The nocebo hypothesis proposes that expectations of sickness and the affective states associated with such expectations cause sickness in the expectant. The nocebo phenomenon is a little-recognized facet of culture that may be responsible for a substantial variety of pathology throughout the world. However, the extent of the phenomenon is not yet known, and evidence is piecemeal and ambiguous. This paper reviews the concept of nocebo and its association with the placebo phenomenon, gives examples of evidence for the nocebo phenomenon, and suggests public health implications.

Key Words: nocebo; placebo; expectation; etiology.

INTRODUCTION

The nocebo hypothesis proposes that expectations of sickness and the affective states associated with such expectations cause sickness in the expectant. Resultant pathology may be subjective as well as objective conditions. Some nocebo effects may be transient; others may be chronic or fatal. An extreme form of the nocebo phenomenon was described in Cannon’s classic paper [7] as “voodoo death.” Because expectations are largely learned from the cultural environment, nocebo effects are likely to vary from place to place.

The nocebo phenomenon, first named by Kennedy [17] and then elaborated by Kissel and Barrucand [19], has not been systematically assessed. In this review, I formulate a working definition of the nocebo phenomenon that relates nocebos and placebos, present a range of examples of nocebo phenomena, and draw several implications for public health.

A WORKING DEFINITION OF THE NOCEBO PHENOMENON

The nocebo effect is the causation of sickness (or death) by expectations of sickness (or death) and by associated emotional states. Two forms of the nocebo effect should be recognized: In the specific form, the subject expects a particular negative outcome and that outcome consequently occurs; for example, a surgical patient expects to die on the operating table and does die—not from the surgery itself, but from the expectation and associated affect [7,35]. In the generic form, subjects have vague negative expectations—for example, they are diffusely pessimistic—and their expectations are realized in terms of symptoms, sickness, or death—none of which was specifically expected. Again, expectation plays a causal role.

The nocebo phenomenon considered in this review is distinct from placebo side effects (Fig. 1). Placebo side effects occur when expectations of healing produce sickness, i.e., a positive expectation has a negative outcome. For example, a rash that occurs following administration of a placebo remedy may be a placebo side effect. Diverse placebo side effects have been documented; one review reports an incidence of 19% in the subjects of pharmacologic studies [29]. In the nocebo phenomenon, however, the subject expects sickness to be the outcome, i.e., the expectation is a negative one. Nocebos may also have side effects, i.e., when negative expectations produce positive outcomes or outcomes other than those expected.

When Kennedy [17] and Kissel and Barrucand [19] first referred to the nocebo phenomenon, they did not distinguish placebo side effects from the effects of negative expectations. However, reference to voodoo death, for example, as an instance of the placebo phenomenon is etymologically inappropriate. Kennedy and Kissel and Barrucand distinguished placebos from nocebos only in terms of positive and negative outcomes, not also in terms of expectations. Kennedy’s examples are all placebo side effects, and Kissel and Barrucand did not separate examples of placebo side effects from an example of nocebo in the sense proposed here: 80% of hospitalized patients given sugar water and told that it was an emetic subsequently vomited. What distin-
guishes nocebos is that the subject has negative expectations and experiences a negative outcome. Schweiger and Parducci [31] refer to nocebos as "negative placebos."

Nocebos are causal in the same way that commonly recognized pathogens are, e.g., cigarette smoke of lung cancer, the tubercular bacillus of tuberculosis [15,38]. That is, nocebos increase the likelihood that the sickness they refer to will occur, and this effect is not the result of confounding, i.e., the empirical association of the hypothesized nocebo with another cause of the condition. None of these exposures is a necessary or a sufficient cause of the given outcome.

**EVIDENCE OF NOCEBO PHENOMENA**

This review of evidence is divided according to the source or manner of acquisition of expectations. It begins with (1) the effects of inner, mental worlds and moves to (2) the effects of nosological categories and self-scrutiny, (3) sociogenic illness, or mass hysteria, and (4) the deliberate induction of sickness or symptoms.

**Inner, Mental World**

Mood, affect, and some psychiatric conditions are often associated with negative expectations [1]. For example, hopelessness is a prominent component of diverse forms of depression. Somatoform disorders such as hypochondriasis and conversion disorder may also be associated with expectations of pathology. Some anxiety disorders, too, may be associated with expectations of pathology. Panic disorder, for example, may involve a sense of "impending doom" and a fear of death [1].

Although several studies indicate an association of negative expectations and affect with psychiatric conditions and pathological outcomes [4–6,13,24,28,36,37], only the study by Anda et al. [2] uses epidemiologic methods to control for the confounding effects of other risk factors. Anda et al. examined the effects of depression on ischemic heart disease (IHD) incidence and mortality among a sample of U.S. adults. They examined persons who were free from heart disease at the outset of the study and excluded subjects whose initial depressed affect might have been the consequence of chronic disease. Depression was assessed from the General Well-Being Schedule [11]. Anda and colleagues found that persons with depressive affect were 1.6 times more likely to have nonfatal IHD and 1.5 times more likely to have fatal IHD than persons who did not have depressive affect, independent of other known risk factors for IHD. These researchers also examined the effects of hopelessness on heart disease incidence and mortality, and found a dose response—a critical criterion in the inference of causality. Greater hopelessness was associated with greater incidence and mortality.

Considering that an 11.1% prevalence of depressed affect was assessed in the study cohort—a sample of U.S. adults—it can be estimated (as the "population attributable risk") that approximately 26,000 deaths a year (i.e., more than 5% of U.S. IHD mortality and more than 1% of all U.S. deaths) may be attributable to depression, independent of other risk factors. Mortality associated with depressive expectations is an example of the generic form of the nocebo phenomenon. The other examples in this review are of specific nocebo phenomena.

**Nosological Categories and Self-Scrutiny**

In one specific form, cardiac neurosis or cardiophobia, patients are persistently fearful of heart attacks or other cardiac symptoms, and report chest pain, described by physicians as "nonspecific." Although these patients may not manifest recognized cardiac symptoms, there is evidence that belief that one is susceptible to heart attacks is itself a risk factor for coronary death. Eaker examined women, 45 to 64 years of age, in the Framingham Study for the 20-year incidence of myocardial infarction and coronary death [12]. Women who believed they were more likely than others to suffer a heart attack were 3.7 times as likely to die of coronary conditions as were women who believed they were less likely to die of such symptoms, independent of commonly recognized risk factors for coronary death (e.g., smoking, systolic blood pressure, and the ratio of total to high-density lipoprotein cholesterol).

**Sociogenic Illness**

Sickness or symptoms may also occur when one person observes or learns of the sickness or symptoms in others. Knowledge of sickness in others fosters an expectation that one may also be subject to the same
condition. Perhaps the best recognized form of contagion by observation are epidemics referred to as “sociogenic,” “psychogenic illness,” “mass hysteria,” or, in the workplace, “assembly line hysteria” [9].

Sirois [32] reviewed 78 documented outbreaks of “epidemic hysteria” reported between 1872 and 1972. Of these, 44% occurred in schools, 22% in towns, and 10% in factories. Twenty-eight percent involved fewer than 10 persons, 32% involved 10–30 persons, and 19% more than 30 persons; 5% were of unreported magnitude. (Whereas the largest outbreak noted by Sirois involved approximately 200 persons, an outbreak has been described that involved 949 persons [23]). Only females were involved in 74% of the outbreaks, only males in 4% [32]. Outbreaks occurred more commonly among persons from lower socioeconomic classes and in periods of uncertainty and social stress. Convulsions were reported in 24% of outbreaks, abnormal movements in 18%, and fainting, globus/cough/laryngismus, and loss of sensation in 11.5% each. Symptomatology changed over the 100 years surveyed, from more globus/cough/laryngismus and abnormal movements to more fainting, nausea, abdominal malaise, and headaches.

Colligan and Murphy [8] point out that sociogenic outbreaks are commonly associated with a source believed to be related to the symptoms, e.g., a strange odor or gas, new solvent, or an insect bite. However, sometimes reported symptoms do not fit biomedical knowledge of associations between potential toxins or pathogens and pathophysiology. Persons affected often have repetitive jobs, are under unusual stress, and/or have poor relations with superiors. They may be in poorer general health and have been absent more often than persons who are not affected. Colligan and Murphy indicate that sociogenic outbreaks in workplace settings are substantially underreported.

Sirois [33] estimates that sociogenic outbreaks occur in approximately 1 of every 1,000 schools per year in the province of Quebec. A review of recent school outbreaks in diverse countries indicates attack rates (i.e., the proportion of persons exposed who experience the condition) of 6–48% [3].

The study of Kerckhoff and Back [18] of the 1962 “June Bug” outbreak in a Montana mill is one of the few to carefully reconstruct social patterns of the spread of a sociogenic condition. In the June Bug event, those affected fainted or complained of pain, nausea, or disorientation. Sixty-two (6.4%) of 965 workers were affected, 59 (95.2%) of them women; all those affected worked in dressmaking departments. Persons affected were 70% more likely than controls to believe that the cause of the outbreak was an insect or other physical object. Persons affected were 62% more likely to have worked overtime at least 2 or 3 times a week than those not affected. Persons affected were less likely to go to a supervisor with a complaint or to be members of the union. They were 2.2 times as likely to be sole breadwinners, 5.6 times as likely to be divorced, and 30% more likely to have a child under 6 years of age. The outbreak began among women who were socially isolated, subsequently spread among women connected by links of close social relations, and finally diffused among women less closely connected. The phenomenon analyzed by Kerckhoff and Back might be described as “mass somatization.”

The effects of a person’s social environment on sickness or illness behavior need not involve direct personal contact. An association has been found between traumatic death or violence in the community environment and subsequent suicide or suicide-like behavior [25–27]. In this instance, the first victim serves as a model with whom others may “identify.” For example, when newspaper or television stories about a suicide are released, the rate of suicide may increase in the following week; the greater the circulation of the newspaper, the greater the increase [25]. After Marilyn Monroe’s suicide in 1962, 197 suicides occurred in the United States during the following week—12% more than the number expected on the basis of past suicide patterns [25]. A recent study indicates that teenagers are more susceptible to televised publicity about suicide and that increases in suicides are greater for girls than for boys [27].

Motor vehicle fatalities also follow newspaper stories of suicide. Phillips [26] calculates that, on average, motor vehicle fatalities increase 9% above the expected rate in the week following front-page reporting of suicides in newspaper stories and that, when the newspaper has greater than average circulation, the increase is 19%.

Sickness/Symptoms Induced

Social psychologists have conducted diverse experiments that demonstrate the effects of negative suggestion on the experience of negative symptoms [16,20, 30,31,34]. In one experiment, 47.5% of asthmatics who were exposed to (normally innocuous) nebulized saline solution and told they were inhaling irritants or allergens experienced substantially increased airway resistance and changes in airway resistance and thoracic gas volume [22]. Controls who did not have asthma were unaffected by exposure to the same stimulus. Twelve asthmatic subjects developed full-blown attacks that were relieved by the same saline solution presented therapeutically. (The researchers also refer to an asthmatic patient in another study whose allergy to roses was induced by plastic as well as natural roses, indicating that the effect of the rose did not result entirely from its botanical properties.)

In a follow-up, double-blind experiment, Luparello et al. [21] randomized asthmatic patients to four conditions: Two groups were given a bronchodilator, the
other two a bronchoconstrictor; half of the group given each substance was told they were being given a bronchodilator, the other half that they were being given a bronchoconstrictor. For each substance administered, expectations induced by misinformation about the substance reduced its physiologic effectiveness by 43% (for the bronchoconstrictor) and 49% (for the bronchodilator).

Another study was designed to evaluate a method for the diagnosis of psychogenic seizures, reported to account for as much as 20% of “refractory epilepsy” [20]. Lancman and colleagues compared the effect of suggestion on the induction of seizure behavior in patients with psychogenic seizures and others with known epilepsy. Patients were told that a medicine administered through a skin patch would induce seizures within 30 sec, and that removal of the patch would end the seizure. Of patients with psychogenic seizures, 77% manifested seizures when the patch was applied, with symptoms such as nonresponsiveness, generalized violent thrashing, and uncoordinated movements; 19% of these patients reported auras, and 44% showed postictal confusion and/or sleepiness. None of the patients with diagnosed epilepsy manifested seizures.

Finally, another study [16], designed to evaluate a controversial method of food allergy testing, compared the effect of injecting the food substances—the test to be evaluated—with the effect of injecting saline diluent without the substance in question on symptoms that included itching of the nose, watering or burning eyes, plugged ears, tight or scratchy throat, nausea, dizziness, sleepiness, and depression. (Patients with a history of anaphylactic reactions or documented cardiac irregularity or other severe reactions to their allergies were excluded.) In this double-blind study, the proportion of patients who experienced symptoms was not statistically different in patients given test (27%) and nocebo diluent injections (24%). “Neutralizing” injections, given to eliminate the reactions, were also equally effective whether they contained the food substance or—in this case—the diluent placebo. An injection becomes a nocebo (or placebo) not because of its contents, but because of the pessimistic (or optimistic) expectations of its consumer.

**DISCUSSION**

I have reviewed a range of studies indicating that socially given negative expectations and their emotional associations facilitate their own realization. Beliefs can make us sick as well as healthy. The nocebo phenomenon is a little-recognized facet of culture that may be responsible for a substantial variety of pathologies intended to be healed. The assessment of the extent of this noxious facet of ethnomedicines, including our own system of biomedicine, is an important public health challenge.

Second, and more immediately practical, if communication about pathological conditions may serve not only to describe, but, in a sense, also to foster sickness by creating expectations, then we must be cautious in both public health communications and in clinical medicine. We need to know more about how health messages affect their audience. Such knowledge may enhance our ability to minimize the pathological consequences of negative messages. The placebo/nocebo phenomenon suggests that it may be healthier to err on the side of optimism than on the side of pessimism.

**REFERENCES**