

RELIGION AND MEDICINE III: DEVELOPING A THEORETICAL MODEL

HAROLD G. KOENIG, M.D.

Duke University Medical Center

GRECC, Veterans Administration Medical Center

Durham, North Carolina

Abstract

In this third of a four-article series on religion and medicine, I describe a theoretical model to illustrate the complex pathways by which religion may influence physical health. Genetic factors, childhood training, psychological and social influences, health behaviors, and healthcare practices are discussed as part of this model. Considerable space is given to recent advances in psychoneuroimmunology and to stress-induced cardiovascular changes that demonstrate physiological pathways by which cognitive, emotional, and behavioral processes may influence susceptibility to disease and disease course. I also discuss research illustrating the important role that social support plays in moderating the physiological effects of stress and improving health outcomes. If religious beliefs and practices improve coping, reduce stress, prevent or facilitate the resolution of depression, improve social support, promote healthy behaviors, and prevent alcohol and drug abuse, then a plausible mechanism exists by which physical health may be affected.

(Int'l. J. Psychiatry in Medicine 2001;31:199-216)

Key Words: religion, psychoneuroimmunology, immunology, social support, health behaviors, substance abuse

In the first article of this *Religion and Medicine* series, I examined the historical background of these twin healing traditions and the reasons for their separation, including the possible negative effects of religion on health. In the second article, I

presented a comprehensive and systematic review of research examining the relationship between religion, mental health, social support, and other behaviors related to mental and social functioning. In this third article in the series, I develop a theoretical model to help explain how religion might impact not only mental health and social functioning, but physical health as well. Models assist in developing research questions, in choosing the appropriate study designs to answer those questions, in understanding and interpreting findings, in organizing a body of knowledge for communication with scientists from different disciplines and for purposes of general education. The model described here (see Figure 1) focuses on known psychological, social, behavioral, and physiological mechanisms by which religion may influence the development and course of various diseases. This model considers five major areas: genetic factors, childhood training, psychological and social influences, health behaviors, and healthcare seeking practices.

GENETIC FACTORS

Heredity has an enormous influence on the onset and course of virtually every disease. If a religious group promotes inbreeding, then certain diseases may cluster in that group. For example, Jewish women have higher rates of familial ovarian cancer [1] and higher rates of familial breast cancer [2]. Likewise, cardiovascular disease is particularly high among Ashkenazi and non-Mizrahi Sephardi Jews [3], and Tay-Sachs disease is more common among Ashkenazi Jews than in the general population [4].

Religion may also influence and be influenced by genetic makeup in ways that appear to operate against the principle of natural selection. Because of religious involvement, people who are physically or mentally “less fit” may be enabled to survive and pass on their genes. For example, if religious beliefs and practices help to prevent depression and suicide, reduce substance abuse, and discourage self-destructive health behaviors associated with early mortality, then religion will provide a force counter to nature’s attempts to weed out the mentally weak from the population. Furthermore, if a physically feeble individual is surrounded by a supportive, caring faith community, then this will increase that person’s ability to survive and reproduce. In these ways, devout religious beliefs and practices could lead to a population that is more susceptible to both mental and physical disease because of the protection that it offers to those who are more vulnerable.

Forgiving or showing mercy to one’s enemies, rather than annihilating them, also appears to go completely against the force of evolution with its rule of survival of the fittest. One would think that such generous practices would lead to the extinction of the group that maintained them. On the other hand, sharing resources and resolving conflict may help bind communities together and enable them to cooperate to achieve goals conducive to propagation of the species. This would

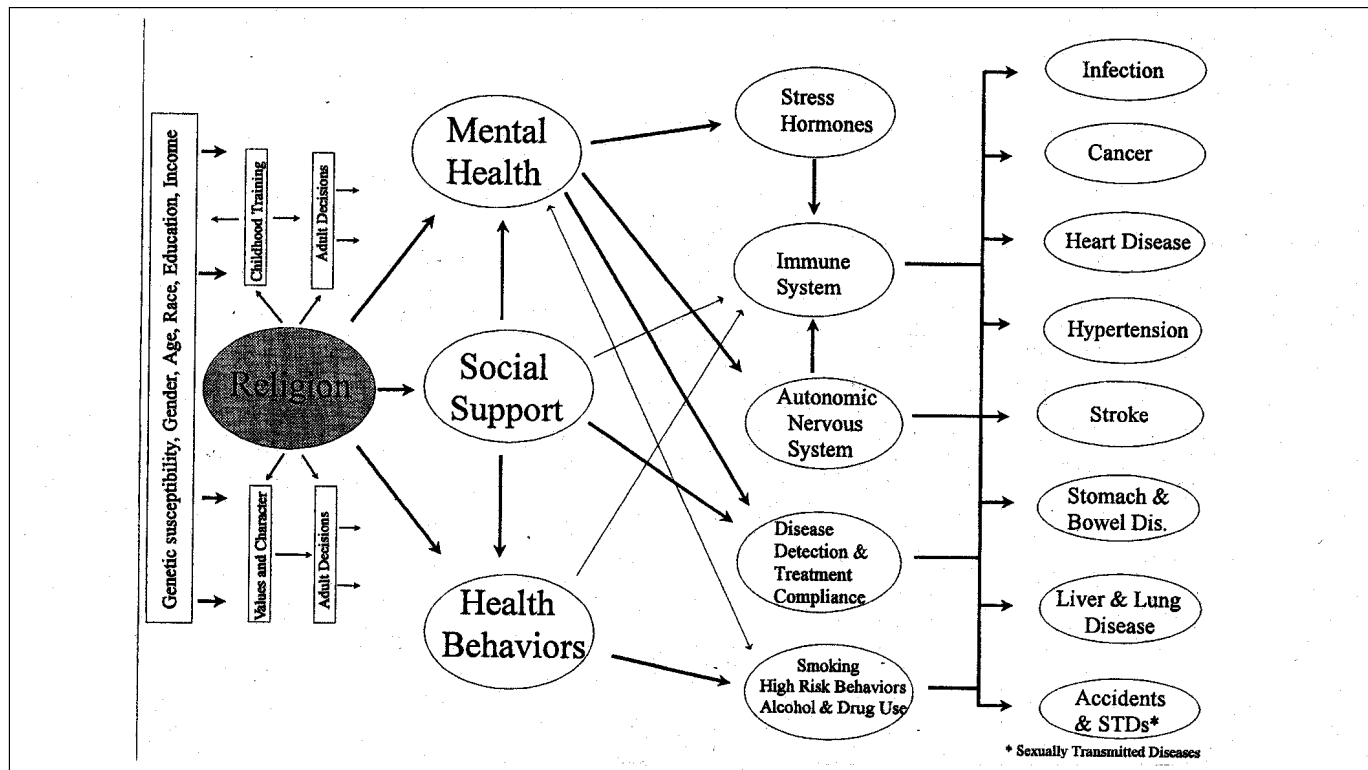


Figure 1. Theoretical model describing how religion affects physical health. From *Handbook of Religion and Health* by Harold Koenig et al., copyright 2001 by Harold Koenig et al. Used by permission of Oxford University Press.

also allow new genetic material to come into the gene pool, increasing genetic variability and resistance to disease. Likewise, if religious involvement increases the stability of families, reduces substance abuse during youth, facilitates other healthy lifestyle practices, and instills values that improve decision-making, then religious persons may be more likely to survive to mate successfully and successfully raise children of their own that become productive members of society.

At least one study suggests that the propensity to engage in religious beliefs and practices may have some genetic basis. In a survey of 1902 twins, Kendler and colleagues [5] found higher correlations for religious characteristics between monozygotic twins than between dizygotic twins. Religious characteristics measured were personal devotion (importance of religious beliefs, seeking religious comfort, and frequency of private prayer), personal conservatism (belief that God rewards and punishes, literal belief in Bible), and institutional conservatism (based on religious affiliation). Correlations between religious characteristics in monozygotic and dizygotic twin pairs, respectively, were $r = .52$ vs. $r = .40$ for personal devotion, $r = .47$ vs. $r = .43$ for personal conservatism, and $r = .63$ vs. $r = .57$ for institutional conservatism. Using statistical modeling investigators found that for personal devotion, family environment and individual-specific influences explained 24 percent and 47 percent, respectively, of the variance in twin resemblance, with genetic factors accounting for the remaining 29 percent. For personal conservatism, percentages were 45 percent for family environment, 55 percent for individual-specific, and 0 percent for genetic influences. For institutional conservatism, the figures were 51 percent for family environment, 37 percent for individual-specific, and 12 percent for genetic.

CHILDHOOD TRAINING

The religious beliefs and practices of parents often influence how they train their children. Religious training during childhood and adolescence may instill values that promote choices that reduce stress, maintain health, and prevent disease in later life. If such training prevents drug use, alcohol abuse, and delinquency in the teen years, then it may also reduce the disruption of education and career development that these problems cause. Likewise, if religious adolescents engage less frequently in pre-marital sexual activity, then teen pregnancy is less likely to arrest the pursuit of higher education and adversely affect later earning capacity. In this way religious training may increase the chances children have when older to afford timely medical care and to acquire knowledge that enables them to identify early symptoms of disease and take preventive measures. Similarly, if a religious training improves adult decisions, then behaviors that lead to substance abuse, divorce, and crime will be less common and less likely to cause psychological and social stress that ultimately impairs health.

On the other hand, poor education, lack of financial resources, stressful life experiences, and physical illness all increase the likelihood that persons will *turn to* religion for comfort or solace. In cross-sectional studies, such dynamic factors involving stress-induced religious change may conceal the positive effects of childhood religious training on health status unless religious history is taken into account.

PSYCHOLOGICAL AND SOCIAL INFLUENCES ON PHYSICAL HEALTH

Recent discoveries in psychoneuroimmunology and cardiovascular physiology have convinced many of the effects that cognitive, emotional, and social factors can have on physical health. These advances provide biological mechanisms by which stress-reducing religious beliefs and practices might impact health by altering the risk of infection, cardiovascular disease, cancer, or influencing the course of illness. Let us now examine some recent findings on how psychosocial stress impacts physical health.

The Fight-Flight Response

Scientists have known for almost 65 years that emotional stress has physiological consequences [6]. The “fight or flight” response, described by Cannon [7], involves a rapid sequence of physiological changes initiated whenever an experience is appraised as threatening—whether that threat is to the physical body or to the *psychological self*. The following is a highly simplistic description of this response. Once the mind interprets an event as dangerous to physical or emotional well-being, signals are sent to at least two areas of the brain—the locus ceruleus (where the cell bodies of autonomic neurons are concentrated in the floor of the 4th ventricle) and the hypothalamus (where neurons that secrete inhibiting and releasing hormones are located in the ventral wall of the 3rd ventricle). These two brain areas then execute a series of commands to the rest of the body.

Autonomic neurons in the locus ceruleus transmit signals to preganglionic sympathetic neurons traveling down the spinal cord and connecting to postganglionic sympathetic neurons located in ganglia along the spinal column. Postganglionic neurons, then, send sympathetic nerve fibers to synapse with smooth muscle in blood vessels, stomach, intestines, the heart, and other vital organs. In addition to connecting with postganglionic sympathetic neurons, preganglionic sympathetic neurons also extended down to the adrenal medulla. When the adrenals are activated by discharges from these nerves, they release large quantities of epinephrine (and smaller amounts of norepinephrine).

While the locus ceruleus is activating the sympathetic nervous system, the hypothalamus is secreting hormones (in particular, corticotropin releasing hormone or CRH) into blood vessels traveling down the infundibular stalk to the pituitary gland. CRH then stimulates the pituitary to release corticotropin (adrenocorticotrophic hormone or ACTH) into blood vessels that carry it to the adrenal cortex, stimulating the release of glucocorticoids. This pathway is known as the hypothalamic-pituitary-adrenal (HPA) axis.

The purpose of this complex series of physiological changes is to prepare the body to either fight or escape from danger. The end result is that blood is redirected to the heart and large muscles (at the expense of less vital organs) and glucocorticoids are made available to enhance muscle function. Hyperactivity of the sympathetic nervous system and HPA axis during psychological stress results in changes that affect heart rate, blood pressure, and coronary artery tone. In addition, alterations of serum cholesterol and blood lipids occur, along with an increased propensity for platelets to aggregate and blood to clot.

Changes also take place in the immune system as part of the fight-flight response. According to Rabin [8], postganglionic sympathetic nerve fibers terminate in secondary lymphoid tissues such as the spleen, lymph nodes, and lymphoid tissue around mucous membranes. It is in these secondary lymph tissues that T lymphocytes are produced and interact with B lymphocytes. The norepinephrine secreted by these sympathetic nerve fibers may bind to lymphocytes and reduce their functioning, or bind to macrophages that produce chemicals such as nitrous oxide which suppress lymphocyte functioning. Other hormones are also released, including opioids, substance P, neuropeptide Y, vasoactive intestinal peptide, and insulin-like growth factor, substances that can alter maturation and release of lymphocytes from primary lymphoid tissue and further affect migration and function of lymphocytes in secondary lymphoid tissue and other organs. Thus, acute stress can impact both primary and secondary immune responses in order to conserve energy needed for the fight-or-flight response (since immune processes require much energy) [8].

The changes induced by the fight-or-flight response are highly adaptive in terms of survival in the acute setting. If, however, a threatening situation continues for days, weeks, or months—as occurs in chronic stress and depression—then these changes may adversely affect body tissues and homeostatic processes in susceptible individuals. By activating the autonomic nervous system, stress may impair gastrointestinal functioning, leading to peptic ulcer disease, irritable bowel syndrome, and possibly pancreatic dysfunction and diabetes. By impairing immune function over the long-term, chronic stress can weaken the body's primary defense against infection, as well as possibly affect the development or spread of malignancy. A growing body of research, as described below, now supports this theory.

PSYCHOSOCIAL INFLUENCES AND IMMUNE FUNCTION

Psychological stress of even brief duration can induce marked physiological changes. Breier and associates [9] demonstrated that lack of control over even mildly aversive stimuli in 10 healthy human volunteers produced alterations in neuroendocrine and autonomic nervous system functioning (elevated ACTH, higher levels of sympathetic nervous system activity, and higher electrodermal activity). In a study of 22 older women, Cacioppo and colleagues [10] also found that brief psychological stress heightened cardiac activity, elevated plasma catecholamine concentrations, and diminished cellular immune responses.

Interpersonal relationships, in particular, may give rise to stress that powerfully affects neuroendocrine and immune function. Studying 90 newlywed couples, Kiecolt-Glaser and colleagues [11] found that those who displayed more negative or hostile behaviors during a 30-minute discussion of marital problems showed greater decreases in natural killer (NK) cell activity, diminished blastogenic responses to mitogens, weaker proliferative responses to monoclonal antibody, and larger and more sustained increases in blood pressure. Effects were stronger in wives than in husbands. Kiecolt-Glaser's team [12] next examined endocrine and immune correlates of marital conflict in 31 couples who had been married an average of 42 years. Marital satisfaction and escalation of negative behavior during conflict correlated with substantial changes in cortisol, ACTH, and norepinephrine levels. These changes were again more likely to occur in wives than in husbands. Both husbands and wives who engaged in negative behaviors during conflict, however, showed weaker immunological responses as measured by T cell blastogenic responses to mitogen stimulation and antibody titers to latent Epstein-Barr (EB) virus.

Depression

Depressive disorder can result from chronic situational stressors, depending on the biological susceptibility of the individual. Depression, in turn, is associated with a variety of neuroendocrine changes, including the elevation of serum cortisol. Numerous studies have found impaired lymphocyte functioning, including reduced NK cell cytotoxicity, in persons with depressive disorder [13, 14]. Bartrop and associates [15] were the first to report impaired lymphocyte functioning in grieving persons who had recently lost a spouse. By the sixth week after bereavement, lymphocyte responses to phytohemagglutinin and concanavalin A were significantly impaired among bereaved subjects compared to controls. More recently, in a 2-year prospective study of 66 HIV-infected gay men, Leserman and colleagues [16] found that stress and depressive symptoms both independently and in combination predicted decreases in immune function (measured by NK cell subsets and CD8-super (+) T cells).

STRESS-INDUCED IMMUNE CHANGES AND HEALTH STATUS

Demonstrating that psychological stress or depression alters immune function does not necessarily mean that such changes will increase the likelihood of disease or worsen prognosis. A number of studies, however, now suggest that stress-induced immune changes are large enough to affect health.

Infectious Diseases

Psychosocial stress may predispose to or influence the course of viral, bacterial, and fungal infections by down-regulating cellular immunity thereby impairing the body's ability to combat infection [17]. For example, Kiecolt-Glaser and colleagues [18] found that stressed caregivers of dementia patients were significantly more likely than age-matched controls to experience depression that was associated with impairments in immune function and increased susceptibility to infection, especially upper respiratory tract infections. In a second study that compared 32 caregivers with 32 sex, age, and SES-matched controls, Kiecolt-Glaser's group [19] found that caregivers showed poorer antibody response following influenza vaccination. In addition, caregivers had decreased in-vitro virus-specific-induced interleukin-2 and interleukin-1 beta levels. This finding suggested that chronic stress down-regulates immune responses to influenza vaccination in older adults, a finding recently confirmed by others [20].

Negative effects of stress may impair immune responses to viral infections in the young and healthy, as well as the old and sick. Vaccinating 48 second-year medical students on the last day of a three-day examination series, Kiecolt-Glaser and colleagues [21] assessed the effects of academic stress on students' ability to generate an immune response to hepatitis B vaccine. Students who developed an immune response were significantly less stressed and anxious than students who failed to do so. Studying stress-induced susceptibility to viral infection more directly, Cohen and colleagues [22] infected 394 healthy volunteers ages 20–55 with a cold virus and an additional 26 subjects with a placebo. Investigators found that both respiratory infections ($p < .005$) and colds ($p < .05$) increased in an almost linear fashion with increases in psychological stress.

Stress may also alter the course of infections. Evans and colleagues [23] examined the relationship between stressful life events and disease progression in 93 HIV-positive homosexual men, assessing subjects and controls over a 42-month period. HIV-positive men with high life stress ($n = 38$) experienced significantly greater HIV disease progression than those with low life stress. The risk of disease progression doubled for each stressful life event per six-month study interval.

Cancer

There is some indication that psychological distress may increase susceptibility to cancer in relatively healthy persons [24, 25]. The evidence to support a role for immune factors in cancer prognosis, however, is stronger than for cancer etiology [26]. Stress-induced suppression of NK cell activity increases the risk of tumor metastasis [27, 28]. In a three-month prospective study of 75 women with stage I-II breast cancer, Levy and associates [28] found that depressive fatigue-like symptoms correlated with NK cell activity both at baseline and three-month follow-up. Depressive-like symptoms at baseline also tended to predict decreases in NK activity at three months even after controlling for baseline NK cell activity. Levy's group [29] next examined mood and time to death following recurrence of breast cancer in 36 women. Positive affect (joy) predicted longer survival after cancer recurrence, controlling for physician-rated prognosis and number of metastatic sites. Similar findings were reported by Roberts and colleagues [30], examining disease progression in women diagnosed with gynecologic cancer. Depressed affect was an independent predictor of positive nodes on follow-up.

Wound Healing

Some of the most exciting research in this area examines psychological stress as a predictor of wound healing, a process dependent on healthy immune function. Kiecolt-Glaser and associates [31] studied 13 elderly female caregivers of demented relatives to determine if the stress of caregiving impaired wound healing in these subjects. Cases and matched controls underwent a 3.5-mm punch biopsy. Wounds in caregivers took significantly longer (24 percent) to heal compared to controls. Similarly, Marucha and colleagues [32] applied two 3.5-mm punch biopsies on the hard palates of 11 dental students. The first wound was made during summer vacation, and the second wound was placed on the opposite side of the palate three days before the first major examination of the term. Students took an average three days longer (40 percent) to heal the wounds during the examination period, compared to wounds made during the summer. In both studies above, peripheral blood leukocytes of stressed subjects produced significantly less interleukin-1 beta mRNA in response to lipopolysaccharide stimulation than did those of control subjects.

Social Support

If social support prevents negative life situations from leading to chronic emotional stress, it may also moderate stress-induced neuroendocrine and immune changes [33]. In one of the first studies supporting this hypothesis, Kiecolt-Glaser's team [34] found reduced immune function in psychiatric patients who complained of feeling lonely compared to those without such feelings. In

another study that assessed the effects of academic stress on medical students' ability to generate an immune response to hepatitis B vaccine [21], these investigators found that students with greater social support had stronger immune responses to the vaccine than those with less support. Cohen and colleagues [35] have now directly demonstrated that social support can increase host resistance to cold virus infection.

Later studies by Kiecolt-Glaser and others have demonstrated a relationship between social support and immune functioning in caregivers. Caregivers of patients with Alzheimer's disease or terminal cancer with low social support experienced greater declines in immune function over time, including NK cell activity, than did those with high support [18, 36, 37]. Similar findings emerge for cancer patients themselves. In Levy and associates' prospective study of women with early breast cancer discussed earlier [28], they found cross-sectional correlations between lack of family support and lower NK cell activity both at baseline and at three-month follow-up. Those who complained about lack of family support at baseline also tended to experience a decrease in NK activity at three months. In another study by this same group involving 66 women with stage I-II breast cancer, they again found that women with higher social support had greater NK cell activity than those with low support [38].

Do interventions that increase social support protect against stress-related decrements in immune functioning, thereby improving clinical outcomes? Spiegel and colleagues [39] conducted a randomized clinical trial to examine the effects of a psychosocial intervention on survival of 86 women with metastatic breast cancer. The one-year intervention consisted of weekly supportive group therapy. At 10-year follow-up, investigators found that subjects in the intervention group survived an average of 36.6 months compared to 18.9 months for controls ($p < .0001$). In a related study, Fawzy and associates [40] randomly assigned patients with malignant melanoma to either a structured group intervention (including stress management and social support) or a control group. Intervention group members experienced significant reductions in psychological stress, increased number of NK cells, increased NK cytotoxic activity, less cancer recurrence and longer survival over six years.

Psychosocial Factors and Cardiovascular Disease

Chronic psychological and social stress may also impact the development and course of cardiovascular disease by adversely affecting serum cholesterol and other blood lipids, increasing the propensity for platelets to aggregate [41], increasing the risk of fatal cardiac arrhythmias [42], and diminishing heart rate variability [43]. Let us now examine a few studies that document a link between psychosocial factors and the most prevalent form of cardiovascular pathology, coronary artery disease (CAD).

Stress, Depression, and CAD

Both psychological stress and depression may impact the development of CAD. For example, Rosengren and colleagues [44] prospectively followed 6,935 middle-aged men for 12 years examining the relationship between psychological stress and the occurrence of myocardial infarction (MI). In men with low stress ratings at baseline, 6 percent experienced a fatal or non-fatal MI compared with 10 percent of men with high stress ratings—a 50 percent increase in risk that remained significant after controlling for relevant covariates. Likewise, in a 13-year study of 1551 subjects *without* history of MI, investigators found that the diagnosis of major depression at baseline increased the risk of MI during follow-up by over 100 percent, independent of other coronary risk factors [45]. Similarly, in a study of 942 middle-aged Finnish men, Everson and associates [46] discovered that those with high levels of despair at baseline experienced a significant 20 percent increase in angiographically-documented atherosclerosis compared to men without despair. Ford and colleagues [47] followed 1190 male medical students at Johns Hopkins between 1948 and 1964, assessing the development of coronary heart disease and risk of MI. While subjects with depression did not differ from non-depressed subjects at baseline on CAD risk factors, they were over twice as likely to develop CAD and twice as likely to have a MI during follow-up. Many other studies document both higher mortality and greater risk of non-fatal cardiac events in depressed patients following acute MI [48-52].

Social Support

There is evidence that social support may counteract the adverse effects that psychosocial stress has on cardiovascular function [53]. Seeman and Syme compared the impact of different types of social support on degree of coronary atherosclerosis in 159 subjects using coronary angiography to assess extent of disease [54]. Quality of social support significantly predicted coronary artery atherosclerosis. Williams and associates [55] studied the effects of social and economic resources on cardiovascular mortality among 1368 patients with CAD undergoing cardiac catheterization. Unmarried patients without a confidant had an unadjusted five-year survival of 50 percent compared with 82 percent among patients who were married, had a confidant, or both. Frasure-Smith [56] randomly assigned 461 men with a prior history of MI to either a social intervention or a control group. Subjects in the intervention group received supportive visits from a nurse during periods when they reported high stress. During the five years of the study, subjects receiving the intervention experienced significantly fewer cardiac events than did those in the control group that did not receive support.

In summary, anything that reduces the responsiveness of the brain to a stressor—through positive cognitive appraisals or increased social support—may decrease the production of stress hormones, decrease sympathetic nervous system

activity, and ameliorate the cardiovascular and immune system alterations that follow. If religious beliefs and practices help to reduce psychological stress, increase social support, prevent depression, or enhance positive emotions like joy, thankfulness, forgiveness, hope, and optimism, then religion may help to moderate or prevent the potentially damaging behavioral and physiological responses to stress described above. On the other hand, religious beliefs that increase psychological stress by instilling fear or arousing guilt may have the opposite effect—stimulating the fight-or-flight response and its long-term negative physiological consequences.

HEALTH BEHAVIORS AND LIFESTYLE CHOICES

Health behaviors have an enormous influence on physical health—particularly those lifelong behaviors practiced since youth. This is especially true for behaviors like cigarette smoking, alcohol or drug abuse, lack of exercise, unhealthy eating habits, or risky sexual practices. Persons under stress are more likely to engage in these negative health behaviors (called the “stress-disinhibition” effect) [57]. Such behaviors may in turn lead to greater stress and poorer quality of life, plunging the person into a downward spiral. Not only do these behaviors lead directly to increased morbidity, they also impair immune responses. Studies in both animals [58] and humans [59] have documented negative effects of alcohol on immunity, particularly cell-mediated immunity. Similarly, cigarette smoking can depress immune functioning [60], whereas smoking cessation can improve it [61]. Drugs like marijuana have also been shown to reduce peripheral blood lymphocytes and impair NK cell activity [62].

If religion can help to prevent the development of unhealthy habits or behaviors in youth and early adulthood, it may have an enormous impact on health over the life span of the individual. A number of reasons exist for the inverse association between religious involvement and negative health behaviors. First, by providing a positive, more optimistic worldview that facilitates coping, religion may lessen the mental stress that sometimes precipitates alcohol abuse, drug use, and other risk-taking behaviors. Second, religious teachings discourage most behaviors that harm the body or control the mind, values that may be instilled early during religious training. Third, religion may reduce negative health behaviors by providing a supportive social network that buffers stress and provides healthier alternatives for coping with stress. On the other hand, if religious beliefs promote unhealthy habits such as neglect of the physical body, overeating, or lack of exercise, then health outcomes will suffer. Similarly, being ostracized from a religious community may drive some individuals to return to a lifestyle of addiction and self-neglect. Finally, rigid religious beliefs may induce or reinforce pathological guilt, which then drives individuals toward self-destructive behaviors to rid themselves of these painful feelings.

HEALTHCARE PRACTICES

Healthcare seeking behaviors influence physical health by at least three pathways: disease prevention, disease detection, and treatment compliance. Religious beliefs and teachings can promote positive healthcare practices in a number of ways. First, religious teachings advocate attention to physical health and respect for health professionals. Christian doctrines prescribe care for the body as the “temple of the Holy Spirit.” Jewish law in early Hebrew times prohibited Jews from living in towns that did not have a physician—underscoring a respect for health care professionals that continues to this day in traditional Jewish communities [63]. Although Islamic holy scriptures (the Qur’an) do not speak specifically of medical treatment, they set a high value on health and the restoration of health [64].

Second, if religious participation increases one’s social network and frequency of social contacts, then this will increase health monitoring. For many, particularly those in minority communities, the church has become an extended family. If a member of one of these close-knit religious communities fails to appear at religious meetings, he or she is likely to be contacted by a member of that community expressing concern. Such support will increase the likelihood that a sick person will be reminded to take their medicine or follow medical advice. Consequently, it is much more difficult for physically ill persons to neglect themselves if they are part of a religious community. Furthermore, being part of a religious community probably improves the likelihood of self-care because there is more reason to do so—perhaps because of the role he or she is playing in the lives of others in that community.

Third, there is some evidence that religious persons may be more compliant in general. Either because they are accustomed to yielding to authority or because of a sense of responsibility to others, religious persons may be more likely to take medication as prescribed [65] and comply with medical appointments [66]. On the other hand, as noted in the first paper of this series, religious beliefs may also prevent the seeking of timely medical care or may promote medication discontinuation, favoring faith-based therapies over medical ones. For the vast majority of persons involved in traditional religious activities, however, such behaviors are rare.

CONCLUSIONS

I have described and discussed a theoretical model that may help explain how religion impacts physical health through *natural* mechanisms. If psychological and social factors influence susceptibility to infection, development and spread of malignancy, speed of wound healing, and risk or course of cardiovascular disorders like hypertension, stroke, and coronary artery disease, then religious factors might also affect these processes. Because religious beliefs impact health

behaviors and lifestyle choices, as well as healthcare practices and compliance with treatment, numerous pathways exist by which physical health may be affected. Whether or not religious involvement is actually associated with better physical health and longer survival is the subject of the final article in this series.

REFERENCES

1. Steinberg KK, Pernarelli JM, Marcus M, Khoury MJ, Schildraut JM, Marchbanks PA. Increased risk for familial ovarian cancer among Jewish women. *Genetic Epidemiology* 1998;15:51-59.
2. Egan KM, Newcomb PA, Longnecker MP, TrenthamDietz A, Baron JA, Trichopoulos D, Stampfer MJ, Willett WC. Jewish religion and risk of breast cancer. *Lancet* 1996;347(9016):1645-1646.
3. Dreyfuss F. The incidence of myocardial infarction in various communities in Israel. *American Heart Journal* 1953;45:749-755.
4. Scriver CR, Beaudet AL, Sly WS, Valle D. *The metabolic and molecular bases of inherited disease*. 7th Edition. New York: McGraw-Hill, 1995:2839-2882.
5. Kendler KS, Gardner CO, Prescott CA. Religion, psychopathology, and substance use and abuse: A multimeasure, genetic-epidemiologic study. *American Journal of Psychiatry* 1997;154:322-329
6. Selye H. Syndrome produced by diverse noculous agents. *Nature* 1936;138:32.
7. Cannon WB. The emergency function of the adrenal medulla in pain and the major emotions. *American Journal of Physiology* 1941;33:356.
8. Rabin BS. *Stress, immune function, and health: The connection*. New York: Wiley-Liss & Sons, 1999.
9. Breier A, Albus M, Pickar D, Zahn TP, Wolkowitz OM, Paul SM. Controllable and uncontrollable stress in humans: Alterations in mood and neuroendocrine and psychophysiological function. *American Journal of Psychiatry* 1987;144:1419-1425.
10. Cacioppo JT, Malarkey WB, Kiecolt-Glaser JK, Uchino BN, Sgoutas-Emch SA, Sheridan JF, Berntson GG, Glaser R. Heterogeneity in neuroendocrine and immune responses to brief psychological stressors as a function of autonomic cardiac activation. *Psychosomatic Medicine* 1995;57:154-164.
11. Kiecolt-Glaser JK, Malarkey WB, Chee M, Newton T, Cacioppo JT, Mao HY, Glaser R. Negative behavior during marital conflict is associated with immunological down-regulation. *Psychosomatic Medicine* 1993;55:395-409.
12. Kiecolt-Glaser JK, Glaser R, Cacioppo JT, MacCallum RC, Snydersmith M, Kim C, Malarkey WB. Marital conflict in older adults: Endocrinological and immunological correlates. *Psychosomatic Medicine* 1997;49:339-349.
13. Schleifer SJ, Keller SE, Bond RN. Major depressive disorder and immunity. *Archives of General Psychiatry* 1989;46:81-87.
14. Irwin M, Smith TL, Gillin JC. EEG sleep and natural killer activity in depressed patients and control subjects. *Psychosomatic Medicine* 1992;54:10-21.
15. Bartrop RW, Lazarus L, Luckhurst E, Kiloh LG, Penny R. Depressed lymphocyte function after bereavement. *Lancet* April 16, 1977:834-836.
16. Leserman J, Petitto JM, Perkins DO, Folds JD. Severe stress, depressive symptoms, and changes in lymphocytes subsets in human immunodeficiency virus-infected men. A 2-year follow-up study. *Archives of General Psychiatry* 1997;54:279-285.

17. Glaser R, Rabin B, Chesney M, Cohen S, Natelson B. Stress-induced immunomodulation: Are there implications for infectious diseases? *Journal of the American Medical Association* 1999;281:2268-2270.
18. Kiecolt-Glaser JK, Dura JR, Speicher CE, Trask OJ, Glaser R. Spousal caregivers of dementia victims: Longitudinal changes in immunity and health. *Psychosomatic Medicine* 1991;53:345-362.
19. Kiecolt-Glaser JK, Glaser R, Gravenstein S, Malarkey WB, Sheridan J. Chronic stress alters the immune response to influenza virus vaccine in older adults. *Proceedings of the National Academy of Sciences* 1996;93:3043-3047.
20. Vedhara K, Cox NKM, Wilcock GK, Perks P, Hunt M, Andersen S, Lightman SL, Shanks NM. Chronic stress in elderly caregivers of dementia patients and antibody response to influenza vaccine. *Lancet* 1999;353:627-631.
21. Kiecolt-Glaser JK, Garner W, Spelcher C. Psychosocial modifiers of immunocompetence in medical students. *Psychosomatic Medicine* 1984;46:7-14.
22. Cohen S, Tyrell DAJ, Smith AP. Psychological stress and susceptibility to the common cold. *New England Journal of Medicine* 1991;325:606-612.
23. Evans DL, Leserman J, Perkins DO, Stern RA, Murphy C, Zheng B, Gettes D, Longmate JA, Silva SG, van der Horst CM, Hall CD, Folds JD, Golden RN, Petitto JM. Severe life stress as a predictor of early disease progression in HIV infection. *American Journal of Psychiatry* 1997;154:630-634.
24. Shekelle RB, Raynor WJ, Ostfeld AM, Garron DC, Bieliauskas LA, Liu SC, Maliza C, Oglesby P. Psychological depression and 17-year risk of death from cancer. *Psychosomatic Medicine* 1981;43:117-125.
25. Prigerson HG, Bierhals AJ, Kasl SV, Reynolds CF, Shear MK, Day N, Beery LC, Newsom JT, Jacobs S. Traumatic grief as a risk factor for mental and physical morbidity. *American Journal of Psychiatry* 1997;154:616-623.
26. Herberman RB. Principles of tumor immunology. In Holleb AI, Fink DJ, Murphy GP, editors. *Textbook of clinical oncology*. Atlanta, GA: American Cancer Society, 1991: 69-79.
27. Akimoto M, Nakajima Y, Tan M, Ishii H, Iwasaki H, Abe R. Assessment of host immune response in breast cancer patients. *Cancer Detection & Prevention* 1986; 9:311-317.
28. Levy S, Lippman M, d'Angelo T. Correlation of stress factors with sustained suppression of natural killer cell activity and predictive prognosis in patients with breast cancer. *Journal of Clinical Oncology* 1987;5:348-353.
29. Levy S, Lee J, Bagley C, Lippman G. Survival hazards analysis in first recurrent breast cancer patients: The seven-year follow-up. *Psychosomatic Medicine* 1988;50:520-528.
30. Roberts D, Andersen BL, Lubaroff A. *Stress and immunity at cancer diagnosis*. Unpublished manuscript. Department of Psychology, Ohio State University, Columbus, Ohio, 1994.
31. Kiecolt-Glaser JK, Marucha PT, Malarkey WB, Mercado AM, Glaser R. Slowing of wound healing by psychological stress. *Lancet* 1996;346(8984):1194-1196.
32. Marucha PT, Kiecolt-Glaser JK, Favagehi M. Mucosal wound healing is impaired by examinations stress. *Psychosomatic Medicine* 1998;60:362-365.
33. Uchino BN, Cacioppo JR, Kiecolt-Glaser JK. The relationship between social support and physiological processes: A review with emphasis on underlying mechanisms and implications for health. *Psychological Bulletin* 1996;119:488-531.

34. Kiecolt-Glaser JK, Ricker D, George J. Urinary cortisol levels, cellular immunocompetence, and loneliness in psychiatric inpatients. *Psychosomatic Medicine* 1984; 46:15-23.
35. Cohen S, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM. Social ties and susceptibility to the common cold. *Journal of the American Medical Association* 1997; 277:1940-1944.
36. Baron RS, Cutrona CE, Hicklin D, Russel DW, Lubaroff DM. Social support and immune function among spouses of cancer patients. *Journal of Personality & Social Psychology* 1990;59:344-352.
37. Esterling BA, Kiecolt-Glaser JK, Glaser R. Psychosocial modulation of cytokine-induced natural killer cell activity in older adults. *Psychosomatic Medicine* 1996; 58:264-272.
38. Levy S, Herberman RB, Lee J, Whiteside I, Kirkwood J, McFeeley S. Estrogen receptor concentration and social factors as predictors of natural killer cell activity in early-stage breast cancer patients. *Natural Immunity & Cell Growth Regulation* 1990; 9:313-324.
39. Spiegel D, Bloom JR, Kraemer HC, Gottheil E. Effect of psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet* 1989;2(8668):888-891.
40. Fawzy FL, Fawzy NW, Hyun C, Elashoff R, Guthrie D, Fahey JL, Morton DL. Malignant melanoma: Effects of an earlier structured psychiatric intervention, coping, and affective state on recurrence and survival six years later. *Archives of General Psychiatry* 1993;50:681-689.
41. Musselman DL, Tomer A, Manatunga AK, Knight BT, Porter MR, Kasey S. Exaggerated platelet reactivity in major depression. *American Journal of Psychiatry* 1996; 153:1313-1317.
42. Veith RC, Lewis N, Linares OA, Barnes RF, Raskind MA, Villacres EC. Sympathetic nervous system activity in major depression—basal and desipramine-induced alterations in plasma norepinephrine kinetics. *Archives of General Psychiatry* 1993; 50:1-12.
43. Carney RM, Saunders RD, Freedland KE, Stein P, Rich MW, Jaffe AS. Association of depression with reduced heart rate variability in coronary artery disease. *American Journal of Cardiology* 1995;76:562-564.
44. Rosengren A, Tibblin G, Wilhelmsen L. Self-perceived psychological stress and incidence of coronary artery disease in middle-aged men. *American Journal of Cardiology* 1991;68:1171-1175.
45. Pratt LA, Ford DE, Crum RM. Depression, psychotropic medication, and risk of myocardial infarction. *Circulation* 1996;94:3123-3129.
46. Everson SA, Kaplan GA, Goldberg DE, Salonen R, Salonen JT. Hopelessness and 4-year progression of carotid atherosclerosis. The Kuopio Ischemic Heart Disease Risk Factor Study. *Arteriosclerosis, Thrombosis & Vascular Biology* 1997; 17:1490-1495.
47. Ford DE, Mead LA, Chang PP, Cooper-Patrick L, Wang NY, Klag MJ. Depression is the risk factor or coronary artery disease in man. *Archives of Internal Medicine* 1998;158:1422-1426.
48. Ahern DK, Gorkin L, Anderson JL, Tierney C, Hallstrom A, Ewart C. Biobehavioral variables and mortality or cardiac arrest in the Cardiac Arrhythmias Pilot Study (CAPS). *American Journal of Cardiology* 1990;66:59-62.

49. Kennedy GF, Hofer MA, Cohen D, Shindledecker R, Fisher JD. Significance of depression and cognitive impairment in patients undergoing programmed stimulation of cardiac arrhythmias. *Psychosomatic Medicine* 1987;49:410-421.
50. Carney RM, Rich MW, Freedland KE, Sanini J, teVelde A, Simeone C. Major depressive disorder predicts cardiac events in patients with coronary artery disease. *Psychosomatic Medicine* 1988;50:627-633.
51. Barefoot JC, Helms MJ, Mark DB, Blumenthal JA, Califf RM, Haney TL. Depression and long-term mortality risk in patients with coronary artery disease. *American Journal of Cardiology* 1996;78:613-617.
52. Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction: Impact on 6-month survival. *Journal of the American Medical Association* 1993;270:1819-1825.
53. Greenwood DC, Muir KR, Packham CJ, Madley RJ. Coronary heart disease: A review of the role of psychosocial stress and social support. *Journal of Public Health Medicine* 1996;18:221-231.
54. Seeman T, Syme SL. Social networks and coronary artery disease: A comparison of the structure and function of social relations as predictors of disease. *Psychosomatic Medicine* 1987;49:341-354.
55. Williams RB, Barefoot JC, Califf RM, Haney TL, Saunders WB, Pryor DB, Hlatky MA, Siegler IC, Mark DB. Prognostic importance of social and economic resources among medically treated patients with angiographically documented coronary artery disease. *Journal of the American Medical Association* 1992;267:520-524.
56. Frasure-Smith N. In-hospital symptoms of psychological stress as predictors of long-term outcome after acute myocardial infarction in men. *American Journal of Cardiology* 1991;67:121-127.
57. Marlatt GA. Relapse prevention: Theoretical rationale and overview of the model. In Marlatt GA, Gordon JR, editors. *Relapse prevention*. New York: Guilford Press, 1985:3-70.
58. Anonymous. Alcohol effects on the immune system: Third Annual Meeting of the Alcohol and Drug Abuse Immunology Symposium, Vail, Colorado, March 25-29 (abstracts). *Alcohol* 1993;10:335-342.
59. MacGregor RR. Alcohol and immune defense. *Journal of the American Medical Association* 1986;256:1474-1479.
60. Holt PG. Immune & inflammatory function in cigarette smokers. *Thorax* 1987;42:241-249.
61. Meliska CJ, Strunkard ME, Gilbert DJ, Jensen RA, Martinko JM. Immune function in cigarette smokers who quit smoking for 31 days. *Journal of Allergy & Clinical Immunology* 1995;95:901-910.
62. Friedman H, Klein T, Specter S. Immunosuppression by marijuana and components. In Ader R, Felten DL, Cohen N, editors. *Psychoneuroimmunology*. San Diego, CA: Academic Press, 1991:66-85.
63. Dorff EN. The Jewish Tradition. In Numbers RL, Amundsen DW, editors. *Caring and curing: Health and medicine in the western religious traditions*. Baltimore: Johns Hopkins University Press, 1998.
64. Rahman F. Islam and health/medicine: A historical perspective. In Sullivan LE, editor. *Healing and restoring: Health and medicine in the world's religious traditions*. New York: Macmillan Publishing Co., 1989.

65. Koenig HG, George LK, Cohen HJ, Hays JC, Blazer DG, Larson DB. The relationship between religious activities and blood pressure in older adults. *International Journal of Psychiatry in Medicine* 1998;28:189-213.
66. Koenig HG. Use of acute hospital services and mortality among religious and non-religious copers with medical illness. *Journal of Religious Gerontology* 1995; 9(3):1-22.

Direct reprint requests to:

Harold G. Koenig, M.D.
Box 3400
Duke University Medical Center
Durham, NC 27710