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ФИЗИКАЛЬНЫЕ МЕТОДЫ ДИАГНОСТИКИ ПРИ ЗАБОЛЕВАНИЯХ СИСТЕМЫ ДЫХАНИЯ И ИХ ПАТОФИЗИОЛОГИЧЕСКИЕ ОСНОВЫ. I. АНАМНЕЗ И ОСМОТР

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Резюме: Данная публикация продолжает цикл статей, посвященных вопросам пропедевтики внутренних болезней и ее патофизиологическим основам, в первую очередь — на материале бронхолёгочной патологии. Пропедевтика толкуется авторами широко, как введение во внутреннюю медицину, поэтому статьи содержат и терапевтический, и клинико-патофизиологический материал. Статья сопоставляет достижения и традиции отечественной терапевтической школы с принципами преподавания внутренней медицины, сложившимися в практике зарубежного медицинского образования. В данной публикации рассматривается методология сбора анамнеза болезни и жизни, а также методология визуального обследования пациента при пульмонологических заболеваниях, анализируются патофизиологические основы интерпретации этих данных. Рассмотрены механизмы и феноменология одышки, в том числе — периодического дыхания, кашля, лихорадки, боли в груди и других симптомов, важных для диагностики бронхолегочной патологии (10 рис., библиография: 44 ист.).

Ключевые слова: анамнез; боль в груди; бронхолёгочные заболевания; врачебные ошибки и халатность; деформации грудной клетки; жалобы больного; кашель; коммуникативные навыки врача; одышка; периодическое дыхание; физикальное обследование.

PHYSICAL METHODS OF DIAGNOSIS IN DISEASES OF RESPIRATORY SYSTEM AND THEIR PATHOPHYSIOLOGICAL BASIS: I. INTERVIEW AND VISUAL EXAMINATION

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Abstract: This publication continues a series of papers devoted to questions of Propaedeutic of Internal Diseases and its pathophysiological basis, primarily based on the material of bronchopulmonary pathology. Propaedeutic is widely interpreted by authors as an Introduction to Internal Medicine; therefore, these articles also contain clinical pathophysiological material. The article compares the achievements and traditions of Russian therapeutic school with the principles of Internal Medicine that have evolved in the practice of foreign medical education. The article is devoted to doctor-patient communication as regards to case and life history and technique of visual examination in pulmonological patients as

well as to pathophysiological basis for correct interpretation of these data. The article analyzes the mechanisms and phenomenology of dyspnea, including periodic breathing, cough, fever, chest pain and other symptoms important for the diagnosis of bronchopulmonary pathology (10 figs, bibliography — 44 refs).

Key words: Anamnesis; Bronchopulmonary Diseases; Chest pain; Communicative skills; Cough; Dyspnea; Malpractice; Patient's Complaints; Physical Examination; Periodic Respiration; Thoracic Deformities.

Previously, in 2017–18 we have published in "Russian Biomedical Research" the cycle of methodological articles in physical diagnosis of cardiovascular diseases with its pathophysiological basis [1–5].

Here is the continuation of series expanding it over the methodology of the physical diagnosis in the diseases of respiratory system.

INTERVIEW AND VISUAL EXAMINATION

In bronchopulmonary patients the diagnostics starts with interview. First, the character of patient's complaints is to be clarified. Then traditionally goes *anamnesis morbi et vitae* or case and life history. After that medical doctor starts physical investigation of respiratory system which proceeds according common sequence of visual examination, palpation, percussion, auscultation, and special symptoms' checking, completed with proper laboratory and instrumental methods of respiratory system investigation. A physician establishes the correct diagnosis by means of analysis and synthesis of the data obtained.

The complaints of a bronchopulmonary patient are quite typical for the set of respiratory system disorders. They include dyspnea, cough, chest pain, fever, and general sickness [6–7].

DYSPNEA

Dyspnea is most important disorder of normal respiration. Nevertheless, the breathlessness may be of not only pathologic origin, but also physiologic one. The disturbance of respiratory rhythm and breath rate is common in heavy physical strain, even in healthy and well-trained individuals. In this case, however, dyspnea is transient and changes rapidly for normal breath. The last phenomenon in Sports Medicine is known under traditional name «second wind». If second wind does not come in physical strain or comes too late, this may witness for pathologic dyspnea of pulmonary or cardiac origin. Dyspnea has subjective and objective sides. As a subjective feeling, dyspnea belongs to the same group of emotionally negative feelings, as thirst, pain and hunger — and, like other phenomena of this group, it originates with crucial participation of paleomammalian cortex (limbic system) and hypothalamus. According current consensus-approved definition, dyspnea is: "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" [8]. If patient complains of dyspnea, but its visible signs are absent — the dyspnea is designated as "subjective". Objective dyspnea is a registered complex of disorders in breath rate, depth and rhythm as well as in relative duration of breathing phases, resulting from the sum of many interoceptors, nociceptors, cortical, and emotional stimuli, with crucial roles of sino-carotid chemoreceptors sensitive to blood pO_2 and central sensitivity of appropriate neurons to pH of cerebrospinal fluid which follows the levels of pCO_2.

Surely, in overwhelming majority of cases objective side of dyspnea comply with subjective feeling of dyspnea. Subjective dyspnea without objective one may occur, most often, in neurotic patients (i.e. in those with distress-related somatoform behavioral disorders).

The mechanism of dyspnea is related with poor alveolar ventilation and subsequent gases exchange disorder resulted in hypoxemia (when arterial pO_2 falls at least below 80 mm Hg). Typically, although not always (for example, not in high altitude disease), it is accompanied by hypercapnia and other pathologic metabolites collected in blood. Combination of hypoxemia and hypercapnia is known as asphyxia. Due to above mentioned shifts of gaseous metabolism respiratory center, being irritated both *via* neural reflex (hypoxemia) and humoral (hypercapnia and cerebrospinal fluid pH shift) pathways, changes the program of breathing and provokes dyspnea [9]. Sudden paroxysmal dyspnea (regardless of its pathogenesis!) in medical practice is referred to as "asthma". It manifests in attacks of breathlessness. Sometimes in shortness of breath respiration is accompanied with noises and even vocalization. Such a course of dyspnea is called distant, because medical doctor can notice it distantly.

Commonly, dyspnea is divided on 3 types, depending on the prevailing disorder of alternative breath phases — inhalation or expiration. These are: Inspiratory dyspnea. (characterized by difficult inhales), expiratory dyspnea (appeared during expiration) and combined (with both phases of breathing suffering).

The inspiratory dyspnea develops, commonly, in stenosis of the gross airways. Its etiology may be either inflammation or tumor; sometimes it is derived from compression of lung or bronchi by neighboring organs, by either goiter, or aortic aneurism etc.

Another reason may be paralysis of vocal cords, laryngeal oedema (for example, in diphtheria ("true croup"), either in viral/allergic inflammatory oedema ("false croup"), or finally — an alien body occluding a bronchus. All this and similar conditions are characterized by difficult inhalation and more active work of inhaling muscles compared to healthy mode of breathing. Efficiency of breath decreases, oxygen cost of breathing increases. If the extent of stenosis is considerable, inhalation is accompanied by specific sound of high-pitched noisy respiration — so called *stridor*, which is easily audible from some distance [9–10].

The bright example of stridor is so called «reprise» in whooping cough patients — the musical noisy inhalation after the attack of cough.

Inspiratory dyspnea usually is accompanied by normal breath rate (16–18 breaths per min for adults). The equation of breath to pulse rates usually is 1:4, like in healthy adults.

Expiratory dyspnea mostly is caused by obstructive syndrome resulted from congestion and collection of secrete excess as well as smooth muscle spasm in lower respiratory airways, e.g. in minor bronchi and/or bronchioles (distal bronchitis and/or bronchiolitis).

Oedema of mucous membranes, shedding of dying epithelial cells which together with mucous plugs may obstacle a lumen of airways, and spasm of finest bronchi (in bronchiolitis and bronchial asthma) or loss of normal pulmonary tissue elasticity and lack of spring effect, causing the impossibility of passive expiration (in pulmonary emphysema) — may also result in expiratory dyspnea [8–9].

In cases like these constricted or dropsy bronchioles are still able to dilate during inhalation and give the way to the airflow, reaching alveoli. But, during an exhale, which normally should be passive (driven by string effect of normal lung tissue and thoracic wall plus gravitation — without additional muscle efforts), the expiration of air through the narrowed airways is retarded and obstructed. It is accompanied by generation of specific musical sounds, even whistling. Efficiency of breath in expiratory dyspnea decreases drastically, oxygen cost of breathing increases rapidly and greatly [8, 10]. This type of dyspnea is by far more energetically costly compared to inspiratory one, it is tolerated much worse and the body can sustain it without profound changes of acid-alkaline balance for short time only, unlike purely inspiratory dyspnea which is better and for a longer time tolerated [9]. Breathing rate increases and the equation of breath to pulse rates disturbs [10].

Combined dyspnea with both breath phases disturbed is characteristic for the restriction of pulmonary area (surface) of gas exchange (that happens in pneumonia, exudative pleuritis, pneumothorax, atelectases, and high position of phrenic muscle).

It must be clarified during patient interviewing, what phase of breathing is more difficult to produce for him/her — expiration, inhalation or both.

Ask the patient, when the dyspnea use to occur: In resting state or only during and after exercise (physical work, running, bicycle riding, hill climbing or walk upstairs). It is also important to check if the patient himself hears some whistling or wheezing noises when breathing [1, 6–7, 10].

COUGH

The cough is meaningful complaint in many bronchopulmonary diseases. It is the defensive reflex, maintained with key roles on caudal nucleus tractus solitarii and caudal ventral respiratory group of nuclei. Biomechanically it consists of forced expiration after deep inhalation in closed or considerably narrowed true glottis [10–11]. Besides purely neural mechanisms, some humoral signals, first of all — neuroimmune ones, brought in by pro-inflammatory autacoids are also essential for the development of cough symptom. For example, angiotensin facilitates cough that is why ACE-inhibitors provoke it as an adverse effect. Inflammatory autacoids can “sensitize and activate the neural pathways regulating cough, leading to excessive and nonproductive coughing that serves little protective utility” [12]. The last mechanism is especially potent in allergic and allergoid bronchopulmonary diseases.

The biomechanics of coughing produces so called «push of cough», which is helpful in cleaning up the airways from the excess of sputum or alien/rejected substances (like caseation masses in caseous necrosis, food, drink, blood, and pus). Cough may be permanent or occurs in episodes. It may come in attacks (like in whooping cough or tracheobronchial alien bodies). The permanent sound cough is most common in patients with chronic bronchopulmonary diseases (laryngitis, bronchitis, bronchiectasis, tuberculosis, and pulmonary tumors). However, cough also may be very weak and even soundless in vocal cords lesions (due to syphilis or tuberculosis), in vocal ligaments palsy (due to compression or surgical impairment of *n. laryngeus recurrens*). In vocal cords swelling resulted from inflammation, cough may be «barking» (e.g., in measles). Barking cough may be observed without any signs of inflammation in some hysteric individuals. The cough may be wet (with some sputum expectoration) or dry. Dry cough is resulted from swelling of bronchial mucous membrane, when meagre and viscous sputum is delayed in the lumen of bronchi and hardly finds the way out. It is observable in laryngitis, tracheitis, pneumosclerosis, dry pleuritis, and in bronchial asthma. In light forms of respiratory tract inflammation commonly cough is weak and occurs in slight coughing. Wet cough always has some specific timbre, influenced by the noise, produced by movement of secrete excess along the bronchi added to the very sound of cough push [13].

The cough accompanied with sputum (secrete) expectoration is observed in pneumoniae, chronic bronchitis, pulmonary abscesses, tuberculosis and, especially, in bronchiectatic disease, when the amount of sputum expectorated may be enormously great, up to 1 liter per day.

The smell of sputum is very peculiar in lung abscess opened in the airways (fig. 1). The classics of Medicine emphasized that the diagnosis of an opened lung abscess can be established even in the complete darkness, without seeing the patient, by the fetid smell of discharging sputum.

There is a medical proverb, often mentioned, that the first sign of illness can be found in the cuspidor.

And this is true, because after a breakthrough of abscesses through the respiratory tract a lot of specific sputum is discharged. The discharge after prolonged standing in a tube gives under gravitation influence three layers of liquid — yellow mucus, pus and a watery layer (the lower layer is more dense and thick). This sputum has a sharp putrid odor, so the patient has to be provided with a separate ward. Sometimes a small amount of blood is admixed to purulent sputum.

Checking the characters of sputum is very significant to distinguish various reasons of cough. Ask the patient about the amount,

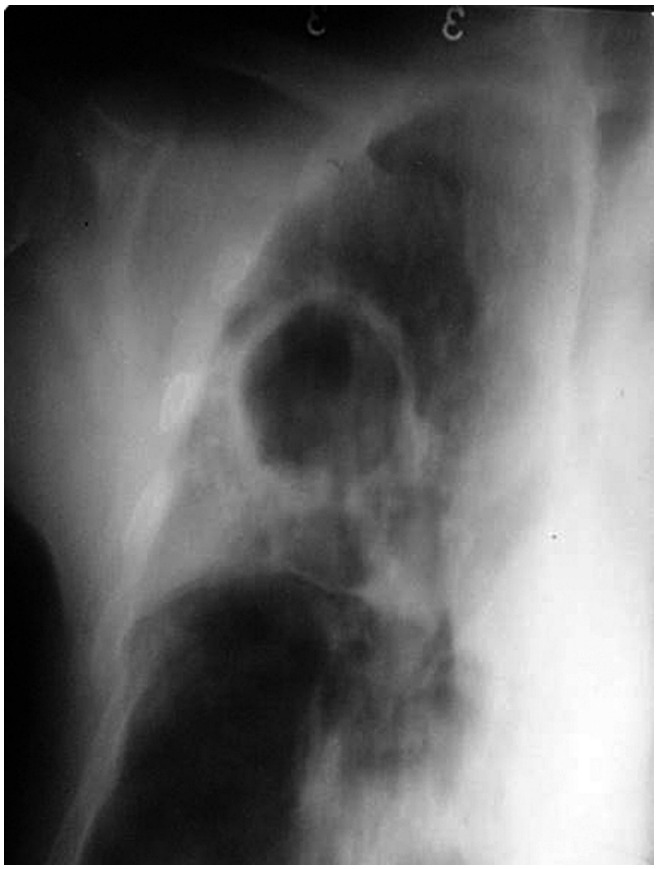

Fig. 1. Tomogram of the pulmonary abscessus in upper lobe of right lung, opened into the bronchus. Case observed by Y.I. Stroev

consistence, scent, color, and also about presence of the streaks of something, e.g. blood — in sputum. Blood-streaked sputum witnesses for hemoptysis, which may be either self-limiting or recurrent.

Blood may present in sputum in different forms, depending on its quantity: Most often as blood-streaked sputum or rusty sputum, as well as in separate blood spites or massive hemoptysis. Sometimes hemoptysis results in prune-juice sputum observed. Blood expectoration may result from tuberculosis of the lungs, but also occurs in bronchiectatic disease, lobar pneumonia, lung abscess or gangrene and in cancer of the lung, in viral pneumoniae, in pneumothorax, in pulmonary arteries embolism (pulmonary infarction), in chest trauma, and in systemic hemorrhagic syndromes. Do not forget that blood expectoration may accompany mitral stenosis, myocardial infarction, and in *periarteriitis nodosa*. Moreover, blood may come to sputum from damaged gingivae (ulorrhagia during brushing teeth), from inflamed nasopharynx, from disturbed telangiectasia elements (Osler–Weber–Rendu disease), from bleeding damaged adenoids or polyps [10, 14]. The reasons may be clarified after special stomatological and ENT examination of a patient.

The sputum may have some blood derived from gut organs. Commonly, in gastric or esophageal bleedings the blood, mixed with acid gastric secrete is dark in color ("coffee dregs" color) and sputum has acid pH; at the same time blood in true hemoptysis is scarlet and with alkaline pH. The sputum in last case usually is foamy. The rusty sputum is common in croupous (lobar) pneumonia, mitral valve disease and in expectoration of the pulmonary hemorrhage remnants [14].

CHEST PAIN

The chest pain usually may witness for pleura involvement, because pleural sheets have many pain sensors, but can be registered also in pulmonary diseases (lobar pneumonia, pulmonary infarction, lung cancer, and tuberculosis) although in these cases pain nevertheless also results from involvement of pleura. Pleural pain usually is related to inhale, especially deep one (in dry pleuritis, in the very beginning of adhesive pleuritis, in pleural mesothelioma). The inflamed pleural layers are rubbing each other, thus producing pain. That's why, the patients try to breath shallow, avoid coughing, protecting themselves from the pain [7, 14]. This type of breathing (tachypnea) is known in domestic medical thesaurus as "the breath of the driven beast" and also under internationall eponym: Corrigan's[1] respiration [9, 15].

Pleural cancer (mesothelioma) and pulmonary infarction (brought in by pulmonary artery embolism) both produce extremely severe pain resistant to narcotic drugs. The involvement of phrenic pleura may spark abdominal pain, which sometimes mistakenly interpreted as a sign of appendicitis or cholecystitis. Lobar pneumonia of inferior pulmonary lobes results in such diagnostic mistakes quite regularly. Severe chest pain is characteristic also for pneumothorax.

Herpes zoster infection also may be the reason of chest pain, often of unilateral character, even in prodromal stage, when its typical rush is still absent and especially — in its overt stage (fig. 2).

Sometimes chest pain is produced by costal trauma, periostitis, intercostal neuralgia, myositis, and myocardial infarction, it may occur in some hematological diseases (like multiple myeloma, megaloblastic anemia, and leukemiae). Chest pain may be of reflex origin: It is observed in pancreatitis, cholecystitis, and cholelithiasis [7, 14].

FEVER AND ACUTE PHASE RESPONSE

Fever very often occurs in patients with bronchopulmonary diseases. It is a typical pathological process, the result of the hypothalamic effect of endogenous pyrogens, mostly, cytokines produced by the cells of immune system in response to the ligands of their Toll-like receptors. The major part of these ligands, so called exogenous pyrogens (or obligatory pathogenic patterns), is of microbial origin [9]. That is why most frequently, it is infectious pneumonia, which causes fever. Pneumonia by definition is always infectious. The most pronounced fever is characteristic for heaviest lobar pneumonia. Body temperature may reach 39–40°C. The chills usually accompany its initial phase. In focal

[1] Sir Dominic John Corrigan (1802–1880) — an Irish physician, famous also for his trope: "The trouble with doctors is not that they don't know enough, but that they don't see enough". Here and everywhere below in footnotes information refers to [15].

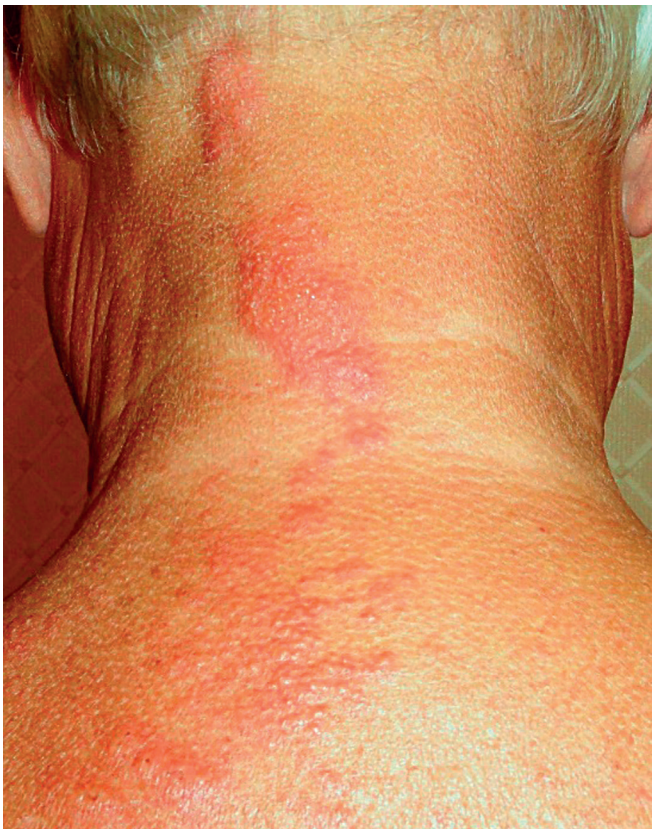

Fig. 2. Herpes zoster of chest and neck, with left side involvement. A case observed by Y.I. Stroev

bronchopneumonia and in pleuritis — body temperature rises slightly and not so sharply as in croupous (lobar) pneumonia [10].

High body temperature, fever, chills and excessive sweating — are typical for such diseases as lung abscess, pleural empyema, and lung gangrene. Purulent lung and pleural illnesses are accompanied by remittent temperature curve, with big swings between morning and evening values of body temperature. In tuberculosis body temperature may be slightly raised above normal (subfebrile) or sometimes high. High body temperature along with excessive sweating is typical for severe, disseminated forms of tuberculosis [7, 10, 14].

Most of the tuberculosis patients have subfebrile temperature, up to 37, 5°C. But, it is distinguished for its constant character, ongoing for weeks and even months. Evening fever of this kind requires profound examination for the exclusion of tuberculosis. The combination of similar fever with sweating and weight loss is observable also in hyperthyroidism (resulting from either toxic thyroid adenoma or Graves' — von Basedow disease), which case demands the special distinguishing investigations [14].

General malaise and nonspecific dizziness — are characteristic for pulmonary patients' complaints, they reflect the existence of acute phase response due to excess of pro-inflammatory autacoids in systemic circulation [9]. It may be both in acute and chronic bronchopulmonary diseases. In acute pneumonia headache, poor appetite, and constipation — are not rare. As a rule in pneumonia these manifestations correlate with increase in serum concentration of acute phase reactants, especially, C-reactive protein, which level in pneumonia is typically > 100 mg/l [16].

The noticeable weakness is typical in lung tumors and *cor pulmonale*. Evening weakness and exhaustion after working day may present in lung tuberculosis patients.

ANAMNESIS

Anamnesis is registered in order to check how the disease started (abruptly or gradually, did the fever present from the very beginning, or the body temperature in initial period of the illness was normal, did the patient suffer from night sweats, side pain on breathing and in resting state, cough of some kind; did he/she expectorate some sputum etc.) [1, 7, 17].

The disease could be triggered by cold exposure in case of improper cloth or cold shower after sports exercises and heavy work, or by exposure to draught.

In croupous (lobar) pneumonia as a rule the patient can indicate the exact hour of disease onset, while in pleuritis the disease sets in gradually, little by little, with rising complaints (side pain on breath, cough, dyspnea, and fever) [14].

Checking of childhood anamnesis and interview about previous diseases is important. Even pediatric infections like measles, whooping cough, roseola, scarlet fever and rubella (German measles) and, especially parvovirus and herpes virus group diseases, e.g. *roseola neonatorum* — may be of large subsequent meaning, for example in provocation of autoimmune disorders [18]. It is advisable to check in every concrete case probable contact with tuberculosis patients and with other contagious diseases involving respiratory tracts. Ask the patient about possible self-treatment on initial stage of disease before calling a doctor in (what drugs were taken, in what doses, were the antipyretics and antibacterial remedies used, were some herbs or traditional ethnic medicine remedies in use, was it effective or not).

Collecting information from *anamnesis vitae* doctor must reveal how did the patient grow up and develop, were the infections, common colds and sore throat episodes frequent in his/her childhood and previous life, or not [1, 7, 10].

There exist certain genetic predispositions to bronchopulmonary diseases. It requires careful taking of genetic and family anamnesis. Case histories of relatives are important also for tuberculosis patients because of close family contact. Medical doctor must be advised about patient's living conditions [18]. Humid air, poor ventilation of the room, smoking and housing with smokers, work at the same room with smokers, living in bad climate — may increase the risk of pulmonary diseases. Passive smoking is almost as dangerous as active one. It is especially true for epidemiology of lung cancer. It has been demonstrated, for example, that the smokers have 50 times greater lung cancer morbidity rate than non-smokers [19]. Besides, now it is common knowledge that smoking facilitates citrullination of many autoantigens, especially — in lungs and blood, which perfuse lungs [20]. Citrulline-containing peptides are involved in provocation of many autoimmune diseases, not only pulmonary (like,

"idiopathic" pneumofibrosis), but also systemic ones (rheumatoid arthritis and systemic sclerosis) [20–21].

Alcohol abuse is also a risk factor of certain bronchopulmonary diseases, i.e. purulent pulmonary processes and tuberculosis. It is related with diminished resistance of alcoholics to infection and poor diet and social condition in many them [22]. Occupational hazards are of great importance in Pulmonology [10]. The following occupations are especially hazardous [23]:

— Requiring work in dusty rooms (weaving mills, mills, mains, building materials production — sand, concrete, cement, bricks);
— Associated with air contact with inhalable pollutants. For example, work with asbestos is considered to be associated with higher risk of mesothelioma.

Higher risk of sarcoidosis was recently registered in those individuals professionally working with printers and their toners, as well as with various kinds of metal-containing dust [24].

Car-road complex, producing plenty of solid dust particles is very considerable source of air pollution increasing risk of bronchopulmonary diseases for those persons, who lives and works in highly urbanized regions, not only *via* their own action as alien bodies and adjuvant-likwe agents, but also because of their ability to harbor microorganisms [25]. Neglecting of safety rules in industry may lead to the cases of occupational bronchitis, and even to pneumoconioses, because alveolar macrophages after phagocytosis of solid particles and crystals of minerals are not able to digest them and undergo chronic stimulation with resulting hyperproduction of inflammatory autacoids including fibrogenic cytokines (these are: Lung silicosis, anthracosis and talcosis) (fig. 3). Silicates involved in etiology of this group of diseases dysplay adjuvant-like properties. Talcosis was described not only in Occupational Medicine, but also among the heroin addicts inhaling the street drug with talc used by vendors as an adulterant.

Professional bronchitis is described even in dentists, who neglected the protective respirators and inhaled for a long time the dental dust, produced by drilling machines.

Allergological anamnesis is of immense significance for bronchopulmonary diseases. Check, if the patient suffered previously from bronchial asthma or some bronchospasm, provoked by any drug, food or smell idiosyncrasy, hay fever or atopic rhinitis/rhinosinusitis; how he/she responded the immunizations, did he/she get any vaccinations recently. It has been proven that certain lung diseases are of autoimmune and/or autoinflammatory origin. One of the most actual current problems is caused by autoimmune interstitial pneumoniae, provoking severe shifts of gaseous parameters in blood with dangerous hypoxia, but having scarce local physical manifestations, compared to common airspace pneumoniae [26].

Of course, physician must ask patient about probable previous and currently diagnosed diseases of other organs and systems, besides current bronchopulmonary disorder. The cardiovascular diseases, diabetes mellitus, and systemic autoimmune disorders — all are of special interest for pulmonological diagnosis. It is well-known, for example, that the diabetic patients are liable to tuberculosis, as well as those with vitamin D deficiency.

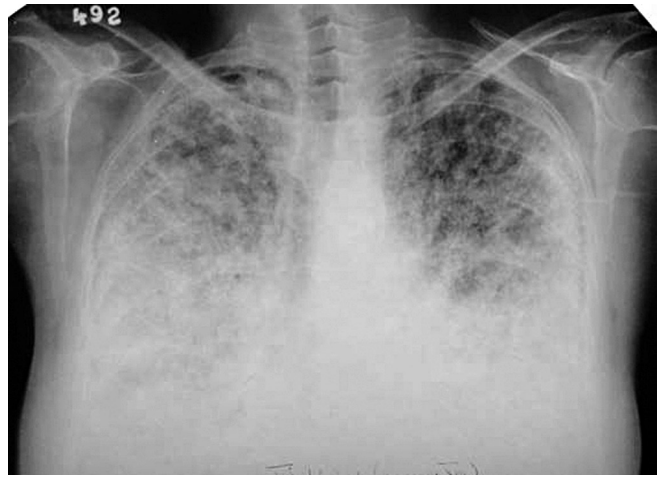

Fig. 3. Chest X-ray in occupational lung talcosis. Female patient with long exposure to talc while working at rubber factory. A case observed by Y.I. Stroev

VISUAL EXAMINATION

Examination of a patient is to be started from visual inspection. Visual examination may reveal objective dyspnea, cyanosis or marked flush on chicks. In croupous (lobar) pneumonia flush is more pronounced on the side of lesion [7]. It is noticed that the people with long eyelashes are more liable to tuberculosis. Feverish flush and eye glitter may present in both tuberculosis and thyrotoxicosis patients. Skin may have bluish color typical for hypoxemia, but also pallor. The last is common in exudative pleuritis or in pulmonary hemorrhage. *Herpes labialis et nasalis* is common finding in pneumonia as non-direct sign of decreased immunity. The cyanosis of skin and mucous membranes is characteristic for hypoxemia in pneumoniae, chronic bronchitis, and purulent processes of the lungs. The overt non-compensated *cor pulmonale* produces dramatic cyanosis with almost black skin. In Ayerza[2] disease, atherosclerotic pulmonary artery stenosis, the cyanosis is equally terrific. It is accompanied by marked dyspnea, getting worse in slightest efforts. Acute development of cyanosis is typical for thromboembolism of the pulmonary artery branches, as well as for pneumothorax and alien body within main bronchi [27–29].

Patient's posture in pulmonary diseases may be forced; some of the patients are sitting with their hands leaning on the bed (in bronchial asthma attacks); others are laying horizontally (in *cor pulmonale*) or lay with involved side down (in unilateral exudative pleuritis), trying to provide more effective respiratory excursions for healthy side).

Never limit the visual examination of bronchopulmonary patient with local chest area only, but always perform the general inspection.

Some chronic processes in bronchopulmonary system (e.g. bronchiectases, suppurative lung diseases, non-small cell bronchopulmonary cancer, interstitial lung fibrosis, complicated tuber-

[2] Ayerza Abel, 1861–1918, an Argentine physician.

culosis and severe sarcoidosis) are accompanied by formation of characteristic "drum stick-shaped" fingers and "watch glass-shaped" nails (common medical term is clubbing of nails and fingers) [7, 14, 29–30]. There is also systemic disorder — hypertrophic pulmonary osteoarthropathy (Bamberger — Marie disease[3]) regularly accompanied by similar nail clubbing and drum stick fingers. This manifestation was first described and associated with chronic disease as early as in Ancient Greece by Hippocrates of Cos[4], that's why the eponym given to the phenomenon is Hippocratic fingers (fig. 4). Pathogenesis of Hippocratic fingers is still debated, but there is strong support in favor of concept relating it with excessive local production of platelet growth factors. The megakaryocytes, normally trapped out of systemic circulation in healthy lungs, in case of bronchopulmonary disorders mentioned above bypass the lesser circulation and enter systemic circulation, trapped there in digital/nail capillary bed. Platelet clumps produced there emit excessive amounts of growth factors stimulating the clubbing formation [31].

Visual examination allows estimating patient's general condition, which may be satisfactory or heavy, down to the status of coma.

Visual examination allows determining patient's somatotype and state of nourishment [2]. It was noticed, that the persons with asthenic (aka: ectomorph) body constitution and poor nourishment state are more inclined to bronchopulmonary diseases [7]. But, severe obesity, regardless of somatotype, also may be accompanied by lung ventilation disorders with cyanosis, dyspnea and marked somnolence (patient may fall asleep when eating or even driving). This is known as "pickwickian[5] syndrome" (a variety of *cor pulmonale*) [32].

PATTERNS OF RESPIRATION IN HEALTH AND DISEASE

Visual examination enables medical doctor to diagnose presence and type of dyspnea and respiratory rhythm disorders. There is a family of respiratory patterns (formally all of them can be listed as kinds of dyspnea), some of them are controlled by physiologic pacemaker of respiration, which means they are regular and adapted to changes in metabolic requirements. Other ones are driven by non-physiologic peacemakers or not entirely controlled by physiologic one, hence they belong to periodic breathing and do not satisfy metabolic and homeostatic needs of the body, at least for prolonged time.

Normal respiration (both its rate and pattern) is controlled by supreme integrative pneumotaxic centre, located in the upper part of the *pons Varolii*. It consists of the subparabrachial nucleus and the parabrachial nuclei complex, including subparabrachial *Köllikер-Fuse*[6] *nucleus [9, 33–35].*

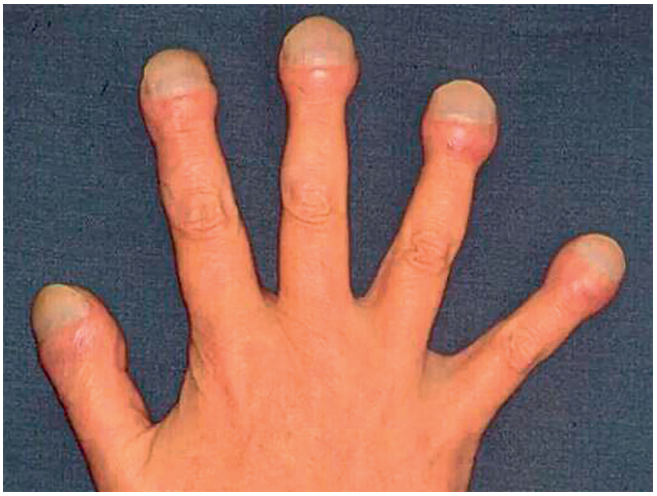

Fig. 4. Hippocratic fingers (source: https://fb.ru/misc/i/gallery/102987/3008212.jpg)

The centre tends to select optimal respiration pattern according dynamically changing requirements and conditions (fig. 5 below). The main principle is that respiratory invoice of the body should be equal to minute volume of ventilation, with minimal possible oxygen cost of breathing in order to prevent fatigue of respiratory muscles. If neither intrabronchial, nor extrabronchial losses of energy are not critically increased — pneumotaxic centre chooses version of dyspnea with both deep and frequent breathing — so called *hyperpnoea*, since it is most effective pattern in terms of the ratio of tidal volume and dead space, which is ventilated but not perfused. But if intrabronchial or extrabronchial losses for friction become critically high because of some bronchopulmonary disorders, hyperpnoea response may loss its effectiveness. In restrictive syndrome (limitation of lung distention and/or volume of ventilation and surface of gas exchange) extrabronchial energy losses for inhalation may critically increase. In this case it is optimal for pneumotaxic centre to drift towards more frequent, but shallow pattern of dyspnea (see above Corrigan's breathing or tachypnoea). This pattern occurs in pneumonia, pneumothorax, hydrothorax, exudative pleuritis, pneumosclerosis, rib fractures, pleural adhesions — and in any restricting limitations of ventilation.

And *vice versa* in obstructive syndrome (limitation of exhale speed and/or impossibility of passive expiration due to obstacles or loss of elastic string effect of lung tissue) intrabronchial energy losses for exhalation may critically increase. In this case it is optimal for pneumotaxic centre to drift towards more rare, but deep pattern of dyspnea (*bradypnoea* or *stenotic breathing*), because maximal losses of energy within bronchi correspond to the turbulent regime at the moment of airflow turn and number of such turns is equal to the number of breath cycles per minute or to respiration rate). Stenotic breathing (bradypnoea) was first described in 1849

[3] von Bamberger Eugen, 1858–1921, an Austrian internist, described the disease in 1889, Marie Pierre, 1853–1940, a French internist and neuropathologist, in 1890 distinguished the disease from acromegaly.

[4] Hippocrates of Cos, 460–377 B.C., ancient Greek physician and philosopher.

[5] The name was given by Canadian physician and pathologist William Osler (1849–1919) in honor of the hero of the novel by Charles Dickens "Notes of the Pickwick Club" (1837), where chapter 54 describes «fat guy Joe», often falling asleep in broad daylight.

[6] Kölliker Rudolf Albert, 1817–1905, a German histologist and embryologist; Fuse Gennosuke, 1880–1946, a Japanese anatomist.

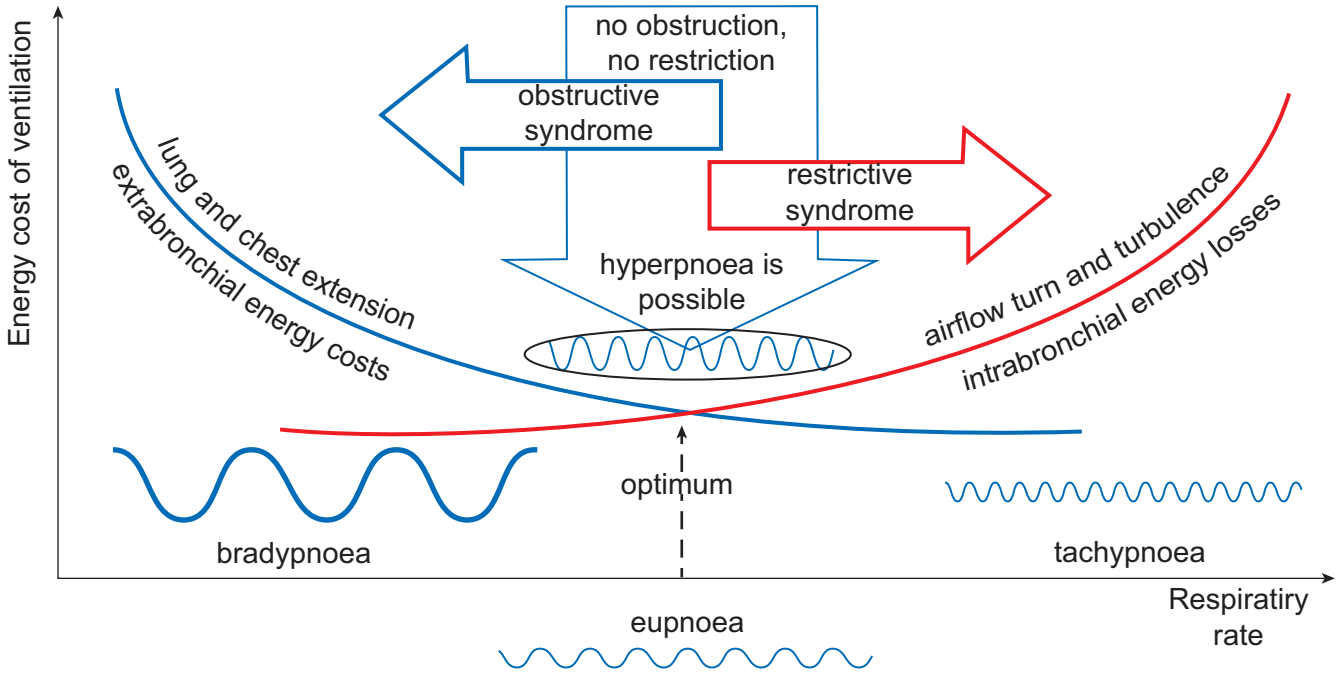

Fig. 5. How does pneumotaxic centre chooses appropriate optimal pattern of breath (explanations in the text)

by L. Traube[7] and is known under eponym "Traube's respiration". This pattern occurs in stenosis of gross airways, in emphysema, bronchial asthma — and in any obstructive disorder of ventilation. *Hyperpnoea, tachypnoea* and *bradypnoea*, although look differently and vary in effectiveness, but all belong to continuous regular patterns of dyspnea, still driven by physiologic respiratory pacemaker — pneumotaxic centre. It does not mean that all these patterns of dyspnea are associated with normal conditions. The last is true only for hyperpnoea which can be physiologic dyspnea (see above). The remaining patterns accompany either marked restrictive or marked obstructive bronchopulmonary disorders (fig. 5).

If pneumotaxic centre is damaged or at least exhausted and no longer able to maintain its physiologic role of respiration pacemaker, the pattern of respiration may loss its continuous regularity and thus *periodic respiration* occurs [9].

There are various kinds of pathological periodic respiration, depending on which abnormal (archetypic) pacemaker takes the baton from silent or exhausted pneumotaxic centre [35].

Periodic Biot's[8] respiration is characterized by several normal inhales, followed by apnea of varying duration (fig. 6).

It is a kind of pathological periodic breathing under the supervision of an apneustic center of lower pons, an emergency expiratory dyspnea, with delay on the top of inhale, characterized by a rare frequency and small minute volume of ventilation. Several convulsive exhalation attempts occur at the height of the inspiration, these episodes are interspersed with pauses of apnea. It reflects the pontine dysfunction, and often accompanies severe

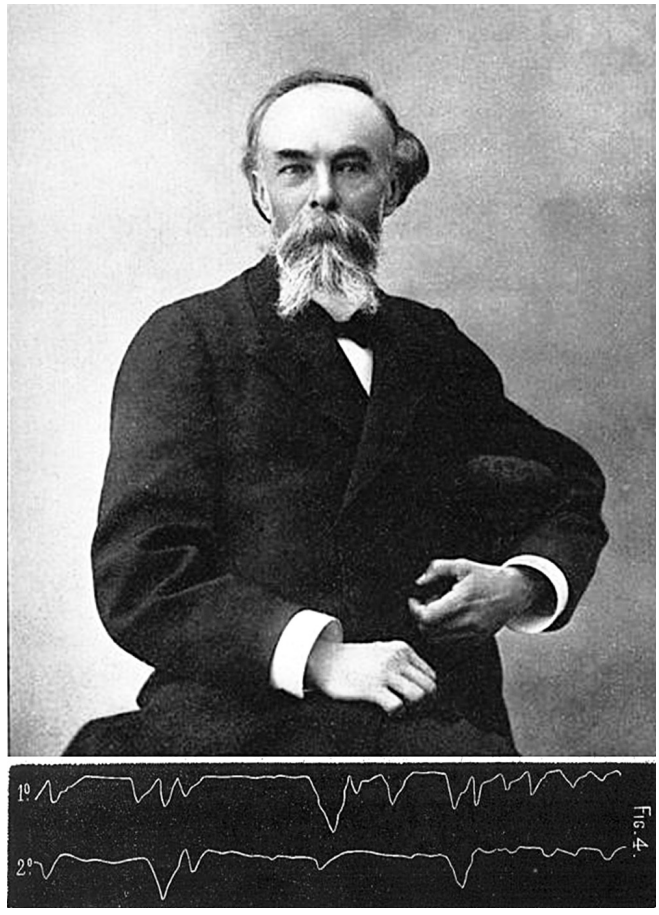

Fig. 6. Camille Biot and his original record of spirogram in periodic respiration of a tuberculosis meningitis patient [38]

[7] Traube Ludwig, 1818–1876, an Austrian (after 1869 — German) internist and clinical pathophysiologist.

[8] Biot Camille, 1850–1918, a French physician.

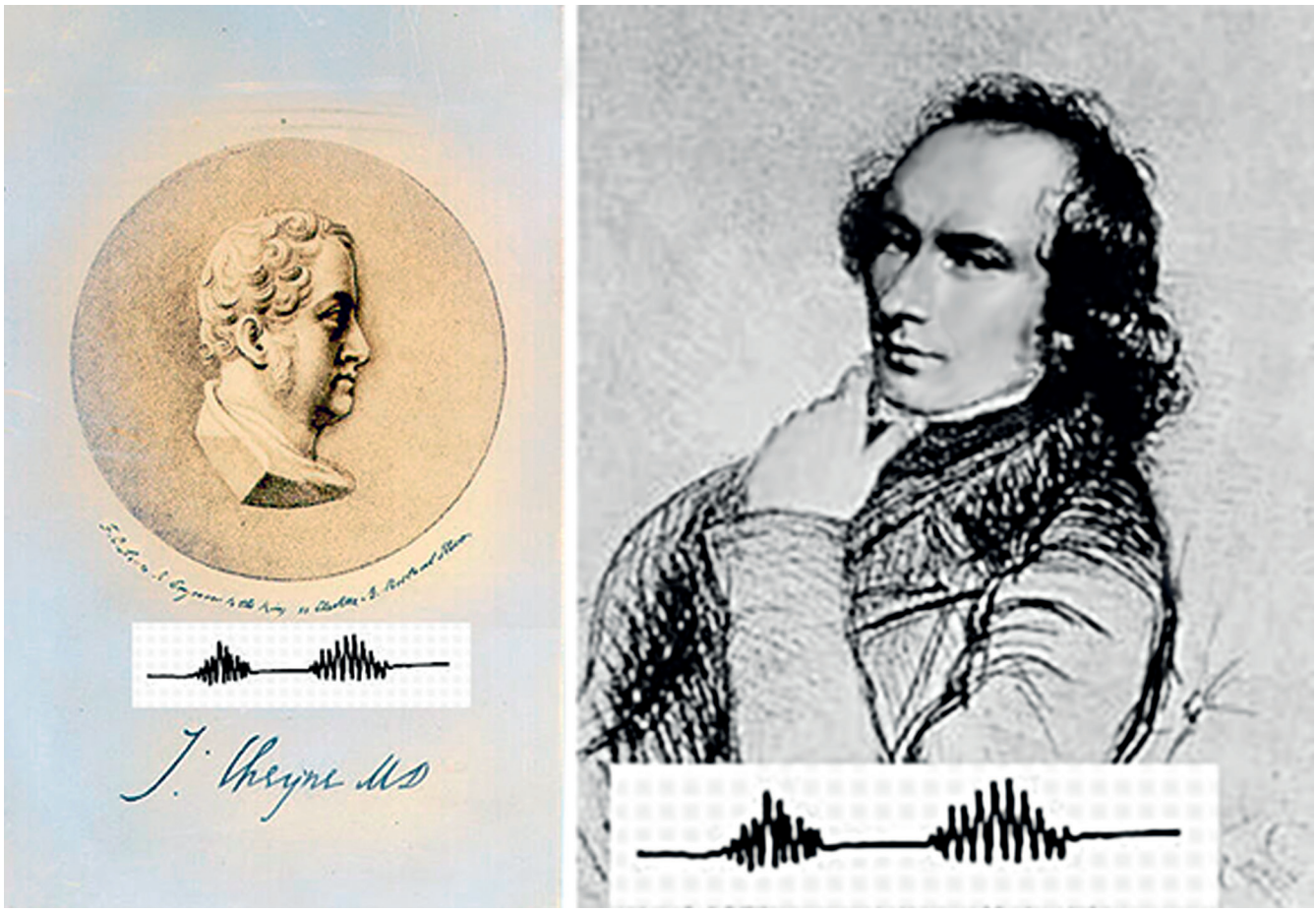

Fig. 7. Left: John Cheyne, right: William Stokes, bottom: spirograms of periodic respiration they described

intracranial hypertension and sometimes is observed in opiate poisoning [9, 34–36]. With a further disorder in the regulation of ventilation, it proceeds into so called ataxic respiration, characterized by completely irregular breaths and pauses with the absence of periodicity [36–37]. The phenomenon (fig. 6) was first described in 1876 — in a pre-agonal case of tuberculous meningitis [38]. This type of respiration may reflect the severely decreased pneumotaxic centre excitability caused by hypoxic necrobiosis of its neurons (described in meningitis, brain tumors, strokes, and comas) [35, 37–38].

Another type of periodic breathing, which is sometimes, but not always, a witness of fatal disorder, is the Cheyne–Stokes[9] respiration. It is characterized by periods of apnea and hyperpnoea, but during hyperpnoea the breath rate and depth gradually increases, reaching certain level, then, *vice versa*, decreases down to new apnea pause (fig. 7).

This sequence is repeated several times. It is considered to be the result of neural parabiosis in pneumotaxic centre due to its fatigue or initial stages of its degradation [9, 33–35]. The lack of hypoxemic reflex drive is also of utmost significance for Cheyne–Stokes respiration. Having hypercapnia-driven stimulation only, the pneumotaxic centre behaves like its threshold of sensitivity to inhalation stimuli has been increased. Hence, there is no inhale in spite of elevated pCO_2, until CO_2 concentration will reach quite high level, enough to overcome the "laziness" of the centre. Then the respiration resumes, but its frequency corresponds to very high levels of carbon dioxide, which ensures the transition from apnea immediately to hyperpnoea [39]. This type of respiration is considered by some internists to be bad for case prognosis, reflecting the deep disorders of central respiratory regulation. It's true that the Cheyne–Stokes breathing may occur in serious disorders, for example in pre-agonal states and in severe atherosclerosis of aorta and sino-carotid reflex trigger zones, making hypoxemic drive from its interoceptors less or non-efficient. It may also occur in cranial trauma, stroke, and in various comas, e.g. uremic one. It is worth to notice, that Biot's and Cheyne–Stokes respirations may be observed even in full conscious patients suffering from marked cerebral atherosclerosis. Nevertheless, Cheyne–Stokes respiration has better prognosis than above mentioned Biot's and apneustic/ataxic patterns of breathing. Moreover, sometimes it is observed in situations which do not belong to critical pathology: In deep sleeping, especially in infants and in very old persons with their less effective sino-carotid drive, or in severe alcoholic intoxication [9–10]. Moreover — recent studies gave a basis for a hypothesis of compen-

[9] Cheyne John, 1777–1836, a Scottish physician, described the phenomenon in 1818; Stokes William, 1804–1878, an Irish physician, completed its description in 1854.

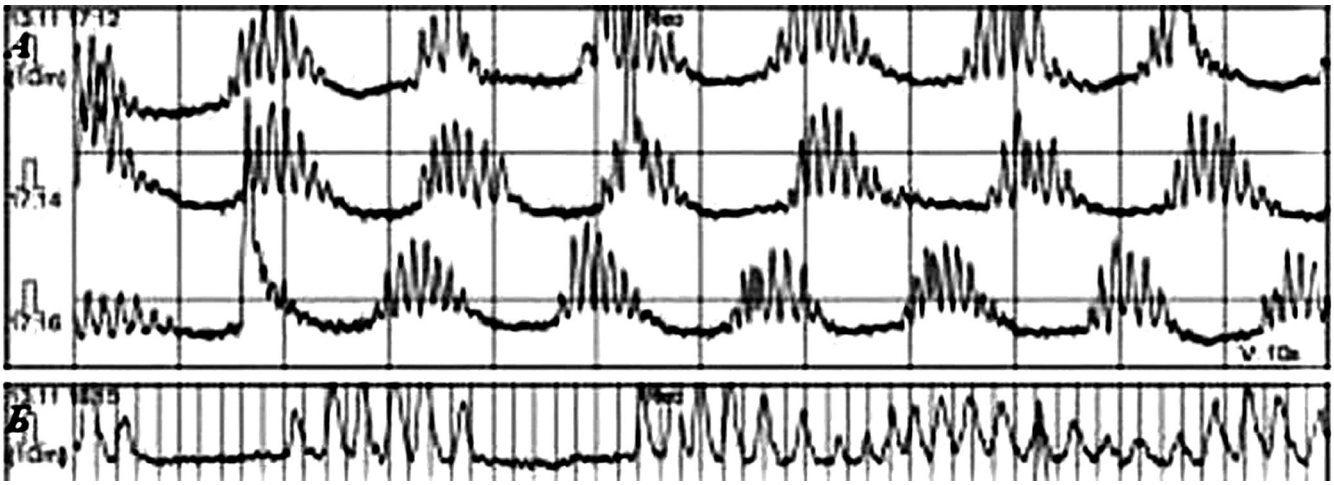

Fig. 8. Patterns of periodic respiration in a premature baby with cerebral ischaemia, pneumopathy and birth vertebral trauma. А — Cheyne–Stokes type; Б — Biot's type [37]

satory character of Cheyne–Stokes breathing for congestive heart failure patients, while asleep.

Thus, this pattern of respiration to a certain degree and till some extent may be not only "foe", but also "friend", although deceiving one in chronic perspective [40]. During provisional apnea in these periodic patterns of respiration some accompanying phenomena like loss of consciousness, bradycardia, and pupil's narrowing may be observed in patient.

A variety of patterns of the periodic breathing as well as their dynamic transformations commonly are observed in premature babies, especially under severe hypoxia, which is routine situation in neonatal resuscitation wards. The witness is shown in (fig. 8), taken from [37].

Another type of pathological dyspnea or periodic respiration driven by pathological pacemaker is so called *gasping respiration*, or *Kussmaul's respiration*. It is pre-agonal and agonal type of inspiratory dyspnea, when pneumotaxic center delegated its pacemaker function to gasping center in upper part of *medulla oblongata*. Pattern of breathing in Kussmaul's respiration is rare and very deep, with long and noisy inhale (agonal inspiratory dyspnea), which sounds were gloomily characterized by old classics of therapy as "death-bell sounds". The Kussmaul's respiration is a result of severe acidosis and was first reported by its discoverer Adolf Kussmaul[10] in a patient with terminal diabetic ketoacidotic coma [41] (fig. 9). Not necessarily ketoacidosis may provoke this disorder, but any kind of acidosis, including deep combined hypoxic acidosis in the terminal stage of heavy hypoxial diseases, metabolic, renal and combined acidoses and exogenous acidoses in poisonings.

Fig. 9. Adolf Kussmaul and spirogram of periodic respiration described by him. Notice that even autograph of this person resembles a little bit the graphic line of his discovery

[10] Kussmaul Adolf, 1822–1902, a German internist, clinical pathophysiologist and poet; known not only for many medical discoveries and innovations, but also for the following verse, translated by H. Waine from German:

"It seems that happenings of yore
Might have occurred the day before
But what transpired yesterday
Already wants to fade away".

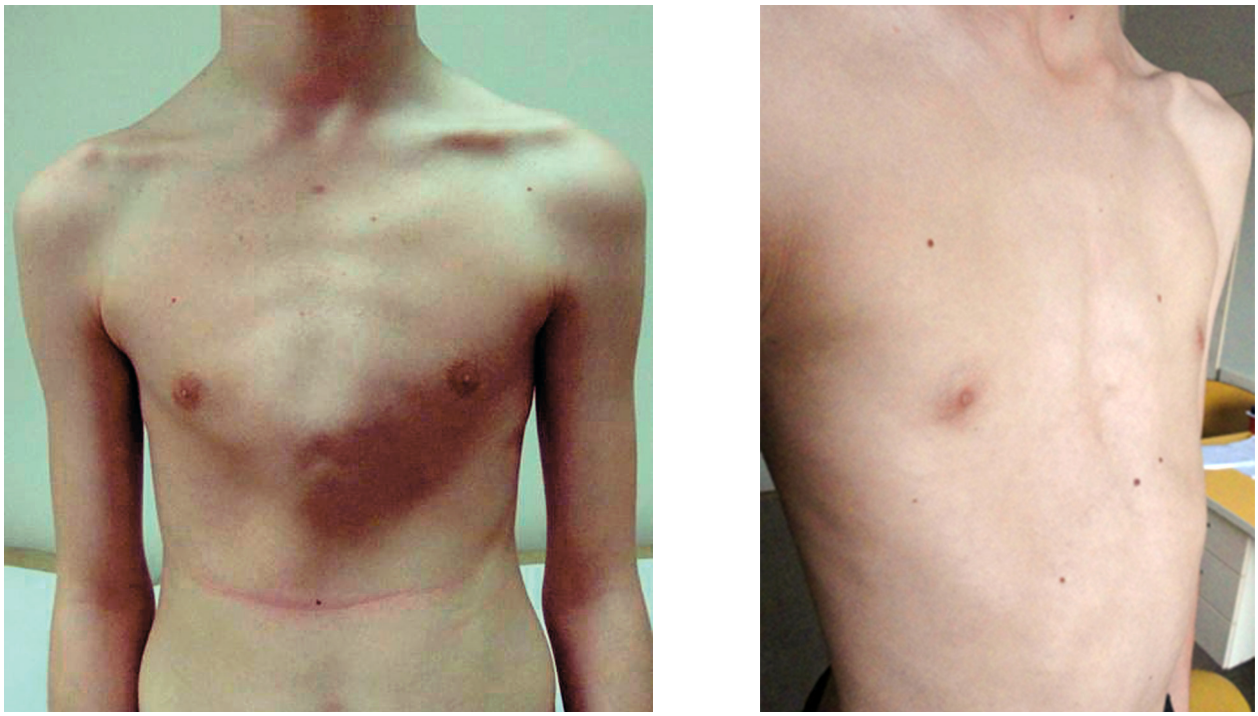

Fig. 10. Left: Keel-shaped chest deformity; right: funnel-shaped chest deformity ("shoemaker's chest"). The cases observed by Y.I. Stroev

Last breaths of a dying person (by the way, as well as first breath in healthy neonate!) are very typically driven by gasping centre. But, besides the pre-agony and agony, Kussmaul's breathing is observed in many situations, which are treatable in spite of severe acidosis of various etiologies [42].

To memorize them, English speaking medical students invented the following mnemonic acronym: **K**etosis, **U**remia, **S**epsis, **S**alycilate, **M**ethanol, **A**ldehyde (poisonings), **U**nd (because of German origin of the discoverer!)… **L**actate-acidosis. In Kussmaul breathing ventilation requirements of the body, dictated by metabolism and internal respiration, are poorly satisfied, so without treatment of its reason it progresses towards complete apnea. Dissociated respiration by Grocco–Frugoni[11] is related to discoordination of phrenic muscle and intercostal muscles' contractions [7, 9, 15, 28, 35]. In extreme cases it may look as a paradoxical of simultaneous inhale movement of upper chest and exhale movement of abdomen. This disorder also regarded as a witness for the bad case forecast (observed, for instance, in severe meningitis, brain tumors or abscesses, uremia and diabetic coma).

Visual examination of a patient is determining not only the shape of his/her thorax (normal, emphysematous, or pterygoid), but also chest deformations, both those derived from skeleton diseases and those brought in by pleuropulmonary diseases.

Pterygoid (alar) chest is usually elongated, flattened and narrowed in both transverse and sagittal dimensions. Shoulders position is oblique and «hanged», scapulae are wing-shaped and lag behind the thorax, intercostal corner is sharp, supraclavicular and infraclavicular pits are eye-catching, intercostal spaces draw in during inhalation The changes like this may be produced by tuberculosis or inflammatory process in lungs and pleura with pneumosclerosis and wrinkled lungs.

Asthenic type of chest shape resembles closely pterygoid one. It is not a result of disease, but a constitutional sign of borderline somatotype, prone to general weakness, pallor, and anemia, poor state of nourishment, weak muscles, and visceroptosis [7].

Emphysematous chest is characteristic for increase of sagittal dimension; horizontal ribs position, dilated intercostal spaces, and intercostal corner greater than 45°. Old physicians use to call it "barrel chest". The pits over and below the clavicles and the intercostal spaces may be almost not observable and even protruding. Barrel chest looks like being in the state of constant inhalation. This shape of thorax may result from the loss of lung elasticity (in emphysema or chronic bronchitis), when residual lung volume is enlarged [9]. In majority of cases it is acquired, but, sometimes, may be of congenital origin.

There may be registered also partial deformities of the chest: Protrusion of one half or drawing some part(s) in. Unilateral protrusion may be derived from air or fluid collection in corresponding pleural cavity. It will disturb the mammal gland nipples symmetry, and may cause the rise of shoulder on damaged side and scoliosis, convex towards the damaged side. Intercostal spaces in such cases are broadened and protruded. If one side of the chest lags behind during respiration and has some portion(s) drawing in, it may witness for unilateral pleuropulmonary lesion, lung atelectasis, dry pleuritis, croupous pneumonia, rib fracture, or rough

[11] Grocco Pietro, 1856–1916, an Italian internist; Frugoni Cesare, 1881–1978, an Italian physician.

pleural adhesion. Severe unilateral chest pain may lead to reflex muscular contraction on damaged side and produce visual chest asymmetry. Besides the most typical chest deformities described above, there may be noticed funnel-shaped deformity (syn.: paralitic chest or "shoemaker's chest"), keel-shaped deformity (which often occurs in marfanoid phenotype — see fig. 10), and kyphotic chest [7, 10] or even so called gibbus cardiacus.

These deformities may facilitate the development of thoracic-phrenic pulmonary heart, and due to that relation may be also significant for case prognosis.

The deformity of cardiac hump (*gibbus cardiacus*) may occur in some congenital heart diseases (like, in patent ductus arteriosus).

The measurements and visual evaluation may register the absence of proper chest expanding on inhalation. It may result from disorders of respiratory muscles (e.g. in myasthenia, especially in advanced autoimmune *myasthenia gravis*), also it occurs in ankyloses of the costovertebral joints (an early and quite characteristic symptom of autoimmune ankylosing spondylitis (also called Bekhterev spondylitis, deforming spondylitis, or Marie-Strümpell arthritis)[12] [43].

Visual examination of the chest may register vein broadening (resulted from either initial stage of congestion in lesser circulation or from vein compression by intrathoracic tumors or lymph nodes enlarged). The last phenomenon may occur in pulmonary tuberculosis or in lung cancer and alternatively — in lymphogranulomatosis. The presence of mesh consisting of small broadened veins in upper third of the chest, especially, in posterior interscapular area, is referred to as positive Frank's symptom[13] [44]. This is connected with bronchial lymph nodes enlargement and subsequent compression of veins by these nodes. Frank's symptom is believed to be one of important diagnostically valuable signs of intrathoracic tuberculosis lymphadenitis, as regards, in particular, to its pediatric cases.

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ЛИТЕРАТУРА

1. Stroev Y.I., Churilov L.P. Selected lectures in internal medicine for m.d. students. Part I. introduction. Patient interviewing and complaints. Rus. Biomed. Res. 2017; 2(4): 33–41.
2. Stroev Y.I., Churilov L.P. Visual examination in cardiovascular diseases. Rus. Biomed. Res. 2018; 3(1): 9–17.
3. Stroev Y.I., Churilov L.P. Palpation in cardiovascular diseases. Rus. Biomed. Res. 2018; 3(2): 9–17.
4. Stroev Y.I., Churilov L.P. Auscultation in cardiovascular diseases. Rus. Biomed. Res. 2018; 3(3): 3–13.
5. Stroev Y.I., Churilov L.P. Percussion in cardiovascular diseases. Rus. Biomed. Res. 2018; 3(4): 3–7.
6. Бокарев И.Н., Попова Л.В. Внутренние болезни. Дифференциальная диагностика и лечение. Учебник. М.: Медицинское информационное агентство; 2015: 776.
7. Василенко В.Х., Гребенев А.Л., Голочевская В.С., Плетнева Н.Г., Шептулин А.А. Пропедевтика внутренних болезней: Учебник. 5-е издание, переработанное и дополненное. М.: Медицина; 2001: 592.
8. Parshall M.B., Schwartzstein R.M., Adams L., et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med. 2012; 185(4): 435–452. doi:10.1164/rccm.201111–2042ST.
9. Чурилов Л.П.(ред.). Практикум по экспериментальной и клинической патологии. Издание 3-е, испр. и дополн. СПб.: СпецЛит., 2018: 321–3.
10. Окороков А.Н. Диагностика болезней внутренних органов. Руководство в 10 томах. Т. 3. Диагностика болезней органов дыхания. М.: Медицинская литература; 2013: 464.
11. Mutolo D. Brainstem mechanisms underlying the cough reflex and its regulation. Respir Physiol Neurobiol. 2017;243:60–76. doi:10.1016/j.resp.2017.05.008.
12. McGovern AE, Short KR, Kywe Moe AA, Mazzone SB. Translational review: Neuroimmune mechanisms in cough and emerging therapeutic targets. J Allergy Clin Immunol. 2018;142(5):1392–1402. doi:10.1016/j.jaci.2018.09.004
13. Громнацкий Н.И. Внутренние болезни. М.: Медицинское информационное агентство; 2010: 688.
14. Мадьяр И. Дифференциальная диагностика внутренних органов. Пер. с венг. — Будапешт: Изд-во Академии наук Венгрии. 1987; Т. I–II: 1155.
15. Enersen O.-D. (Ed.) Whonamedit? A Dictionary of Medical Eponyms. URL: http://www.whonamedit.com/(accessed 10.06.2019).
16. Luna C. M. C-Reactive Protein in Pneumonia. CHEST, 2004; 125(4): 1192–1195.
17. Маев И.В., Шестаков В.А. (ред.) Пропедевтика внутренних болезней. 2-е изд. М.: Академия. 2012; Т. I: 376.
18. Hunter S.F., Hafler D.A. Ubiquitous pathogens: links between infection and autoimmunity in MS?. Neurology. 2000; 55(2): 164–5. doi:10.1212/wnl.55.2.164
19. de Groot P., Munden R.F. Lung cancer epidemiology, risk factors, and prevention. Radiol Clin North Am. 2012; 50(5): 863–76. doi:10.1016/j.rcl.2012.06.006
20. Valesini G., Gerardi M.C., Iannuccelli C., Pacucci V.A., Pendolino M., Shoenfeld Y. Citrullination and autoimmunity. Autoimmun Rev. 2015; 14(6): 490–7. doi:10.1016/j.autrev.2015.01.013
21. Ummarino D. Rheumatoid arthritis: Smoking influences autoimmunity to vimentin. Nat Rev Rheumatol. 2016; 12(11): 624. doi:10.1038/nrrheum.2016.160

[12] Bekhterev Vladimir Mikhailovich, 1857–1927, a Russian psychiatrist and neuropathologist; Marie Pierre — see footnote 3 above; von Strumpell Ernst Adolph Gustav Gottfried, 1853–1925, a German internist and neuropathologist, native of Russia.

[13] Frank A. Erich, 1884–1957, a German (after 1934 — Turkish) physician.

22. Lorenz J., Ferlinz R. Bronchopulmonale Erkrankungen bei Alkoholismus. Dtsch Med Wochenschr. 1985; 110(27): 1086–88. doi:10.1055/s-2008–1068964
23. Fazen L.E., Linde B., Redlich C.A. Occupational lung diseases in the 21st century: the changing landscape and future challenges. Curr Opin Pulm Med. 2020; 26(2): 142–8. doi:10.1097/MCP.0000000000000658
24. Starshinova A., Malkova A., Basantsova N., Zinchenko Y., Kudryavtsev I., Ershov G., Soprun L., Mayevskaya V., Churilov L.P., Yablonskiy P. Sarcoidosis As An Autoimmune Disease (literature review). Front. Immunol. 2019; 10: 2933. doi: 10.3389/fimmu.2019.02933.
25. Сопрун Л.А., Акулин И.М., Лукашенко М.В., Чурилов Л.П., Старшинова А.А., Яблонский П.К.. Твердые пылевые частицы и проблема их определения при бронхолегочной патологии. Медицинский альянс, 2019; 7(4): 69–76.
26. Wilfong E.M., Lentz R.J., Guttentag A., et al. Interstitial Pneumonia With Autoimmune Features: An Emerging Challenge at the Intersection of Rheumatology and Pulmonology. Arthritis Rheumatol. 2018; 70(12): 1901–13. doi:10.1002/art.40679
27. Яковлева А. Ю. Пропедевтика внутренних болезней: Конспект лекций. М.: Эксмо; 2007: 160.
28. Милькаманович В.К. Методическое обследование, симптомы и симптомокомплексы в клинике внутренних болезней: Руководство для студентов и врачей. Минск: ООО Полифакт-Альфа; 1994: 672.
29. Отто В., Хамбш К., Тройтлер Г. Медицинская поликлиническая диагностика. Пер. с нем. М.: Медицина; 1979: 479.
30. Хегглин Р. Дифференциальная диагностика внутренних болезней. Пер. с нем. М.: Триада-Х; 2015: 800.
31. Dickinson C.J., Martin, J.F., Megakaryocytes and platelet clumps as the cause of finger clubbing. Lancet. 1987; 2 (8573): 1434–5. doi:10.1016/s0140–6736(87)91132–9
32. Littleton S.W., Mokhlesi B. The pickwickian syndrome–obesity hypoventilation syndrome. Clin Chest Med. 2009; 30(3): 467–viii. doi:10.1016/j.ccm.2009.05.004
33. Urfy M.Z., Suarez J.I. Breathing and the nervous system. Handb Clin Neurol. 2014; 119: 241–50. doi:10.1016/B978–0-7020–4086–3.00017–5
34. Бреслав И.С., Глебовский В.Д. Регуляция дыхания. Л.: Наука; 1981: 280.
35. Бреслав И.С. Паттерны дыхания: Физиология, экстремальные состояния, патология. Л.: Наука; 1984: 206.
36. Wijdicks E.F. Biot's breathing. J Neurol Neurosurg Psychiatry. 2007; 78(5): 512–13. doi:10.1136/jnnp.2006.104919
37. Лышова О.В. Варианты дыхательных паттернов при функциональной незрелости дыхательной системы у человека. Вестн. аритмологии, 2005; 39: 43–8.
38. Biot MC. Contribution a l'étude du phénomène respiratoire de Cheyne-Stokes. Lyon Med. 1876; 23: 517–28, 561–7.
39. Lange R.L., Hecht H.H. The mechanism of Cheyne-Stokes respiration. J Clin Invest. 1962; 4 1(1): 42–52. doi:10.1172/JCI104465
40. Oldenburg O., Spießhöfer J., Fox H., Bitter T., Horstkotte D. Cheyne-Stokes respiration in heart failure: friend or foe? Hemodynamic effects of hyperventilation in heart failure patients and healthy volunteers. Clin Res Cardiol. 2015; 104(4): 328–33.
41. Kussmaul A. Zur Lehre vom Diabetes mellitus. Über eine eigenthümliche Todesart bei Diabetischen, über Acetonämie, Glycerin-Behandlung des Diabetes und Einspritzungen von Diastase in's Blut bei dieser Krankheit. Deutsches Archiv für klinische Medicin (Leipzig), 1874; 14: 1–46.
42. Fukui T. [Respiratory regulation system]. Nihon Rinsho. 1992; 50(9): 2077–81. (in Japanese)
43. Kanathur N., Lee-Chiong T. Pulmonary manifestations of ankylosing spondylitis. Clin Chest Med. 2010; 31(3): 547–54. doi:10.1016/j.ccm.2010.05.002
44. Корецкая Н.М. Туберкулез у детей и подростков в современных условиях. Сибирское медицинское обозрение. 2010; 2(62): 105–9.

REFERENCES

1. Stroev Y.I., Churilov L.P. Selected lectures in internal medicine for m.d. students. Part I. introduction. Patient interviewing and complaints. Rus. Biomed. Res. 2017; 2(4): 33–41.
2. Stroev Y.I., Churilov L.P. Visual examination in cardiovascular diseases. Rus. Biomed. Res. 2018; 3(1): 9–17.
3. Stroev Y.I., Churilov L.P. Palpation in cardiovascular diseases. Rus. Biomed. Res. 2018; 3(2): 9–17.
4. Stroev Y.I., Churilov L.P. Auscultation in cardiovascular diseases. Rus. Biomed. Res. 2018; 3(3): 3–13.
5. Stroev Y.I., Churilov L.P. Percussion in cardiovascular diseases. Rus. Biomed. Res. 2018; 3(4): 3–7.
6. Bokarev I.N., Popova L.V. Vnutrennie bolezni. Differencialnaya diagnostika i lechenie. Uchebnik [Internal Medicine. Differential diagnosis and treatment]. M.: MIA Publishers; 2015: 776. (in Russian).
7. Vasilenko V.H., Grebenev A.L., Golochevskaja V.S., Pletneva N.G., Sheptulin A.A. Propedevtika vnutrennih boleznej.[Propaedeutics of internal diseases]. Uchebnik. 5-e izdanie, pererabotannoe i dopolnennoe. M.: Medicina Publishers; 2001: 592. (in Russian).
8. Parshall M.B., Schwartzstein R.M., Adams L., et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med. 2012; 185(4): 435–52. doi:10.1164/rccm.201111–2042ST.
9. Churilov L.P.(Ed.). Praktikum po eksperimental'noj i klinicheskoi patologii. [Practicum in Experimental and Clinical Pathology]. Izdanie 3-e, ispr. i dopoln. Saint Petersburg: SpezLit Publishers, 2018: 321–3. (in Russian).
10. Okorokov A.N. Diagnostika boleznej vnutrennih organov. Rukovodstvo v 10 tomah. T. 3. Diagnostika boleznej organov dyhanija [Diagnosis of diseases of the internal organs]. M.: Medicinskaja literatura Publishers; 2013: 464. (in Russian).
11. Mutolo D. Brainstem mechanisms underlying the cough reflex and its regulation. Respir Physiol Neurobiol. 2017; 243: 60–76. doi:10.1016/j.resp.2017.05.008.
12. McGovern A.E., Short K.R., Kywe Moe A.A., Mazzone S.B. Translational review: Neuroimmune mechanisms in cough and emerging therapeutic targets. J Allergy Clin Immunol. 2018; 142(5): 1392–1402. doi:10.1016/j.jaci.2018.09.004
13. Gromnackij N.I. Vnutrennie bolezni [Internal illnesses]. M.: MIA Publishers; 2010: 688. (in Russian).
14. Magyar I. Differencial'naja diagnostika vnutrennih organov. [Differential diagnosis of internal organs]. Per. s veng. Budapest: Akadémiai Kiadó Publishers. 1987; T. I–II: 1155. (in Russian).

15. Enersen O.-D. (Ed.) Whonamedit? A Dictionary of Medical Eponyms. URL: http://www.whonamedit.com/(accessed 10.06.2019).
16. Luna C. M. C-Reactive Protein in Pneumonia. CHEST, 2004; 125(4): 1192–95.
17. Maev I.V., Shestakov V.A. (Eds) Propedevtika vnutrennih boleznej. [Propaedeutics of internal diseases]. 2-e izd. M.: Akademija Publishers. 2012; T. I: 376. (in Russian).
18. Hunter S.F., Hafler D.A. Ubiquitous pathogens: links between infection and autoimmunity in MS?. Neurology. 2000; 55(2): 164–5. doi:10.1212/wnl.55.2.164
19. de Groot P., Munden R.F. Lung cancer epidemiology, risk factors, and prevention. Radiol Clin North Am. 2012; 50(5): 863–76. doi:10.1016/j.rcl.2012.06.006
20. Valesini G., Gerardi M.C., Iannuccelli C., Pacucci V.A., Pendolino M., Shoenfeld Y. Citrullination and autoimmunity. Autoimmun Rev. 2015; 14(6): 490–7. doi:10.1016/j.autrev.2015.01.013
21. Ummarino D. Rheumatoid arthritis: Smoking influences autoimmunity to vimentin. Nat Rev Rheumatol. 2016; 12(11): 624. doi:10.1038/nrrheum.2016.160
22. Lorenz J., Ferlinz R. Bronchopulmonale Erkrankungen bei Alkoholismus. Dtsch Med Wochenschr. 1985; 110(27): 1086–88. doi:10.1055/s-2008–1068964
23. Fazen L.E., Linde B., Redlich C.A. Occupational lung diseases in the 21st century: the changing landscape and future challenges. Curr Opin Pulm Med. 2020; 26(2): 142–8. doi:10.1097/MCP.0000000000000658
24. Starshinova A., Malkova A., Basantsova N., Zinchenko Y., Kudryavtsev I., Ershov G., Soprun L., Mayevskaya V., Churilov L.P., Yablonskiy P. Sarcoidosis As An Autoimmune Disease (literature review). Front. Immunol. 2019; 10: 2933. doi: 10.3389/fimmu.2019.02933.
25. Soprun L.A., Akulin I.M., Lukashenko M.V., Churilov L.P., Starshinova A.A., Yablonskiy P.K. Tverdye pylevye chastitsy i problema ih opredeleniya pri bronholegochnoj patologii. [Solid dust particles and the problem of their determination in bronchopulmonary pathology]. Meditsinskiy Alliance [Medical Alliance], 2019; 7(4): 69–76. (in Russian).
26. Wilfong E.M., Lentz R.J., Guttentag A., et al. Interstitial Pneumonia With Autoimmune Features: An Emerging Challenge at the Intersection of Rheumatology and Pulmonology. Arthritis Rheumatol. 2018; 70(12): 1901–13. doi:10.1002/art.40679
27. Yakovleva A. Y. Propedevtika vnutrennih boleznej. Konspekt lekcij [Introduction into Internal Medicine]. M.: Eksmo Publishers; 2007: 160. (in Russian).
28. Mil'kamanovich V.K. Metodicheskoe obsledovanie, simptomy i simptomokompleksy v klinike vnutrennih boleznenj. [Methodical investigation, clinical symptoms and symptomocomplexes in internal medicine]. Rukovodstvo dlja studentov i vrachej. Minsk: OOO Polifakt-Al'fa. Publisher, 1994: 672. (in Russian).
29. Otto W., Hambsch K., Treutler H. Medicinskaja poliklinicheskaja diagnostika. [Medical outpatient diagnosis]. Per. s nem. M.: Medicina Publishers; 1979: 479. (in Russian).
30. Hegglin R. Differencial'naja diagnostika vnutrennih boleznej. [Differential diagnosis of internal diseases]. Per. s nem. M.: Triada-H Publishers; 2015: 800. (in Russian).
31. Dickinson C.J., Martin J.F. Megakaryocytes and platelet clumps as the cause of finger clubbing. Lancet. 1987; 2 (8573): 1434–5. doi:10.1016/s0140–6736(87)91132–9
32. Littleton S.W., Mokhlesi B. The pickwickian syndrome–obesity hypoventilation syndrome. Clin Chest Med. 2009; 30(3): 467–viii. doi:10.1016/j.ccm.2009.05.004
33. Urfy M.Z., Suarez J.I. Breathing and the nervous system. Handb Clin Neurol. 2014; 119: 241–50. doi:10.1016/B978–0-7020–4086–3.00017–5
34. Breslav I.S., Glebovskiy V.D. Regulyatsija dykhanija [Regulation of Respiration]. Leningrad: Nauka Publishers; 1981: 280. (in Russian).
35. Breslav I.S., Patterny dykhanija. Fiziologija, ekstremal'nye sostojanija, patologija [Patterns of respiration. Physiology. extreme states, pathology]. Leningrad: Nauka Publishers, 1984: 206. (in Russian).
36. Wijdicks E.F. Biot's breathing. J Neurol Neurosurg Psychiatry. 2007; 78(5): 512–13. doi:10.1136/jnnp.2006.104919
37. Lyshova O.V. Variant dykhatel'nykh patternov pri funktsional'noj nezrelosti dykhatel'noj sistemy u cheloveka [Variants of respiratory patterns in functionally immature human respiratory system]. Vestnik aritmologii. 2005; 39: 43–8. (in Russian).
38. Biot M.C. Contribution a l'étude du phénomène respiratoire de Cheyne-Stokes. Lyon Med. 1876; 23: 517–28, 561–7.
39. Lange R.L., Hecht H.H. The mechanism of Cheyne-Stokes respiration. J Clin Invest. 1962; 4 1(1): 42–52. doi:10.1172/JCI104465
40. Oldenburg O., Spießhöfer J., Fox H., Bitter T., Horstkotte D. Cheyne-Stokes respiration in heart failure: friend or foe? Hemodynamic effects of hyperventilation in heart failure patients and healthy volunteers. Clin Res Cardiol. 2015; 104(4): 328–33.
41. Kussmaul A. Zur Lehre vom Diabetes mellitus. Über eine eigenthümliche Todesart bei Diabetischen, über Acetonämie, Glycerin-Behandlung des Diabetes und Einspritzungen von Diastase in's Blut bei dieser Krankheit. Deutsches Archiv für klinische Medicin (Leipzig), 1874; 14: 1–46.
42. Fukui T. [Respiratory regulation system]. Nihon Rinsho. 1992; 50(9): 2077–81. (in Japanese)
43. Kanathur N., Lee-Chiong T. Pulmonary manifestations of ankylosing spondylitis. Clin Chest Med. 2010; 31(3): 547–54. doi:10.1016/j.ccm.2010.05.002
44. Koretskaya N.M. Tuberkulez u detej i podrostkov v sovremennyh uslovijah [Tuberculosis in children and adolescents nowadays]. Sibirskoe medicinskoe obozrenie, 2010; 2(62): 105–9. (in Russian).