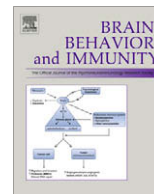


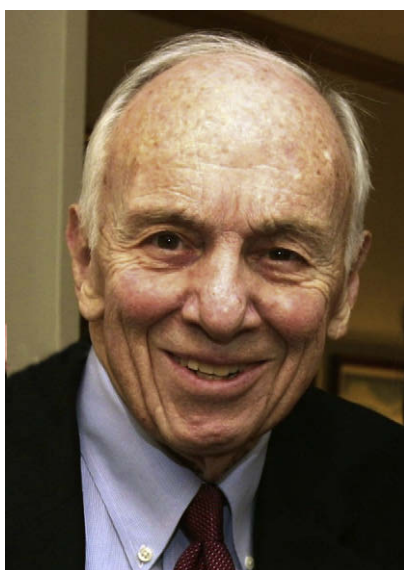
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In Memoriam

Marvin Stein, M.D. (1923–2009)



Dr. Marvin Stein, who died this past May 16 at the age of 85, was one of the remarkable small group of clinically oriented scientists who contributed to the establishment of the modern field of psychoneuroimmunology in the United States. Marv, as did Bob Ader and George Solomon, found his way somewhat circuitously during the 1960s and 1970s into studies of brain and behavioral influences on the immune system. On the way, research publications appeared in journals ranging from *J Clin Endocrinol Metab* (1952), the *Am J Physiol* (1964–1991), *J Comp Neurol* (1964), and *Cell Immunol* (1980), to *Science* (1981–1983) and *JAMA* (1983), but also the *Arch Gen Psychiatry* (1966–1989) and *Psychosomat Med* (1953–1969), (1953–1969), and, yes, *BBI*, of which he served on the founding Editorial Board (1988). Marv's journey took him to many disciplines, drawing insights from many and leaving contributions of uncompromising scientific rigor along the way.

Born in St. Louis, home of his beloved Cardinals, and completing undergraduate and medical degrees as well as postgraduate training in psychiatry at Washington University, Marv took up two lines of study that may seem incongruous today: an NIMH Fellowship with Arthur Mirsky in endocrine physiology and psychosomatic medicine, and formal psychoanalytic training. While he loved to debunk its eccentricities, Marv's psychoanalytic background provided a context for serious consideration of the influence of mental and brain processes on physical states. His lab, however, was classic physiology. I was not the only one who wondered, upon first

meeting him and his work in the early 1970s, what in the world it had to do with psychiatry. By that time, Marv and his lab had moved from Penn to Cornell, to SUNY-Downstate, where he served as Professor and Chair of Psychiatry, and then to Mount Sinai, where he became the second Chair of the Department of Psychiatry in a vigorously new medical school, a position he held for 16 years.

Marv's lab was modest in scale, by design. He would work with one, at most several, co-investigators extraordinarily closely, examining every detail, even as he carried the growing academic and clinical responsibilities of his medical school department. Science, however, was never relegated to "the left hand". Studies from Marv's lab were exquisitely focused and carefully designed, "tight". His was a linear path of investigation, always building on the last experiment. And it was the data that led Marv from the lung to the immune system. To understand how psychological states influenced asthma, a classic psychosomatic illness, with behavioral conditioning of allergic asthma as a model, Marv and several of his earliest collaborators, Raul Schiavi and Tom Luparello, developed a guinea pig model of lethal anaphylaxis. Together with their long time assistant Maria Camerino, they found themselves exploring the intricacies of lung compliance in the guinea pig. Only then could they investigate the effects of hypothalamic lesions on anaphylaxis, demonstrating lesion localization among other effects (and publishing a stereotactic atlas of the guinea pig hypothalamus along the way). These studies forced a major shift in focus as it began to appear that brain effects on pulmonary anaphylaxis were related not so much to intrinsic aspects of lung compliance but rather to the mediating effects of brain states on immunologic processes.

Marv and his collaborators had come to an unexpected place. While concepts of psychoneuroimmunology (as yet unnamed) had a long history in the Eastern European Pavlovian tradition, and were being explored in the US by Solomon and by Ader, that the brain might play an important role in regular activities of the immune system was viewed as curious, strange, even preposterous by many organ-system-oriented clinicians and scientists at the time (and maybe even a few today). Marv worked in the shadow of early 20th Century studies he loved to quote, which demonstrated that the immune system continued to function in the decerebrate animal. He loved to recount receiving back a manuscript sent to the *Am J Physiol* with an editor's scribble, inadvertently unerased (well before the days of word processors), asking if anybody knew anything about this immunology.

At around that time, Steve Keller, an immunologist–pathologist, and I joined Marv's lab. The lab moved to exploring a range of immune processes that might be affected by brain states and a range

of brain states that might affect immunity. Studies examined hypothalamic effects on delayed cutaneous hypersensitivity and on *in vitro* models of “cell mediated immunity”, especially mitogen induced lymphocyte proliferation. The anaphylaxis-oriented guinea pig model no longer had unique advantages for studying brain-immune effects, and the studies shifted to the rat as a better model for behavioral effects, especially those of acute stress. A now classic series of papers in *Science* and *PNAS*, collaborating with Jay Weiss and Neil Miller at Rockefeller University, demonstrated that acute stress could result in a profound suppression of lymphocyte activity that was largely adrenal independent. With some trepidation, we also began to consider whether similar processes might be demonstrable in humans, examining effects of a profound stressor, the death of a spouse, on lymphocyte activity. Along the way, Marv led the group into studies of bench immunology methodology and of novel statistical approaches to the daunting challenge of immune assay variability over time (in collaboration with Jacob Cohen).

The finding of an apparent suppressive effect of bereavement on lymphocyte activity led to what may have been Marv's most challenging area of PNI research, that of immunity in clinical depressive disorders. The logic of the work rested on the hypothesis that immune effects of bereavement were associated with the induction of depressive states—curiously a return to the classic psychoanalytic theme of mourning and melancholia. While early studies found decreased lymphocyte activity in some depressed patients, the field Marv helped create turned out to be far more complex than anticipated, with more than its share of seemingly inconsistent observations. It is a story that remains incomplete 25 years later. Still seeking to understand the data, Marv's last PNI studies, working with Andy Miller and Bob Trestman in collaboration with Bruce McEwen's group, returned to a classic theme of stress, depression and immunity: the role of adrenal receptors in immunomodulation.

One cannot leave Marv's story without recognizing another context for his work, that of his family and his deeply held personal values. How often would he reference his most trusted consultant, his wife Ann, or speak with pride of his daughters and son. The pursuit of truth transcended science; there was a right and a wrong

that needed to be discovered for every aspect of life, and action was required, not optional.

Marvin Stein was a devoted skeptical scientist who believed that scrupulous attention to experimental design and method transcended all other considerations, and would reveal the truth. Nothing left his office without having been examined to the highest level of tolerance available. Every word was measured, every angle explored. Always a doubter, he entered an unnamed field that few took seriously, and left a legacy in which few express doubt that brain and behavior influence the immune system.

Further reading

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