Integrating the Incompatible
The Rise of the Incorporated Immune System

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In the mid 1990s, Alan Leschner, the director of the National Institute of Drug Abuse, opened a lecture by stating that dualism was dead. He was referring to the idea that the mind and body were separate entities, a practice that not only pervades Western science but also Western culture. Although dualism’s death is questionable, given its long history and firm hold on Western thought, it may well have received a blow from the biomedical community. The 1970s brought a scientific revolution in the way researchers perceived mind-body interactions. This change challenged the belief that the immune system was an autonomous, self-regulating organ system. The reasoning behind this paradigm was that the cells of the immune system worked in culture, devouring microbes as they did in vivo. Therefore, the brain would have nothing to do with immune response, an idea perpetuated in medical literature and textbooks. The idea of an independent immune system extended to the vast majority of immunologists, who, if asked in 1970 if the immune system interacts with the nervous system, would have given a resounding no. So deeply entrenched was this belief which experiments that illuminated a link between the mind and immune system were denounced as rubbish in the 1970s and 1980s. Despite this resistance, these experiments introduced a new scientific paradigm.

Along with the skepticism of many scientists, there were internal rifts among the forthcoming revolutionaries of the new school of immune research, leading to the establishment of five definable, and often competing, sub-schools. “Neural-immune interactions” (NII), as the overarching school is often called, will serve as an appropriate title for the purposes of this paper because it avoids the politicization of many other contemporary expressions that signify the entire field. “Neural” encompasses the central nervous system, the endocrine system, and behavior, allowing the term to touch on all aspects of the overarching school. This school, as well as the sub-schools beneath it, is the result of a scientific revolution whose basic pattern fits Thomas Kuhn’s model of scientific change in his essay, The Structure of Scientific Revolutions.

Kuhn’s Paradigm
Kuhn’s theory offers an excellent conceptual framework against which we can view the emergence and development of NII. Kuhn believed that science does not advance in a steady march toward truth, but instead progresses in occasional spurts followed by more extended periods of stability. The stable periods are times of puzzle solving, where the details of a science are examined and explained and advances are made within a “paradigm.” Scientists doing research within a paradigm operate in a microculture with a specific theoretical and methodological orientation. Their standards of excellence and rigor are implicitly agreed upon and are so embedded that they are not usually acknowledged. The paradigm is a requirement of science, because “[no] scientific group [can] practice its trade without some set of received beliefs.”

When the paradigm fails to explain newly discovered and yet unexplained phenomena, new schools and theories emerge to account for these discrepancies. But the rise of new paradigms is no smooth progression, for “in science…novelty emerges only with difficulty, manifested by resistance, against a background provided by expectation.” The change does not follow the progression of anomaly, to crisis, to establishment, and finally to acceptance of a new paradigm in one fell swoop; thus, ‘revolution’ is a somewhat misleading but necessary term that describes radical changes in the scientific process. Since scientific revolutions shift paradigms and therefore change commonplace facts, rules, and standards taken for granted by scientists, they meet with incredible resistance from proponents of established paradigms. Yet, inasmuch as theory and fact must eventually become compatible again, new schools begin theory creation and shuffle to establish themselves as the new paradigm.

Although Kuhn’s theories make up the bulk of our conceptual framework, there are areas where we must stray from his ideas to explain the development of NII. Kuhn never explicitly states that scientific revolutions are self-contained and limited strictly to the scientific community involved, but he makes such an implication. As we will see later, external forces including the lay public and various government institutions, as well as general medical trends and fads influenced the development and acceptance of NII.

The Beginnings of NII
1975 was a benchmark year for NII. Robert Ader, an experimental psychologist

A small discovery at the University of Rochester sparks a revolutionary way of understanding the immune system.
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at the University of Rochester, demonstrated a mind-immune link. Meanwhile in Switzerland at the Schweizerisches Forschungsinstitut, Hugo Besedovsky, an endocrinologist, performed experiments confirming the thymus’s influence on the neuroendocrine system. Simultaneously George Solomon of Stanford University was writing papers that discussed the correlation between stress and immunologic parameters. A new school developed in the mid 1970s because these and other research-ers discovered, or in some cases stumbled across, a link between the nervous system and the immune system. This school was a direct challenge to the long-standing paradigm of the isolated and self-regulating immune system.

For a paradigm to be questioned and discarded, an anomaly must emerge and be incompatible with the current paradigm. Robert Ader’s unfamiliarity with the autonomous immune paradigm was the very reason he discovered an anomaly. As an experimental psychologist, Ader had no idea that the immune system was considered an independent system. His education and experience made him think that every disease had a psychosocial aspect. Ader performed classical conditioning experiments on rats, which, as originally designed, had nothing to do with the immune system or immune function. His research was akin to that of Ivan Pavlov, who conditioned dogs to salivate at the ring of a bell. Likewise, Ader conditioned rats to develop an aversion to water sweetened with saccharin. To do this, he fed the rats saccharin water and then injected them with cyclophosphamide, a nausea inducing drug. Contrary to expectation, some of the rats died after Ader provoked the conditioned response. As Ader soon learned, cyclophosphamide was an immuno-suppressant and through conditioning he assumed the rats had suppressed their immune systems, a process leading to overwhelming infection and, ultimately, death. He did not know how the observed phenomenon worked or if he had committed a simple error in experimental design.

With immunologist Nicholas Cohen’s help, Ader designed a new experiment that challenged the immune system with antigen to show the rats did indeed suppress their immune systems.6 At the time, no one could conjecture how conditioning compromised the immune response; nevertheless, the improbable experimental results amazed many and therefore received heated criticism. To a large extent, Ader and Cohen’s individual reputations as conservative, rigorous researchers legitimized the results; as George Engel, the principal architect of the biopsychosocial model of medicine, told Ader: “Your conservatism is going to pay off because people are going to believe this because you said it.”5

George Solomon published many similar papers on the effects of stress on immunity. A 1969 paper of his, titled “Stress and Antibody Response in Rats,” tested various types of stressors on antibody production. Solomon concluded that “the central nervous system might play a role in control of immune response.”6

Because of advances in medical technology in the 1970s, specifically in the extraction and detection techniques of peptides, researchers from various fields discovered more evidence for an integrated immune system. D. C. Dumonde’s work was particularly monumental: he classified a group of non-antibody signal molecules secreted by activated lymphocytes, which he named “lymphokines.”7 In 1974, the term “cytokine” was introduced and by 1979 researchers again changed the name to “interleukin.”8 The discovery of signal molecules secreted by leukocytes created a real possibility for an interactive immune system for scientists skeptical of psychology and stress research, which seemed full of ambiguous ideas. Dumonde’s and others’ work laid the groundwork researchers needed to demonstrate communication between the immune system and the brain. Convincing skeptical scientists of this relationship depended largely on clarifying the role of cytokines.

The endocrinologist, Hugo Besedovsky, brought a neuroendocrine perspective and “hard science” legitimacy to the field in 1975 with his research on the thymus’s effects on the neuroendocrine system. The thymus, an ontologically important immune organ in the middle part of the chest, is the site of T-lymphocyte development. In 1975, Walter Pierpaoli and Besedovsky measured the effects of a missing thymus on the neuroendocrine system.9 Besedovsky’s research suggested that the immune system had a role in neuroendocrine regulation. Two years later he made clear what he and Pierpaoli had suggested in their aforementioned paper: “In order to bring the self-regulated immune system into conformity with other body systems its functioning within the context of an immune-neuroendocrine network is proposed.”10 If taken with previous research, Besedovsky’s work allowed for communication and regulation between systems as well.

J. Edwin Blalock’s research on lymphocytes, done early in 1981, focused on communication in the same way Besedovsky’s did. He and Eric Smith found that lymphocytes produced andrenocorticotropic hormone, previously thought to be made solely by the pituitary gland and to have functioned only in the neuroendocrine system.11 These results suggested a “circuit” between the neuroendocrine and immune systems and the possible existence of immune regulation of neuroendocrine function.12

These major findings of the 1970s and early 1980s constituted the first inklings of a paradigm shift from the autonomous to the integrated immune system. Their immediate significance, however, was the development of a new school of research to challenge the existing paradigm.

**Sub-schools Emerge**

The first edition of *Psychoneuroimmunology*, edited by Robert Ader, established a new school, NII. The book presented a formal challenge to the autonomous immune system paradigm, and forced researchers from varied disciplines working to bring the subject matter of disparate specialties together. The school had no official members; there was nothing to take membership in, except a belief that the immune system was not self-controlled.

The unity that developed the first edition of *Psychoneuroimmunology* would not last. It was a temporary alliance between individu-
als from different fields with very different scientific backgrounds who were attracted to the possibility a non-autonomous immune system. These researchers shared glimpses of a common vision but had little else that bound them together. In fact, there were rifts between the contributors of Psychoneuroimmunology even before the first edition was published.

The existing differences between NII researchers and their methodologies became a greater issue once the field emerged. The paradigms in which they worked could not be avoided or overcome. That one scientist was a psychologist by training and another an endocrinologist made a difference. More important, however, were each researcher’s preconceptions of the importance of demonstrable mechanisms or their ideas on the methodology of research; these became some of the important and controversial lines of delineation between sub-schools.

At least five distinct research “approaches” emerged in the 1980s that would eventually become sub-schools. There were scientists who took a psychological approach and asked how stress could alter the immune response. They started from psychology and behavior, and then moved into biological aspects. The neuroendocrine approach did not go higher than the hypothalamus; these scientists looked at the interplay between hormones originating from the hypothalamus, pituitary gland, and the immune system. Neuroanatomists searched for the expression of immune molecules in the brain and other physical connections. A fourth approach was made by scientists who researched sickness behavior; they measured the effects of cytokines on behavior. Finally, the neuroimmunologists who managed to stay outside the politicization of NII made up the fifth approach. They isolated themselves from the other approaches because their research did not cross the blood-brain barrier. Neuroimmunologists measured the effects of immune cells and molecules that were physically in the brain, focusing mainly on multiple sclerosis.

Through development, competition, and external influence these approaches hardened into sub-schools. Some had names reflecting the overall school of NII, whereas others did research under the name of their original discipline. Since fluidity marked the progression of the field, especially in its advance from scattered points of research to definable sub-schools, there are no set dates for when approaches became confirmed sub-schools, only general trends. Scientists, as well as the lay public and media, lumped these approaches under the newly emerging names that the field’s leaders created, such as psychoneuroimmunology (PNI), neuroimmunomodulation (NIM), or psychoimmunology.

All of these approaches had roots in the 1970s, and most, with the exception of sickness behavior (which did not appear until the late 1980s), did not realize their boundaries enough to be called sub-schools until the early to mid 1980s. But even as they gained recognition, these research areas transitioned from approaches to sub-schools. In the rest of this section, I use sub-school to refer to the transitional approaches and emerging sub-schools.

The boundaries between sub-schools were often blurred throughout the development of NII in the 1980s and early 1990s. The participants did not live in a vacuum; the crossing of scientific disciplines led to cooperation and communication among researchers, often producing stunning results. Sub-schools are fluid structures whose most defining aspect stems from the paradigm under which its members are trained, whether it is psychology, neurology, medicine, or something else. It must be stressed that the central defining characteristic separating the sub-schools was the content of their science. Neuroimmunology, for example, separated itself from the other sub-schools because its science did not leave
The emergence of NII has changed our concept of disease and opened up new ways that we can use to preserve health.

In the 1970s, and even today, the idea that the immune system could be taught was considered an outrageously heretical notion by most classical immunologists. Immune cells respond to molecules that crash up against them, get stuck to proteins protruding on their surfaces, get gobbled up into the cell's interior, and cause other molecules to be made in the cell's protein factories and spit out-magic antibody bullets that surround the prey and destroy it. There is no room for learning here.15

So strange were Ader’s results that even supporters of the NII school were skeptical. The neuroendocrine sub-school, called neuroendocrinimmunology, rose simultaneously as the PNI sub-school with Hugo Besedovsky’s research. As early as 1971, Besedovsky had published a paper measuring the influence of glucocorticoids on the lymphoid organs of pregnant rats.16 His later papers were direct attacks at the paradigm of an isolated immune system.17,18

The neuroanatomy sub-school, which often paralleled and progressed with the neuroendocrinimmune sub-school, started in the early 1980s. Many different groups, among which Karen Bulloch’s was prominent, started to identify innervations of immune tissues.19,20,21 These observations provided preliminary evidence for a direct, physical, hard-wired link between the two organ systems. Jean-Michel Dyer’s was one of the first to demonstrate the presence of interleukin-1 in the brain and also its in vivo synthesis.22 Bill Farrar and Candace Pert took the next step by identifying interleukin-1 receptors in the brain.23

Of the first papers to mark the beginning of the sickness behavior sub-school was a review article by B. L. Hart titled “Biological basis of the behavior of sick animals.”24 The sub-school did not really take off until Robert Dantzer and the team of Steven Maier and Linda Watkins joined the scene in the early 1990s. Dantzer’s first papers linking interleukins to sickness behavior were published in the early 1990s;25,26 the researchers injected animals with synthetic interleukins and measured changes in behavior.

Maier’s and Watkins’ team did work similar to the Dantzer group. Their studies in the early 1990s helped illuminate the mechanisms of acute responses: fever, fatigue, decreased sexual activity, loss of appetite, and decreased social interaction. By injecting synthetic proinflammatory molecules such as interleukin-1, they elicited acute responses and later found that these responses were largely mediated via the vagus nerve, which connects the gut to the brain (cytokines can either stimulate the vagus nerve and trigger communication or travel to the brain via the blood stream).27

The neuroimmunology sub-school was tightly bound with multiple sclerosis and other diseases of the central nervous system. Its roots started in the late 1970s with the work of Henry McFarland and Dale McFarlin. Neuroimmunology dealt mainly with immune effects in the brain, and therefore it did not seriously consider many interactions that the other schools considered relevant. Neuroimmunology gained acceptance from the biomedical community rather early on in the 1980s. The Journal of Neuroimmunolgy started circulation in 1981 and quickly gained respect.

All of this work sprouted from different research approaches and backgrounds of individuals. Through refining these works, researchers exploring the nervous-immune connection funneled into sub-schools at different rates. As the field of NII germinated, the singular approaches of exploration turned into sub-schools with more defined methodologies.

**COMPETITION BETWEEN SUB-SCHOOLS**

That different sub-schools of NII developed is not surprising given the history of competition within medical science. Increasingly, in post World War II United States, medical specialties and subspecialties formed and found their own niches. Medicine transformed from one connected field to many related ones, each steeped in its own methodology. Thus, when NII emerged, each researcher brought her or his own traditions, technologies, and research styles.
The five NII sub-schools drifted apart from each other throughout the 1980s. Subtle scientific difference governed the separation, with each field seeing its specific methodology and pathways of neural-immune communication as the most important. As the incredible ramifications of the field became apparent, NII entered the biomedical research milieu, with all its politicization, research grants, and opportunities for career advancement. The adherents to the new school were treading the dangerous waters associated with competition for scarce resources and recognition. Egos flared as scientists vied to create new ideas and position their work as central to the development of a major new science.

PNI, as a sub-school, was soon isolated from other sub-schools and shunned by mainstream biomedicine, which perceived it as “soft science” psychology, “strategically located at the nexus of natural, biomedical, and social science.” The historical marginalization of psychology led to a “physics envy” among psychologists. As far as the other natural sciences were concerned, psychology was a black sheep, “its subject matter...unquantifiable and its methods mired in a metaphysical morass.” PNI, because it contained “psycho-,” caused a knee-jerk reaction in mainstream biomedicine, which was concerned with the single cause-single effect “just-associations” provided by molecular mechanisms and not the “simple-associations” psychologically oriented research provided. PNI, as seen by some of the other sub-schools, was not rigorous enough despite Robert Ader’s and Nicholas Cohen’s reputations as rigorous NII researchers.

The stakes of association with PNI were raised by scientists outside NII; some of the most scathing remarks were directed against the psychological aspects presumed to characterize the overarching school. Two articles represented the criticism against PNI. One was in the New England Journal of Medicine and the other in Nature, which repeatedly refused to print PNI research because “...the precise mechanisms involved in the phenomenon” observed were not identified. As the editor of Nature argued, not only were mechanisms and thus just-associations not identified, but also the science of PNI falsely sustained the hopes of the ill. This editor, John Maddox, argued that the likelihood of a link binding the nervous and immune systems was high, but that not “enough is yet known to sustain people’s hopes of explanation.” His skepticism was aimed at the prospect of the seriously ill finding hope in applications of an unproven science, which, under Maddox’ interpretation, claimed that a person’s state of mind was the road to either health or disease. This view was reflected throughout the biomedical community despite repeated statements by advocates of PNI that the psychological aspects of immunity were just some of the many contributing factors leading to disease. As Robert Ader wrote, “it is unreasonable to suppose that stressor-induced perturbations of the immune system could, by themselves, be of clinical significance.”

In her 1985 article, “Disease as a Reflection of the Psyche,” Marcia Angell recalled the history of scourges such as tuberculosis and the myths that arise with misunderstanding disease. Since incurable diseases are feared, people attach psychosocial causes to them in an attempt to gain control over the disease. But, as Angell points out, nothing other than a tubercle bacillus causes tuberculosis; she drew a similar parallel to cancer and the 20th Century, recalling that “most reports of such a connection [between state of mind and disease onset and progression] are anecdotal.”

Angell’s criticism relied heavily on popularizations of PNI since the new research gave an air of legitimization to the already standing biopsychosocial model of medicine. These popularizations ran far ahead of the science of the new field. As the sub-schools were fragmenting in the mid-1980s, magazines were peppered with headlines such as, “Got a Cold? Have you Tried Willing it Away?” and captions such as, “Can you marshal your moods to fight disease? Scientists are discovering the pathways that link your brain with your body’s lines of defense.” Such media claims made PNI seem ungrounded in the lofty annals of the hard sciences. The neuroendocrine, neuroanatomy, and neuroimmunology sub-schools, however, were not highlighted by the media because their language would not popularize easily; it did not contain explicit references to emotions and stress. Even though their aim was ultimately the
same as PNI, to show bi-directional communication between the immune and nervous systems, the other sub-schools stayed outside the public view throughout the 1980s. Thus, popularization exposed the sub-school containing the psychological aspects of NII even further than its psychological stance would have by itself. PNI research seemed to give legitimacy to what many in the public wanted to hear. Modern purveyors of “snake oil” even used PNI to give credence to odd curatives, such as crystal therapy.

External criticism of PNI paralleled its internal problems with the other sub-schools and the general field of biomedical research. Ader summed up some of the major differences in his 1979 Presidential Address to the American Psychosomatic Society:

One simple, universal observation underlies psychosomatic research: that when a population of individuals is exposed to the same environmental pathogens only some individuals manifest disease. Despite the most sophisticated strategies designed to achieve uniformity, variability remains one of the ubiquitous results of all natural and contrived biological experiments. The biomedical scientist, operating within the conceptual and technical constraints imposed by the disciplinary boundaries of a reductionistic philosophy, attempts to control or minimize (or ignore) variability. For the psychosomaticist, such variability is the starting point of his research: it defines the operation of variables with which to be concerned.39

This type of statement seriously discouraged mechanism-oriented researchers who had to limit variables in order to observe cause-effect type relationships on the molecular level. In terms of scientific content, the stance on variability and PNI’s unquantifiable aspects were the major reason for tension between it and the other sub-schools. Thus members of the other sub-schools, in particular the neuroendocrine sub-school, tried to distance themselves from PNI.

Outside influence did not serve a strictly negative role in setting PNI off from the other sub-schools; special funding opportunities arose because of this sub-school’s stress oriented research. The military financed a great deal of PNI research because they had encountered illness among members of the armed forces that if not caused by stress, were at least exacerbated by it. More important for PNI’s growth, however, was the immense amount of money made available in the late 1980s for AIDS and HIV research. The disease and the research sub-school became intertwined for a brief period of time into the early 1990s until the “unrealistic expectations” projected onto the possibilities of PNI treating AIDS did not yield incredible results.40

Novera Herbert Spector, who held an administrative role at the NIH throughout the 1980s, coined “neuroimmunomodulation” (NIM) in 1979 as a substitute for “nervous system influences upon immune responses,” a cumbersome term that researchers in the emerging field of NII frequently used.41 As tensions between the sub-schools ran high, many researchers distanced themselves from the science of PNI as well as the word by using NIM in reference to the overarching school. Both expressions were, and still are, used to signify NII or certain combinations of sub-schools. PNI and NIM also function as benchmarks demonstrating the union of the overarching school in the very early 1980s and the separation and politicization of sub-schools shortly thereafter; NIM appeared in the first addition of Psychoneuroimmunology. It was only afterward that proponents of each term began to actively avoid the other term. And as will be shown later, when the sub-schools started to accept each other’s work as complementary to their own, PNI papers constituted a significant portion of the meetings of the International Society of Neuroimmunomodulation and appeared very often in their journal, Neuroimmunomodulation.42

Of the other sub-schools, neuroimmunology and sickness behavior hold special positions, the former because it effectively separated itself from the rest of the sub-schools by virtue of its scientific content and the latter because it did not fully develop until the early 1990s. There is no evidence of the neuroimmunology sub-school interacting with the other sub-schools until the mid 1990s. The constituents of this sub-school were either pure immunologists or neurobiologists who extensively researched multiple sclerosis and other neurological diseases of the central nervous system; thus they were able to insulate themselves from the mind-body controversy the other sub-schools dealt with.

Solidification and Acceptance

As sub-schools distinguished themselves, their members conducted research, thus creating a sound foundation upon which they could establish a paradigm. Little of this research represented a collaboration between sub-schools; each traveled down its own road of solidification beyond the original introductory experiments described earlier. The body of research under the NII school burgeoned in the mid-1980s through the 1990s, each experiment reinforcing another so that, when taken in totality, the findings explained to even the most skeptical of critics that the immune system was integrative. Solidification was a requirement for paradigm establishment because scientists are skeptical people who need irrefutable evidence that an established paradigm is obsolete. Initial experiments created an introduction but were not convincing on their own; it was only when these experiments were repeated with greater precision, or simply repeated by different researchers, that skeptics considered them sound. Introduction of a new concept concerning the immune system eventually led to rigorous experimentation and thus solidification and acceptance. Some experimental results seemed so outlandish, as conditioned immune responses did, that no matter how rigorously carried out, they had to be repeated by a variety of people, many of whom aimed to refute the original results.43

Solidification of the neuroanatomical and neuroendocrinimmune sub-schools came in two waves, a supplement to the August 1, 1985 issue of the Journal of Immunology and three influential articles in the October 23, 1987 issue of Science. The supplement contained 28 diverse papers that
centered mainly on the neuroendocrine-immune and neuroanatomy sub-schools, but they also addressed PNI.

Perhaps the most striking of the articles and what constituted a landmark achievement of the neuroanatomy sub-school, as well as that of the NII school, was David Felten’s “Noradrenergic and peptidergic innervation of lymphoid tissue.” The paper solidified Karen Bulloch’s earlier work and thus achieved greater acceptance. The Felten group firmly established an anatomical connection between the immune and nervous systems. Also in the same issue was a paper by Candace Pert, “Neuropeptides and their receptors: a psychosomatic network,” in which her group “develop[ed] the concept that neuropeptides and their receptors form a network of information exchange which extends throughout the brain and body, including the immune system.” The paper furthered Jean-Michel Dayer’s identification of interleukins in the brain, because they now had an identified target in the brain upon which to act.

The October 23, 1987 issue of Science convinced many skeptical neuroendocrinologists with its mechanistic evidence for neuroendocrine-immune communication. The research in all three papers, printed in succession, was made possible by the cloning of the interleukin-1 gene, first done by Charles Dinarello. By injecting pure, recombinant interleukin-1 into mice, researchers could measure the effects on the neuroendocrine system and establish a direct cause and effect relationship between the nervous and immune systems.

The three independent papers constituted an enormous landmark in the progression of NII. However, there were still many scientists, especially immunologists, who found these studies to be incomplete or unconvincing. This is evidenced by the small amount of attention given to NII in immunology textbooks up to the present. While immunologists were willing to accept that the immune system was integrated into the rest of the organism, they questioned the immunological importance of the communication. As immunologists argued, just because there is an interaction between the nervous and immune system, even if it produces statistically large variation in immune cell and antibody populations, does not necessarily mean the interaction is immunologically important. The immune system’s flexibility, its overabundance of leukocytes and antibodies, allows for a drastic fall in immune cell number without affecting immune efficacy. The importance, however, lies in the combination of multiple inputs leading to compromised immunity and, ultimately, the difference between health and disease.

Other researchers, who did not author papers in either of the two above landmark issues but were of incredible scientific and political importance to the neuroendocrine sub-school, included Samuel McCann, Seymour Reichlin, Alan Munc, Esther Sternberg, Robert Dantzer, and Janice Kiecolt-Glaser. The first two men contributed to NII in both research and funding areas. Munc produced important work on the role of glucocorticoids, steroid substances released when we are under stress that have an anti-inflammatory role; 55,56 Sternberg established the biological and immunological importance of the nervous immune connection, 51,52,53 Dantzer illuminated some of the mechanisms of sickness behavior, 7 and Kiecolt-Glaser added legitimacy to PNI and the link between stress and repressed immune responses. 55,56 All of these experiments and discoveries, along with more persuasive research of the 1990s, legitimized the field of NII and allowed it to achieve paradigm status. Each study fed off the previous one, creating an exponentially growing body of research that gained viability with each passing year. New journals that contained research strictly from the sub-schools of NII started to appear and gain respect in the 1980s. Ader and Cohen started Brain, Behavior, and Immunity in 1987; The Journal of Neuroimmunology began circulation in 1981 and became a highly respected and cited journal; and in the winter of 1988, the first volume of Progress in NeuroEndocrinology, which later switched names to Neuroimmunomodulation in 1999, debuted.

PARADIGM ACHIEVED

The revolutionary period of the 1970s and 80s finally led to NII’s establishment as a new paradigm in the early 1990s. But this was only the beginning of paradigm status: it would take more research for the paradigm to eventually solidify in the late 1990s. The struggle to convince skeptics that the nervous and immune systems did communicate was not completely over; the extent, pathways, and importance of the interaction remained hotly debated. Some researchers, though fewer than in the 1980s, still questioned the existence of bi-directional communication between the nervous and immune systems. However, the communication between two organ systems, previously thought to be autonomous, was accepted by a majority of the biomedical community, leaving only details to be resolved.

One of the best indicators of NII’s raise to paradigm status appears in the 1992 Encyclopedia of Immunology with the entry on “Neuroendocrine Regulation of Immunity.” This entry, along with the huge number of publications printed in prestigious journals such as Science and The New England Journal of Medicine, marked NII’s into mainstream legitimate, paradigm-driven science. We also see recent immunology texts with references to modulation of the immune system, especially through the use of cytokines; some texts even include small sections on the neuroendocrine modulation of immune function. Although immunologists were the most skeptical about the integration of the immune system, their questioning faded to an eventual acceptance of communication between the nervous and immune systems.

SCIENTIFIC DETENTE

As NII became paradigmatic, the sub-schools started to accept each other. The pressure for precedent faded, and internal differences made way for cooperation as each sub-school acknowledged the varying, yet complementary, pathways of communication between the immune and nervous systems. The science binding the two most complex parts of human beings attained ever-greater clarity from the early 1990s, and by the mid-1990s on the various sub-schools saw more similarities than dif-
ferences between their research. However, tensions still run high within the field, especially among pioneers, and NII remains the subject of criticism, although it no longer has to fight for survival.

In 1993, Seymour Reichlin published an article in the *New England Journal of Medicine* reviewing some of the important pathways of communication associated with NII. He identified research from most of the sub-schools and synthesized a broad overview of their contributions, though he did manage to identify Ader and Cohen’s conditioning experiments as “neuroimmunomodulation.” His professional position and the article’s publication in the *New England Journal of Medicine* gave credence to a template of cooperation and synthesis of varied research for NII that coincided with its rise to paradigm status.

**“Dualism is dead”—Alan Leschner**

Some researchers who started investigating areas within NII in the late 1980s and 1990s were able to move between sub-schools and in doing so consolidated the field. Chief among these was Esther Sternberg whose education and background in immunology made her research acceptable to the other subschools. Her book, *The Balance Within*, a personal account of her experiences with NII, included all of the sub-schools and adamantly emphasized that they all worked toward the same goal.

Younger researchers entered the field by the late 1990s and received training under an integrated rubric, one furthered by trainee grants issued by the National Institutes of Health. These students of the new paradigm are now learning within an integrative field and are being taught to conduct research in an integrative manner, thus allowing them to bring together not only the scientific aspects of NII but also aspects of all the sub-schools.

Yet the most convincing marks of détente are the scientific content and members of meetings, societies, and most importantly, journals like *Brain, Behavior, and Immunity* and *Neuroimmunomodulation*. The editorial boards of these two journals exemplify détente quite well. The editors of *Neuroimmunomodulation* are Samuel McCann and Jim Lipton. Robert Ader serves as the editor-in-chief of *Brain, Behavior, and Immunology*. The two journals, whose principle editors were among the leading figures of some of the sub-schools (Ader of PNI, McCann of neuroendocrinimmunology), have many common associate editors and editorial board members: Hugo Besedovsky, Robert Danzler, Adrian Dunn, Kieth Kelly, Seymour Reichlin, Eric Smith, and Esther Sternberg, who serves as an associate editor for both journals.

Reports such as *Neuroimmunology and Mental Health*, put out by the National Institutes of Health in 1994 and edited by Ljubisa Vitkovic and Stephen Koslow also hint at the beginnings of integration of sub-schools. Some of the notable names previously mentioned were on the advisory panel: David Felten, Ronald Glaser, and Samuel McCann. More importantly, the subject matter of the report covered all of the sub-schools and consolidated the pathways and outcomes of integration.

**CONCLUSION**

Scientific revolutions are long processes with neither clear beginnings nor endings but with distinguishable trends that let us mark their progression despite their fluid nature. They are a broad series of events with numerous inputs and ramifications, not only for the science involved, but also for society at large. The emergence of NII has changed our concept of disease and opened up new ways that we can use to preserve health. While NII has not completely matured into a fully developed field of science, there still remains controversy about its efficacy, and a textbook, which Kuhn suggests is the mark of a matured science, is not evident. There are many proto-textbooks, such as Bruce Rabin’s *Stress, Immune Function, and Health*, but they are neither comprehensive nor fully integrative. There remains room for even greater integration.

NII has blurred the duality of mind and body, showing us that they are indeed two parts of a whole that are entirely reliant on one another. If we expand on the findings of the past three decades and view them in totality, we can see that the state of the immune system affects our emotions and vice versa. This is not, in any way, to say that emotions and the stresses they cause lead to or cure disease, but that they are one aspect of health and illness and belong with the other inputs modern medicine considers when treating a patient. Emotions should be considered along with genetic predisposition to disease and the pathological basis of disease when a physician makes a diagnosis and prescribes therapies. NII, by providing the pathways and outcomes of neutral-immune communication, allows us to seriously consider the mental and social circumstances underlying the disease process. The body of research is, at this time, so large that it cannot and must not be ignored.

David Felten questioned our ignorance in the second edition of *Psychoneuroimmunology* and asked, “Can we afford to ignore the role of emotions, hope, the will to live, the power of human warmth and contact, just because they are difficult to investigate scientifically and our ignorance is so overwhelming?” The research is certainly abundant and the ramifications of NII are now seen in policy decisions about healthcare and even in the medical school curriculum, although they still represent only the slightest inklings of influence.

The mind and body, held in separate regard for centuries and therefore believed to be incompatible, have been integrated. Thus, the development of NII did much to integrate the incompatible by changing our conceptions of mind and body, nervous system and immune system, and the specialties and divisions within medicine. The recent entrance of NII into the biomedical milieu marks the beginning of change. Whether these changes will manifest themselves in any revolutionary manner outside the annals of science (or even outside NII) remains to be seen.

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This article is an abridged version of Sahand Boorboor’s senior honors thesis, for which he received the Wilton Coates Award for the most outstanding senior honors thesis in history. Sahand received a B.A in history from the University in 2002. He is currently at the University of Cologne (Germany) studying German literature and the German healthcare system.