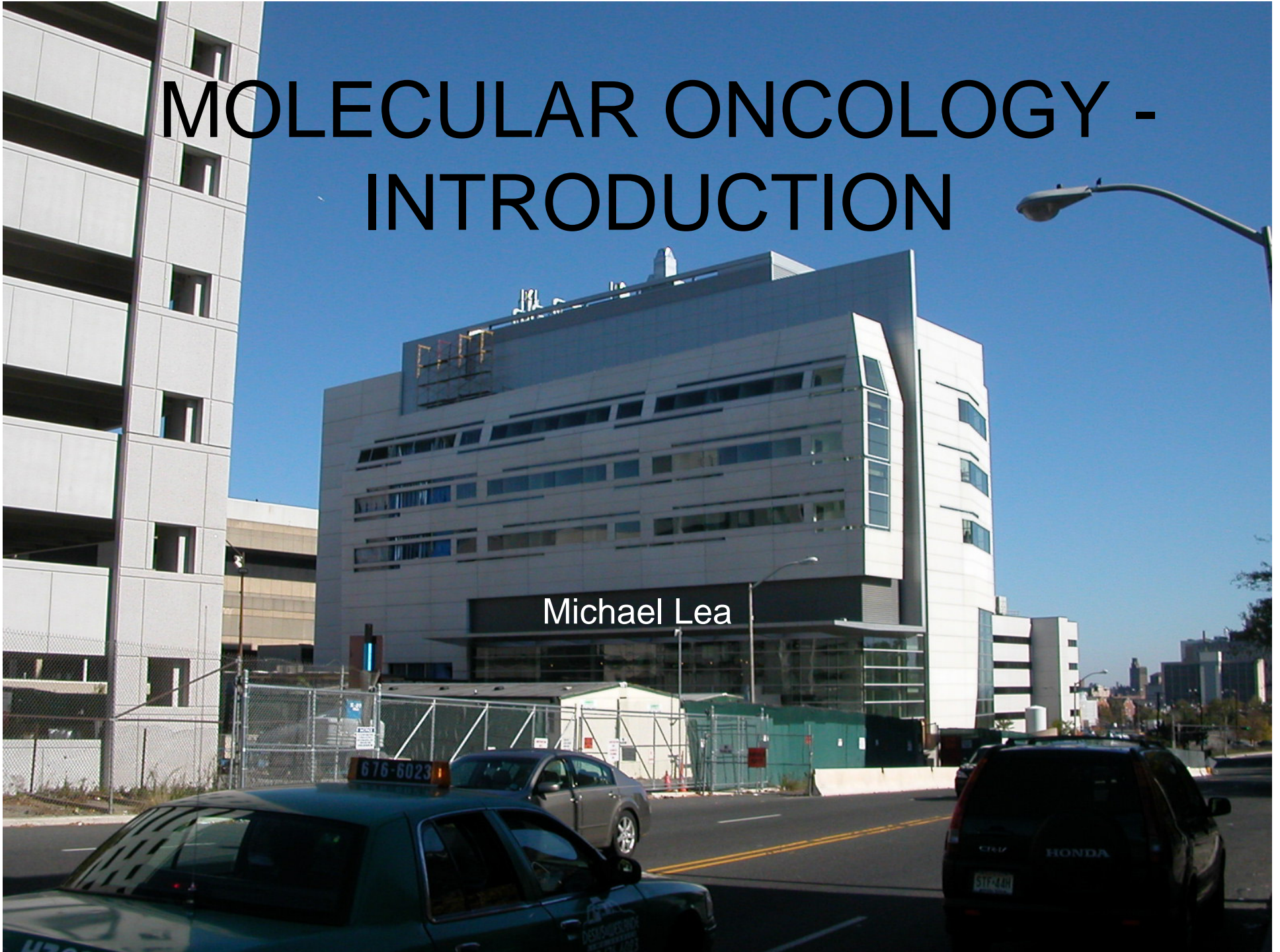


MOLECULAR ONCOLOGY - INTRODUCTION

Michael Lea



GOALS OF THE MOLECULAR ONCOLOGY COURSE

- **To describe the nature of cancer (what is cancer?)**
- **To review the causes of cancer (what starts cancer?)**
- **To distinguish the biochemistry of normal and cancer tissue (what is different about cancer cells?)**
- **To consider the treatment of cancer (how can we cure cancer?)**
- **To discuss measures for the prevention of cancer (how can we prevent cancer?)**

Peyton Rous – Nobel Lecture, December 13, 1966
The Challenge to Man of the Neoplastic Cell

Tumors destroy man in a unique and appalling way, as flesh of his own flesh which has somehow been rendered proliferative, rampant, predatory and ungovernable.

MOLECULAR ONCOLOGY LITERATURE

There is no required text for the course. The recommended text is R.A. Weinberg, *The Biology of Cancer*, Garland Science, New York, NY (2007). The following texts provide a reference list for those who wish to read further. The most relevant texts for this course are given in bold.

DeVita, V.T., Hellman, S. and Rosenberg, S.A. (editors), *Cancer Principles and Practice of Oncology*, 6th edition, Lippincott, Williams and Wilkins: Philadelphia, 2001.

Franks, L.M. and Teich, N.M., (editors) *Introduction to the Cellular and Molecular Biology of Cancer*, 3rd edition, Oxford University Press: Oxford and New York, 1997.

Greenstein, J.P., *Biochemistry of Cancer*, 2nd edition, Academic Press: New York, 1954.

Kufe, D.W., Frei, E., Hollander, J.F., Weichselbaum, R.R., Pollock, R.E., Bast, R.C., Gansler, T.S., (editors): *Holland-Frei Cancer Medicine*, 6th edition, B.C. Decker: Hamilton, Ontario, 2003. *Available on line through the Smith Library*

MOLECULAR ONCOLOGY LITERATURE (CONTINUED)

McKinnel, R.G., Parchment, R.E., Perantoni, A.O., Damjanov, I. and Pierce, G.B., *The Biological Basis of Cancer* (2nd ed.), Cambridge University Press, Cambridge and New York, 2006.

National Program for the Conquest of Cancer. Report of the National Panel of Consultants on the Conquest of Cancer. Part 2. U.S. Government Printing Office: Washington D.C. 1970.

Pitot, H.C., *Fundamentals of Oncology*, 4th edition, Marcel Dekker: New York and Basel, 2002.

Ruddon, R.W., *Cancer Biology*, 4th edition, Oxford University Press: Oxford and New York, 2007.

Robbins and Cotran, *Pathologic Basis of Disease* (7th edition) Edited by Kumar, Abbas and Fausto, Elsevier Saunders,\: Philadelphia, PA, 2005, Chapter 7.

JOURNALS PUBLISHING RESEARCH ON CANCER

Anticancer Research
BBA Cancer Reviews
British Journal of Cancer
Cancer
Cancer Chemotherapy and Pharmacology
Cancer Letters
Cancer Research
Carcinogenesis
Clinical Cancer Research
European Journal of Cancer
International Journal of Cancer
International Journal of Oncology
Journal of the National Cancer Institute
Molecular Cancer Research
Molecular Cancer Therapeutics
Nature Reviews, Cancer
Oncogene
Oncology

THE NATURE OF CANCER

Cancer is a disease of multicellular organisms in which there is an uncontrolled proliferation of cells. The cardinal features of cancer are **growth, invasion and metastasis**. The term metastasis is given to the formation of secondary tumors at sites distant from the primary tumor. No morphological or biochemical change has been identified that is present in all cancer cells and has not been seen in any normal cell.

THE NATURE OF CANCER

An increase in tissue size can result from an increase in cell size (hypertrophy) or an increase in cell number (hyperplasia). The term **neoplasia** is used when the proliferating cells are morphologically abnormal. Such proliferation will usually give rise to a tissue mass which is described as a **tumor**. Although increased cell numbers are a feature of cancer, the rate of cell division is not always greater than for normal cells. An increased life span, as in leukemic cells, will result in a selective increase in numbers. However, neoplastic tissue usually grows more rapidly than the normal tissue of origin. This may arise from a shortening of the cell cycle or from an increase in the proportion of cells undergoing division.

Terms related to normal and abnormal cell growth

- **Anaplasia: Loss of differentiation of cells and/or tissues**
- **Aneuploidy: Possessing an abnormal number of chromosomes**
- **Carcinoma: Malignant neoplasm of endodermal or ectodermal origin**
- **Dysplasia: Abnormal tissue development**
- **Hyperplasia: Increased number of cells in a tissue**
- **Hypertrophy: Increase in the size of a tissue**
- **Metastasis: Growth of cells distant from the site of origin**
- **Neoplasm: An altered, relatively autonomous tissue growth**
- **Papilloma: Benign epithelial tumor**
- **Sarcoma: Malignant neoplasm of connective tissue origin**

BENIGN AND MALIGNANT TUMORS

The table below is taken from Pitot, Fundamentals of Oncology, 4th edition, 2002, p. 34. The table indicates the features which distinguish benign and malignant tumors:

| | <u>Benign</u> | <u>Malignant</u> |
|----|------------------------|-------------------------------|
| 1. | Usually encapsulated | Non encapsulated |
| 2. | Usually non invasive | Invasive |
| 3. | Highly differentiated | Poorly differentiated |
| 4. | Rare mitoses | Mitoses relatively common |
| 5. | Slow growth | Rapid growth |
| 6. | Little or no anaplasia | Anaplastic to varying degrees |
| 7. | No metastases | Metastases |

Properties of Transformed Malignant Cells Growing in Cell Culture and/or in Vivo (Table 9-1 from Ruddon in Kufe et al., Holland-Frei Cancer Medicine)

A. In vitro alterations

1. Cytologic changes resembling those of cancer cells in vivo include:

increased cytoplasmic basophilia

increased number and size of nuclei

increased nucleus:cytoplasmic ratio

formation of clusters and cords of cells.

Properties of Transformed Malignant Cells Growing in Cell Culture and/or in Vivo

(Table 9-1 from Ruddon in Kufe et al., Holland-Frei Cancer Medicine)

A. In vitro alterations

2. Alteration in growth characteristics:

- a. "Immortality" of transformed cells in culture. Transformed malignant cells become "immortal" in that they can be passaged in culture indefinitely.**
- b. Decreased density-dependent inhibition of growth or loss of "contact inhibition." Transformed cells frequently grow to a higher density than their normal counterparts, and they may 'pile up' in culture rather than stop growing when they make contact.**
- c. Decreased serum requirement. Transformed cells usually require lower concentrations of serum or growth factors to replicate in culture than nontransformed cells require.**
- d. Loss of anchorage dependence and acquisition of ability to grow in soft agar. Transformed cells may lose their requirement to grow attached to surfaces and can grow as free colonies in a semisolid medium.**
- e. Loss of cell-cycle control. Transformed cells fail to stop at cell-cycle checkpoints in the cell cycle when they are subject to metabolic restriction of growth.**
- f. Resistance to apoptosis (programmed cell death).**

Properties of Transformed Malignant Cells Growing in Cell Culture and/or in Vivo (Table 9-1 from Ruddon in Kufe et al., Holland-Frei Cancer Medicine)

- 3. Changes in cell membrane structure and function, including increased agglutinability by plant lectins; alteration in composition of cell surface glycoproteins, proteoglycans, glycolipids, and mucins; appearance of tumor-associated antigens; and increased uptake of amino acids, hexoses, and nucleosides.**
- 4. Loss of cell-cell and cell-extracellular matrix interactions that foster cell differentiation.**
- 5. Loss of response to differentiation-inducing agents and altered cellular receptors for these agents.**

Properties of Transformed Malignant Cells Growing in Cell Culture and/or in Vivo (Table 9-1 from Ruddle in Kufe et al., Holland-Frei Cancer Medicine)

6. Altered signal-transduction mechanisms, including constitutive rather than regulated function of growth factor receptors, phosphorylation cascades, and dephosphorylation mechanisms.

7. Ability to produce tumors in experimental animals. This is the sine qua non that defines malignant transformation in vitro. If the cells believed to be transformed do not produce tumors in appropriate animal hosts, they cannot be defined as "malignant." However, failure to grow in an animal model does not mean that they may not be tumorigenic in a different type of animal (eg, syngeneic vs allogeneic).

Properties of Transformed Malignant Cells

Growing in Cell Culture and/or in Vivo (Table 9-1)

from Ruddon in Kufe et al., Holland-Frei Cancer Medicine)

B. In vivo alterations

1. Increased expression of oncogene proteins as a consequence of chromosomal translocation, amplification, or mutation.
2. Loss of tumor-suppressor gene protein products because of deletion or mutation.
3. Alterations in DNA methylation patterns.
4. Genetic imprinting errors that lead to overproduction of growth-processing substances (eg, IGF-2).
5. Increased or unregulated production of growth factors (eg TGF- α), tumor angiogenesis factors, PDGF, hematopoietic growth factors (eg, CSFs, interleukins).

Properties of Transformed Malignant Cells Growing in Cell Culture and/or in Vivo (Table 9-1 from Ruddle in Kufe et al., Holland-Frei Cancer Medicine)

B. In vivo alterations

6. Genetic instability leading to progressive loss of regulated cell proliferation, increased invasiveness, and increased metastatic potential. "Mutator" genes may be involved in this effect.
7. Alteration in enzyme patterns. Malignant cells have increased levels of enzymes involved in nucleic acid synthesis and produce higher levels of lytic enzymes (eg, proteases, collagenases, glycosidases).
8. Production of oncodevelopmental gene products. Many cancers produce increased amounts of oncofetal antigens (eg, carcinoembryonic antigen), placental hormones (eg, human chorionic gonadotropin), or placental-fetal type isoenzymes (eg, placental alkaline phosphatase).
9. Ability to avoid the host's antitumor immune response.

Cellular origin and nomenclature of tumors



Sometimes a distinction is made between solid tumors and those tumors of the hemopoietic and immune system in which there is an increase in circulating abnormal cells.

A neoplasm is termed a **carcinoma** if it arises from tissue derived from embryonic ectoderm or endoderm. Those tumors of epithelial cells may be distinguished from tumors of connective tissue which are described as **sarcomas**. Most human neoplasms are carcinomas.

CANCER INCIDENCE AND MORTALITY

CA Cancer J Clin 2005;55:10-30

Estimated New Cases*

| | | | Males | Females | | | |
|-------------------------|----------------|-------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------|----------------|-------------|
| Prostate | 232,090 | 33% |  |  | Breast | 211,240 | 32% |
| Lung and Bronchus | 93,010 | 13% | | | Lung and Bronchus | 79,560 | 12% |
| Colon and Rectum | 71,820 | 10% | | | Colon and Rectum | 73,470 | 11% |
| Urinary Bladder | 47,010 | 7% | | | Uterine Corpus | 40,880 | 6% |
| Melanoma of the Skin | 33,580 | 5% | | | Non-Hodgkin Lymphoma | 27,320 | 4% |
| Non-Hodgkin Lymphoma | 29,070 | 4% | | | Melanoma of the Skin | 26,000 | 4% |
| Kidney and Renal Pelvis | 22,490 | 3% | | | Ovary | 22,220 | 3% |
| Leukemia | 19,640 | 3% | | | Thyroid | 19,190 | 3% |
| Oral Cavity and Pharynx | 19,100 | 3% | | | Urinary Bladder | 16,200 | 2% |
| Pancreas | 16,100 | 2% | | | Pancreas | 16,080 | 2% |
| All Sites | 710,040 | 100% | | | All Sites | 662,870 | 100% |

Estimated Deaths



| | | | Males | Females | | | |
|----------------------------------|----------------|-------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|--------------------------------|----------------|-------------|
| Lung and Bronchus | 90,490 | 31% |  |  | Lung and Bronchus | 73,020 | 27% |
| Prostate | 30,350 | 10% | | | Breast | 40,410 | 15% |
| Colon and Rectum | 28,540 | 10% | | | Colon and Rectum | 25,750 | 10% |
| Pancreas | 15,820 | 5% | | | Ovary | 16,210 | 6% |
| Leukemia | 12,540 | 4% | | | Pancreas | 15,980 | 6% |
| Esophagus | 10,530 | 4% | | | Leukemia | 10,030 | 4% |
| Liver and Intrahepatic Bile Duct | 10,330 | 3% | | | Non-Hodgkin Lymphoma | 9,050 | 3% |
| Non-Hodgkin Lymphoma | 10,150 | 3% | | | Uterine Corpus | 7,310 | 3% |
| Urinary Bladder | 8,970 | 3% | | | Multiple Myeloma | 5,640 | 2% |
| Kidney and Renal Pelvis | 8,020 | 3% | | | Brain and Other Nervous System | 5,480 | 2% |
| All Sites | 295,280 | 100% | | | All Sites | 275,000 | 100% |

FIGURE 1 Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths, by Sex, US, 2005.

*Excludes basal and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates are rounded to the nearest 10.

Note: Percentage may not total 100% due to rounding.

American Cancer Society, Surveillance Research, 2005

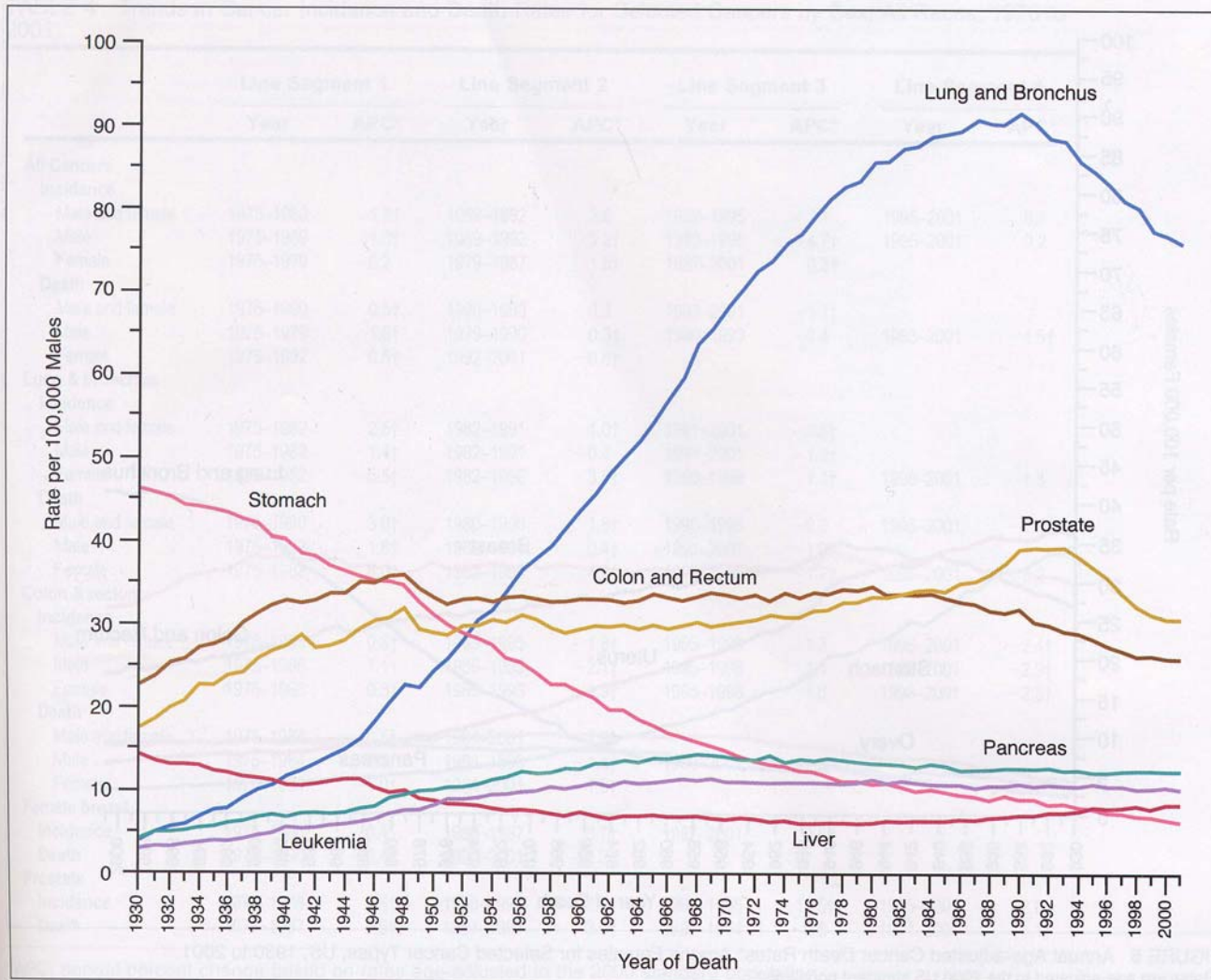


FIGURE 4 Annual Age-adjusted Cancer Death Rates* Among Males for Selected Cancer Types, US, 1930 to 2001.

*Rates are age-adjusted to the 2000 US standard population.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the lung and bronchus, colon and rectum, and liver are affected by these changes.

Source: US Mortality Public Use Data Tapes, 1960 to 2001, US Mortality Volumes, 1930 to 1959, National Center for Health Statistics, Centers for Disease Control and Prevention.

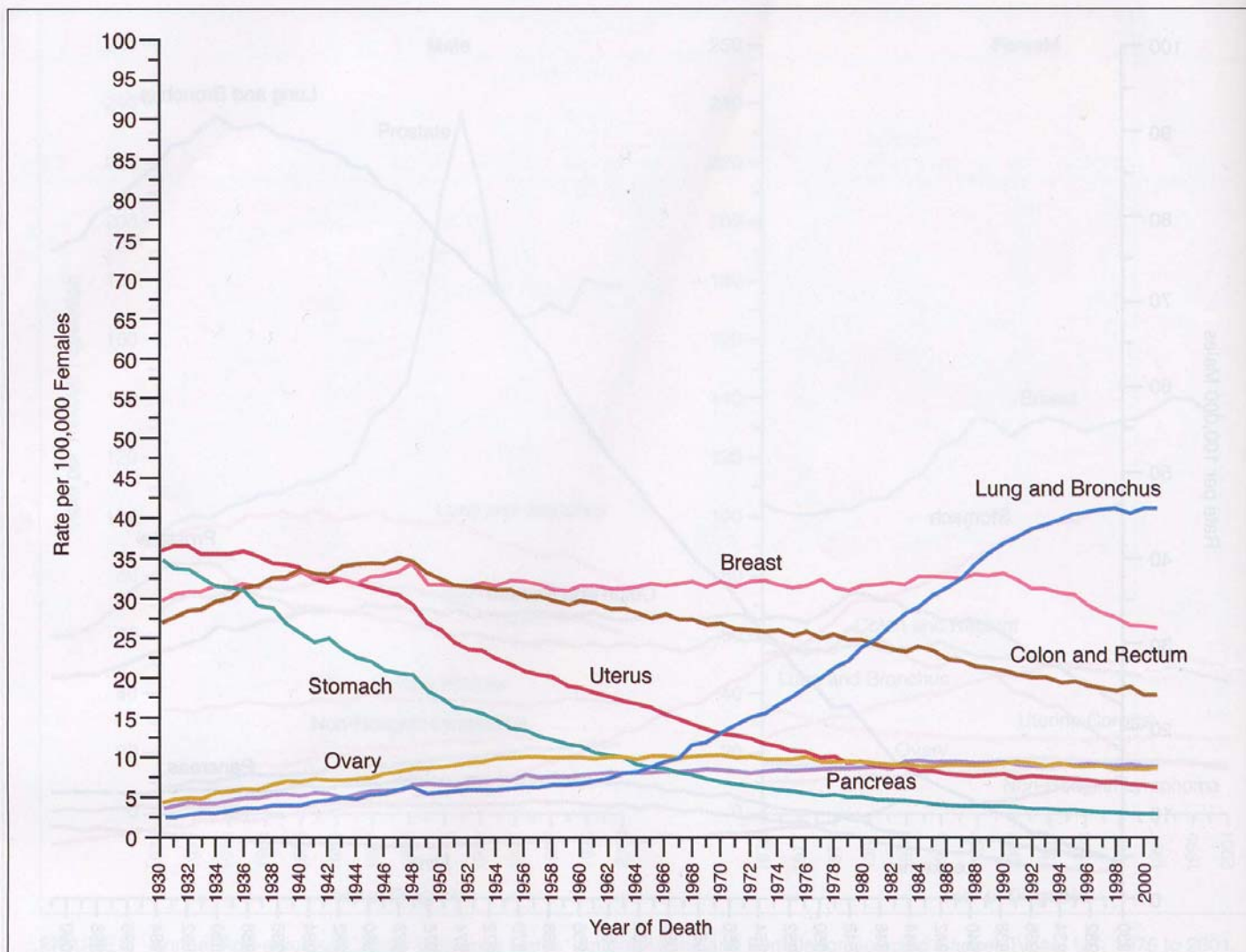


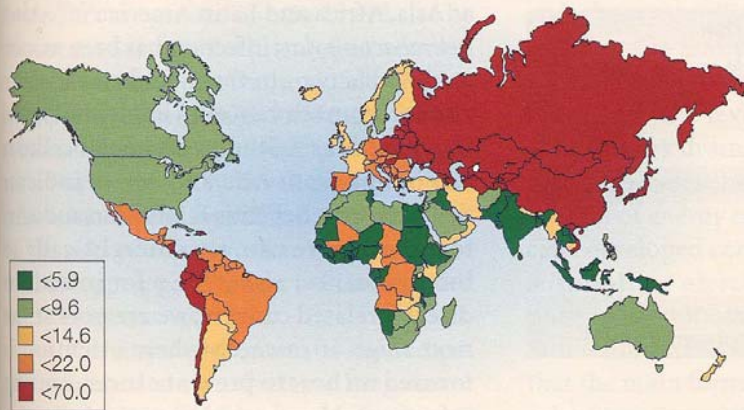
FIGURE 5 Annual Age-adjusted Cancer Death Rates* Among Females for Selected Cancer Types, US, 1930 to 2001.

*Rates are age-adjusted to the 2000 US standard population.

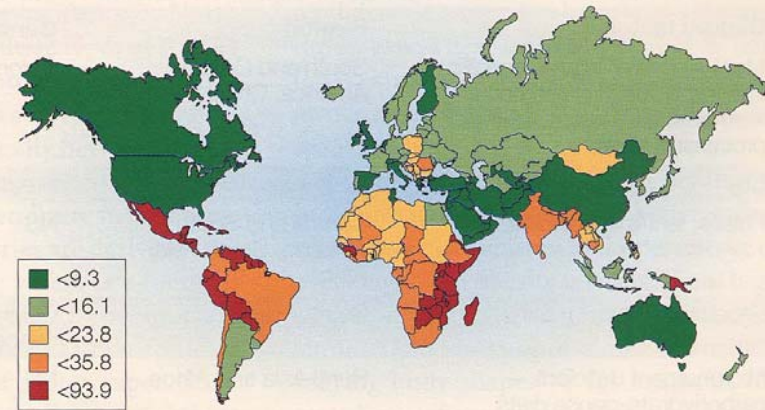
Note: Due to ICD coding, numerator information has changed over time. Rates for cancers of the uterus, ovary, lung and bronchus, and colon and rectum are affected by these changes. Uterus cancers are for uterine cervix and uterine corpus combined.

Source: US Mortality Public Use Data Tapes, 1960 to 2001, US Mortality Volumes 1930 to 1959, National Center for Health Statistics, Centers for Disease Control and Prevention.

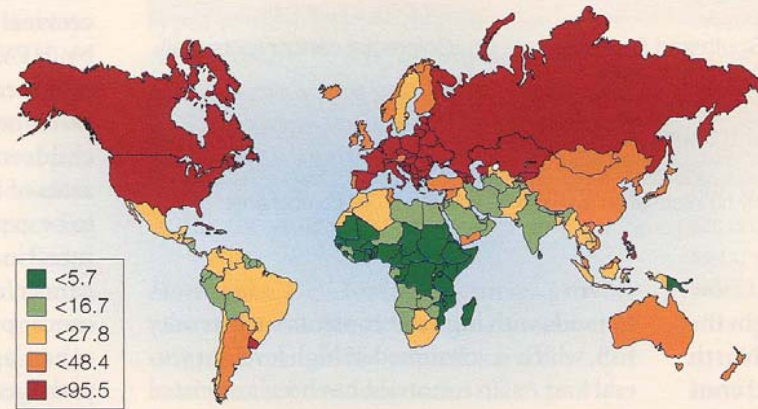
a Incidence of stomach cancer



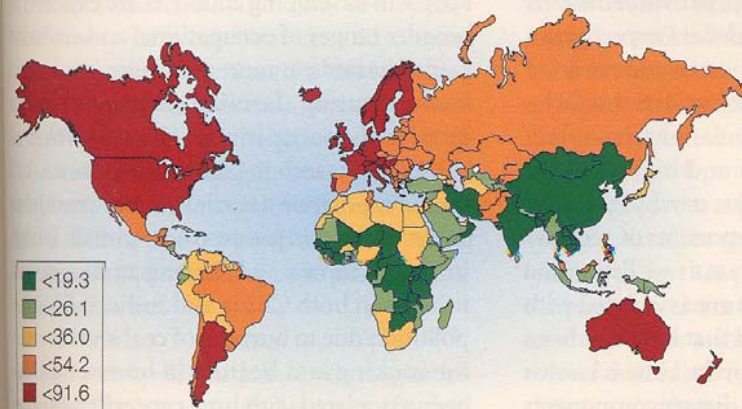
b Incidence of cervical cancer



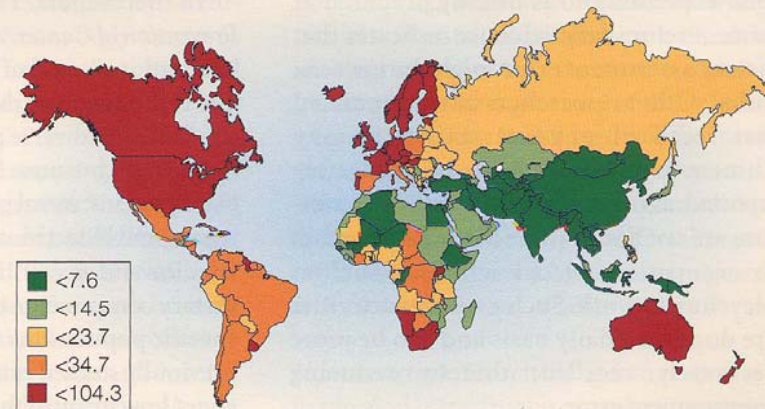
c Incidence of lung cancer



d Incidence of breast cancer



e Incidence of prostate cancer



HISTORY OF ONCOLOGY - 1a

The term carcinoma was described by Hippocrates (460-377? B.C.). Galen (131-201? A.D. used the term cancer. He attributed cancer to an excess of black bile (melancholia). In 1775, a London surgeon, Percival Pott, recorded the high incidence of cancer of the scrotum in chimney sweeps. He attributed the condition to prolonged exposure to soot. In 1802, a Medical Committee of the Society for Investigating the Nature and Cure of Cancer met in London and formulated the following thirteen queries:

Query 1st: What are the diagnostic signs of cancer?

Query 2nd: Does any alteration in the structure of a part take place, preceding that more obvious change which is called cancer; and if there be an alteration, what is its nature?

Query 3rd: Is cancer always an original and primary disease; or may other diseases degenerate into cancer?

Query 4th: Are there any proofs of cancer being an hereditary disease?

Query 5th: Are there any proofs of cancer being a contagious disease?

Query 6th: Is there any well-marked relation between cancer and other diseases? If there be, what are those diseases to which it bears the nearest resemblance in its origin, progress, and termination?

HISTORY OF ONCOLOGY - 1b

Query 7th: May cancer be regarded at any period, or under any circumstances, merely as a local disease? Or does the existence of cancer in one part afford a presumption that there is a tendency to a similar morbid alteration in other parts of the animal system?

Query 8th: Has climate or local situation any influence in rendering the human constitution more or less liable to cancer, under any form, or in any part?

Query 9th: Is there any particular temperament of body more liable to be affected with cancer than others? If there be, what is the nature of that temperament?

Query 10th: Are brute creatures subject to any disease resembling cancer in the human body?

Query 11th: Is there any period of life absolutely exempt from the attack of this disease?

Query 12th: Are the lymphatic glands ever affected primarily in this disease?

Query 13th: Is cancer, under any circumstances, susceptible of a natural cure?

HISTORY OF ONCOLOGY - 2a

Johannes Muller was the first person to describe cancer as an **abnormal growth of cells** (1838). This abnormal growth was attributed by Rudolf Virchow to chronic irritation. The nature of the cells which give rise to cancer has long been debated. Cohnheim (1877) suggested embryonic rest cells were responsible while others favored changes in mature cells.

Progress in experimental tumor research has often been achieved using **transplanted tumors**. In 1875, Novinsky transplanted a sarcoma in dogs. However, this peculiar tumor was capable of venereal transmission. In 1889, more conventional tumors were transplanted in rats by Hanau and in dogs by Wehr. At the beginning of the twentieth century tumors were being transplanted in several species.

HISTORY OF ONCOLOGY - 2b

Epidemiological evidence has been important in detecting carcinogenic substances. Rehn (1895) reported an increased incidence of bladder cancer in aniline dye workers in Germany. The major **carcinogen** involved is now believed to be 2-naphthylamine. Work with radium suggested the induction of skin cancer by repeated X-ray burns and in 1910 to 1912, Marie, Clunet and Raulot-Lapointe reported the induction of sarcoma in rats by the application of X-irradiation. The first chemical induction of cancer in laboratory animals was achieved by Yamagiwa and Ichikawa (1915) by painting coal tar on the ears of rabbits every 2-3 days for more than a year. The first pure carcinogen, 1,2,5,6-dibenzanthracene, was synthesized in 1929 and in the 1930s Kenneway and Cook and their associates isolated carcinogenic polycyclic aromatic hydrocarbons including benzo(a)pyrene from coal tar.

HISTORY OF ONCOLOGY 3a

Evidence for a **viral induction** of cancer was obtained in 1908 when Ellerman and Bang demonstrated that cell-free filtrates of a chicken leukemia would transmit the disease. In 1910, Rous published work on a viral agent causing sarcomas in chickens. In the 1930s, there were publications on the oncogenic viruses, such as the Shope papilloma virus and the Bittner milk factor for mammary tumors in mice, but it was not until the early 1950s that the possibility of oncogenic viruses became generally accepted.

HISTORY OF ONCOLOGY 3b

In the early 1900s, Boveri proposed a **mutation theory of carcinogenesis** but at that time it was not amenable to chemical investigation.

Later theoretical approaches to carcinogenesis reflected advances in basic biochemistry.

From his work on the glycolysis and respiration of tumors, Otto Warburg concluded in the 1920s that cancer arose from damaged respiratory mechanisms.

HISTORY OF ONCOLOGY 3c

The possibility of a **two-step mechanism for cancer** was noted by Berenblum in 1941.

In the 1940s, Greenstein concluded that there was a tendency for tumors to resemble each other biochemically which gave rise to the **convergence theory** of cancer.

The Millers, Van Potter and their associates placed emphasis on deletions in cancer.

Investigations on the so-called minimal deviation hepatomas, induced by Harold Morris in the 1960s, suggested that many biochemical features of tumors were not essential features of the neoplastic transformation.

HISTORY OF ONCOLOGY - 4

Cancer chemotherapy has made notable progress since the introduction of methotrexate by Sidney Farber in 1947. Treatment with combinations of drugs has proved efficacious for some types of cancer.

Carcinogen metabolism and the interaction of carcinogens with genetic material are areas of current interest. The identification of oncogenes and tumor suppressor genes has shown the importance of both positive and negative regulatory influences on the initiation, promotion and progression of cancer. The development of improved short term tests for carcinogens and the identification of environmental carcinogens remain important goals.