REVIEWS

Pathogenesis and Morphogenesis of Alcoholic Disease

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Experimental, autopsy, and clinical findings call for a new clinical entity, namely, alcoholic disease. The disease has three stages: I) repetitive acute alcohol intoxications; II) drunkenness; and III) alcoholism and alcoholism-related complications. The organs determining the pathogenesis and outcome of alcoholic disease are the liver, heart, lungs, and brain. In chronic alcohol intoxication, lesions in these organs develop in a cascade manner according to the principle of a vicious circle. Pathological changes in the internal organs arise against the background of progressive microangiopathy that by itself is an important pathogenic component of the disease. The results obtained show that changes developing in the internal organs during the second stage are reversible or well compensated, whereas those occurring at the third stage are irreversible in a vast majority of cases and often fatal. There are reasons to consider the problem out of the context of the fight against alcoholism, which, in principle, is an irreversible pathological condition, but from the viewpoint of the proposed concept of alcoholic disease.

Key Words: *alcoholic disease; pathogenesis; morphogenesis*

Alcoholism and alcohol-related complications continue to cause increasing concern all over the world, since they pose a high risk of adverse and irreversible changes in human genome and lead to a great number of medical and social problems [14]. In Russia, a governmental system to combat alcoholism has been established. It includes a network of narcological clinics, dispensaries, narcological centers, etc. The preventive measures and treatment of alcoholism are based on guidelines and recommendations developed by psychiatrists and/or narcologists and are implemented under their supervision. The efficacy of these measures is very low: at the global level, the rates of radical cure of alcoholism range from 3% to 8%, these figures refer to men [4,10]. It should be stressed that the term "cure" is understood as it is interpreted by psychiatrists and narcologists who regard suppression of the desire to drink as the top priority.

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Historically, the situation has developed in such a way that the individuals constantly consuming alcohol are only noticed when the signs of mental disorder appear. Thus, alcoholics and chronic alcohol intoxication (AI) become a psychiatric problem. After studying this disease for about two centuries, psychiatrists came to the conclusion that the problem is associated with the development of mental and physical alcohol dependence, which determines the uncontrollable desire for alcoholic drinks. Consequently, suppression of this desire and elimination of alcohol dependence become the major priorities in the therapy of alcoholic disease. The effectiveness of the cure is defined according to the degree to which the desire to drink has been suppressed. However, many former alcoholics die within 10-12 years from illnesses related to chronic AI, such as cirrhosis of the liver and its complications, alcoholic cardiomyopathy, etc. [19]. In fact, even individuals cured of alcoholism according to psychiatric criteria often remain seriously and irreversibly ill. Therefore, the

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outcome of the current treatment of alcoholism can be regarded as social rather than medical. Obviously, alcoholism is an advanced stage of the disease at which the possibility of a cure in its general medical sense becomes questionable. This was confirmed by clinical and morphological research [1,11,15,21]. Alcoholics are known to suffer from diseases related to chronic AI, such as hepatitis, cirrhosis, pancreatic induration, recurrent pneumonia with abscess formation, chronic encephalopathies, including Gayet—Wernicke's encephalopathy, and alcoholic cardiomyopathy. Since numerous organs are affected and the rates of cure of alcoholic disease are very low, it could be said that the current level of understanding of the disease and, consequently, of therapy lead to a dead end.

If alcoholism is an advanced stage of the disease, then it should be preceded by earlier stages with less pronounced morphological changes and mental disorders. The concept of "social drinking" is based on very vague criteria. According to this concept, alcohol abuse is perceived as a social phenomenon but not as a disease. Generally, alcoholism is associated with drunkenness even by physicians; therefore, campaigns are launched against "drunkenness and alcoholism." However, these two conditions differ fundamentally from each other. Drunkenness involves only the desire to drink, while alcoholism is characterized by alcohol dependence. It was reported that only about 10% of drunkards become alcoholics [10,27]. Hence, the social aspect of alcohol-related problems is associated predominantly with drunkenness rather than with alcoholism. Bearing in mind the high prevalence of alcohol abuse, it can be stated that the proportion of drunkards among those who are ill or die from excessive alcohol consumption is greater than that of alcoholics. However, psychiatrists show little or no interest in drunkards because no obvious manifestations of mental illness are present. Therefore, drunkards are not included in health statistics as alcohol abusers, and general practitioners who treat these people for somatic diseases generally do not associate these diseases to prolonged alcohol abuse. The patients do not consider themselves as drunkards and are treated without taking the etiology of the disease(s) into consideration and without linking the disease with general chronic ethanol intoxication. After therapy, the patients continue excessive drinking, and somatic diseases become recurrent and progressive. Obviously, for effective control of alcoholism it is necessary to study chronic AI. In order to find out at which stage of the disease preventive and curative measures are most effective the mechanisms whereby internal organs and systems are affected by alcohol should be elucidated.

We modeled acute and chronic AI on 483 male albino rats. Chronic AI was performed with and without discontinuation of alcohol consumption, i.e., we attempted to reproduce the states similar to the withdrawal syndrome (the most reliable sign of alcoholism) and drunkenness in humans.

Intoxication with acetaldehyde was investigated in a separate study. Various organs and tissues were examined using histological, electron microscopic, and morphometric methods. The results were analyzed using statistical methods.

Analysis of the pathogenesis and morphogenesis of chronic AI led us to the conclusion that a new clinical entity, alcoholic disease, should be introduced to gain a better understanding of the problem of alcoholism. However, we do not equate this term with the term "alcoholic disease" proposed in 1849 by M. Guss who regarded it as a synonym of "alcoholism." Later, other researchers regarded different manifestations of alcoholism as forms of alcoholic disease [1,9,21]. According to the latter interpretation, the cases of severe generalized lesions are defined as "alcoholic liver disease", "alcoholic heart disease", etc., although there is no alcoholic heart damage without alcoholic liver damage and vice versa [19,22]. Unfortunately, this approach not only has direct academic but also practical implications, since pulmonary and cardiac disorders are then treated without taking into account the condition of the liver. However, blood concentrations of ethanol and acetaldehyde strongly depend on the basal liver metabolism, which determines the effect of these substances on the heart and lungs. We believe that repeated ethanol intoxications over a prolonged period provoke changes in organs and systems. These changes range from minimal microcirculatory disorders to massive damage to the internal organs, which is accompanied by specific clinical manifestations and symptoms (including psychic manifestations). The pathogenesis of alcoholic disease can be divided into three stages: I) repetitive acute AI, II) drunkenness, and III) alcoholism with complications (withdrawal syndrome, psychoses, etc.). Each stage is characterized by specific morphological features.

Our experimental studies and analysis of mortality among drunkards and alcoholics confirm the importance of the liver, heart, lungs, and brain in the pathogenesis and thanatogenesis of alcoholic disease, although AI induces pathological changes in all the body's organs and systems. During the stage of repetitive acute AIs, ethanol is rapidly and completely absorbed from the gastrointestinal tract and is accumulated in the internal organs proportionally to their water content [24]. Blood (predominantly erythrocytes [6]) and vascular walls are the first

targets of alcohol. Plethora occurs in visceral veins and capillaries of the microcirculatory bed (MCB), which leads to the development of stasis and erythrocyte sludge. Endothelial cells become edematous and show signs of intense pinocytosis and mitochondrial degradation. In capillaries and venules, the basement membrane swells, and destructive foci appear in it. Perivascular edema and mucoid swelling of the perivascular stroma are observed [16].

Electron microscopy reveals moderate destruction of the glycocalyx (particularly in cardiomyocytes) and the presence of colloidal lanthanum on mitochondrial membranes, indicating a marked increase in the permeability of sarcolemma. Consequently, the blood-tissue barrier is the first "victim" of acute AI. As a result, cells are invaded not only by ethanol, which causes fluidization of their membranes and inhibits in a dose-dependent manner the membrane-bound enzymes [29,32], but also by degradation products and "ballast" substances such as various metabolites cleared from the circulation. Fluidization and destruction of cell membranes by ethanol impairs the mechanisms responsible for the transmembrane transport of metabolites, including energy substrates and oxygen. Moreover, microcirculation disorders lead to hypoxia which inflicts damage to tissues and particularly to the plasma membrane structures [25]. Astrocytes are the major cell type of the blood-brain barrier transferring ethanol to the cerebrospinal fluid preventing it from reaching the neurons [13]. Ethanol and hypoxia induce pronounced degenerative changes in astrocytes. The ethanol concentration in the brain cannot be high, judging from the relatively low alcohol dehydrogenase (ADH) activity in the brain. Presumably, brain neurons are affected by hypoxia but not by ethanol, therefore, their specific density remains practically unchanged.

Thus, ethanol-induced alcoholic microangiopathy provides the basis for all subsequent changes in internal organs. During stage I, i.e., when ethanol is consumed from time to time in moderate doses, changes in the MCB are reversible. During this stage, granular degeneration of hepatocytes and plethora develop in the liver due to intense metabolization of ethanol. ADH activity rises considerably, and ethanol is completely oxidized, as evidenced by the absence of acetaldehyde from the blood. Cardiomyocyte mitochondria are the primary target of ethanol in the heart. The activities of mitochondrial enzymes (succinate dehydrogenase and NADH) decrease. It should be noted that the activity of mitochondrial enzymes positively correlated with that of liver ADH. An increase in the intracellular content of ethanol and massive destruction of the mitochondria may cause energy deficiency and impair myocardial contractility. This will aggravate hypoxia of the brain, lungs, and heart.

Thus, the first stage of alcoholic disease is characterized by the development of pathological changes in the internal organs. These changes are particularly pronounced in the heart.

If the episodes of acute AI are frequent, pathological changes occur in the neurotransmitter systems: the release of norepinephrine into the bloodstream and its degradation cause a compensatory increase in its synthesis [2,3]. Clearance of excessive norepinephrine is stimulated by increased consumption of alcohol. This leads to the second stage of alcoholic disease, drunkenness.

Stage II is characterized by progression of dystrophic, atrophic, and sclerotic processes in the endothelial cells of MCB. In venules and capillaries, the density of luminal membranes and endothelial cells increases, the basement membrane is thick and hyalinized, and pinocytic activity decreases. Deendothelialized areas and vacuolization of the smooth muscle cells can be observed in small and medium blood vessels. The permeability of these vessels for plasma proteins increases. Dystrophic and atrophic changes become more pronounced in pericytes. In larger vessels, atrophic and sclerotic changes occur in the tunica media, and perivascular fibrosis develops. Acute AIs against the background of drunkenness initiate the development of fibrinoid necrosis in the walls of arterioles and small arteries; in this case perivascular hemorrhages are possible. Generally, chronic and acute vascular changes occur simultaneously, triggering an onset of alcoholic macroangiopathy along with progressing microangiopathy.

At the stage of drunkenness, the liver is the major target organ. The intensity of its basal metabolism determines the progression of pathological processes in other internal organs, and, to a certain extent, the duration of this stage. The level of basal metabolism in the liver is determined primarily by the activities of NAD-dependent ADH and acetaldehyde dehydrogenase which convert alcohol to acetaldehyde and to acetate [4,6,11]. During stage II, the synthesis of fatty acids in the liver is enhanced, while the rate of mitochondrial oxidation of fatty acids drops [5,11,23,30]. Regular consumption of alcohol causes fatty hepatosis which transforms into alcoholic hepatitis. As a result, some hepatic functions become impaired, namely, triglyceride oxidation, amino acid and antioxidant turnover, synthesis of proteins, carbohydrates, hematopoietic and coagulation factors, and surfactant components [5,8,19]. The rate of ethanol oxidation in the liver determines the degree of damage to other organs caused by AI. The processes

developing in the liver stimulate changes in other organs and inhibit synthetic reactions. Brain astrocytes are destroyed. The contacts between astrocytes and neurons are disrupted, which leads to the development of astrocyte-neuron blocks. Neurons suffer from hypoxia and substrate deficiency, become atrophic, and die. Morphometric studies have shown that the specific density of neurons markedly decreases, while the numbers of shrunken neurons and ghost cells increase. These changes occur not only in the cortex, but also in the subcortical centers regulating various functions of the organism, including breathing and blood circulation. Chronic alcoholic encephalopathy develops. It is characterized by microangiopathy with pronounced changes in the blood-brain barrier, gradually progressing atrophic processes in the brain, and moderate fibrosis of the pia mater. Acute AI exacerbates chronic alcoholic encephalopathy, inducing acute vascular and rheological changes and increasing the permeability of the blood-brain barrier. The electrolyte balance is no longer regulated by astrocytes, implying that neurons become accessible to ethanol. As a result, neurons swell, develop total chromatolysis, and die. In this situation, respiratory standstill or cardiac failure can be fatal.

Drunkenness leads to progression of alcoholic cardiomyopathy [7,18,26]. It should be stressed that not only mitochondria but also myofibrils become involved in this process. The foci of overcontraction appear in myofibrils. Fatty degeneration of the myocardium progresses due to aggravation of hypoxic, metabolic, synthetic, and hematopoietic changes in the liver and probably due to impaired CNS regulation [20]. Cardiomyocyte hyperfunction due to hypoxia results in depletion of myocardial reserves and suppression of resynthesis, which may cause sudden death from heart failure.

Since about 10% of ethanol is eliminated through the lungs, changes in type II pneumocytes and surfactant occur at stage II, when some liver functions are impaired. Destruction of the surfactant is accompanied by formation of microatelectases and weakening of antimicrobial defense. Together with gradual progression of immunodeficiency and impaired central regulation of respiration this creates favorable conditions for the development of focal alcoholic pneumonia. Changes occurring in other organs, including the stomach and pancreas, play no decisive role in the pathogenesis of alcoholic disease.

Thus, the stage of drunkenness is characterized by the development of pathological changes in the internal organs and systems according to the vicious circle principle: damage to one organ or system triggers pathological changes in other organs and systems.

Drunkenness may progress to alcoholism. This is the last stage of alcoholic disease characterized by mental and physical dependence on alcohol. In our view, this stage starts with a considerable decrease in the rate of basal liver metabolism and marked rise of blood concentration of acetaldehyde, a primary metabolite of ethanol. Although acetaldehyde appears in the blood during the second stage, its concentration is too low to exert serious adverse effects on internal organs. Elevation of blood acetaldehyde is linked to clinical manifestations of alcoholism thus distinguishing it from drunkenness. We think that high blood concentration of acetaldehyde indicates the transition from stage II to stage III. Acetaldehyde produces a specific effect on the synaptic membranes in the brain, which causes an increase in the CNS tolerance to alcohol [3,22,31,33]. Consequently, more alcohol must be consumed to reach inebriation, so the load on the liver increases. This aggravates structural and metabolic changes in hepatocytes, hyaline foci appears, and the level of basal metabolism progressively decreases with consequent elevation of blood acetaldehyde. Reacting with catecholamines, acetaldehyde gives rise to morphine-like substances that not only increase the tolerance to alcohol but also initiate the development of mental and physical alcohol dependence [3,28,31-33]. The vicious circle closes.

Severe damage to the blood-brain barrier results in albuminous degeneration, atrophy, and the death of brain neurons. Moreover, acetaldehyde may promote the emergence of toxic proteins contributing to the destruction of brain neurons [34], thus aggravating alcoholic encephalopathy. The density of brain neurons decreases more significantly than during stage II, while the numbers of dark neurons (including shrunken ones) and ghost cells increase. The high blood concentration of acetaldehyde as well as frequent and severe AI lead to degradation of cardiomyocyte mitochondria, lysis of myofibrils, and destruction of Z line. A reduction in the activity of hepatic ADH is accompanied by a decrease in the content of mitochondrial enzymes in the heart and brain. Together with impaired central regulation of cardiac functions, progressive alcoholic cardiomyopathy provokes disorders in the cardiac conduction system and development of arrhythmias leading to death from heart failure. Aggravated hypoxia in association with reduced myocardial contractility enhances atrophic and sclerotic processes in the lungs, brain, and liver. Progressive impairment of hepatic functions, including the synthesis of glucose from lactate, results in energy metabolism disorders, while disturbances in the hematopoietic system regulation provoke anemia and aggravate hypoxia [5,22]. In the lungs, pronounced

changes occur in the surfactant system, and a focal-confluent bronchopneumonia (usually bilateral) is often complicated by abscesses [8,17,21], which exacerbates hypoxia and intoxication.

At the stage of alcoholism, severe organic and tissue changes become irreversible and potentiate one another even in the absence of alcohol. Therefore, in somatic terms cure from alcoholism is virtually impossible.

The above-mentioned data make it possible to describe the course of alcoholic disease. It should be stressed that stage I of this disease is characterized by the emergence of pathological changes in the MCB, heart, and lungs. At this stage, clinical signs are not pronounced, except the occurrence of marked short-term manifestations of intoxication as a result of excessive alcohol intake. Morphological changes in organs are reversible after the patient had stopped drinking. The duration of stage I varies from person to person and precedes drunkenness (stage II).

Stage II is characterized by severe changes in organs and tissues. Although many organs are affected, the target organs are the heart, liver, lungs, and brain. Microangiopathy becomes much more pronounced, and sclerotic changes progress in the arteries. Clinically, changes in the target organs are manifested as an active persistent hepatitis, cardiac arrhythmias, frequent episodes of bronchopneumonia, etc. Generally, regular drinking is neglected as an etiological factor. The psychiatric symptomatology of drunkenness [4,12] is not taken into consideration by general physicians; these patients do not receive psychiatrist consultation. Moreover, psychiatric aspects of drunkenness receive little attention from researchers.

Our studies and those of others have shown that basal liver metabolism in drunkards is essentially high, while changes in organs and systems are either reversible or well compensated. Drunkards can adequately perceive their situation. At this stage the disease is curable, providing that the general physician and psychiatrist choose an adequate strategy of therapy.

Unfortunately, the stage of drunkenness is often unnoticed, which in turn leads to alcoholism. It should be noted that a relatively small proportion of drunkards become alcoholics, but each alcoholic has passed through the stage of drunkenness. The stage of alcoholism starts when blood concentration of acetaldehyde reaches a high level. In addition to aggravating the severe changes that have already developed in vessels and internal organs, acetaldehyde radically changes the situation by contributing to the synthesis of morphine-like substances and toxic proteins. Alcoholic encephalopathy progresses, and cardiac dysfunction due to alcoholic cardiomyopathy reaches a critical level. Acetaldehyde may contribute to hyalinization of the liver, brain, and kidneys as well as to the development of fibrinoid necrosis in the vascular wall and the progression of microangiopathy and arteriosclerosis.

At stage III, changes in the internal organs are practically irreversible, and individual compensatory reactions are inhibited by increased amounts of alcohol against a background of irreversible damage to the vital organs. Consequently, stress caused by the withdrawal syndrome often leads to complete suppression of compensatory reactions and is often fatal. Irreversible changes in internal organs (for example, cirrhosis of the liver) progress even if the alcoholic has stopped drinking, leading to death. Neither physicians nor narcologists can do anything at this stage. The efficiency of therapies prescribed to alcoholics is very low. Therefore, special attention should be focused on the problem of drunkenness, i.e., the curable stage of alcoholic disease. This is the only way to control alcoholism and reduce its morbidity and mortality to sufficiently low levels. These goals can be achieved if fundamentally new approaches to the prevention and treatment of alcoholic disease are developed and introduced through sustained efforts of the entire society.

Thus, experimental results supported by autopsy and clinical findings [15] suggest a new nosological entity, alcoholic disease. Its pathogenesis includes the three above-mentioned stages. The organs determining the pathogenesis and outcome of alcoholic disease are the liver, heart, lungs, and brain. In chronic AI, pathological changes in these organs develop in a cascade manner according to the principle of a vicious circle. These changes arise in the internal organs against the background of progressive microangiopathy which by itself is an important pathogenic component of the disease. Changes developing in internal organs at the stage of drunkenness are reversible or well compensated, whereas those occurring at the stage of alcoholism are irreversible in a vast majority of cases and often fatal. Therefore, there are reasons to consider the problem not in the framework of the fight against alcoholism, which is an irreversible pathological condition, but rather on the basis of the proposed concept of alcoholic disease.

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