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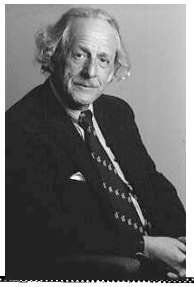

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Of Sea Snails and Science Reviews: Neurobiologist Eric R. Kandel Receives the 1988 NAS Award for Excellence in Scientific Reviewing

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The 1988 National Academy of Sciences Award for Scientific Reviewing has been awarded to neurobiologist Eric R. Kandel. Kandel's influence on the study of the cellular basis of behavior is traced through ISI® research fronts on both the sea snail *Aplysia* as well as earlier work on the mammalian hippocampus. Kandel's thoughts on his research work, as well as scientific review, are highlighted.

The 1988 National Academy of Sciences (NAS) Award for Scientific Reviewing has been awarded to Eric R. Kandel, University Professor, Columbia University College of Physicians & Surgeons, and Senior Investigator, Howard Hughes Medical Institute, New York. Kandel was recognized by the NAS for "greatly influencing modern study of the cellular basis of learning through his outstanding reviews relating findings in simple systems to those obtained in higher forms."[1]

ISI® and Annual Reviews Inc., Palo Alto, California, established the NAS award in 1977 (although it was not actually awarded until 1979) and have cosponsored the $5,000 honorarium ever since. The award honors James Murray Luck, who founded Annual Reviews and served as its editor-in-chief until his retirement in 1969. Although ISI and Annual Reviews contribute jointly to the award, winners are selected independently by committees appointed by the NAS. The discipline from which recipients are chosen rotates annually among the biological, physical, and social and behavioral sciences. Last year's recipient was psychologist and educator Gardner Lindzey, president and director, Center for Advanced Study in the Behavioral Sciences, Stanford, California.[2] The 1989 award will be for reviews in the physical sciences.

Biographical Information

Kandel was born in Vienna, Austria, on November 7, 1929. He received his BA from Harvard College, cum laude, in 1952 and an MD in 1956 from the New York University (NYU) School of Medicine, New York. Highlights of his career to date include positions at the Laboratory of Neurophysiology, National Institute of Mental Health (NIMH), Bethesda, Maryland (1957-1960); clinical training in psychiatry at the Massachusetts Mental Health Center, Harvard Medical School, Boston, Massachusetts (1960-1962); a postdoctoral fellowship at the College of France, Paris (1962-1963); instructor, Harvard Medical School (1963-1965); head, Division of Neurobiology and Behavior, NYU School of Medicine (1965-1974); director, Center for Neurobiology and Behavior, Columbia University College of Physicians & Surgeons (1974-1983); University Professor, Columbia University (1983-present); and Senior Investigator at the Howard Hughes Medical Institute (1984-present). Honorary degrees include ones conferred by Johns Hopkins University, Baltimore, Maryland; the State University of New York, Stony Brook; the Mount Sinai Medical Center, New York; Hahnemann University, Phila-

delphia; and the Jewish Theological Seminary of America, New York.[3]

Kandel has garnered several prestigious awards, including the 1983 Albert Lasker Basic Medical Research Award (given by the Albert and Mary Lasker Foundation, New York), the 1984 Lewis S. Rosentiel Award for Distinguished Work in Basic Medical Research (given by Brandeis University, Waltham, Massachusetts), the 1987 Gairdner International Award for Outstanding Achievement in Medical Science (given by the Gairdner Foundation, Willowdale, Ontario, Canada), and the 1988 Gold Medal for Scientific Merit (given by the Giovanni Lorenzini Foundation, Milan, Italy).[3] He was also a recipient of this year's National Medal of Science, awarded by the president of the US.[4]

Kandel is a member of NAS, the American Philosophical Association, and the American Academy of Arts and Sciences. He served as president of the Society for Neuroscience from 1980 to 1981 and is former associate editor of the *Journal of Neurophysiology*, the *Annual Review of Neuroscience*, and the *Journal of Neuroscience*. Currently, Kandel is review editor of the journal *Neuron*. He is also a member of the Board of Trustees of the Cold Spring Harbor Laboratories, New York.[3]

Scientific Reviewing: Significance, Audience, and Unpublished Peer Reviewing

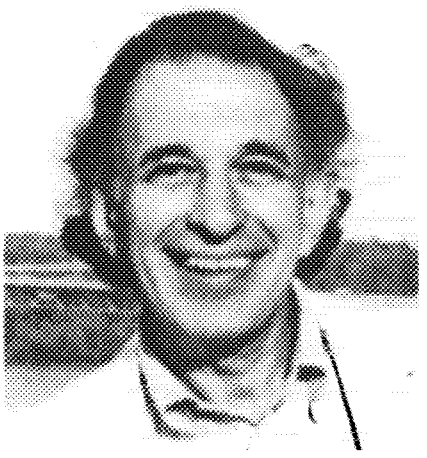
Recently, we spoke at length to Kandel about his reviews, as well as his viewpoints on his work, and how reviews reflect on primary research.[3] Excerpts from that conversation appear throughout this essay.

Q: What are your ideas on the significance of scientific reviewing?

Kandel: A critical review should serve a function both for the reviewer and for readers, for the people in the field. A review ideally allows the reader to learn, from one person, the outlines of the field: what the major issues are and what directions are most profitable to follow. In turn, the writing of the review forces a reviewer to master a subcomponent of the discipline and to set priorities for what is important and what is not. The reviewer needs to outline the directions that are likely to be most productive for the next round of research—directions that are both interesting and doable—and to explain these directions clearly to the reader. A good review is particularly worthwhile and important in newly emerging areas that lie between traditional disciplines.

Q: What initially led you to write review papers? Is there a particular audience that you write for?

Kandel: The first review that I wrote was with Alden Spencer [then at the NYU School of Medicine], called "Cellular neurophysiological approaches in the study of learning."[5] [This paper has accumulated over 250 explicit citations since it appeared in 1968.] At the time we wrote it, most cellular neurobiologists thought that behavior and learning were intractable, by and large, and certainly not accessible to modern cell-biological approaches. Conversely, most psychologists had no interest for or competence in cell biology. We attempted to point out to both neurobiologists and psychologists that the problems of learning could now indeed be tackled profitably from a cellular point of view and that, moreover, this approach was essential if we were to understand elementary mechanisms. Most people were, by and large, not aware that this might be done. We pointed out why the study of learning had become doable: we indicated the systems that were most promising for this sort of study, and we suggested the directions we thought were most interesting. Specifically, we tried to spell out how learning experiments could be translated into cellular neurobiological experiments. We also pointed out the pitfalls and indicated that a great distance still needed to be traversed—a lot of problems had to be overcome and new systems had to be developed—before one could really be in sight of the goal.



Eric R. Kandel

Q: How would you compare the significance of published scientific reviews with that of unpublished peer reviews?

Kandel: They both serve important yet very different functions. Peer reviewing at its best helps make science strong. It sets and maintains standards in the field. You and I may be very good friends, but when I referee your paper or proposal, my obligation to you is to tell you honestly what its weaknesses are. That is the stuff of which science is really made: open, non-ad hominem criticism of each other's works. Scientific reviewing, on the other hand, has an additional function. One function certainly is to provide a critical evaluation of a field. But another, even more important, role is to outline the problems that are interesting and to suggest the mechanisms that might be at work. The function of the review is broader and much more educational than that of an unpublished peer review. The peer review is directed specifically to the author; the scientific review is meant for a much larger audience.

Kandel's Most-Cited Works Dealing with *Aplysia californica*

Kandel has published (as primary author or coauthor) more than 190 papers since 1960, which together have received almost 5,000 citations. He has also, since 1976, authored three books (with nearly 700 scientific works referencing them) on aspects of neural science and neurobiology.

Since 1968, when his first review article was published, Kandel's reviews have had a significant influence on the field of neurobiology. (Table 1 is a list of his most-cited publications.) ISI data have identified nine of his papers as reviews—about 5 percent of his published output since 1968. This is a significantly higher proportion of reviews than the average of other scientists. About 3 percent of currently published papers are classified by ISI as reviews. Many of Kandel's published works involve research results from the study of the neuronal cells of the gastropod *Aplysia*.

There are 35 known species of this hind-gilled sea snail, with approximately two-thirds found in either tropical or subtropical waters (although one species has been found within the Arctic Circle). The species of *Aplysia* most extensively investigated live off the Atlantic and Pacific coasts of the US and the Mediterranean coasts of France, Monaco, and Italy.[6] (p. 40) Kandel has worked mainly with *Aplysia californica*, which was first described in 1863.[6] (p. 29)

In his volume *Cellular Basis of Behavior*, Kandel describes why *Aplysia* is such a useful organism in neural behavior studies.

> The central nervous system of *Aplysia* is remarkably well suited for studies of single cells. Almost all its nerve-cell bodies are large enough to permit the insertion of microelectrodes for intracellular recording. Many of the cells can be individually identified so that identical neurons can be examined in any number of individual animals under a variety of conditions. Single cell bodies can be dissected for biochemical studies. Radioactive chemical substances or dyes can be injected into the cell body and their movement throughout the neuron monitored morphologically and biochemically. Unlike arthropods, the synaptic...connections can often be monitored electrically, with minimal attenuation, by obtaining intracellular recordings in the cell body of the neuron.... The ability to trace connections from cell to cell makes

Table 1: Eric R. Kandel's most-cited publications in the *SCI®*, 1955-1987, and the *SSCI®*, 1966-1987. A = number of citations. B = bibliographic citation. The *SCI/SSCI* research fronts to which the paper is core are included in parentheses.

A	B
707	**Frazier W T, Kandel E R, Kupfermann I, Waziri R & Coggeshall R E.** Morphological and functional properties of identified neurons in the abdominal ganglion of *Aplysia californica*. *J. Neurophysiol.* 30:1288-351, 1967. (87-5739, 86-5651, 85-1230, 76-0789)
455	**Kandel E R.** *Cellular basis of behavior*. San Francisco, CA: Freeman, 1976. 727 p. (87-5739, 86-5651, 84-7783)
348	**Kandel E R & Spencer W A.** Electrophysiology of hippocampal neurons. II. After-potentials and repetitive firing. *J. Neurophysiol.* 24:243-59, 1961. (82-0381, 81-0449)
342	**Kandel E R, Spencer W A & Brinley F J.** Electrophysiology of hippocampal neurons. I. Sequential invasion and synaptic organization. *J. Neurophysiol.* 24:225-42, 1961. (81-0449)
336	**Kandel E R & Schwartz J H.** Molecular biology of learning: modulation of transmitter release. *Science* 218:433-43, 1982. (87-5739, 86-0552, 85-0195)
269	**Spencer W A & Kandel E R.** Electrophysiology of hippocampal neurons. IV. Fast prepotentials. *J. Neurophysiol.* 24:272-85, 1961.
250	**Kandel E R & Spencer W A.** Cellular neurophysiological approaches in the study of learning. *Physiol. Rev.* 48:65-134, 1968. (83-0541)
246	**Klein M & Kandel E R.** Presynaptic modulation of voltage-dependent Ca^{2+} current: mechanism for behavioral sensitization in *Aplysia californica*. *Proc. Nat. Acad. Sci. USA* 75:3512-6, 1978.
185	**Kandel E R & Tauc L.** Anomalous rectification in the metacerebral giant cells and its consequences for synaptic transmission. *J. Physiol.—London* 183:287-304, 1966.
182	**Castellucci V, Pinsker H, Kupfermann I & Kandel E R.** Neuronal mechanisms of habituation and dishabituation of the gill-withdrawal reflex in *Aplysia*. *Science* 167:1745-8, 1970.
167	**Kandel E R.** Electrical properties of hypothalamic neuroendocrine cells. *J. Gen. Physiol.* 47:691-717, 1964.
165	**Kandel E R, Frazier W T, Waziri R & Coggeshall R E.** Direct and common connections among identified neurons in *Aplysia*. *J. Neurophysiol.* 30:1352-76, 1967.
148	**Castellucci V F, Kandel E R, Schwartz J H, Wilson F D, Nairn A C & Greengard P.** Intracellular injection of the catalytic subunit of cyclic AMP-dependent protein kinase simulates facilitation of transmitter release underlying behavioral sensitization in *Aplysia*. *Proc. Nat. Acad. Sci. USA* 77:7492-6, 1980. (82-1472)
136	**Brunelli M, Castellucci V & Kandel E R.** Synaptic facilitation and behavioral sensitization in *Aplysia*: possible role of serotonin and cyclic AMP. *Science* 194:1178-81, 1976.
127	**Kandel E R.** *Behavioral biology of* Aplysia. San Francisco, CA: Freeman, 1979. 463 p.
126	**Eisenstadt M, Goldman J E, Kandel E R, Koike H, Koester J & Schwartz J H.** Intrasomatic injection of radioactive precursors for studying transmitter synthesis in identified neurons of *Aplysia californica*. *Proc. Nat. Acad. Sci. USA* 70:3371-5, 1973.
113	**Kupfermann I, Carew T J & Kandel E R.** Local, reflex, and central commands controlling gill and siphon movements in *Aplysia*. *J. Neurophysiol.* 37:996-1019, 1974.
102	**Kandel E R & Schwartz J H.** *Principles of neural science*. New York: Elsevier/North Holland, 1981. 749 p.

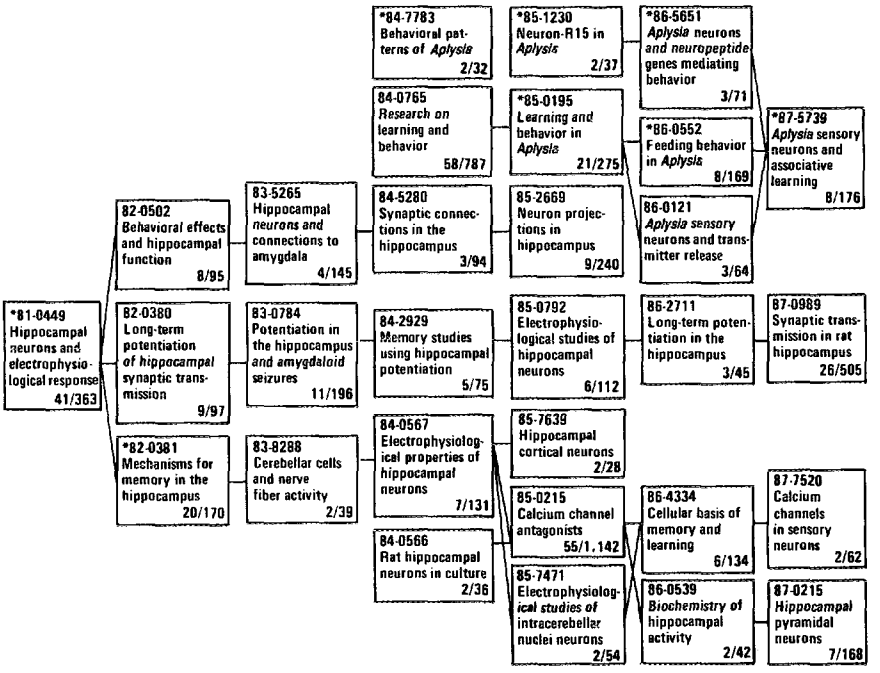
> it possible to relate types of neuronal circuits and types of behavior.... These technical advantages made *Aplysia* attractive for the exploration of the rules governing the patterns of nervous connections and the relationship between different patterns of connections and behavior.[7]

The above excerpt is from the first comprehensive overview of the principles of cell biology underlying behavior and learning, Kandel's second most-cited work (see Table 1). It has been explicitly cited in over 450 publications to date. During the dinner just before the NAS award presentation, Kandel told me that this is his favorite and, to his mind, his best review. It is, in fact, a core publication in three recent annual research fronts involving this organism—"Behavioral patterns and structure of the nervous system in *Aplysia*" (#84-7783), "*Aplysia* neurons and neuropeptide genes mediating behavior" (#86-5651), and "*Aplysia* sensory neurons and associative learning" (#87-5739). These fronts appear along with many others in the historiograph in Figure 1.

Hippocampal Research/Citation Classic

In the late 1950s and early 1960s, before Kandel came to work with neurons of the

Figure 1: Electrophysiology of central neurons and cellular mechanisms of behavior. Historiograph showing developments in this research. Numbers of core/citing papers are indicated at the bottom of each box. Asterisks (*) indicate research fronts in which E.R. Kandel is a core author.



Aplysia, he had worked on the mammalian hippocampus (a curved elongated ridge that extends over the floor of the descending horn of each lateral ventricle of the brain and consists of gray matter covered on the ventricular surface with white matter). This effort resulted in a four-part study published in 1961 in the *Journal of Neurophysiology* and coauthored with his colleague Alden Spencer.[8-11] With well over 1,000 citations collectively, this set of papers has attained *Citation Classic*® status. In his *Citation Classic* commentary, Kandel recalls:

> Reading these papers brings back the sense of privilege and excitement I experienced in collaborating with Alden Spencer. Although we did not collaborate again, we continued our friendship and interacted daily, first at NYU and then at Columbia, where our colleagueship was sadly disrupted by Alden's untimely death of amyotrophic lateral sclerosis in 1977. We met in 1958 at NIH.... From the outset, we sought to bring the methods of cell biology to the study of learning. I had already started work on the hippocampus, the part of the mammalian brain that neurosurgeons had shown to be critically involved in human memory, and, when he arrived at NIH, Alden immediately agreed that this might be a good place to begin. We wanted to see whether the electrophysiological properties of the hippocampal neurons were fundamentally different from those of the only two other vertebrate central neurons that had been studied, the motor neurons of the spinal cord and of the motor cortex.... We were immediately successful in our attempts.... Being young, naive, and brash, we were not reluctant to tackle what appeared to others to be a difficult technical problem: intracellular recordings from cortical neurons in a pulsating brain.[12]

Papers in this highly cited series appear as core documents in research fronts on "Hippocampal neurons and electrophysiological response" (#81-0449) and "Mechanisms for memory in the hippocampus"

(#82-0381) (see Figure 1). Many of the core authors for these fronts continue to show up as core authors up to the present—T.V.P. Bliss, National Institute for Medical Research, London, UK;[13] and R. Llinás, Department of Physiology and Biophysics, NYU Medical Center.[14,15] It is interesting that two of the major systems currently being used in the cellular study of memory were originally developed by Kandel, as Figure 1 shows.

Identification of Nerve Cells

After the series of papers on the hippocampus, Kandel's most-cited single paper, coauthored with colleagues at the NYU School of Medicine and at Harvard Medical School, has gathered over 700 citations to date: "Morphological and functional properties of identified neurons in the abdominal ganglion of *Aplysia californica*." This paper describes the features that allow unique identification of a large number of nerve cells in this ganglion. It formed the basis for all later studies that relate these cells to each other in terms of their patterns of interconnections on the one hand and to the animal's behavior and learning capability, on the other.

This paper is core to several annual research fronts, including the three latest contiguous fronts we have data for—"Neuron-R15 in *Aplysia*" (#85-1230), "*Aplysia* neurons and neuropeptide genes mediating behavior" (#86-5651), and "*Aplysia* sensory neurons and associative learning" (#87-5739). Figure 2 is a graph showing the chronological distribution of the number of papers citing this most cited and the next most cited of Kandel's publications.

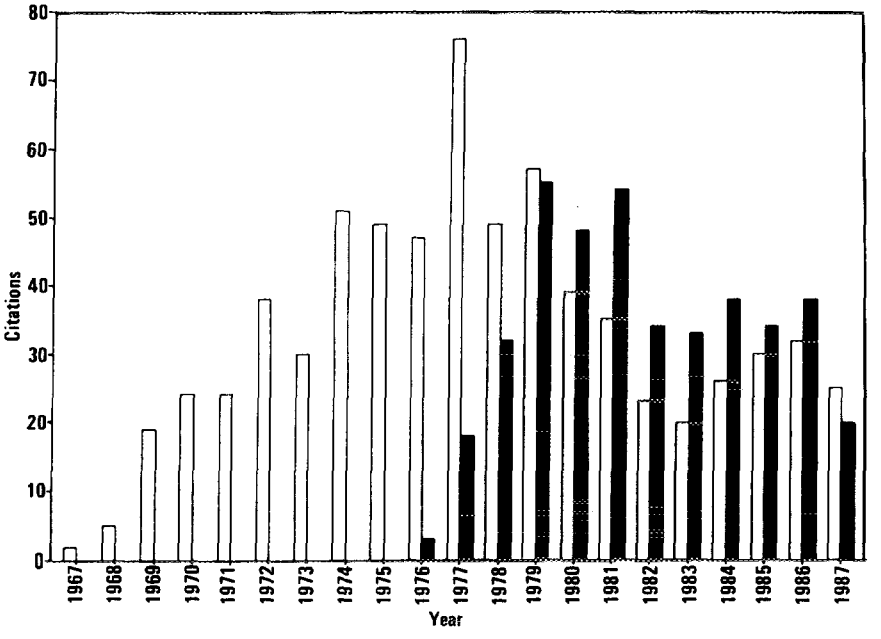
Scientific Reviewing: Invisible Colleges and Nonoriginal Research

In 1963 Derek J. de Solla Price published his landmark book *Little Science, Big Science*.[16] (In previous essays I have discussed both Derek[17] and his most-cited work.[18]) Price redefined the seventeenth-century term "invisible college" as being an informal, widely dispersed group of people with a common scientific interest who "effectively solve a communication crisis by reducing a large group to a small select one of the maximum size that can be handled by interpersonal relationships."[16] (p. 85) These unofficial collectives are important channels for informal and formal communication, where its members exchange data—by preprints or other works in progress. By maintaining communication in the invisible college, the reviewer is expected to include all relevant research, whether it is original scientific effort or otherwise.

Q: What is your view of the significance of scientific reviews in relation to nonoriginal scientific work?

Kandel: I think most people's view of what a review should accomplish has evolved. It once was thought that a good review should be encyclopedic. Such reviews listed, in a scholarly way, every single reference, every single piece of work done in a scientific field. Years ago, many annual reviews were like that. But with respect to the first review I coauthored with Spencer[5] [1968] and the second one [1970] with Irving Kupfermann[19] [NYU School of Medicine]...we tried to take a different approach—one in which we were purposely selective rather than exhaustive. Insofar as one is selective, it's not simply a question of summarizing what others have done. There is an opportunity for a modest amount of creativity. The challenge is to try to put findings and questions together in a somewhat new way. But, having said that, I would emphasize that both levels of scholarship—the exhaustive and the selective review—although valuable for the reviewer, do not, in my mind, reach the originality that is central to independent, original scientific work. If you were to ask me what I think has provided me with greater gratification—the scientific contributions that I and my colleagues have made experimentally or the reviews that I have written—I would say without a doubt it's the scientific research that I've done, hands down. The reviews have contributed importantly to my education and have allowed me to do

Figure 2: Year-by-year citations to E.R. Kandel's two most-cited publications dealing with *Aplysia*, *J. Neurophysiol.* 30:1288-351, 1967 (identified neurons paper) (white bar) and *Cellular basis of behavior*, 1976 (black bar).



the research.... When I want to move into a new field, I think at the beginning, "I have to do an awful lot of reading to get into this area." As I get into it, I sometimes feel, "Gee, this is a nice new field. I really ought to share this with my friends. I have sweated through this and now I begin to understand it." Also, in the course of writing reviews, one gets an idea or two that may lead to an experiment you want to do. One does get many ideas from reading and trying to pull work together in a somewhat new way.

Q: Would you recommend that a person write reviews, then, to be a better scientist?

Kandel: I think writing reviews is a worthwhile scholarly activity and is useful for giving one a grasp of a particular part of the discipline. I don't necessarily recommend it, but I think that I've often come out of review being very grateful that I've done it because I learn a great deal from it. But, as with all things, you have to balance the good of writing a review and the other side—the time it takes. One has to make sure that it does not distract too much from the really important long-term activity of doing the science itself.

Conclusion

The importance of critical reviews in making information accessible and meaningful should not be underestimated. They have become one of our most valuable tools for overcoming information overload. As described in *Current Contents®*, the growth in the review literature is inevitable and parallels the exponential growth of the experimental literature. In addition to the traditional forms, a whole new genre of reviews is emerging. The recent emphasis is on the "minireview," but the need for discursive treatment is still relevant when the right reviewer can be found. Kandel's remark about the time it takes to write reviews brings to mind some observations by Sir Julian Hux-

ley (1887-1975), the noted British biologist. In the preface to his book *Biological Aspects of Cancer* (which is based on two comprehensive reviews that he wrote on the topic in the mid-1950s), he candidly admits:

> I can truthfully say that the preparation of these two reviews involved me in more hard labour than anything I have attempted since I took my Final Honours examination in Zoology at Oxford.... I could never have finished them if I had been occupied with teaching, administration, or the need to produce a stream of research papers. Indeed it may be a good thing to have a few elderly scientists quit of all such professional obligations and free to devote themselves now and again to general surveys.[20]

The profession of science reviewer,[21] the role of the science critic,[22] and the need for well-trained science journalists all form part of the continuing and complex process of reviewing. The NAS Award for Scientific Reviewing, one hopes, is a reminder to the aspiring scientist—young or old alike— that the path taken by Eric Kandel and many others before him is indeed a fundamental service to science.

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My thanks to Peter Pesavento for his help in the preparation of this essay.

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