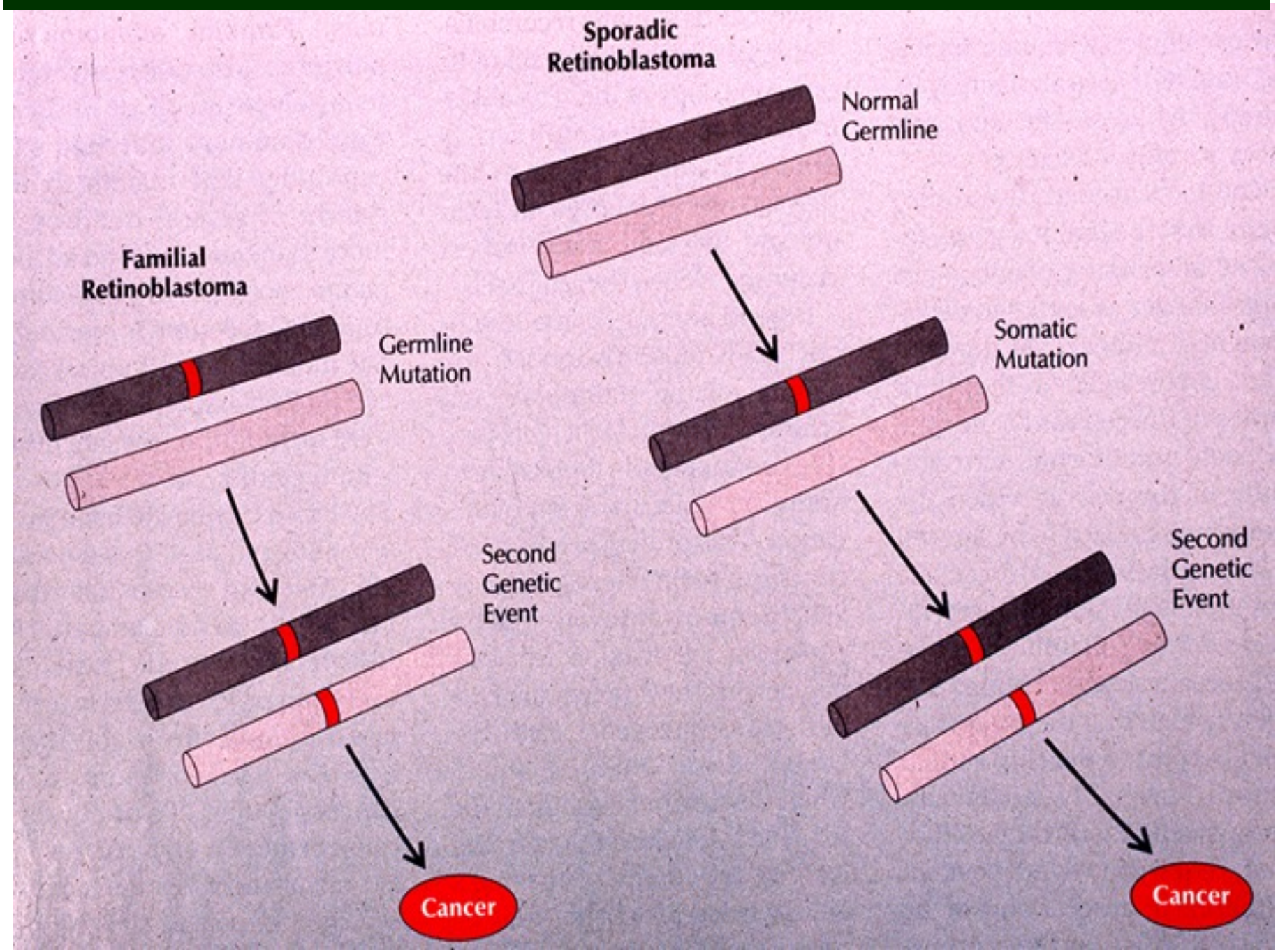
Knudson's insight: eye cancer takes two mutations, not just one, to get started

1976

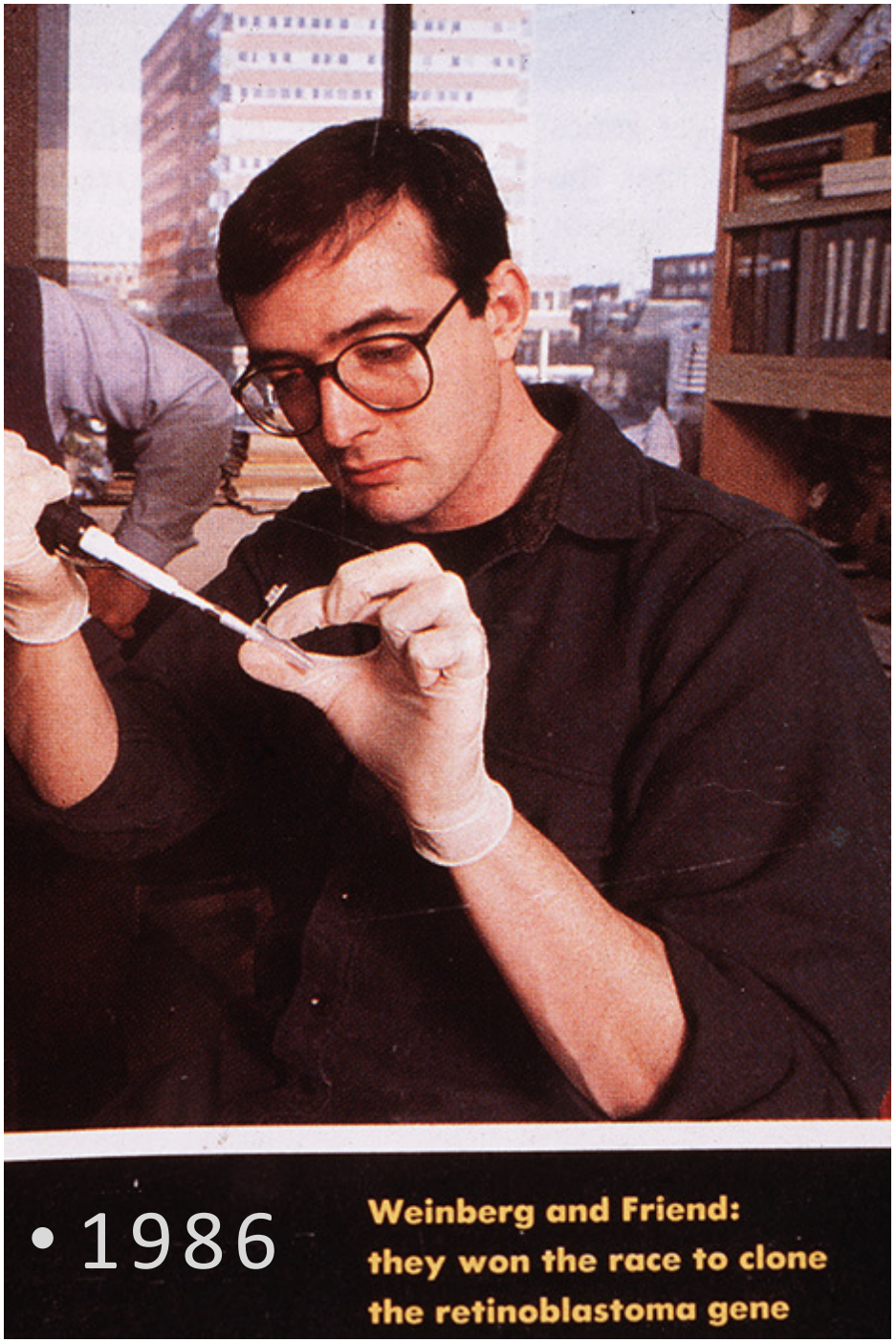


Children who carry the gene for retinoblastoma on chromosome 13 develop the eye cancer sooner and oftener than those who get it by non-hereditary means. The diagrams at right show why.

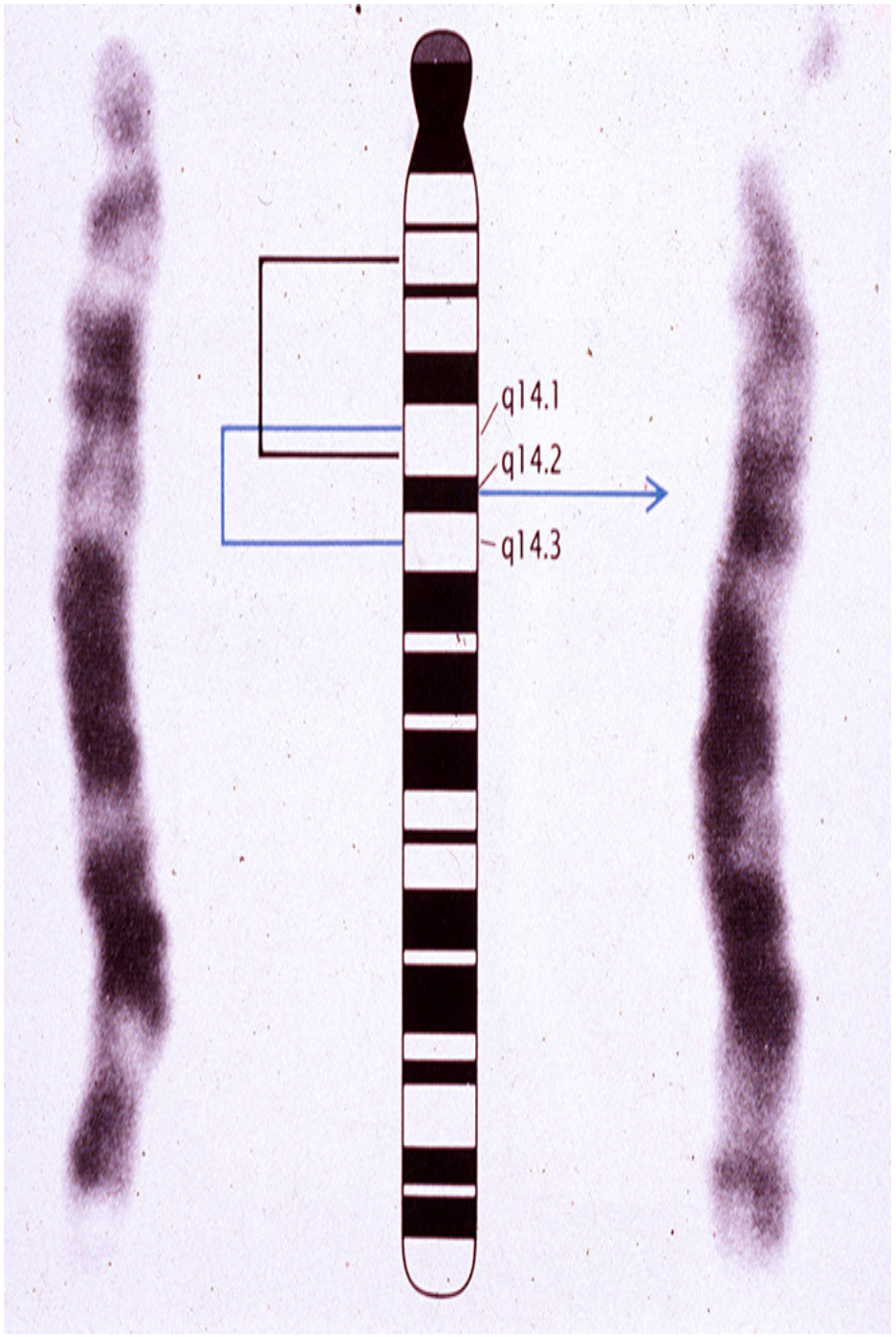
• Two-hit theory of Knudson



• A decade later Dr. Friend proved it right by identified *Rb*

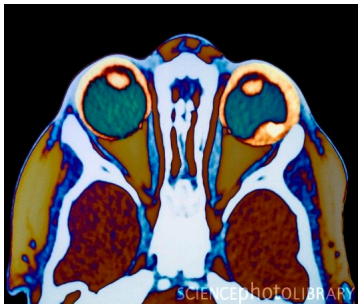


• 1986 **Weinberg and Friend: they won the race to clone the retinoblastoma gene**



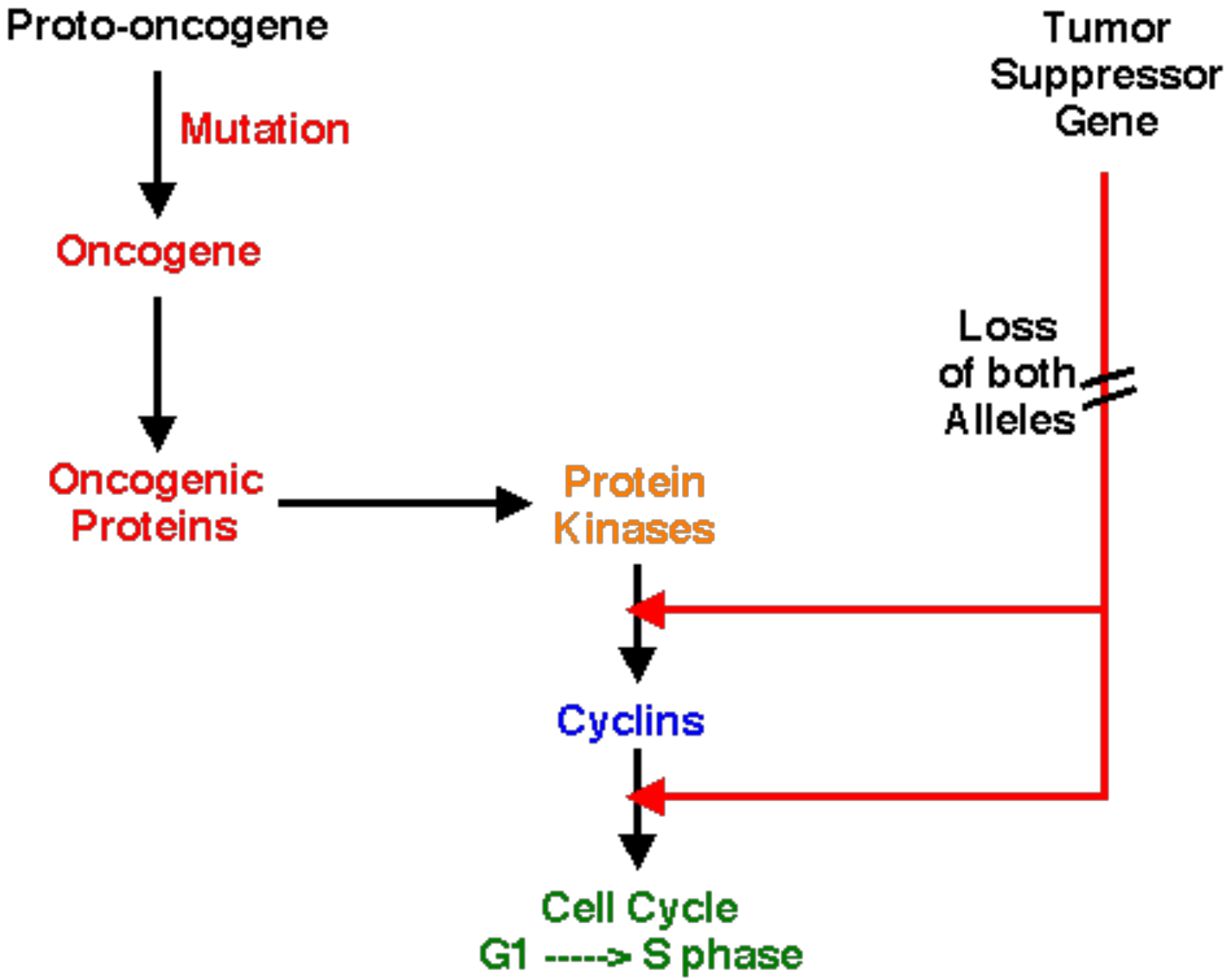
• (1953) Two-hit hypothesis

It takes (at least) two to tango



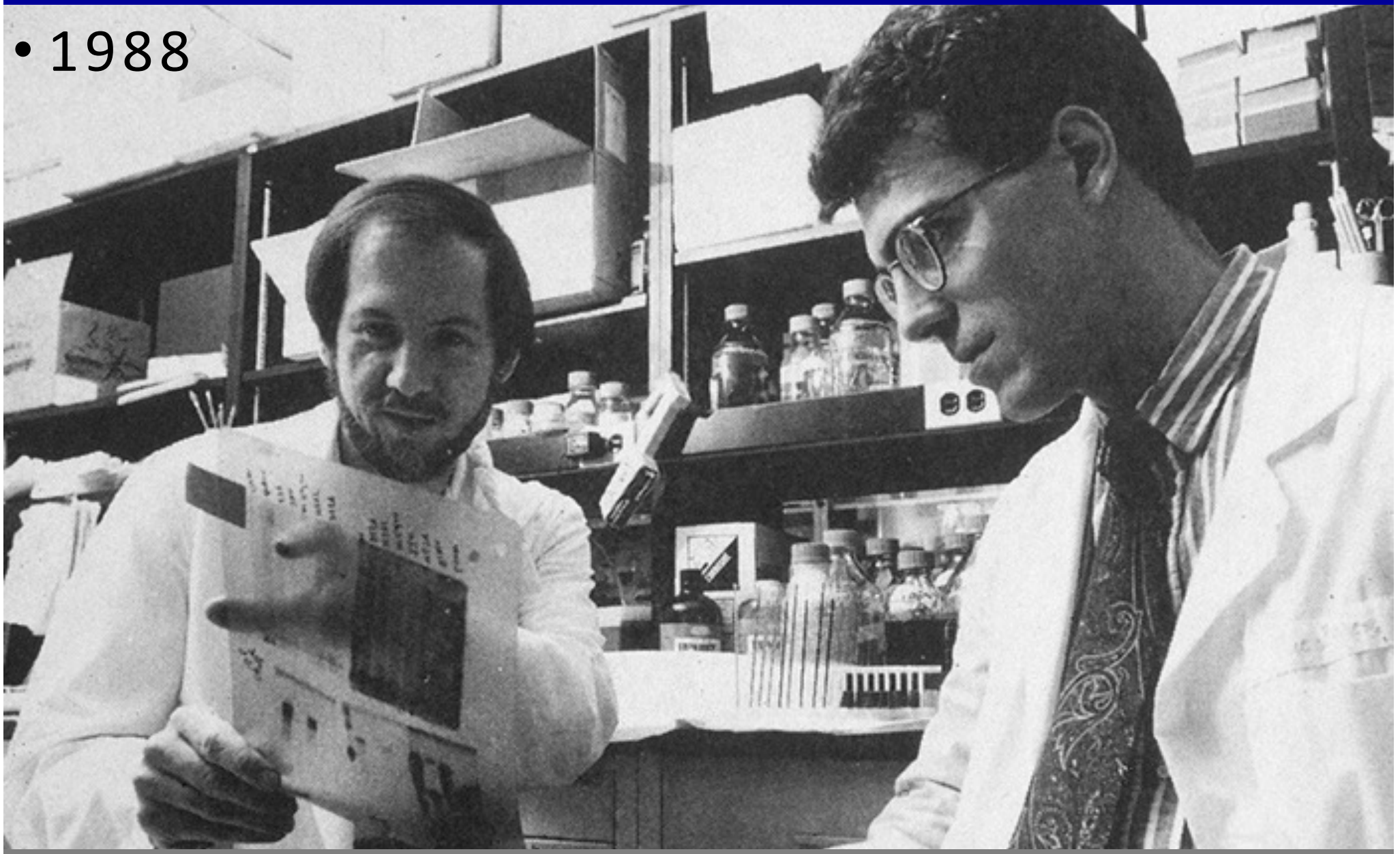
- Alfred Knudson noted that "what is lacking is direct evidence that cancer can ever arise in as few as two steps and that each step can occur at a rate that is compatible with accepted values for mutation rates".
- Knudson analysed 48 cases of retinoblastoma with the presence of a family history of the disease. Using Poisson statistics, he showed that the distribution observed was consistent with retinoblastoma being caused by two mutations.
- In familial cases, one hit was inherited whereas the other one was acquired later; in sporadic tumours, both changes were somatic.
- The now famous **two-hit hypothesis** was, in later years, to merge with the concept of allelic loss of **tumour-suppressor genes.**

- Co-operate function of oncogenes and tumor suppressor genes



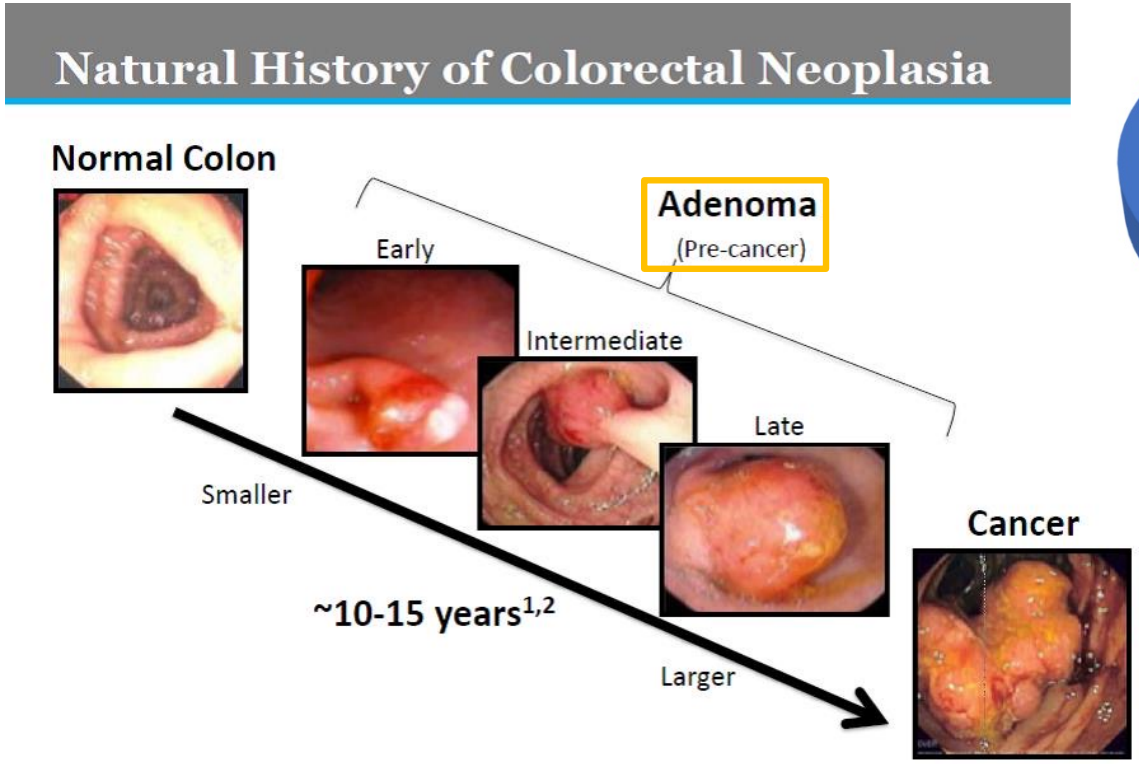
- Standard dogma in molecular carcinogenesis

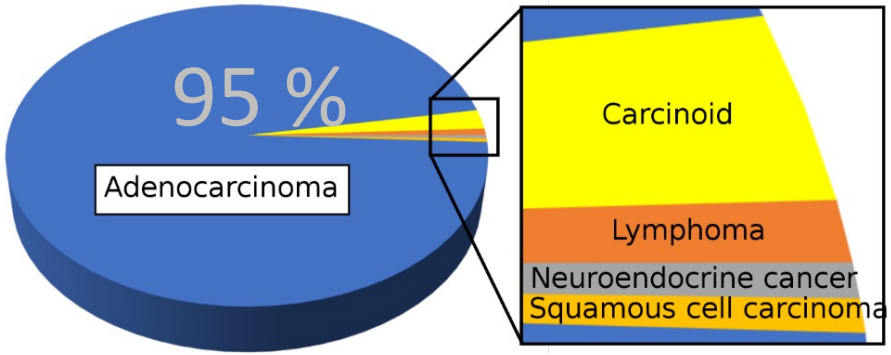
- 1988

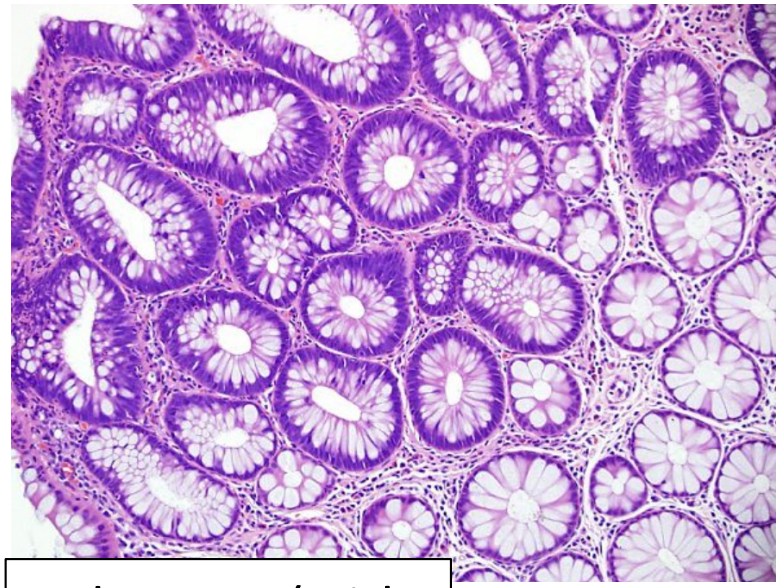


- Vogelstein B, Fearon ER, et al. *Genetic alterations. during colorectal-tumor development.* N Engl J Med 1988

- Adenoma - Carcinoma Sequence :
  Malignant tumor arising from a prior benign tumor







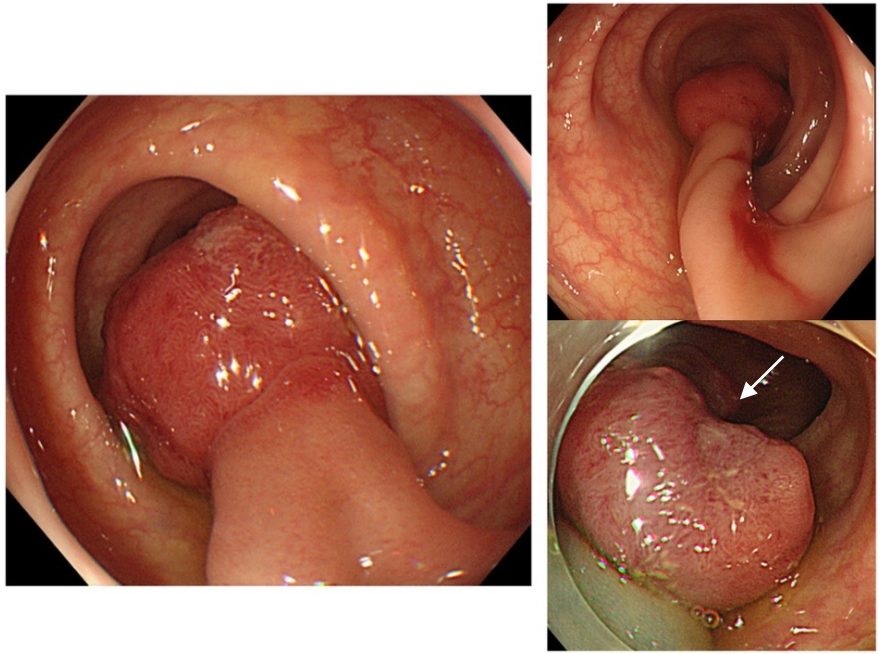
Adenoma (with dysplasia)

- Adenoma – Carcinoma Sequence

- Adenoma –Dysplasia– Carcinoma Sequence

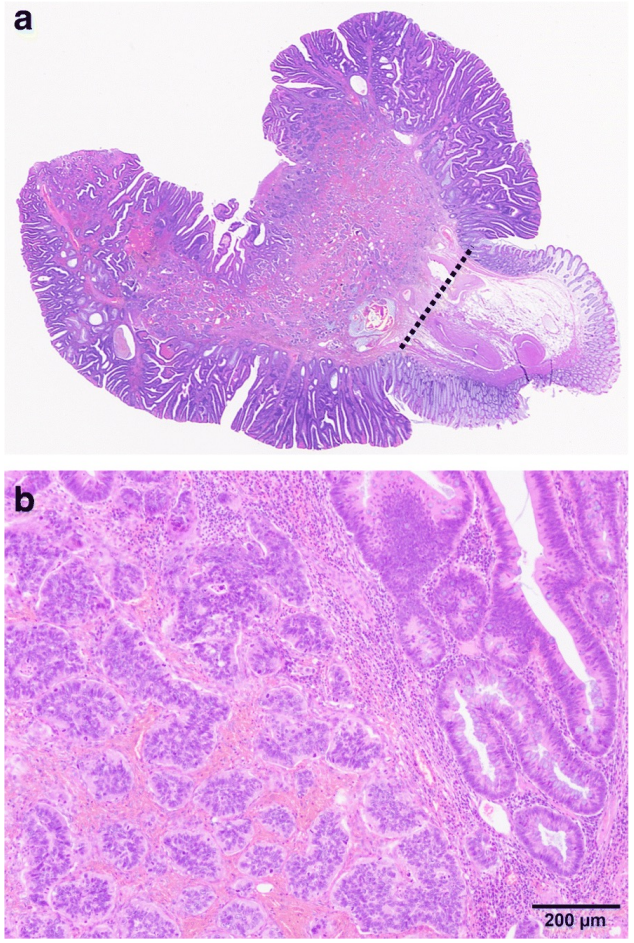
- **Pedunculated early colorectal cancer with nodal metastasis: a case report**

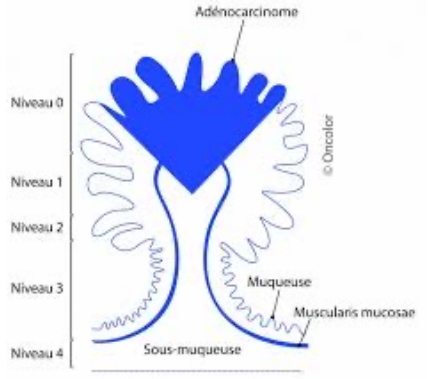
World Journal of Surgical Oncology **volume 19**, : 269 (2021)



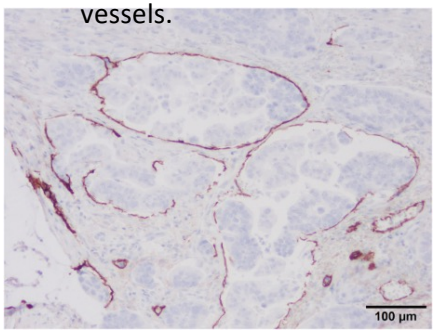
- Colonoscopic findings. A 20-mm pedunculated polyp is present in the descending colon, with a depression at the apex of the head

- *Adenoma – Carcinoma Sequence*



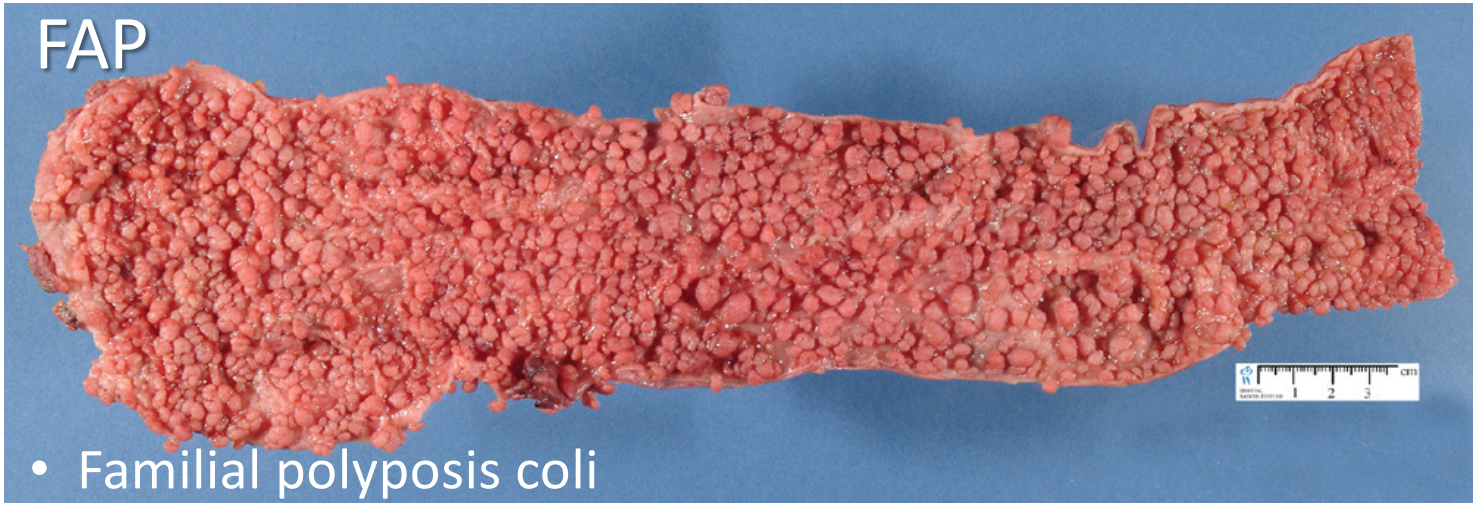


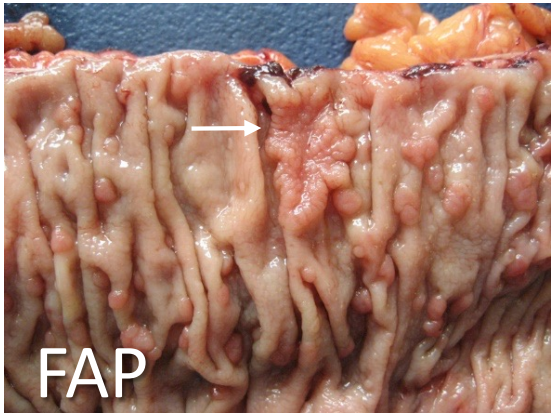
- **Podoplanin** immunostaining. Multiple tumor cells are noted in the lymphatic vessels.

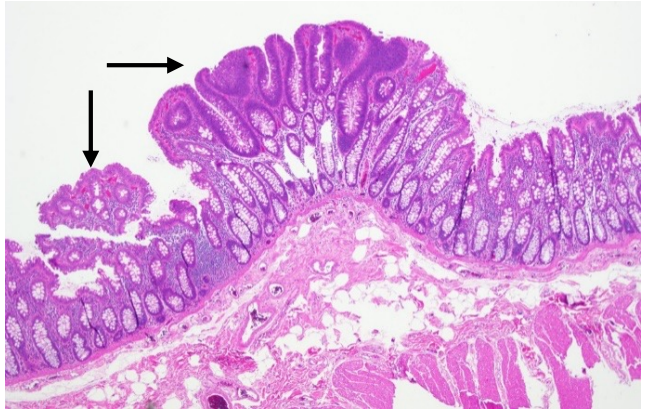


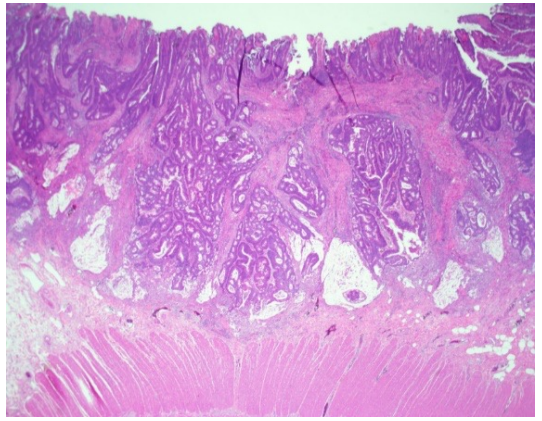
n mainly consists of non-solid, poorly differentiated adenocarcinoma, with surrounding adenoma components. The s do not reach the Haggitt line (dotted line), indicating a level 2 Haggitt lesion. Hematoxylin-eosin staining. **b** There is ent of adenoma in the non-solid, poorly differentiated adenocarcinoma.

• Familial adenomatous polyposis coli (FAP)









- Colon cancer in FAP.

- Smaller polyps demonstrate classical low-grade adenomatous dysplasia.

- Larger polyp demonstrates invasive adenocarcinoma, extending into the submucosa.

• Oncogenes and TSGs involvement in FAP

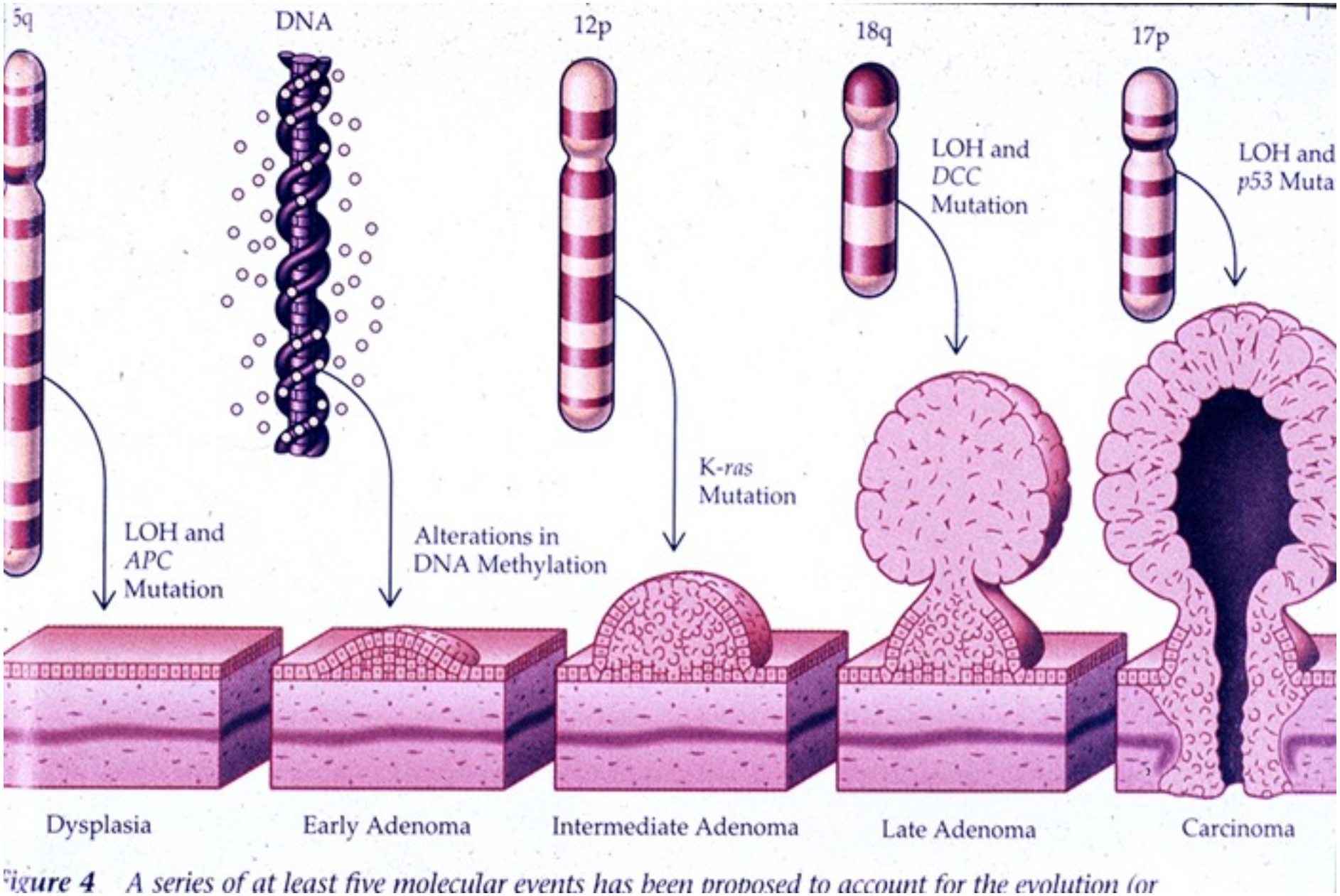
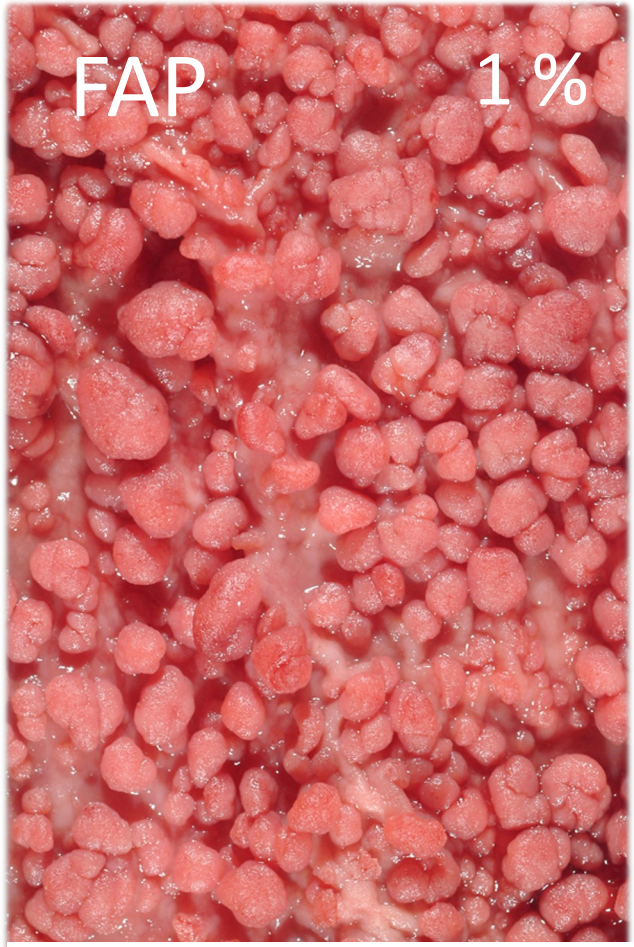
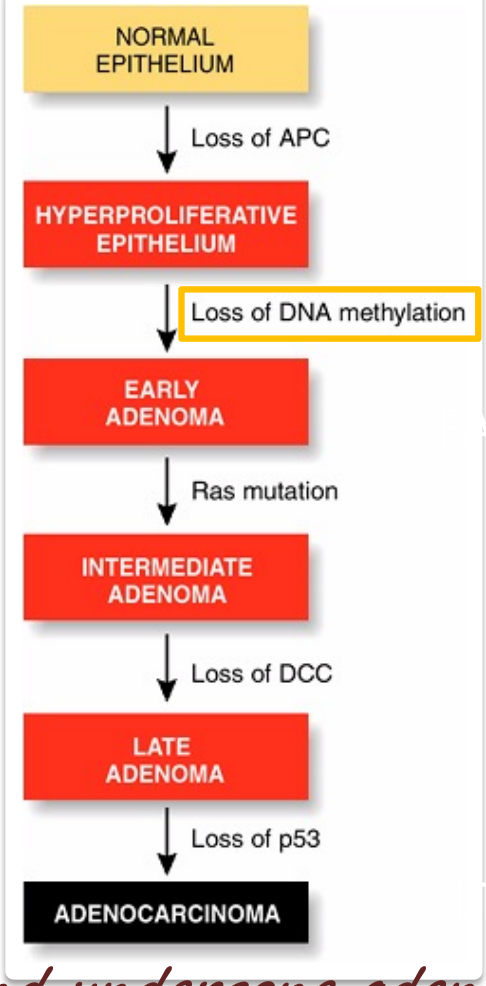


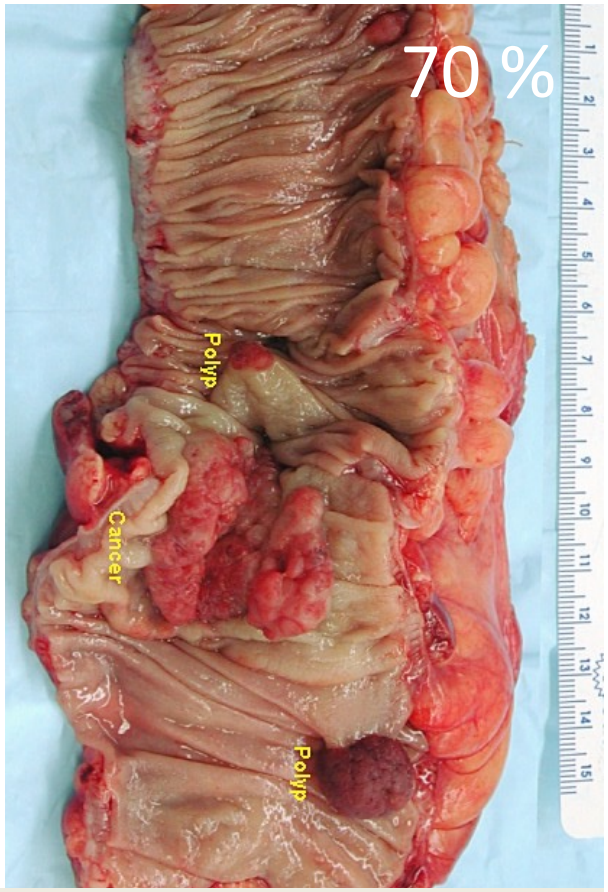
Figure 4 A series of at least five molecular events has been proposed to account for the evolution (or

- *FAP-colon cancer and sporadic colon cancers share mol. genetics….*



Familial Adenomatous Polyposis

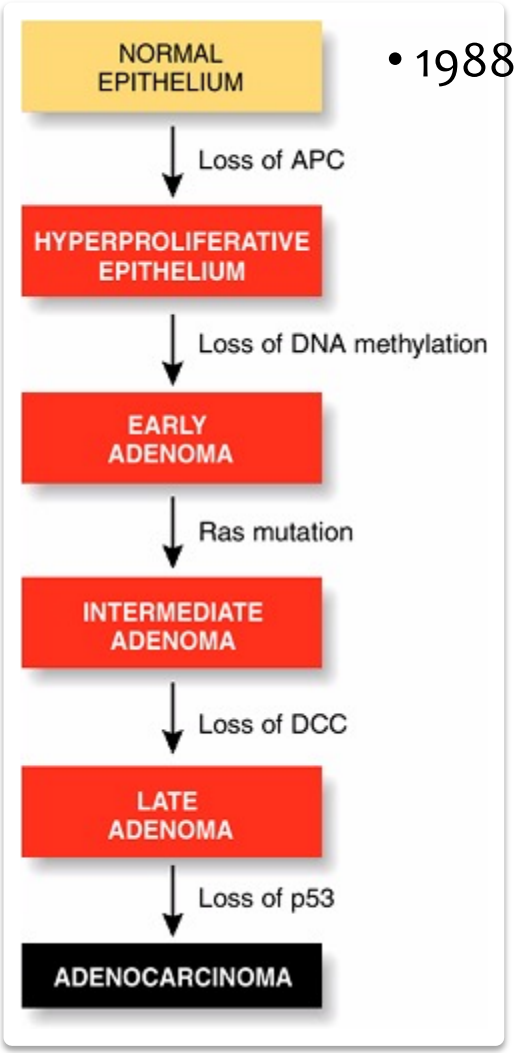




- Left- sided colon cancer

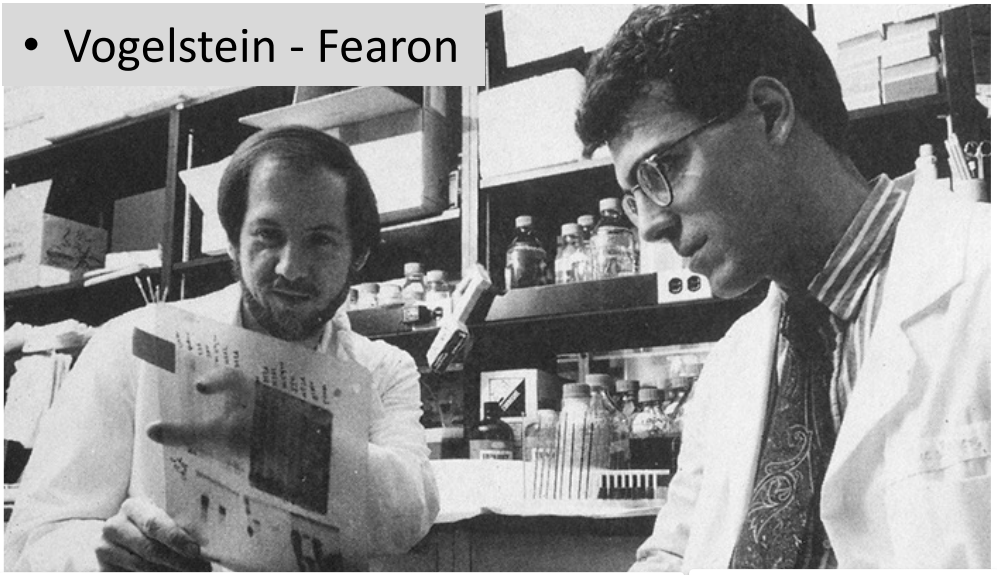
…and undergone adenoma-carcinoma sequence

• ‘ VOGELGRAM ‘ : A standard dogma in CR carcinogenesis



• 1988

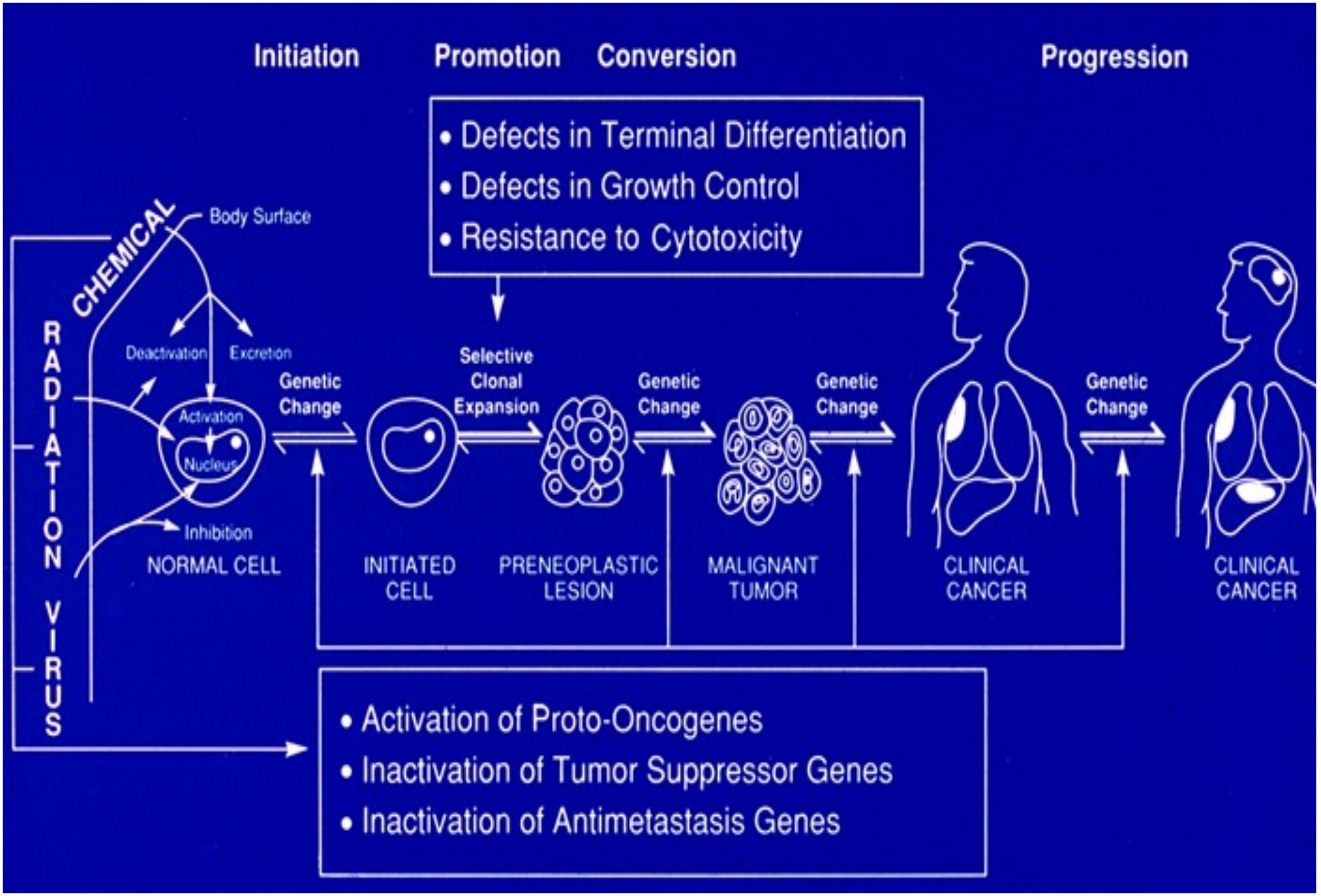
• Vogelstein - Fearon



• FAP

• Yusuke Nakamura

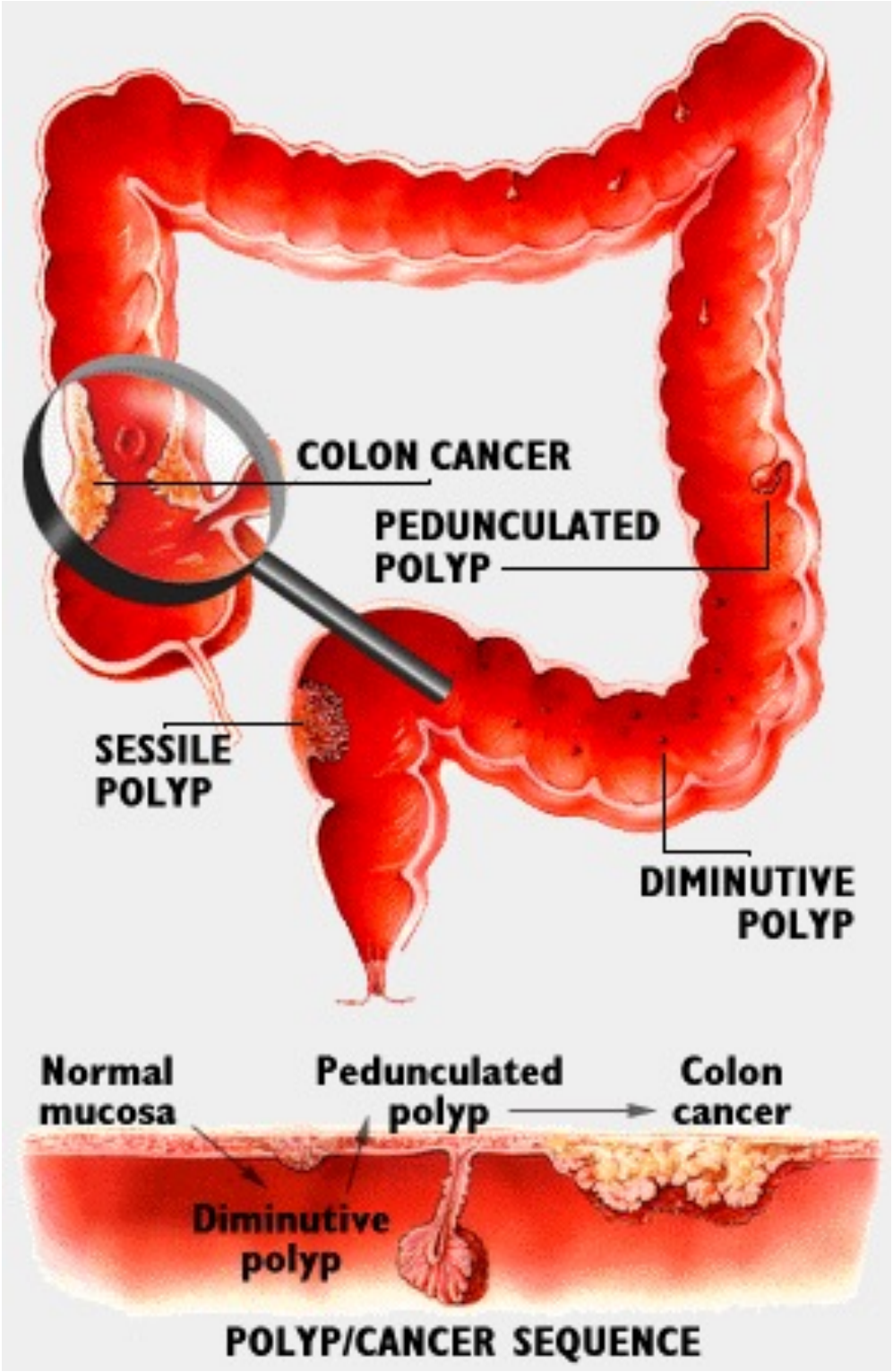
• Multi-stage molecular carcinogenesis

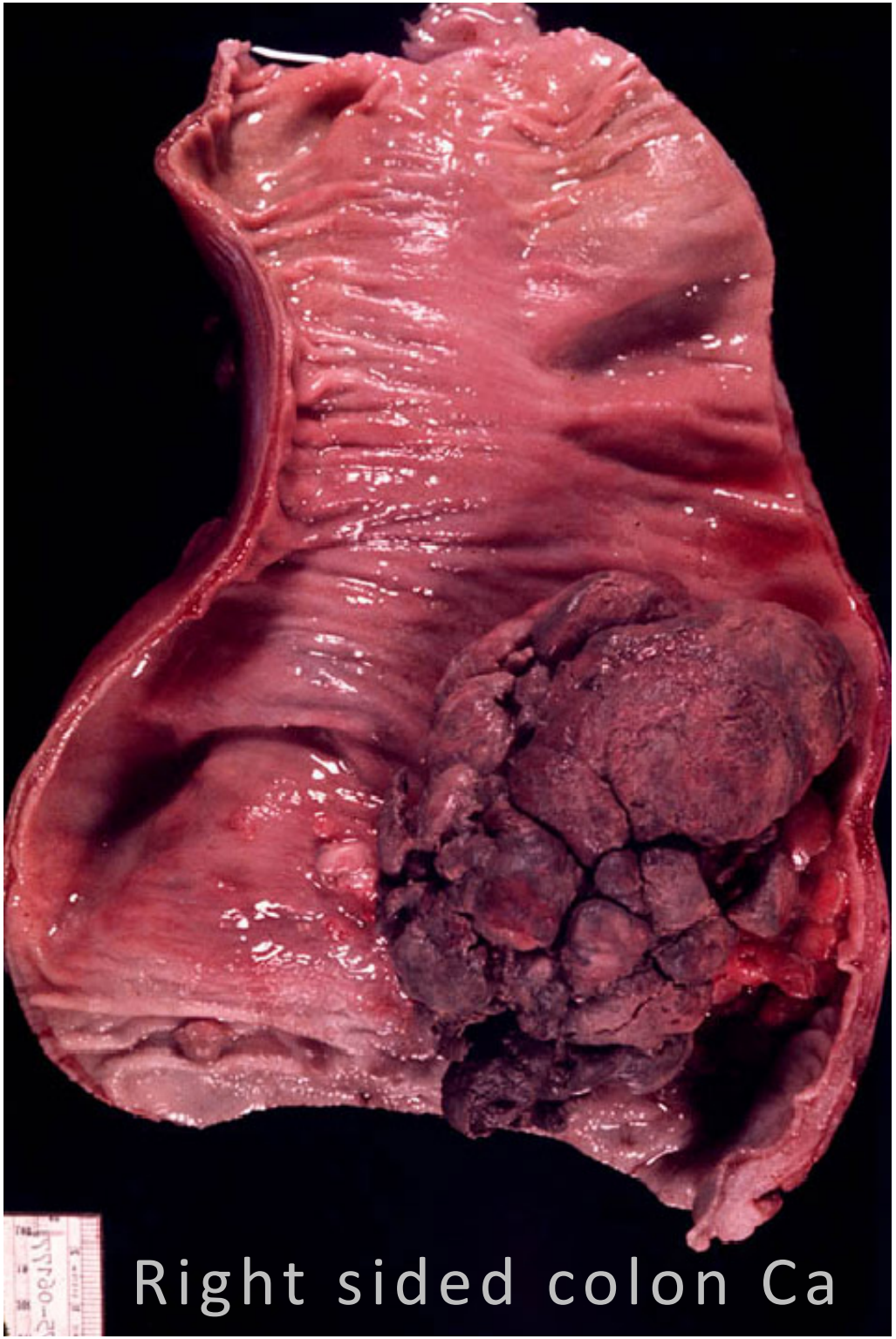


- The cardinal principles of hereditory cancer genetics

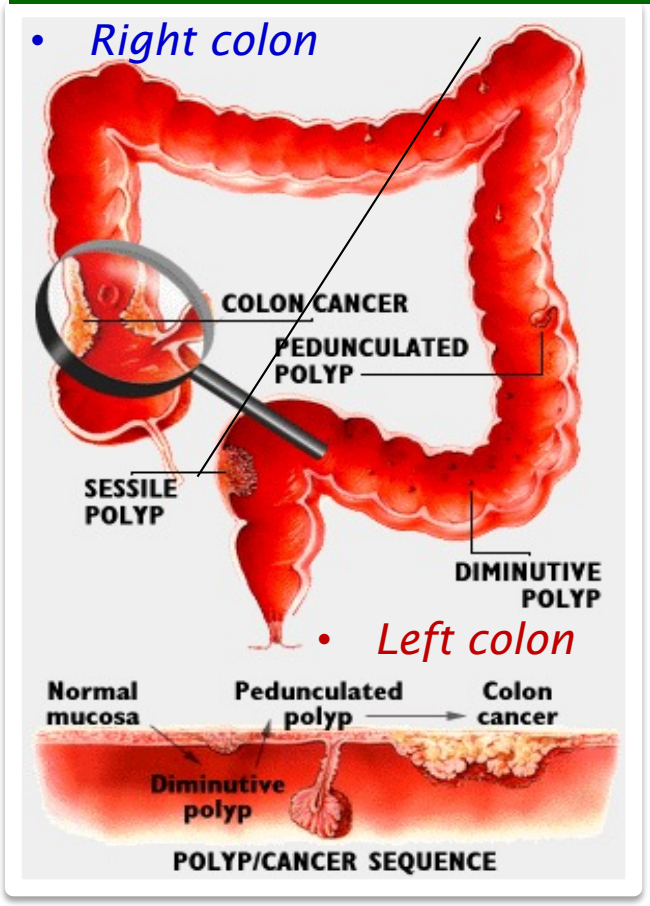
1944 : US Navy
1945 : Professional boxer
1950-60 : Psychology, Genetics, Medicine
1961: Medical genetic team (Ann Krush)
1966 : Family cancer
1970 : Professor Preventive Medicine Creighton
1984 : HNPCC, Lynch syndrome
1993 : MLH1
1996 : PMS2

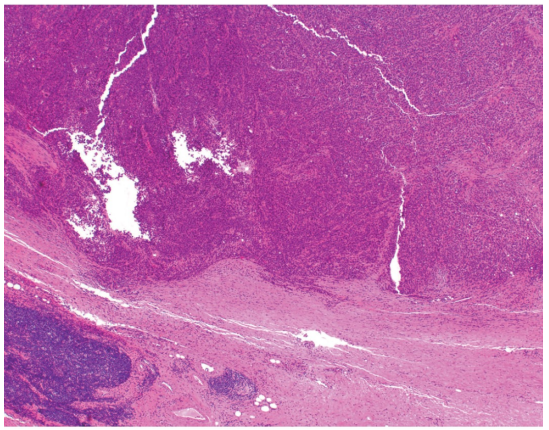
In 1970, NIH rejected the idea that cancer could be hereditary.

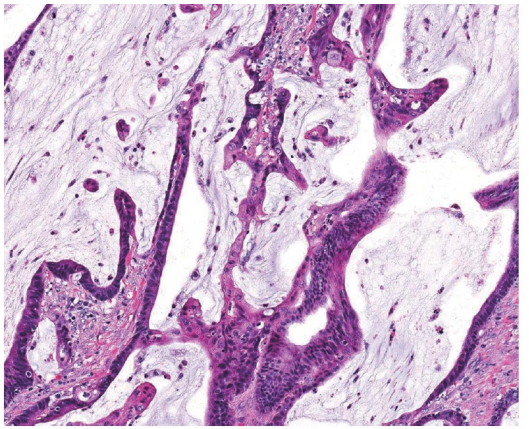

COLON CANCER
PEDUNCULATED POLYP
SESSILE POLYP
DIMINUTIVE POLYP
Normal mucosa
Pedunculated polyp
Colon cancer
Diminutive polyp
POLYP/CANCER SEQUENCE


Right sided colon Ca

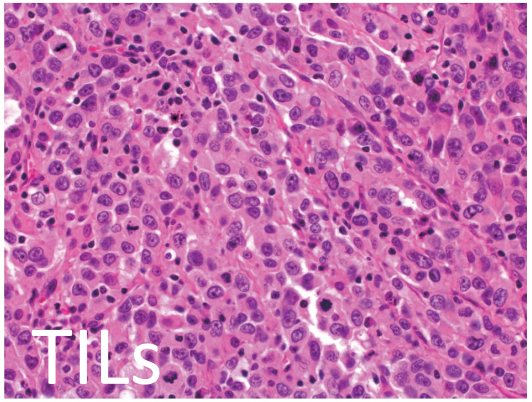
HNPCC, Lynch syndrome ; small "flat" adenoma





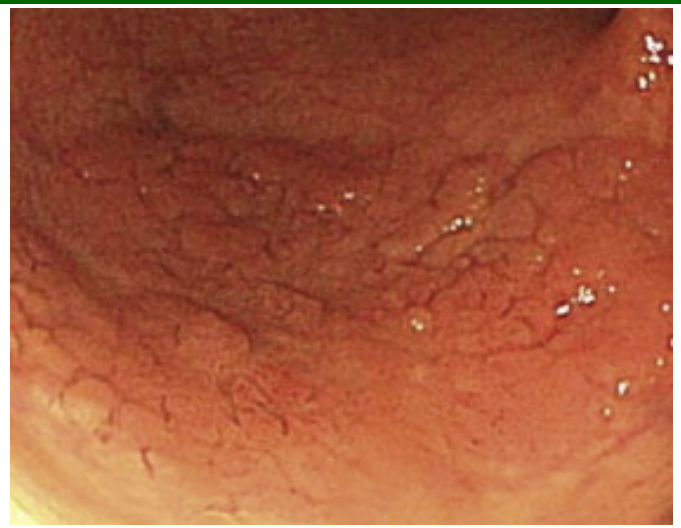


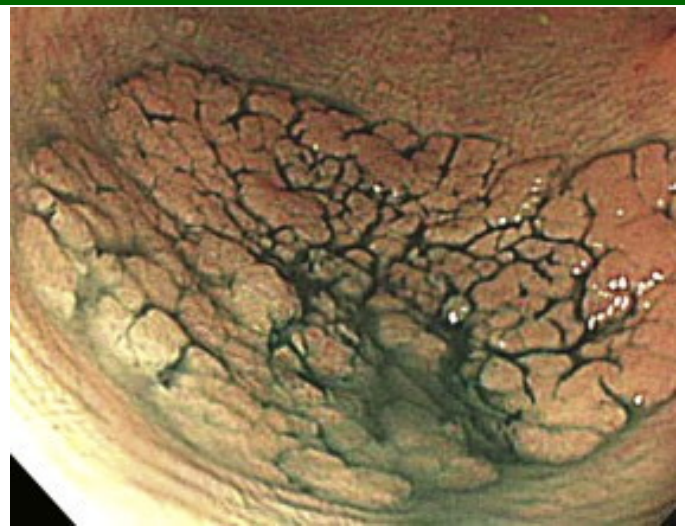
- HNPCC :
- Distinctive histology – *mucinous ,"medullary" or PD, adenocarcinoma*, with 'TIL' (tumor-infiltrating- *lymphocytes)*

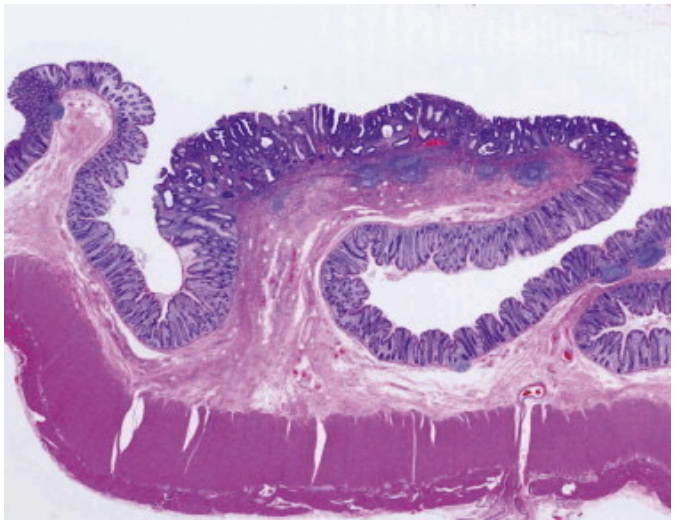


- Lynch syndrome (LS), previously called hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominant condition caused by germline mutations in any one of the mismatch repair genes (MSH2, MLH1, MSH6, PMS2) .

HNPCC, Lynch syndrome ; small “flat” adenoma







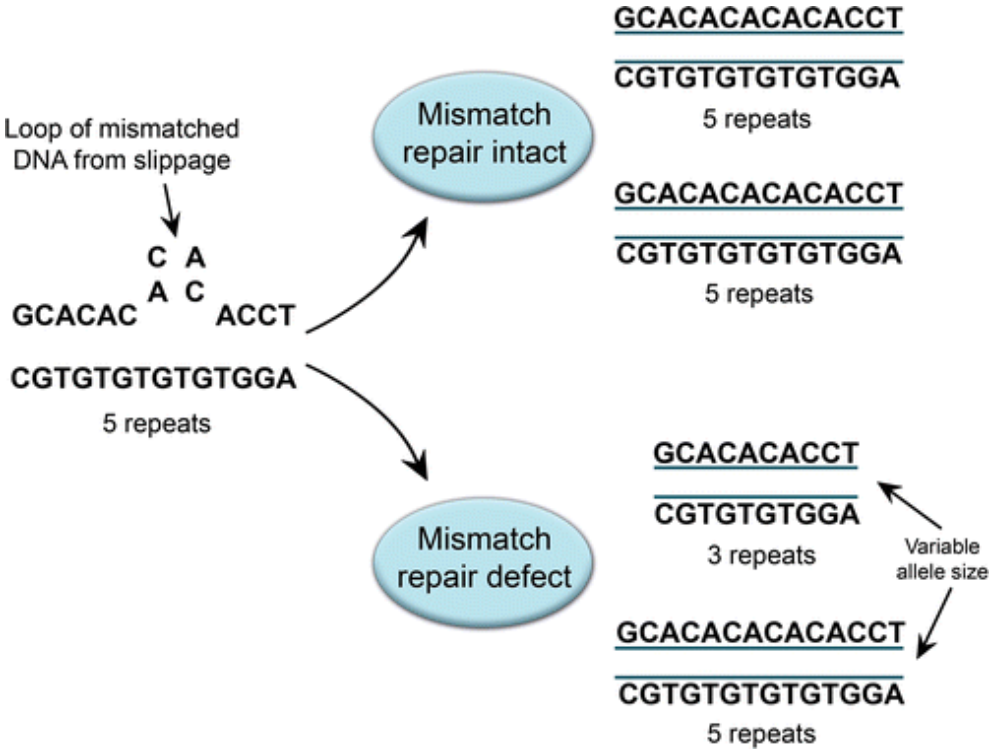
Lynch syndrome: flat lesion noted on conventional colonoscopy and improved visualization with chromo-colonoscopy (indigo carmine)

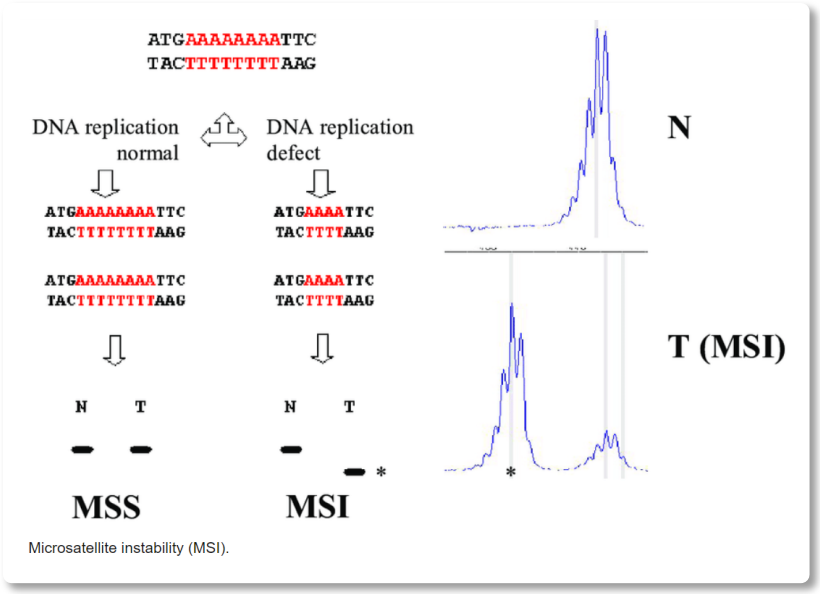
• Lynch syndrome

- Germline mutations of *hMLH1* (50%), *hMSH2* (40%), *hPMS1*, *hPMS2*, *hMSH6*, caretaker tumor suppressors that function in DNA mismatch repair (MMR).
- Characterized by microsatellite instability (MSI-H).

Repair genes : a super- highway to cancer

- Microsatellite instability (MSI) is caused by defective DNA mismatch repair (dMMR) genes and is characterized by a decrease or increase in repeated nucleotide sequences, which can lead to evasion of apoptosis, development of malignant mutations, and tumorigenesis.





Microsatellite instability (MSI).

- MSI is a marker of dMMR.

MLH1 & MSH2

The primary genes that can cause the HNPCC syndrome.

ONE in 740.

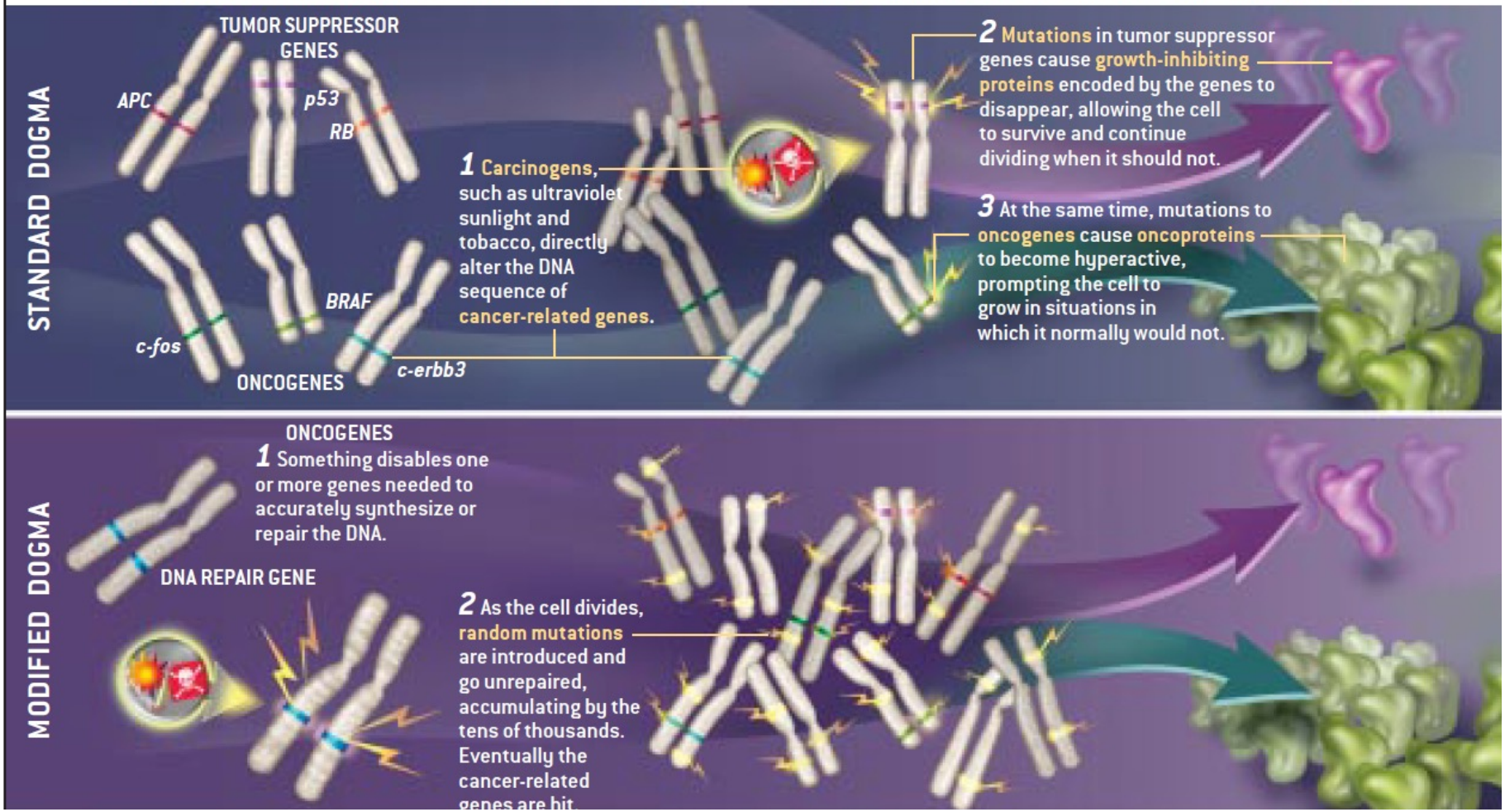
The average number of people carrying mutations in the genes responsible for HNPCC.

HNPCC: Hereditary nonpolyp colon carcinoma

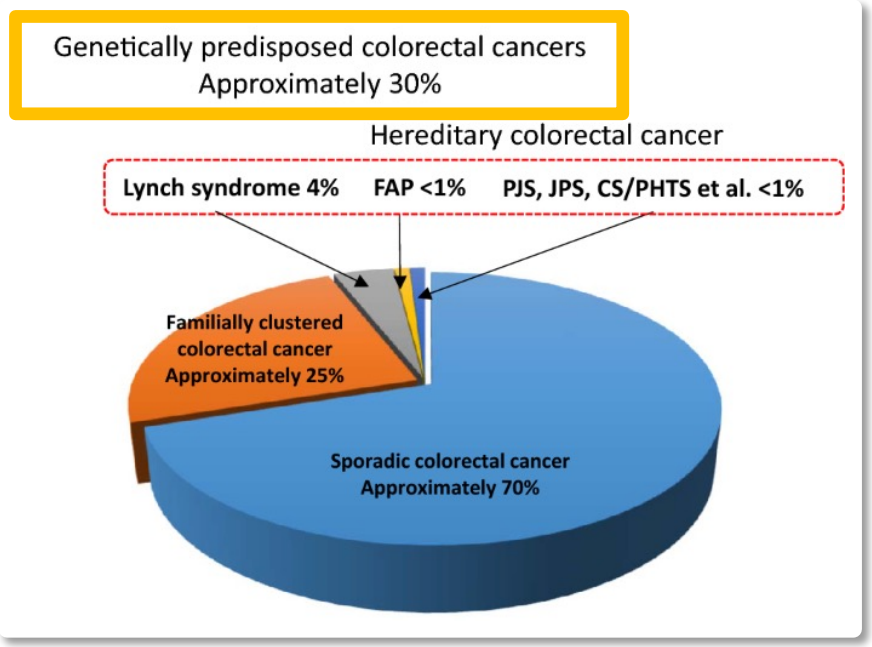
HNPCC Cancer Type	Mutation Carrier Risk[1,35]	General Population Risk
Colorectal	70-82%	2%
Endometrial	42-60%	1.5%
Stomach	13%	<1%
Ovarian	12%	1%
Kidney/ Urinary Tract	4%	<1%
Brain	3.7%	<1%
Biliary Tract	2%	<1%
Central Nervous System	2%	<1%
Small Bowell	1-4%	<1%

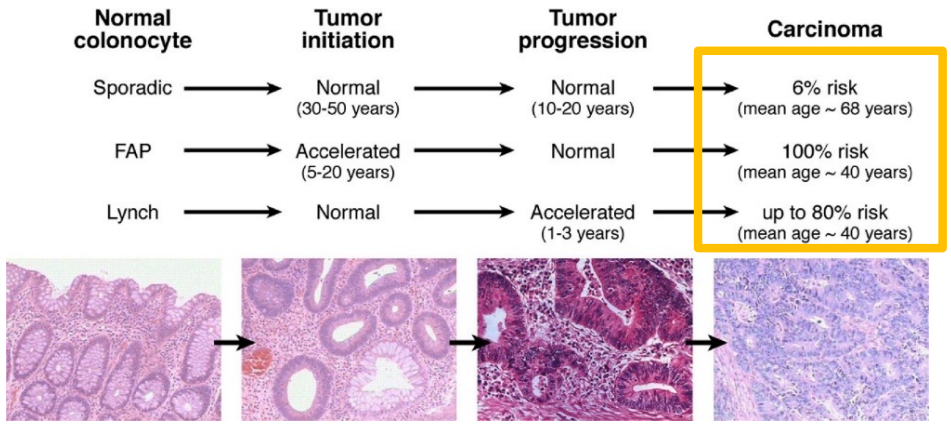
THE GENESIS OF CANCER: FOUR THEORIES

FOR DECADES, the most widely accepted view of how cancer begins has been that mutations to a handful of special genes eliminate tumor suppressor proteins and activate oncoproteins. More recently, three alternative theories have gained currency. One modifies the standard paradigm by postulating a dramatic increase in the accumulation of random mutations throughout the genomes of precancerous cells. Two other theories focus on the role of aneuploidy:



• Who is at highest risk for colon cancer?





- Fig. 1. Depiction of colorectal tumor progression in sporadic and high-risk genetic syndromes. The general paradigm is that a tumor is initiated from a normal colonocyte stem cell that has sustained genetic damage over time due to the local environment and any germline genetic mutation that has been inherited.
- The damaged DNA provides a growth advantage that drives tumor progression as successive clonal outgrowths are generated, ultimately forming carcinoma.
- In FAP, tumor initiation is accelerated with the inheritance of a germline *APC* mutation; in Lynch syndrome, tumor intitiation might be normal to slightly accelerated, but tumor progression is greatly accelerated due to the hypermutable phenotype that occurs with loss of DNA MMR.
- Photomicrographs depict, in order, normal colon, tubular adenoma, high-grade dysplasia, and cancer.

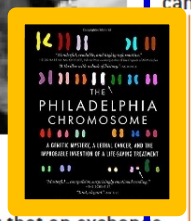
- Cancer campaigner Dame Deborah James died in June 2022, aged 40, after being diagnosed with incurable bowel cancer six years prior. James, who was awarded a damehood last May for her tireless efforts in raising awareness of the disease, was committed to showing that it is possible to live a full life with cancer.

BRANCHING POINTS IN THE EVOLUTION OF CANCER THEORY

1914 Boveri suggests that aberrant chromosomes may cause cancer

1927 Hermann J. Muller observes that radiation mutates cells

1951 Muller proposes theory that multiple mutations turn a cell malignant



1960 Discovery that an exchange of DNA between chromosomes 9 and 22 leads to chronic myelogenous leukemia

1971 Alfred G. Knudson explains different rates of inherited and spontaneous retinal cancer with the hypothesis that two "hits," or damaging mutations, are needed to disable both alleles of the *RB* gene and that one mutation can be inherited

1974 Loeb argues that random mutations must accumulate much faster than is normal inside cells that become malignant

1990 Vogelstein and Eric R. Fearon publish a model of sequential gene mutations that lead to colon cancer

1986 Weinberg and colleagues isolate *RB*, the first tumor suppressor gene

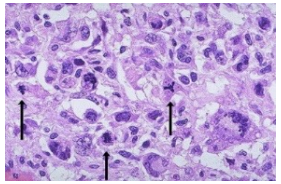
1997 Lengauer, Vogelstein and co-workers demonstrate dramatic increase in gain and loss of chromosomes in colon tumor cells and propose that chromosomal instability is a critical early event that leads to the mutation of oncogenes and tumor suppressor genes

2002 Reid identifies recurrent patterns of aneuploidy in human cervical and colon cancers

2003 The number of identified cancer genes, now well over 100, continues to grow rapidly

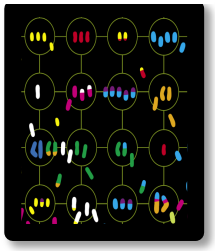
1999 Duesberg and collaborators publish detailed theory of how aneuploidy may be sufficient to cause cancer itself, even without mutations to any particular set of genes

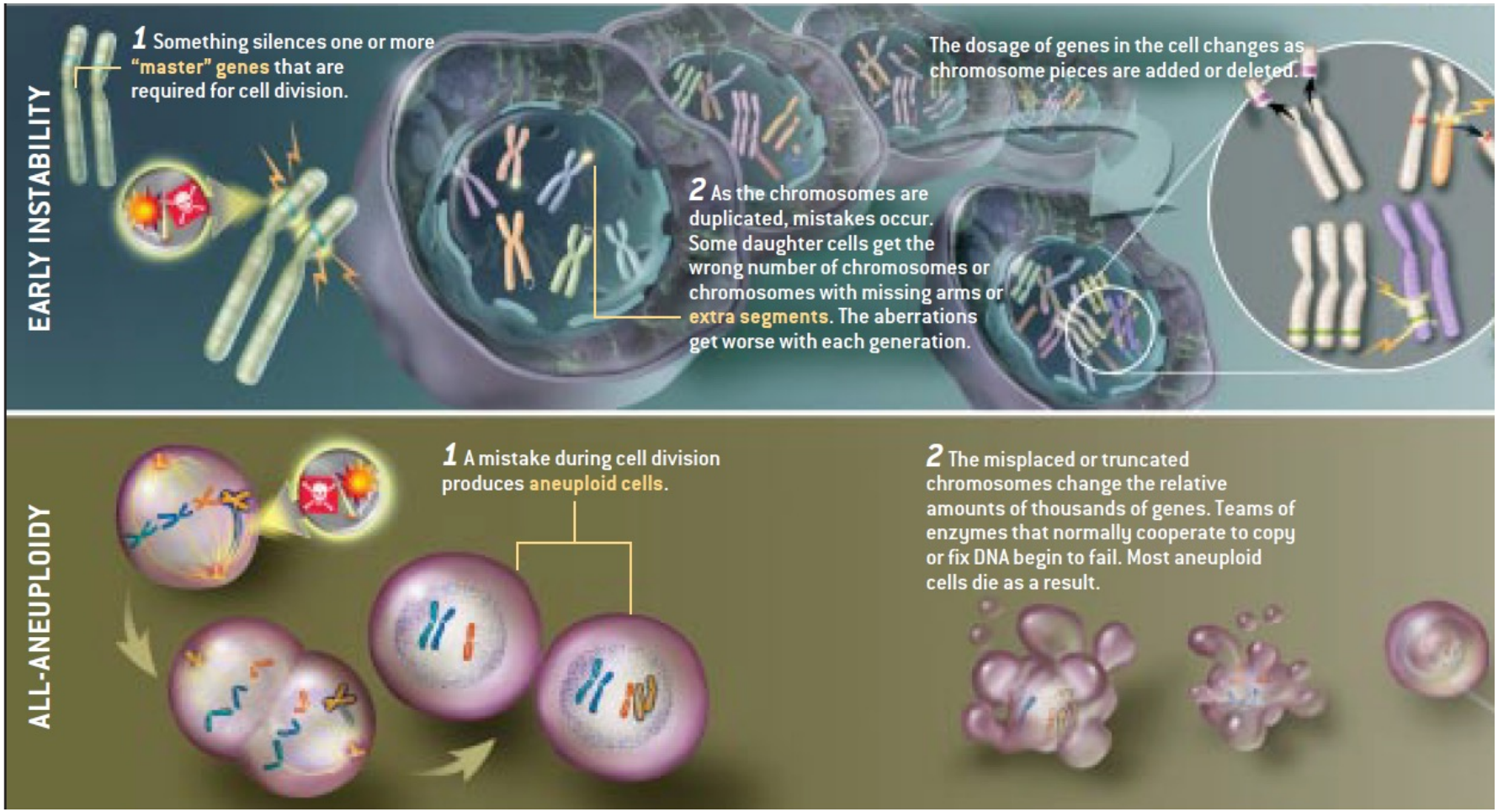
1915 1920 1925 1930 1935 1940 1945 1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000



An important difference

It takes (at least) two to tango




EARLY INSTABILITY
1 Something silences one or more "master" genes that are required for cell division.
2 As the chromosomes are duplicated, mistakes occur. Some daughter cells get the wrong number of chromosomes or chromosomes with missing arms or extra segments. The aberrations get worse with each generation.
The dosage of genes in the cell changes as chromosome pieces are added or deleted.
ALL-ANEUPLOIDY
1 A mistake during cell division produces aneuploid cells.
2 The misplaced or truncated chromosomes change the relative amounts of thousands of genes. Teams of enzymes that normally cooperate to copy or fix DNA begin to fail. Most aneuploid cells die as a result.

THE GENESIS OF CANCER: FOUR THEORIES

FOR DECADES, the most widely accepted view of how cancer begins has been that mutations to a handful of special genes eliminate tumor suppressor proteins and activate oncoproteins. More recently, three alternative theories have gained currency. One modifies the standard paradigm by postulating a dramatic increase in the accumulation of random mutations throughout the genomes of precancerous cells. Two other theories focus on the role of aneuploidy: