Typically, the elderly have a number of concomitant chronic diseases, which most commonly affect the cardiovascular, respiratory and central nervous systems and involve metabolic disorders and cancer. Several lines of evidence indicate that individuals aged ≥65 have at least 3 chronic diseases, while a substantial proportion of these patients suffer from at least 5 chronic diseases.

Modern medicine is focused on narrow specialties and the majority of papers published by experts form the basis for the guidelines for the management and prevention of a single chronic disease, thus limiting their practical application only to the population of the young and the middle aged.

Since most elderly patients suffer from more than 1 chronic disease, such an approach is clearly insufficient. It seems that contemporary medicine should concentrate on readjusting terminology and developing new diagnostic tools to describe the clinical condition of a patient with comorbidities. Only internal medicine might deal with such a task, for it has always been characterized by a holistic approach to the patient with several chronic diseases. The challenge of the task is well reflected in a study conducted by de Groot et al. The objective of the study was to systematically review available methods to evaluate comorbidity, which had been used in clinical studies over the years 1966–2000. The authors identified 13 different methods to measure comorbidity and its effect on the diagnosis, prognosis, therapy and results. Four of those methods (the Charlson Index, the Cumulative Illness Rating Scale, the Index of Coexistent Diseases, the Kaplan classification) were considered valuable and reliable as far as their use in clinical studies was concerned. It has to be stressed that the authors indicated research methods which in carefully designed clinical setting could contribute to the development of practical guidelines for efficient management of a patient with several coexisting diseases. These methods, however, could not guarantee complete resolution of the problem.

Chronic comorbidities in elderly patients inversely affect their clinical condition, exacerbate symptoms and reduce therapeutic efficacy. In such complex circumstances, an accurate diagnosis is both necessary and difficult. Chronic obstructive pulmonary disease (COPD) and chronic...
### TABLE 1 Chronic disease categories

<table>
<thead>
<tr>
<th>I</th>
<th>simple (common pathophysiology)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>coronary artery disease and myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>chronic obstructive pulmonary disease, pulmonary emphysema</td>
</tr>
<tr>
<td>II</td>
<td>complicated</td>
</tr>
<tr>
<td></td>
<td>thromboembolism in chronic heart failure</td>
</tr>
<tr>
<td>III</td>
<td>coexisting (no cause and effect relationship)</td>
</tr>
<tr>
<td></td>
<td>pneumonia in chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td></td>
<td>gastritis and chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td></td>
<td>nephritis and chronic heart failure</td>
</tr>
<tr>
<td>IV</td>
<td>overlapping (acute, limited in time)</td>
</tr>
<tr>
<td></td>
<td>common cold and chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td></td>
<td>influenza and chronic heart failure</td>
</tr>
<tr>
<td>V</td>
<td>multiorgan (low-grade systemic inflammation manifestation)</td>
</tr>
<tr>
<td></td>
<td>chronic obstructive pulmonary disease and chronic heart failure</td>
</tr>
<tr>
<td></td>
<td>hypertension, chronic renal failure, chronic heart failure, chronic obstructive pulmonary disease, diabetes, neoplastic disease, anemia, osteoporosis</td>
</tr>
</tbody>
</table>

Heart failure (CHF), for example, infrequently occur on their own but rather coexist with several other diseases.\(^5\)\(^6\) Considering these complexities, it is particularly difficult to make a precise classification of chronic diseases, which is partly reflected by our attempt to organize the subject as presented in **TABLE 1.**\(^7\) Although the diseases in question pertain to 2 different systems of the body, they have many common risk factors, most importantly cigarette smoking and obesity. One of the most attractive, recently discussed hypotheses is the phenomenon of low-grade systemic inflammation in the pathogenesis of several chronic diseases of the old age.\(^8\)

#### The hypothesis of systemic inflammation in the pathogenesis of chronic multiorgan lesions

A number of studies conducted in recent years provide evidence for great interest in a relation between low-grade chronic systemic inflammation and multiorgan lesions underlying chronic comorbidities. According to this hypothesis, environmental factors, such as tobacco smoke, air pollutants, and pathogens associated with viral and bacterial infections, act locally on respiratory epithelial cells and lung alveolar macrophages, inducing the occurrence of multiple circulating cytokines, chemokines and growth factors which stimulate the bone marrow to produce active inflammation cells, such as neutrophils, monocytes and platelets, which in turn are a source of inflammatory cytokines common for the pathogenesis of several coexisting chronic diseases.\(^1\)

Most evidence indicating a direct effect of systemic inflammation on the pathogenesis of several coexisting chronic diseases refers to pathophysiologic associations between COPD and cardiovascular diseases, especially CVD.\(^9\) Toxic particulates and gases, which by means of generating circulating proinflammatory cytokines, mainly tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6) from lung macrophages and from other respiratory tract structural cells, play a major role in the etiology of COPD and may induce chronic systemic inflammation. These cytokines, occurring locally in the acute phase of the inflammatory reaction, also have the ability to stimulate systemic inflammatory markers in the liver, including C-reactive protein (CRP), fibrinogen and other proteins which stimulate the coagulation system.\(^10\) Systemic inflammation induces the activation of circulating leukocytes and circulatory endothelial cells, and promotes the mechanisms of leukocyte adhesion, migration and accumulation in the atherosclerotic plaque. Moreover, oxidative stress, an important factor in COPD pathogenesis, releases active oxygen free radicals resulting in the occurrence of oxidized lipid fractions, phagocytized by active cells of the monocyte/macrophage series which are transformed into foam cells.\(^11\) This is how microenvironmental conditions occur, which are conducive to the development of arteriosclerosis with all its complications, including acute coronary syndromes, chronic ischemic heart disease, cardiac insufficiency and acute events in other areas such as cerebral or lower extremities arteries.\(^12\) The issue under discussion concerns also the relation between local respiratory tract inflammation in asthma or COPD and systemic inflammation underlying multiorgan lesions in these diseases (**figure**). In genetically predisposed individuals activated macrophages, respiratory epithelial cells, and other respiratory tract cells might continue to produce a set of various transmitters which play an important role in systemic inflammation via recruitment of neutrophils (interleukin-8 [IL-8]), monocytes (macrophage chemotactic protein-1) and lymphocytes (interferon-inducible protein-10). These cells are involved in the synthesis of growth factors, enzymes degrading elastin and metalloproteinases responsible for local lesions occurring during chronic diseases. This shows the complex interrelation between chronic diseases and low-grade systemic inflammation.

#### Multiorgan lesions in chronic respiratory diseases

COPD, comprising several non-specific pathologies of progressive nature occurring in the respiratory tract and caused by COPD type inflammation, is a well-documented example of an age-related disease associated also with a number of other chronic diseases. A potential common pathogenetic factor for both COPD and other multiorgan lesions may be not only a local but also a systemic response to toxic particles and gases, namely the release of markers suggestive of both local and systemic inflammation that in consequence increase the production of CRP, which reflects the systemic nature of the inflammation process.\(^13\) There is a potential relation between local and systemic inflammation in the disease, and evidence of a moderate, low-grade systemic inflammation present in COPD may confirm its contribution to the presence of other diseases, especially in elderly individuals.\(^8\) Therefore,
The cooperation of acute phase proteins (CRP, fibrinogen), active adhesion molecules, released during this process, with monocytes, neutrophils, lymphocytes and the platelet count increases, supports a low-grade systemic inflammation and is responsible for organ damage (activation of i.a. the complement, coagulation system, transcription factors, metalloproteinases). Abbreviations: CHF – chronic heart failure, COPD – chronic obstructive pulmonary disease, CRP – C-reactive protein, GM-CSF – granulocyte macrophage colony stimulating factor, IL – interleukin, MMP-9 – matrix metalloproteinase-9, NFκB – nuclear factor κB, ROS – reactive oxygen species, TNF-α – tumor necrosis factor-α.

**FIGURE** Hypothetic links between local and systemic inflammatory processes in the pathogenesis of multiorgan lesions. Reactive oxygen species, cytokines and growth factors (GM-CSF, TNF-α, IL-1, IL-10, IL-6, IL-8) released during a local inflammatory reaction, stimulate endothelial cells, the liver and bone marrow. The cooperation of acute phase proteins (CRP, fibrinogen), active adhesion molecules, released during this process, with monocytes, neutrophils, lymphocytes and the platelet count increases, supports a low-grade systemic inflammation and is responsible for organ damage (activation of i.a. the complement, coagulation system, transcription factors, metalloproteinases).

**TABLE 2** The most harmful health risk factors among conditions associated with COPD are chronic renal failure, pulmonary hypertension, right ventricular insufficiency and pulmonary vascular lesions.

**Systemic lesions in chronic circulatory system diseases** Coronary and systemic atherosclerosis cause multiple pathologic lesions resulting in the injury to the heart, brain, internal organ and extremities.19 Atherosclerosis does not usually occur only in one vascular bed; atherosclerosis involves peripheral, cerebral and renal arteries, thus providing optimal conditions for a successive occurrence of myocardial infarction, brain stroke, extremity necrosis and renal insufficiency.18 Traditional risk factors of systemic atherosclerosis such as tobacco smoking, diabetes, hyperlipidemia, hyperhomocysteinemia, family history, postmenopausal period or advanced age are closely associated with the development of atherosclerosis.15,16 Vascular lesions in various body areas and organs are accounted for in limited blood supply resulting from age-related conditions such as altered vascular structure and an increased risk of thromboembolic event.17 Structural lesions, caused by chronic ischemia and acute cerebrovascular events related to atherosclerosis, lead to functional disorders of the central nervous system (CNS), mainly cognitive impairment. Atherosclerosis is also associated with the risk of type 2 diabetes. An interesting phenomenon reported in autoimmune diseases, especially in systemic lupus erythematosus and rheumatoid arthritis, is the acceleration of the atherosclerosis associated with systemic inflammation and with the presence of proinflammatory lipid fractions and phospholipid autoantibodies.18 As a result, there is an acceleration of atherosclerotic plaque formation and its destabilization, which stimulates thrombosis in the coronary and carotid arteries.19

CHF, for which the relationship with age is well documented, occurs much more commonly in elderly individuals.1 CHF takes a different course in the elderly compared to other age groups because of concurrent arterial diseases and other conditions unrelated to the circulatory system.20 Various diseases coexist commonly with CHF in older patients because over half of elderly patients have coronary and peripheral artery diseases, about ½ have hypertension, about ½ suffer from diabetes and COPD, and the same proportion suffers from anemia.21 For these reasons, CHF is the main cause for hospitalization and an important risk factor for the rise in mortality and disability rates in the older age group.

Hypertension is a typical medical condition that coexists with the majority of chronic diseases, most commonly COPD, CHF, renal failure and metabolic syndrome (MS).22 Untreated arterial hypertension is associated with a high risk for CHF, myocardial infarction, cerebral hemorrhage and renal insufficiency in older subjects. Moreover, uncontrolled arterial hypertension is the most serious risk factor for stroke, a significant risk factor for coronary atherosclerosis and retinopathy, i.e. retinal arterial and venous lesions and papilledema. Coronary artery disease is a major cause of death observed in hypertensive patients, and high systolic blood pressure constitutes a higher risk factor for mild or life-threatening cardiovascular event than high diastolic blood pressure.1

**Motor system diseases** Osteoporosis usually occurs in association with chronic cardiovascular and respiratory diseases, mainly COPD, in which physical activity limitation, resulting from primary diseases, is also a causative factor.23 It occurs particularly often in elderly individuals with chronic diseases. It is reported in 50% of COPD patients, who have never taken systemic glucocorticoids, while bone mass loss in a similar age group without COPD or chronic diseases is substantially lower.24 Chronic systemic inflammatory processes depend on increased TNF-α and IL-1 levels, which may induce the deficiency in anabolic hormone and insulin-like growth factor-1 (IGF-1), can also take part in the pathogenesis of osteoporosis.25 Moreover, in COPD patients also peripheral monocytes produce larger amounts of TNF-α, which together with IL-1 and IL-6 cause bone resorption and stimulate the formation of osteoclasts, similarly to idopathic osteoporosis, leading to bone mass loss and, above all, to pathologic fractures.26 There is evidence that the systemic inflammatory mediators...
Similarly, bone metabolism, bone mass loss and osteoporosis in the course of CHF, cystic fibrosis and neoplastic disease.27

Muscle mass loss is an important cause of patients’ physical activity limitation and is typically observable in the course of COPD and CHF. Physical loss of muscle strength is a result of the cumulative effect of all medical conditions accompanying the disease and the ageing process. It occurs as a result of low-grade chronic systemic inflammation leading to the loss of type I muscle fibers through apoptosis and inhibiting their regeneration, which results in a significant skeletal muscle dysfunction.28 It is a vicious circle, in which disease-induced muscle mass loss causes physical deactivation, aggravated by the muscle degradation process caused by lack of training. Muscle wasting is mainly responsible for a typical cachexia appearance of an elderly patient with a chronic disease.29

**Hematopoietic system diseases** The main issue concerning the hematopoietic system is anemia of a complex, at least two-factor etiology, including the ageing process and the coexistence of chronic diseases in the old age. The significance of the overlap of these 2 factors is reflected by the fourfold higher risk of anemia associated with chronic diseases in the elderly, which usually meets the criteria for anemia of chronic diseases.30 This type of anemia is caused by CHF, autoimmune diseases (mainly rheumatoid arthritis), chronic infectious diseases and neoplastic disease.1,31 The prevalence of anemia is higher in those elderly patients who also suffer from renal insufficiency and relative or absolute erythropoietin deficiency.30 Hemoglobin concentration, still within normal limits (men <13 g/dl, women <12 g/dl) but slightly above the lower limit of the reference range, increases the risk of death and several coexisting abnormalities, most commonly cardiovascular diseases, CNS cognitive function disorders and osteoporosis which underline frequent falls and fractures.31

Anemia, occurring independently of concomitant diseases and concurrent chronic diseases, presents with such clinical symptoms as fatigue and weakness associated with emaciation or malnutrition. It diminishes muscle strength and physical fitness and extends hospital stays. All this negatively affects elderly patients’ quality of life.32 Despite controversies surrounding the pathogenesis of chronic disease anemia in the elderly, in the majority of reports there is a conformity of opinions on the significance of transmitter dysregulation, the increased effect of proinflammatory cytokines (TNF-α, IL-6, IL-1, IL-1β) and CRP, which may inhibit hematopoiesis by decreasing erythropoietin and other growth factors production and effect on bone marrow progenitor cells.33 A role of nutritional deficiencies, accounting for about 30% of anemia cases in the elderly as a result of iron, B12 vitamin and folic acid insufficient intake, is also highlighted.34 It seems that leptin, the satiety hormone, plays the major role in nutritional deficiency by decreasing the production of appetite stimulating neurohormones (ghrelin, orexin), and increasing the synthesis of the remaining satiety neurohormones (cholecystokinin, YY peptide, glucagon-like peptide-1) and therefore counteracting malnutrition in these patients using diet poses a big challenge.35

**Diabetes mellitus and chronic diseases** Type 2 diabetes mellitus (DM) occurring in the elderly is mainly associated with insulin resistance. This condition also relates to circulating proinflammatory cytokines, indicative of the systemic nature of inflammation, 2 of which (TNF-α and IL-6) play the most significant role, particularly in insulin resistance and postprandial glycemia.36 These cytokines have an indisputable significance in inflammatory processes accompanying COPD, CHF, renal failure, MS and hypertension; and therefore a common coexistence of these diseases, typical of both the elderly age and DM, is observed.37,38 Long-term diabetes is, however, an indirect death risk factor in these patients, occurring finally as a result of respiratory failure in the course of chronic pulmonary diseases, uremia associated with renal insufficiency, or of advanced heart failure.37 In COPD, the degree of a reduction in values of a ventilation parameter, forced expiratory volume in 1-second (FEV1) measured annually is larger in patients with concomitant DM. Moreover, in such patients a decrease of FEV1 correlates with insulin resistance, and glycated hemoglobin level correlates with death rate, risk of exacerbations, length of hospital stays and lack of therapeutic benefits.39

**Chronic diseases and kidneys** In the majority of patients with chronic renal failure the disease leads to death in the old age. Two thirds of end-stage chronic renal failure cases are caused by diabetes and hypertension.1 Regarding the time of patient discharge from the hospital,
during COPD exacerbation, chronic renal failure associated with CHF is an important prognostic factor in COPD. Coexistence of hypertension and CHF in patients with COPD seems indicate a poor prognosis during COPD exacerbations, and mortality in this disease.

Systemic syndromes  MS, associated with 5 cardinal features (insulin resistance, dyslipidemia, hypertension, acute phase reactants, hypercoagulability), may also be characterized by low-grade systemic inflammation. Acute phase proteins including CRP reflect systemic inflammatory response in the MS, while increased plasminogen activator inhibitor and fibrinogen levels facilitate thrombus formation. In cases of a concomitant MS, a 2–3 fold higher death risk, elevated risk for acute cardiovascular events, type 2 diabetes risk and metabolic alterations in COPD is understandable given the fact that low-grade systemic inflammation predisposes to the occurrence of typical diseases in the elderly.

Cachexia is associated with a number of chronic diseases, e.g. COPD, CHF, renal failure and cancer. It is mainly due to skeletal muscle wasting, though also adipose tissue loss may result from lipolysis. Cachexia in the elderly patients with chronic diseases poorly responds to dietary treatment, which is probably related to the effect of leptin, which inhibits appetite stimulating neuropeptide release and increases the release of satiety hormones. The background of cachexia in all chronic diseases is similar and is associated with the effect of cytokines specific for systemic inflammation, such as TNF-α and IL-1 which increase skeletal muscle apoptosis. These cytokines also inhibit the skeletal myoblast regeneration process by decreasing IGF-1 and anabolic hormone levels. Dietary deficiencies and muscle wasting are estimated to affect about 50% of patients with severe COPD and 10–15% of individuals with a mild or moderate form of the disease. Similarly to COPD in CHF, an obese patient has a greater chance of survival compared to a subject with cachexia. This paradox results from the effect of excessive nutrition and overweight as the long-term killer, and malnutrition and cachexia as the short-term killer, in both chronic conditions. Systemic inflammation response which is enhanced in cachectic patients most likely plays a key role in survival prognosis (apart from genetic polymorphisms associated with a certain phenotype of the disease), which corresponds to better therapeutic outcomes reported on the administration of appetite stimulants (megestrol, pentoxifyllin), which also demonstrated anti-inflammatory properties.

SUMMARY  Ageing poses a substantial challenge to modern medicine oriented towards narrow specialities. This problem might lead to return to clinical practice which follows the principles of traditional internal medicine. Once called the queen of medical sciences, internal medicine was characterized by a holistic approach to the patient. Such a concept of internal medicine seems necessary as the basis for the dynamic development of geriatrics. Functioning of healthcare system, for example the family doctor, is hardly conceivable without support of an internist, professionally trained to diagnose and treat patients with comorbidity, and fully aware of full responsibilities towards these patients in terms of the complex diagnostic evaluation and pharmacotherapy.

REFERENCES
ARTYKUŁ POGŁĄDOWY

Choroba przewlekła w podeszłym wieku

Ważne uzasadnienie renesansu interny

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SŁOWA KLUCZOWE
choroba przewlekła, choroby wewnętrzne, choroby współwystępujące, geriatria, wiek podeszły

STRESZCZENIE
Zjawisku starzenia się społeczeństw towarzyszy, wśród współcześnie występujących chorób, ogromna przewaga chorób przewlekłych. U osób w podeszłym wieku występują z reguły co najmniej dwie choroby przewlekłe, najczęściej dotyczące układu krążenia, oddechowego, ośrodkowego układu nerwowego, zaburzenia metaboliczne i choroby nowotworowe. Współwystępowanie wielu chorób u osób starszych pogarsza stan kliniczny i utrudnia rozpoznanie oraz terapię. Tymczasem współczesna medycyna, zaabsorbowana wąskimi specjalnościami, odwróciła od wielkiej akademickiej interny, a praktyka kliniczna została zdominowana przez szczególne podejście do jednej choroby, zamiast do pacjenta z wieloma chorobami. W tej sytuacji precyzyjne rozpoznanie, gwarantujące skuteczne leczenie w złożonym, niejednoznaczonym obrazie chorobowym opiera się często na próbie połączenia szeregu specjalistycznych konsultacji, a nie na holistycznej ocenie charakterystycznej dla tradycyjnej interny. Dlatego patofizjologia oraz klima choroby przewlekłej u osoby w podeszłym wieku wymagają renesansu interny, niezbędnego również – jako podstawy – do rozwoju geriatrii.