Hypotheses of Origin of Neoplasia

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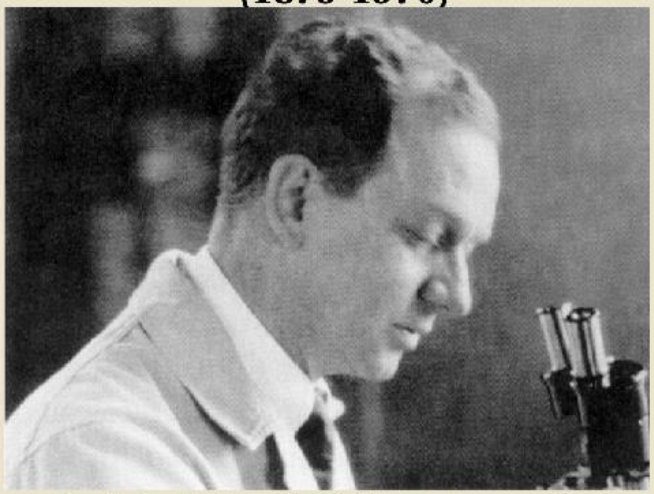
- Several of these hypotheses have enjoyed a phase of respectability, followed by a period of discreditation and then reemergence in modified form.

- Hypotheses of the viral cause of neoplasia . with the demonstration of transmission of certain animal neoplasms by ultrafiltrable agents (Rous sarcoma, 1908; Shope papilloma, 1933; Bittner milk factor, 1935).

- Immunologic hypotheses came to the fore after experiments involving tumor transplantation in animals (Ehrlich, 1908; Immune surveillance, Burnet, 1950s).

- (DNA) mutations (Watson and Crick, 1950s).

Peyton Rous
(1879-1970)



Peyton Rous isolated the first tumor-causing animal virus in 1911 at the Rockefeller Institute.
For his discovery of the **Rous sarcoma virus** he won the Nobel Prize in 1966.

- In 2001, in a landmark paper, Schreiber reported that mice, lacking an innate and adaptive immune system, had a dramatically increased rate of tumor formation

- This study invalidated the conclusions of the Stutman study, and **revived** the idea that the immune system could play a critical role.

- Subsequent work showed that tumors escape immune recognition by losing their antigenicity in a process he named cancer immunoediting.

Two general types of origins proposed for neoplasms

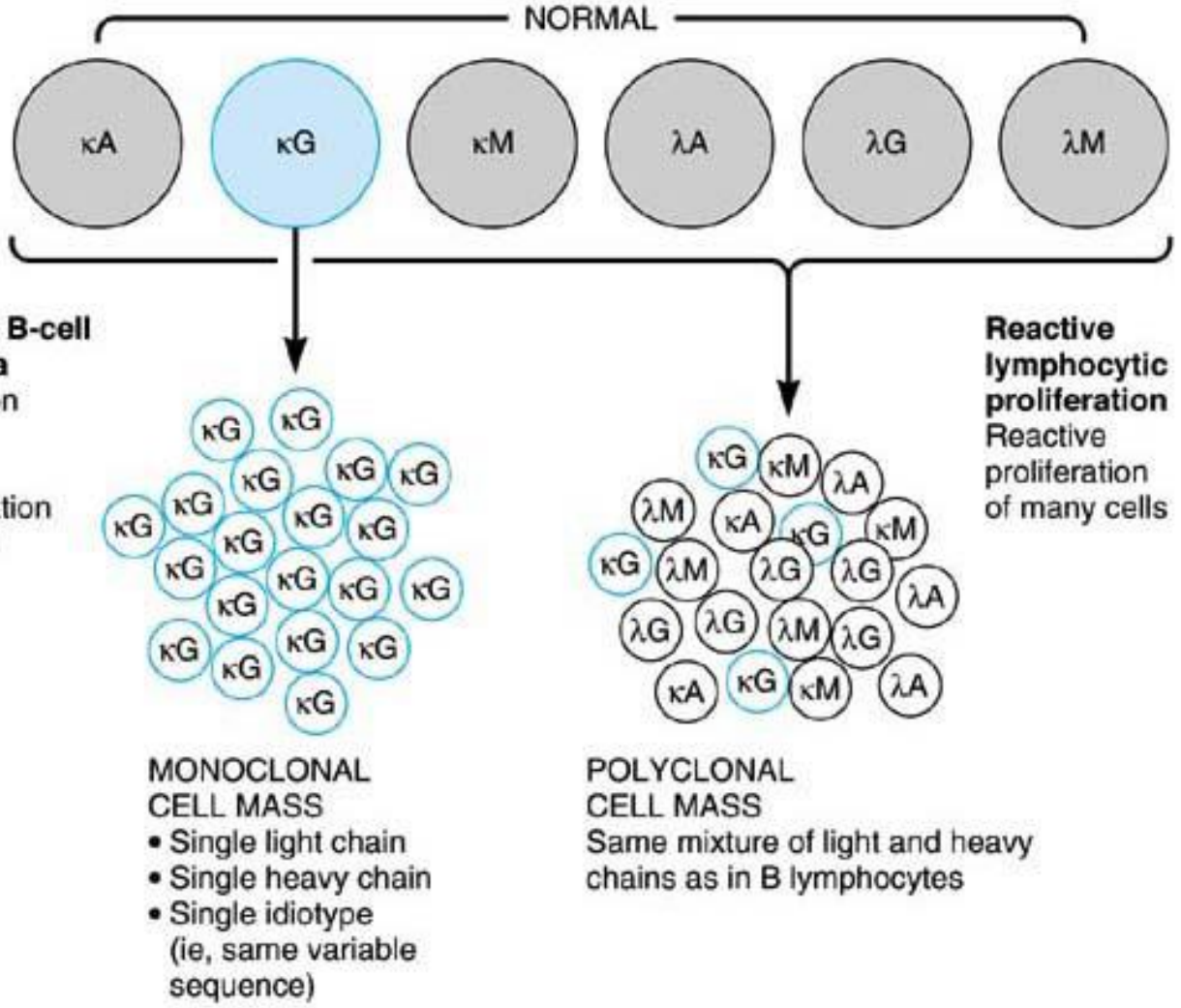
Monoclonal Origin

- The initial neoplastic change affects a single cell,
- Which then multiplies and
- Gives rise to the neoplasm.

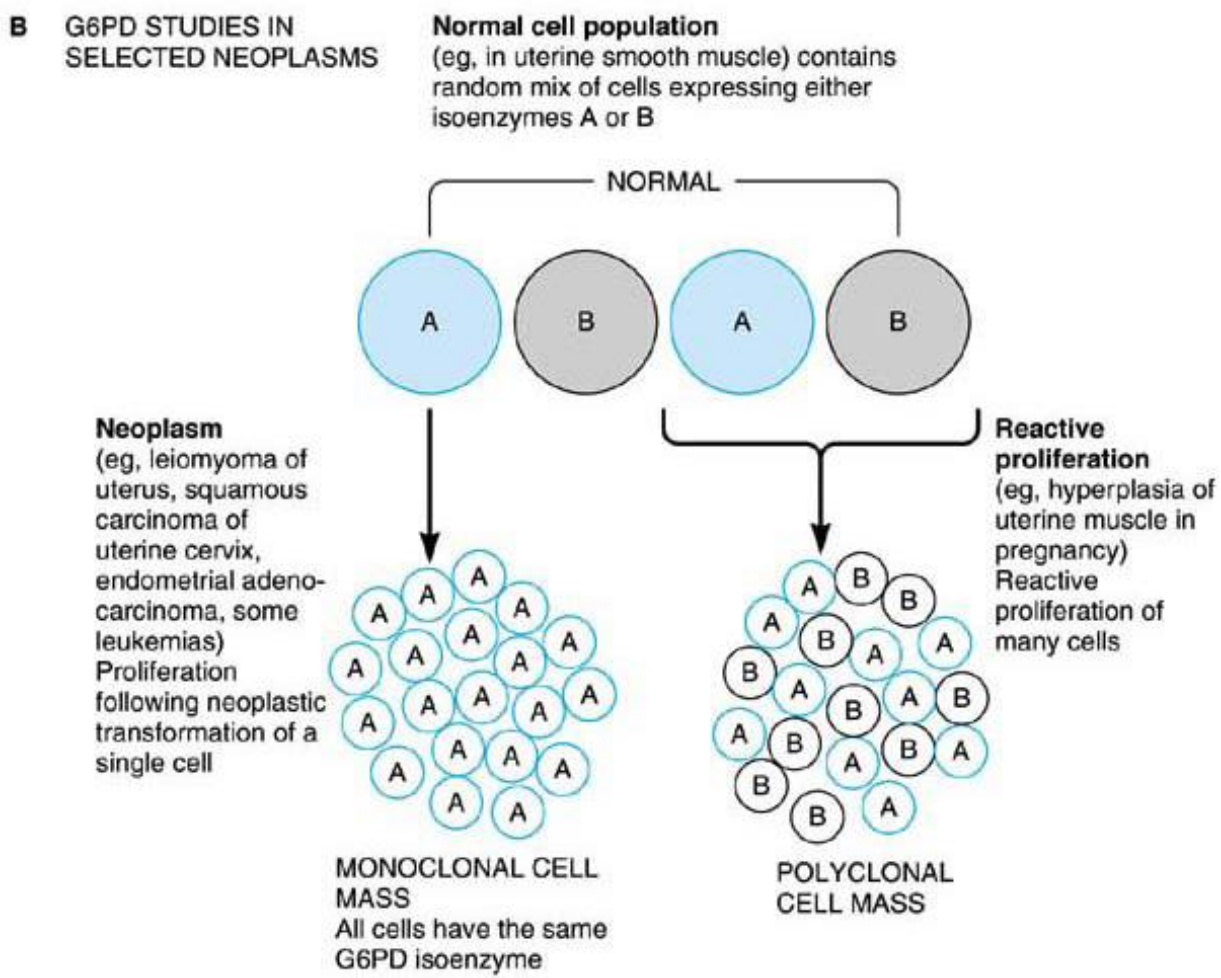
- Clearly shown in neoplasms of B lymphocytes (B-cell lymphomas and plasma-cell myelomas) that produce immunoglobulin and in some other tumor types by isoenzyme studies

A B-LYMPHOCYTE NEOPLASMS

Normal B lymphocytes have kappa (κ) or lambda (λ) light chains and G, M, or A heavy chains



G6PD isoenzyme inheritance is X-linked. In heterozygous females, one X chromosome codes for the A isoenzyme and the other for the B isoenzyme. Because one X chromosome is randomly inactivated in the adult cell, an adult cell will contain only one of the isoenzymes. A polyclonal population will be composed of cells containing both isoenzymes in approximately equal amounts, whereas a monoclonal population will be composed of cells that express only one isoenzyme



Field Origin

- A carcinogenic agent acting on a large number of similar cells may produce a field of potentially neoplastic cells.

- Neoplasms may then arise from one or more cells within this field. In many cases the result is several discrete neoplasms, each of which derives from a separate clonal precursor.

- The field change may be regarded as the first of 2 or more sequential steps that lead to overt cancer (multiple hits).

- Skin, urothelium, liver, breast, and colon.

- Alert the clinician to the possibility of a second similar neoplasm.

- cancer in one breast carries a risk of cancer in the opposite breast that is about 10 times higher than that of the general population.

The Lag Period

The interval (lag period) between exposure and development of the neoplasm

- A constant feature of all known agents that cause neoplasms

- In survivors of Hiroshima and Nagasaki, the largest number of cases of leukemia occurred about 10 years after the event, and some cancers developed as late as 20 years afterward.

- In shipyard workers exposed to asbestos

- However, new cases were identified through the 1970s even though exposure stopped in the 1940s.

- In utero exposure to diethylstilbestrol may give rise to vaginal cancer 15 or more years after birth

During the lag period

- The altered cell may not show any structural or functional abnormality; for example, an epidermal cell that has been exposed to a carcinogen looks and functions the same as surrounding cells.

- Subtle changes are present in such cells, particularly in the genome, but these may not be apparent morphologically

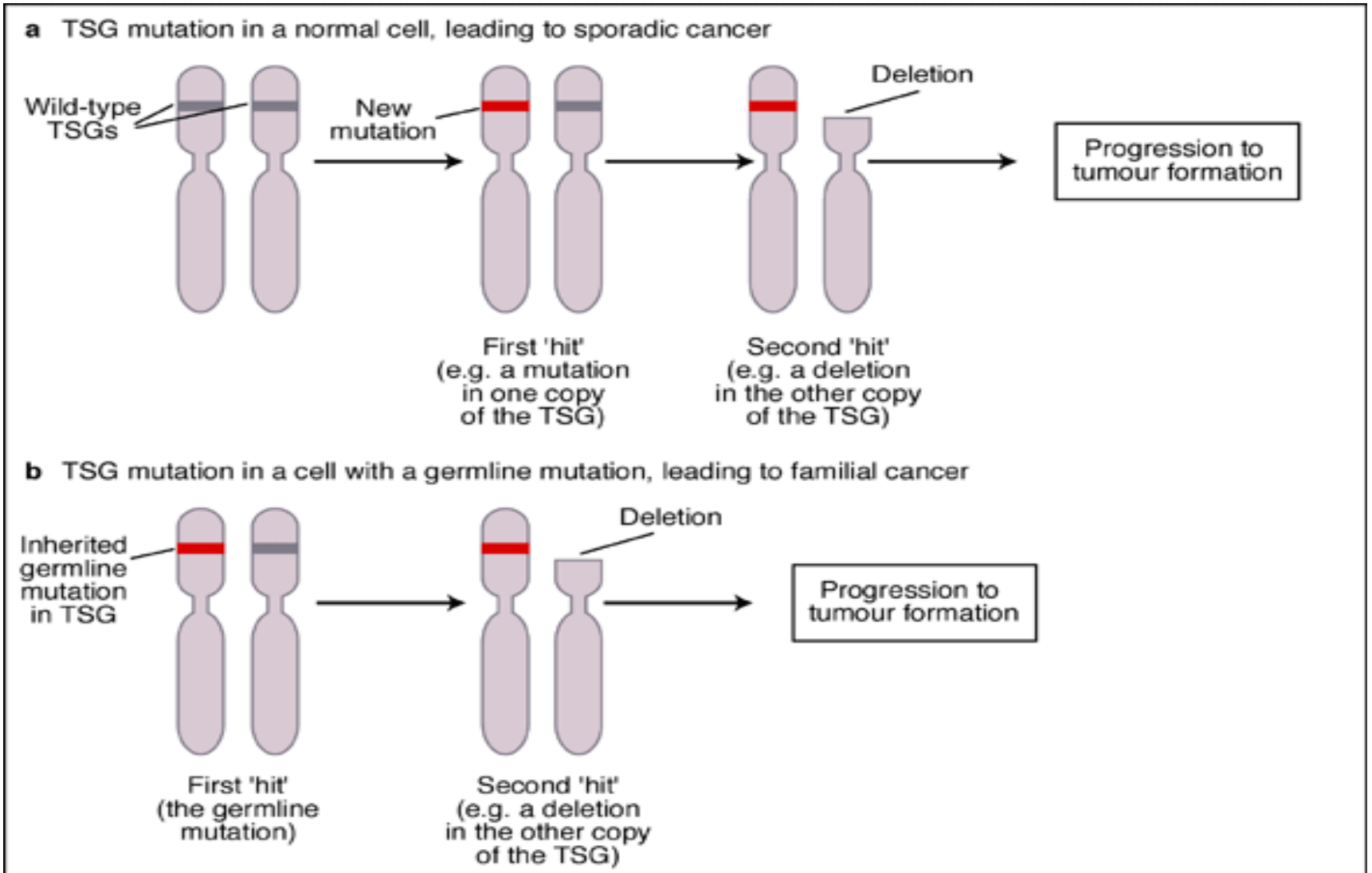

dS/dt = -kS
p(0) = e^-m
p(n) = m^n/n! e^-m

Multiple Hits & Multiple Factors

- Knudson proposed that carcinogenesis requires two hits.

- The first event is **initiation**, and the carcinogen causing it is the **initiator.**

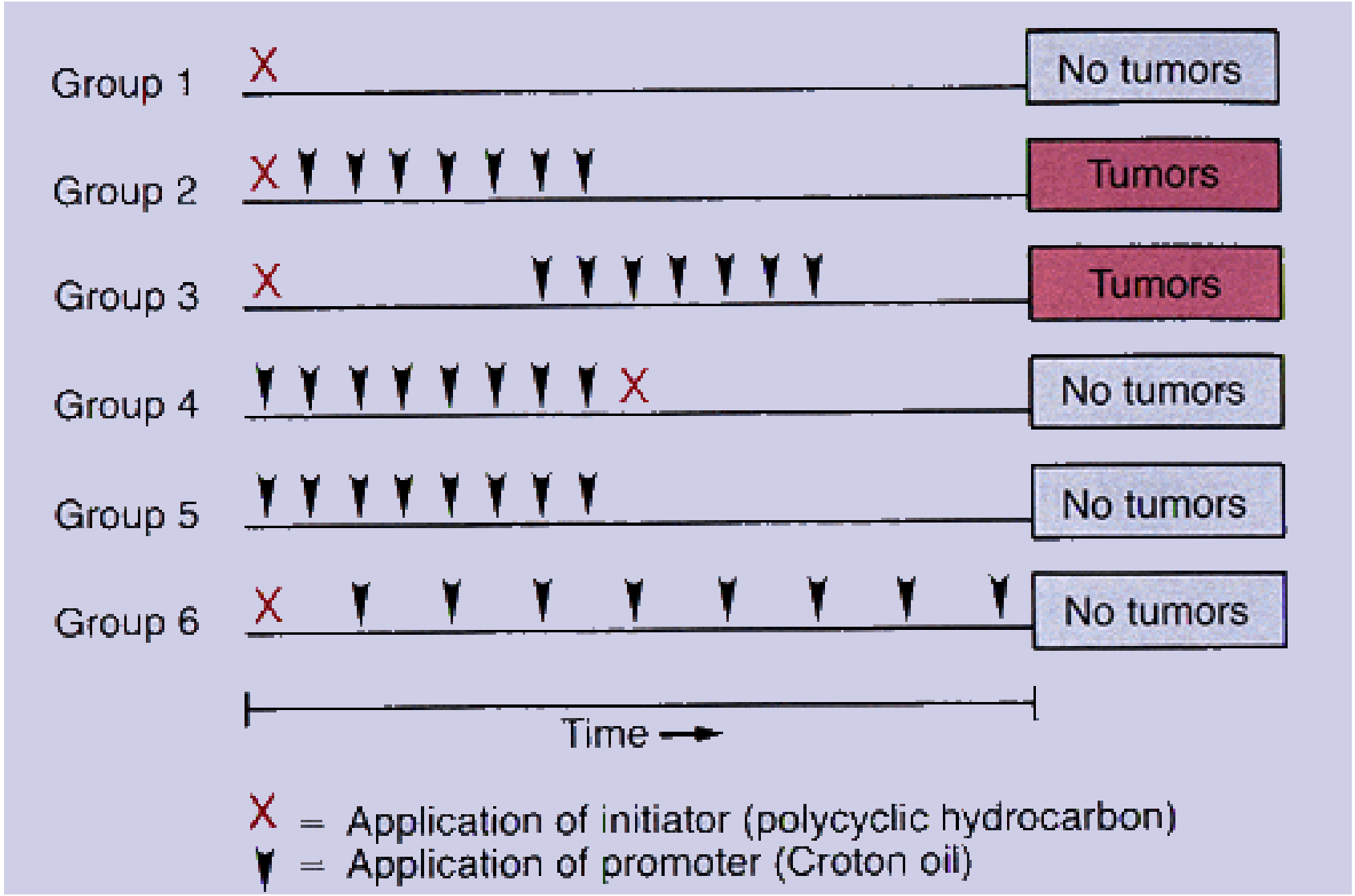
- The second event, which induces neoplastic growth, is **promotion,** and the agent is the **promoter.**



Knudson's two-hit hypothesis for tumourigenesis involving a tumour suppressor gene (TSG)

- It is now believed that in fact multiple hits occur (five or more),
- That multiple factors may cause these hits, and
- That each hit produces a change in the genome of the affected cell
- That is transmitted to its progeny (ie, the neoplastic clone).

- The period between the first hit and the development of clinically apparent cancer is the **lag period.**


Group 1
Group 2
Group 3
Group 4
Group 5
Group 6
No tumors
Tumors
Tumors
No tumors
No tumors
No tumors
Time
X = Application of initiator (polycyclic hydrocarbon)
= Application of promoter (Croton oil)

The multistep process involves

Initiation & Promotion

Classical experiments performed on mouse skin.

- Initiation results from the exposure of cells to a certain doze of a carcinogen (initiator).

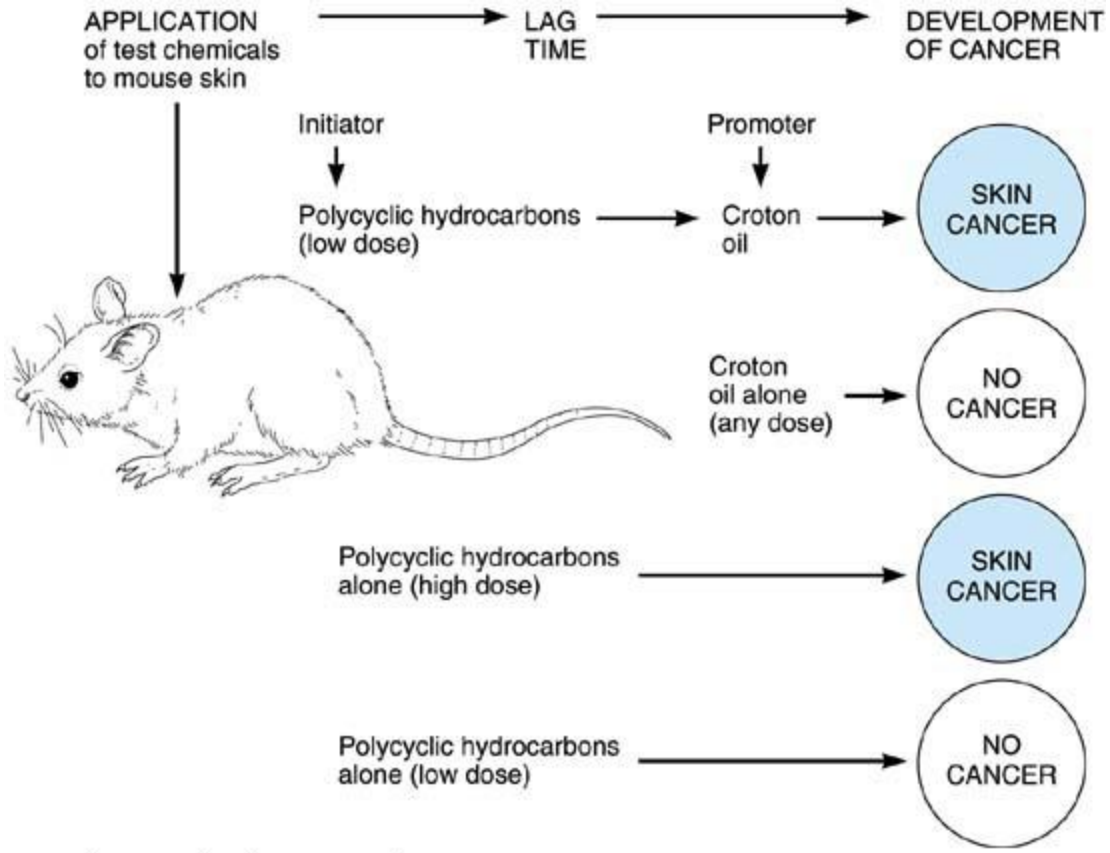
- An initiated cell is altered making it more likely to give rise to a tumour (if exposed to another agent; group 2 &3).

- Initiation alone is not sufficient for tumour formation (group 1).
- Initiation cause permanent DNA damage (mutations).
- Thus it is rapid irreversible and inheritable (group 3).
- In this group tumours were produced even if the application of the promoting agent was delayed for a long period of time after a single application of the initiator.
- Initiators can themselves bind and change DNA(direct acting) or procarcinogens, which require metabolic conversion in vivo to produce ultimate carcinogen

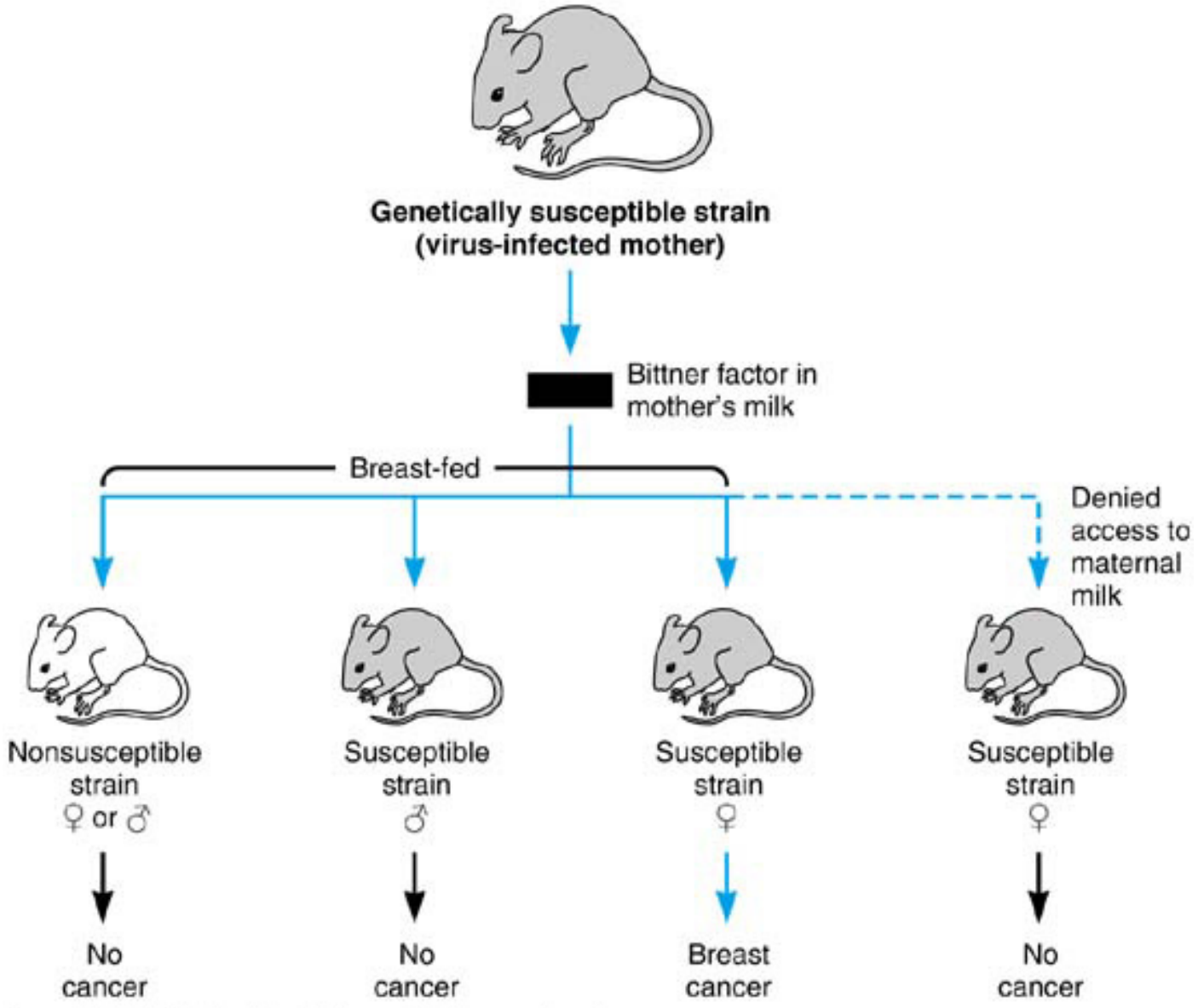
- Promoters can induce tumours in initiated cells, but they are non-tumourigenic by themselves (group 5).

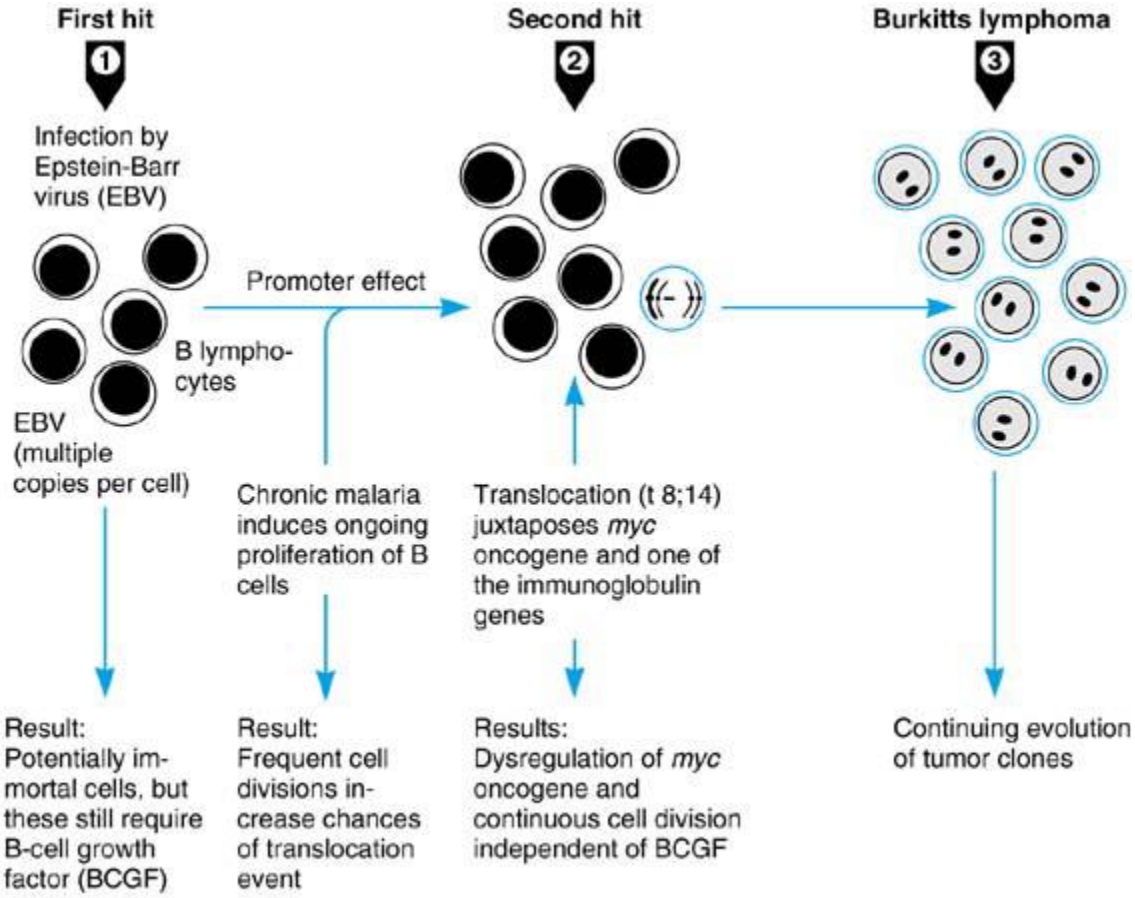
- Also, tumours do not result when the promoting agent is applied before the initiating agent (group 4).

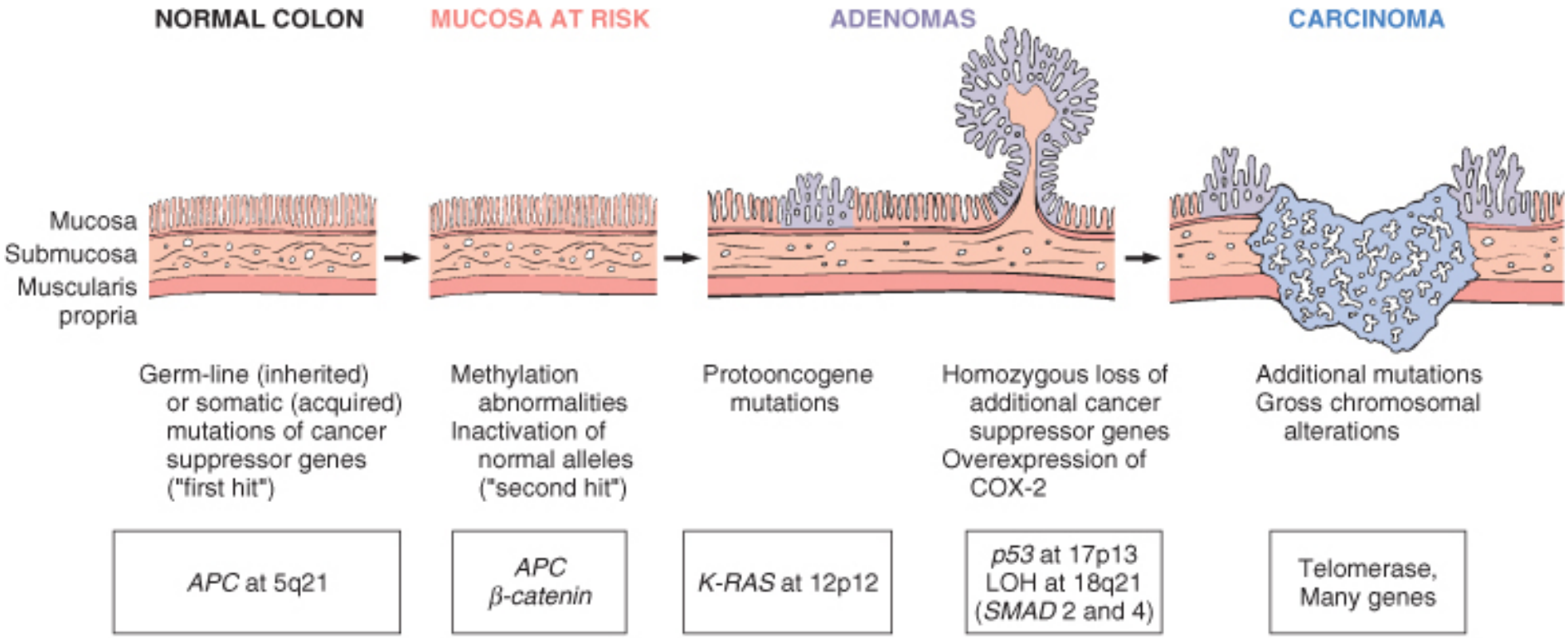
- This indicates that unlike initiating agents, promoting agents do not affect DNA directly and are reversible (group 6).



The role of the Bittner milk factor ([RNA] virus) in mouse mammary carcinoma







Normal →	Hyperplasia →	Adenoma →	Adenoma and Dysplasia →	Carcinoma →	Metastasis
Chromosome	5q	12p	18q	17p	
Change	m/del	m	del	m/del	?
Gene	*APC*	*Kras*	*DCC*	p53	?

Hypothesis of Failure of Immune Surveillance

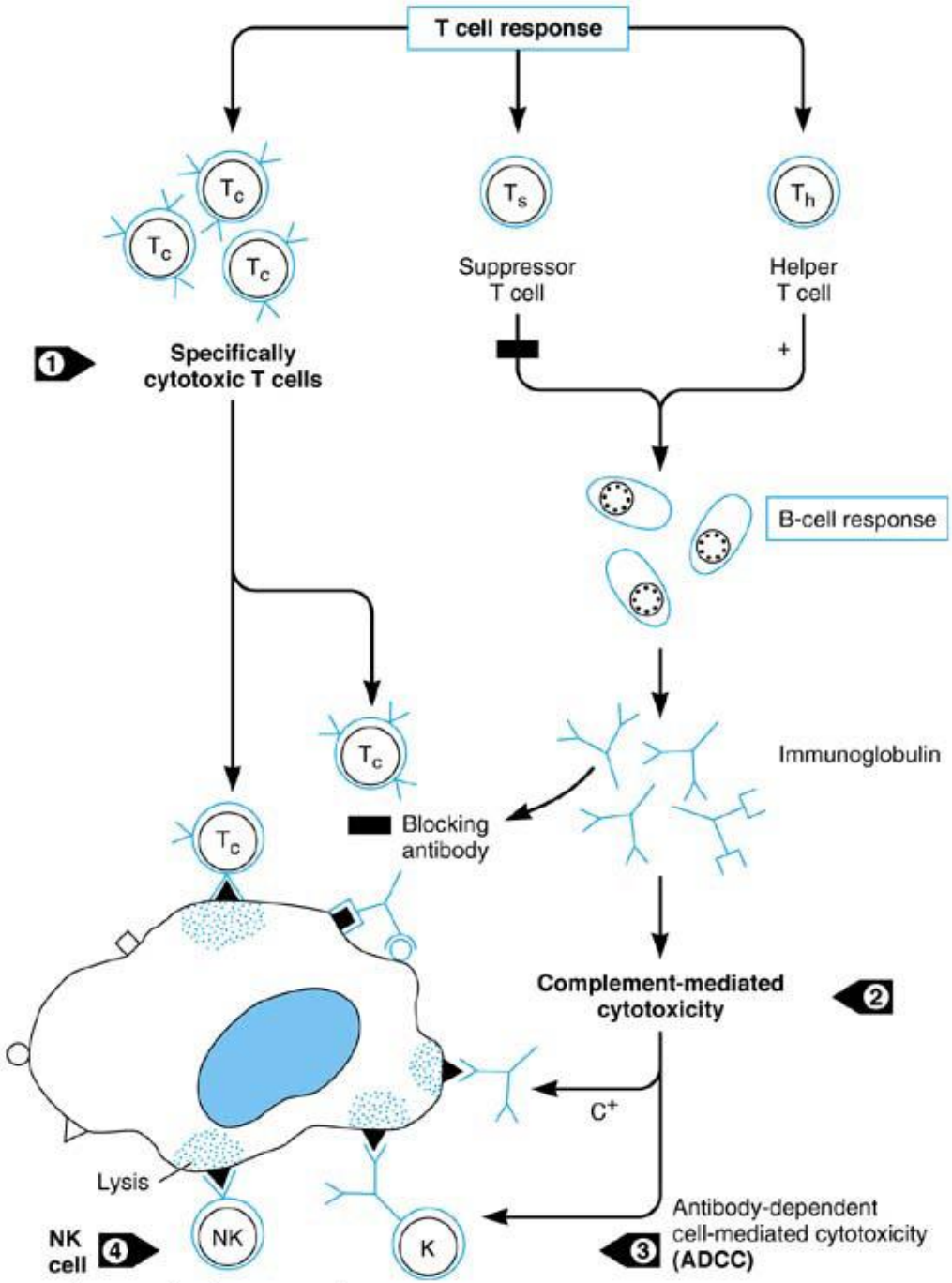
The hypothesis of immune surveillance encompasses several concepts:

(1) Neoplastic changes frequently occur in the cells

(2) DNA alteration => neoantigens

(3) The immune system => cytotoxic immune response destroying the neoplastic cells

(4) Neoplastic cells produce clinically detectable neoplasms only if they escape recognition and destruction by the immune system.



Challenges to this hypothesis are based on several findings:

- (1) T cell-deficient strains of mice do not show higher rates of neoplasia;
- (2) Immunodeficient humans or transplant recepients mainly lymphomas and not a full spectrum of different cancers
- (3) Thymectomized humans do not show an increased incidence of neoplasia; and
- (4) although many tumors do possess tumor-associated antigens and an immune response can often be demonstrated, the response is clearly ineffective at the time of clinical expression of the cancer.