ЗМІСТ

Oncology: textbook

Про книгу

The first part of the textbook examines the issues of general oncology, aetiology, pathogenesis of malignant tumours, as well as the basic principles of diagnosis and treatment of cancer patients. In the second part 16 cancer localisations, risk factors, diagnostics, classification and treatment are considered. The textbook is intended for English-speaking fifth- and sixth-year students of Ukrainian higher medical education establishments.

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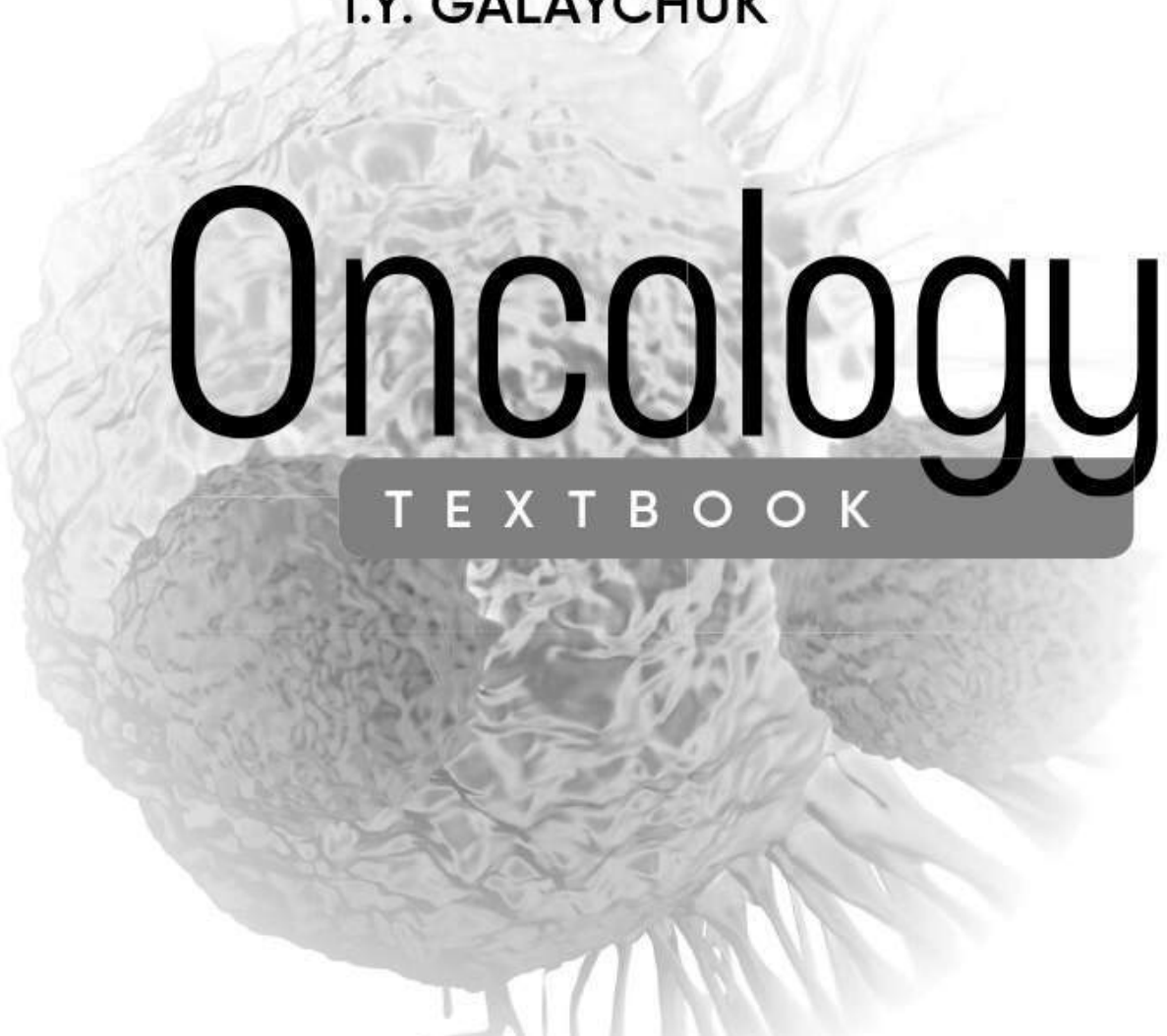
Oncology

TEXTBOOK



APPROVED
by the Academic Council of Kharkiv National Medical University and is recommended for the fifth- and sixth-year students of medical faculties

Kyiv
AUS Medicine Publishing
2019

UDC 616-006(075.3)
LBC 55.6ya73
S77

Approved by the Academic Council of Kharkiv National Medical University and is recommended for the fifth- and sixth-year students of medical faculties (minutes No. 5, 17 May 2018)

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S77 Oncology : textbook / V.I. Starikov, A.S. Khodak, I.Y. Galaychuk. — Kyiv : AUS Medicine Publishing, 2019. — 216 p. + 4 p. colour insert.

ISBN 978-617-505-722-3

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Introduction

Malignant tumours are the second only to heart and vessel diseases as a cause of death in the most highly developed countries. However, the existing tendency of malignant neoplasms to increase makes it possible to predict that malignant tumours will be the main cause of population death throughout the world, so we can say that the problem of malignant neoplasms is not only medical, but also a social one.

A rapid increase in the incidence of malignant tumours of almost all localisations was recorded at the end of the 20th and the beginning of the 21st centuries.

Moreover, the incidence of the most frequent localisations (lung, breast, skin, prostate and uterine body) of malignant tumours has been constantly increasing.

It happens because of the ruinous influence of carcinogenic factors on the human body. Different pathogenic factors: chemical, physical and biologic cause malignant cell transformation.

Cancer has been known to be widespread in multicellular plants, insects, birds. This ancient disease is much older than man.

Scientific and technical progress has induced the explosive growth of knowledge and thus the possibility to study tumours at the cell genome level.

This textbook has been aimed at partial presentation of general aspects about carcinogenesis and treatment modalities, since it is recommended first of all for the students of medical universities studying a course of oncology. The textbook can be helpful to young medical specialists: oncologists, surgeons, therapeutists and students of biological faculties.

Part I

GENERAL ONCOLOGY

Oncology is the science that deals with tumours, discloses the causes and establishes general regularities of their origin (etiology) and the mechanism of their pathogenesis, preventive measures, diagnosis and treatment.

Oncology, as a general biological problem, is closely connected with different branches of natural sciences: molecular cell biology, social hygiene and ecology.

Oncology is a branch of medical science that studies a definite scientific problem. Specialisation according to problems is very up-to-date and promising, as it makes it possible to use different methods of research and treatment. Over the last years, it has begun to develop into oncogynaecology, mammology, otolaryngological oncology, thoracal oncology, abdominal oncology, oncourology, oncoproctology, oncopaediatry, drug therapy etc.

A simplified definition of malignant tumour is as follows: tumour is unlimited growth of tissue with loss of its differentiation (plus tissue, minus differentiation). But sometimes, this definition is not true, because in some cases, tumour growth and healthy tissue destruction are observed, but there is no increase in the size of the tissue or organ.

A tumour grows from a primary neoplastic bud and does not involve the surrounding unchanged cells in the process. Infiltrative growth and metastasising are characteristic of malignant tumours. It is characterised by unlimited and relatively autonomous growth and duplication of cells in the focus of the disease.

Tumours, especially malignant tumours, are accompanied by changes throughout the body.

We will give a definition of malignant tumour and point out only its main biologic properties.

A **malignant tumour** is a biologic tissue with unlimited proliferation of transformed cells, losing morphologic parameters of histogenesis and capable of dissemination and implantation into other tissues and formation of new foci of tumour growth.

Benign tumour is characterised by higher cell differentiation, slow non-infiltrative growth and absence of metastasising.

The names of different tumours are usually formed from those of the tissue, from which the tumours are derived (cell, tissue, organ) and the suffix *-oma*, which means "tumour". For example, fat tissue tumour — **lipoma**, bone tissue tumour — **osteoma**, glandular tissue tumour — **adenoma**. The name of the tumour may indicate cell structure (e. g., tumour developing from histocytes is called **histocytoma**). Also, the site of the tumour may be indicated in the tumour name (e. g., shoulder lipoma, breast fibroadenoma). Tumour containing elements of embryonal tissue is called embryoma or teratoma.

Tumour may be derived from the epithelial, connective, nervous and muscle tissue.

There are special names for malignant tumours — carcinoma or **cancer** for tumours derived from the epithelial tissue and **sarcomas** for those derived from the connective tissue. About 90 % of all malignant solid tumours in adults are cancers, and about 10 % are sarcomas. In children, everything is vice versa, sarcomas account for 90 % of all solid tumours and cancers account for less than 10 %.

Systemic tumours of the haemopoietic tissue are called **haemoblastoses**. There is a small group of tumours called **herminogenic**, they are tumours from the testicles and ovaries.

Epidemiology of Malignant Tumours

Epidemiology is a brach of oncology studying variations in disease incidence in population groups. It identifies cancer risk in populations, the rate of affected and dead patients from malignant tumours for a certain period of time on a specific territory and applies preventive measures.

It has been estimated that about 90 % of all malignant tumours are due to environmental factors (exogenous), the rest 10 % are caused by genetic factors, hormones and viruses (endogenous).

It has been proved that malignant tumours have been registered in every nationality and ethnic group. However, the geographic and ethnic differentials for most cancers appear largely determined by environmental influences. Rates for stomach cancer in different counties vary greatly in line with socieconomic differences in the use of alcohol and tobacco and nutritional patterns. The Japanese, Icelanders, Chileans experience elevated rates for stomach cancer. Americans, Indoneseans and Egyptians have low rates of this disease. These variations in cancer occurrence can be explained by genetic and dietary factors.

Correlation of microelements in the soil and drink water are of great importance.

Some regions have exceptionally high rates of certain cancers. Africans have high rates for Burkitt's lymphoma. African populations experi-

ence elevated rates for primary liver cancer in comparison with American or European populations.

There are two main methods of malignant tumour epidemiologic investigations. They are **descriptive** and **analytic** studies.

Descriptive studies measure the number of persons affected by the disease, the length of the period covered and the population from which they are derived. These studies can be useful in generating aetiologic hypotheses. Cancer shows variations according to age, sex, race, geographic location, socioeconomic class and marital status. Descriptive studies employ mainly population-based statistics on mortality, incidence and survival to calculate rates.

Analytic studies test aetiology hypotheses, involving cohort or case-control designs. These studies allow estimating the risk of disease associated with exposure. Retrospective and prospective analyses are used in these studies.

The incidence and death rates according to sex are of great interest in the epidemiology of malignant tumours. In males, malignant tumour incidence (cancer of the lung, stomach, larynx, oral cavity and oesophagus) is higher than in females. In females, malignant tumour incidence in the thyroid gland, liver and gallbladder is higher than in males.

Most often, the incidence and death rates are expressed in new registered cancer cases calculated per 100,000 population. Incidence rates may be crude (for all ages) or age-specific (standard). When summary figures are necessary to compare rates between population groups with different age distribution, they should be age-adjusted; this is done by multiplying each age-specific rate by the percent of individuals in a standard population with the same age and then summing to produce a single value.

For several cancers with poor survival, mortality rates nearly equal incidence rates. The combined analyses of incidence, mortality and survival statistics provide valuable data on the patterns of cancer. There are European, world and other standards.

According to the registered data, a crude incidence rate of malignant tumours has increased in Ukraine to 375.7 cases per 100,000 population in 2015; in comparison with 2005 it was 348.0 cases.

The incidence rate has increased for oral cavity, lung, colon and rectum, skin, breast, uterine body, prostate, bladder, thyroid cancers. Incidence rates have risen the most for malignant tumours of the thyroid — 40 %, skin — 26 %, prostate — 25.4 % in comparison with 1997. Notable declines are apparent for lip, oesophagus, stomach and larynx cancers.

The rank of different cancers in male and female in Europe and Ukraine is different (see the Fig. 1, 2 on the colour inset). The crude incidence rate of malignant tumours in Ukrainian males is 349.1 per 100,000 population, in females — 304.1 per 100,000.

Among males aged 30–34 to 60–64, the incidence rates of cancer increase in the following age group two-fold in comparison with the preceeding one. Incidence rates decrease after 80 years.

Among females aged 25–29 to 65–69 years, the rate of cancer incidence has been rising rapidly (1.5–1.8-fold), risk decreasing steadily thereafter, becoming very small by the age of 80 years. So, the incidence rate in Ukraine has a stable tendency to increase.

The highest incidence rates are for lung, breast, skin, stomach, colon, prostate, uterine body cancers.

Advancing age increases susceptibility to cancer. We suppose that in case people do not die from heart disease and other diseases, the leading cause of death can be cancer as a result of the ageing process.

The leading causes of cancer deaths are:

— lung cancer — 20.1 %;
— stomach cancer — 13.6 %;
— colorectal cancer — 11.2 %;
— breast cancer — 7.8 %;
— malignant neoplasms of the lympatic and haemopoietic tissue — 5.3 %.

Aetiology and Pathogenesis of Malignant Tumours

The aetiology of malignant tumours is a science of the causes of disease and of the conditions, under which the disease develops. One of the main objectives of aetiology is establishment of general regulations of cancer origin and the study of cancer causes.

Different theories concerning the aetiology of neoplastic growth have been proposed, many of them explain the origin of tumours and have been proved in practice.

The most studied theories are: chemical, viral (biologic), physical and genetic theories of carcinogenesis.

According to the WHO (World Health Organization), carcinogen (physical, chemical or biological) is the agent capable of causing or accelerating the neoplastic growth, regardless of the mechanism of its action or the degree of effect specificity. Carcinogen is an agent, which due to its physical or chemical properties can cause irreversible change or damage in those parts of the genetic apparatus, which realise homeostatic control over the somatic cells. Mutation transforms normall cells into malignant ones, it can be proved by the fact that the change of only one nucleotide in human protooncogenes can make them function as oncogenes and in some cases can cause malignant cell transformation.

Procarcinogens are chemical substances, which after a series of metabolic processes are capable of causing malignant tumour development.

Factors Involved in the Causation of Cancer

Chemical Theory of Carcinogenesis

According to chemical theory, the transformation of normal cells into blastomatous ones is caused by cancerogenic substances, which have either gained entrance into the body from the outside or have been possibly formed in the body as a result of deep changes in metabolism.

Percivall Pott published in 1775 his findings that working as a chimneysweeper led to scrotal cancer. However, only K. Yamigawa and K. Ichikawa were the first to report in 1915 that coal tar could cause skin cancer in laboratory animals. They induced skin tumours in mice by systematic rubbing the coal tar into the skin of the auricle.

The number of known carcinogenic substances capable of causing neoplastic growth by action from without has now considerably increased (more than 2000 chemical substances). According to the chemical structure, the carcinogens belong to different classes of inorganic and organic compounds.

Chemical carcinogens can be divided into the following groups: organic, inorganic and endogenous substances. Organic carcinogens are polycyclic aromatic hydrocarbons (coal carbonisation products and some mineral oils). They are the products of incomplete combustion contained in tobacco smoke, in the exhaust gases of motor vehicles, in the smoke of blast furnaces.

Aromatic nitrogen compounds are contained in large quantities in the nitrogen dyes used for dyeing natural and synthetic fabrics, for colour printing and graphic arts industry, in cosmetics. Aromatic amine compounds are responsible for the development of the so-called “aniline cancer” of the bladder in the workers of aniline dyeing industry.

N-nitroso compounds and nitramines are chemically stable in the body. Their biologic effect is due to the action of the active metabolites formed under the influence of oxides. Nitrosamines are used as intermediates in the synthesis of dyes, drugs, plastics, pesticides. Nitrosamines are used as solvents in printing inks, anticorrosion agents, intermediates for herbicide synthesis. A human can be subjected to nitrosamine action not only due to occupational exposure, but also because of the chlorinated water and foodstuff quality. Nitrites are widely used as preservatives, so one of the tasks is to reduce their content in the foodstuffs.

Studies of animals show that a number of metals and metalloids have carcinogenic activity. They include nickel, chromium, arsenic, cadmium, beryllium, cobalt, lead, titanium, zinc, iron.

The study of occupational groups has indentified more carcinogens than any other branch of cancer epidemiology and has led to cancer pre-

vention by reducing or eliminating hazardous exposures in the workplace. Most carcinogenic exposures in the workplace were noticed initially by epidemiologists as in the case of asbestos (lung cancer and pleural mesothelioma), nickel, haematite (iron dioxide), chromium and its salts, arsenic (lung cancer and stomach adenocarcinoma in experimental animals) and leather industry (nasal cancer).

Asbestos represents the major occupational carcinogen due to its induction of lung cancer and pleural mesotheliomas. Asbestos is a naturally occurring hydrated mineral silicate. A relation of asbestos to the development of gastrointestinal tract tumours has been claimed.

Along with the existence of antropogenic carcinogens there are more than 20 carcinogens of natural origin. The most potent hepatocarcinogens appear to be natural products that occur in the environment and are synthesised by plants, fungi and bacteria.

Probably the best studied natural chemical carcinogen is aflotoxin, a product of the Aspergillus fungus. Aspergillus flavus mold and aflotoxin product have been found in a variety of stored grains, peanuts, particularly in hot humid parts of the African continent, where most village-based grains can be seen covered with a white layer. This layer contains high levels of aflatoxin and is consumed after months of storage.

Endogenous carcinogens can also cause a number of malignant tumours. The appearance of these carcinogens is associated with genetic, hormonal and metabolic disorders. Blastomogenic properties of endogenously produced substances such as metabolites of tryptophan and tyrosine have been proved. In particular it has been revealed that tryptophan metabolites participate in the development of bladder, lung, liver, uterus and ovary cancer and leukaemia.

Nowadays, it has been proved that some hormones: oestrogens, androgens and corticosteroids are capable of causing a carcinogenic effect. It has been supposed that the excess function of the pituitary gland has a direct carcinogenic effect.

Physical Theory of Carcinogenesis

Malignant tumours can be induced by physical agents: ultraviolet radiation and ionising radiation, which can be electromagnetic (photon) and corpuscular. X- and γ-rays are electromagnetic radiations. Elementary particles such as electrons, protons, neutrons or alpha particles are corpuscular radiation.

Life on Earth has always been exposed to ionising radiation in the form of cosmic rays or radioactivity in the earth, man-made radiations from medical radiology and nuclear power and man-enhanced sources (naturally occurring radon). Radon concentrates in the houses and decays.

Along with ionising radiation, cancer can be induced in humans endogenously by ingested radionuclides.

Long before the discovery and testing of nuclear weapons, two American researchers March and Ulrich had analysed the causes of radiologists deaths and came to a conclusion that they had died from leukaemia 9 times more often than doctors of other specialisations.

The incidence of leukaemia, lung cancer, breast cancer and thyroid gland cancer was increased manyfold in atomic bomb survivors in Japan. Both chemical carcinogens and ionising radiation are polytropic, i. e. can induce cancer almost in every tissue and organ (skin, lung, liver, thyroid, breast cancers, bone tumours, leukaemia).

External ultraviolet radiation from sunlight induces the tendency of tumours to arise within the irradiated tissue on sun-exposed sites, but radionuclides induce tumours on the sites of deposit. There are different kinds of radionuclides. They are osteotrop radionuclides (strontium, radium), thyroid (iodine) and other radionuclides. For example, incorporated osteotropic radionuclides ^{90}Sr, ^{89}Sr, ^{140}Ba, ^{45}Ca can induce tumours of the bones and surrounding tissues. Hepatropic radionuclides ^{144}Ce, ^{140}La, ^{147}Pm, ^{232}Th, ^{198}Au are deposited in the liver and bones and induce tumours of the liver, bones, haematopoietic tissue, stomach and colon.

The carcinogenic effect of ionising radiation is independent of the dose, although the probability of its occurring increases with dose. Any dose carries with it some risk of inducing cancer. Radiation has "no threshold". Radiation given gradually over time may cause less cancers overall than if the same radiation dose were given over a brief interval.

Ultraviolet (UV) radiation from sunlight has been known to be responsible for carcinogenesis. In experimental animals, repeated doses of UV radiation, particularly in the UV-B spectral range (280 to 320 nm), can induce skin cancer. It is the most biologically effective wavelength of UV radiation. Long-term sun exposures appear closely related to the development of malignant epithelial (cancer) and connective tissue (sarcoma) tumours on sun-exposed body sites.

Epidemiologists have noticed that the incidence of skin cancer is higher in persons living in the southern regions of Ukraine (the Crimea, Odessa region) and exposed to long-term insolation. There is a good evidence to believe that an increase in the incidence of skin melanoma occurs from repeated exposures to sunlight. It is suspected that the mechanism of action of ionising radiation and UV rays is associated with activation of lipid peroxidation due to the formation of highly active radicals by hydrolysis of water in the cell.

There is no incontestable proof of the trauma aetiology of a tumour. Some data on the origin of tumours suggest that tumours may apparently

be caused by a preceding trauma: mechanical, thermal or chemical. Trauma can predispose to the development of cancer in the areas of keloid scars of burns and oesophagus chemical burns. Development of osteosarcoma and Ewing's sarcoma appear to be associated with mechanical trauma. Many cases of neoplasm development in case of a long-term stay of a calculus in the gall bladder, renal pelvis, urinary bladder have been described. Trauma may play a mediate role in causing cancer.

Biological (Viral) Theory of Carcinogenesis

The biological carcinogens include a large group of viruses and some protozoa (infectious agents (*Helicobacter pylori* infection raises the risk of gastric cancer).

F. Peyton Rous was the first to prove in 1911 by his experiments the aetiologic role of the virus in the occurrence of malignant tumours. He showed that cell-free extracts from a sarcoma in chickens could induce tumours in injected chickens within a few weeks, even when passed through filters that retained bacteria. P. Rous pointed out that this infectious agent was not only capable of inducing tumours, but also imprinted the phenotypic characteristics of the original tumour on the recipient cell.

In the 1930s, Richard Shop described cell-free transmission of tumours in rabbits. Ludvig Gross in 1950s discovered the murine leukaemia viruses and described retroviruses that could cause tumours in mice. After these findings many virologists supposed that human tumours might have a viral origin. The field of viral oncology lay dormant until the discovery of Bittner virus causing breast cancer, the murine leukaemia viruses and mouse pappilomavirus. Virologists proved that oncogenic viruses can be transmitted by horizontal and vertical ways, i. e. from mother to her offspring when feeding with milk or transovarially.

Nowadays, more than 150 types of RNA- and DNA-containing viruses have been discovered and described to have oncogenic activity. They induce tumours, generally leukaemias and sarcomas in birds, reptiles, mammals (rats, mice, hamsters, dogs, monkeys).

The discovery of oncogenic viruses in birds and mice was the basis for the creation the virusogenetic theory by L.A. Zilber in 1966, according to which virally-linked tumours transform normal cell into a malignant one and this change is hereditary. The virus associated with this transformation is involved only at an early step in carcinogenesis and plays no role in the further development of the tumour.

According to L.A. Zilber's theory, as a result of virus contact with the virus-susceptible cell occurs virus deproteinisation, nucleic acid release and invasion into the cell cytoplasm and then into the nucleus. The viral genome or its part is integrated into the host cellular genome as part of

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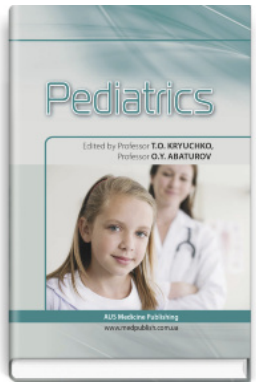

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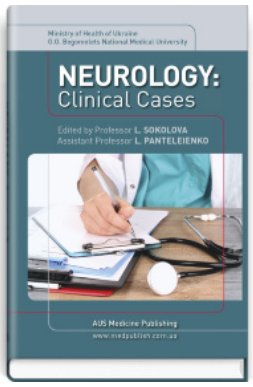

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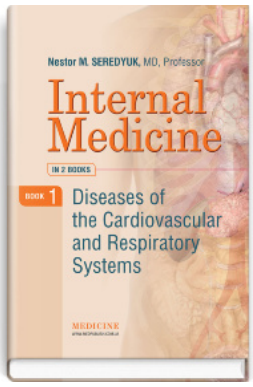

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Перейти до категорії
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