A troubled pilgrim's progress

The compelling personal journey of a founding father of cellular immunology.

Science as Autobiography: The Troubled Life of Niels Jerne
by Thomas Söderqvist
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Gustav J. V. Nossal

The central puzzle of the immune system is how it can react specifically to virtually any microbe or foreign molecule. How is it possible, with a large but limited number of genes, to produce billions of different sorts of antibody? Before revealing the answer, we must pay tribute to Niels Kaj Jerne (1911–94), the Danish-born immunologist who unquestionably deserves the credit for creating a theoretical framework within which the matter could be pursued.

The steps along the path are elegantly described in this biography by Thomas Söderqvist, first published in Danish in 1998 and recently revised and translated into English. But if the reader is expecting a typical scientific biography, in which the research of a famous person is catalogued and explained, a rude shock awaits. After more than ten years of meticulous examination of Jerne's extensive papers, and 160 hours of interviews with him, Söderqvist presents a thought-provoking, surprisingly frank account of Jerne's personal life and philosophy.

The controversial justification for this approach is Söderqvist's belief that the source of Jerne's creativity lay in his personal experiences; that his scientific work was an inseparable part of his life as a whole. Thus, Söderqvist embarks on what he terms new biographical territory, namely existential biography. As a result, we are given both an authoritative presentation of Jerne's scientific achievements and a penetrating survey of this troubled pilgrim's progress.

Jerne's parents were Danish, but lived successively in England, Germany and the Netherlands. The young Niels became fluent in Danish, English, German and Dutch, never feeling rooted anywhere. He gradually assumed the mantle of an élitist, epicurean, deeply cultured European intellectual. A 'bookworm' from a very young age, he steeped himself in Kierkegaard, Bergson, Nietzsche, Proust and Gide. Paradoxically, he felt himself to be insecure, alienated and a misfit while at the same time enjoying conversation, longing for the sublime and, convinced of his superior gifts, eager to make an impression on the world.

He took a long time to find his *métier*. After school, he worked in business in Rotterdam, then moved to Leiden to study mathematics and physics, dropping out after a couple of years. At 22, he decided to study medicine in Copenhagen, but again could not commit himself to it. He failed in a job with a publishing house, then worked for his father for three years — helping him to find better ways of curing bacon. Only at the age of 28 did he begin to study medicine seriously, graduating eight years later, and starting research at the State Serum Institute in Copenhagen.

Source of inspiration? Niels Jerne's personal life may have contributed to his scientific work.

At 23, Jerne had married his first wife, Tjek Wahl, a German art student who established a successful painting career and bore him two sons. Marriage problems began seven years later, when Jerne had a two-year affair with a physician whose erotic arts included sado-masochism. Although Tjek knew of this and of two other brief liaisons, she was unable to accept it when Niels started an affair with her close friend Adda.

As Tjek's own infidelities became clear, Niels believed divorce to be the only option. But after ten years of marriage, Tjek could not bear this thought and committed suicide. Jerne never forgave himself. In time he married Adda, who was soon reduced to the role of stepmother and housekeeper. In his mid-forties, Jerne began an affair with a 19-year-old girl who (after divorce from Adda) became his third wife. Add in a relationship with an American woman who bore his third child, and one sees the complexity of this man's private life.

Jerne's first major scientific achievement was in formulating the natural-selection theory of antibody formation, published in 1955. He postulated that millions of different kinds of antibody are synthesized naturally, without previous exposure to foreign antigens, and that their diversity is due to a random process. The antigen, rather than being involved in moulding the antibody, is only a catalyst. David Talmage and Frank Macfarlane Burnet refined the theory, proposing that the natural antibody is a surface receptor on white blood cells known as lymphocytes, with the antigen needing only to encounter the 'right' cell to stimulate the immune response and increase the number of appropriate cells. This clonal-selection theory turned out to be correct. Regarding the antigen as playing a selective rather than an instructive role was a true paradigm shift.

Jerne made two other profound contributions. He devised a simple and elegant technique (known as the haemolytic plaque technique) for determining the number of antibody-forming cells. This added a vital quantitative element to cellular immunology, and facilitated the development of hybridoma technology for producing monoclonal antibodies — antibodies with predetermined exquisite specificity. Jerne shared the 1984 Nobel prize with its inventors, Georges Köhler and César Milstein. He was also the founding director of the Basel Institute for Immunology which, within a decade, he made into a Mecca of European immunology and a cauldron of intellectual ferment. It must have been a source of great satisfaction to Jerne that it was at this institute that the nature of the generator of random antibody diversity was discovered by Susumo Tonegawa, leading to another Nobel prize. Each antibody-forming cell develops from a unique recombination event that assembles functional antibody genes from a pre-existing array of minigenes. The combinatorial element of antibody-gene production thereby creates the huge number of different end products.

Jerne also deserves credit for setting up an immunology unit within the World Health Organization to promote research and teaching in developing countries. But his network theory of immune responses proved less successful, and his impatience with experimental details lessened the impact that he might otherwise have had on the development of immunology as the science reached maturity. As Söderqvist remarks: "Jerne never took satisfaction from small discoveries — in this respect he resembled an artist more than a biomedical researcher — and he struggled to formulate theories of great breadth, wishing to impose his own worldview and his personality on nature." Later in life, Jerne complained that

immunology was becoming too complicated and technical. His dismissal of the reductionist approach to the discipline prevented him from appreciating the amazing discoveries made in immunology during the last 15 years of his life.

Is Söderqvist successful in his attempt at existential biography? The answer must be hedged in uncertainty. Did Jerne use the experiences of his inner life, his understanding of himself, to construct the natural-selection theory? It seems far-fetched, but who has the right to be dogmatic about the wellsprings of human creativity? Where Söderqvist has undoubtedly succeeded is in revealing the startling personal journey of one of the twentieth century's great biological thinkers, and in sketching the milieu within which cellular immunology came of age. This serious work of scholarship will be devoured both by immunologists and by a wide general readership. ■

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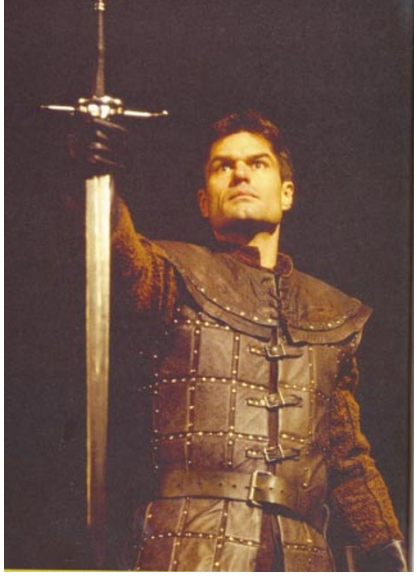
Scanning Shakespeare

The Bard on the Brain: Understanding the Mind Through the Art of Shakespeare and the Science of Brain Imaging
by Paul M. Matthews & Jeffery McQuain
Dana Press: 2003. 192 pp. £24.50
University of Chicago Press: 2003. 192 pp. $35

Kevan A. C. Martin

Every now and then, an editor will come up with what seems to them to be a brilliantly original wheeze. Here, Jane Nevins of the Dana Press persuaded Paul Matthews, a neurologist, and Jeffery McQuain, an English scholar, to use Shakespeare's plays as a vehicle for describing the brain correlates of cognitive function. Perhaps she was prompted by the popular success of the 1998 film *Shakespeare in Love*, in which the audience meets the young Shakespeare, then struggling with writer's block and trying to meet a deadline for his new play, *Romeo and Ethel the Pirate's Daughter*, whose plot is suggested to him by his rival, Christopher Marlowe. More significantly, the film conveys the powerful effect of a live theatre performance on an audience. How does theatre weave its magic spell? In the film, Phillip Henslowe, director of The Rose Theatre, gives his answer: "I don't know. It's a mystery."

The connection between theatre and the brain explored in this book is less mysterious when we learn that the remit of the Dana Alliance for Brain Initiatives is to publicize



"Once more unto the breach": Shakespeare's Henry V used mental imagery to rally his troops.

information about the benefits of brain research. The most visible and successful of the initiatives is Brain Awareness Week, a popular event held annually in many centres worldwide. It provides an invaluable forum for members of the public to meet patient-support organizations and local brain scientists, who usually cover a wide breadth of basic and clinical research.

Square and 'coffee table' in its aspect, there is much that is artful in this book. It is itself a play in seven 'acts'. Each act covers different topics, such as "Minds and Brains", "Our Inner World" and "The Seventh Age of Man", and each contains a number of 'scenes', whose titles range from the straightforwardly banal, "The Wonder of the Human Brain", to the dramatic, "Let Me Clutch Thee", to the boggling, "Putting an English Tongue in a French Brain". Each scene begins with a précis of a plot or subplot from one of the plays, which is followed by an excerpt from a scene and finally a commentary that interweaves topics evoked by the excerpt and its speculative neurological correlate. With 34 such scenes, this unrelenting format does wear a little thin. Writing anything worth reading alongside an excerpt from Shakespeare is a challenge, but here even the shortest sentences can somehow contrive to emphasize the difference, as in "Shakespeare has Juliet ponder what defines a 'Montague'".

The subsequent analyses are largely unrevealing: "Shakespeare was a keen observer of human nature", or "some of his characters talk to themselves in sonnets". Unfortunately, much of the commentary on Shakespeare's text is reminiscent of the cribs one crammed the night before the English literature examination in the hope of impressing the teacher with such pearls as "Shakespeare lived intimately with a rich world of imagination, which he communicated to others through words and stage action".

The book's illustrations are prodigal. The full-page photographs of performances of Shakespeare's plays appear without context or connection to the text. The neurological illustrations are small, 'arty' graphics of the computer-generated variety, a technique that has too easily enabled images of the brain, each postage-stamp-sized, to multiply on obscure and complicated backgrounds. Again, the repetition of style makes these brain images interchangeable. What's actually being illustrated is not only hard to see, but is poorly explained, despite lengthy captions, albeit of variable fidelity. The caption of figure 9, for example, implying that the right and left visual fields map onto the primary visual cortex of the same hemisphere, could be written off as a schoolboy howler, were it not that the accompanying text confirms that the authors really have misinterpreted the experiment illustrated, which shows the distribution of cortical visual areas and not, as they state, the well-known 'ocular dominance columns' of the primary visual cortex, which are beyond the spatial resolution of the scanners used.

The neurological material is restricted mainly to functional imaging of the human brain, principally the "folded surface of the brain (called the cortex) … where neurons are found". Unfortunately, the different imaging methods — for example, positron-emission tomography (PET) and functional magnetic resonance imaging (fMRI) — used in the various studies referred to in the book are not properly explained. There is no doubt that fMRI has revolutionized cognitive neuroscience. The method, however, does not actually detect "the amount of fresh blood flow", but records changes in the levels of the paramagnetic molecule deoxyhaemoglobin. How this blood-oxygen-level-dependent signal (the so-called BOLD signal) correlates with neural activity has been the subject of intense and technically difficult invasive experiments with animals, but such experiments are vital steps in developing a deeper understanding of the basic physiology and anatomy underlying human brain function.

This information would help lay readers to understand why the non-invasive techniques now used in human studies cannot, on their own, "define the brain mechanisms responsible for thoughts, emotions, and disorders that Shakespeare wonderfully described". The reader is left with the impression that imaging techniques all produce multiple images of tiny brains decorated with rainbow-coloured blobs of unknown significance. This is a missed opportunity to explain why different techniques of brain imaging are used in the clinical setting, and how the images are interpreted.

A danger inherent in popular science books is that they try to be popular and so simplify too much. The lesson we learn from the theatre, and from Shakespeare's plays in particular, is that complex ideas and emotions can be effectively communicated to a receptive audience, even if the language is