19 Effect of Nutrition on Stress Management

Ali Reza Waladkhani and Michael Roland Clemens

CONTENTS

ABSTRACT

Persistent mild to moderate hypothalamic-pituitary-adrenal axis activation associated with depressive illness is a well-documented phenomenon. Clinical studies have shown that during periods of depression this results in persistent hypercortisolism of varying degrees that is sufficiently chronic to induce adaptive changes in the hypothalamic-pituitary-adrenal axis function. Animal studies suggest that chronic stress causes high basal cortisol and low cortisol response to acute stressors and that such changes may contribute to disease states. Components of the diet such as protein and carbohydrate, even when the intakes of fat and energy remain unchanged, can produce consistent changes in concentrations of cortisol and its binding globulin, CBG. Further, the fat content of the diet plays a critical role in CBG and cortisol concentration. Also, addition of monounsaturated and polyunsaturated free fatty acids to purified human CBG enhances CBG binding activity in a concentration-dependent fashion. Other important factors are micronutrients, e.g., vitamins and phytochemicals. Studies indicate that persons who eat green or yellow vegetables every day show a lower incidence of stress

syndrome (irritation, sleeplessness) than those who do not eat them regularly. Also, dietary modification may reduce stress susceptibility and improve the stress management.

19.1 INTRODUCTION

Persistent mild to moderate hypothalamic-pituitary-adrenal (HPA) axis activation associated with depressive illness is a well-documented phenomenon and can be demonstrated in approximately half of patients suffering from major depression.[1] Clinical studies have shown that during periods of depression this results in persistent hypercortisolism of varying degrees that is sufficiently chronic to induce adaptive changes in HPA axis function.[1] Many investigators have speculated that subtler, subclinical changes related to HPA axis activation may occur in depression.

Because cortisol is critically involved in the regulation of immune function, many investigations have focused on aspects of immune function in patients with depression.[2] Psychosocial stress may be associated with a process of premature aging in middle-aged males, corresponding to a hypogonadal state as well as to indirect signs of increased insulin resistance.[3] The steady-state blood glucose levels were significantly higher after stress, demonstrating impairment of the insulin sensitivity by mental stress.[4] It is documented from vitamin deprivation studies that alterations in behavior and mental performance arise in early stages of vitamin deficiency.[5]

The increase in the circulating glucocorticoid signal associated with acute stress endures well beyond the period of increased total corticosterone levels.[6] After an acute stressor termination, glucocorticoid-sensitive targets are exposed to high levels of free corticosterone for several days. The long-term increase in free corticosterone may play an important role in mediating some of the effects produced by acute stressor as well as those produced by other acute stressors.[7]

In most species, as much as 68% of plasma CBG remained free of cortisol under physiologic conditions.[8] Also, in addition to its role as a transport protein, CBG plays an active role in determining the disposition of cortisol in humans.[9] $\mathrm{Acu_{te}}$ exposure to a stressor is able to decrease CBG levels provided that duration of exposure to the stressor and its intensity are high and that the effect is tested at least 6 h after the onset of stress. The effect appears to be mediated by some adrenal factor(s) other than glucocorticoids.[10] Further, psychological stress seems to increase oxidative stress.[11] Early studies indicate that psychological stress decreases DNA repair[12] and inhibits radiation-induced apoptosis[13] in human blood cells. This may mean that oxidative damage may persist during psychological stress and may increase the likelihood of a pathological development. [11]

In contrast to the tendency of chronic stress to elevate baseline cortisol, it appears to decrease testosterone, both in animals and humans (Figure 19.1).[14,15]

19.2 MEAL FREQUENCY

Timing and the nutritional composition of the meal can influence the effects of meals on cognitive behavior. Using a cross-over design, Simeon and Grantham-McGregor[16] found that stunted and previously malnourished 9- and 10-year-old

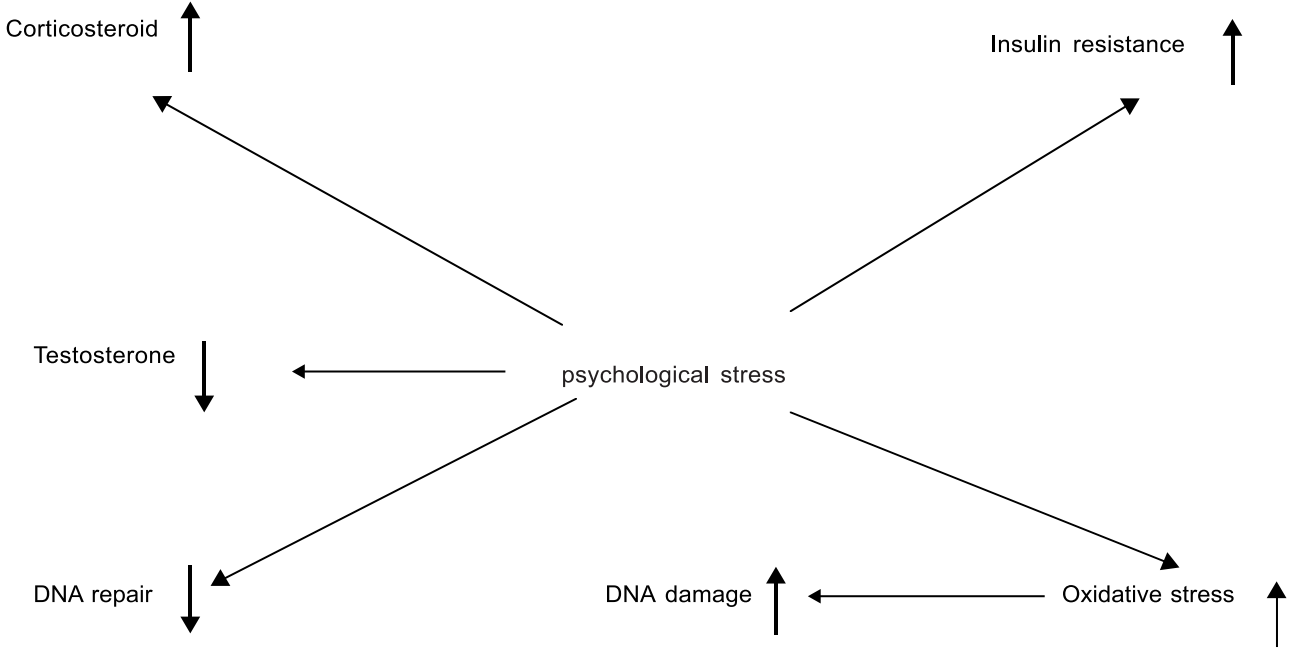

FIGURE 19.1

Jamaicans performed less well on tests of short-term memory and problem-solving ability when they had not eaten breakfast than when they had eaten a morning meal. Undernourished children's performance on a test of verbal fluency was significantly better when they had consumed a school breakfast than when they had not.[17] Experimental evidence suggests that omitting breakfast negatively affects cognitive functioning.[18]

The degree to which lunch moderates subsequent cognitive performance and mood may be mediated by a number of factors. One of the most obvious of these factors is meal size. In a study investigating the effect of meal size on attention and mood, Smith et al.[19] reported that subjects who ate a larger than usual lunch made more errors on attention and search tasks than those who ate a normal-sized lunch, or one smaller than usual. No differences in mood were noted as a function of meal size. Craig and Richardson[20] found that relative to their performance before lunch, young men made significantly more errors on a letter-cancellation project after eating a large lunch, but tended to make less errors after a small lunch. Changes in performance were greater when subjects ate a meal similar in size to their normal lunch. Performance improved to a greater degree after the small lunch in subjects who typically ate a heavy lunch than in those who ate a light lunch. Afternoon snacks may also have positive effects on cognitive performance.[21]

Smith et al.[22] addressed the effects of an evening meal on cognitive performance and mood. After 1-3 h, subjects who consumed the meal reported feeling stronger, more proficient, and more interested than subjects who did not consume the meal. Additionally, 90 min after the meal, the subjects who had eaten completed more sentences on a logical-reasoning task than those had not eaten.

19.3 CARBOHYDRATES

Components of the diet, such as protein and carbohydrate, even when the intakes of fat and energy remain unchanged, can produce consistent changes in concentrations of cortisol and its binding globulin. The isocaloric change from a high protein to a high carbohydrate intake was associated with decreases in plasma cortisol and corticosteroid binding globulin, with reciprocal changes in plasma testosterone and sex hormone binding globulin.[23] Also, a carbohydrate-rich, protein-poor diet may increase personal control in subjects with a high stress proneness.[24] An abnormal rhythm of glucocorticoids combined with elevated cortisol concentrations has also been reported in pathological situations involving an elevation of free fatty acid, such as in insulin-dependent diabetes mellitus or acquired immune deficiency syndrome.[25]

An improvement in memory in those who had eaten breakfast has been found to correlate with the levels of blood glucose.[26] The impression that memory, rather than other aspects of cognition, is more susceptible to changes in blood glucose levels is unavoidable. A glucose-containing drink has been found to improve memory in both young healthy adults[27] and the elderly.[28] The mechanism by which an enhanced provision of glucose might facilitate memory and the possibility that

cholinergic activity is enhanced has attracted particular attention; an association between acetylcholine-mediated neurotransmission and memory is well documented.[29] Acetylcholine is formed by choline acetyltransferase from the precursors choline and acetyl-CoA; glucose is the main source of the acetyl groups used in the formation of acetyl-CoA.[30] One situation associated with a high demand for acetylcholine is learning. Durkin et al.[31] produced the first direct evidence that raised glucose levels facilitate acetylcholine synthesis, by measuring its release from the rat hippocampus under conditions of increased neuronal activity.

19.4 FAT

Fat content of the diet plays a critical role in CBG and cortisol concentration. Early studies in burn patients indicated patients fed the low-fat solutions (15% kcal as fat) had higher serum CBG than patients fed the standard solution (35% kcal as fat) and that higher levels of CBG resulted in a lower free serum cortisol.[32] Not only the fat amount but also the fat deposition is effective in corticosteroid bioavailability. Also, free fatty acids modulate the action of steroids mainly by inhibiting their binding to specific plasma and tissue proteins such as the human sex steroid binding protein.[33] *In vitro* studies have also shown that free fatty acids modulate the functionality of human CBG positively or negatively, depending on their molar ration to CBG.[34] *In vivo*, the release of free fatty acids consecutive to heparin-induced lipoprotein lipase activation mediates conformational changes, causing a reduction of CBG binding in suckling rats.[35] *In vitro* addition of physiological concentrations of exogenous free fatty acids confirms that the stimulation of CBG binding properties is mainly due to monounsaturated free fatty acid classes. Oleic acid alone mimicked the *in vivo* situation by increasing the affinity constant of CBG for cortisol (three-fold) and reducing the number of binding sites (two-fold), whereas saturated fats did not enhance the binding.[36] Addition of monounsaturated and polyunsaturated free fatty acids to purified human CBG enhanced CBG binding activity in a concentration-dependent fashion.[34] Garrel et al.[32] showed that CBG and cortisol levels did not indicate any changes by the consumption of n-3 and n-6 fatty acids (Figure 19.2).

19.5 VITAMINS

In the presence of a chronically insufficient vitamin supply verified by repeated measurements of the vitamin parameters, many unfavorable psychometric findings in the corresponding deficiency groups were obtained for vitamin C, thiamin, riboflavin, cobalamin, and folate, depending on the degree of insufficient vitamin supply.[5] Administration of folic acid, vitamin C, and to a lesser extent thiamin, as compared to placebos, in men with an initial suboptimal folate status, led to a decreased emotional lability, increased activeness and concentration, higher extroversion and lower introversion, greater self-confidence, and a markedly improved mood.[5] In volunteers with an initial mild-to-moderate vitamin C deficiency, supplementation led to decreased nervousness, less depression, and increased emotional lability.[5]

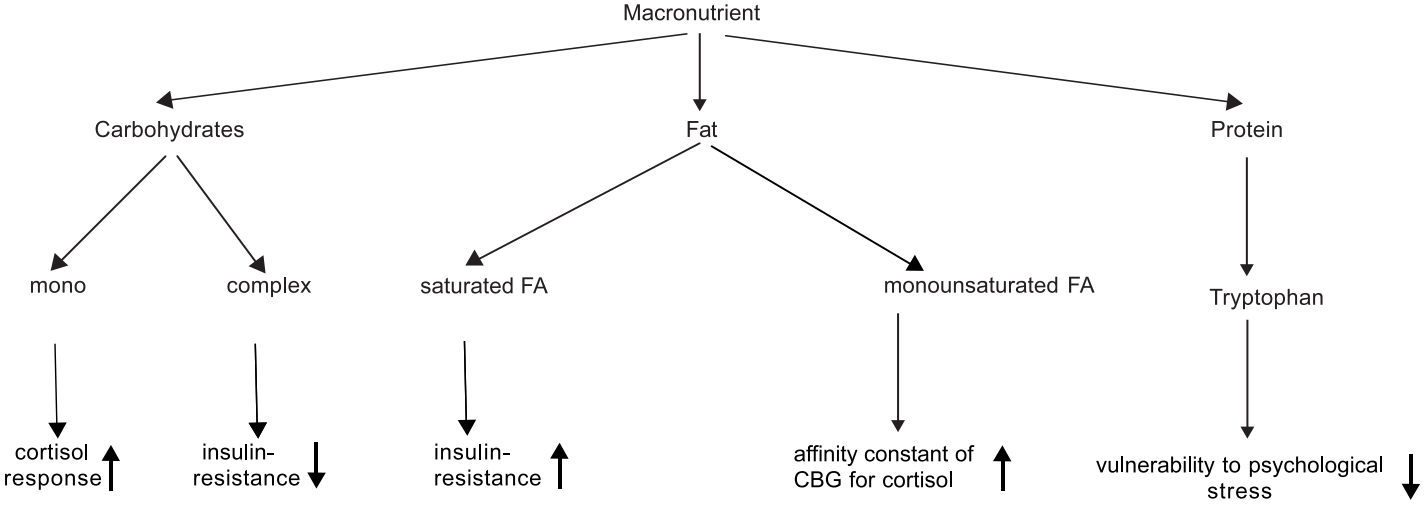

FIGURE 19.2

19.5.1 Vitamin C

It has long been known that endocrine organs are exceedingly high in the concentration of vitamin C per weight of tissue as compared with nonendocrine organs.[37] Ascorbic acid exceeds the functions of a vitamin, since it not only has its known cofactor roles for several enzymes, but also affects the regulation of the levels of the circulating thyroid and adrenal cortical hormones.[38] Differing plasma concentrations of ascorbic acid regulate *in vivo* steroidogenesis by altering the activity of the membrane-bound enzyme adenylate cyclase.[39] Ascorbic acid is essential for optimal steroid hormone functions and this suggests an involvement of ascorbic acid in steroid synthesis mechanisms.[40] Vitamin C depletion led to a significant increase in plasma cortisol without an increase in ACTH.[41] In animal studies, ascorbic acid deficiency caused an increase in plasma cortisol concentration.[42] In humans there was a distinct increase of plasma cortisol about 2 h after vitamin C application. This increase was concomitant with an increase in urinary 17-hydroxycorticosteroids.[43] In rats, vitamin C pretreatment enhanced the release of endogenous glucocorticoid such as to delay the turnover of the tracer cortisol in plasma.[44]

Vitamin C depletion led to a significant increase in plasma cortisol without an increase in ACTH.[41]

19.5.2 Vitamin B_6

There are *in vivo* effects of steroids that are altered depending on vitamin B_6 status. The *in vivo* action of pyridoxal phosphate does not appear to involve a change in receptor number or binding capacity of the hormone.[45] Evidence accumulated over the past decade suggests that vitamin B_6 may function as a physiological regulator of steroid hormone action.[46] Induction of vitamin B_6 deficiency in rats altered the function of the glucocorticoid receptor such that at low cellular concentrations of pyridoxal phosphate there was an increased translocation of the receptor complex to the nucleus, whereas at normal or high levels nuclear translocation of steroid receptor complex was diminished.[47]

High concentrations of pyridoxal phosphate suppress activation of transcription, while vitamin deficiency enhances responsiveness to steroid hormone.[48] Further, pyridoxine deficiency states are associated with decreased GABA and increased central nervous system irritability.[49] Also, pyridoxine is essential in the conversion of L-dihydroxyphenylalanine to dopamine. Side effects of excessive L-dihydroxyphenylalanine include dystonia and dyskinesia (Figure 19.3).[49]

19.5.3 Vitamin E

Vitamin E, as the major chain-breaking lipid-soluble antioxidant, would be expected to be important for functional integrity of all biological membranes. A deficiency of vitamin E results in an number of pathological changes in muscle, reproductive, cardiovascular, and nervous systems.[50] Animal studies indicated that chickens raised on a vitamin E-deficient diet developed cerebellar encephalomalacia.[51] Einarson and Telford[52] found that prolonged vitamin E-deficiency in the rat caused demyelination of axons and gliosis in the gracilis and cuneate nuclei.

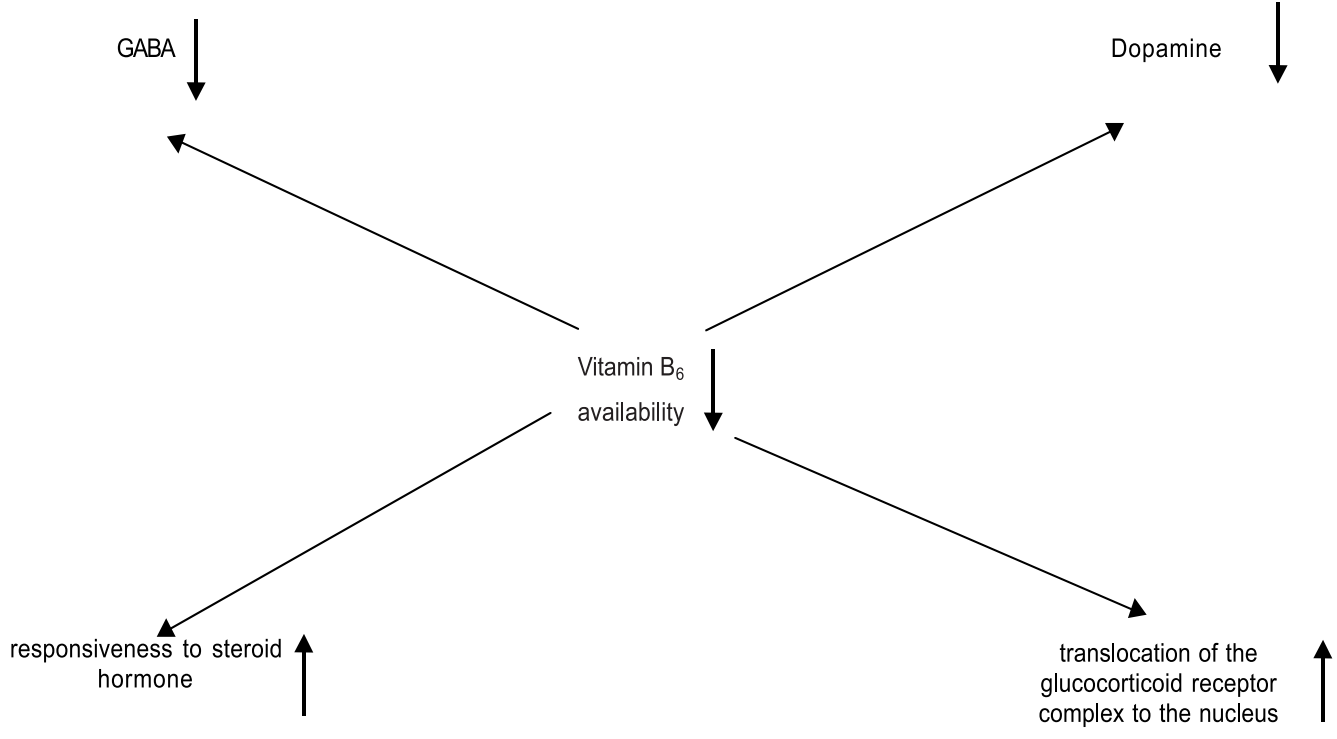

FIGURE 19.3

The importance of vitamin E for maintaining the structural and functional integrity of nervous system in humans has now been well established. Clinical data on the role of vitamin E in nervous system diseases indicate that even though a dietary vitamin E deficiency is very rare in humans, a symptomatic vitamin E deficiency exists in association with abetalipoproteinemia, chronic cholestatic hepatobilliary diseases, cystic fibrosis, short bowel syndrome, and isolated vitamin E deficiency syndrome.[53]

The neuropathologic changes of vitamin E deficiency in humans are very similar to those in rats and rhesus monkeys,[53] and the resulting neurological syndrome is characterized by areflexia, peripheral neuropathy, cerebellar involvement with gait and limbo ataxia, and decreased propioception and vibration sense.[54]

Nelson et al.[55] compared the neuropathologic changes in vitamin E-deficient rats and monkeys and described the process as a distal and dying-back type of axonopathy. Concentrations of α-tocopherol in the distal and proximal parts of the sciatic nerve are not different. This suggests that susceptibility of the distal portion of peripheral nerves to vitamin E deficiency must be due to reasons other than lower levels of tocopherol in distal regions.[56] A defect in the fast anterograde and retrograde axonal transport has been reported in vitamin E-deficient rats.[57]

Cerebellum seems to be active in the metabolic utilization of vitamin E. This could be the reason for cerebellar damage during experimental vitamin E deficiency and for the incidence of cerebellar symptoms in clinical vitamin E deficiency.[56]

19.6 PHYTOCHEMICALS

Persons who eat green or yellow vegetables every day show a lower incidence of stress syndrome (irritation, sleeplessness) than those who do not eat them daily.[58] Plant foods contain a wide variety of phytochemicals that have the potential to modulate stress, e.g., carotinoids, flavonoids, and sulfides.

Human studies indicated that β-carotene suppresses the secretion of CRH dose-dependently.[59] It is also suggested that the effective site of β-carotene is the hypothalamus, where β-carotene suppressed the secretion of CRH induced by exercise stress, and consequently the secretion of ACTH in the pituitary. As CRH stimulates the sympathetic neuron,[60] β-carotene also inhibited the stimulation of noradrenaline and adrenaline secretion through the suppression of CRH secretion.[59]

Rats fed diets containing extracts high in both flavonoid levels as well as total antioxidant activity for 6 weeks before being subjected to 48 h of exposure to 100% normobaric O_2 showed no loss in striatal muscarinic or cerebellar GABAergic receptor sensitivity.[61] These oxygen-induced decreases in neuronal function have been shown to be sensitive to aging and have been associated with behavioral deficits.[62]

Recent studies have indicated that garlic extract was effective in preventing brain atrophy[63] as well as learning and memory impairments[64] in the senescence-accelerated mouse.

19.7 VEGETARIAN DIETS

Nutritional studies suggest that the change from their customary vegetarian diet to a cafeteria-fed Western diet for 3 weeks in a group of 13 elderly black South African men was associated with a decrease in plasma testosterone.[65] Comparisons of hormone levels in vegetarians and omnivores[66] also indicate that steroid hormone metabolism can be influenced by diet. Not only diet but also stress influences testosterone level. Also, chronic stress appears to decrease testosterone both in animals and humans.[14,15] Furthermore, an increase of testosterone in response to acute stress is found in successful (low stress) male baboons, while subordinate (chronically stressed) males show a decrease.[67] Thus, changes in nutritional behavior could cause changes in endocrine balance and eventually in stress response.

19.8 ALCOHOL

Alcohol affects the endocrine system in healthy subjects. Earlier studies showed that a high dose of ethanol stimulates adrenal catecholamine secretion and urinary excretion[68] but inhibits luteinizing hormone (LH) secretion.[69] Also, alcohol affects cortisol[70] and dehydroepiandrosterone sulfate.[71] In the premenopausal women alcohol consumption did increase the concentrations of cortisol.[72] Detoxified alcoholics and controls had similar baseline cortisol levels; the alcoholics showed an attenuated cortisol response to the combined stressors. Therefore, higher stress cortisol values were seen in the patients with the most severe withdrawal symptoms.[73]

Animal models of alcohol dependence demonstrated decreased sensitivity to GABAergic agonists and enhanced sensitivity to GABA inverse agonists.[74]

19.9 CONCLUSION

Modification of the diet and changes in frequency of the diet intake may be helpful in stress management. It is of great importance to eat properly. A large part of the diet has to be of complex carbohydrates. In general, foods of plant origin have to be preferred. Reduction and modification of dietary fat may be helpful. In particular, a diet rich in monounsaturated and n-3 fatty acids is advisable. These modifications can produce consistent changes in concentrations of cortisol and its binding globulin. Further, plant foods are rich in phytochemicals, trace elements, and vitamins, which show a variety of positive effects on health. Also, consumption of green or yellow vegetables every day may lower the incidence of some stress syndromes (e.g., irritation and sleeplessness).

REFERENCES

1. Gold, P. W., Goodwin, F. K., and Chrousos, G. P., Clinical and biochemical manifestations of depression. Relation to the neurobiology of stress. *N. Engl. J. Med.,* 319, 348 and 413, 1988.

2. Michelson, D. and Gold, P. W., Pathophysiologic and somatic investigations of hypothalamic-pituitary-adrenal axis activation in patients with depression, in *Neuroimmuno-Modulation. Molecular Aspects, Integrative Systems, and Clinical Advances*, McCann, S. M., Sternberg, E. M., Lipton, J. M., Chrousos, G. P., Gold, P. W., and Smith, C. C., Eds., New York Academy of Sciences, New York, 1988, 722.
3. Nilsson, P. M., Moller, L., and Solstad, K., Adverse effects of psychosocial stress on gonadal function and insulin levels in middle-aged males. *J. Intern. Med.*, 237(5), 479, 1995.
4. Moberg, E., Kollind, M., Lins, P. E., and Adamson, U., Acute mental stress impairs insulin sensitivity in IDDM patients. *Diabetes,* 37(3), 247, 1994.
5. Heseker, H., Kübler, W., Pudel, V., and Westenhöffer, J., Psychological disorders as early symptoms of a mild-to-moderate vitamin deficiency, in *Beyond Deficiency. New Views on the Function and Health Effects of Vitamins*, Sauberlich, H. E. and Machlin, L. J., Eds., New York Academy of Sciences, New York, 1992, 352.
6. Tannenbaum, B., Rowe, W., Sharma, S., Diorio, J., Steverman, A., Walker, M., and Meaney, M. J., Dynamic variations in plasma corticosteroid-binding globulin and basal HPA activity following acute stress in adult rats. *J. Neuroendocrinol.,* 9(3), 163, 1997.
7. Fleshner, M., Deak, T., Spencer, R. L., Laudenslager, M. L., Watkins, L. R., and Maier, S. F., A long-term increase in basal levels of corticosterone and a decrease in corticosteroid-binding globulin after acute stressor exposure. *Endocrinology,* 136(12), 5336, 1995.
8. Gayrard, V., Alvinerie, M., and Toutain, P. L., Interspecies variations of corticosteroid-binding globulin parameters. *Domest. Anim. Endocrinol.,* 13(1), 35, 1996.
9. Bright, G. M., Corticosteroid-binding globulin influences kinetic parameters of plasma cortisol transport and clearance. *J. Clin. Endocrinol. Metab.* 80(3), 770, 1995.
10. Marti, O., Martin, M., Gavalda, A., Giralt, M., Hidalgo, J., Hsu, B. R., Kuhn, R. W., and Armario, A., Inhibition of corticosteroid-binding globulin caused by a severe stressor is apparently mediated by the adrenal but not by glucocorticoid receptors. *Endocrine,* 6(2), 159, 1997.
11. Moller, P., Wallin, H., and Knudsen, L. E., Oxidative stress associated with exercise, psychological stress and life-style factors. *Chem.-Biol. Interact.,* 102, 17, 1996.
12. Kiecolt-Glaser, J. K., Stephens, R. E., Lipetz, P. D., Speicher, C. E., and Glaser, R., Distress and DNA repair in human lymphocytes. *J. Behav. Med.,* 8, 311, 1985.
13. Tomei, L. D., Kiecolt-Glaser, J. K., Kennedy, S., and Glaser, R., Psychological stress and phorbol ester inhibition of radiation-induced apoptosis in human peripheral blood leukocytes. *Psychiat. Res.,* 33, 59, 1990.
14. Allen, P. I. M., Batty, K. A., Dodd, C. A. S., Herbert, J., Hugh, C. J., Moore, G. F., Seymour, M. J., Shiers, H. M., Stacey, P. M., and Young, S. K., Dissociation between emotional and endocrine responses preceding an academic examination in male medical students. *J. Endocrinol.,* 107, 163, 1985.
15. Leedy, M. G. and Wilson, M. S., Testosterone and cortisol levels in crewmen of U.S. Air Force fighter and cargo planes. *Psychosom. Med.,* 47(4), 333, 1985.
16. Simeon, D. T. and Grantham-McGregor, S., Effects of missing breakfast on the cognitive functions of school children of differing nutritional status. *Am. J. Clin. Nutr.,* 49, 646, 1989.
17. Chandler, A. M., Walker, S. P., Connolly, K., and Grantham-McGregor, S. M., School breakfast improves verbal fluency in undernourished Jamaican children. *J. Nutr.,* 125, 894, 1995.

18. Kanarek, R., Psychological effects of snacks and altered meal frequency. *Br. J. Nutr.,* 77(1), 105, 1997.
19. Smith, A., Ralph, A., and McNeill, G., Influences of meal size on post-lunch changes in performance efficiency, mood and cardiovascular function. *Appetite,* 16, 85, 1991.
20. Craig, A. and Richardson, E., Effects of experimental and habitual lunch-size on performance, arousal, hunger and mood. *Int. Arch. Occup. Environ. Health,* 61, 313, 1989.
21. Kanarek, R. B. and Swinney, D., Effects of food snacks on cognitive performance in male college students. *Appetite,* 14, 15, 1990.
22. Smith, A., Kendrick, A., Maben, A., and Salmon, J., Effects of breakfast and caffeine on cognitive performance, mood and cardiovascular functioning. *Appetite,* 22, 39, 1994.
23. Anderson, K. E., Rosner, W., and Khan, M. S., Diet-hormone interaction: Proteins/carbohydrate ratio alters reciprocally the plasma levels of testosterone and cortisol and their respective binding globulin in man. *Life Sci.,* 40, 1761, 1987.
24. Markus, C. R., Panhuysen, G., Tuiten, A., Koppeschaar, H., Fekkes, D., and Peters, M. L., Does carbohydrate-rich, protein-poor food prevent a deterioration of mood and cognitive performance of stress-prone subjects when subjected to a stressful task? *Appetite,* 31(1), 49, 1998.
25. Christeff, N., Michon, C., Goertz, G., Hassid, J., Martheron, S., Girard, P. M., Coulaud, J. P., and Nunez, E. A., Abnormal free fatty acids and cortisol concentrations in the serum of AIDS patients. *Eur. J. Cancer Res. Clin. Oncol.*, 24, 1179, 1988.
26. Benton, D. and Sargent, J., Breakfast, blood glucose and memory. *Biol. Psychiatry,* 33, 207, 1992.
27. Parker, P. Y. and Benton, D., Blood glucose levels selectively influence memory for word list dichotically presented to the right ear. *Neuropsychology,* 33, 843, 1995.
28. Craft, S., Dagogo-Jack, S. E., Wiethop, B. V., Murphy, C., Nevins, R. T., Fleischman, S., Rice, V., Newomer, J. W., and Cryer, P. E., Effects of hyperglycemia on memory and hormone levels in dementia of the Alzheimer type: a longitudinal study. *Behav. Neurosci.,* 107, 926 1993.
29. Kopelman, M. D., The cholinergic neurotransmitter system in human memory and dementia: a review. *Q. J. Exp. Psychol.,* 38A, 535, 1986.
30. Tucek, S., Acetylcoenzyme A and the synthesis of acetylcholine in neurones: a review of recent progress. *Gen. Phys. Biochem.,* 2, 313, 1983.
31. Durkin, T. P., Messier, C., de Boer, P., and Westernik, B. H. C., Raised glucose levels enhance scoplamine-induced acetylcholine overflow from the hippocampus: an in vivo microdialysis study in rat. *Behav. Brain Res.,* 49, 181, 1992.
32. Garrel, D. R., Razi, M., Larivire, F., Jobin, N., Bonneton, A., and Pugeat, M., Improved clinical status and length of care with low fat nutritional support in burn patients. *J. Parenteral Enteral Nutr.,* 19(6), 482, 1995.
33. Martin, M. E., Vranckx, R., Benassayag, C., and Nunez, E. A., Modifications of the properties of human sex steroid-binding protein by nonesterified fatty acids. *J. Biol. Chem.,* 261, 2954, 1986.
34. Martin, M. E., Benassayag, C., and Nunez, E. A., Selective changes in binding and immunological properties of human corticosteroid binding globulin by free fatty acids. *Endocrinology,* 123, 1178, 1988.
35. Haourigui, M., Vallette, G., Martin, M. E., Sumida, C., Benassayag, C., and Nunez, E. A., In vivo effect of free fatty acids on the specific binding of glucocorticoids to corticosteroid binding globulin and liver receptors in immature rats. *Steroids,* 59, 46, 1994.

36. Haourigui, M., Sakr, S., Martin, M. E., Thobie, N., Girard-Globa, A., Benassayag, C., and Nunez, E. A., Postprandial free fatty acids stimulate activity of human corticosteroid binding globulin. *Am. J. Physiol.,* 269(6, Pt. 1), E1067, 1995.
37. Giroud, A., Repartion de la vitamin C dans l'organisme. *Ergeb. Vitam. Hormonforsch.,* 1, 68, 1938.
38. Degkwitz, E., Neue Aspekte der Biochemie des Vitamins C. *Z. Ernahrungswiss,* 24(4), 219, 1985.
39. Doulas, N. L., Constantopoulos, A., and Litsios, B., Effect of ascorbic acid on guinea pig adrenal adenylate cyclase activity and plasma cortisol. *J. Nutr.,* 117(6), 1108, 1987.
40. Goralczyk, R., Moser, U. K., Matter, U., and Weiser, H., Regulation of steroid hormone metabolism requires L-ascorbic acid, in *Beyond Deficiency. New Views on the Function and Health Effects of Vitamins,* Sauberlich, H. E. and Machlin, L. J., Eds., New York Academy of Sciences, New York, 1992, 349.
41. Redmann, A., Mobius, K., Hiller, H. H., Oelkers, W., and Bahr, V., Ascorbate depletion prevents aldosterone stimulation by sodium deficiency in the guinea pig. *Eur. J. Endocrinol.,* 133(4), 499, 1995.
42. Enwonwu, C. O., Sawiris, P., and Chanaud, N., Effect of marginal ascorbic acid deficiency on saliva level of cortisol in the guinea pig. *Arch. Oral Biol.,* 40(8), 737, 1995.
43. Kodama, M., Kodama, T., Murakami, M., and Kodama, M., Autoimmune disease and allergy are controlled by vitamin C treatment. *In Vivo,* 8, 251, 1994.
44. Kodama, M., Inoue, F., Kodama, T., and Kodama, M., Intraperitoneal administration of ascorbic acid delays the turnover of 3H-labelled cortisol in the plasma of an ODS rat, but not in the Wistar rat. Evidence in support of the cardinal role of vitamin C in the progression of glucocorticoid synthesis. *In Vivo,* 10(1), 97, 1996.
45. Leklem, J. E. and Reynolds, R. D., *Clinical and Physiological Applications of Vitamin B_6.* Allan R. Liss, New York, 1988.
46. Compton, M. M. and Cidlowski, J. A., Vitamin B_6 and glucocorticoid action. *Endocrinol. Rev.,* 7, 140, 1986.
47. DiSorbo, D. M., Phelps, D. S., Ohl, V. S., and Litwack, G., Pyridoxine deficiency influences the behavior of the glucocorticoid receptor complex. *J. Biol. Chem.,* 255, 3866, 1980.
48. Allgood, V. E., Powell-Oliver, F. E., and Cidlowski, J. A., The influence of vitamin B_6 on the structure and function of the glucocorticoid receptor, in Vitamin B_6, Dakshinamurti, K., Ed., New York Academy of Sciences, New York, 1990, 452.
49. Bernstein, A. L., Viatmin B6 in clinical neurology, in *Vitamin B_6,* Dakshinamurti, K., Ed., New York Academy of Sciences, New York, 1990, 250.
50. Scot, M. L., Studies on vitamin E and related factors in nutrition and metabolism, in *Fat Soluble Vitamins*, Deluca, H. F. and Suttie, J. W., Eds., The University of Wisconsin Press, Madison, WI, 335, 1969.
51. Pappenheimer, A. M. and Goettsch, M., A cerebellar disorder in chicks, apparently of nutritional origin. *J. Exp. Med.,* 53, 11, 1931.
52. Einarson, L. and Teleford, I. R., Effect of vitamin E deficiency on the central nervous system in various laboratory animals. *Dan. Videnskabernes Selskab,* 11, 1, 1960.
53. Sokol, R. J., Vitamin E and neurologic function in man. *Free Rad. Biol. Med.*, 6, 189, 1989.
54. Muller, D. P. R., Lloyd, J. K., and Wolff, O. H., Vitamin E and neurological function. *Lancet,* 1(8318), 225, 1983.

55. Nelson, J. S., Fitch, C. D., Fischer, V. W., Broun, G. O., and Chou, A. C., Progressive neuropathological lesions in vitamin E-deficient rhesus monkeys. *J. Neuropathol. Exp. Neurol.,* 40, 166, 1981.
56. Vatassery, G. T., Vitamin E, neurochemistry and implications for neurodegeneration in Parkinson's disease, in *Beyond Deficiency. New Views on the Function and Health Effects of Vitamins,* Sauberlich, H. E. and Machlin, L., Eds., New York Academy of Sciences, New York, 1992, 97.
57. Southam, E., Thomas, P. K., King, R. H. M., Gross-Sampson, M. A., and Muller, D. P. R., Experimental vitamin E deficiency in rats. *Brain,* 114, 915, 1991.
58. Hirayama, T., Personal communication, 1992.
59. Hasegawa, T., Anti-stress effect of β-carotene, in *Carotenoids in Human Health*, Canfield, L. M., Krinsky, N. I., and Olson J. A., Eds., New York Academy of Sciences, New York, 1993, 281.
60. Kurosawa, M., Sato, A., Swenson, R. S., and Takahashi, Y., Sympatho-adrenal medullary functions in response to intracerebroventricularly injected corticotropin-releasing factor in anesthetized rats. *Brain Res.,* 367(1-2), 250, 1986.
61. Chadman, K., Joseph, J. A., Shukitt-Hale, B., Prior, R., Taglialatela, G., and Bickford, P. C., Diets high in antioxidant activity prevent deleterious effects of oxidative stress on signal transduction and nerve growth factor. *Soc. Neurosci. Abstr.,* 23, 348, 1997.
62. Joseph, J. A., Shukitt-Hale, B., Denisova, N. A., Prior, R. L., Cao, G., and Martin, A., Long-term dietary strawberry, spinach, or vitamin E supplementation retards the onset of age-related neuronal signal-transduction and cognitive behavioral deficits. *J. Neurosci.,* 18(19), 8047, 1998.
63. Moriguchi, T., Saito, H., and Nishiyama, N., Anti-aging effect of aged garlic extract in the inbred brain atrophy mouse model. *Clin. Exp. Pharmacol. Physiol.,* 24, 235, 1997.
64. Nishiyama, N., Moriguchi, T., and Saito, H., Beneficial effects of aged garlic extract on learning and memory impairment in the senescence-accelerated mouse. *Exp. Gerontol.,* 32, 149, 1997.
65. Hill, P., Wynder, E. L., Garbaczewski, L., and Walker, A. R. P., Effect of diet on plasma and urinary hormones in South African black men with prostatic cancer. *Cancer Res.,* 42, 3864, 1982.
66. Goldin, B. R., Adlercreutz, H., Gorbach, S. L., Warram, J. H., Dwyer, J. T., Swenson, L., and Woods, M. N., Estrogen excretion patterns and plasma levels in vegetarian and omnivorous women. *N. Engl. J. Med.,* 307, 1542, 1982.
67. Sapolsky, R. M., The endocrine stress-response and social status in the wild baboon. *Horm. Behav.,* 16, 279, 1982.
68. Adams, M. A. and Hirst, M., Ethanol-induced cardiac hypertrophy: correlation between development and the excretion of adrenal catecholamines. *Pharmacol. Biochem. Behav.,* 24, 33, 1986.
69. Pohl, C. R., Guilinger, R. A., and van Thiel, D. H., Inhibitory action of ethanol on luteinizing hormone secretion by rat anterior pituitary cells in culture. *Endocrinology,* 120, 849, 1987.
70. London, S., Willett, W., Longcope, C., and McKinlay, S., Alcohol and other dietary factors in realtion to serum hormone concentrations in women at climacteric. *Am. J. Clin. Nutr.,* 53, 166, 1991.
71. Longcope, C., Adrenal and gonadal androgen secretion in normal females. *Clin. Endocrinol. Metab.,* 15, 213, 1986.

72. Reichman, M. E., Judd, J. T., Longcope, C., Schatzkin, A., Clevidence, B. A., Nair, P. P., Campbell, W. S., and Taylor, P. R., Effect of alcohol consumption on plasma urinary hormone concentrations in premenopausal women. *J. Natl. Cancer Inst.,* 85, 722, 1993.
73. Bernardy, N. C., King, A. C., Parsons, O. A., and Lovallo, W. R., Altered cortisol response in sober alcoholics: an examination of contributing factors. *Alcohol,* 13(5), 493, 1996.
74. Buck, K. J. and Harris, R. A., Benzodiazepine agonist and inverse agonist actions on GABAa receptor-operated chloride channels II chronic effects of ethanol. *J. Pharmacol. Exp. Ther.,* 253, 713, 1990.