Diagnosis of Stress

Rudolf E. Noble

Stress is defined as a disruption of normal homeostasis. During exposure to stress stimuli, the body responds physiologically by increased activity of both the hypothalamic-pituitary-adrenal (HPA) axis and the sympathoadrenal system (SAS). Stress also gives rise to a number of characteristic behavioral responses. Diagnosis of stress, therefore, depends on a multitude of factors and is complex. A variety of approaches to the diagnosis of stress have been employed, including the use of questionnaires, biochemical measures, and physiologic techniques. Most of these methods are subject to experimental error and must be viewed with caution. A thorough, stress-oriented, face-to-face medical interview is currently the most practicable way to diagnose stress and its effects. It remains for future research to develop a cleaner methodology to diagnose this elusive, yet, all too common medical entity.

STRESS IS DEFINED as "reactions of the body to forces of a deleterious nature, infections, and various abnormal states that tend to disrupt its normal physiologic equilibrium (homeostasis)."[1] Thus, Hooke's law of elasticity (Stress = K $\times$ Strain) applies here. K is a constant, called *Young's modulus*, and strain is the reaction of the body to the stress. The diagnosis of stress is hence multifactorial, complex, and often uncertain. There are currently 3 main methods used clinically for the diagnosis of stress: questionnaires, biochemical measures, and physiological measures.

QUESTIONNAIRES

One can use questionnaires and checklists such as the Life Stress Inventory,[2] the Perceived Stress Scale (which appears to match well with clinical findings),[3] Social Readjustment Rating Scale (SRRS),[4] etc. If the stress is due to post-traumatic stress disorder (PTSD) one may use the Davidson Trauma Scale (DTS),[5] Penn Inventory (PI),[6] Peritraumatic Distress Inventory (PDI),[7] Short Post-Traumatic Stress Disorder Rating Interview (SPRINT),[8] Acute Stress Disorder Scale (ASDS),[9] etc. If the stress reaches anxiety/depression levels, use may be made of the Profile Moods Survey (POMS),[10] Minnesota Multi-Phasic Personality Inventory (MMPI),[11] Beck's Depression Inventory (BDI),[12] Traumatic Stress Symptom Checklist (TSSC),[13] etc. However, most all of these tests are time-consuming and unwieldy, given the time limitations imposed on doctors, their assistants, and patients. A thorough, stress-oriented medical history is currently the best way to uncover stress and its effects. One can inquire about stressful life events, work events, finances, marital problems, natural disasters, and such and note their effects. Time permitting, one may have the patient list these items, as shown in Fig 1, and rate his/her ability to cope with these events.[2]

BIOCHEMICAL MEASURES

The body responds to stress by increased hypothalamic-pituitary-adrenal (HPA) axis activity, which involves the release of corticotropin-releasing hormone (CRH) from the hypothalamus. CRH acts on the adenohypophysis, causing release of corticotropin (ACTH). ACTH then acts on the adrenal cortex inducing increased secretion of corticosteroid hormones, which can be measured in various body fluids (eg, blood, saliva, urine).

In individuals under stress, adrenocortical output of cortisol may increase from the norm of 25 mg/d to as high as 300 mg/d.[14] Adrenocortical hormones, however, are not released in a constant fashion but are secreted in episodic bursts and are subject to negative feedback regulation. Circulating levels of the hormone generally are higher during sleep than during the day. Hence, a randomly obtained result is difficult to interpret because it may represent a peak, a trough, or some point in-between. Furthermore, even a mild stress such as a venipuncture may elevate these values.

A more elegant method is to place an indwelling catheter in an individual's vein and obtain specimens hourly over a 24-hour period. Each specimen is then analyzed, with concentration of the hormone(s) plotted against time. The area under the curve is reported as an index of hormone production.[14] Measurement of urinary free cortisol is especially useful because cortisol-binding globulin, which attaches to one cortisol molecule per molecule of protein, is approximately saturated at the peak morning cortisol concentration. Free, unbound cortisol is then filtered off at the glomerulus such that an elevated 24-hour urine free cortisol determination provides a more accurate assessment.[15]

To assess the sympathoadrenal system's response to stress, one can measure plasma catecholamine levels in a supine, resting patient in whom an indwelling antecubital venous cannula has been in place for at least 15 minutes. The catecholamines are stable within the storage granules of the adrenal medulla but are released by stress, muscular exertion, hypotension, etc. The usual normal blood resting level of epinephrine ranges from 20 to 60 pg/mL, and that of norepinephrine from 200 to 400 pg/mL. The upper limit of both these catecholamines is less than 1,000 pg/mL.[15] However, values between 1,000 and 2,000 pg/mL may be present during mental/emotional stress.[15] The pathways of synthesis of these hormones and their metabolites, and their urinary excretion products are shown in Fig 2. One can measure free catecholamines in the urine (only 2% of total catecholamine output),[14] or urinary metanephrine or normetanephrine (20% of catecholamines).[14] Most of the catecholamines are further converted to vanilly-

From the Cathedral Hill Obesity Clinic, San Francisco, CA.
Address reprint requests to Rudolf E. Noble, MD, PhD, Cathedral Hill Obesity Clinic, 20 Gough St, San Francisco, CA 94103.

0026-0495/02/5106-1008$35.00/0
doi:10.1053/meta.2002.33190

Stress Inventory

List below the stresses that currently exist in your life and your ability to cope with them.

Stress	Ability to cope
	1 2 3 4 5 6 7 8 9 10
	← →
	within your control outside your control
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	

Fig 1. Stress inventory. (With permission of J.F. Christensen and McGraw-Hill Companies from: Feldman MD, Christensen JF (eds): Behavioral Medicine in Primary Care, 1997, Appelton & Lange.[2])

mandelic acid (VMA) by the combined action of catechol-O-methyl-transferase and monoamine oxidase, and VMA can also be measured in the urine.

Other measures that have been used to diagnose stress include levels of prolactin,[16] ACTH,[16] growth hormone,[16] gonadotropins,[16] insulin,[16] dihydroxyphenylalanine (DOPA),[17] and dehydroepiandrosterone (DHEA).[18]

PHYSIOLOGIC MEASURES

The autonomic nervous system is the axis activated most rapidly during the stress response. The balance between the sympathetic and parasympathetic components is quickly disrupted, with sympathetic nervous activity becoming predominant. Hence, one can use various physiologic measures of sympathetic nervous system (SNS) activity in the diagnosis of stress. We list here certain noninvasive techniques that clinicians can use; however, for their proper interpretation, all require baseline, pre-stress measurement.

Heart Rate

Heart rate is determined by auscultation, palpation of peripheral pulses, or electrocardiogram (ECG). However, this indicator of autonomic activity can be confounded by the "white-coat" effect, circadian variation, body posture, environmental conditions, medications, etc, all of which must be taken into account when heart rate is being evaluated.

Heart Rate Variability

With increased sympathetic nervous activity, a reduction in cardiac variability occurs. To assess this variable, a continuous ECG recording is made (only the QRS complexes need be analyzed). Again, many conditions may affect the reliability of this measure, including medication, body posture, and age.

Blood Pressure

Blood pressure is the resultant of cardiac output and peripheral vascular resistance, both of which are regulated by autonomic nervous activity. During periods of acute stress, the systolic blood pressure changes more rapidly than the diastolic blood pressure. For example, changes in systolic blood pressure can be detected within 1 to 2 minutes of the cold pressor test. The effect of chronic stress on blood pressure is less obvious, primarily because there is adaptation of the blood pressure–controlling mechanisms. The accuracy of blood pressure measurements is subject to many errors, including instrument-related and user-related artifacts. The mercury sphygmomanometer is generally considered more accurate than the aneroid device, and one should consistently follow the recommendations of the American Heart Association for measuring blood pressure.

Heart Rate–Blood Pressure Product

Increased levels of circulating epinephrine and norepinephrine cause an increase in heart rate, peripheral vascular resistance, and force of myocardial contraction, all of which result in an increase of oxygen demand by the heart. A reliable indicator of myocardial oxygen demand is the heart rate–blood pressure product (HRBPP), which is calculated by multiplying heart rate by systolic blood pressure.[19] Again, this method is

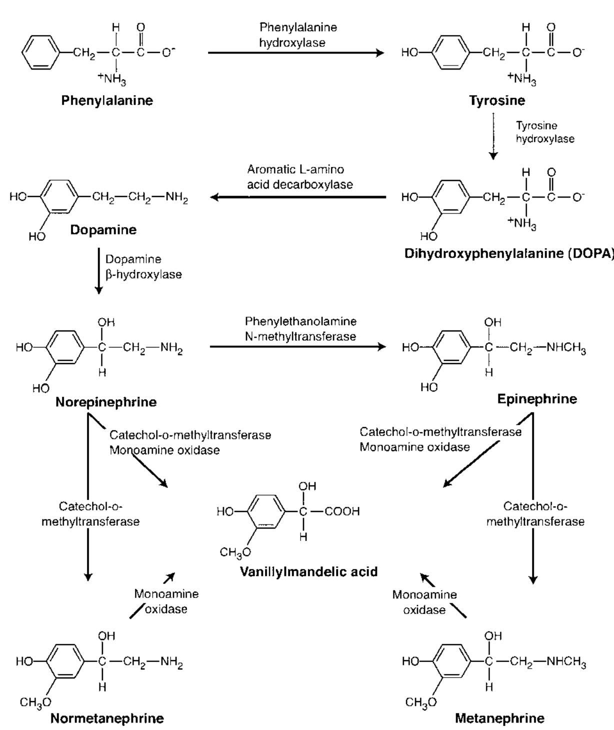

Fig 2. Synthesis and metabolites of catecholamines.

susceptible to all the errors that may cause heart rate and blood pressure variability.

Electrodermal Activity (Galvanic Skin Resistance)

Measurement of electrodermal activity may be useful in the diagnosis of stress,[20-24] but this indicator of SNS activity requires specialized instruments not currently available in the usual clinical setting. This method is imprecise because electrodermal activity possesses both tonic and phasic properties, and electrode size can affect skin potential conduction.

CONCLUSION

Many diagnostic tests may be used to assess stress and its effects. However, most are subject to experimental error of one sort or another and must be viewed with caution. Currently, a thorough, stress-oriented, face-to-face medical interview is probably the best way to diagnose stress. Owing to methodologic constraints, only measurements of peripheral hormones can be used at this time to diagnose stress. It remains for further research to develop a cleaner method to diagnose this elusive, but all too common medical entity.

REFERENCES

1. Stedman TL: Stedman's Medical Dictionary (ed 25). Baltimore, MD, Williams & Wilkins, 1990, p 1487
2. Boone JL, Christensen JF: Stress and disease, in Feldman MD, Christensen JF (eds): Behavioral Medicine in Primary Care. Stamford, CT, Appleton & Lange, 1997, pp 265-276
3. Cohen S, Kamarck T, Mermelstein R: A global measure of perceived stress. J Health Soc Behav 24:385-396, 1983
4. Holmes TH, Rahe RH: The Social Readjustment Rating Scale. J Psychosom Res 11:213-218, 1967
5. Davidson JR, Book SW, Colket JT, et al: Assessment of a new self-rating scale for post-traumatic stress disorder. Psychol Med 27: 153-160,1997
6. Scragg P, Grey N, Lee D, et al: A brief report on the Penn Inventory for posttraumatic stress disorder. J Trauma Stress 14:605-611, 2001
7. Brunet A, Weiss DS, Metzler TJ, et al: The Peritraumatic Distress Inventory: A proposed measure of PTSD criterion a2. Am J Psychiatry 158:1480-1485, 2001
8. Connor KM, Davidson JR: SPRINT: A brief global assessment of post-traumatic stress disorder. Int Clin Psychopharmacol 16:279-284, 2001
9. Bryant RA, Moulds ML, Guthrie RM: Acute Stress Disorder Scale: A self-report measure of acute stress disorder. Psychol Assess 12:61-68, 2000
10. McNair DM, Lorr M, Droppleman LF: Manual for the Profile of Mood States. San Diego, CA, Educational & Industrial Testing Service, 1996
11. Dahlstrom WG, Welsh GS, Dahlstrom LE: An MMPI handbook, vol 1: Clinical Interpretation. Minneapolis, MN, University of Minnesota Press, 1972
12. Beck AT: Depression: Causes and Treatment. Philadelphia, PA, University of Pennsylvania Press, 1967
13. Basoglu M, Salcioglu E, Livanou M, et al: A study of the validity of a screening instrument for traumatic stress in earthquake survivors in Turkey. J Trauma Stress 14:491-509, 2001
14. Kaplan LA, Pesce AJ: Clinical Chemistry. Theory, Analysis, Correlation (ed 3). St Louis, MO, Mosby-Year Book, 1996
15. Goldman L, Bennet JC: Cecil. Textbook of Medicine (ed 21). Philadelphia, PA, Saunders, 1995
16. Conte-Devolx B, Guillaume V, Grino M, et al: Stress, neuroendocrine aspects. Encephale 1:143-146, 1993
17. Kvetnansky R, Noskov VB, Blazicek P, et al: New approaches to evaluate sympathoadrenal system activity in experiments on earth and in space. Acta Astronaut 34:243-254, 1994
18. Kanter ED, Wilkinson CW, Radant AD, et al: Glucocorticoid feedback sensitivity and adrenocortical responsiveness in posttraumatic stress disorder. Biol Psychiatry 50:238-245, 2001
19. Gobel FL, Nordstrom LA, Nelson RR, et al: The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. Circulation 57:549-556, 1978
20. Guzzetta CE: Effects of relaxation and music therapy on patients in a coronary care unit with presumptive acute myocardial infarction. Heart Lung 18:609-616, 1989
21. Rief W, Shaw R, Fichter M: Elevated levels of psychophysiological arousal and cortisol in patients with somatization syndrome. Psychosom Med 60:198-203, 1998
22. Seibt R, Boucsein W, Schuech K: Effects of different stress settings on cardiovascular parameters and their relationship to daily life blood pressure in normotensives, borderline hypertensives and hypertensives. Ergonomics 41:634-648, 1998
23. Steptoe A, Cropley M, Joekes K: Job strain, blood pressure and response to uncontrollable stress. J Hypertens 17:193-200, 1999
24. Vogele C: Serum lipid concentrations, hostility and cardiovascular reactions to mental stress. Int J Psychophysiol 28:167-179, 1998