ANALYTIC REVIEW

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An Epigenetics-Based, Lifestyle Medicine–Driven Approach to Stress Management for Primary Patient Care: Implications for Medical Education

Abstract: *Over 75% of patients in the primary care setting present with stress-related complaints. Curiously, patients and health care providers all too often see stress as a relatively benign sequela of many common illnesses such as heart disease, cancer, lung disease, dementia, diabetes, and mental illness. Unfortunately, various day-to-day lifestyle choices and environmental factors, unrelated to the presence of any disease, can cause stress sufficient to contribute to the development of various diseases/disorders and suboptimal health. There is evidence suggesting that counseling in stress management–oriented therapeutic interventions (as offered by lifestyle medicine–oriented practitioners) may prevent or reduce the onset, severity, duration, and/or overall burden of stress-related illnesses. Such counseling often involves considerations such as the patient's nutrition, physical activity, interest in/capacity to meditate, drug abuse/cessation, and so on. Unfortunately, lifestyle medicine–oriented approaches to stress management are rarely offered in primary care—the patient care arena wherein such counseling would likely be best received by patients. Would health care outcomes improve if primary care providers offered counseling in both stress management and positive lifestyle choices? The purpose of this article is to provide both primary care practitioners and educators in health care training programs with an introductory overview of epigenetics. An emerging field of science offering insights into how factors such as stress and lifestyle choices interact with our genes in ways that can both positively and negatively impact the various micro (eg, cellular) through macro (eg, physiologic, pathophysiologic) processes that determine our tendencies*

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toward illness or wellness. A deeper understanding of epigenetics, as provided herein, should enable primary care providers and medical educators to more confidently advocate for the primary benefits associated with counseling in both stress reduction and the pursuit of healthy lifestyle choices.

Keywords: epigenetics; lifestyle medicine; stress; patients; medical education

Over 75% of patients visit their primary care physicians (PCPs) for stress-related complaints.[1,2] Stress (physiologic, pathophysiologic, and psychologic) is associated with many of the leading causes of morbidity and mortality in the United States (eg, cardiovascular disease,[3-5] cancer,[6,7] chronic respiratory disease,[8,9] cerebrovascular disease,[10,11] Alzheimer's disease,[12,13] diabetes,[14] influenza and pneumonia,[15-17] depression,[18-20] suicide[21]), suboptimal health, and a shortened lifespan.[22] Unfortunately, often overlooked is the fact the stress responses associated with many diseases can induce negative lifestyle choices that both worsen the severity and duration of disease states while also triggering the deterioration of an individual's overall health. For example, job loss (not an uncommon sequela of chronic disease) can trigger numerous maladaptive psychosocial and physiologic responses leading to adverse lifestyle behaviors, such as abuse of alcohol and drugs, poor nutrition, physical inactivity, sleep deprival, etc.. These factors may in turn trigger conditions such as oxidative stress, metabolic syndrome, and/or a predisposition to other diseases/disorders later in life.[14,23,24]

Unfortunately, stress management–oriented therapeutic interventions are often inadequate or nonexistent in contemporary health care.[2,25,26] For example, despite the long recognized association between depression and stress, only 3% of patients with depression are likely to receive stress-related counseling.[18] Evidence also suggests that while over 90% of PCPs believe stress management to be an important component of health promotion and disease prevention, almost half rarely or never discuss stress with patients.[27]

The authors suggest that PCPs who have a deep understanding of how stress can be both the sequela and precipitant of illness will be well positioned to mitigate a patient's stress-related tendencies toward those maladaptive lifestyle practices that lead to further worsening of their health. More specifically, they can provide their patients with an evidence-based approach to stress management via a form of health care increasingly referred to as lifestyle medicine, which is defined as "the application of environmental, behavioral, medical, and motivational principles to the management of lifestyle-related health problems."[28-30] However, it is also important for PCPs to understand that many of the health promotion and disease prevention benefits associated with a lifestyle-oriented approach to patient care are based on a body of evidence emerging from a field of science referred to as epigenetics. Simply put, epigenetics offers insights into how factors such as stress and lifestyle choices regulate the level of activity of our genes and, subsequently, our genes' capacity to both positively and negatively affect the various micro (eg, cellular) through macro (eg, physiologic, pathophysiologic) processes that determine our tendencies toward illness or wellness.

The purpose of this article is to provide primary care practitioners and medical educators with an introductory overview of both epigenetics and lifestyle medicine. The authors suggest that such an understanding can overcome two barriers that impede the PCP's capacity to optimize the health and welfare of their patients: (1) a suboptimal understanding of how stress-induced biochemical and physiologic factors can increase both the severity of ongoing disease states, and a tendency to precipitate the onset of disease,[31-38] and (2) lack of confidence in their ability to offer effective, evidence-based lifestyle-oriented counseling.[2,27] With such an understanding, medical educators can design rudimentary course offerings in epigenetics and lifestyle-oriented health care so that tomorrow's health care providers might more efficiently and effectively optimize the heath of their patients. Hopefully, as more practitioners adopt a lifestyle medicine–based approach to patient care, and demonstrate improvements in patient care outcomes, medical school and residency curricula will increasingly provide training in both epigenetics and lifestyle medicine sufficient to assure optimal health care for all.

Background: A Broad Overview of Epigenetics

The evidence introduced in this article is derived from a targeted literature search of MEDLINE conducted via the PubMed interface. The search was limited to English language articles published from 2007 to 2017 and was based on keywords and phrases such as stress, stress management, epigenetics, epigenetic literature related to these keywords and phrases, along with an informal scanning of related literature.

Broadly stated, the field of epigenetics attempts to provide an evidence-based understanding of how internally (eg, thought, perception, feeling, nutrition, movement, sleep, stress) and externally (eg, social relationship, shift-work, pollutions, light, stressor) induced lifestyle and environmental factors change our biochemical landscape. These biochemical changes subsequently lead to the epigenetically mediated regulation of gene activity, function, and expression, and thereby contribute to both illness and health without inducing changes in the genetic code.[31-38] Some of these biochemical reactions include DNA methylation, histone acetylation, miRNA, and non-coding RNAs—reactions that play a significant role in promoting health or tendencies towards illness.

Epigenetically induced biochemical changes can also lead to changes in molecular memory through transcription changes within the genome, changes that can serve as biomarkers for adaptive and maladaptive physical and behavioral phenotypes.[39,40] Epigenetically induced biochemical changes can also cause transgenerational effects such as tendencies or predispositions toward certain diseases in offspring.[41-46]

More narrowly stated, epigenetically induced biochemical reactions continuously shape, and/or are shaped by, behavioral, psychological, lifestyle, and environmental factors. Examples of these factors include poor nutrition,[34,47,48] obesity,[49,50] tobacco,[51,52] alcohol consumption,[53,54] psychosocial stress,[55-57] sleep deprivation,[58,59] and environmental pollution.[60,61] Similarly, a variety of socially determined factors such as poverty, low social status, low educational level, and living in disadvantaged neighborhoods contribute to an increase in the occurrence of disease.[62-64] The epigenome can also be positively affected by health-promoting lifestyle choices (ie, fruit and vegetable intake,[65,66] drinking green tea,[67-69] exercise,[70-75] meditation and relaxation,[76,77] and a positive outlook on life[78]) and social factors (ie, prosocial behavior,[79,80] comforting social relationships,[81] and social support networks[63,82]).

In summary, the field of epigenetics is increasingly appreciated as a primary means of understanding how stress and maladaptive lifestyles induce genome-wide changes in gene expression, which can negatively affect the trajectory of our lives. Epigenetics is also informing us about how stress management techniques and positive lifestyle health behaviors can induce genetic expression contributing to positive health outcomes and an improved quality of life. A broad understanding of how epigenetics can induce both negative and positive health outcomes should motivate tomorrow's PCPs to incorporate stress management interventions and the promotion of positive lifestyle choices among their patients. The following provides a sampling of how epigenetically induced biochemical changes can lead to very specific, maladaptive, and deleterious responses to stress.

Epigenetic Evidence of Biochemically Mediated Responses to Stress

Epigenetics and HPA

Stress is defined as any stimulus (internally or externally induced) that disrupts the body's homeostasis; disruptions affecting the body's ability to maintain a steady state of balance within and between organ systems.[83,84] The hypothalamic-pituitary-adrenal (HPA) axis has long been understood as the body's primary means of responding to stressful stimuli.[85] In response to stress, there is an upregulation of gene expression of HPA axis–mediated hormones.[86,87] Some of these changes involve increased catecholamine and cortisol production, and the transcription of pro-inflammatory molecules; changes intended to optimize the body's capacity to overcome stress and thereby regain homeostasis. From an epigenetic perspective, these biochemical changes influence gene activity, function, and expression (ie, influence one's epigenetics) and ultimately the body's capacity to mitigate and/or overcome stress and illness, and regain health and wellness.

Prenatal Stress and Outcomes

Maternal stress produces hormones that inform the fetus in terms of how to adapt its phenotype to the environment.[88] These adaptations are thought to be carried out by epigenetic changes that alter fetal HPA axis development,[88,89] immune system function,[16,90-92] and nervous system development.[91,92] Distress in pregnancy is also associated with defects in fetal cognitive development and subsequent childhood behavioral problems, exemplifying epigenetically modifiable relationships between prenatal stress and fetal phenotype outcomes. Fetal alcohol syndrome also has an epigenetic impact through DNA methylation of POMC (Proopiomelanocortin) neurons, which are regulators of HPA axis, immunity, and energy homeostasis, thus further exemplifying the relationship between perinatal stress and phenotype outcomes.[93]

Early Life Stress and Outcomes

Stress during infancy and childhood greatly increase the risk of chronic disease morbidity and mortality.[94-96] A variety of perinatal and postnatal stresses such as adverse living conditions, drug use, malnutrition, and trauma; experiences impacting the infants' mothers, can lead to epigenetic changes that affect the lives of their offspring.[95-97] For example, children of maternal Holocaust survivors report greater use of medications for hypertension, lipid disorders, as well as a greater tendency to develop psychological disorders as adults.[97] Additional studies of perinatal maternal stress revealed increased DNA methylation in 1675 CGs affiliated with over 900 genes related to immune function.[98] Research also suggests that childhood stress is encoded in macrophages via epigenetic, posttranslational, and tissue remodeling changes. Changes which result in exaggerated pro-inflammatory responses and decreased sensitivity to inhibition, and further worsened by dysregulated hormones and abhorrent behavioral tendencies.[94] Childhood stress also negatively affects social skills, relationships, self-regulation, and lifestyle.[34,37,55]

The Epigenetic Clock and Stress

Average methylation levels at CpG sites can be used as a means of estimating DNA methylation, a metric that may represent one's epigenetic clock (a metric referred to as DNA methylation age).[22,99] An individual's epigenetically mediated rate of aging is estimated via assaying factors reflecting the amount of extrinsic epigenetic age acceleration (EEAA) and intrinsic epigenetic age acceleration (IEAA) in blood cells. Researchers are attempting to determine

the relationship between epigenetic age (via EEAA and IEAA levels in blood cells) and a variety of lifestyle factors such as diet, alcohol consumption, physical activity, educational attainment, obesity, and lifetime stress.[99] Current evidence suggests that elevated systolic blood pressure and C-reactive protein levels associated with oxidative stress[100,101] were found to increase the level of EEAA and IEAA factors in blood cells and, thereby, advance the age of our epigenetic clock. An increased BMI (body mass index) and waist-to-hip ratio has been found to be significantly associated with increased IEAA, thus providing new insights into how increased weight is deleterious toward health as a function of lifestyle-induced epigenetic change.[101] There is also evidence suggesting that obesity is characterized by chronic low-grade inflammation with permanently increased oxidative stress.[102] Other researchers are beginning to suggest that EEAA and IEAA levels might be broadly predicative of morbidity and mortality, the development of specific diseases and disorders, and alterations in cognitive ability and physical functioning.[22,100] In essence, such research may ultimately demonstrate how an individual's chronologic age might be compared with their epigenetic age and thereby produce an estimate of one's relative health and/or tendency toward early aging and disease.

Epigenetics and the Glucocorticoid Receptor Gene

The glucocorticoid receptor (GR) gene NR3C1 plays a role in controlling the development and metabolism of the immune system and HPA axis regulation. Psychological stress has been shown to have increased rates of DNA methylation within the GR gene. A meta-analysis of over 900 individuals born to mothers who experienced perinatal psychosocial stress identified significant DNA methylation at 5 consecutive CpG sites of NR3C1, which has been suggested to serve as a determinant of aberrant neurobehavior and cortisol reactivity of newborns.[103] In another study involving women exposed to extreme psychosocial stress, their offspring had increased methylation of NR3C1 as well as decreased birth weight.[104] The authors suggested NR3C1 methylation suppress plasticity of GR, which contributes to chronic disease development due to decreased adaptability to stress. Another study showed that traumatic events during childhood and stressful life events in adolescence resulted in higher rates of NR3C1 methylation in females, which was associated with increased co-stress in adolescence.[105] Furthermore, cumulative lifetime stress in African Americans living in urban areas was associated with increased methylation of glucocorticoid response elements and accelerated aging.[106] These findings clearly demonstrate the impact of psychosocial stress resulting in epigenetic changes of the NR3C1 glucocorticoid receptor, which may be an ideal biomarker to study the relationship between DNA methylation and stress.

Additional Epigenetic-Induced Methylation Changes Resulting From Stress

Stress can produce alterations in methylation of the SKA2 gene, which is implicated in altering the HPA axis and thereby an increased risk of suicide completion and the development of PTSD (posttraumatic stress disorder).[107] Furthermore, SKA2 methylation measured in saliva and blood are significantly predictive of lifetime suicide attempts, likely making it a useful biomarker for suicide risk. Fetal alcohol syndrome (FAS) also has an epigenetic role through DNA methylation of pro-opiomelanocortin (POMC) neurons, which are regulators of HPA axis, immunity, and energy homeostasis.[93] Hypermethylation of POMC neurons results in their decreased expression and subsequently increased responsiveness to stress in adulthood. Differential methylation and histone modifications of the glial cell-derived neurotrophic factor (GDNF) also play a role in mouse response to stress.[108] These findings suggest that higher DNA methylation as a result of stress, and subsequently a decreased expression of neurotrophic factors, contribute to neural disorders, mental health issues, and other unhealthy, stress-related outcomes. Methylation changes at the CpG sites of corticotropin-releasing factor (CRF) gene have been described in response to chronic stress and depression.[109] Hypermethylation of the tyrosine hydroxylase (TH) gene is correlated with both occupational stress and an overall elevation of stress levels.[110]

Epigenetics and Genetic Polymorphisms

Polymorphisms within the genome can explain how epigenetically mediated biochemical changes induce variations in health and disease-related outcomes. That is, individuals may respond differently to the same stress due to their unique genetic code and associated epigenetic changes. A review of the relationship between variable phenotypes of FKBP5, a co-chaperone involved in modulation of glucocorticoid receptor activity and stress revealed diverse responses ranging from mood disorders, cardiovascular disease, cancer, PTSD, and adaptive responses including improved response to antidepressants.[111] This also highlights the role that genetic variability, particularly at FKBP5, plays in differential responses to similar stressors and how some individuals are more prone to disease versus adaptation. Differences in SLC6A4 serotonin transporter gene DNA methylation were shown to contribute to stress response resulting in increased susceptibility or resilience to stress depending on 5-TTLPR polymorphism at the gene.[112] Decreased methylation of CpG residues of SLC6A4 promoter in shift-work nurses with stressful jobs has also been noted, which would account for decreased SLC6A4 expression among others performing shift-work.[113] However, there was no significant change in 5-HTLPR polymorphism in relation to stress. The varied stress responses due to different SLC6A4 methylation patterns warrants further investigation to see if this may be a useful biomarker in stress management.

Epigenetic Evidence of the Benefits of Stress Management–Oriented Interventions

In this section, we describe epigenetic evidence demonstrating how beneficial lifestyle behaviors modulate gene expression that attenuate the stress response. An understanding of the positive benefits of healthy lifestyle choices, especially those interacting with epigenetic activities, should enable PCPs to more aggressively, assertively, and confidently promote stress management techniques and positive lifestyle choices among their patients.

Mindfulness

A single day of intensive mindful meditation reduced the expression of pro-inflammatory genes (COX2, RIPK2, and histone deacetylase genes 2, 3, and 9) while also promoting a more rapid recovery of appropriate cortisol levels.[114] Another mindfulness-based study directed at improving coping skills and cognition of women with stage 0-III breast cancer resulted in over 50% reduction in the expression of unfavorable alterations in 91 genes compared to controls at 6 and 12 months.[115] More specifically, this study demonstrated that training in mindfulness resulted in downregulation of epigenetically expressed pro-inflammatory cytokines, prostaglandin-synthesis enzyme COX2, inflammatory chemokines, chemokine receptors, as well as upregulation in epigenetically expressed wound healing and immune-protective interferon-related genes. A systematic review of MBSR (mindfulness-based stress reduction) interventions demonstrated that such practices were associated with downregulation of nuclear factor κB (NF-κB) pathway, a transcription factor for inflammatory gene expression, which is upregulated as part of chronic stress.[116]

Meditation and Lifestyle Modification Education

A small randomized clinical trial looked at the diet, regular exercise, meditation, weight reduction, and sodium restriction in a hypertensive cohort.[117] In addition to mitigating stress levels, both groups saw a decrease in systolic blood pressure. Furthermore, both groups also showed significantly increased telomerase gene expression, which is inversely related to chronic stress. This study further supported existing evidence that telomerase expression is tied to the mechanics of stress levels. In this instance, lifestyle modification, including meditation, positively spurred telomerase expression.[117] In another study, stress management techniques involving 3 months of education directed at the adoption of a positive lifestyle, paced respirations, and relaxation techniques designed to reduce stress and anxiety, were associated with the decreased transcription of pro-inflammatory NF-κB, pro-sympathetic CREB, and oxidative stress marker NFR2 among transplant patient caregivers.[118] Furthermore, genome profiling showed 57 health-promoting genes with over 1.5 times upregulation in the intervention group compared to control.

Lifestyle Choices Intended to Slow the Epigenetic Clock

Several studies have been directed at determining the relationship between positive lifestyles/stress management and the slowing of our epigenetic clock/age. It was found that EEAA was decreased with a diet consisting of fruits, vegetables, fish, whole grains, and dietary fiber (very similar in scope to the Mediterranean diet[119]), along with physical activity and moderate alcohol consumption, indicating that healthy lifestyle choices decrease the production of EEAA and thereby are likely to slow our epigenetic clock.[99] Fish consumption on its own, has also been demonstrated to be protective against age-related pathology.[99] High blood carotenoid levels may be useful in quantifying fruit and vegetable intake, while also exhibiting an inverse correlation with EEAA. Interestingly in this study, metformin, a front-line medication for the treatment of type 2 diabetes, does not appear to reduce/delay advances in epigenetic age/clock.[99]

Nutrient Availability, Caloric Restriction, and Tea

In both human and animal studies, caloric restriction has been shown to delay the incidence of age-related chronic diseases such as cancer, cardiovascular disease, and diabetes.[120-122] For example, it has been estimated that 30% to 35% of cancers are associated with overnutrition (excessive nutrient and calorie consumption). Overnutrition has been demonstrated to induce oxidative stress, which disrupts oxidative homeostasis, thereby increasing the epigenetic expression of the histone deacetylase SIRT1 and increased DNA methylation.[121] SIRT1 plays a critical role in the longevity response to caloric restriction. Also, compounds that mimic caloric restriction like resveratrol, a natural polyphenolic compound, induces protective antioxidant effects and positive health benefits including cardiovascular health and anti-aging benefits.[123] Investigations into the molecular mechanisms of compounds contained in tea showed benefits in terms of the prevention of cancer and various inflammatory and metabolic diseases (eg, cardiovascular disease, obesity, metabolic syndrome, and neurodegenerative diseases).[124-130] More specifically, these studies found that the polyphenols, such as theaflavins and catechins contained in green and black tea, are effective in reducing oxidative stress and inflammation by activating Nrf2 transcription factors. Activities that upregulate detoxifying and antioxidant enzymes and downregulate NF-κB, the master transcription factor that regulates inflammation.

Regular Exercise

Stress induces both an inflammatory response and atherosclerosis.[131,132] It was found that acute bouts of exercise such as intensive cardiac endurance training induces an immediate pro-inflammatory response including alteration of gene expression in leukocytes.[133,134] However, the prolonged and regular exercise led to an anti-inflammatory environment in the peripheral blood cells and tissues, which reduce the risk of developing

inflammatory-related diseases such as atherosclerosis by mediating the gene expression of pro-inflammatory markers.[134-136]

Yoga

Eight weeks of yoga meditation in subjects suffering from stress (ie, caregivers for family members with dementia) resulted in decreased depression, and improved mental health and cognition along with beneficial changes in the epigenetic expression of 68 genes.[118] Through yoga, there was also an upregulation of the caregivers immunoglobulin-related transcripts including antiviral response interferon regulatory factor 1 (IRF1) and downregulation of pro-inflammatory NF-κB-associated genes—clear evidence that yogic meditation can mitigate maladaptive gene expression in stressed individuals. A systematic review found that yoga, in a manner similar to other mind-body interventions, aided in downregulation of NF-κB pathway, a transcription factor for inflammatory gene expression, which is upregulated as part of chronic stress.[116]

Discussion

There is a growing body of evidence suggesting that stress management and healthy lifestyle practices such as mindfulness, exercise, a nutritious diet inclusive of whole foods and plant-based intake, physical activity, adequate sleep, positive psychology, social support, higher levels of education, weight reduction, meditation, and yoga provide positive health benefits and an increased quality of life. These benefits appear to be the result of lifestyle medicine mediated (eg, stress reduction, healthful living), epigenetically induced, biochemical changes.

Curiously, only a small number of PCPs appreciate the epigenetic factors underlying patient tendencies toward both health and illness. However, any increase in the number of PCPs who confidently and proactively offer their patients an informed, evidence-based approach to stress management and the pursuit of positive, health and wellness–oriented lifestyles, will be largely dependent on continuing education programs and undergraduate and residency curricula offering training in both epigenetics and lifestyle medicine.

The content and concepts put forward in this article should assist both today's PCPs and medical educators in more deeply and confidently understanding the positive benefits to be gained by the incorporation of lifestyle medicine in the practice of contemporary health care. As more practitioners adopt a lifestyle medicine–based approach to patient care, and demonstrate improvements in patient care outcomes, medical educators will likely be more willing to seriously consider the development of curricula providing training in both the biochemistry of epigenetics, lifestyle medicine, and stress-management techniques. Imparting such training to tomorrow's health care providers will likely lead to an increase in knowledge and confidence with which they offer counseling directed at improving their patient care outcomes.

One approach to the development of such curricular offerings could come in the form of what is often referred to as an active (as opposed to a passive) training environment. In such an environment, learners would be exposed to patient scenarios (real, computer-driven, standardized patients, etc), wherein they are given the opportunity to diagnose the disease or disorder causing the patient's medical presentation and treat it with conventional therapies. They would also be required to develop a lifestyle-oriented therapeutic intervention based on current epigenetic theories, evidence, and outcomes-oriented clinical findings. Schools interested in offering epigenetic training and lifestyle-oriented therapeutic interventions would face considerable resistance in the form of faculty concerns suggesting that their curriculum is already overburdened with too many concepts and topics. In anticipation of such barriers and concerns, initial curricular initiatives in epigenetics and lifestyle medicine could be directed at launching a small initiative such as five, 2-hour long modules with each focused on one of the more common, important, and "high impact" diseases or disorders likely to benefit from such training and interventions. Furthermore, such training could be delivered by a team of educators comprised of faculty representing (1) traditional medical specialties, (2) health promotion and disease prevention, (3) biochemistry, (4) genetics/epigenetics, (5) psychiatrists, behavioral psychologists, and counselors, and (6) lifestyle medicine practitioners.

Currently, there are only a handful of postgraduate medical training programs that teach lifestyle medicine, including Loma Linda University, Harvard University, and University of Florida.[28,29,137] Furthermore, there appears to be only 5 medical schools that formally incorporate a biopsychosocial or lifestyle and environmental focus into their undergraduate medical curriculum.[30] For those schools unable to adopt a major change in their current undergraduate training programs, another method of incorporating a lifestyle medicine training model would be to develop an optional, parallel "optional" curriculum for students interested in lifestyle medicine.

Summary

The frequency and severity of stress poses a largely unmanaged threat to health. More specifically, evidence suggests that stress: (1) represents a frequently encountered, yet unaddressed sequela of disease, (2) is likely to worsen the severity of disease, and (3) has the capacity to induce disease. The field of epigenetics is in part oriented to providing an evidence-based explanation of how internally and externally induced stress influences the biochemically medicated processes that regulate gene activity, function, and expression, and thereby contribute to both illness and health. Epigenetics also provides biochemical and genetically based evidence of the benefits of stress management and lifestyle-oriented

techniques such as those involving mindfulness, meditation, yoga, exercise, breathing techniques, sleep hygiene, social connectedness and support, smoking cessation, and the reduction and/or elimination of alcohol and drug use. The authors suggest that the adoption of curricular changes inclusive of training in the role of epigenetics-based lifestyle medicine should enable tomorrow's PCPs to make more intelligent, meaningful, and insightful inquiries into their patients' medical histories for stress and stress-inducing lifestyle choices. And when appropriate, confidently prescribe those specific stress-management and positive lifestyles considerations likely to lead to improved health outcomes. By counseling patients in how to reduce stress and adopt healthy lifestyles, tomorrow's PCPs can alter a patient's epigenetic landscape, thereby promoting healing and optimal health, and subsequently improved patient care outcomes.

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