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BOB ADER ON PLACEBOS & PSYCHOSOMATIC DISEASE

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Many people, including physicians, may not know who Robert Ader is, but almost everyone is familiar with psychoneuroimmunology, a tongue twisting term he coined over three decades ago to describe his ability to condition the immune system, just as Ivan Pavlov had done with the gut. Pavlov's classical conditioning study was based on his observation that if a dog saw a piece of meat, it would sniff it and immediately start to salivate. If someone rang a bell, the animal would simply turn around to see where the sound was coming from. However, if he repeatedly rang the bell first and immediately followed this by giving the dog some meat to eat, after repeating this several times, simply ringing the bell was sufficient to promote salivation. And since this sound was a signal that the meat would soon be coming, the dog's body reacted as if it were already there, with an increase in gastrointestinal secretions and motility.

Also Included In This Issue

- The Birth Of Psychoneuroimmunology
And Its Skyrocketing Growth.....2**
- Engel's Biopsychosocial Model,
Psychosomatic Medicine And Stress.....8**
- Has Psychoneuroimmunology Research
Resulted In Any Clinical Benefits?.....10**
- Why Do You Believe That Placebo
Effects Are Conditioned Responses? ...11**
- Some Ader And Selye Parallels —
Psychoelectoneuroimmunology?14**

Similar conditioned responses were subsequently demonstrated in other animals as well as humans, and Ader, a psychologist, wondered how long this conditioning effect would last. He injected rats with Cytoxan, which causes nausea, and simultaneously fed them water containing saccharin. The association of nausea with saccharin's sugary taste resulted in subsequent avoidance of the sweetened water, a conditioned response. But the rats had to drink it when this aversion was overcome by severe thirst. Some avoided drinking longer than others, and a few died, not from dehydration, but infections.

In point of fact, deaths seemed to occur in those animals that drank the most saccharin-laced water on the single conditioning trial. Cytoxan was used in such taste aversion experiments because it predictably made the

animals feel sick. Cytoxan is used to treat certain cancers since it suppresses specific immune system components, which improves results. Unfortunately, like other chemotherapy drugs, patients who are sensitive or receive too much may be at increased risk for infections due to lowered immune system defenses. Although these influences did not seem to apply to this study since the rats were no longer receiving Cytoxan, was it possible that the sweetened water somehow continued to suppress their immune systems?

The Birth Of Psychoneuroimmunology And Its Skyrocketing Growth

Along with Nicholas Cohen, an immunologist, Ader did subsequent studies that confirmed this by measuring the amount of antibody that was produced in conditioned and unconditioned littermates. Others had previously suspected that the brain could influence the immune system, and George Solomon had actually established a "psychoimmunology" laboratory. However, this was first scientific proof that a nervous system signal (taste) could dramatically affect the immune system. The subsequent explosion of interest in this was unprecedented in my opinion. Some indication of this is evident in the first edition of Ader's Psychoneuroimmunology in 1981, which had no references to AIDS. The second edition 10 years later, co-authored with Felten and Cohen, was dedicated to George Solomon, who was the senior author of the concluding chapter. This was entitled "Psychoneuroimmunologic Aspects of Human Immunodeficiency Virus Infection", and its 32 pages included 150 references. The 2001 third edition was so huge that it required 2 volumes and the last in 2006 was even larger. I had been planning to do a Newsletter interview with Bob Ader for some time to discuss the above and recent advances in this field as well as his views on psychosomatic disease, stress, placebos and other mind/body issues. This was delayed because of various scheduling and health glitches, so without further ado, let me begin as follows:

PJR: I would like to make sure that my brief description of what led up to your groundbreaking discovery is accurate. There are undoubtedly other important details that were omitted and would be grateful if you could fill in the blanks. I suspect many of our readers would be curious as to when you coined the term psychoneuroimmunology. How can you explain the dramatic escalation of interest in this discipline and its continuing upward spiral?

RA: Notwithstanding its corrupted use by some clinical practitioners, psychoneuroimmunology, simply stated, is the study of the interactions among behavior, neural and endocrine function, and immune system processes. The term was first used in 1980 in my presidential address to the American Psychosomatic Society. Its most conspicuous use was as the title of my edited volume in 1981, reviewed and prophetically described as "The signature volume of a new field of research." The central premise of this interdisciplinary field is that adaptation is the product of a single, integrated

network of defenses. Each component of this network evolved to serve specialized functions. These are the parochial interests of the "disciplines" into which we have divided the biological sciences. At the same time, though, each component of this defensive network monitors and responds to information derived from the others. Thus, we cannot fully understand immunoregulatory processes without considering the organism and the internal and external milieu in which immune responses take place.

As you know, the immune system was once considered a self-regulating, autonomous agency of defense, critical in defending the organism against the invasion of foreign material. At one time, the immune system was defined as that agency of defense that was independent of the nervous system. Research, most of which has been conducted over the past 30 years, however, has revealed that immunoregulatory processes are, in reality, influenced by the brain and, conversely, that neural and endocrine functions and behavior are influenced by the immune system.

With respect to filling in some blanks about the background of psychoneuroimmunology, and others who made significant contributions, we were not aware of it at the time, but Russian scientists had conducted studies on the classical conditioning of immune responses in the 1920s. Indeed, that was the first sustained program of research on brain-immune system interactions. A conditioned stimulus (e.g., heat, tactile stimulation) was repeatedly paired with injections of foreign proteins. Subsequent exposure to the conditioned stimulus alone was thought to have induced antibody production. Although it was reviewed in English language journals by the eminent Clark Hull in 1934, it attracted little attention outside the Soviet Union. Within the Soviet Union, it provoked heated arguments since some investigators believed (but the scientific community rejected the notion) that an antibody response was the direct result of neural activity, i.e., that the nervous system, by itself, could stimulate antibody production. Other early indications of CNS influences on immunity came from Szentiványi's studies in the late 50s showing that hypothalamic lesions could prevent anaphylactic shock in animals. Similar lines of research were initiated sporadically following this.

One of the earliest pioneers in the study of behavioral influences on immunity was Fred Rasmussen, a microbiologist at UCLA. Intrigued by the possibility that emotional states could influence the course of infectious illness, Rasmussen teamed up with Norman Brill, a psychiatrist—probably the first such collaborative team—to start a program of research on stress and infectious disease. During the 1950s and 60s, Rasmussen and his colleagues examined the effects of various stressors on mice inoculated with different viruses. Susceptibility to infections was increased or decreased, depending on the nature of the stressor. These studies, with obvious implications for the neuroendocrine modulation of immunity, also failed to attract much attention, although they were forerunners of some of the research on early life experiences and disease susceptibility initiated by Stan

Friedman, a pediatrician, and myself and by George Solomon and Alfred Amkraut in the mid 60s. George Solomon was one of the real pioneers in the development of psychoneuroimmunology. His initial research examined the life histories and personality characteristics of patients with autoimmune disease. In the best known of their studies, Solomon and Moos compared rheumatoid arthritis patients with their "at risk," but healthy, relatives. Their analysis also included the presence or absence of rheumatoid factor, an anti IgG antibody characteristic of rheumatoid arthritis. Compared to the patients, rheumatoid factor positive relatives were psychologically "healthy," lacked anxiety, depression, or alienation and reported good relationships with spouses, relatives and friends. Psychological well being seemed to have had a salutary effect in the face of a genetic predisposition to autoimmune disease. George was convinced that experimental research would be more persuasive, so, as you indicated, he established a "psychoimmunology" laboratory and studied the effects of behavioral, social and endocrine manipulations in animals on immune function and responses to a bacterial antigen, virus-induced tumors, and adjuvant-induced arthritis. As in other such studies, the results varied depending on the stressor and the outcome measure. Solomon thought that "nobody was listening," and, in the early 1970s, he had to discontinue this line of research—temporarily. Ten years later, he returned to it and adopted a psychoneuroimmunologic perspective in his clinical research program on AIDS.

During the 1970s, Hugo Besedovsky, another very prominent figure in the development of what would later be called "psychoneuroimmunology," was beginning to construct a neuroendocrine-immune system network with his studies of the effects of immune responses on neural and endocrine function. If, as he believed, immune function was integrated with other physiological processes, exposure to an antigen should evoke changes in neuroendocrine activity that, in turn, should have feedback effects on immunoregulatory processes and host defenses. There followed an innovative program of research that provided dramatic demonstrations that the nervous and endocrine systems could perceive and respond to signals emitted by an activated immune system.

The novel studies of several other figures played critical roles in the growing acceptance of this new discipline. There was the research of Ed Blalock who found lymphocytes could be a source of brain peptides and pituitary hormones. Now, it's accepted that brain peptides and their receptors exist within the immune system and that the products of an activated immune system can function as neurotransmitters. Another critical link was forged by investigators such as Karen Bulloch and David Felten who described "hard-wired" connections from the nervous system to the immune system. At a behavioral level, Roger Bartrop described immunologic changes associated with the bereavement that followed the sudden death of a spouse and several other laboratories launched studies of the immune changes associated with stressful life experiences and emotional states. Marvin Stein,

for example, who had studied the effects of hypothalamic lesions and stimulation on anaphylactic reactions in guinea pigs during the 1960s, returned to psychoneuroimmunology in the 1980s with a program of animal research on the immunologic effects of stressful experiences as well as human studies of the immunologic changes associated with loss and depression. Another interdisciplinary collaboration between Ronald Glaser, a virologist, and Janice Kiecolt-Glaser, a psychologist, developed an extremely productive research program beginning with studies of stress-induced immune function and the reactivation of latent viruses.

The research initiated in the 1970s and early 1980s was apparently "the right stuff at the right time!" It is likely that no one research program would have had quite the same impact had it not been for the converging evidence of brain-immune system interactions that was appearing in the literature at the same time. These initial studies legitimized questions that had not been asked before. And if the questions—and, sometimes, the questioners—were disparaged, a common experience, the data were compelling and then, undeniable. Thus, the coalescence of research initiated during the 1970s—and the identity provided by the label, psychoneuroimmunology—reactivated latent interests and attracted new investigators to this hybrid field.

In 1976, our research on behaviorally conditioned immunosuppression was the only NIH grant in this area. Today, there are hundreds of NIH grants from different Institutes that deal with psychoneuroimmunology. In 1984, Academic Press approached me about editing a new journal in the field. Initially, I thought it might be too early and could give other journals an additional excuse not to publish our material. I relented, however, and, in 1987, I became the Editor-in-Chief of *Brain, Behavior and Immunity*. I remained Editor-in-Chief until 2002 when I turned 70. According to 2009 figures, the Citations Index Impact Factor for this journal now places it in the top 16% of all immunology journals and the top 17% of all neuroscience journals. During this time, our informal meetings also included discussions of forming a scientific society representing psychoneuroimmunology. In 1993, I was elected founding President of the Psychoneuroimmunology Research Society and in 2003, *Brain, Behavior and Immunity* became its official journal. I am frequently asked, "Did you have any idea of what you had started or where your studies would lead?" I did know the concept challenged immunological dogma and could be very important, but never anticipated how rapidly or how large the field would grow, and I continue to be amazed by the number of scientists working in various psychoneuroimmunology laboratories—named as such—all over the world.

PJR: I presented a brief description of your initial discovery, but you and Nick went on to conduct other experiments that contributed greatly to our understanding of relationships between the brain and immune system and the effects of conditioning. As you look back, what do you think was your

greatest contribution and was their much opposition to your theories?

RA: My role in developing this new field will always be associated with a very controversial paper that Nicholas Cohen and I published in *Psychosomatic Medicine* in 1975. Our research had demonstrated a functional link between the brain and the immune system, which shouldn't happen, because there were no connections between the brain and the immune system. In the early 1970s, I was studying taste aversion conditioning in rats. This is a variant of classical Pavlovian conditioning as you described it earlier. It is an extremely robust one-trial, passive avoidance learning situation in which a novel, distinctively flavored drinking solution, the conditioned stimulus (CS), is paired with the unconditioned effects of a drug with noxious gastrointestinal consequences, the unconditioned stimulus (UCS). Under these circumstances, the rat will learn, after a single CS-UCS pairing, to avoid consumption of the CS solution. In our study, rats drank different volumes of a saccharin solution and were then injected with a constant dose of Cytoxan, an immunosuppressive drug used in studies of taste aversion learning because it induces the desired gastrointestinal upset. As expected, the magnitude of the conditioned aversive response was directly related to the volume of saccharin consumed on the single conditioning trial. Also, repeated CS presentations without the drug extinguished the avoidance behavior, and the rate of extinction was inversely related to the magnitude of the CS. Unexpectedly, animals began to die during the course of these extinction trials—a troublesome but not particularly interesting observation. It became evident, however, that, like the magnitude of the conditioned response, mortality rate varied directly with the amount of saccharin the rats consumed on the one conditioning trial—a troublesome but very interesting observation.

As a psychologist, I was unaware that there were no connections between the brain and the immune system so I was free to consider any possibility that might explain this orderly relationship between the magnitude of the conditioned response and the rate of mortality. A hypothesis that seemed reasonable to me was that, in addition to conditioning the avoidance response, we were conditioning the immunosuppressive effects of Cytoxan. If reexposure to a CS previously paired with an immunosuppressive drug evoked a conditioned immunosuppressive response, and if the strength of the conditioned response was related to the magnitude of the CS, these animals might have been more susceptible to otherwise subthreshold levels of pathogenic stimulations in the laboratory environment. Thus, the serendipitous observation of mortality in a simple conditioning study and the need to explain an orderly relationship between mortality and the conditioned avoidance behavior prompted the hypothesis that immune responses could be modified by classical conditioning. Colleagues persuaded me to write a letter to *Psychosomatic Medicine* describing these observations and the

hypothesis that immune responses were subject to conditioning. I asked George Engel to read a draft of the letter (from which I had deleted the title). Engel, who usually criticized the Discussion sections in my research papers for being overly cautious, predicted that my conservative reputation was now going to pay off: people were going to believe this just because I was the one who said it. Although it was meant as a compliment, I found the prospect somewhat unnerving. I wanted my ideas to be considered, of course, but I also wanted to retain my right to be wrong.

I learned, however, that if you say something that's not especially important, it doesn't really matter whether you're right or wrong; but, if you say something that could be important, you had better be right! The Letter to the Editor in *Psychosomatic Medicine* did not, as far as I know, attract much attention or generate any interest in testing the hypothesis. The exception was Nick Cohen, an immunologist, who thought these preliminary observations should be pursued. Using the taste aversion conditioning model, he and I designed a study to determine if immune responses could be modified by classical Pavlovian conditioning. The results: conditioned animals that were reexposed to a CS, saccharin, previously paired with the immunosuppressive effects of Cytoxan showed an attenuated antibody response to sheep red blood cells compared with (a) conditioned animals that were not reexposed to the CS, (b) nonconditioned animals that were exposed to saccharin and (c) a vehicle-treated control group. With some evident apprehension on the part of the Program Committee as well as the Editor of *Psychosomatic Medicine*, the manuscript entitled "Behaviorally Conditioned Immunosuppression" was presented at the 1975 meeting of the American Psychosomatic Society and published in the journal that year.

This initial experiment demonstrated that, like other physiological processes, the immune system was subject to classical conditioning, thereby documenting a functional relationship between the brain and the immune system. In that paper, we wrote that

...there may be an intimate and virtually unexplored relationship between the central nervous system and immunologic processes and that the application of behavioral conditioning techniques provides a means for studying this relationship in the intact animal. Confirmation of the capacity of behavioral conditioning procedures to suppress (or elicit) immune responses would raise innumerable issues regarding the normal operation of and modifiability of the immune system in particular and the mediation of individual differences in the body's natural armamentarium for adaptation and survival in general. Such data also suggest a mechanism that may be involved in the complex pathogenesis of disease and bear eloquent witness to the principle of a very basic integration of biologic and psychologic function.

Over the next several years, there were replications and extensions of the work on conditioned alterations of immune function resulting in an extensive literature documenting the acquisition and/or extinction of conditioned nonspecific host defense responses and different antibody- and cell-

mediated responses using different conditioned and unconditioned stimuli—and this includes the conditioned enhancement of antibody production using antigen, itself, as the UCS.

Engel's Biopsychosocial Model, Psychosomatic Medicine And Stress

PJR: I'm glad you mentioned George Engel's influence for several reasons. He was your immediate superior, and it is hard to think of anyone better equipped to objectively criticize your hypotheses or provide support if he thought they were correct. A towering figure in medicine as well as psychiatry, George is best known for proposing a biopsychosocial model of health in a 1977 article in Science. It posited that health was best understood in terms of a combination of biological, psychological, and social factors, rather than purely biological terms. This was in sharp contrast to the traditional medical belief that every illness or disease was due to some pathogen, injury, genetic or developmental abnormality. I had the pleasure of meeting him when you invited me to give a talk on Stress and Cancer at the University of Rochester, which was attended by Art Schmale and some of the other pioneers in this field. George Engel drove me back to the airport, during which we discussed mutual friends, like Stewart Wolf, who was his classmate at Johns Hopkins, my views on Hans Selye's contributions, and so many other topics that the time flew and we continued our conversation for another five or ten minutes after we reached our destination. He eagerly accepted my invitation to do a Newsletter interview and I always regretted that his untimely death prevented this.

*You became the George L. Engel Professor of Psychosocial Medicine at Rochester, and I always thought this was particularly appropriate, since so many of your views were similar, if not congruent. For example, back in 1974, before biopsychosocial and psychoneuroimmunology were invented, both of you published separate papers in different journals, which essentially argued that **psychosomatic research does not deal with psychosocial factors as a cause of disease, but rather in altering the individual's susceptibility to disease**. The term psychosomatic was introduced into American medicine by Flanders Dunbar around the same time as Hans Selye's initial publication on stress and I was privileged to work and co-author articles with both of these luminaries. Dunbar founded what would later be the American Psychosomatic Society as well as its journal, Psychosomatic Medicine, and served as its editor for the first eight years. Her research focused on an attempt to relate different disorders to specific emotional conflicts and/or personality patterns. Like Selye's concept of non-specific responses to stress as a cause of disease, her views, such as the notion that rheumatic fever was largely due to autoeroticism and homosexuality, were also later rejected. This led to considerable controversy, especially when psychosomatic illnesses began to be viewed as a form of malingering. Psychosomatic was replaced by somatoform, neurotic and stress-related disorders by the World Health Organization and*

Psychosomatic Medicine is now often referred to as Behavioral Medicine. Among your many honors, like George Engel and Stewart Wolf, you also served as President of the Psychosomatic Society, and I wondered what your current views were on psychosomatic disease and the role of stress.

RA: There is no such thing as psychosomatic disease! Modern psychosomatic medicine deals with the role of psychosocial factors (including stressors) that contribute to (but not by themselves, cause) the development and/or progression of disease. If I were to accept the argument that a particular disease was psychosomatic, I would, by definition, have to agree that some diseases were not psychosomatic. If, however, it can be shown that psychosocial factors can influence one particular disease, I must allow for the possibility that the interaction among biological, psychological and social variables could, to a greater or lesser extent, influence the course of all diseases. In the search for single causes for single effects, *H. pylori* was identified and labeled as the cause of duodenal ulcers. However, most people harbor *H. pylori* but only a fraction of these develop duodenal ulcers. Thus, *H. pylori*, the ostensible cause of ulcers, may be a necessary component, but it is not sufficient—its mere presence does not mean that an ulcer will develop. Psychosocial and biological factors can also be essential ingredients.

For the most part, the mechanisms underlying the effects of stressors or stress on immune function and disease can only be outlined in general terms. Affective responses to what are perceived to be stressful circumstances are accompanied by autonomic nervous system and neuroendocrine changes capable of influencing immune function and thereby altering susceptibility to a variety of diseases. The majority of stress research emphasizes the common responses to stressors (e.g., adrenocortical responses). If these were the changes responsible for changes in disease susceptibility, we would expect that all stressors would exact the same effects. In fact, different stressors have different effects on the same experimentally induced disease process in animal studies and the same stressor can have different effects on different disease processes. It would seem, then, that it is not the common, nonspecific effects but the uncommon, idiosyncratic effects of stressors that are responsible for the alterations in susceptibility to different disease processes.

Has Psychoneuroimmunology Research Resulted In Any Clinical Benefits?

PJR: The discovery that H. pylori was the cause of peptic ulcers, led many to conclude that the prior widespread belief in the role of stress was hogwash, despite abundant anecdotal support and Stewart Wolf's direct observation of this. But stress lowers resistance to bacterial infections, so its contributory role seems quite plausible. Similarly, tuberculosis cannot occur unless the tubercle bacillus is present, but many individuals who harbor this organism do not develop clinical tuberculosis, or do so only after exposure to an

*increase in stress related hormones like cortisone. Stress has also been shown to be associated with an exacerbation in autoimmune inflammatory diseases like psoriasis. As you may recall, I had invited you to organize a session on "How Can Basic Psychoneuroimmunology Research Be Put To Practical Use" at our 1995 International Congress on Stress in Switzerland. Unfortunately, you could not attend due to illness but did arrange to have Nick Cohen chair this session. It included presentations on the effect of psychological intervention on immune and inflammatory responses, psychoimmune factors in juvenile rheumatoid arthritis and the impact of emotional status on cancer. Although these confirmed the important effects that the mind and emotions could have on immune system function, how could these assist physicians in their efforts to prevent or treat disease? As Nick noted, **"despite the large body of evidence validating psychoneuroimmunology as a bona fide interdisciplinary field with potential clinical relevance, the current applications of research in this area are still more in the realm of wishful thinking than in reality."** I was therefore pleased to see your recent paper in Psychosomatic Medicine dealing with psoriasis and wondered if you could tell us about this and any other future clinical applications.*

RA: In the paper you referred to, we hypothesized that psoriasis patients treated under a partial schedule of pharmacologic (corticosteroid) reinforcement would show less severe symptoms and relapse than patients given the same amount of drug under standard conditions (continuous reinforcement). To paraphrase our abstract, this was a double blind, simple randomization intervention conducted with 46 patients from Stanford and Rochester. Initially, lesions were treated with 0.1% acetone triamcinolone under standard treatment conditions. Thereafter, a Standard Therapy group stayed on continuous reinforcement (active drug every treatment) with 100% of the initial dose; Partial Reinforcement patients received a full dose 25-50% of the time and placebo medication other times; Dose Control patients received continuous reinforcement with 25-50% of the initial dose. Severity of disease was rated weekly on a 9-point Psoriasis Severity Scale. Severity scores in California neither supported nor refuted the hypothesis. In New York, partial reinforcement effected a greater reduction in lesion severity than Dose Control conditions and did not differ from Standard Therapy patients receiving 2-4 times more drug. For the entire population, the incidence of relapse under partial reinforcement (26.7%) was lower than in Dose Control patients (61.5%) and did not differ from full-dose treatment (22.2%). It appeared that a partial schedule of pharmacotherapeutic reinforcement could maintain psoriasis patients with a cumulative amount of corticosteroid that was relatively ineffective when administered under standard treatment conditions. It is conceivable that corticosteroid administration only one quarter or half as frequently as currently prescribed is sufficient to treat psoriasis and that possibility will be addressed in future

studies. We posit, however, that these preliminary observations implicate conditioning processes in (and for the design of) pharmacotherapy regimens.

Adding a behavioral dimension to the design of drug treatment protocols changes the equation for understanding drug effects and is likely to stimulate new interdisciplinary research in neuropharmacology and behavioral pharmacology. Partial schedules of reinforcement might:

- Reduce the total amount of drug required for treating various disorders
- Reduce deleterious side effects and thus increase adherence to treatment
- Extend pharmacotherapeutic effects (increase resistance to extinction)
- Reduce very substantially the cost of long-term drug treatments

Reducing costs may be the most important benefit and in some instances this and the other rewards noted above have already been achieved.

Why Do You Believe That Placebo Effects Are Conditioned Responses?

PJR: At our 2000 International Congress On Stress in Hawaii, we devoted a session to "The Power Of The Placebo" that was chaired by Karen Olness and featured presentations by Stewart Wolf, Herb Benson, Wayne Jonas and other notables. You were again unable to attend but submitted an abstract entitled "Are Placebo Effects Conditioned Responses?" in which you wrote

If the response to placebo is a conditioned response, there is an alternative to the typical administration of drug or placebo; namely, administration of drug *and* placebo — a partial schedule of reinforcement. In effect, reinforcement schedule, or the "active drug:placebo ratio," represents an additional dimension of drug treatment protocols and an alternative means of titrating cumulative drug dose that may enable one to maintain some physiological responses within homeostatic limits using lower cumulative amounts of active medication.

Karen's presentation was also entitled "Are Placebo Effects Conditioned Responses? (The Macadamia Chocolate Decaf Effect)". In it, she described an 11-year-old girl with systemic lupus and severe complications, for which she was to receive intravenous Cytoxan. Her mother, who was a psychologist, had read the study you and Nick did on applying conditioning in a mouse model of systemic lupus being treated with Cytoxan paired with a saccharin solution as the conditioned stimulus. You showed that the saccharin solution alone could delay the onset of disease and reduce the dose of Cytoxan needed to have a therapeutic effect. The mother wanted the doctors to use a similar protocol on her daughter when she received the intravenous Cytoxan. In this case, the conditioned stimuli were cod liver oil (taste) and the scent from a rose perfume (smell). As I recall, the conditioned stimuli were given over a 15-month period during which it was possible to present only the conditioned stimuli and thereby reduce the frequency of intravenous Cytoxan infusions, and her daughter did well for 8 years. However, I find it hard to believe that all placebo phenomena fall under the category of conditioned responses. For example, how would this apply to Stewart Wolf's study demonstrating the antinausea effect of ipecac

in pregnant women with morning sickness? Has your position on placebos and conditioning changed over the past decade?

RA: No, my position has not changed. Well, actually, it has changed: I'm now more convinced that placebo effects are learned responses and that some placebo responses reflect conditioned pharmacotherapeutic effects. This hypothetical statement is not restricted to placebo responses involving the immune system—nor by the sensory modality of the conditioned stimuli, all of which are, by definition, nervous system stimuli. Indeed, we may have to distinguish between different kinds (and "explanations") of placebo effects such as faith healing, belief systems, verbally-induced expectations, direct instruction, authority pronouncements, observation and conditioning, all of which can induce expectations. **While all placebo responses do not involve conditioning, it seems to me that, in the final analysis, they all involve learning; they are derived from experience.** Who on this earth, for example, has not been helped by somebody (physician, shaman, witch doctor, teacher, parent) at some time? The attempt to attribute a particular placebo response to one or another of these explanations is complicated by the fact that more than a single kind of learning may be involved. Studies that attempt to pit one explanation against another can be difficult to unravel because there is no way to equate, for example, the amount or value of the information communicated by a verbally-induced expectation with the information value of prior conditioning.

As you pointed out, clinical research and drug evaluation studies have, for the most part, adhered to the model in which a placebo is administered in order to evaluate the efficacy of pharmacotherapies or to define the pharmacologic (as opposed to the psychologic) action of a drug. Thus, research has been directed to characterizations of beliefs and expectancies, including those induced by the instructions to subjects, and characterizations of the subjects who respond to placebos. Much placebo research also derives from an effort to define the "true" unadulterated action of a drug, rather than an effort to understand the nature of the placebo effect and its therapeutic actions. There have been repeated but unanswered calls for studies of the placebo effect as a phenomenon that may have clinical implications in its own right. And that's what we're trying to do by exploring the clinical implications of placebo responses from a learning perspective.

The conditioning model of placebo effects challenges the very definition of a placebo response as a nonspecific response to an inert agent. Perhaps the response to a placebo is a two-stage process. The initial response satisfies the definition of a placebo response as a nonspecific response to a therapeutically neutral stimulus based, perhaps, on the individual's experiences with healers of one sort or another. As a second stage, I would suggest that some placebo responses are neither nonspecific nor are placebos (conditioned stimuli) inert. If a conditioned stimulus can evoke a response that approximates the results seen with the unconditioned

stimulus, you could hardly call it neutral or inert. And if that conditioned stimulus, over time, elicits conditioned physiological responses that resemble the responses unconditionally elicited by a drug or other therapeutic intervention, the response can hardly be called nonspecific. I can refer to it as a conditioned pharmacotherapeutic response. The clinical community may or may not want to call it a placebo response. They may wish to retain an entrenched concept and definition that has not, however, clarified our understanding of the placebo effect or its therapeutic potential and has, I believe, misdirected the search for models amenable to experimental analysis and from which new, testable hypotheses can be derived.

Some Parallels With Selye And Stress And Psychoelectroneuroimmunology?

PJR:I see certain intriguing similarities between you and Hans Selye. Both of you described your discoveries as "serendipitous", which implies that they were simply lucky accidents. However, as Pasteur emphasized, "Chance only favors the prepared mind". Both of you introduced novel concepts that launched such a huge avalanche of research that it became impossible to keep up to date. Stress became a popular buzzword that was used to describe very different things and psychoneuroimmunology is at risk for suffering a similar fate, as the allure of its cachet is abused by charlatans who want to profit from its credibility and scientific patina.

In 1972, Selye developed a reticulosarcoma, a normally fatal malignancy, from which he completely recovered. He refused chemotherapy, and attributed his good fortune not to any other treatment received, but rather his very firm determination to continue living so that he could complete his important research activities. Based on reports of similar experiences and spontaneous remissions, he was convinced that a firm faith and fierce determination could retard or reverse cancer growth. I vividly remember getting the news about your pancreatic cancer but it's hard to believe that this was over five years ago since normal life expectancy is a year or less after detection. Before that you suffered a heart attack from which you were not expected to recover, and subsequent by-pass surgery. Since then, you have had one or more defibrillators implanted, several bladder cancers removed, a pulmonary embolism and most recently, a gastrectomy for a stomach tumor. Could your amazing ability to overcome all these obstacles also stem from a strong desire to continue your research, similar to Selye's? How such effects are mediated is not clear, but as you may recall, I used the term psychoelectroneuroimmunology to refer to subtle energy communication pathways in a book we both contributed to.

*As Thoreau wrote, "To know that we know what we know, and **that we do not know what we do not know, that is true knowledge.**" I suspect that the second half of this aphorism is particularly pertinent to the present situation, and in the limited space available, wondered what your speculations might be on the future of psychoneuroimmunology.*

RA: I could go on and on reciting what we have yet to learn, what needs to be done and how to do it. But that would be my conservative self. Given the space that remains, let me look further ahead and speculate very broadly, but briefly, on the potential health implications of psychoneuroimmunology. First, I would repeat the central premise of psychoneuroimmunology, which is that immunoregulatory processes are part of a single complex interacting network of adaptive responses. As such, psychoneuroimmunology does not recognize the arbitrary and illusory boundaries of the disciplines into which we have divided the biomedical sciences. We know a great deal about the actions of different components of the immune system and about the neuroendocrine responses to stressors, but we are only just beginning to understand how these systems interact in health and disease. Or, as Lewis Thomas put it: "You'll never understand how bees make honey no matter how carefully you dissect a single bee."

If you really accept the proposition that there's only a single, integrated defense system, new questions emerge. Central among these may be the need to reconsider the "cause" or development and the treatment of what we now speak of as "neurological" diseases, "endocrine" diseases or "immune system" disorders. How do early life experiences, including stress, influence the development of the immune system? Conversely, how do immunological challenges early in life or prenatally influence subsequent behavior and neuroendocrine function? Research in these areas has already begun. And what about a focusing on neuroendocrine interventions in the treatment of autoimmune disorders or the applicability of immunological interventions in the treatment of neuroendocrine disorders? It seems to me that basic research on the interactions among behavior, neuroendocrine and immune processes has a bright future that promises new developments in our understanding of adaptive processes with profound consequences for the maintenance of health and for the treatment of disease.

PJR: Many thanks, Bob, for this trip down memory lane and sharing your thoughts for the future. It is unfortunate that we have run out of space since there is much more that could be said — so stay tuned for future updates.

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Editor-in-Chief

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