The Mind-Body Connection Behind Holistic Approaches to Health

Recent Advancements and Current Limitations

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Preface

When our family of three became sick in 2007 with temperatures of 104F, at least one of us felt at some point that we were all going to die–not because of the sickness itself, but because of the lack of support we provide to one another. Thanks to the help of our relatives and friends, we recovered after several weeks of struggle. We realized that our immunity was down due to a lot of work prior to the sickness. The turning point came when we were able to laugh at ourselves, as one with a slightly lower fever offered help for the other. None of us sought medical intervention.

Every instance of a healing process like this makes us think about how we get sick and how, most of the time, we recover. Of course, it would be far more difficult if the situation were really life-threatening. What can we do? What would be the impacts of our feelings and thoughts? This booklet is a result of our own (preliminary) journey regarding these questions. Since these are deep questions, we know that our understanding is quite limited. However, we thought it would be good to share with others what we have found in the literature.

We would like to thank many people, especially those who helped us when we were sick. Without their help, there would not be this booklet, nor would there be "us."

1. Introduction

As more and more people become frustrated with the current state of "conventional" Western medicine primarily based on the so-called biomedical model, many turn to "alternative"/"complementary" approaches to health (Tindle et al., 2005). Many (but not all) such approaches are also characterized as holistic. A common theme of holistic health approaches is to view the whole person in context, not just a single organ or system, e.g., the heart, in isolation. Another focus of holistic health approaches is the interconnectedness of the mind and the body, in contrast to conventional medicine's tendency to separate the two. While it is our common experience that our bodies affect our minds as in illness, influence in the other direction has been more controversial. The conventional medical community tends to assume that our minds do not affect our health. For example, it had been believed that the immune system functions independently from the nervous system (so-called the autonomy of the immune system). However, this counterintuitive belief turned out to be false, as shown by psychoneuroimmunology researchers (as will be discussed in more detail in this booklet). Then, we are at least in a position to believe that our minds affect our health to some extent. This point, the most critical part of the mind-body problem relevant to holistic health approaches, will be referred to in this booklet as the problem of "mind over health," narrower than "mind over body." Some other questions in this category include whether just thinking positively could make us healthy, and whether one could heal with inert pills, the so-called placebo effect. Although the conventional medical community is slowly accepting some aspects of mind over health, there still are skeptics, partly because they have not seen as much research supporting mind over health.

Set in this context, the main question of this booklet is, "What do we know about the problem of mind over health, particularly regarding (1) *to what extent* and (2) *how* does it work?" Since this is a difficult problem, it is expected that the currently available research would be rather limited. So, we are also interested in the limitations associated with the current research. An answer to our main question is important for all of us. Alternative health practitioners could support some of their practices with research evidence. The skeptics

might need to revise some of their beliefs. Lay-people could make better informed decisions about health care and their well being.

As one of the strongest supports of mind over health, the field of psychoneuroimmunology will be reviewed first. Since this relatively new field has grown so much, we chose to base our review on three recent, readily available introductory textbooks discussing psychoneuroimmunology (Daruna, 2004; Freeman, 2004; Wisneski and Anderson, 2005), which will be referred to as the main references in this booklet. Psychoneuroimmunology clearly shows that the nervous, immune, and endocrine systems interact with one another, especially with respect to stress. Furthermore, recent placebo studies provide additional insights into the mechanism behind mind over health. However, we also recognize two main limitations of the current research: the complexity of the domain and the subjectivity involved in the mind. We note that these limitations are associated with scientific research methods in general. Then, to deepen our understanding of mind over health, we propose to broaden our investigation with other approaches as well, e.g., phenomenological approaches including the use of narratives.

Before proceeding, a few qualifications are in order. First, due to the vastness of the topic, it is impossible to cover relevant fields exhaustively. Thus, our discussion of psychoneuroimmunology is mainly based on the three main references mentioned earlier as well as some additional references relevant to the topic. Second, our use of the term "holistic health" refers to abstract concepts not tied to specific "alternative" (i.e., non-conventional) health approaches. There are conventional physicians who promote holistic health in our sense, while there are alternative health practitioners who are not holistic. In this sense, our use of the term is not radically different from another related term: "integral medicine" (e.g., Schlitz et al., 2005).

This booklet is organized as follows. Section 2 reviews psychoneuroimmunology, focusing on stress and its connection to immune functions. In Section 3, we review more recent work on placebo effects and also explore cognition and emotion as underlying components. Then, in Section 4, we discuss the two main issues involved in holistic health, complexity

and subjectivity, and introduce narratives as a means to investigate the problem of mind over health.

2. Advancements in Psychoneuroimmunology: Focus on Stress and Immunity

This section reviews the state of psychoneuroimmunology and its contributions. For many lay-people, it is common sense and first-hand experience that our minds affect our bodies. Then, the findings in psychoneuroimmunology, that the immune system interacts with other parts of the body, comes as no surprise. What is actually surprising is that psychoneuroimmunologists had to make great efforts to get their results published and acknowledged by the conventional medical community. To demystify the situation, we start with the historical background. The section continues with discussions of stress, stress response, relevant medical conditions, and the mechanism behind bodily interactions.

Historical Overview

The first successful attempt to challenge the idea of the autonomy of the immune system was by Robert Ader and his colleagues in the 1970s. Ader (1996, p. 1) recalls that, despite some research and common sense, few researchers paid attention to the topic and no mechanistic explanations were known. Indeed, the lack of scientific explanation or ignorance was sufficient for immunologists to *assume* the autonomy of the immune system. Ader also coined the term, psychoneuroimmunology first used in 1980 as "the study of the interactions among behavioral, neural and endocrine (or neuroendocrine), and immunological processes of adaptation." We include a historical summary in Table 1. All of these results explore the interaction between the nervous and the immune systems involving different aspects of the nervous system, e.g., conditioning (memory/learning) and stress.

By now, these results are well recognized by the scientific community. But the agony of psychoneuroimmunologists can be felt as Ader (1996, p. 15) quotes a textbook in immunology published in 1991: "Clinical and experimental

Years	Principle investigators	Summary
1920s	Metal'nikoff, Chorine	Preliminary findings of immune response conditioning, introduced to the research community in the 1930-40s but largely ignored
1950s	Rasmussen	Effects of stress on herpes simplex and other conditions in mice
1960s	Solomon, Moos	Psychological factors in autoimmune diseases, e.g., systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA)
	Hadden	Brain lesions and immune reactions in guinea pigs
1970s	Ader	Effect of an immunosuppressive drug elicited by the taste of saccharin after conditioning in mice
	Besedovsky	Connection between antigen (cause of antibody production), the immune system, the central nervous system (CNS), and the endocrine system in animals
	Blalock	Lymphocytes (immune cells) as a source of chemicals (i.e., peptides, neurotransmitters, and pituitary hormones) in the brain
1980s	Felton	Signaling from the sympathetic nerve fibers to the immune system
	Stein	Effects of stress on immune system in animals and humans (in particular, the impacts of loss and depression)
	Kiecolt-Glaser, Glaser	Effects of stress on the immune system demonstrated by recruiting medical students during exams

Table 1 Early History of Psychoneuroimmunology

psychoneuroimmunology studies to date confirm *the long-standing belief* that the immune system does not function completely autonomously" (italics in the original). His quote of Schopenhauer also expresses his feeling: "All truth passes through three stages. First it is ridiculed. Second it is violently opposed. Third it is accepted as being self evident."

So, why did it take so long to convince the mainstream medical community about the connection between the immune system and the rest of the body? One possibility is that medicine is heavily anatomically oriented (Sternberg, 2000, p. 10). That is, unless one can identify a problematic organ or system, one cannot be convinced. More generally, the shortsighted views of the medical community may be due to its reductionistic orientation (Daruna, 2004, p. 229). Since the immune system alone is already so complex, scientifically rigorous

studies controlling a few variables may not reveal the true story (Daruna, 2004, especially Ch. 12). We will come back to this point later in this booklet.

Stress

Stress is one of the most explored topics in psychoneuroimmunology, first systematically studied by Selye (1976) in the 1920s. Selye characterized stress as the common response of organisms to a variety of noxious events, including physical, chemical, and radiation threats; infections; and challenging and life-endangering conditions (Daruna, 2004, p. 101). This is a rather broad characterization and some later attempted to define it more specifically. However, those attempts have not been very successful. For example, Daruna (2004, Ch. 6) also tries to define stress, as contextual change. He includes the person herself as part of the context and considers a disease as contextual change. However, this definition is problematic in at least two ways. First, the common use of the term "context" contrasts the "foreground" (focal point) and the "background" (context). By combining both the foreground (person) and the background (environment) as context, the term can no longer retain the intended common-sense meaning involving the contrast. Second, a certain context change could be more stress-relieving than stressing. In a sense, Selye's contribution to identify the common symptoms related to various conditions may be best captured by his broad characterization.

After Selye's discovery, the connection between stress and health has been discussed extensively (e.g., Hafen, 1996), although there is a cautious meta-analysis (Miller and Cohen, 2001) as well. As pointed out by Selye, stress is a complex concept related to a variety of events. Due to their impacts on our lives, diseases can also be considered as stress (Daruna, 2004, p. 149). In addition to prototypical examples of facing dangerous situations, certain natural and artificial environmental factors can also be stressors, possibly even a small amount of electromagnetic radiation from a cell phone (Daruna, 2004, pp. 110-111).

As mentioned above, there are many types of stressors. Even though all the types of stressors would have similar responses, the most important class of stressors for our discussion of mind over health is psychological stress,

involving stressors such as predictability, control, outlet of frustration, and social impacts (Sapolsky, 2004a, Ch. 13). This is because other types, e.g., physical stress, may be unconscious and not involve the mind to activate the immune system. Among the factors of psychological stress, control is discussed as one of three real-life elements, along with commitment and challenge, in Wisneski and Anderson (2005, p. 92). One relevant primate study is included in Daruna (2004, p. 120), which says that lower-ranking primates are more stressed out, reflecting a higher cortisol (hormone produced in the adrenal gland) level. However, there also is an opposite statement (Rabin, 1999, pp. 22-23). The situation turns out to be more complex. Sapolsky (2004a, pp. 44, 361) notes the following, citing Jay Kaplan: within a stable hierarchy, dominant individuals have the healthiest stress response; within an unstable hierarchy, the situation is not the same.

Stress Response

Even though there are a variety of stressors, individuals respond to stress in a fairly consistent manner. Thanks to psychoneuroimmunologists, we now understand a great deal about this process. Before reviewing this complex topic, it is important to note the following. From an evolutionary perspective, (acute) stress response is a normal biological response to noxious events (Wisneski and Anderson, 2005, p. 34). However, it has been argued that in modern human history, stress becomes increasingly chronic, for which human bodies have not evolved. Thus, it is chronic stress that is problematic for us.

Stress response takes place through neural and chemical pathways (Wisneski and Anderson, 2005, Sec. 1.3). The neural pathway is faster (seconds) and the chemical pathway is slower (minutes) but more sustaining. The neural pathway actually relies on both the nervous and endocrine systems as described in Daruna (2004, pp. 122-123) and Wisneski and Anderson (2005, pp. 32-34). A stressor eventually activates the hypothalamus, which releases corticotropin-releasing hormone (CRH). This activates the sympathetic branch of the nervous system, reaching the adrenal medulla (inner part of the adrenal gland), which releases epinephrine (formerly known as adrenaline); nerve terminals release norepinephrine (NE). While epinephrine prepares the body for quick reaction, e.g., an increase in heart rate, NE induces arousal. This stage also

involves various peptides (chemicals consisting of amino acids), such as a higher level of substance P (involved in pain transmission) when anxious or discomfort. Then, acetylcholine (ACh) is released from the sympathetic postganglionic neurons, which innervates the sweat glands. But ACh from the parasympathetic branch is decreased. The situation also increases 5-hydroxytryptamine (5-HT or serotonin), which regulates emotional tone.

The chemical pathway relies on the endocrine system. This is the well-known hypothalamus-pituitary-adrenal (HPA) axis, discussed in Daruna (2004, pp. 120-121, 123-129) and Wisneski and Anderson (2005, pp. 32-34). In this pathway, too, a stressor activates the hypothalamus, which releases CRH and antidiuretic hormone (ADH). This activates the pituitary gland, which in turn releases adrenocorticotropic hormone (ACTH). This stimulates the adrenal cortex (outer part of the adrenal gland), where glucocorticoids/corticosteroids (hormones such as cortisol in humans and corticosterone in rats) are released. Note that the adrenal medulla is activated neurally. Corticosteroids have multiple effects. First, they prepare the body for coping with the stress by generating more energy. Second, they suppress the immune system so that the immune system will not become overexcited (negative feedback). In addition, the pituitary gland releases endorphins and enkephalins, which reduce pain perception (Sapolsky, 2004a, p. 32). They also inhibit systems non-essential for the stress, including the digestive and reproductive systems. Note again that before modern times, stress was supposed to be short-term, and the slower-acting chemical pathway is expected to wind down the immune system.

As mentioned above, the contrast between acute stress response (evolutionally natural) and sustained stress response (evolutionally more recent) is a crucial one. First, we discuss the contrast with respect to nonspecific/innate immunity (Daruna, 2004, pp. 124-125), which involves natural killer (NK) cells (immune cells to clean infected cells). Acute stress increases NK cells, which is considered good because the increased level may be the consequence of the mobilization of nonspecific immunity in preparation for possible injury. On the other hand, chronic stress in general decreases the NK cell level. For example, worry-prone individuals had a lower NK cell level; the NK cell level is lower in depressed or lonely people. However, this is not always the case. For example,

the NK cell level is increased in war situations and in lab tests. So, the impact of chronic stress on nonspecific immunity is not so clear-cut.

Second, we briefly discuss the contrast with respect to acquired immunity, targeting specific, predisposed pathogens. One aspect of this type of immunity, humoral immunity (involving antibodies) is in general diminished due to stress, and this may be the main source of immune suppression (Daruna, 2004, pp. 125-126, 128). The other aspect, cell-mediated immunity (handled by immune cells) has mixed results on acute stress and consistently lower results on chronic stress, e.g., caring for chronically ill relatives, job stress, exams (Daruna, 2004, pp. 126-127). These results show that chronic stress impairs acquired immunity.

In summary, stress response initiates immune mobilization; the immune cells (NK and some other types of immune cells) in the peripheral circulation tend to increase, thus boosting the immunity preparing for potential injuries. With sustained stress, there may be a decrease in all types of lymphocytes and associated phagocytes (immune cells that absorbs waste). Then, impairments in cellular immunity appear to be crucial, especially for a novel antigen. Even more NK cells could be less cytotoxic (having a toxic effect on cells), but there are individual differences, and details are still lacking even today (Daruna, 2004, p. 128, 130).

In addition to its impacts on immunity, stress response also has other consequences. For example, chronic stress also affects the brain. A higher level of cortisol may result in cell death (apoptosis) of the neurons in the hippocampus. This in turn leads to sustained HPA axis activation (Wisneski and Anderson, 2005, pp. 97-103), forming a vicious cycle. Thus, stress truly damages the brain (Bremner, 2002). Stress is also relevant to pain. During the initial period of a highly stressful experience, our pain perception may be controlled by stress hormones (Wall, 2000). Furthermore, while we discussed the traditional "fight or flight" stress response, it has also been pointed out that stress response, especially in females, may take the form of "tend and befriend" (Taylor et al., 2000; Taylor, 2002). Finally, although not discussed as much as the stress system, it has also been noted that there is contrasting response to relaxation (Benson, 1975).

Relevant Medical Conditions

Psychoneuroimmunologists also explore various medical conditions relevant to the stress-immunity connection. Some representative cases are discussed below.

Cardiovascular problems are one of the most common diseases normally associated with high blood pressure and coronary artery problems. We also know that acute stress can cause sudden cardiac deaths, and chronic stress can cause various cardiac problems (Sapolsky, 2004a, Ch. 3). However, the involvement of immune activities in these diseases has also been recognized, and thus it is natural to regard the mind-body connection more broadly for these diseases as discussed in Daruna (2004, pp. 138-139) and Wisneski and Anderson (2005, pp. 92-94).

Rheumatoid arthritis (RA), an autoimmune disease, can also be triggered by infection (Daruna, 2004, pp. 167-168). Then, the impact of the mind-body connection cannot be ignored. For example, personality and relationships are shown to be important factors (Daruna, 2004, p. 171), and even emotional inhibition has been associated with RA (Daruna, 2004, p. 176).

Cancer, as a genetic neoplastic disease, has been suspected as caused by the impact of stress probably more than other disorders. In fact, 15% of cancer is estimated to be due to chronic infection (Daruna, 2004, p. 135), although direct attempts to investigate the connection are scarce (Daruna, 2004, p. 162). However, the situation seems rather complicated. For example, non-virally induced cancers may even stop growing under stress (Daruna, 2004, p. 176). It is not clear how stress affects it in such a case.

Gastrointestinal (GI) disorders, such as gastric ulcers, are another common problem. Until relatively recently, stress was considered as the main factor in these disorders. However, after the recognition of *Helicobacter pylori* as *the* main component of ulcers, the role of stress has since been overlooked. The CDC even distributed information to ignore the stress factor (Sapolsky, 2004a, p. 87). Psychoneuroimmunologists point out that not everyone infected with *H. pylori* suffers from the disorder and thus re-emphasize stress as an important factor (Weiner and Shapiro, 2001). Although it is said that nearly everyone in the

Western world has *H. pylori* (Sapolsky, 2004a, p. 86), these types of infections (as well as GI ulcer cases) may be decreasing (Kolata, 2006).

Asthma, a non-infectious, allergic disease, has a history analogous to GI disorders with respect to the effect of stress. From the 1930s to 1950s, it was thought of as a nervous disorder, possibly caused by a problematic mother-child relationship. Once the mechanism of immune response is better known, asthma was categorically classified as an allergic disease, and psychosocial factors are ignored. However, it has since been established that allergic conditions can be conditioned (Daruna, 2004, pp. 148-149). More specifically, allergy treatment by glucocorticoids can enhance immunoglobulin E (IgE, a type of antibody) and aggravate the underlying problem (Daruna, 2004, p. 150). In both GI disorders and asthma, the complex, overall picture has been reduced solely to physical causes. This is the pattern consistently observed in conventional medicine, a concern of holistically minded people.

General Mechanism Underlying the Bodily Interconnection

The main mechanism behind stress response is the nervous-immune system interaction (Daruna, 2004, Ch 5), which has many aspects. A brief summary is given below; additional details are available in Maier (2003).

First, the process involves a variety of chemicals (Wisneski and Anderson, 2005, p. 47) as messengers, and their respective receptors (site of the cell membrane that binds with chemicals for some action) as interpreters. This process is described in Lipton (2005) in a very accessible manner. The immune system heavily depends on releasing and binding chemicals. Even the nervous system relies on the same mechanism, especially at synapses between neurons. Thus, the immune system can release cytokine (a chemical to signal immune functions) in the central nervous system (CNS), which can induce sickness behavior. Such a process has measurable effects within the CNS, e.g., electrical activities, alterations in neurotransmitter (type of chemical) levels in the CNS (Daruna, 2004, pp. 94-96). For example, Besedovsky and his colleagues showed that neural activities in the hypothalamus increased during peak antibody

response to a vaccination (Wisneski and Anderson, 2005, p. 51). The receptor binding process is in reality extremely complex. The lymphocyte reveals its receptor for insulin (hormone to metabolize sugar) only after the presence of an antigen (Wisneski and Anderson, 2005, p. 46). In many cases, receptors are shared by multiple chemicals (Wisneski and Anderson, 2005, pp. 49-64). Furthermore, the immune signal may take a pathway from the abdominal area traveling through the vagus nerve, which connects the brain and the internal organs (Sternberg, 2000, p. 186). Due to the complexity of the mechanism, it is no wonder that it was discovered only recently by psychoneuroimmunologists.

Second, the nervous system also affects the immune system in various ways. For example, peripheral nerve endings appear not only in the primary lymphoid tissues but also in *all* the tissues where immune responses are involved. This ensures the role of the neural component to the endocrine effects on immune responsiveness (Daruna, 2004, p. 101). Through this route, the limbic system, including the amygdala and the hippocampus, modulate the immune system. This brain location is essential for emotional processing, and thus the involvement of emotion is suggested (Daruna, 2004, pp. 95-96). Additional evidence can be found in lesion studies. Lesions to either neocortical hemisphere affect immune response. While lesions to the left hemisphere tend to be immunosuppressive, such as decreased T-cell (immune cells that mature in the thymus) numbers, lymphocyte proliferation, and NK cell activity, lesions to the right hemisphere tend to be immune-enhancing, such as increased T-cell numbers and no effect on NK cell activitiy (Daruna, 2004, pp. 95-97). This suggests a cognitive link. That is, as the right hemisphere is considered to be associated with negative emotion (Davidson, 2003), negative emotion could suppress immune function. Another aspect of neural effects on the immune system is classical conditioning, such as the experiments by Ader on mice and by others on humans as discussed earlier. However, Daruna (2004, pp. 98-99) notes that specific pathways are still unknown; we will explore more recent results in the following section.

In this section, we reviewed the contributions of psychoneuroimmunology mainly based on our main references. As a result, we gain a partial answer to our main question of mind over health. Regarding the first part of the question–"to what extent"–we know that certain mental states, such as those

due to psychological stress, can impair our health at a measurable level by contributing to reduced immune functions. Since psychological stress is relevant to many other common medical conditions, wherever this type of stress is suspected, analogous health impairment is also possible. As psychological stressors involve predictability, control, outlet of frustration, and social impacts, it is fair to say that we have a scientific basis for believing that these factors are crucial for our health. Regarding the second part of the question–"how"–we have fairly detailed knowledge of how the nervous, endocrine, and immune systems interact mainly through various chemicals, their receptors, and other pathways within each system. However, how psychological stress actually initiates the process is not discussed in our main references.

3. More Recent Advancements: Placebo Effects and the Underlying Mechanisms

In the previous section, we reviewed a partial answer to our main question surrounding the stress-immunity connection. While it is a crucial first step, the problem of mind over health is much broader than that. For example, we did not discuss placebo effects, even though the conditioning studies have shown a strong connection to this topic. This reflects the limited coverage of placebo effects in our main references. Wisneski and Anderson (2005, p. 135) even propose that placebo *is* psychoneuroimmunology. Such an oversimplification is not at all helpful. In this section, we extend our inquiry into placebo effects and relevant concepts such as cognition and emotion, bringing in more recent advancements in placebo research.

Placebo Effects

Here is a simplified example of the "placebo effect." For a supposedly incurable disease, a physician gives a patient sugar pills (with supposedly no positive impacts on the disease). Even without any "medical" reasons to believe that the sugar pills would cure the disease, the patient may be improved or cured. Although placebo effects have been documented abundantly, both the term itself and the idea have been shunned by the conventional medical community. This is partly due to the difficulty associated with understanding the mechanism behind the placebo effects and partly due to the ethical question of whether physicians are allowed to "lie" about their treatment (i.e., referring to sugar pills as drugs). The opposite of placebo, "nocebo" (e.g., voodoo death), has received even less attention. However, nocebo effects may be observed when, for example, physicians "determine" their patients' time to live, which seems to happen fairly commonly. In short, placebo is something the conventional medical community always wanted to eliminate.

Despite the resistance of the conventional medical community and the individual variability associated with placebo effects, the topic has been researched seriously and placebo effects have been known to be real based on the research (e.g., Harrington, 1997). In a sense, the current situation

surrounding placebo effects is analogous to that surrounding stress before the advancements in psychoneuroimmunology. As more and more research results accumulate, people's perception and understanding of placebo effects may well follow the path of stress research. We can no longer ignore placebo effects; we need to squarely face them and take advantage of the findings where possible.

Distinct Aspects of Placebo Effects

Placebo effects can be observed in a variety of contexts, as in the case of stress. Thus, it is extremely difficult to pin down the underlying mechanisms. However, we now have substantially more detailed knowledge about it than, say, even a decade ago. In the following, we discuss three aspects of placebo effects: conditioning, expectation, and meaning. The majority of the current literature focuses on the distinction between the first two.

Ader's pioneering work (i.e., the effect of an immunosuppressive drug elicited by the taste of saccharin after conditioning, as mentioned in the previous section) identified the conditioning aspect of placebo effects. That is, a placebo (e.g., sugar pill) is considered as conditioned stimulus (CS) and the placebo effect (e.g., healing) as conditioned response (CR). For example, the side effects of cancer chemotherapy (CR) may be triggered even before the patient actually receives the treatment (unconditioned stimulus; UCS) as the patient approaches a hospital (CS). Conditioning is the most well-studied aspect of placebo effects. Many researchers may only discuss this aspect of placebo effects (e.g., Freeman, 2004, pp. 84-86). Some would even argue that all placebo effects are conditioned (e.g., Ader, 1997).

Next, note that Ader's experiment was on mice, and the effect must be considered in principle *unconscious*. Many cases of documented placebo effects appears to involve *consciousness* in a more complex way. For example, Mr. Wright healed from cancer with a new, experimental drug, became ill again after learning FDA reported that the drug is ineffective, healed again with placebos introduced as a stronger version of the drug, and died after reading a newspaper story reporting that the drug is completely worthless (e.g., Newberg and Waldman, 2006). Here is another example. If one expects the effect of caffeine in coffee, the positive effect might appear even if she drinks a decaffeinated

coffee (Moerman, 2002, p. 125). In order to explain cases like these, Kirsch (1997) proposes to explain placebo effects as expectation. While conditioning and expectation must be distinguished, many real cases of placebo effects may involve both of them and it may be difficult to separate them. Note that the discussion of placebo effects in Daruna (2004, p. 210-213) does not clearly distinguish these aspects.

Then, Moerman (2002, p. 126) discusses an example that even expectation may not be able to explain. Patients who take four inert pills would heal faster than those who take two inert pills. These two classes of patients may never have *expected* the consequence differently. However, they *recognized* the quantitative difference and reacted accordingly. To this end, Moerman proposes that placebo effects are what people respond to as the meaning relevant to the situation, which is referred to as "meaning response." This aspect of placebo effects has received much less attention in the literature. In a more recent work, Thompson (2005) refers to Moerman, but he does not seem to go beyond Moerman with respect to the essence of placebo effects.

Mechanisms Underlying Placebo Effects

In Section 2, especially in connection to stress, we reviewed the mechanism of how our health depends on immune functions. When placebo effects have an impact on our health, an analogous mechanism must be involved. In addition, recent research results provide insight into how conditioning and expectation might be linked to the immune system.

The "conditioning" aspect of placebo effects has been studied extensively by psychoneuroimmunologists, though not specifically labeled as such (reviewed in Freeman, 2004, Ch. 3). As a result, we have a better understanding of this aspect of placebo effects; this is why Wisneski and Anderson (2005, p. 135) equate placebo effects with psychoneuroimmunology. However, we are still in an early stage of an extremely challenging project. Recently, Pacheco-López et al. (2006) concluded the "Brain Mechanisms of Placebo" series in *Brain, Behavior, and Immunity* with a summary article. According to the article, parts of the brain, including the insular cortex (lateral part of neocortex hidden by the temporal lobes) and the amygdala appear to be involved in the conditioning

type of immunomodulation. That is, the information goes through these areas to the hypothalamus to activate the stress response (as reviewed in Section 2) as well as through the vagus nerve.

The research on the "expectation" aspect of placebo effects has a much shorter history, mostly within the past decade. Again, according to the same article (Pacheco-López et al., 2006), the reward/dopamine circuitry through the prefrontal cortex and the limbic system is the key to the expectation-based immunomodulation. Note that the reward circuit is also called the SEEK system and is considered one of the basic emotion systems (Panksepp, 1998). The level of certainty about the expected situation is also relevant; a particular level of uncertainty may increase the expectation in this circuitry, with a positive effect. Since negative expectation is naturally associated with fear, the role of the amygdala may be crucial for declined health.

Although conditioning and expectation are discussed as distinct aspects of placebo effects with distinct underlying mechanisms (prior to the stress response part, which must be common), it would be difficult to separate the two in real cases. Even carefully designed studies (e.g., Lorenz et al., 2005) may not be as successful separating the two as they claim. In this connection, the distinction between conditioning and expectation as the distinction between unconscious and conscious, respectively, may be too simplistic and premature.

As for the "meaning" aspect of placebo effects, there is virtually no comparable research. This is understandable because the notion of meaning is far too complex for the current approaches. However, it seems that the notion of meaning subsumes the notion of expectation, although both of them are complex cognitive processes. Then, we can speculate that the mechanism underlying the meaning aspect may be similar to the mechanism underlying the expectation aspect. In addition to the cognitive components, both the expectation and the meaning aspects must involve emotional components. This is consistent with the brain studies for the expectation aspect, which appears to involve the limbic system, an area highly relevant to emotional processing. The conditioning aspect too must involve emotional components because it involves the limbic system (the amygdala in particular) as described above. However,

conditioning proper may not involve as much cognitive components, as it is associated with more unconscious effects.

Cognition and Emotion in Mind-Over-Health Research

As reviewed above, we are beginning to understand the brain mechanisms of placebo effects, especially for the conditioning and expectation aspects. Through this exploration, we realize that placebo effects involve both cognition and emotion, which in turn affect the immune system. In the previous section, we discussed psychological stress (due to predictability, control, outlet of frustration, and social impacts), which also involves cognition and emotion. Thus, in order to explore the problem of mind over health, we need to have a solid understanding of cognition and emotion, especially in connection to the immune system and other possible health functions. Unfortunately, the discussion of cognition and emotion in our main references and also other relevant references is fairly limited as reviewed below. In fact, it has even been argued that the current mind-body research is "mindless" (Dienstfrey, 1999).

The importance of expressing emotions for reducing stress has been noted in the main references (e.g., Daruna, 2004, pp. 213-214, 221). However, emotion itself is not really explored in the same literature. As for how it relates to health, some fragmental ideas can be found. For example, Sapolsky (2004a, pp. 51, 350-351) states that certain opposite emotions, e.g., extreme forms of pleasure and shock, have similar physiological mechanisms. He also comments on the connection between emotion and cognition (Sapolsky, 2004a, pp. 5-6, 411-412); cognitive control is possible for better stress management dealing with emotional aspects.

Another point about emotion is its chemical basis, involving neurotransmitters and hormones (Wisneski and Anderson, 2005, p. 268). We are aware of the use of exogenous (derived from outside the body) chemicals for control of certain emotions as well as pain. Noting that opiate receptors exist throughout the body, Pert and her colleagues (1997; 2005) argue that emotions are felt in the whole body and thus affect health. Yet another possibility of how emotion affects health is through developmental stages from infancy through childhood (e.g., Lewis, 2002). Citing Antonio Damasio, Wisneski and Anderson (2005, p. 268) state that neural patterns of emotions reveal that "the subjective process of

feeling emotions is partly grounded in dynamic neural maps." However, the subjectivity of emotion is an area still actively debated; we will return to this point later. Additional information on the emotion-health connection (both directions) can also be found in Booth and Pennebaker (2000).

As for cognition, the literature has some details on the effects of stress on cognition (Sapolsky, 2004a; b), as well as on psychopathology (Daruna, 2004, Ch. 10). The other direction, i.e., how various cognitive factors affect our health, is not explored in detail, even though that is more relevant to our main problem of mind over health. One exception is about a special case of learning, i.e., immune conditioning (e.g., Daruna, 2004, pp. 98-99). Another example is learned helplessness, i.e., a subject heavily exposed to uncontrollable stressors would fail to learn even simple cues to avoid new stress (Sapolsky, 2004a, pp. 300-304). However, these types of limited learning mechanisms must be happening unconsciously and would be quite different from more complex forms of cognition. Sternberg (2000, Ch. 9) describes the effects of belief and expectation in length, writing that "the healing effects of belief and expectation might come only through the removal of stress and the reduction of the immune-suppressing hormonal burst." In particular, she describes the mechanism of learning (conditioning) and pain control, e.g., for child birth. However, there actually is no discussion of how higher cognition, e.g., belief, would affect health. In this respect, Newberg and Waldman (2006) is not helpful either, despite their attempt to explain the mechanism of beliefs. Although emotion, belief, suggestion, and expectation are mentioned in our main references (especially Daruna, 2004, pp. 208-212), there are very few discussions of how they affect health. In addition, although meditation is reported to reduce emotional reactivity (Freeman, 2004, p. 523), there is no discussion of what aspects of meditation, e.g., emotion and/or cognition, would be affecting the outcome.

One interesting idea about the effects of belief is put forward by Lipton (2005). He argues that the membrane of each cell has receptors which respond to energy, citing the work of Tsong in 1989. These receptors control how the cell behaves in its physical, chemical, and electromagnetic environment. He further argues that thoughts are the mind's energy, which eventually controls those

receptors. Although this is an intriguing idea, the latter part of his argument does not yet seem to be supported by research.

Finally, let us note the following statement of Freeman (2004, p. 57): "The ultimate goal of mind-body research is to determine under what conditions and to what degree stressors and conditioning factors alter immunity. Once this information is elucidated, new methods for the management of immune dysfunction can be developed." This seems to illustrate how limited the researchers' view of mind over health could be.

Further Exploration of Emotion and Cognition

In order to expand our understanding of cognition and emotion, we will briefly review the literature in these areas. We will focus on emotion; but we will also discuss its connection to cognition.

Since emotions are often considered the irrational part of mind, scientists tend to exclude or ignore them from their studies. However, it seems that there is a recent revival in this topic, especially thanks to advancements in neuroscience. Since emotion, as well as cognition, is a huge topic, this booklet will only be able to scratch the surface so that the information can be used for later discussion. Much of the discussion on emotion is based on Plutchik (2003), but more information can be found in Lewis and Haviland-Jones (2000). Note that some argue that the terms "feeling" and "thought" are linguistic and thus conscious (Booth and Pennebaker, 2000). But we will not necessarily stick to this idea, because emotions are notoriously difficult to express in language and thus we need to consider emotions regardless of their linguistic connection.

As summarized in Plutchik (2003), the first well-known modern theories are proposed by William James and Walter Cannon. James considered emotion cognitive appraisal of the body as functions of the neocortex. Cannon tried to refute James' idea proposing that emotion occurs in special emotion circuits in the brain, pointing out that the cognitive process is too slow as an emotional experience. Since then, there are many more theories affected by these two. Partly due to the advancement of neuroscience, we now know that neither James nor Cannon alone was completely right.

Then, it has been shown that there are brain sections which activate heavily during emotional experiences, e.g., the amygdala for fear/anxiety (LeDoux, 2000); see also his other work (LeDoux, 1996; 2002). In general, the area called the limbic system and its vicinity (e.g., ACC) appears to activate during various emotional experiences (Panksepp, 1998). From the evolutionary perspective, this area is classified as old-mammalian brain (by Paul MacLean as reviewed in Plutchik, 2003). This contrasts with the neo-mammalian brain, i.e., neocortex.

One of the implications of this finding is that the brain areas specialized for emotions can respond quickly to various types of information, including sensory and visceral. This would involve appraisal (an idea of Richard Lazarus) and readiness for action (an idea of Nico Frijda), as reviewed in Plutchik (2003). For different emotional experiences, there often are different responses, e.g., physiological and facial expressions. However, this aspect of emotion is relatively inflexible. As certain mammals evolved further, emotion also evolved so that individuals can respond to various situations in more flexible ways. What is involved in this is cognition (e.g., LeDoux, 2000; Phelp, 2004). It is even argued that what distinguishes human beings from other primates is the higher-level awareness of "self," based on the cognitive function to inhibit emotions (Solms and Turnbull, 2002). In fact, emotion and cognition are both essential aspects of the development of the human mind (Engel, 2005; Siegel, 1999) and thus need serious attention. The bidirectional nature of the emotion-cognition connection is discussed in Johnson-Laird and Oatley (2000). Another concise summary of the connection between emotion and cognition is in Buck (2000). All of these point to the complexity involved in the interconnectedness and interaction between emotion and cognition. In a sense, the distinction between the fixed and the flexible parts of emotion roughly correspond to the distinction between unconscious and conscious sides of emotion; the latter is discussed in Lane (2000). However, such distinction may diminish if we follow an idea that emotion always involve cognition (Clore and Ortony, 2000).

Although some biological analyses of emotion focus on the central nervous system (CNS), that is not the only element involved in emotion. As Pert and her colleagues (1997; 2005) argue, there are receptors for a whole range of chemicals in various parts of the body. For example, opiate receptors can be

found not only in the brain but also in other parts of the body, all of which may cause some emotional reactions. On the other hand, Panksepp (1998) points out that certain chemicals have related but different functions in the brain and in other parts of the body. For example, oxytocin works for birthing and milk letdown peripherally, while it also works for maternal acceptance and readiness centrally.

An important aspect involved in both emotion and cognition is subjectivity, as each person feels and thinks differently. For example, Damasio (2000) distinguishes between emotion and the *feelings* of emotions (see also his other work Damasio, 1994; 1999; 2003). Then, stress research based on cortisol levels may be measuring some physiological aspects of emotions but not necessarily the subjective feelings. He writes, "Discovering chemicals involved in emotions and moods is not enough to explain how we feel." Naturally, the subjective "feeling" part would rely on cognition to access the more flexible, reflective processing of emotion.

In the above, we noted (1) the complex interaction between emotion and cognition, and (2) the subjectivity involved in both emotion and cognition. Unfortunately, there is little research that addresses these points in connection to their impact on health. In a sense, the placebo research reviewed earlier seems to be the best we can get at this point.

Integration: Cognition, Emotion, and Immunity

Before closing this section, we propose to integrate what we reviewed in this and the previous section (mainly based on Pacheco-López et al., 2006; Panksepp, 1998; Solms and Turnbull, 2002). We have identified the expectation aspect of placebo effects as one case of the mind part involved in mind over health. Since expectation is a kind of belief with the addition of the temporal dimension (more on this in Section 4), and some psychological stressors such as predictability and control also involve these components, all of these cognitive phenomena must be closely related. Then, expectation/belief, as a conscious activity, initiates in the prefrontal cortex and then invokes the reward/SEEK system, whose main neurotransmitter is dopamine (DA). This system projects to areas including the amygdala, where DA may reduce fear, especially with

positive expectations. Such an emotional state could reduce the stress response, which in turn supports immune functions.

However, as mentioned in Lipton (2005, p. 127-128), positive thoughts alone are not sufficient for a positive health outcome. Sapolsky (2004a) points out that it is erroneous to believe that our thoughts alone can cure disease. Particularly when the health condition becomes worse, it would be difficult to maintain positive thoughts. One possibility is the involvement of another basic emotion system, the pleasure or LUST system, which is more or less reciprocal to the reward/SEEK system. Depending on how one's expectation is met (naturally after a certain amount of time), this system interacts with the hypothalamus through the key neurotransmitter endorphin, where the stress response is controlled. Thus, positive emotions after one's expectation is met could be another element in mind over health. However, it is not that negative emotions are categorically bad (Pert et al., 2005). Acknowledging negative emotions can have a positive outcome with respect to health (Hafen, 1996, citing Rachel Naomi Remen), and the existence of an outlet of frustration is another factor in psychological stress. Since positive (pleasant) and negative (unpleasant) feelings are associated with the direction toward and away from homeostasis, respectively (Panksepp, 1998, p. 182), the ability to recognize and accept emotional fluctuation may actually invoke a kind of satisfaction in the pleasure/LUST system, which could in turn result in a good health outcome.

In this section, we reviewed placebo effects and their underlying mechanisms, which led to further exploration of cognition and emotion. As a result, we have gained a more refined answer to our main question of mind over health. Regarding the first part of the question, i.e., "to what extent," we know that our expectations too have measurable impacts on our health. Although this suggests other forms of cognition including beliefs and meaning in general, this possibility has not been confirmed by research at a comparable level. Regarding the second part of the question, i.e., "how," we now know that expectations emerging in the prefrontal cortex can influence the limbic system, which in turn can modulate the immune system through stress response.

4. The Limitations of the Current Research: Complexity and Subjectivity

In the previous sections, we reviewed the current research to find an answer to our main question. However, our knowledge is still far from what we would really like to gain. In the previous section, we also pointed out two major issues involved in this pursuit: complexity and subjectivity. In this section, we start with general ideas about complex systems, which leads to the notion of holistic health, as well as the limitations of psychoneuroimmunology in particular and scientific methods in general. Then, after backing off, we will note a complementary approach to the question of mind over health.

Properties of Complex Systems

Throughout this booklet, we face a recurring theme, complexity, for example in the immune system, or emotion/cognition. Complexity is indeed a major obstacle to our pursuit of knowledge. On the other hand, our curiosity and ability to address many interesting questions are the results of the complexity of the brain. In this subsection, we will discuss a way to deal with complexity.

Many aspects of our modern life take advantage of the idea of "reductionism" (in the most common sense), i.e., a position that the whole can always be understood by analyzing its components and the relations among the components. This is an extremely powerful idea because it allows us to distribute tasks and processes so that a large project can be completed through division of labor. Reductionism is naturally one of the main assumptions in the modern scientific and technological approaches. We owe a lot to reductionism regarding our knowledge of, say, the human body. Thanks to reductionism, a broad range of subjects can be studied in academia, i.e., the existence of many academic disciplines. Even in holistic health, we would rely on reductionism where applicable. However, there are limits to reductionism. Despite the success of reductionism, virtually no complex systems can be *completely* understood reductionistically. We can easily recall the conventional medical community's false belief–in the autonomy of the immune system. Also note the comment of Panksepp (1998) that psychological studies often ignore

neuroscience and cognitive science customarily ignores emotion. Possibly reflecting this situation, psychoneuroimmunology too has fairly fragmental treatment of the mind, as reviewed in the previous section. Also if we look at the state of higher education, it is obvious that colleges and universities are highly departmentalized and there are very few integral or holistic approaches to various complex problems (e.g., health, globalization).

In contrast, "holism," the term coined by Smuts (1961) in the 1920s, is an idea that rejects the assumption of reductionism; i.e., the whole can *not* always be understood by analyzing its components and the relations among the components. In general, complex systems exhibit other properties (e.g., Corning, 2003). For example, it is possible that some unpredictable properties emerge out of the interaction of a complex body of components (e.g., Kennedy et al., 2001). Another important property is that the interactions are nonlinear, e.g., a small change could result in a large consequence as often exemplified in social contexts (e.g., Eve et al., 1997). Furthermore, complex systems will self-organize as in many biological systems (e.g., Camazine et al., 2001).

As demonstrated in psychoneuroimmunology, the human body is a complex system by itself and also in the context of its environment. Thus, when we consider health in a realistic manner in context, properties of complex systems are extremely important. Even just emotion, simultaneously involving several brain structures and functions, is a complex system as well.

The idea of complex systems can also be applied to the discussion of the mind-body connection, e.g., the contrast between "dualism" and "monism." Dualism, most commonly associated with Descartes, asserts that mind and body are separate *substances*. Dualists consider that mental activities are inexplicable supernatural phenomena, which is subject to no scientific research. The practice of conventional medicine appears to be dualistic (although medicine aspires to be scientific, this aspect differs from many scientists' beliefs, as described below). On the other hand, monism asserts that there is only one substance. Note that there actually are many different versions of monism. The most extreme case is called physicalism (or materialism), which asserts that everything can be explained by understanding physical substance (and possibly energy); i.e., the mind is considered *nothing more than* brain activities. Note that

this point is commonly coupled with reductionism. Physicalism is the view held by many scientists, including cognitive scientists.

Between the extreme forms of dualism and monism, there are many intermediate positions. One is called "anomalous monism" (Davidson, 1970), also considered a non-reductive physicalism. In this view, mental events are considered identical as physical events; however, it also asserts that mental events are not strictly regulated by physical events, i.e., the whole may not be governed by rules. As a result, it would be impossible to reduce mental events to physical events. Thus, certain phenomena may be out of the reach of reductionistic approaches. Another is called "dual-aspect monism" (Solms and Turnbull, 2002). In this view, the mind is considered a way of perceiving the self through first-person experience, cf. objective ways to perceive the same self. Although neither of these views could really nail down the gap between the mind and the brain, they are consistent with complex systems ideas.

Notion of Holistic Health

Considering the complexity of the human body and mind in their environments, we cannot help but be amazed by the simple fact of survival and reproduction. Health is also far too complex to fathom completely reductionistically, as noted by Wisneski and Anderson (2005, p. 63) and further emphasized by Daruna (2004, p. 229). While Freeman (2004, p. 91) discusses the possibility of applying psychoneuroimmunology to pharmacology (citing Robert Ader), how a chemical interacts with the whole body is in general extremely complex and must be done very carefully. Often, alternatives to pharmacological approaches are more desirable. We actually know that there is a long history of dangerous side effects overlooked or intentionally ignored for the sake of the profit of some corporations/individuals.

Then, it would be natural to consider health in a holistic way, i.e., in connection to the principles of complex systems. On the web site of the American Holistic Health Association, the first bullet of holistic approach reads: "Balance and integrate your physical, mental, emotional and spiritual aspects" (Walter, 1996). This concise description is a useful starting point because it refers to the three components of mind, body, and spirit in contrast to just body as in the

biomedical model. In addition, it also refers to the balance and integration of mind, body, and spirit. However, as we reviewed earlier in the paper, the balance and interconnectedness are observed on various levels. We will elaborate this point further in the following.

Here, we consider the interconnectedness and balance along *multiple* dimensions including individual, spatial, and temporal ones. Even within the body of an individual, the interconnectedness and the balance of various systems, organs, and other components must be taken into consideration, as pursued in psychoneuroimmunology. This holistic approach is in stark contrast with the conventional medicine (biomedical model), which adopts a more analytic, reductionistic approach (divide and conquer). In addition, interconnectedness and balance is naturally considered within the *whole* individual, i.e., including both the mind and the body. This point actually predates conventional medicine and was valued in ancient civilizations in Greece, India, and China (Daruna, 2004, pp. 12-14). For example, it would not be sufficient to assess the health condition of an individual by, say, measuring a few parameters (e.g., blood pressure) associated with a specific organ or system.Another notion relevant to balance and often discussed in medicine is homeostasis (coined by Walter Cannon), which is a mechanism to maintain stability within a system. For example, there is an argument that pleasant/unpleasant feelings are associated with movement toward/away from homeostasis (Panksepp, 1998, p. 182). More recently, this notion has been extended to "allostasis," a more complex form of homeostasis (McEwen and Lasley, 2002; Sapolsky, 2004a).

The idea of interconnectedness and balance can also be extended along the dimensions of space and time. This is somewhat related to but broader than Dossey's (1999) classification of medical systems between mechanical, mind-body, and non-local (spatial). The spatial extension covers the relatedness of an individual with the outside world, including other people and the environment. For example, psychoneuroimmunologists are interested in the impact of social relation. As human cultures expand with seemingly no limit, we are also more and more concerned about the changing environment.

Along the temporal dimension, we can think of an idea that there is a natural course of state transition for each individual. Subject to all sorts of individual

contexts, an organism would develop in a way typical of that species; in general, earlier stages affect later ones. Eventually, every living organism will die. From this point of view, it does not sound natural if a physician insists that her mission is to prolong every single life regardless of the circumstance. Although it does not need to be deterministic, a holistic approach would seek a way to respect the natural course of life. This point is close to Maslow's (1968) definition of health as "what human beings are at their best," through realizing what they already are, and in contrast with the biomedical notion of health as lack of illness. In this sense, even with biomedical disorders, some people could be "healthier" than others who have no apparent disorder.

The temporal dimension is also relevant to the notion of expectation, an important aspect of placebo effects discussed in the previous section. When one expects something, she certainly has a belief that a certain event might happen in the future. That is, an expectation is a special form of belief which involves a temporal dimension. If one's expectation is close to her natural course of state transition, she will most likely be satisfied; otherwise, the opposite would happen. This process must involve the emotional parts of the brain for evaluation of the situation. Thus, the significance of the expectation aspect of placebo effects may just be the significance of her natural course of state transition with respect to her beliefs.

Regarding the notion of holistic health, there are a few caveats. Our understanding of holistic health is general, cf. more specific characterization referring to energy and spirit (Lewis, 2002, pp. 310-313), and as mentioned earlier not associated with specific approaches, e.g., acupuncture, yoga, biofeedback. It is not labels that distinguish holistic health from others; it is the meaning behind how we think and practice. Then, as long as there are benefits, it is an individual's preference of how she realizes her own holistic health. As Sapolsky (2004a, pp. 178-182) warns, there are inherent limitations to curing and there are suspicious approaches. On the other hand, we may not be able to discount potentially positive impacts of possibly questionable approaches. Recall that the stress-immunity connection was considered questionable or ridiculous before the advancements in psychoneuroimmunology. As a reminder, we note the story of a Native American who was suspicious of the shamans' tricks but eventually became a shaman himself, because his "tricks"

worked (Claude Levi-Strauss and Franz Boas via Moerman, 2002). Another caveat is that if one claims to be a holistic "healer," others might suspect such a claim. In fact, the whole point of holistic health is to focus on the balance on various levels, including the inner healing ability of an individual. Thus, healing processes would not take place in a single direction as if a healer heals a patient. Considering the cognition-emotion-immunity connection reviewed in the previous section, it is clear that the patient's mind must take the initiative.

Limitations of Psychoneuroimmunology

Comparing the notion of holistic health with the current state of psychoneuroimmunology, we are forced to admit to a wide gap. Since psychoneuroimmunology is a relatively young field, it is natural that the accumulation of knowledge would be rather limited. For example, much of what we know in the field is through in vitro (lab) experiments and not sufficiently examined in vivo (real life) (Daruna, 2004, p. 92). As a result, regarding stressors and sample characteristics, we depend on the opportunistic nature of human study, i.e., special population for that kind of stress, which is frequently confounded (Daruna, 2004, pp. 123, 128-130). In addition, it is very difficult to test internal immune function (e.g., lymphoid tissues), and thus, many tests are usually done only peripherally (Daruna, 2004, pp. 125, 128). There also are some concerns about immune measurements, indicating that these measurements and the actual immune functions may not correlate so well (Booth and Pennebaker, 2000). Of course, these limitations may be overcome in the long run with further advancements in the field. However, we will also need to be open-minded with respect to the limitations associated with the current scientific practice.

Limitations of Scientific Methods

Psychoneuroimmunology offers us information generally consistent with our intuition about the effects of mind over health. This is an essential point to begin with. However, it has also been brought to our attention that the psychoneuroimmunological inquiry may not yield complete information. In the

previous section, we mentioned two obstacles to fully answering our main questions: complexity and subjectivity. While these will remain as the principle limitations of psychoneuroimmunology, they are actually limitations of scientific methods in general. Strictly speaking, these limitations discussed here are due to the assumptions of "scientific materialism," while science itself can be more open with respect to such assumptions (for detailed discussion, see Wallace, 2000).

In order to attain scientific rigor, many studies suffer from inevitable oversimplification (Sapolsky, 2004a, pp. 160-164). Here is an example. When a chemical called GLP-1 was considered as a diet pill, it did effectively reduce the appetite of the subjects. However, it turned out that the chemical worked by actually invoking anxiety, a "side effect" nobody would tolerate (Panksepp, 1998, p. 172). Such a problematic proposal would not have been made, if a broader context had been considered. While reductionistic traditions have advanced so much that they can deal with even fairly complex phenomena very well, there still are limitations (Daruna, 2004, p. 229). As another example, placebo research tends to focus on the more manageable conditioning aspect, much less on the expectation aspect, and virtually none on the meaning aspect, which is crucial but not easily measurable. In psychoneuroimmunology, researchers deal with not only individual minds, but also social engagement, which is even more complex (Daruna, 2004). Daruna (2004, p. 5) states "[d]isease emerges as a result of complex interactions among many variables — clinical care should be guided by the fact that disease is a multidimensional condition that is not adequately confronted using one-dimensional treatments." We could also say that the threshold for the HPA axis activation appears to be nonlinear (Wisneski and Anderson, 2005, p. 60), a property of complex systems. As explored in the complex systems literature (e.g., Corning, 2003), it would be impossible to reduce everything.

The impossibility of reducing everything is clearly put forward by Varela et al. (1991). They point out the problem with the current approach of cognitive science, i.e., the environment is predetermined and the observer perceives the environment as given. This position views perception as if scientists observe the environment objectively, which is by no means warranted as can be seen in quantum physics (briefly discussed later). In contrast, Varela et al. view the

connection between the environment and the observer more as an interactive one. Perception can be seen as directed by the observer through her goals and actions. Due to such complex interaction, they conclude that it is impossible to "ground" everything to some fundamental item.

Next, if we tackle the mind-over-health problem and realize that cognition and emotion involve subjectivity, it is straightforward to accept that the concept of health is by itself subjective (Sagan, 1987, p. 9). Thus, subjectivity is inevitable in our pursuit. But subjectivity is by all means an obstacle to scientific methods, which pursue "objectiveness." Certain studies might manipulate a human body electrically or chemically and collect subjective reports. Or, one might analyze pain based on a purely biologically complex theory (Hardcastle, 1999). However, that would ignore subjectivity as an essential component of our experience, including pain. People who do not feel pain cannot live long; perception of pain has survival advantages. We also note that Searle (1998) argues that subjectivity (as part of consciousness) can be studied scientifically. However, Searle states that only statements which are "not a matter of opinion" can be scientific. But the notion of health and one's beliefs and expectations *are* all a matter of opinion. In a sense, if we ignore subjectivity from physicalism, it appears so much like dualism, because the most important part of the mind would be completely left out and can be considered even mystical. In this sense, both the medical and scientific communities are alike, ignoring subjectivity involved in the mind.

Related to both complexity and subjectivity, we also consider individual differences. Regarding the cases studied in psychoneuroimmunology, this problem has already been noted (Sapolsky, 2004a, p. 160). For example, Daruna (2004, pp. 99-101) discusses personality and immune function. But he mainly refers to "temperament," e.g., citing Davidson concerning brain development including the amygdala. Individuality is much broader, including more developmental (and environmental) aspects such as child-caregiver "attachment" as well as a variety of personal styles. In many cases, individual differences can be seen in terms of the form-content connection. That is, the same form (symbol, situation, context, etc.) can have radically different content (meaning, response, etc.). How *each* (unique) person can improve her health by changing how she feels and thinks is highly contextual (Sapolsky, 2004a, p. 268),

especially in the sense of control. For example, one may not necessarily combat her own death, but may well accept it in a certain way. When one faces a difficult situation, generic results based on "averaged" scientific studies may make little sense to that person; it is clear that there is no "average" person. Thus, an intervention based on a hypothetical, average situation would never completely match a real person.

Another related issue is the context of a person. Again for the sake of generalizability, scientific research attempts to *control* the context. However, no two cases have the identical context. Then, even for a single individual, the same approach may not work for the next time (for a comment on intra-individual difference, see Maier, 2003). For a topic as complex as health, in many cases, we need to see each individual in a specific context. Conventional medicine, based on science, certainly underestimates this point.

As with any other research, scientific inquiry also consists of a research question and its significance (Booth et al., 2003). If scientists are preoccupied with their research questions, but overlook the *significance* of their questions, they could easily be affected by external forces, e.g., a funding source. Unfortunately, such a situation has led to many cases of fraud (e.g., Altman and Broad, 2005). This is one example of overemphasizing the "form" (e.g., symbol, procedure, etc.) and ignoring the "content" (e.g., meaning, response, etc.). For example, Sapolsky (2004a, p. 395) discusses the effects of the Lamaze technique during child birth. However, if such a technique is taught simply as a procedure without sufficient explanation of the *meaning* behind it, the students may well be stuck with the procedure itself and may not be able to get the real benefits. Another example is the individual difference in stress response; it depends on what kind of meaning one attaches to a stressor (Sapolsky, 2004a, p. 263). We can also recall that placebo effects can be considered as meaning response (Moerman, 2002). It is how one perceives the procedure that makes a difference. Again, the same symbol can have completely different meanings to different individuals. Unfortunately, many scientific studies tend to deal with symbols with extra care but not their meanings with the same kind of care.

Although conventional medicine aspires to be scientific (Morris, 1998) and tends to obscure its limitations, some other branches of science are more eager

to accept their own limitations. For example, in physics, Heisenberg's uncertainty principle states that one cannot measure the position and momentum of an object with an arbitrary precision. Thus, it is in general impossible to completely identify the state of an object. Even logic, arguably the foundation of mathematics and science, suffers from inherent limitations. For example, logical theories sufficiently powerful to be able to count, such as arithmetic theories (as collections of statements) in first-order logic, cannot prove certain true statements, for example, Gödel's incompleteness theorem (as discussed, .e.g., in Enderton, 2001). This suggests that formal scientific theories cannot exactly represent the truth. In a sense, it is healthy and respectable that logic can reveal its own limitations from within the logical tradition. Science, or any field based on logic, must as well be able to recognize its limitations from within. Another limitation inherent to logic is that it starts with axioms (assumptions), which must be accepted as true and cannot be proven. Thus, if one starts with false axioms, consequences can be wrong even with a correct reasoning process. Naturally, it is crucial to identify correct axioms (or those at least consistent with our observation, experience, etc.).

Phenomenological Turn

With inherent limitations of scientific methods, should we give up our search for an answer to the mind-over-health problem? If we step back and look at the issue at hand more openly, we actually notice that people have always dealt with the issue from ancient times even without science, e.g., narratives as discussed in the next subsection. The attitude of suspending presupposition (e.g., the primacy of scientific methods) is one of the main components of "phenomenology," a philosophical position often in contrast with more "logical" or "analytical" traditions (as introduced, e.g., in Stewart and Mickunas, 1990). It is also important to note that before conducting meaningful research, we must actually go through phenomenological stages to identify meaningful hypotheses (for relevant points, see, e.g., Komagata, 2004). Many researchers do not even realize that they do this implicitly (and thus with little paper trails), except possibly certain qualitative researchers. As a related note, it would be illuminating to point out that Ader noticed the immune conditioning effect by mistake (Ader, 1996). If he had not stepped back and re-examined his assumptions, he would not have had his theory.

As an example of phenomenological inquiry, let us revisit the evolutionary perspective of chronic stress response. The most common explanation of the damaging effects of chronic stress found in most of the current literature is repeated as follows. Stress response is designed for physical stress more appropriate to the days of hunter-gatherers (or other mammals). Since the human body has not evolved since then for the modern life, our bodies cannot deal with a broader range of stress. This explanation must be questioned. As has been documented in the literature (e.g., de Waal and Tyack, 2003), many non-human mammals have very complex social lives. It seems highly likely that they have all sorts of stress including chronic stress, e.g., involving various social relationships (Sapolsky, 2004a, p. 357). In fact, baboons and other mammals have been studied with respect to their chronic stress response (Sapolsky, 2004a). Then, instead of tens of thousands of years, there would have been millions of years for Homo sapiens and other mammals (at least primates) to have developed better biological mechanisms for chronic stress. Here is one possibility. Chronic stress itself may not be that bad; it may even be an essential part of our lives. In other mammals, if they suffer from chronic stress, they may need to live shorter. But since the contexts involving chronic stress are so complex, no specific avoidant patterns may have evolved biologically. Homo sapiens has extended its life expectancy only during recent years. It might be the case that those suffering chronic stress who could not expect to live longer are now living much longer, with more prolonged suffering. Since chronic stress itself is not new to the *modern* human life and is too diverse for biological evolution, no adaptive mechanism may evolve, even with millions of more years. The only way to deal with chronic stress may be for each individual to pay attention to it and adjust to her life accordingly. This is typically what conventional medicine has been avoiding.

Narratives: A Phenomenological Approach to Holistic Health

Now, considering the limitations of scientific approaches and the real need to address complexity and subjectivity in health situations, we will need to step back and address the problem by suspending certain presuppositions. One

approach taken by many people is to use narratives in a variety of ways. It is not important to be stuck with the term "narrative." For our purposes, it is basically synonymous to "stories." It is also referred to as "clinical tales" by Oliver Sacks (Morris, 1998). In any case, narratives have been used to describe health conditions and all sorts of other ideas. The use of narratives is considered also as a key milestone in the evolution and development of the human mind (Donald, 1991; Engel, 2005; Siegel, 1999) and also language acquisition (Nelson, 1996). The importance of narratives in dealing with the holistic health of an individual cannot be underestimated. Narratives can reveal different perspectives of different people, even for a single situation (Morris, 1998). We know that personal stories (e.g., Cousins, 1979; Groopman, 2004) have inspired many people. In particular, the story of Norman Cousins has a strong influence on the advancement of psychoneuroimmunology.

Before proceeding, we should note a few qualifications regarding the use of narratives. First, some would question the accuracy of self reports (e.g., Panksepp, 1998). It is true that narratives do not always reflect the truth. However, scientific research too progresses through revising incorrect theories. Many of the problems associated with the use of narratives are actually due to the lack of interest in and the inability to deal with subjectivity in the scientific community (Varela et al., 1991; Wallace, 2000). For future advancements in the areas involving subjectivity, we must develop a more refined way of integrating narratives. One such possibility would be to use narratives at a higher level. For example, although not exactly on subjectivity, attachment theorists analyze not only the content but also the manner of delivery with respect to principles in linguistic pragmatics (Hesse, 1999). Second, some might complain that stories are weaker than controlled studies because of the lack of generalizability. However, we must note that the information gathered in stories is not to *prove* hypotheses, but is an essential step before designing controlled studies. Furthermore, in order to complement the current weakness of conventional medicine, we really need the rich contexts that stories can provide.

While narratives have a low place in conventional medicine, there still are physicians who rely on narratives. For example, Kleinman (1988) uses narratives to understand the psycho-social aspects of chronic illness. He distinguishes "illness" with complex meaning and "disease" with biomedical

diagnosis, and emphasizes health needs to address illness, not just disease. In this regard, WHO's definition of health makes sense: "a state of complete physical, mental and social well-being and not simply the absence of disease or infirmity" (the 1958 version via Sagan, 1987). Kleinman notes that chronic illnesses are in many cases abandoned by conventional medicine because they cannot be "cured" by medication or surgery. He points out that illness has multiple meanings (to the patient, family, caregivers, etc.), and that the interpretation of illness meaning is an essential part of dealing with chronic illness. Certain diseases are incurable and hopeless; certain conditions appear unfair. How should we deal with such cases? Without first listening to the people involved in such a situation, it would be impossible to derive the meaning. A resolution of such a situation could lead to a better way to cope with chronic illness, even without conventional medical interventions. The emphasis on the meaning instead of the appearance of illness is an essential point of the use of narratives.

Mehl-Madrona, with his use of Native American stories as well as his own experiences, also employs narratives as the main resources both from patients' points of view (Mehl-Madrona, 2003) and from caregivers' point of view (Mehl-Madrona, 2005). He warns against the use of "universal" treatment because each individual is different. He argues that the mechanism of story-telling is by itself a healing process. That is, through the process of *negotiating* stories among the involved people, the patient could find what he needs in order to deal with the situation in a meaningful way. In fact, the healing power of telling a story has been researched, e.g., in the form of journal writing (e.g., Pennebaker, 1993). This might appear close to placebo effects discussed earlier, where Moerman (2002) referred to it as meaning response. Although narratives are used also in psychoanalysis, the approach of Mehl-Madrona seems to respect patients more as active participants.

Here is a relevant example. To reverse heart disease, Dr. Dean Ornish (1990) proposes a very strict program, which is claimed to be "scientifically proven." Still, not all patients benefit from it. Some patients (as can be seen on a video recording) show apparent frustration with the strictness of the program. In such a case, the meaning of the program may not be a treatment but could be a source of chronic stress. Toward the end of this exploration of

psychoneuroimmunology and the mind, we came to realize the importance of meaning. Our impression is that conventional medicine has consistently been ignoring meaning. On the other hand, in the holistic view of health, meaning is everything. To deal with meaning, we need to choose appropriate tools which would reveal and appreciate meaning (interesting approach in Freeman, 2000). That is not possible, even with state-of-the-art medical technology (a similar point in Dossey, 1995).

The conventional medical community and scientists may reject the use of narratives as the single source of information. It is true that narratives alone are not sufficient for understanding complex topics such as mind over health. However, as noted above, scientific methods alone cannot achieve the same goal either. Thus, it is natural that we need to be open-minded and embrace multiple perspectives to tackle the problem of mind over health and other complex issues, including consciousness. For example, collaboration between psychoanalysts and neuroscientists could bring in their respective strengths and may yield new insights into the mind-body problem in general (Solms and Turnbull, 2002). The essence of such collaboration is that psychoanalysis (or narratives) provides subjective experience, and neuroscience provides objective analyses. This point can easily be mistaken even by a Nobel laureate such as Eric Kandel; he encourages that psychoanalysis be more "blind" (Solms and Turnbull, 2002, p. 305). The point of this subsection is that we do need an approach which promotes *awareness*, instead of blindness or objectiveness, as also pointed out by Varela et al. (1991) and Wallace (2000).

Through the discussion of the limitations of psychoneuroimmunology in particular and scientific methods in general, we actually came to realize that our ancient methods make sense. Although we may never completely understand the complexity and subjectivity behind mind over health, especially in a systematic manner, narratives could be used for each individual to make sense of her health and its meaning.

5. Conclusion

Recent advancements in psychoneuroimmunology clearly support the possibility of mind over health by demonstrating the interaction between the nervous and the immune system, especially in the context of psychological stress and the expectation aspect of placebo effects. This is certainly consistent with holistic health. Since both this type of *integrative* research and holistic health focus on the whole person, future research in this direction is expected to be consistent with the notion of holistic health. However, our understanding of mind over health is still rather limited. As two major obstacles to scientific approaches taken by most of the current research, we identify the properties of complex systems, e.g., irreducibility of the whole, and subjectivity involving individual differences. One way to complement this situation is to rely on narratives as both a healing process and research data of the qualitative type. If our goal is to seriously think about each individual's health in a holistic manner, what matters most to the person may not be the rigor and predictability of scientific methods but may be the openness and flexibility of phenomenological approaches.

By understanding the advancements and limitations of the current research, we will be able to position ourselves at the right place to move forward. For example, alternative health practitioners could use the scientific information in this booklet in support of some of their practices, while they also need to recognize the limit of the current research. Skeptics need to accept the fact that certain aspects of mind over health have been demonstrated with scientific rigor. They may also need to realize the inherent limitations of scientific methods and the difficulty associated with *rigorously* disproving certain "exotic" approaches. The general audience could benefit from the relatively up-to-date review of the literature, and could organize their minds to apply the ideas of mind over health to their own health situations. In the end, it is not an either-or situation between conventional medicine and alternative approaches. We can easily imagine (or even recall) situations such as alternative health practitioners flocking to hospitals and conventional physicians relying on beliefs and expectations. Furthermore, this booklet also tries to bridge the gap between the psychoneuroimmunology literature and the emotion-cognition literature. Although each is a huge area, the intersection of these areas seems to remain

very small. We hope that this booklet initiates further discussions on this connection.

There are several directions in which we can proceed from here. Since the field is rapidly evolving, it would be interesting to revisit the same question in the future. Another possibility is to include spirituality in our investigation, as holistic health often concerns the idea of "mind-body-spirit." Here are a few comments relevant to this direction. First, we need to distinguish between religion and spirituality (Freeman, 2004, p. 529), a topic which also invites a book-length discussion (e.g., Fuller, 2001). Then, we can be free from the religious (e.g., procedural) aspects of "spirituality" and focus on the *meaning* of spirituality. We notice that there are some limited aspects of spirituality which can be discussed from the mind-body view point (as in this booklet). This falls in the domain of *conscious* effects of, say, distant praying. That is, if a subject knows that someone is praying for her, this *knowledge* could certainly affect her health. On the other hand, if a subject does not know that someone is praying for her, such a case would involve *unconscious* effects, certainly beyond the scope of this booklet. However, such a phenomenon could still be discussed in terms of notions such as "nonlocal" (Dossey, 1999) and "transpersonal" (Lawlis, 1996). It would also be worthwhile to explore mindfulness meditation as practiced by Buddhists (Varela et al., 1991), which could overcome the limitations of scientific methods.

We could also explore the mind-body connection behind energy medicine, which has been attracting some researchers (e.g., Oschmn, 2000). An interesting starting point could be Lipton's (2005) idea that energy mediates the cognitive brain activities, e.g., beliefs, and the cell membrane activities throughout the body, also possibly in connection to ideas in quantum physics.

Yet another direction is a careful investigation of "meaning" associated with various forms: symbols, behaviors, ideas, lives, etc. Earlier, we noted the importance of meaning in the context of placebo effects (Moerman, 2002). But the notion of meaning is far broader. One important point again is that a symbol (or any other form) can be interpreted by different people in different ways. Thus, if a person pays attention only to a form, she may well miss the importance of how it *affects* other people. For example, certain life styles

(possibly as a cause of health and illness) and medical interventions may or may not be good for a person. Furthermore, we could analyze why some "irrational" behavior, e.g., teen smoking, continues.

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