MICRONUTRIENTS AND STRESS

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The term stress is used in a variety of contexts and may have different meanings to different people. It is widely accepted that both mental stress and nutritional factors are associated with the risk for a number of diseases, and that stress relief measures and dietary or nutritional interventions form part of the management of these diseases.[1] However, scientific evidence of a direct link between stress and nutrition is lacking, except in the case of the eating disorders and a few other psychiatric conditions.[2] To answer the question as to whether psychological stress influences micronutrient requirements or whether micronutrient interventions alleviate the effects of stress, it is necessary to study the common biological pathways whereby these factors influence health.

DEFINITION OF STRESS AND NATURE OF THE STRESS RESPONSE

One of the pioneers of modern stress research, the physician/physiologist Hans Selye, was the first to invoke the concept of a physiological response to a wide variety of stressors, both psychological and physical.[3] He coined the term 'general adaptation syndrome' (GAS) to describe the physiological process by which the organism responds to stressors and attempts to re-establish homeostasis.[4,5] The syndrome consists of three phases: alarm, resistance and exhaustion. During the alarm stage the organism detects a stressor and responds with activation of the sympathetic nervous system and adrenal medulla, the so-called 'fight or flight reaction' during which the body's defences are mobilised. The second stage — resistance — recruits the pituitary-adrenocortical axis to permit the organism to achieve optimal adaptation and maintain homeostasis. Exhaustion results when the organism depletes its adaptive resources and may give rise to disease or even death. Selye identified 'diseases of adaptation,' including hypertension, cardiovascular disease, kidney disease, peptic ulcer, hyperthyroidism and asthma.[4,5] In the past few decades a large body of research has confirmed a connection between stress and disease, and between stress management and reduced risk of, or reduced morbidity and mortality from, certain diseases.[3,6,7]

The neuro-endocrine response to psychological stress is extensively documented.[3,4,6-9] A twofold cascade of responses is triggered by higher brain centres in response to stimulation from a stressor, which involves the sympathetic nervous

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system and the hypothalamic-pituitary-adrenal (HPA) axis. Recent research has demonstrated that activation of the above pathways is not unitary and nonspecific. The response varies according to the nature and severity of the stimulus.[3,4] Psychological stress may be acute or chronic, positive or negative, minor or major. Most life stress, however, is caused by a combination of stressors, including those of a physical nature. Acute stress, if quickly resolved, does not appear to threaten health; in fact it may be beneficial.[3] On the other hand, prolonged severe stress has been shown to result in tissue damage and disease. It must also be borne in mind that people differ in their responsiveness to environmental threats and how they compensate.[3,10] Psychologists prefer to apply what is termed a 'multimodal-transactional model of stress'. This model comprises external pressures (stressors), internal pressures (individual perceptions, beliefs and characteristics) and coping resources, for example material or social. These three together will determine the individual's response: cognitive, sensory, behavioural and biological.[10]

A number of micronutrients have well-described functions concerned with the body's neuro-endocrine and metabolic response to stress. Consequently, certain micronutrients, notably vitamin C and some B vitamins, have been popularly labelled 'anti-stress factors'. The pill-popping 'mania' that has ensued in the USA and other developed countries has been harshly criticised by some experts.[1] The truth is that there are virtually no scientific data concerning micronutrient metabolism or requirements during psychological stress. Regarding the potential of micronutrients to modulate the stress response, or enhance coping with stress, occasional clinical trials, usually administering orthomolecular doses of certain vitamins, have yielded unconvincing results, and have largely been ignored by health scientists.[2]

Psychological stress and illness

Until the 1980s the medical profession favoured the opinion that most diseases were purely organic. A few disorders were acknowledged to be 'psychosomatic' in origin, particularly gastric ulcers, hypertension, asthma and migraine. In 1985 an editorial in the *New England Journal of Medicine* dismissed most reports of psychological influence on physical health as anecdotal and concluded ' . . . it is time to acknowledge that our belief in disease as a direct reflection of mental state is largely folklore'.[11] Just 4 years later the *Lancet* published a report of a carefully controlled study showing that breast cancer patients who were given supportive group therapy in addition to their medical treatment, survived twice as long after commencement of treatment as those who did not receive group therapy.[12] Two years after that the *New England Journal of Medicine* published the findings of a study by Cohen and colleagues, showing a highly significant association between reported exposure to stressful events and the incidence of the common cold.[13] As research continues the number of specific diseases that can be linked to stress grows. Those that have been most extensively researched are infectious diseases, cancer and coronary heart disease.[3,4] The effects of stress on relevant risk factors for these diseases — immunosuppression, oxidative stress, and elevations in blood pressure and blood lipids — are also well documented. It is noteworthy that both stress and nutritional imbalances are established risk factors for the above disorders, although neither stress nor malnutrition *per se* are regarded as causes. Other health states influenced by both stress and nutrition include psychiatric disorders and growth and development.

The immune system and infectious disease

Stress and the immune system

The past 15 years have seen the development of a new science, psychoneuroimmunology (PNI), which has been defined as 'the study of interactions between behaviour, the brain and the immune system'.[14-16] The main findings[17-21] indicate that in general, stress — particularly sustained, negative stress — has been shown to cause immunosuppression. In addition, certain personality types are associated with greater susceptibility to immunosuppression. Stress levels of cortisol suppress immune function in several ways, for example suppression of macrophage function, cytokine production (interleukin-1, interleukin-2), production of T-lymphocyte subsets (CD4 cells), B-lymphocyte activity and natural killer (NK) cell activity.[3] A recent meta-analysis has shown that suppression of NK cell activity is a reliable correlate of acute and chronic life stress.[15] However, reduced lymphocyte response is a more reliable marker for chronic stress alone.[22] Researchers in this field have focused extensively on the association between stress and infectious illnesses. At least seven human studies which used experimental inoculation (viral challenge) with rhinovirus or influenza virus, demonstrated significant associations between high levels of psychological stress and incidence of upper respiratory tract infections.[15] Regarding latent viral infections, 16 human studies so far have shown that acute or chronic psychological stressors are associated with high antibody levels and recurrent outbreak of symptoms of herpes simplex virus, Epstein-Barr virus (in association with elevated cortisol levels), cytomegalovirus and infectious mononucleosis.[15]

Evidence for an association between stress and bacterial infections is convincing in animal studies, but only weakly so in human studies.[15] Nevertheless, a few studies have shown an association between tuberculosis and severe emotional stress, such as bereavement.[9,15]

Micronutrients and the immune system

The role of micronutrients in immunity has recently been reviewed.[23] As far back as the 1960s, Scrimshaw and co-workers noted that 'no nutritional deficiency is more synergistic with

infectious disease than that of vitamin A'.[24] It has been repeatedly associated with major morbidity and mortality from infectious diseases, particularly measles and diarrhoeal disease in young children in developing countries. Many studies have shown that high-dose vitamin A supplements reduce the occurrence and severity of measles and its complications, and improve survival in children. It has also recently been reported that vitamin A speeds up recovery from measles in well-nourished children. Maternal health and survival also improve significantly with supplementation before, during and after pregnancy.[25,26] Furthermore, recent research has shown that vitamin E plays an important role in immune function.[23] Several animal and human studies have shown that vitamin E deficiency is associated with an inadequate immune response, while higher than recommended amounts have enhanced the immune response in healthy infant and elderly populations. Both humoral and cell-mediated responses appear to benefit, while an anti-oxidant cocktail enhances this effect. Of all the vitamins, vitamin C is probably the most controversial because of the public interest aroused by Linus Pauling's claims that it can prevent the common cold. However, more than a dozen clinical trials have failed to show a beneficial effect of vitamin C in this regard. One recent study has shown that ascorbic acid supplements reduced the rate and severity of upper respiratory tract infections in endurance athletes.[27] Vitamin C's claimed beneficial effects on health are probably mainly due to its anti-oxidant functions.

CANCER

Psychological stress and cancer

The belief that psychosocial factors play a role in cancer has been evident throughout the documented history of medicine, going back at least to the second century AD.[14] Epidemiological studies conducted since the 1950s have confirmed that intense emotional stress and certain personality characteristics (introverted, depressed, obsessive) increase the risk for several types of cancer.[14,28] Also, adverse psychosocial factors such as stress, poor coping skills and social isolation reduce survival rate in cancer patients.[12,14,28] Since the mid-1980s, several carefully controlled interventions have shown that psychosocial support enhances survival in patients receiving cancer treatment. The study by Spiegel and co-workers[12] showed that 10 years later patients with breast cancer who received group therapy, mental relaxation and development of coping skills had twice the survival rate compared with the controls.[12] Several studies have also demonstrated enhanced immune function in cancer patients receiving psychological intervention.[14]

Micronutrients and cancer

Vitamin A deficiency is associated with a higher incidence of cancer and increased susceptibility to carcinogens, whereas increased levels of retinoids can mediate resistance to some carcinogenic agents.[23] Supplements of vitamin A and related retinoids, for example all-*trans* retinoic acid, appear to reduce the risk of breast cancer in women with very low intakes and are beneficial for the treatment of some leukaemias.[23,29] Several mechanisms may be responsible for this enhanced tumour immunity: enhanced T-cytotoxic lymphocyte activity, NK cell activity, macrophage activity and apoptosis.[23] Cancer, as well as a number of other chronic diseases, have been linked to oxidative stress in the tissues.

OXIDATIVE STRESS

Oxidative stress may be defined as 'a cellular or physiological condition of elevated concentration of reactive oxygen species (ROS) that cause molecular damage to vital structures and functions'.[30] This implies a serious imbalance in the tissues between ROS generation and anti-oxidants. There is a mounting body of evidence that oxidative stress contributes to the development of a number of chronic diseases, including cancer, cardiovascular disease, chronic inflammatory diseases, neurodegenerative diseases and the ageing process.[31] Conversely, the production of ROS is enhanced by disease and environmental stressors, for example acute infections, chronic inflammatory diseases, cancer, psychological stress, protein-energy malnutrition, low intake of dietary anti-oxidants, cigarette smoke, air pollution, industrial toxins, insecticides, anticancer drugs and radiation.[32]

Psychological stress and oxidative stress

The idea that psychological stress may give rise to oxidative stress is a novel one, and emerges from the evidence of a few animal and human studies. The first evidence that oxidative damage to nuclear DNA is induced by psychological stress was observed in the livers of rats exposed to conditioned emotional stimuli.[33] Two recent human studies have also demonstrated enhanced production of ROS, including lipid peroxides, during periods of psychological stress.[33,34] One of these, a controlled trial, showed a significant reduction in serum lipid peroxide levels in subjects enrolled for a stress reduction programme involving transcendental meditation.[33] Although this field is nascent, it appears to warrant further investigation.

Anti-oxidant nutrients and oxidative stress

The anti-oxidant nutrients, vitamin E, vitamin C, β-carotene and selenium, have been the focus of a large body of research, with specific regard to their functions in the human body and their potential for disease prevention.[31] This interest has arisen, firstly because anti-oxidant defences within the body have been shown to play an important role in preventing molecular damage by reactive oxygen species, and secondly, because of the consistent observation from epidemiological studies that diets rich in plant foods, and therefore anti-oxidants, appear to reduce the risk of certain diseases.[31] In general, the findings

from basic research and observational epidemiological studies support the hypothesis that anti-oxidant vitamins protect against coronary heart disease (CHD) and cancer. This is particularly true for vitamin E and CHD.[31] Two recent heart trials have demonstrated beneficial effects of vitamin E in patients with established coronary heart disease. In one study of men who had previously had coronary artery bypass surgery, patients who took more than 100 IU of vitamin E daily demonstrated less coronary artery lesion progression as observed angiographically, than patients who took less than 100 IU daily.[35] In the Cambridge Heart Antioxidant Study (CHAOS), vitamin E supplementation (400 - 800 IU over 18 months) achieved a 77% reduction of risk of non-fatal myocardial infarction, but did not reduce overall cardiovascular mortality.[36] Regarding cancer, there is limited evidence for a beneficial effect of a combination of anti-oxidants. The Chinese Cancer Prevention Study (Linxian study) showed a 13% reduction in total cancer mortality, and a significant 21% reduction in gastric cancer mortality, in the group of subjects assigned to the combination of β-carotene, vitamin E and selenium.[37] This region had one of the world's highest rates of oesophageal and gastric cancer, and dietary intake of a number of micronutrients is known to be very low. Other studies have not confirmed that anti-oxidants hinder the progression of cancer.[31]

The human studies concerning the benefits of anti-oxidants reported to date have received wide criticism from reviewers, partly because of inconsistencies and weaknesses in study design, but also because of overemphasis on single nutrients taken over a relatively short period of time,[38] and on anti-oxidants in isolation from other food components.[31] Much more research needs to be done to provide the general public with scientifically valid recommendations regarding the optimal intake of anti-oxidant nutrients.[30] There is, however, strong support for raising the RDA for vitamin C from 60 mg/d to 200 mg/d.[39] This would probably help attenuate lung damage in smokers, and would be achieved by dietary means alone (about five servings of fruit and vegetables). In this regard, research has shown that consumption of an anti-oxidant-rich diet can reduce levels of oxidative stress and raise anti-oxidant status.[40]

CARDIOVASCULAR DISEASE

Stress and cardiovascular disease

Recent research has examined susceptibility to heart disease in persons experiencing stressful life events. Kawachi and colleagues have shown that nurses who perform rotating shift work for more than 6 years of their working lives have a significantly higher risk of heart disease and heart attack than nurses who work normal daytime shifts.[41] The work of Friedman and Rosenman demonstrated that the so-called type A personality is particularly prone to heart disease.[4] Subsequent research, however, has shown that this definition is an over-simplification. Only certain aspects of the type A personality appear to be harmful to health, namely, hostility, cynicism and impatience.[4] A recent study has found that type D personality was a significant predictor of long-term mortality in patients with established CHD, independent of biomedical risk factors.[42] Type D personality is characterised by the chronic suppression of negative emotion, and is associated with depression and social isolation. The authors caution that their findings cannot prove a cause-effect relationship between personality and mortality, but have established the prognostic power of type D personality. Stress or personality may promote heart disease through several pathophysiological mechanisms. It is well established that acute stress elevates blood pressure[3] and that chronic stress may give rise to hypertension,[6,7] a major risk factor for CHD. Recent models of the atherogenic process give a major role to the immune and inflammatory processes. One of the earliest events in arterial lesion formation is the adhesion of monocytes and T lymphocytes to the endothelium. Cytokines and other chemicals are mediators in this process.[23,31] Mental stress may also elevate serum lipids,[4] and by potentiating coronary spasm and platelet release, give rise to silent myocardial ischaemia.[42] Stress and personality type may also promote disease indirectly by influencing lifestyle and health-related behaviours. For example, a recent Australian study in male and female office workers showed that maladaptive stress-related coping scores were strongly associated with obesity, alcohol consumption, 'atherogenic' diet and low physical activity. Blood pressure was significantly correlated with all the above lifestyle measures, particularly in males, but not with stress *per se*. Females had lower blood pressures, better coping scores and healthier lifestyles, although their stress scores did not differ from male scores.[43]

Micronutrients and cardiovascular disease

Vitamin E is of particular interest, not only because of its anti-oxidant properties, but also because of a newly emerging role in immune function. Basic research has shown that vitamin E is involved with cytokine production, production of lipid mediators, platelet function, proliferation of smooth-muscle cells, control of vascular tone, as well as the interaction of the endothelium with immune and inflammatory cells.[23,31] The vitamin E modulation of these functions provides a compelling mechanistic link for the beneficial effect of vitamin E on atherosclerosis that has been observed in animal, human and epidemiological studies.

In addition to the role of the anti-oxidant nutrients, there is some evidence supporting a preventive role of calcium and magnesium in hypertension. A recent meta-analysis of calcium supplementation studies between 1966 and 1994 found that calcium supplementation may lead to a small reduction in systolic but not diastolic blood pressure. It is possible that calcium supplementation could lead to a larger and important

effect of calcium on blood pressure in subpopulations, and ongoing research is expected to clarify this.[44] An inverse relationship has been reported between dietary magnesium and blood pressure.[45] Magnesium is an inhibitor of vascular smooth-muscle contraction and thus could act as a vasodilator. However, clinical trials involving magnesium supplementation have yielded conflicting results, possibly because of confounding variables. Routine supplementation is therefore not recommended.

Comprehensive lifestyle changes

Most coronary heart disease prevention programmes now incorporate multiple intervention strategies, including stress management and dietary modification. The Lifestyle Heart Trial has shown convincingly how a comprehensive intervention package was able to bring about regression of coronary atherosclerosis.[46] In a prospective, randomised control trial, patients in the experimental group were instructed to follow a programme which included a very low-fat (10% of total energy) vegetarian diet, moderate aerobic exercise, stopping smoking, stress management training and group support. The experimental group patients had a 91% reduction in angina after 1 year and 72% after 4 years. Quantitative coronary angiography showed a significant reduction in stenosis after 1 year and an even greater improvement after 4 years. All these measures showed an overall progression of atherosclerosis in the control group. Also, the number of coronary events was more than twice as high in the control group as in the treatment group.

MENTAL HEALTH

Depression is now regarded as one of the world's major disorders. A recent article in a national Sunday newspaper reported that depression in the USA is more widespread than cancer, AIDS and heart disease.[47]

Stress and depression

Although depressive illness results from an interaction between genetic predisposition and environmental stress, for the commonest forms of depression the influence of environmental stress is believed to be the greater of the two.[48] The mechanisms whereby stress induces depression are currently the subject of a large body of research. The neuro-endocrine response to severe negative stressors has been shown to be driven by the HPA axis.[48] In humans, there is evidence of increased adrenocortical activity and altered immune function following bereavement. Hypertrophy of the adrenal gland and a reduction in both glucocorticoid and mineralocorticoid receptor numbers have been reported in chronically stressed patients.[48] Alterations in acute-phase proteins have also been shown to occur.[49] Long-lasting brain changes involve neurotransmitters, neuropeptides and receptors. Although only limited data are available, early research suggests that long-term consequences could translate into changes at the gene level.[48]

Micronutrients and depression

Vitamins in general, and B-group vitamins in particular, play important metabolic roles in the nervous system. The use of B vitamins in the treatment of psychiatric conditions has been described previously, for example vitamin B_6 in depression[50] and niacin in schizophrenia.[51] However, clinical application of nutritional protocols in the mental health field remains minimal. A recent publication provides a comprehensive review of this field.[2]

Evidence that folate may have a role in alleviating depressive illness has recently been discussed.[52] Clinical trials have shown that when folate-deficient depressed patients are given folate in addition to antidepressant medication, they show a significantly better clinical response than patients who receive a placebo.[53] Moreover, in elderly patients with depressive disorders but no evidence of folate deficiency, folate alone was associated with an 81% response rate after 6 weeks.[54] The mechanisms whereby folate exerts its neuropsychiatric effects are believed to involve the one-carbon-cycle required for many transmethylation reactions in the central nervous system (CNS). These include the metabolism of monoamine neurotransmitters and melatonin and the synthesis, repair and recombinations of nucleic acids.[52]

Micronutrients and mood

In a recent double-blind controlled trial, healthy young adults took a vitamin supplement (10 times the RDA of 6 B vitamins, ascorbic acid and *dl*-α-tocopherol and 3 334 IU of vitamin A) or placebo for one year.[55] The 'mood' and 'mental health' of women improved significantly after 12 months. This improvement correlated best with the biochemical status of riboflavin and pyridoxine. Women in the lowest quartile of initial thiamin status showed significant improvements in thiamin status and mood after 3 months.

No significant changes in any of the variables were seen in the placebo group. Interestingly, women showed a significantly greater response to the supplements than men. Earlier studies have shown that dietary modifications induce serotonin-mediated neural responses in females, but not in males.[56] Also noteworthy is the time it took for a significant change to occur.

CORRELATIONAL STUDIES LINKING DIET, STRESS AND HEALTH

Is there evidence that dietary factors can enhance the individual's stress-coping capacity and decrease the negative effects of stress on health? A mere handful of studies have been reported in the literature. A recent study of nearly 3 000 Japanese factory workers showed that 'better nutritional balance' and 'eating breakfast regularly' were two of the five lifestyle factors that were negatively associated with the grade

of psychological distress reported by workers, after the effects of confounding variables were controlled for.[57] A USA study of the dietary intakes of adult clients enrolled for psychotherapy found that clients with higher intakes of vitamin C and B-complex vitamins had lower anxiety levels and better stress-coping scores.[58] The difficulty with such studies is that they do not clearly differentiate between cause and effect. It is well established that stressful life situations influence dietary behaviour in various ways which may have negative health consequences.[1,10,43,59] It has also been reported that poor dietary habits correlate with high levels of family conflict.[60] Specifically, dependent or controlled wives were found to have poor dietary habits, whereas the independent wives tended to have better diets. In families with high degrees of cohesion, wives had diets with more protein and micronutrients.[60]

Biomarkers of chronic stress

Since it is widely acknowledged that chronic stress may be a risk factor for several diseases, it would be advantageous to identify physiological markers of chronic stress for use in population health surveys. A recent review in a public health journal has examined all the available scientific evidence and suggested that the following measures meet the criteria for such markers:[22] (*i*) elevated glycosylated haemoglobin; (*ii*) depressed lymphocyte stimulation; (*iii*) abnormal immunoglobulin G concentrations; and (*iv*) elevated plasma fibrinogen. Other potential biological markers include increased antibody titres for latent viruses, elevated peripheral benzodiazepine receptors and a high waist-hip-circumference ratio. Regarding NK cell activity, the authors concluded that this responds rapidly to both acute and chronic stress stimuli and could therefore not be recommended as a marker for chronic stress.

Micronutrient intake for optimal health

Dietary guidelines

Virtually all dietary guidelines in use for the past four decades have advocated the intake of more fruits, vegetables and grains, and a reduction of fat intake. At present the dietary guidelines of most countries advise people to eat at least five portions of fruit and vegetables daily.[61] The basis for this advice is the finding from numerous epidemiological studies that diets rich in plant foods are associated with a reduced risk of certain chronic diseases, particularly cardiovascular disease and certain cancers.[61-63]

It is clear from recent reviews that nutrition experts are not in complete agreement on the specifics of this guideline.[31,61] Nevertheless, there is broad agreement that, within the context of the overall healthy dietary pattern advocated by the dietary guidelines, eating more plant foods is beneficial.[61,64] Such a diet is rich in many micronutrients, including folate and anti-oxidant vitamins, as well as fibre. Also, plant foods are known to contain a considerable number of chemicals which do not have nutrient functions, but may be beneficial for health. These include several hundred carotenoids, phytochemicals[65] and plant sterols and sterolins.[66] Finally, diets high in plant foods usually provide less fat and energy. Surveys have shown that about three-quarters of the population in the USA does not achieve the recommended intake of fruit and vegetables per day.[62] The situation in South Africa appears to be no better.[67]

Recommended dietary allowances: are they adequate?

RDAs are guidelines intended for use in apparently healthy populations.[68] They are not intended to represent the actual physiological requirements of individuals, and do not take into account the metabolic effects of any form of stress. It has been documented that physiological stress affects the metabolism and blood levels of several micronutrients,[69,70] but the implications of this with regard to psychological stress remain to be determined. However, there is a growing body of expert opinion that questions whether the current RDAs for certain micronutrients are optimal for the prevention of disease. Some of these experts have recently proposed guidelines for the determination of 'optimal' RDAs.[30,39]

Micronutrient supplements — do we need them?

Given our current knowledge of micronutrient requirements, expert opinion does not advocate the taking of micronutrient supplements by apparently healthy individuals.[30,71] There is simply not enough evidence on which to base recommendations at this stage. On the other hand, there is good evidence to show that a healthy lifestyle, including a well-balanced, varied, prudent diet, will help prevent disease and promote well-being.

Micronutrient supplementation is therefore only advocated where deficiency is known to be present, or prophylatically in individuals or populations known to be at risk of deficiency. In addition, there are several clinical indications for the prescription of supplements. Expert bodies in the USA have recently provided guidelines for the use of micronutrient supplements.[72] Regarding the general public, it is recommended that if individuals choose to take supplements, they should be advised preferably to take a multivitamin and mineral supplement which is well balanced and provides not more than 50 - 150% of the RDAs.

Conclusions

Research has shown that both stress and micronutrients have a significant and demonstrable effect on body function and health. The effects of stress and micronutrients overlap in many areas of physical and mental well-being, and it is reasonable to assume that they have a synergistic effect and that each impacts on the other. While micronutrient requirements to

counter effects of stress are unknown, it is evident from research that a healthy lifestyle, including diet, exercise, adequate relaxation, social support and abstinence from harmful substances, is beneficial. Interventions should therefore be 'holistic' at the individual and community level, and also with regard to both developed and developing communities. Ongoing research is needed: (*i*) to elucidate the mechanisms whereby micronutrient- and plant-rich diets promote well-being; (*ii*) to provide information whereby nutrient requirements for optimal health, and thus appropriately revised RDAs, can be estimated; and (*iii*) to determine indications, if any, for micronutrient supplementation to alleviate stress.

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