REVIEWS

Theory of Functional Systems and Human General Pathology

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We analyze the role of the theory of functional systems for human general pathology and the necessity of integration of this theory with the concepts of pathological and ambivalent systems. Multiple (qualitatively heterogeneous) nature of system-forming factors and principle possibility of the formation of physiological, pathological, and ambivalent systems by the same factors are discussed. These theses broaden the application of the theory of functional systems as the fundamental basis for studies of informational mechanisms of vital activity under normal and pathological conditions.

Key Words: *theory of functional systems; human general pathology; system-forming factor; result of activity*

General pathology considers the most fundamental relationships of the onset, development, and outcome of pathological processes and diseases and creates on this basis the modern theory of medicine [7,16,31,32]. This is an interdisciplinary and even supradisciplinary conceptual system on "the most general regularities of pathological processes and most important features underlying various diseases irrespective of their cause, individual features of the organism, specific environment, and research methods" [24]. The principal basis of this science is systemic approach [32], which plays the key role in the study of the mechanisms underlying the development of any (normal and pathological) manifestations of vital activity (from the molecular to the organism and social levels), in assessment of their role for the individual, and in the creation of adequate correction methods. In addition to fundamental works of N. Wiener, L. Bertalanffy, I. Prigozhin, K. Pribram, G. Kryzhanovskii, and other scientists, works of P. K. Anokhin's scientific school on the theory of functional systems (TFS) are of special importance. Until now, TFS remains a striking example of a universal approach to the study of mechanisms of regulation of vital activity. P. K. Anokhin introduced a classical concept of system-forming factor and defined the universal elements (stages) of systemic activity: afferent synthesis, decision-making mechanism, acceptor of the result, and parameter of the result. On the basis of this theory, K. V. Sudakov advanced the concept of quantization of vital processes. These concepts are widely used in normal physiology, psychology, biology, pedagogic, and other sciences [1-4,26-29]. At the same time, despite the fact that the concept of functional system appeared during systemic research of disturbed functions [4], the potencies of classical TFS are limited if this theory is applied to analysis of vital activity during pathology. Moreover, obstacles appear even in scientific fields where TFS is widely recognized.

Our aim was to analyze the possibilities of using classical TFS in the studies of human general pathology and possible ways of further development of this theory.

Classical interpretation of the role of adaptive results limits the field of application of TFS

The concept of system-forming factor is fundamental concept in the analysis of vital activity under normal

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and pathological conditions. According to common interpretation of TFS, this universal and unique factor is attainment of an adaptive result [3]. According to P. K. Anokhin, adaptive result (more correctly, the process of its attainment) is a kind of a categorical imperative for the assembling of the integral system from its parts. This factor determines the rate of realization of individual mechanisms and the moment of termination of further mobilization of system's components when the result is attained [4]. According to K. V. Sudakov, the latter is the leading factor of organization of the functional system at various levels. When the organism attains an adaptive result, all elements mobilized by initial requirement are consolidated within the functional system. This determines the system-forming role of the result [28]. However, this interpretation significantly impedes the analysis of many physiological and pathological manifestations of vital activity.

According to the concept on system-forming factor the functional system can be formed only after first attainment of the corresponding adaptive result. Indeed, during acquisition of a conditioned response the useful result is first occasionally attained in the course of random orienting and exploratory activity [18-20]. However, many systems possess "monopoly" for a particular result, because without them no random attainment of the result is possible. In these cases, the first results cannot play the system-forming role, but they are attained via realization of preexisting specialized systems. This is true for all congenitally determined functional systems responsible for metabolisms, homeostasis, and instinctive behavior; it is also applicable to the most complex forms of purposeful activity beyond the limits of conditioned and unconditioned reflexes [22,23]. Specifically, the reproductive systems in plants and animals are formed long before their participation in fertilization, *i.e.* before attainment of any (at least intermediate) adaptive result. Moreover, in some cases the action of preexisting systems leads to disadaptive effects (including the first ones). For example, male deer can be wounded during nuptial tournament, newborn chickens can peck poisoned grains [14], humans can purpose a false goal, whose attainment impedes satisfaction of the dominant requirements, and so on.

It is noteworthy that the authors of TFS indirectly assumed the development of functional systems (except for conditioned reflexes) before the moment of attainment of the first useful results. "For example, immediately after hatching a chicken pecks grains spread on the floor, while rook nestlings passively receive food from their parents for a long time, albeit they have *absolutely ready system* (emphasized by us) opening the beak in response to adequate stimuli" [3]. Another example is characteristic of the development of complex forms of purposeful activity: "… Any decision made after the end of afferent synthesis is the search for the most suitable degrees of freedom in those components, which should compose *the actuator part of the system* (emphasized by us). In their turn, these remaining degrees of freedom enable effective realization of the actionleading to the programmed result… It is noteworthy, that the interval between these events can be equal to a minute or to a year" [2]. Again, this means the possibility of forming a functional system (its "actuator part") during the decision-making stage, *i.e.* before the attainment of the first useful result. K. V. Sudakov directly indicates that "*After the first attainment of the useful result by the functional system* (emphasized by us), this result possesses a unique property: when the definitively developed functional system attains useful result, which satisfies the initial requirement of the organism, its dynamic architectonics is composed and fixed" [27].

Therefore, from P. K. Anokhin to modern time, *even classical TFS admits the development of functional system before the attainment of the first adaptive result*. Paradoxically, contradiction of this admission with the cornerstone TFS postulate is persistently ignored. Consider the last citation again: its first part ascertains attainment of *primary result* by preliminary developed *functional system*, but then classical system-forming role of this result is confirmed ("dynamic architectonics is composed and fixed at the moment of attainment of the result"). Thus, *the notion on universal system-forming role of the result is internally contradictory, and it impedes further development and application of TFS*. It was emphasized several times in literature, that it is necessary to reject this TFS basic postulate in order to analyze congenitally determined systems [22,23] and the most complex forms of behavioral activity that are realized on the basis of consciously determined goal [5,13,22,25]. In addition, this postulate is at variance with some other scientific statements, as considered below.

First, classical interpretation of the system-forming factor principally excludes the formation of systems whose activity is not aimed at a positive result, because "it is evident that the concept of a system cannot exist without its useful result" [3]. However, the concept of pathological system is now widely spread [9-12], "whose activity is biologically negative and pathogenic for the organism" [11]. Such systems can be formed due to existence of abnormal hyperactive generator (pathological determinant), and they can work for a long time, even throughout the lifetime (Parkinson's disease, pathological scratch reflex, some forms of epilepsy, *etc.*). In other words, the result of systemic activity is not obligatorily adaptive. Exist-

ence of stable pathological systems directly contradicts the basic postulate of classical TFS. According to G. N. Kryzhanovskii: "A concept took root that functional system always produces biologically or socially useful result. Moreover, an opinion exists that if the system dose not ensure useful result, it is not a system. This is a mistake, because functional system can be either physiological or pathological" [12]. It should be noted that *the result of activity (function) is a decisive criterion to define a pathological system, and in this sense, the pathological systems are functional to the same degree as the Anokhin's classical systems. This is why G. N. Kryzhanovskii proposed to compare the physiological (not functional) systems to the pathological ones*. Of course, this does not mean that functional changes are not underlain by the structural transformations. We agree with this view and refer to the classical (Anokhin's) functional systems as physiological.

Second, *Anokhin's theory ignores the possibility of ambivalent results (intermediary or final), which are simultaneously characterized by adaptive and pathological features.* By contrast, this theory allows insufficient correspondence of intermediary results to acceptor parameters. In other words, Anokhin's theory admitted insufficient degree of useful result but rejected existence of disadaptive component in it. This problem is of principle importance for TFS, because it indicates absence of clear demarcation line between *physiological and pathological systems*. Indeed, the decisive criterion to separate both systems is the final result of their work (adaptive or disadaptive). However, if the result is ambivalent, the system assumes mixed features and turns into a *pathophysiological* one. Such systems are described elsewhere [7,24,29, 31]. For example, allergic damage to tissues during Arthus—Sakharov (Gell-Coombs II) phenomenon is accompanied by elimination of allergen and preservation of antigen homeostasis, albeit in a pathological way. Some forms of pathological scratch reflex, alimentary obesity, and alcoholism have also pronounced adaptive component — at least, at initial stages of their development (for example, moderation of psycho-emotional stress) [33]. How the corresponding systems should be termed? Evidently, they are ambivalent, since any of them incorporates (to various degrees) the signs of pathological and physiological systems. The same approach can be used to analyze conscious behavior of humans, which is based on erroneously chosen goal (attainment of this goal will not satisfy the initial requirement). Should be the system, which underlies this purposeful activity, termed as pathological? On the one hand, obtaining of the corresponding result leads to neutral or even obviously disadaptive consequences. However, in a wider sense, such results can be considered as the stages of trial and error period, which yields experience needed for future satisfaction of dominant requirement. Indeed, it is not possible to acquire even the simplest conditioned reflex without trials and errors. In addition, a rapid transformation of one kind of systems into other is also possible. For example, a sudden termination of reinforcement of a conditioned reflex immediately "converses" the corresponding system into pathological or ambivalent, since the result of its activity becomes more disadaptive than adaptive. The most important is the fact that clinical practice acquired many examples of the development of relatively stable systems, which are ambivalent according to the results of their activity (sickle-cell disease, stimulation of rhythmogenesis of the heart during insufficiency of its contractile activity, many neurotic variants of behavior, *etc*. [25,30,35,36].

Some disputable aspects of modern theory of functional systems

"The theory of functional system underwent… a number of modifications from the moment, when it was initially formulated" [3]. At present, essential modifications of TFS are made continuously [11,12,18,19, 21-23]. Nevertheless, the mechanisms of systemic activity are little known yet, which is indicated by a moiety of various opinions (sometimes opposite) on the role of actual requirements, dominating motivation, the goal of activity, emotions, coherent electrical activity of various subdivisions of the brain, *etc*. [8,15, 25-29]. The views diverse even on the problem, what an object should be called a system [6,8,15]. However, most approaches are characterized by similar efforts to reveal some universal system-forming factor, which is characteristic of any system or at least of a greatest variety of systems: attainment of positive (useful, adaptive) result, existence of abnormal hyperactive generator (in pathological systems), *etc*. Unfortunately, few attempts are made to formulate the general rules (a kind of "boundary conditions"), which would elucidate the mechanisms of system formation and the very concept of a "system". Here we consider some opinions, which hopefully would deepen our knowledge and extends the fields of constructive application of TFS — above all, in general pathology.

The decisive criterion to mark something as a system is the results of its activity (function), and in this sense, all systems are functional. This statement, which was originally advanced in classical TFS, seems to be true provided the corresponding morphological basis of the function is taken into consideration. However, the concept of functional system should be drastically widened. Since any "true systems in an

organism are functional in essence" [3], one should agree with G. N. Kryzhanovskii [12] that antithesis to pathological system is physiological (not functional) one. We assume that *depending on the result of activity, not only physiological and pathological systems should be defined, but also the ambivalent systems*. In other words, the adequate definition of functional system is "a complex of selectively involved components, whose interaction interrelationships assume the character of mutual co-action of the components" [3] aimed to obtain adaptive, disadaptive, or ambivalent results.

The decisive role in formation of any system belongs to system-forming factor, which organizers the controlled interaction between initially unorganized components. It should be noted that this statement was also advanced for the first time within the framework of classical TFS. "A specific mechanism of interaction of the component parts is elimination of their superfluous degree of freedom, which are not needed to attain a particular goal, and preservation of those degrees of freedom, which participate in attainment of the result" [3]. At the same time, it is reasonable *to stop searching for some universal and single system-forming factor*. In particular, this factor cannot be the adaptive result, because many functional systems are formed before its first attainment. This peculiarity, as well as availability of pathological and ambivalent systems indicate existence of a set of system-forming factors. Presumably, any of these factors can form functional systems, which significantly differ from each other in the results of their activity for organism and population.

One and the same result of systemic activity can significantly change its biological and social role depending on environmental conditions, modification of metabolism, *etc*. This fact eliminates the boundary between various types of functional systems indicating compliance of their properties to the law of unity and conflict of the opposites. It is also corroborated by the presence of different variants of transformation of the same system into physiological, pathological, or ambivalent one. For example, the results of activity of several physiological systems of tropic animals are ambivalent or even disadaptive under the conditions of colder climate. This fact shows that *one and the same system-forming factor can initiate the development of various functional systems (physiological, pathological, and ambivalent)* depending on environmental conditions, peculiarities of homeostasis, *etc*. Otherwise, nature of the system-forming factor would depend entirely on the results of systemic activity, which can vary in a very wide range (for example, a newborn chicken pecks normal grains in some cases and poisoned grains on other cases).

Taking into consideration the above statements, we consider several possible variants of system-forming factors. One should agree with Anokhin's theory, that in the cases of conditioned reflex training, such a factor is accidental achievement of useful result, which organizers intrasystemic activity in the following period. We suggest that this process may produce not only physiological, but also ambivalent or even pathological systems (some variants of narcomania, alcoholism, *etc*.). To exemplify this statement, consider the classical experiment with electrodes implanted into hypothalamic areas, where stimulation produces the positive emotions. By stimulating this area with a lever, the animal attains a subjectively positive result, although long-term stimulation usually resulted in exhaustion and even death. What kind of functional system was formed during this experiment? On the one hand, this system was physiological, because it resulted from initially acquired routine conditioned reflex, where positive reinforcement is a classical system-forming factor considered in TFS [1-4, 26-29]. On the other hand, this functional system should be termed as pathological, because a long-term self-stimulation produces severe negative consequences. In this example, the development and consolidation of the pathological determinant are the consequences of repeated attainment of subjectively positive results. Moreover, at the first stage, the "objective" positive changes are also evident — for example, moderation of emotional stress. It seems that the very result of instrumental activity (not secondary formed abnormal hyperactive generator!) is the true system-forming factor, which determines the most specific features and directs further transformations of the system. Namely, "the result of activity is intrinsic and decisive component of functional system" [2]. Withdrawal of such factor triggers relatively rapid elimination of intrasystemic connections. Thus, a paradoxical situation emerges: *a pathological system can be gradually formed due to persistent and repeated attainment of subjectively (and, to some degree, objectively) positive result*. In other words, the system-forming factor of pathological system is a positive result considered within classical TFS.

Probably, the system-forming factors of all congenitally determined systems are mutations [22,23]. Beneficial mutations form physiological systems, while harmful mutations produce pathological systems; in some cases, the development of ambivalent systems is possible [33,34]. Specifically, the harmful mutations underlie many congenital metabolic diseases in population. The role of such mutations is indisputable in the development of congenital heart disease, susceptibility to schizophrenia, *etc*. However, unusual situations are also possible. For example, the pathological

mutation, which produces sickle-cell disease, yields also immunity against malaria. Therefore, in unfavorable epidemiological environment, sickle-cell disease can widely spread by the mechanism of natural selection.

Probably, the system-forming factor of most complex variants of purposeful behavior, which exceed the bounds of congenital or conditioned reflexes, is the goal of activity [22,23]. This statement more or less agrees with the views of most authors [5,13,23,25], and it looks logical if we assume possibility of a long-term realization of purposeful activity before attainment of the first adaptive result. Indirectly, the system-forming role of a goal was admitted by P. K. Anokhin: "The afferent synthesis, which prepares the organism for solving the problem on what result should be obtained at a particular moment, *sets the goal, so all further system logic will be devoted to attain it*" (emphasized by the present authors) [1]. It is the aim, and not the dominant requirement, which determines specificity of the developing system. By contrast, actualization of the same requirement may develop essentially different systems depending on accumulated experience, subjective assessment of own physical state, *etc*. [17,18,21]. The development of necessary system is evidently performed by trial and error method on the basis of "inner" model of future result (goal). P. K. Anokhin assumed that "one of the most characteristic properties of functional system is dynamic changeability of its integral components, which exists until the corresponding adaptive result is attained" [2]. Activity of the last successful variant of the system makes it possible to obtain the adaptive result programmed at the goal-setting stage. However, before the moment of appearance of this successful variant, the development of several "intermediate" pathological and ambivalent systems is possible, and some of these systems can be stable. For example, behavioral activity can be guided by false aims, whose attainment does not promote satisfaction of the dominant requirement and which is predominantly disadaptive. In this case, there is evident analogy with congenitally determined functional systems, which are also developed by trials and errors, but realized via mutagenesis, a principally different mechanism.

In some cases, such as described by G. N. Kryzhanovskii [9-12], the role of system-forming factor can be played by abnormal hyperactive generator (a pathological determinant). It is interesting that in such cases, the boundary between the basic systems, qualitatively different by the result of their activity, is also fuzzy. In particular, "every pathological system (PS) has its structure-functional antipode, the specific antisystem, which counterbalance PS, restricts and inhibits its activity, and participates in elimination of PS. Activity of such system is exemplified by antinociceptive and antiepileptic antisystems" [11]. These antisystems can be justly termed physiological (or functional, according to original Anokhin's version of TFS), since their activity is evidently adaptive. Hence, the *pathological* morphofunctional structures are closely connected with corresponding physiological ones. Interaction of these structures indicates existence of greater mixed (pathophysiological, ambivalent) systems.

Summary

The key sign of any system is activity of all its parts, which is "focused" on attainment of the corresponding result. Depending on the role of this result for an organism, the systems are subdivided into physiological, pathological, and ambivalent ones. There are several variants of system-forming factors, and any of these factors can develop qualitatively different systems. Existence of the results of activity, which are ambivalent for an organism, is an additional argument in favor of the concept that interrelations of physiological and pathological systems (and some of their variants manifested under normal and pathological conditions, such as noci- and antinociceptive systems, stressor and antistressor systems, *etc*.) should be considered on the basis of dialectic unity, their commonality in the developmental regularities, and their contrast in the results of activity. This approach eliminates intrinsic conflict of classical Anokhin's theory and simplifies the analysis of all manifestations of vital activity. Of particular importance is the fact that it eliminates the major hurdle in the way of integration of TFS with the concepts of pathological and ambivalent systems, which males it possible to use modernized theory as a fundamental basis of human general pathology and many other disciplines.

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