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SYSTEMATIC APPROACH TO THE ANALYSIS OF CARDIORENAL RELATIONS AS A FIRST STEP TOWARDS NEPHROLOGY P4 FORMAT

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ABSTRACT

The problem of cardiorenal relationships is considered from the point of view of the system approach. It is assumed that over the next 5-20 years the advances in computer technology and their approach to the analysis of complex biological systems inmedicine will reach a level that will significantly change the traditional approaches. Medicine in general – and one should think of nephrology as part of it – will become personalised, predictive, preventative and participatory, i.e. it will acquire the P4 format.

Keywords: nephrology, cardio-renal relationships, system approach

Historically, the advancement of scientific knowledge concerning any object has always occurred through its division, since it is a priori believed to be easier to learn about and thus come to know part of some phenomenon (process or object) than the whole. Almost all sciences – and medicine in particular – have been successfully developed in this way. In medicine, the extent of division (or reduction) across different historical periods has depended on the state of the basic scientific disciplines of the corresponding era. The principle of reduction to individual organs in the disclosure of the pathogenesis of disease in the 18th century (Morgagni) was replaced by reduction to the level of the cell (Virchow), and then, in the contemporary period, the molecular (biochemical, genetic) level. The culmination of this process of division was achieved with the disclosure of the sequence and function of genes at the level of the human genome [1].

The science of genetics was the first in which it was acknowledged that it is impossible to know the whole phenomenon by studying its individual parts exclusively at the cellular or sub-cellular levels. Even so-called monogenic diseases, caused by a defect in a single gene, may have different phenotypes; this applies to a greater degree when it comes to the multifactorial (polygenic) causes that characterise most chronic human diseases. However, it is not possible to assess the disease as a whole by only studying information encoded in genes. For example, the process of reading information from a gene depends on the interaction of many transcription factors, which in turn are products of other genes, as well as on the synthesis of the matrix and the activity of the transport RNA. This insight led to the creation of a new field in genetics – transcriptomics. However, it is not only the genetic and transcription processes themselves that are affected, but also their products. From this insight emerged the new scientific discipline of proteomics, which consists in an evaluation of the function of the genome according to its protein product, considering possible changes in the latter at the post-translational level. Proteomic analysis includes three stages: isolation of individual proteins, quantification of each protein and identification of individual proteins including evaluation of their post-translational modifications [2].

In metabolic disorders, the known genotype does not always lead to the formation of the expected phenotype, which depends on numerous intermolecular interactions that can compensate (or, conversely, strengthen) the defective function of some enzyme. From this set of problems emerges the scientific discipline of metabolomics (the study of the metabolome). It includes not only the study of individual products of biochemical reactions in the cell, but also the establishment of the character and dynamics of the connection between metabolites depending on the mutations or polymorphism of genes and the processes of their transcription (transcriptomics), as well as epigenetic (for example, changes in DNA structure due to methylation by products of biochemicalreactions) of changes (epigenomics) [2]. Over the past few years, it has become apparent that all biological systems must be viewed as an integrative whole, functioning within a system of interrelated components. Analogously, it

is impossible to evaluate a symphonic work on the basis of studying only individual instrumental parts without listening to the orchestral performance.

This view on the design and functioning of biological systems turned out to be identical to the basic provisions of the general system theory used in system engineering, on the basis of which a network approach (sometimes referred to in terms of a neuronal network) was constructed. The most striking example is the global network known as the internet. Any complex biological phenomenon involving multiple elements that regulate each other (as seen in the example of the genome, transcriptome, proteome, metabolome), can be mathematically represented as a scale-free graphical network consisting of interconnected heterogeneous nodes (Bayes probability theory of events). The degree of heterogeneity of the nodes is determined by the number of interconnections. The nodes of the network having the largest number of connections are called nuclei, network centres or hubs [3]. The study of biological networks comprises the topic of systems biology. It is important to emphasise that the links between the elements (nodes) of a biological network system contain additional (and sometimes extremely important and decisive) information. Having mathematically constructed a system network from separate heterogeneous nodes, the researcher can detect previously unknown connections (phenomena) and thus acquire knowledge about the object as a whole. The study of biological network systems has led to an understanding of the high resistance of intermolecular intracellular processes to random external influences. This is explained by the fact that most of the external affects apply to small nodes with a negligible number of connections, which does not violate the integrity of the entire network (for example, the random mutation of one of the genes). Of course, this rule does not apply to cases of external influences on the core (hubs) of the network.

P. Sobradillo. et al. [4] explain this network principle by the following example. It is known that numerous European airports (nodes) are involved to varying degrees (number of connections) in the organisation of air travel (comprising the network). During the recent emission of ash during the eruption of the Icelandic volcano, many of these nodes were closed down. However, the collapse of air transportation came only when London Heathrow Airport (hub) ceased to function. In recent years, the system biological approach has been increasingly applied in medicine. By analysing the OMIM online database of hereditary human diseases, K.I. Goh et al. [5] established that, out of 1777 genes studied, 1377 were interrelated. It is apparently the case that many human diseases, although having a different clinical phenotype, can share the same genes. The “Diseasome” network created by the authors was used to establish the existence of a large number of connections between cancer and neurological diseases at the genetic level. At the same time, such connections between metabolic diseases and diseases of the skeletal system turned out to be less significant at the genetic level. The results of the study also showed that two diseases are connected in the network to the extent that at least one gene is shared in common. In the research based around the network created by the authors, obesity was associated with seven nosologies, among which “nonclassical variants” of asthma, lipodystrophy and glioblastoma appeared. Thus, one of the new methods (means) for studying the relationship between various diseases is the formation of networks of their interactions on the basis of genetic commonality (common genes), physiology or metabolism. The creation and study of the metabolic network of pathological processes made it possible to establish comorbidity between diseases that previously were considered independent (Fig. 1) [6]. Recently, the system biological approach has been applied to analysing the relationship of diseases with a wide variety of clinical phenotypes.

On the basis of an analysis of an electronic database (Medicare), which included more than 30 million patients with a variety ofdiseases, C. A. Hidalgo et al. [7] developed a network called the PhenotypicDisease Network (PDN); Fig. 2).

Such a scientific approachpermitted the establishment of extremely important facts (bothfrom the theoretical and practical points of view): firstly, diseases that are distinct in terms ofclinical presentation (phenotype) and etiologycan nevertheless be closely interrelated. Secondly,the mortality rate of patients whose diseaseshad multiple connections in the network was higher in comparison with those who had the samediseases, but having fewer connections with other pathologies.Thirdly, the diseases that were precededby other diseases had more connections and were characterised by high mortality. Fourth,the progression of various diseaseswas largely dependent on gender and ethnicity. The network approach in medicinecan also be used to assess the impact of social factorson the origin of the disease. N.A.Christakis and J.H. Fowler [8] used theFramingham database to studythe influence of social factors on obesity. They foundthat the risk ofobesity increased by40% in the presence of a genetic predisposition,but increasedby 171% if the person includedin the study had close friendswith obesity.The application of the network

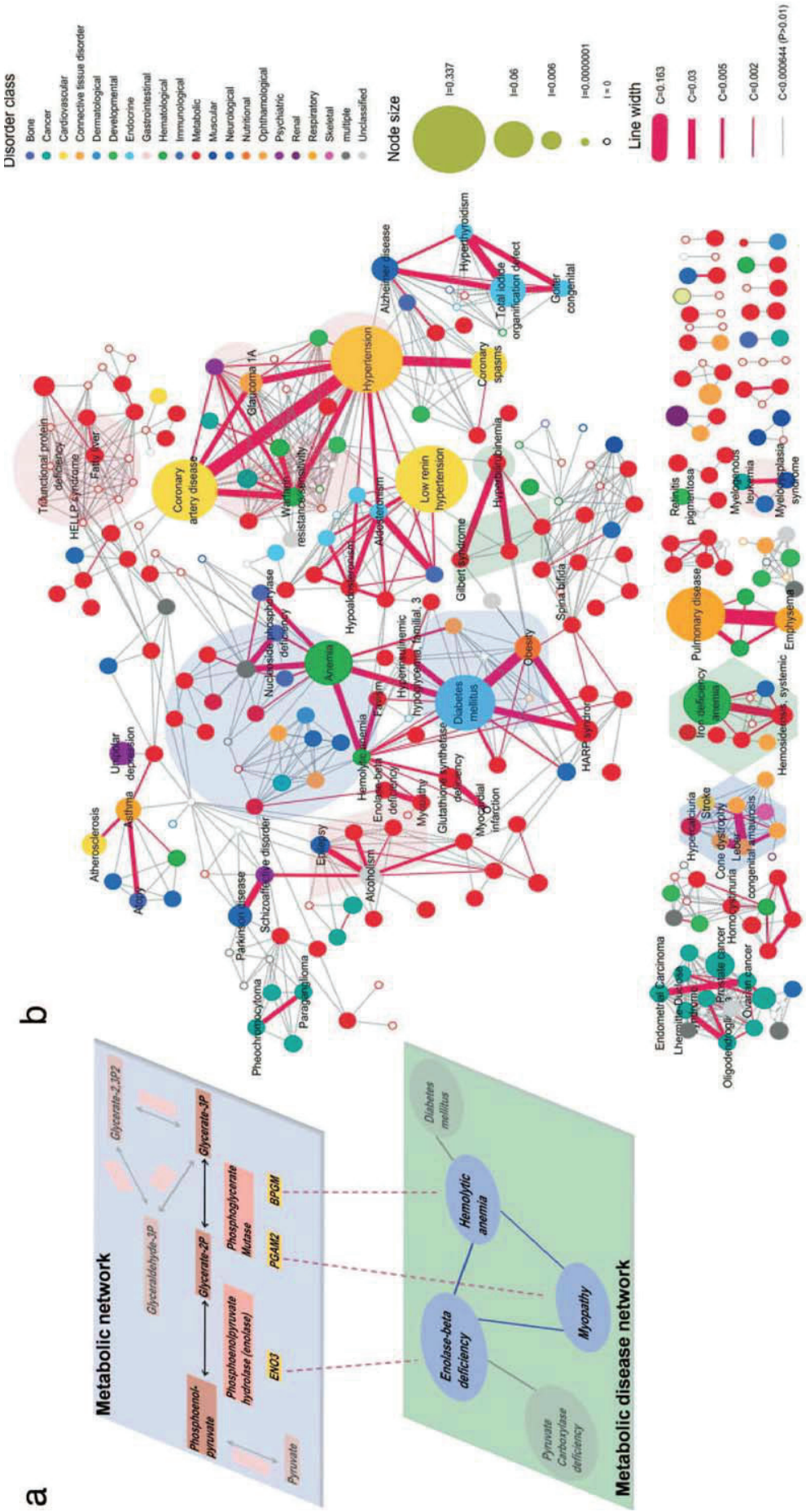

Fig. 1. Metabolic disease network (MDN). **(a)** Construction of MDNs. Above: the area of glycolysis in which catalytic enzymes are highlighted in red and the corresponding genes are marked in orange. Below: adjacent metabolic diseases (blue colour), associated with biochemical reactions. The EN03 gene encodes an enzyme that catalyses the reaction between phosphoenolpyruvate and glycerol-2F, its mutation is associated with the development of enolase-β deficiency. The products of the PGAM2 and BPGM genes that catalyse the reaction involving glycerate-2F and glycerate-3F are associated with myopathy and haemolytic anaemia. Two diseases are associated with each other, including through a system of biochemical reactions associated with enolase-β deficiency. **(b)** A network is presented in which 308 non-isolated diseases (nodes) connected through 878 metabolic links demonstrate the possibility of additional connections, determined during the reconstruction of the data of the electronic Kyoto Encyclopaedia of Genes and Genomes (KEGG) and Online Mendelian Inheritance in Man (OMIM) databases. The colour of the nodes indicates the class of the disease; their size is proportional to the frequency of the disease in the population according to the Medicare database. The width of the lines characterising the relationship is proportional to the comorbidity frequency. The colour red indicates associations with significant comorbidity ($p < 0.01$). Clustersof diseases associated with purine metabolism are highlighted in blue; those associated with the exchange of fatty acids are marked in red; and those associated with porphyrin metabolism are marked in green (figure from the paper of D.S. Lee et al. [6] published with the permission of the editorial board of ProcNatlAcadSci USA).

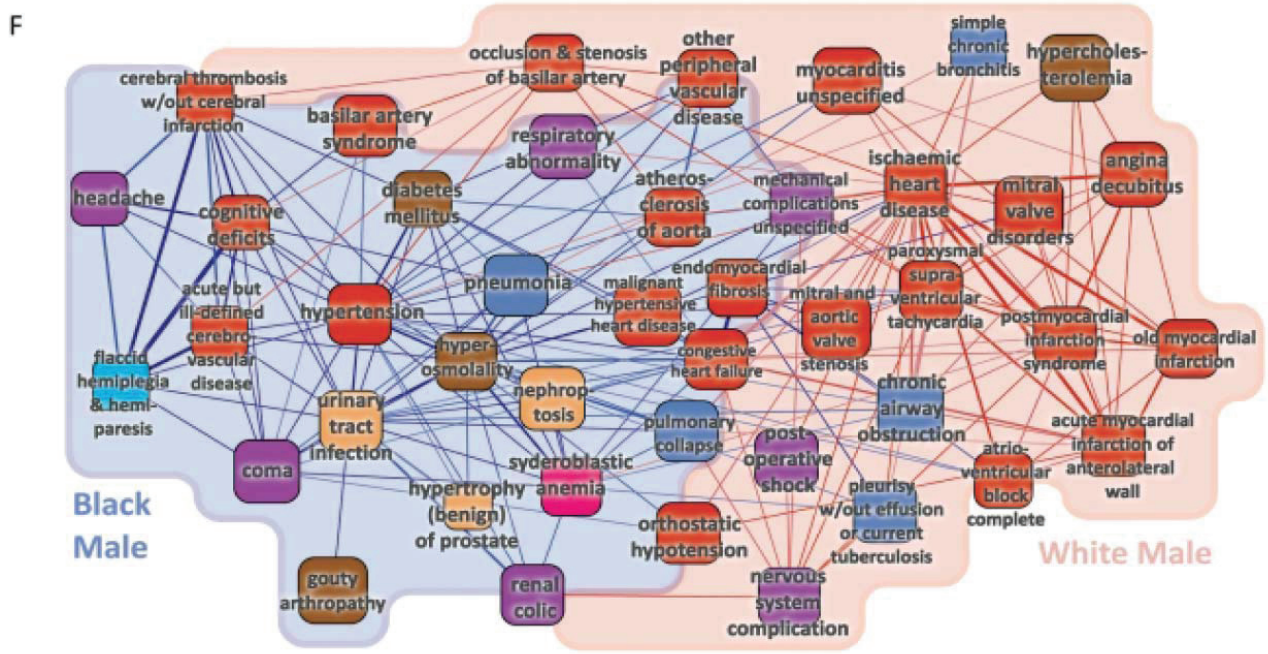

Fig. 2. Network of the phenotype of disease (figure from the work of C.A. Hidalgo et al. [7] published in accordance with the editorial policy of the journal)

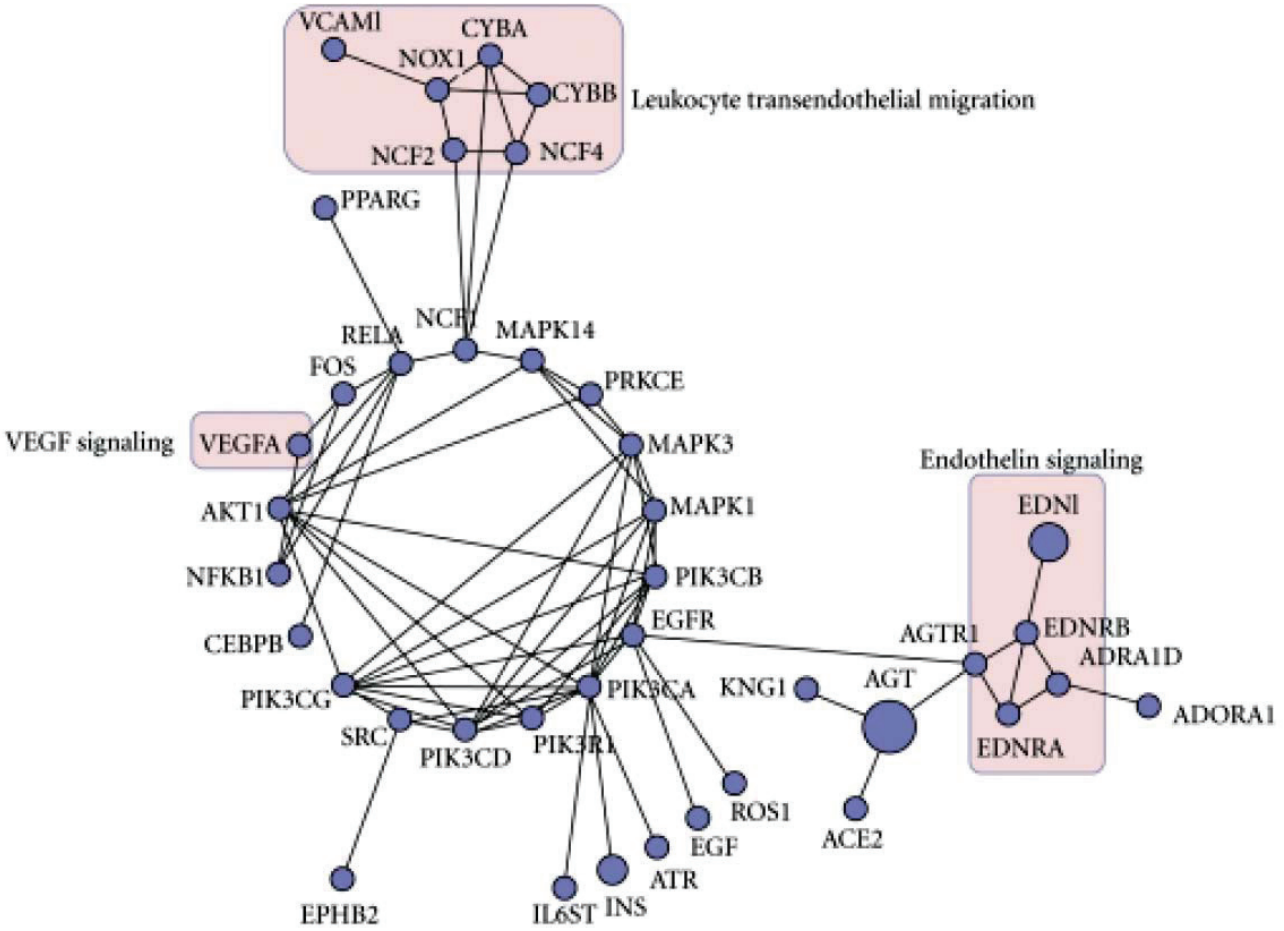

Fig. 3. Network of interrelation of proteins associated with cardiorenal syndrome. The nodes represent by genes (denoted by symbols) and the lines represent functional connections between them. Pink-coloured nodes represent proteins that are specific for signals of vascular endothelial growth factor (VEGF), leukocyte transendothelial migration or endothelin signalling (figure from I. Muhlberger et al. [40] published in accordance with the editorial policy of the journal.

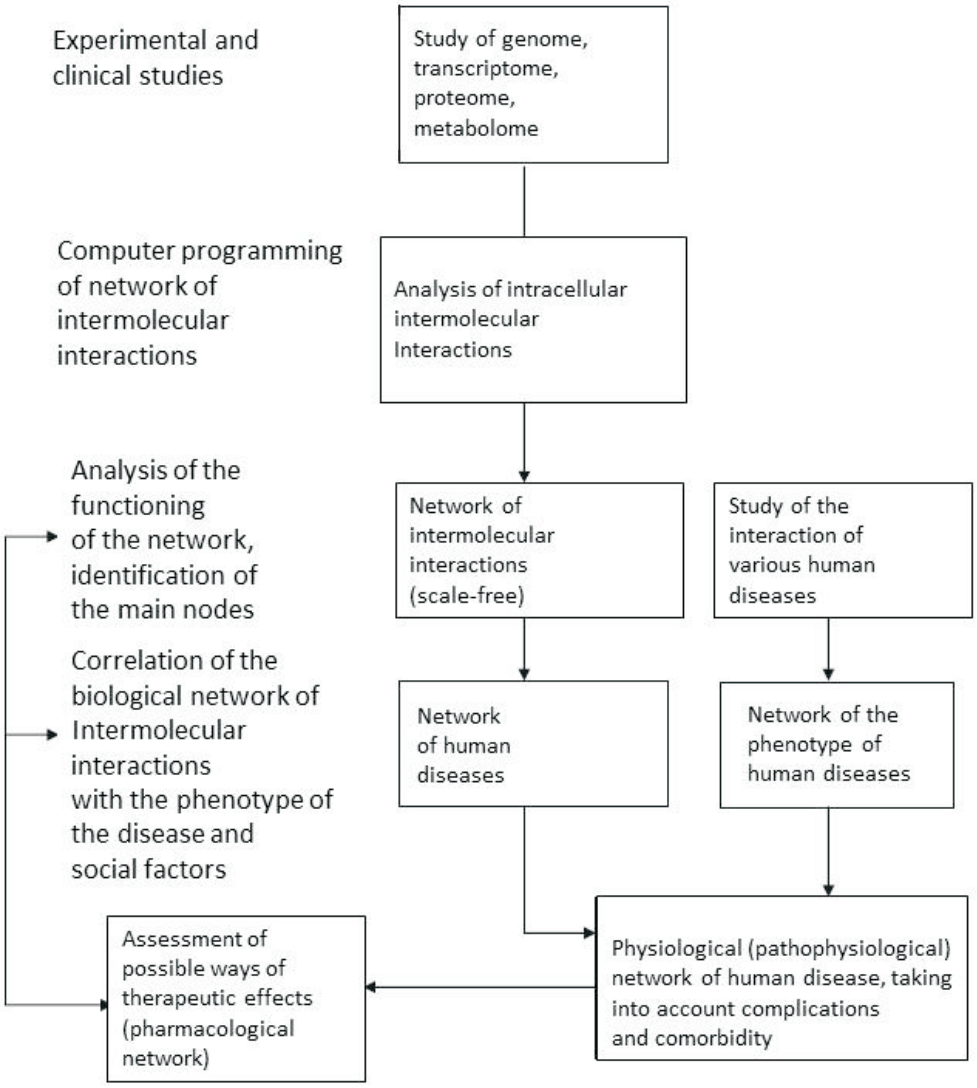

Fig. 4. System biological approach to the analysis of human diseases

approach in this work revealed the influence of the social environment on the occurrence of obesity (in this connection, we may recall the proverb: "birds of a feather…").

Thus, a systematic biological approach to the analysis of human diseases can be realised at various levels: subcellular, cellular, organ-, organism- and social (Figure 4).

When the pathways of intracellular regulation become clear, a scale-free network (map) of intermolecular interactions is created on the basis of the study of the functional activity of the genome, transcriptome, proteome and metabolome (Fig. 3). Such a network not only permits an understanding of the nature of interactions, but also an identification of the main hubs of the system, to which pharmacological network influences can be directed. A human disease network is created by connecting the intermolecular network interaction data to the phenotype of the disease. With regard to human diseases, an alternative approach, combining a study of the phenotype of the disease and the character of comorbidity with an assessment of the influence of external risk factors informing the compilation of a phenotypic disease network, is also possible [9].

The network approach in medicine permits us to state that two diseases (with different phenotypes) can be closely related to each other if at least one commongene is shared or associated with the same metabolicpathways or co-expressed in a significantnumber of patients in the population [4, 10, 11].

In clinical nephrology, the most striking example of co-expression of two diseases is the combination of cardiovascular and renal pathologies, the relationship between which has been (and is being) considered by a number of researchers at different levels. The most

Table 1

Classification of cardiorenal syndrome [19]

Type	Name of type	Pathogenesis
1	Acute cardiorenal syndrome	Acute heart failure, leading to acute renal failure
2	Chronic cardiorenal syndrome	Chronic heart failure leading to the development of CKD
3	Acute renocardiac syndrome	Acute renal dysfunction (acute renal injury) leading to development of acute heart failure
4	Acute renocardiac syndrome	CKD leading to impaired cardiac function (left ventricular hypertrophy, diastolic dysfunction) and to the development of cardiovascular complications
5	Secondary cardiorenal syndrome	Systemic disease (e.g. sepsis) leading to heart and kidney damage

traditional, long-lived and "obstinate" point of view consists in an analysis of the relationship between the two systems at the level of hemodynamic changes caused by cardiac or renal insufficiency. The focus is on reducing cardiac output in acute [12] or chronic [13, 14] heart failure, which causes a decrease in renal blood flow as well as in the glomerular filtration rate (GFR). Obviously, such a physiological mechanism is present in severe cases of acute heart failure and is the cause of acute renal damage (prerenal kidney failure). However, in chronic conditions, it is not possible to ignore the presence of a powerful mechanism of a myogenic autoregulation of the renal blood flow at the level of the arterioles that carry it [15], which is able to compensate for violations of central haemodynamics (low cardiac output and / or reduction in blood pressure) for a long time. Over time, when the processes of autoregulation are disrupted (especially in patients with diabetes mellitus), glomerular hypertension is formed. Hydrodynamic damage of glomerular podocytes causes their apoptosis and mopping to the capsular space. Sclerosis (focal-segmental glomerulosclerosis) is formed in the exposed parts of the glomerular basement membrane, which subsequently causes local ("glomerular") hypoxia that damages not only the structure of the glomerulus, but also tubulointerstitia, which, as is known, is fed from capillaries originating in the glomerulus [16]. In chronic, congestive heart failure, there is a more prosaic explanation for the decline in GFR, associated with a decrease in transrenal perfusion pressure (AD minus the central venous), due to stagnation of blood in the circulatory system (as previously understood) or an increase in central venous pressure (as is generally stated today). Surprisingly, this mechanism is rarely considered in serious scientific reviews; however, it is precisely for this reason that, in the case of congestive heart failure with a decrease in GFR and the presence of resistance to the action of loop diuretics, the most effective therapeutic measures are those leading to a decrease in the central venous pressure: vasodilators (nitrates) oxygen therapy, hardware ultrafiltration. In former times, bloodletting could be included amongst these measures. In those cases when there were no irreversible destructive changes in the renal parenchyma, the complex of these medical measures leads to an increase in GFR, restoration of diuresis the "appearance" of sensitivity to diuretics. Obviously, venous hypertension and renal hyperaemia lead to the appearance of morphological changes, such as mesangiolysis, which some authors have previously suggested to be considered as a specific morphological criterion of kidney damage in severe heart failure [17]. At the present time, when the concept of chronic kidney disease has already been developed, there is no reason to return to the question of the nosological isolation of "cardiac nephropathy" [18]. By examining cardiorenal relationships at the level of haemodynamic factors, some researchers were able to propose the theory and classification of cardiorenal syndrome, which earned its due recognition in the international consensus (Table 1) [19].

It is quite understandable that the diversity and complexity of the relationship between cardiovascular and renal systems is not capable of being explained in terms of haemodynamic causes. In connection with this, the pathogenesis of chronic cardiorenal syndrome (type 2) was supplemented by such common risk factors for heart and kidney damage as obesity, diabetes, dyslipoproteinemia, arterial hypertension, oxidative stress and endothelial dysfunction (the so-called "common soil" hypothesis) [20]. However, in addition to pathogenetic discrepancies, the presented classification has a number of internal logical contradictions. Essentially, it is necessary to consider each of the five types of cardiorenal syndrome as an independent pathophysiological condition. It is no accident that, both in the title of their work and in the texts of the articles, the developers of the concept indicate cardio-renal *syndromes* (in the plural!). It remains to be seen how conducive to progress or practically convenient the introduction of the concept of cardiorenal syndrome into nephrology will be. However, for now it is possible only to state the difficulty and ambiguity in the interpretation of its types. Thus, some authors, in distinguishing the concept of cardiorenal syndrome

as a whole, unite its 2nd and 4th types (see Table 1) on the basis of a single pathogenesis (?!) in the general concept of "chronic cardiorenal syndrome", thus contradicting the original classification of syndromes [18].

Another level of analysis of cardiorenal relationships was provided from the point of view of remodelling the cardiovascular system in chronic renal pathology. This idea of the cardiovascularis the most completerelationship reflected in the works of N.A. Mukhina et al. [21]. For the first time, a renin-angiotensin-aldosterone system and generalised endothelial dysfunction were indicated as a link between the two pathologies, determining, on the one hand, the maladaptive remodelling of the cardiovascular system, and, on the other, the progression of renal injury (fibrosis). In 2005, we proposed the concept of a pathogenetic continuum for explaining the coexpression and mechanisms of interrelation between cardiovascular pathology and chronic kidney damage (in the form of chronic kidney disease) in patients without primary renal pathology referred to in terms of cardiorenal continuum [22].

Among its principal provisions, the following should be noted. Firstly, the blurred concept of cardiovascular pathology has acquired a specific definition in the form of the internationally recognised pathophysiological term cardiovascular disease (in the singular!), by which is understood the atherosclerotic damage of the vessels of various anatomical regions (coronary, carotid, cerebral arteries, aorta, peripheral arteries of the lower extremities). Secondly, renal pathology also received a specific definition in the form of chronic kidney disease, a supranosological concept, which should be understood as chronic damage to the renal parenchyma (irrespective of aetiology and pathogenesis) leading to the development of renal fibrosis and loss of all essential renal functions. Thirdly, based on the principled position of the St. Petersburg School of Physiology-Nephrology headed by Yuri Natochin, Academician of the Russian Academy of Sciences, we presented the kidney not as a target organ (as was done, for example, in the cardiovascular continuum of Braunwald), but as an actively functioning organ, the non-excretory functions of which are directly involved in atherogenesis – and, consequently, in the pathogenesis of cardiovascular disease itself. Fourthly, dividing the opinion of the majority of scientific researchers, we emphasised the fact that the traditional risk factors for atherogenesis (Table 2) simultaneously act as damaging factors for the renal parenchyma, causing it to develop fibrosis. Fifthly, for the first time, based on our own research and the literature sources, we proposed the (then) hypothesis, according to which damage to the renal parenchyma (in the first instance, to the cells of the proximal tubule epithelium) as a result of exposure to traditional risk factors leads to a decrease in the non-excretory functions of the organ (including metabolic, as the most vulnerable). This causes the development in the body of metabolic shifts, which in classical cardiology are associated with unconventionalatherogenesis risk factors (see Table 2).

Table 2

Risk factors for atherogenesis

Traditional risk factors:	
	• age
	• male sex
	• diabetes mellitus
	• arterial hypertension
	• smoking
	• obesity
	• dyslipoproteinemia
	• sedentary lifestyle
Nontraditional risk factors:	
	• hypergastrinemia
	• inflammatory stress (hc_CRP) *
	• oxidative stress (ADMA**, AGE***)
	• endothelial dysfunction
	• protein-energy insufficiency
	• indoxyl sulphate
	• anaemia
	• coagulopathy
	• other

Note: * Highly sensitive C_reactive protein; ** asymmetric dimethylarginine; *** advanced glycation end-products.

Not only did the past six years not result in any changes being made to our ideas, but also brought new data confirming our primary hypothesis.

The results of prospective follow-up of more than 1.5 million representatives of the general population of the population finally confirmed the opinion that a moderate decrease in GFR (up to 60 ml / min) and microalbuminuria (MAU) (more than 10 mg / day) is associated with a high risk of general and cardiovascular mortality [23, 24]. Moreover, the decline in GFR is a "direct" consequence of the degree of severity and prevalence of coronary atherosclerosis [25, 26].

It is important to understand that a moderate decrease in GFR and / or microalbuminuria is nothing but markers of kidney damage. The most important role in atherogenesis is played by the proximal tubules, the dysfunction of which causes oxidative and inflammatory stresses, hyperhomocysteinemia, an increase in the concentration of asymmetric dimethylarginine (NO antagonist), an increase in the level of indoxyl sulphate, a decrease in production of 1.25 (OH)2D3 etc. [27–32]. Acceleration of atherogenesis was noted in polycystic kidney disease in pa-

tients with a completely preserved excretory function [33]. The name of the quoted work is noteworthy: "... autosomal-dominant polycystic kidney disease: from tubular insufficiency to defective coronary and carotid arteries." Autosomal-dominant polycystic kidney disease is attributed by some authors to the prototype of cardiovascular syndrome of the 4th type [34]. The pathogenesis of microalbuminuria is currently associated not with generalised endothelial dysfunction, but with damage to podocytes [35] and / or epithelium of the proximaltubules [31, 36]. Of course, GFR and microalbuminuria cannot be classified as highly sensitive markers for chronic damage to the kidney parenchyma; however, they are the earliest and only witnesses to the presence of CKD available to nephrologists at the present time. It can be stated that the kidney is at the same time "the perpetrator and the victim of atherosclerosis". The early stages of non-obstructive atherosclerosis of the renal arteries are accompanied by an increase in the density and tortuosity of the vascular bed, which appears to be a compensatory response aimed at maintaining adequate organ perfusion [37]. However, over time, such changes cause a decrease in kidney size (renal fibrosis) as well as an increase in their dysfunction with age [38]. This leads to the conclusion that there is practical significance to a patient with atherosclerosis affecting any location if microalbuminuria and / or a decrease in GFR is observed since this indicates an advanced (and not an initial) stage of atherogenesis requiring active treatment. This is why the recommendations that all patients with cardiovascular pathology be systematically screened for the presence of CKD (control of microalbuminuria and GFR) should be given serious attention.

There is no doubt that the system approach currently being developed for analysing pathogenetic relationships in the body, which was discussed at the beginning of the article, will highlight new facets of the problem; however, it can be said that with complete certainty that its solution will not be found in the framework of one of the types of cardiorenal syndrome.

The first attempts to establish a systematic approach to the analysis of cardiorenal relationships have appeared in recent years. On the basis of a detailed review of the literature, I. Muhlberger et al. [40] established the presence of 280 genes that are important in the formation of cardiorenal connections; as was to be expected, the genes of the renin-angiotensin system took the first place. The non-extensive network of relationships between genes and their products is shown in Fig. 4. It is certain that other works based on the system biological approach will appear in the near future.

David Galas and Leroy Hood of the Institute of Systems Biology in Seattle predict that advances in computer technology and their approach to the analysis of complex biological systems in medicine will reach a level over the next 5-20 years that will permit significant changes to traditional approaches taken to medicine [41]. Medicine as a whole – and one should think of nephrology as part of it – will become: personalised, predictive, preventive and participatory; i.e. it will acquire the P4 format.

Until the inauguration of the nephrological P4 format, we join the opinion of A. Shutov and V.A. Serov, who correctly pointed out that "cardiorenal syndrome does not completely replace the concept of the "cardiorenal continuum" but only clarifies the situation concerning cardiorenal relationships in the continuum at the stage of development of heart failure" [42].

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