REVIEWS

The Basic Clinical Concepts of Syndrome, Disease Entity, and Disease Group: Biomedical Assessment

V. V. Serov

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 123, No. 3, pp. 244-247, March, 1997
Original article submitted November 20, 1995

Further development of nosology as part of general pathology and theoretical medicine should be based on the recent molecular biology and pathology data.

Clinical medicine developed from efforts to comprehend syndromes and symptoms to elucidation of causes and essence of diseases. In the 1990s, profound insights into the delicate mechanisms underlying functional disorders in the body have been gained at the molecular and supramolecular levels. The data collected by molecular biologists, geneticists, and immunologists have made possible both genotypic (nosologic) and phenotypic (syndromic, pathogenetic) evaluations of the events occurring in disease. It would seem that the progress achieved by theoretical medicine and biology has afforded clinical medicine a good opportunity to enter the 21th century with firmly established concepts of syndromology and nosology. Yet this opportunity has not been fully utilized because analytical thinking predominated to the detriment of synthetic thinking whereby generalizations are made, based on consideration of practical data in order to understand the essence and principles of disease processes.

Consider the concept of **syndrome**. This concept is far from being interpreted unequivocally, even in reference books. According to the Greater Medical Encyclopedia (Vol. 23, p. 779 [in Russian]), a syndrome is not equivalent to a disease (nosologic) entity, for "it may be associated with various diseases." The Encyclopedic Dictionary of Medical Terms (1984, Vol. 3, p. 102 [in Russian]) defines syndrome as "the sum of symptoms having a common pathogenesis" and adds that this term may sometimes be used "to designate a nosologic entity." The "nosologization" of syndromes, as well as the bringing nosologic entities together as a syndrome, represents an attempt to promulgate the syndromologic approach to the evaluation of disease. Thus, a World Health Organization (WHO) expert, commenting on the new International Classification of Chronic Hepatitis (1994), wrote that chronic hepatitis is not a disease entity but a syndromic concept [11].

Preoccupation with the syndromic approach is also evident among clinicians in this country. There are textbooks of internal medicine [1] in which the syndromic principle is often replaced by a nosologic one. A question arises: on what grounds the "manifestations of occupational allergy" such as dermatitis, eczema, urticaria, or bronchial asthma are referred to as a "nonspecific syndrome" rather than a disease entity? Another question is why joint lesions occurring in nonspecific ulcerative colitis and Crohn's disease are not regarded as a manifestation of these diseases, as a "joint syndrome," but as a "disease entity" in the group of rheumatic diseases?

For example, in the Vestnik RAMN (Journal of the Russian Academy of Medical Sciences), hypertension, diabetes mellitus, and atherosclerosis are described as clinical manifestations of the metabolic syndrome X [7]. A report at a meeting of the Moscow Therapeutic Society was entitled "Hypertensive Disease as a Syndrome".

I. M. Sechenov Moscow Medical Academy

0007-4888/97/0003-0209$18.00

In Russia, the practice of replacing nosologic entities by syndromes is rooted in the past when this replacement was probably justified because much less was known about the "etiological principles" than at the present time. For example, M. P. Konchalovskii wrote half a century ago that clinical medicine "moves away from the immovable organic diagnostics toward the formulation of syndromes and symptom complexes" [3,4].

This thesis is unacceptable because a syndrome as the sum of symptoms with a common pathogenesis is often shared by various diseases. This is not a nosologic and, hence, not an etiologic concept, but rather a pathogenetic one. For this reason, there are only about 1500 syndromes and more than 20,000 disease entities "covered" by these syndromes.

It is important to note that some of the recognized syndromes can claim to be nosologic entities. This is so because many syndromes named after their discoverers in the past have since then acquired, owing to the achievements of biomedical sciences that have identified their etiologies, the status of nosologic entities, although they continue to be called syndromes in the nomenclature. One example is the Zollinger—Ellison syndrome caused by non-beta cell adenoma of pancreatic islets (Zollinger—Ellison-I) or a gastrinoma of the gastroduodenal system (Zollinger—Ellison-II). The pathogenesis of this syndrome is well understood, and its clinical and morphological manifestations have been defined. Another example is Goodpasture's syndrome and many more can be given. Unfortunately, the terms "syndrome" and "disease" are still perceived as synonyms by some compilers of reference books of symptoms and syndromes [5].

Turning to the concept of **disease**, i.e., of nosologic entity, it is easy to see that its definitions are vague. A nosologic (disease) entity has been defined as "a particular disease identified on the basis of its established etiology and pathogenesis and/or its characteristic clinicomorphological picture" (The Encyclopedic Dictionary of Medical Terms, 1988, Vol. 1, p. 148 [in Russian]). However, the etiology of more than 20,000 disease entities is unknown; therefore, the identification of an overwhelming majority of disease entities is based on the characteristic clinicomorphological picture. It should be noted that this criterion envisages consideration not only of the symptoms and syndromes peculiar to a given disease, but also the location and pattern of pathological process [8].

What are the specific reasons for the existence of controversial questions concerning the identification and classification of nosologic entities?

One reason is that "established" nosologic entities are fragmented and then combined in "nosologic groups of diseases" as a result of progress made by molecular biology, genetics, immunology, biochemistry, and cellular pathobiology. It allowed generalization of etiological, pathogenetic, and clinicomorphological heterogeneity into particular nosologic entities. For example, chronic gastritis is no longer a nosology entity, but a group concept. Each of its forms has its distinctive features, either etiological (gastritis B caused by *Chelicobacter*) or pathogenetic (autoimmune gastritis A and reflux gastritis C). Pyloroduodenal ulcers and ulcers of the gastric body can also be regarded a nosologic entity since they are pathogenetically distinct diseases. Widely different, both etiologically and patho- and morphogenetically, are central and peripheral lung cancers. Five types of viral hepatitis have already been identified (A, B, C, D, and F), each as an independent disease entity. Finally, the group of so-called acute respiratory viral infections includes at least four nosologic entities (influenza, parainfluenza, adenoviral infection, and respiratory syncytial infection).

A second reason is the failure to take into proper consideration the nature (essence) of the underlying pathological process in defining a disease entity or disease group, which leads to the creation of incorrect and, hence, unacceptable classification schemes. One example is the classification of chronic glomerulonephritis proposed by WHO experts. According to the WHO classification, chronic glomerulonephritis includes proliferative (endocapillary, extracapillary, mesangioproliferative, mesangiocapillary) and sclerotizing (fibroplastic) varieties, as well as minimal changes, membranous nephropathy, and focal segmental sclerosis/hyalinosis. Yet the immunoinflammatory nature of glomerulonephritis, which is its essence, can be demonstrated only for proliferative nephritis and sclerotizing nephritis. All other conditions are not glomerulonephritis but represent degenerative and dysplastic changes of the glomerular basement membrane and abnormalities of podocyte receptors. The inclusion in the glomerulonephritis group of minimal changes, membranous nephropathy, and focal segmental sclerosis/hyalinosis is therefore unjustified.

Another example of grouping diseases in which the underlying pathological process does not correspond to the respective nosologic entities is provided by rheumatic diseases. Until recently, these were considered, and still are by some, as diseases of systemic connective tissue disorganization involving an immunopathological mechanism. The morphogenesis of this disorganization was thoroughly explored, its successive phases were identified, features of the immune inflammation accompanying the disorganization were investigated, and generalized

vasculitis was shown to be implicated in these changes. A group of rheumatic diseases, i.e., the connective tissue and immunologic disorders, was then formed on the basis on the etiology (roles of infection and heredity), their pathogenesis (immunopathological mechanism), and clinical and morphological manifestations. This group included rheumatism, rheumatoid arthritis, ankylosing spondylitis (Bekhterev's disease), systemic lupus erythematosus, scleroderma (progressive systemic sclerosis), periarteritis nodosa, dermatomyositis (?), and (without taking morphogenesis into account) Sjögren's syndrome.

By the present time, rheumatic diseases have become a collective, chaotic, polyetiologic, polypathogenetic, and polymorphogenetic concept, as evidenced by the working classification of these diseases developed by All-Union Society of Rheumatologists (1985) in line with International Classification. This working classification is used in expounding the relevant material in textbooks and monographs.

This classification includes relapsing panniculitis (Weber—Christian's disease) appearing near systemic lupus erythematosus (probably because the panniculitis is nonsuppurative); Schönlein—Henoch's syndrome and Goodpasture's syndrome placed near all systemic vasculites; gout, amyloidosis, and hemochromatosis grouped together, although they are diseases of a metabolic-degenerative rather than immunoinflammatory genesis; and, finally, osteoporosis, osteomalacia, and even osteochondropathy of the tibial tuberosity. Such a classification could be proposed primarily because the historic experience of research into rheumatic diseases was ignored, the syndromic approach prevailed over the nosologic one, and the morphogenetic features of the diseases concerned were buried in oblivion.

A third factor that has undermined the rationale for identifying nosologic entities is the validation of the concept of "secondary diseases." Particular interest in these diseases has been shown in our times, most likely because of the increased incidence of iatrogenic conditions. It was revived in the late 1970s by A. V. Smol'yannikov [10] who maintained that the term "secondary disease" should be interpreted to cover, first, any morbid condition that is pathogenetically associated with another disease or is accidentally superimposed on it and, second, any disorder resulting from physician's intervention in another disease which is not pathogenetically related to the iatrogenic disorder. Thus, a secondary disease is a second nosologic entity arising in the course of or in relation to the primary disease and developing independently of the primary disease. An example of secondary disease is the secondary amyloidosis developing many years after tuberculosis; its major manifestation is progressive renal failure. An example of secondary disease in a surgical clinic is postoperative "complications" due not so much to surgical mistakes as to peculiarities of the individual tissue response to the intervention (e.g., adhesive inflammation after appendectomy or laparotomy).

The concept of secondary disease calls for special attention to iatrogenic disorders which have now reached epidemic proportions and are regarded as an aftermath of scientific and technological progress. Iatrogenies were broadly defined by the WHO as "any undesirable or adverse consequence of preventive, diagnostic, and/or therapeutic interventions or procedures leading to impaired bodily functions, limited habitual activities, disability, and death" [6]. There are good grounds for such a definition. Indeed, according to WHO's estimates for 1986, iatrogenies occurred in 20% of patients and accounted for 10% of hospital deaths. In the USA, infections related to drug therapy or surgery affect annually 5-6% of hospitalized patients, 1% of whom die, while 3-5% of hospitalized patients develop adverse reactions to drug therapy. Importantly, about one-third of iatrogenies are not recognized in living patients [9].

All this completely justifies the recommendation of WHO experts to consider as the underlying disease (as the cause of death) any iatrogeny that has led to death, regardless of whether the treatment that a patient has received was appropriate or inappropriate, whether it was given with or without due consideration of the indications for it, and whether it was based on correct or an incorrect diagnosis [9].

It follows that "secondary diseases" and iatrogenies, by violating the canons underlying the identification of nosologic entities, enable complications to be elevated to the rank of nosology. This has serious implications because there may be other reasons for justifying such a situation. One reason may be the social factor referred to by Russian pathologist I. V. Davydovskii [2] who wrote that "... human activities, substantially changing human ecology, impart new features to the lifestyles of people, their physiology and psychology, and, consequently, to pathology and nosology," and that this is why "the social factor colors in peculiar and specific ways many facets of human pathology."

The augmented role of the social factor is becoming yet another, obligate criterion for the identification of nosologic entities and groups such as ischemic heart disease (IHD) and cerebrovascular disease (CVD). These diseases account for more than 50% of deaths in industrialized countries. A similar situation has developed in this country. According to the Center for Preventive Medicine of the Ministry of Health of the Russian Federation, cardiovascular

diseases were responsible for 45% of deaths among men and 68% of deaths among women in 1988, with IHD and CVD accounting for about 90% of all deaths from these diseases.

Not surprisingly, although IHD and CVD are complications of atherosclerosis or hypertension, the WHO considered it possible and necessary to regard them as independent nosologic groups. Accordingly, IHD was included in the Eighth Revision of the International Classification of Diseases (published by WHO in 1965) and CVD in the Ninth Revision of this classification (published in 1977). However, IHD and CVD are group concepts rather than nosologic entities, and for this reason no patient should have a diagnosis of IHD or CVD.

Ischemic hear disease has been recognized for about 30 years and CVD for at least 20 years, and yet the problem of whether or not IHD and CVD should be recognized as nosologic groups is debated by Russian clinicians, although the arguments adduced by opponents of this recognition are rather weak. It is appropriate to recall here the I. V. Davydovskii's words that "the quality of physician's work is largely determined by the extent to which he has succeeded in freeing himself of ... nosologic dogmatism with "rounded off" pictures of disease."

It can be concluded from the foregoing discussion that the three interrelated concepts of syndrome, nosologic (disease) entity, and nosologic (disease) group can be adequately assessed only in the context of the current status of medicine, and it is very important, first, to interpret them from a general biological viewpoint, based on the doctrines of etiology, pathogenesis, and nosology, and second, to give due consideration to the pertinent historic experience.

In summary, the idea is that the advances in the fields of molecular biology and pathology, in addition to elucidation of delicate mechanisms underlying vital processes, allowing deeper insights into the etiology and pathogenesis of human diseases and favoring the development of improved methods for their treatment, also have direct relevance for resolving issues of general pathology such as those of nosology and syndromology and others that are of paramount importance for further progress of theoretical medicine and, in particular, of the doctrine of disease.

REFERENCES

1. A. V. Sumarokov (Ed.), *Diseases of Viscera* [in Russian], Vol. 1-2, Moscow (1993).
2. I. V. Davydovskii, *General Human Pathology* [in Russian], Moscow (1969).
3. M. P. Konchalovskii, *A Textbook of Internal Medicine* [in Russian], Moscow - Leningrad (1939).
4. M. P. Konchalovskii, *Selected Works* [in Russian], Moscow (1961).
5. I. R. Lazovskis, *A Handbook of Clinical Symptoms and Syndromes* [in Russian], Moscow (1981).
6. J. Last, *Vsemirnyi Forum Zdravookhraneniya* (*World Health Forum*) [in Russian], **6**, No. 2, 40-48 (1986).
7. V. S. Moiseev, A. Ya. Ivleva, and Zh. D. Kobalova, *Vestn. Ross. Akad. Med. Nauk*, No. 5, 15-18 (1995).
8. V. V. Serov, *General Pathologic Approaches to the Understanding of Disease* [in Russian], Saratov (1992).
9. V. V. Serov, M. S. Popov, and O. V. Zairat'yants, *Arch. Pat.*, No. 5, 11-16 (1988).
10. A. V. Smol'yannikov, in: *The Greater Medical Encyclopedia* [in Russian], 3rd ed., Vol. 7, Moscow (1977), pp. 243-246.
11. Y. V. Desmet, *Hepatology*, **19**, No. 6, 1513-1520 (1994).