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Review

METHODOLOGICAL ASPECTS OF USING ALLOSTATIC LOAD ANALYSIS IN ASSESSING HEALTH OF WORKING POPULATION EXPOSED TO ADVERSE OCCUPATIONAL FACTORS (ANALYTICAL REVIEW)

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Preventive medicine of pathogenetically based technologies for prenosological diagnostics of health risks at the stage of reversible physiological dysregulation is being introduced into practice as a relevant strategy for preserving population. It provides suitable conditions for timely prevention of chronic diseases and reducing risks of premature mortality among working age population. Using resources of the scientific information systems CyberLeninka, eLibrary, PubMed and Google scholar, the authors analyzed and summarized scientific literature data on methodological aspects and problems related to practical application of the concept of allostasis and allostatic load (AL) in assessing and predicting health risks for working population

The review focuses on the main causes of physiological dysregulation leading to AL formation under environmental exposures, including occupational ones; presents the most popular biomarkers of the functional state of the neuroendocrine, immune-inflammatory, cardiovascular and metabolic systems included in the sets of variables for determining the AL index. The review also provides the description of the most common algorithms for calculating the AL index used in preventive examinations of workers and highlights methodological approaches to the correction of AL values with regular intake of medicines. The sex-specific age dynamics of AL is presented; attention is drawn to the aggravating effect produced on AL by negative behavioral factors.

The review shows that it is still difficult to introduce this methodology into routine practices of preventive medical examinations of working population despite the proven diagnostic and prognostic significance of the prenosological diagnosis of health disorders based on AL. This is mostly due to lack of consensus on standardized approaches to creating sets of biomarker scales and a method for calculating the AL index, as well as considering the sex factor and contribution of therapeutic effects to cumulative assessment of risks of developing physiological dysfunctions.

Keywords: *homeostasis, allostasis, allostatic load, allostasis biomarkers, allostatic load index, prenosological diagnostics, working population, working conditions, adaptation, occupational stress.*

Contemporary global challenges determine priority trends in the state policy of the Russian Federation. These priorities include health protection, improvement of life quality, and growth in welfare of the country population based on birth rate growth, growth in life expectancy at birth, longer years of active life, decline in mortality and disability as well as on creating suitable conditions for timely disease prevention and formation of healthy lifestyles[1].

Results obtained by recent studies in hygiene and occupational medicine obviously indicate that existing and new occupational factors emerging in the 21st century able to affect workers' life and health are caused by

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exponentially growing use of new technologies, first of all, digital ones; key changes in workplace structures and design and organization of work processes as well as employment structure given the global trend of workforce ageing [1, 2]. All this is accompanied with growing biological and psychosocial occupational hazards [3] that create additional risks of somatic (essential hypertension, coronary heart disease, obesity, type 2 diabetes mellitus, nonalcoholic fatty liver disease, dorsalgia, and neoplasms) and mental (depression-like states, actual depression) health issues in workers of various occupational groups [4–6].

Given that, it is important to rely on the complex system of social-hygienic monitoring that involves analysis of effects produced by working conditions on workers' health, occupational risk assessment, prediction of progression of occupational and work-related diseases [7] as well as general somatic pathology that affects work ability. This requires farther development of a methodology for prenosological diagnostics of diseases in workers in order to achieve their early detection and provide timely personalized and group prevention [8, 9]. The World Health Organization (WHO) gives recommendations how to determine early signs of negative effects produced by occupational environment and work processes on workers' bodies. They should be determined relying on pathogenetically grounded informative diagnostic methods eligible for detecting disrupted mechanisms of adaptation to external exposures at the stage when physiological deregulation can still be reversed prior to the development of nosologic syndromes and clinically identifiable occupational and general somatic diseases [10].

Over the last decades, methodical instruments based on the concept of allostasis and allostatic load (AL) have been successfully used in complex assessments of intensity of physiological deregulation caused by occupational factors including psychosocial, physical, chemical, biological and some others [11]. These instruments allow estimating adaptability to chronic occupational stress per combined changes in the circulatory, respiratory, and immune systems, metabolic processes and anthropometric data [12]. At present, although the AL model is in great demand in foreign epidemiological studies [13–15], it still has not been actively employed in Russian hygiene and occupational medicine within prenosological diagnostics and prediction of occupational or work-related diseases.

The aim of this study was to summarize and analyze available literature data on up-to-date methodical aspects and issues of using the concept of allostasis and allostatic load in practice to assess and predict risks of diseases in working population.

Materials and methods. Russian and foreign studies were searched in relevant databases including RSCI, eLibrary, CyberLeninka, PubMed and Google scholar. Search requests included the following keywords and their combinations: 'allostasis', 'allostatic load', 'allostasis biomarkers', 'allostatic load index', 'homeostasis', 'prenosological diagnostics', 'adult population', 'working population', 'working conditions', 'adaptation', 'occupational stress', 'occupational burnout', 'age', 'biological sex'. The search depth covered the period between 1997 and 2024. The review covers 55 studies selected from preliminarily analyzed 207 foreign and Russian scientific publications.

Results and discussion. Homeostasis primarily maintains dynamic internal stability of the body. In contrast to that, allostasis is a process aimed at effective regulation of adaptability to new emerging environmental challenges (stressors) through change that makes the body more resistant to new environmental conditions [16]. Over time, 'wear and tear' of this compensatory-adaptive mechanism of response to stressor exposures may lead to subclinical accumulation of dysfunction in some regulatory systems in the body. This state is known as allostatic load [17]. Homeostasis is maintained by each involved functional system in the body performing

physiological control of its indicators through negative or positive feedback providing metabolism stability. In contrast, allostatic reactions are regulated by the central nervous system that makes constant corrections in changes of the body physiological state occurring due to stressor exposures [18]. I.N. Karatsoreos and B.S. McEwen believe allostasis to be a dynamic, integral and adaptively plastic mechanism that combines sensory perception and cognitive assessment of risks related to stressor exposures and initiates a cascade of typical stress-mediated responses [19].

B.S. McEwen described four models of body responses to changes in the environment, allostatic load or even overload being their outcome: 1) frequent or permanent exposures that induce chronic stress and repeated physiological agitation; 2) absence of stable adaptation to persistent stressors; 3) persisting elevated levels of compensatory-adaptive reactions after a stressor exposure has ended; 4) inadequate and / or insufficient adaptation mechanisms that should fight against a stressor. These four types of overactive or ineffectively managed compensatory-adaptive reactions can exist separately or in their combinations [11, 20]. Any chronic or frequently repeating stressor exposures are able to induce AL growth when body adaptive reserves are depleted and compensatory-adaptive pathways of basic allostasis-regulating systems (the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system, immune-inflammatory system) become non-coordinated. This can ultimately manifest itself as stress-related disease [21, 22]. Therefore, under persisting stressor exposures, AL-related adaptive changes at best mitigate induced metabolic and functional disorders; at worst, they lead to chronic diseases, accelerated ageing and premature all-cause mortality [11, 23].

Environmental factors, occupational ones included, produce certain effects on the body that are determined by genesis and levels of stressor exposures. Identification of their impacts, either cumulative or combined ones, involves certain difficulties associated with multiple variable existing pathogenetic ways of disease progression and their interplay as well as with individual susceptibility and adaptability to the environment [24]. At the same time, results obtained by foreign epidemiological studies indicate that use of allostatic load as a poly-system indicator of chronic physiological dysfunction allows investigating multiple stressors in their integrity and quantifying their influence on population incidence and mortality [11, 25].

Initially, the allostatic load index (AL index) was suggested by T.E. Seeman with colleagues as an instrument to measure subclinical health impairments[2]. It was calculated based on biomarkers presented by primary mediators of stress-related responses, including dehydroepiandrosterone sulfate (DHEA-S), cortisol, adrenalin and norepinephrine, and biomarkers of secondary chronic stress outcomes that manifest themselves in the cardiovascular (systolic and diastolic blood pressure, total cholesterol, high density lipoproteins) and metabolic (waist-to-hip ratio, glycated hemoglobin) systems. Later the authors admitted that this set made of 10 indicators was not meant to become a standard AL index scale and could not be considered comprehensive. The reasons are that it was based on biological data available to its developers and therefore it can be altered and added with other markers of body regulatory and functional systems depending on specific research aims [26].

At present, more than 70 biomarkers of various functional systems have been suggested to determine the allostatic load index. The neuroendocrine, cardiovascular, metabolic and immune-inflammatory systems are the basic ones used in allostatic load calculation [15, 27, 28] (Table 1).

[2] Seeman T.E., Singer B.H., Rowe J.W., Horwitz R.I., McEwen B. Price of adaptation – allostatic load and its health consequences. MacArthur studies of successful aging. *Arch. Intern. Med.*, 1997, vol. 157, no. 19, pp. 2259–2268.

Table 1

Biomarkers employed to calculate allostatic load

Functional system	Biomarkers
Neuroendocrine	adrenalin, cortisol, dehydroepiandrosterone sulfate, epinephrine, norepinephrine, testosterone, thyrotrophic hormone
Parasympathetic	heart rate variability
Immune-inflammatory	erythrocyte sedimentation rate, white blood cell count, C-reactive protein, fibrinogen, interleukin 1 receptor antagonist, beta interleukin, interleukin 6, interleukin 8, interleukin 10, interleukin 12p70, tumor necrosis factor alpha, E-selectin, intercellular adhesion molecule type 1, total immunoglobulin E, insulin-like growth factor 1, herpes I and II antibodies
Cardiovascular	resting heart rate, pulse wave velocity, systolic and diastolic blood pressure, pulse pressure
Metabolic	total cholesterol, high density lipoproteins cholesterol, low density lipoproteins cholesterol, CS-HDL / TCS ratio, triglycerides, apolipoprotein A1, apolipoprotein B, fasting glucose, glycated hemoglobin, insulin, HOMA-IR, adiponectin, leptin, body mass index, waist circumference, waist-to-hip ratio, waist-to-height ratio
Respiratory	peak expiratory flow rate, the forced expiratory volume in 1 second to forced vital capacity ratio
Urinary	creatinine, cystatin C
Hepatobiliary	albumin, aspartate aminotransferase, alanine aminotransferase, gamma-glutamate aminotransferase, alkaline phosphatase

In various epidemiological studies, multi-system models for AL assessment may include, as a rule, between 5 and 26 physiological biomarkers to describe health; on average, 9 indicators [29]. In practice, AL scales have often been added with highly correlated variables such as systolic and diastolic blood pressure; total cholesterol (TCS) and low density lipoproteins cholesterol (LDL-CS); fasting glucose in blood serum and glycated hemoglobin (HbA1c); body mass index and waist-to-hip ratio. Another widespread practice is to include primary mediators of stress reactions into analysis that reflect recent stress events and not a cumulative effect of stressor exposures [13]. Some researchers believe that such practices are able to reduce the statistical significance of prognostic AL models due to increasing measurement inaccuracies [30, 31].

It is noteworthy that despite growing numbers and diversity of biomarkers included into allostatic load assessment by different researchers, a consensus has not been reached yet as regards what biomarkers are the most eligible for such assessments [18, 19, 29]. C. McCrory with colleagues aimed to create the most effective set of AL biomarkers. To do that, they took data obtained by 13 cohort medical and preventive examinations of working population in Western European countries, the USA and South Africa and performed comparative meta-analysis of strength of correlations between 40 biomarkers describing the functional state of the neuroendocrine, parasympathetic, immune-inflammatory, cardiovascular, metabolic, respiratory, urinary, hepatobiliary and antioxidant systems and general health measures of 67,126 examined participants such as walking speed [32], handgrip strength [33] and self-rated health. The study results showed significant correlations between integrated health measures and only 9 out of 40 analyzed biomarkers: DHEA-S, heart rate variability (HRV), C-reactive protein (CRP), resting heart rate (HR), peak expiratory flow rate (PEFR), high density lipoproteins cholesterol (HDL-CS), waist-to-height ratio (W/H), HbA1c and cystatin C. In addition to that, the

authors established that the AL index based on only five biomarkers (CRP, HR, HDL-CS, W/H and HbA1c), which were present in each analyzed cohort study, had a significant correlation with high mortality risk, just as more complex sets of AL biomarkers [15]. It is noteworthy that three variables, namely CRP, HbA1c and HR, which were analyzed in a cohort of Great Britain's National Child Development Study (NCDS) (7981 participants were examined at the age of 44–45 years and 54–55 years), had an authentic correlation with elevated risks of cardiovascular mortality and premature all-cause mortality over a 10-year period whereas the cortisol level did not have any prognostic value [23, 34].

It should be noted that not only validity of variables that are suggested for inclusion in an AL scale is considered significant in accomplishing periodical check-ups of working population. Other important aspects are economic costs related to testing AL indicators as well as correctness and standardization of taking biosamples within a mass outpatient examination, first of all, those aimed at analyzing primary stress mediators (cortisol, adrenalin, noradrenalin, dopamine, and DHEA-S) [12, 35]. At the same time, relying on population data analyses, researchers more often believe it is possible to exclude these primary indicators from an AL scale since they have a lower prognostic value as compared to biomarkers of the immune, metabolic and cardiovascular physiological systems [36–38]. D. Mauss with colleagues took workers employed at industrial enterprises in Germany as an example to develop a simplified approach to AL index assessment. It was based on five routine indicators including diastolic blood pressure, HbA1c, LDL-CS, WC and HRV and showed a strong correlation with workloads in a model that described an imbalance between efforts and remuneration [35].

Apart from selecting relevant variables, another significant issue is to select a method for AL index calculation, which should be relevant to research aims [31]. At present, there are approximately 15 algorithms for AL index estimation. The method suggested by T.E. Seeman with colleagues[3] is the most popular. According to this algorithm, intensity of cumulative health impairment is determined by total dichotomous manifestation of disease risk through risk quartiles. Biomarker values that fall within the high risk quartile (the upper 75 % percentile) are assigned score 1 whereas all the others are estimated as zero (low risk). The only exclusion are some indicators since even their low values (the lower 25 % quartile) create high risks of physiological dysregulation, for example, HDL-CS or DHEA-S. After code values have been assigned to all biomarkers, an individual AL index is calculated by simply summing up the scores assigned to each biomarker [39]. Similar to the foregoing algorithm, the AL index can be calculated based on values of biomarkers falling within the upper (90 % percentile) and lower (10 % percentile) decile of high subclinical health risks [40]. Experts believe that regardless of a combination and quantity of variables employed to calculated AL, its total index as possible predictor of disease in long-term outlook is better than any other biomarkers when analyzed separately [15, 27].

Use of quartiles / deciles to identify high risks of biomarkers included into an AL scale means that each of them makes an even contribution to this multisystem model. However, each physiological system is described with different numbers of variables, and this, especially in a situation when all variables are strongly correlated, can lead to inaccuracy in AL index calculations [41]. As a rule, the metabolic and cardiovascular systems [15, 27] are described with a greater number of indicators. To eliminate any shifts towards them, a weighted estimation of average system risk was suggested. It allows uniform presentation

[3] Seeman T.E., Singer B.H., Rowe J.W., Horwitz R.I., McEwen B. Price of adaptation – allostatic load and its health consequences. MacArthur studies of successful aging. *Arch. Intern. Med.*, 1997, vol. 157, no. 19, pp. 2259–2268.

Table 2

Clinically relevant cut points for high-, moderate-, and low-risk categories of specific biomarkers by E.J. Rodriquez et al. [31]

System	Marker	Risk categories		
		High	Moderate	Low
Cardiovascular	Systolic blood pressure, mmHg	≥ 150	120–149	< 120
	Diastolic blood pressure, mmHg	≥ 90	80–89	< 80
	Total cholesterol, mg/dL	≥ 240	200–239	< 200
	HDL cholesterol, mg/dL	< 40	40–59	> 60
	Total/HDL cholesterol ratio	> 4.0	3.0–4.0	< 3.0
Metabolic	Glycated hemoglobin, %	≥ 6.5	between 5.7 and < 6.5	< 5.7
	Waist-hip ratio (women)	≥ 0.85	between > 0.80 and < 0.85	≤ 0.80
	Waist-hip ratio (men)	≥ 1.0	between 0.95 and < 1.0	≤ 0.95
	Body mass index, kg/m^2	≥ 30	between 25 and < 30	between 18 and < 25
	Albumin, g/dL	< 3	between 3 and < 3.8	≥ 3.8
Inflammatory	C-reactive protein, mg/L	> 3	1–3	< 1

of all functional systems in the ultimate AL index regardless of how many biomarkers were assessed for each of them [42].

Another way to calculate an AL index is an algorithm based on clinically established reference threshold values of biomarkers. It is primarily implemented within mass preventive medical check-ups of adult people in outpatient clinics and relies on the following scale that estimates risks of physiological 'wear and tear' on the body: low risk, 0 score; moderate risk, 0.5 score; high risk, 1 score [43] (Table 2).

It is noteworthy that the AL calculation method based on clinical measurements has some limitations. They reduce its potential eligibility as an indicator of subclinical health impairment, first of all, due to absence of established risk category ranges for most biomarkers included into extended sets of AL index variables. Another reason is identification of high risks of dysfunction at values corresponding to a clinical phenotype, for example, metabolic syndrome [43]. Given that, it does not seem advisable to employ clinical measurements in allostatic load assessment when examining people from specific occupational groups (military, rescue workers, firefighters, and law enforcement personnel) since their occupational activities make high demands of their physical and mental health [18]. As a rule, these occupational groups have lower incidence rates and levels of physiological deregulation as opposed to general population due to strict tests taken before entering an occupation [44].

Selection of a method for calculating the AL index sensitive to system prenosological changes in health becomes important in comparative examinations of physiological adaptability to environmental factors in different occupational groups. Most researchers believe the z-score analysis to be the most informative in this respect [18, 39]. The z-scores are assigned to AL biomarkers depending on the number of standard deviations from the relevant average in a sample identified for each variable; deviations above the average are considered positive and below the average, negative. For biomarkers, low levels of which correspond to high risks of physiological deregulation, an additive inverse value of an indicator is included into the AL index. Higher total scores per selected continuous values of variables correspond to the greatest physiological deregulation [45]. This method allows estimating allostatic load for various population groups even when different thresholds of its subclinical risks are employed in each analyzed sample [18]. This makes for wide use of the z-score analysis in longitudinal studies [46].

Regular drug administration remains an open question in allostatic load assessment. This concerns therapies with drugs aimed at stabilizing the cardiovascular system (hypotensive drugs, beta blockers, and calcium blockers), lipid (statins) and carbohydrate (hypoglycemic drugs) metabolism. The expert society has not yet reached any consensus on the matter [31, 39]. In earlier research, the prevailing opinion was that administration of drugs that normalize functional state of the body systems and reduce risks of chronic pathology does not require any changes in a current AL index assessment [47]. Later on, more and more researchers started to believe that even though supportive drug therapy reduces individual health risks its use already indicates existing physiological deregulation in the compromised systems. This deregulation cannot be considered completely reversible if constant drug therapy is needed [42].

Different approaches are employed to adjust the AL index for people who take drugs aimed at maintaining values of diagnostic biomarkers within their reference ranges. Most frequently, relevant data on drug administration are included into AL index calculations, the cardiovascular system, glucose and lipid metabolism being the primary targets for drug therapy. System risk for those drug-taking patients who participate in epidemiological studies is assigned into the quartile of high health risk regardless of actual values identified for indicators of the systems supported by drug therapy [48]. E.J. Rodriquez and others offer a compromise that involves adding a half-score to the total indicator of a functional system supported by drug therapy [31]. We should also mention high prevalence of blood pressure (BP) indicators in clinical measurements of the AL index. Given that, T. Robertson and E. Watts recommended adjusting systolic and diastolic BP for patients who take hypotensive drugs by adding 10 and 5 mmHg respectively to their actual levels. This allows more accurate prediction of subclinical risks [49].

Epidemiological studies usually cover established hygienic (physical, ergonomic, chemical, and biological) and psychosocial occupational factors that promote chronic occupational stress [21]. In addition to them, it is recommended to consider several indicators able to independently influence regulatory allostasis systems when examining working population. These indicators are conventionally considered secondary determinants of adaptation processes [44]. Age and sex are two non-modifiable factors that play the most significant role in use of the allostatic load model within preventive medical heck-ups of adult population [30, 50].

The allostasis theory considers the AL model as a general physiological mechanism of cumulative body ‘wear and tear’ due to accumulated stressor exposures that occur through the lifetime [18, 21, 23]. On this basis, most researchers consider the AL index a universal indicator that describes age-specific changes in functional systems and has a strong correlation with biological ageing [39, 49]. Age dynamics in allostatic load is a nonlinear process; the rate at which system dysfunctions accumulate in the body has a positive correlation with risks of adverse vital outcomes, primarily, all-cause mortality [17]. Results obtained by epidemiological studies in various occupational groups show a slow rise in AL starting from the age of 20–25 years with a subsequent drastic rise in its growth rate at the age of 35–65 years. Next, the plateau is reached and after that an insignificant decline is possible during a period with the highest mortality risks (people older than 90 years) [13]. Stabilization of AL population values at the end of lifetime is assumed to be due to selective premature deaths at working age when people with the highest AL do not live long enough to reach late maturity or old age [18]. On the other hand, peculiarities of AL age dynamics emphasize how important it is to monitor it throughout the whole period of working, even in workers who do not have any health-related complaints. This opens an almost 40-year long

'window of opportunity' to correct physiological dysfunctions by using medical and preventive technologies and commitment to healthy lifestyles [13].

Biological sex and sex dimorphism of cognitive assessment of biopsychosocial risks can influence AL, either independently or in synergy. Multiple studies performed in various occupational groups and adult population in general report that higher AL is typically detected in men younger than 45–50 years than in women of the same age. Sex-specific differences in AL tend to smooth out with age [11, 13, 51]. Sex-related variability in AL can be caused by multiple factors. The most significant ones include immune-, cardio- and neuroprotector effects of estrogen as well as higher biological sensitivity to stressor exposures, which is typical for men [52]. Sex dimorphism in AL is mostly considered within the approach to its assessment based on clinical measurements due to sex-specific differences in reference ranges established as physiological norms for certain biomarkers of chronic stress. In case other methods are used to identify the AL index, sex-dependent risk of physiological dysfunctions is analyzed rarer despite its significance and a necessity of such analysis is usually determined by research aims [36, 39, 49].

Apart from age and sex, some other well-known modifiable risk factors of chronic diseases have significant influence on AL dynamics. Primarily, we should mention behavioral ones (unhealthy diets, low physical activity, smoking, and alcohol intake) [53], which increase AL levels and growth rates [11, 18, 24]. The latter, together with working conditions, is recommended to be considered when analyzing current health of working population, predicting vital impairments and premature mortality as well as when developing health recovery programs and preventive and therapeutic measures to prolong healthy and active working life.

Conclusions. The review has presented the results obtained by retrospective and instant studies that focus on practical use of the allostasis concept in prenosological health assessment in various occupational groups and adult population in general. These results show that allostatic load is an effective marker of cumulative physiological deregulation at the multisystem level and can be used as a predictor of poly-morbid states and premature all-cause mortality. At the same time, despite its verified diagnostic and prognostic significance, it would be difficult to integrate AL into the standard of preventive medical check-ups for working population since there is still no consensus as regards standardized approaches to creating a biomarker scale or selecting a method for AL calculation. Other unresolved issues are related to considering sex factor and contributions made by therapeutic interventions into cumulative assessments of physiological dysfunctions.

The most disputable issue is whether any primary mediators of stress-related responses (adrenalin, noradrenalin, or cortisol) should be mandatorily included into an AL scale. However, results obtained by population studies clearly show that these neuroendocrine biomarkers tend to have daily fluctuations in their activity caused by routine daily stresses. They correlate with risks of subclinical health impairments and adverse outcomes of occupational stresses to a lesser extent than biomarkers of various functional systems (cardiovascular, metabolic, or immune-inflammatory). This allows excluding these biomarkers from AL panels without any reduction in their diagnostic and prognostic value.

At present, the analysis of the continuous z-scores is considered by most experts to be the most informative methodical approach to allostatic load quantification. At the same time, this method involves additional statistical unification of initial data just as AL index calculations based on quartiles / deciles of the highest risks of multisystem dysfunctions. Hence, they allow stratifying health impairments only within one selected population and exclude comparison with population groups, for which other sets of AL biomarkers were

employed. Given that, it seems more advisable to employ the AL estimation method, which is based on clinical measurements, when conducting mass preventive medical check-ups of working population. This method relies on using verified sex-specific reference ranges of routine clinical-laboratory, functional and anthropometric indicators that correspond to low, moderate and high risks of physiological dysfunctions.

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