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Volume 5

Edited by Larry R. Squire



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The History of Neuroscience in Autobiography

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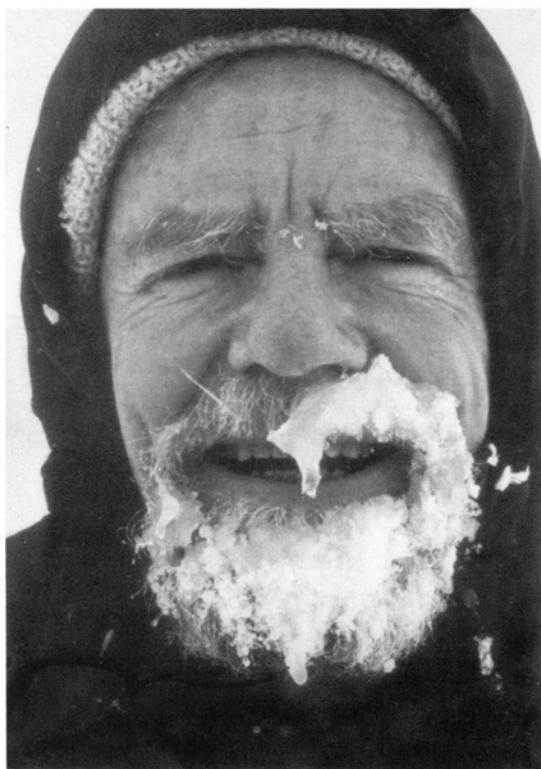
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John S. Edwards

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November 25, 1931

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John Edwards has worked throughout his career on aspects of insect physiology and ecology and especially on neural development. He pioneered the use of an insect system, the cercus-to-giant interneuron connectivity, in the analysis of sensory regeneration. He also discovered the pioneer role of insects in ecosystem regeneration after the 1980 eruption of Mount St. Helens.

John S. Edwards

The invitation to contribute to this autobiographic series was as intimidating as it was tempting. Intimidating because of the eminence of so many contributors, beside whom my own contributions seem, without false modesty, rather trivial. Tempting because I had often spoken with colleagues about the value of putting on record our lives in science during the second half of the 20th century, a period that will surely come to be seen as the coming of age of biology in general and of developmental neuroscience in particular, but perhaps also the zenith of science as a profession if we are indeed living in the twilight of the Enlightenment, a possibility raised recently by a distinguished invertebrate neuroscientist (Kennedy, 2005). It is all too easy to procrastinate the act of writing, no matter how many ideas swirl through one's cortex, until senility creeps on and it is too late. The editor has provided a deadline for that effort, and I thus offer my thanks at the outset to Larry Squire.

My life in science was best characterized early on by the admonition leveled at me by my dreaded undergraduate adviser: "Mr. Edwards, you suffer from responding to an excessive diversity of stimuli." I have never quite mastered that defect, so I must preface my story with the warning that my neuroscience will be studded (or stunted) with diversions and tangents. It is said that moles know one big thing, whereas foxes know lots of little things. I am vulpine. If there is a theme in what follows, it stems from Wigglesworth (1939) that "Insects provide an ideal medium in which to study all the problems of physiology."

Origins

I was born in Auckland, New Zealand on November 25, 1931, in the shadow of the worldwide Great Depression that hit New Zealand hard. Neither of my parents had more than primary schooling but they were avid readers; my father could recite Shakespeare and Wordsworth at great length and enjoyed word play. Their love of music left its mark on me. My mother, a second- or third-generation New Zealander, whose pre-antipodean ancestry we do not know, was born in Waikino, a small town in the gold fields of the North Island where her father owned a chain of butcher shops and the first model T Ford in the region. She was an able pianist and for some years worked in a music store as a sight reader of sheet music for prospective

buyers. She later moved to Auckland where she worked as a stenographer and met my father. His father emigrated to New Zealand from Iffley, near Oxford, where he was a champion sculler and a skilled woodcarver. He created many elaborate ornaments in the Victorian style for churches and public buildings in Auckland. His father, my great-grandfather, was a servant at Balliol College Oxford. My father's apprenticeship as a pharmacist was interrupted by the First World War, for which he traveled to England as a cellist in the New Zealand Army Band. He never saw action, unlike his elder brother who was a victim of gas in the trenches of France from which he never fully recovered. On his return to New Zealand my father took a job in a retail business in Auckland, rising there over the years to general manager. In the 1920s he played cello 3 nights a week in a silent movie theater pit to pay the mortgage on their modest suburban home where I was born and spent my first decade. Several years of my early schooling required a long bicycle ride because the local school was taken over by the American military as a recuperation center for U.S. forces in the Pacific theater. Three memories stand out from schoolboy views of the GIs: We never found a real cowboy despite persistent questions, the women did not look at all like Hollywood beauties, and they were all so generous with candy and gum to pestering kiwi kids. Boy Scouts played a key role in nurturing my love of field biology. My parents were resolutely suburban and the "bush" was to them a hostile place. My happiest days were on Scouting forays (however tame in retrospect) into the native forest and that joy in wilderness has remained with me throughout my life. I am sure that my current activities with the North Cascades Conservation Council aimed at protecting what little remains of northwest wilderness springs from those early experiences. During much of my childhood my parents and younger brother suffered from various illnesses that occupied most of their attention. I think I learned to be self-sufficient during those years.

School and College

Early childhood memories are few, but one that I am reminded of these days on regular visits to my dermatologist is of the association of appallingly painful sunburn with midsummer antipodean Christmases at the seaside, for which 60–70 years later my dermis is paying.

The Auckland Boys Grammar School was modeled on strict English traditions. Uniforms and strong discipline, with a stout cane to the backside for even minor infringements, was the rule. I did not excel in school but I found my niche as a lab assistant, paid a pittance to prepare materials for the next day's lessons. There I met some of my life-long friends, fellow refugees (nerds in today's parlance) from the macho rugby football hierarchy of the school. Most of those school pals went on to distinguished careers in science in New Zealand or overseas. We were culpably free to use

the lab equipment unsupervised after school hours and there were some miraculous escapes from disaster, for example a rocket that went off prematurely through the school roof, and the successful x-ray photography of a lizard, using an ancient x-ray tube from a museum cabinet, which we connected to a chain of military surplus high-tension batteries. It was a relief years later, when my offspring were born apparently normal.

An early fascination with insects and with growing plants was fostered during school years by sympathetic teachers and by the Curator of Birds and Insects at the Auckland Museum where Graham Turbott, a respected ornithologist, gave me the run of the insect collection and its care. Science as a research career was unknown to my parents who urged me to choose a practical profession. My dream then was to practice veterinary medicine in a dairy farming area. I worked as a farm hand during school holidays, milking cows, delivering calves, making hay, and castrating hundreds of piglets and that framed my ambitions. Having survived grammar school I began university studies in Auckland, majoring in Zoology and Botany. Zoology was my first love but the head of the small department was a pompous tyrant (or so it seemed) who concealed his incompetence behind a glowering, humorless presence. Failure to take dictated notes (we had no textbooks) was met with a reproachful eye and, other than his clipped dictation, sepulchral silence was to be maintained—no questions asked. I once won a dare by eating a raw carrot in the front row during his exposition of the skeletal anatomy of some obscure fish.

Botany on the other hand was a lively place under V.J. Chapman, an ebullient new arrival from Cambridge. Animals, for all we were taught, had only anatomy and fossils but plants had thrilling physiology, genetics, and ecology. Peer learning played a major role through the activities of the student-led Field Naturalists Club that organized expeditions to offshore islands to collect and record and live camp life with a zeal that endowed us as graduates with a thorough knowledge and love of the New Zealand flora and fauna. Despite our total innocence of much of the science that was current in those immediately pre-Watson-Crick days, I believe that our thorough organismal training served us well. In my senior year I was awarded the Botany Book Prize, for which I chose, to the consternation of the Botany faculty, the newly published *Insect Physiology* edited by Kenneth Roeder (1953).

Plans for a career in veterinary medicine faded partly for financial reasons and partly from the epiphany of finding V.B. Wigglesworth's newly published studies (Wigglesworth, 1959) on the insect nervous system. A Masters in Zoology then seemed to be the alternative track. I was advised against attempting it under W.R. McGregor, the head of the mausoleum-like Zoology Department, but the return to Auckland of two Imperial College entomological PhDs Tom Woodward and Jim Pendergrast made graduate work feasible and in the end McGregor graciously supported my next step

overseas to Cambridge. My master's work focused on the reproductive biology of a large native longhorn timber beetle that was thriving on the dead wood of extensive exotic *Pinus radiata* plantations. The thrill of discovery came early when I found evidence that the female beetles had an olfactory sex attractant. That thrill was short-lived when I found the literature on pheromones that dated back to Fabre, but it primed the pump.

Graduate School on the Other Side of the World

The Master's thesis was almost done when I read invitation notices to apply for Research Studentships at several Cambridge colleges. Having scant hope of success, and unwilling then to take a technical position in New Zealand entomology, I began planning to travel in Canada, attracted by both forest entomology and mountains to climb. At that time, New Zealand was so anglocentric that graduate study in North America was rare. But the improbable happened and I was accepted by Gonville and Caius College, to do my PhD with V.B. (later Sir Vincent) Wigglesworth, whose papers, models of clarity, so elegant in style and so beautifully illustrated, had become my beacon. Appointed Quick Professor in the Department of Zoology and author of *The Principles of Insect Physiology*, he became known as the founder of the field (Edwards, 1998). The 6-week trip to England in 1956 as a steerage passenger on the *Tamaroa*, a wallowing frozen meat ship, gave me some time to cover my nakedness in insect physiology. In these days of easy flight it is hard to believe that England was then so far away and at the same time so much a foundation of all our myths. Arriving in London was like stepping into reality after a quarter century on vacation in the colonies. I was finally *in* history, *in* the nursery rhymes, and among the symbols of Britain that had loomed so large in our early education, especially through the war years of my childhood that were so filled with pro-British, anti-Nazi, and later anti-Japanese propaganda.

Life as a graduate student in Cambridge was at first overwhelming. My congenital response to an "excessive diffusivity of stimuli" proved insurmountable. Who could not leap at the opportunity to attend lectures on nerve and muscle from Hodgkin and Huxley, respiratory enzymes from David Keilin, Chinese science from Joseph Needham, or architecture from Nicholas Pevsner? I had hoped to combine field study with bench physiology but I was dissuaded by Wigglesworth who cautioned that seasonal field work dependent on Britain's fluctuating weather was too risky a project. Instead he proposed that I work on a predatory insect in the assassin bug family (Reduviidae), a relative of *Rhodnius prolixus*, the blood-sucking insect made famous through his pioneer work on the hormonal basis of insect development.

The first few months at the bench were troubled. Wigglesworth expected his students to find their own question and pursue it; he regarded

his advisory role as inhibitory, "to help students avoid making fools of themselves." But my assigned animal seemingly raised no experimental potential until I began to closely observe their predatory behavior. They were fed on moth larvae that could outweigh the predator a hundredfold and yet succumb in seconds. The mouthparts of assassin bugs, as with all in the order Hemiptera, are modified from chewing units to form a hypodermic needle. Saliva is injected through one barrel, while fluid food is ingested through the other. When a prey is captured, the injected assassin bug saliva causes immediate convulsive thrashing followed within seconds by flaccid paralysis. Their saliva had obvious analogies to that of neurotoxic snake venoms. The composition of insect saliva was known at best superficially for very few species and was certainly quite unknown for assassin bugs, so I decided to explore this vacant frontier. It soon became clear however that "my" animal, *Rhinocoris carmelita* was a poor source of pure saliva. Only minute quantities could be harvested and, given analytical techniques then available, there was little to be learned. But serendipity struck while I was summoning the resolve to take my case to Wigglesworth for a change of topic. Thumbing through an economic entomology journal I found an account of a large African assassin bug that attacked chestnut-sized rhinoceros beetles in the coconut plantations of Zanzibar. Rhinoceros beetles were destructive pests and *Platymeris* was considered a potential biological control agent, but it was also notorious for causing disabling pain in bitten coconut harvesters. Not only did it bite, but it also could spit, using its saliva as a defense against would-be predators. Inquiries to the author F.L. Vanderplank in Zanzibar led to the delivery by mail of a small batch of eggs from which I started a colony. These evil-looking insects with adults the size of a large cockroach, black with two menacing red spots on the wings, were raised on cockroaches from the departmental culture. Their spitting behavior enabled me to collect tens of milligrams of dried saliva. The technique of starch gel zone electrophoresis had only recently been introduced by Smithies (1955) and having found a source of DC current in the basement of the Zoology building I was, to my delight, able to separate six protein bands. Hydrolyzing starch and pouring a layer on a sheet of glass was a delicate art but persistence paid off and, armed with data, I managed to convince Wigglesworth, who was famed for his "string-and-sealing wax" approach to experimentation, that I needed a controllable DC supply unit and that gave me the springboard for my thesis work. I isolated three endopeptidases comparable in specificity to trypsin and chymotrypsin, hyaluronidase, and weak phospholipase (Edwards, 1961). None of these, according to work then published, could account for the rapid lethality of the whole saliva, and the mystery of the mode of rapid neurotoxic action remained when I submitted my thesis. By that time I had become intensely allergic to the assassin bugs, probably from careless handling of the saliva powder, and I could no longer work with them.

I cannot leave an account of my graduate student time in Cambridge without a comment on the Agricultural Research Council's Insect Physiology Unit headed by Wigglesworth on the top floor of the Zoology Department. The staff included John Treherne who was to become a leader in insect neuroscience, A.D. (Tony) Lees, whose brilliant experimental work on photoperiodic control of aphid polymorphism involved piping light through fine polystyrene threads to different regions of free-living aphids' brains, and John Kennedy, a pioneer in the analysis of aphid migratory flight behavior and a resolute mechanist who was skeptical of ethological metaphors. Lees and Kennedy did not have graduate students but were always ready to listen to the woes of graduate students too intimidated to take their problems to Wigglesworth who was perceived by the student mind as somewhat remote and of the "sink or swim" persuasion. He presided over the ritual Monday afternoon tea, a time for discussion of latest developments and publications after which students and some of the staff adjourned to the Bun Shop, a neighboring pub, where the discussion became less inhibited and where we learned so much about the sociology and politics of research in the UK.

Unlike United States practice, the PhD thesis was submitted for examination as a bound volume and the award decision was "up or down." My external examiners were Sir Rudolph Peters, an eminent Oxford biochemist known for his synthesis of dimercaprol or "British anti-Lewisite," an antidote to a very potent arsenic-based chemical warfare agent, and David Keilin, the discoverer of the cytochrome respiratory chain system. Weeks went by without an appointment for the final oral exam and my apprehension grew exponentially until I learned that Keilin had been ill. Eventually the exam went well, again thanks to serendipity. I had bought a copy of *Scientific American* to read on a train trip to London the previous day. It carried an article with all the latest on the actions of biological toxins, so by chance I appeared to be fully *au fait*, and I enjoyed the afternoon-long discussion with these two remarkable men.

The next move had been looming: where to go and what to do? The university system in New Zealand at that time was in a lamentable state, with limited research and travel opportunity, heavy teaching, and meager salaries. The opportunity to spend a couple of years in the School of Agriculture in Cambridge postponed the decision. I joined an aphid research unit directed by Claude Ribbands, better known for his honeybee studies at Rothamstead, in which my task was to find a technique for plucking a migrating aphid from the air and determine which of many potential plant hosts it had sprung from. The question had immediate significance for British agriculture because the aphids in question are notorious vectors of debilitating plant viruses that affect the productivity of crops such as sugar beet and potatoes. What was the source of virus bearing aphids that infested each new spring crop? Immunological techniques had recently

been used to determine the hosts of tsetse flies in areas of Africa ravaged by sleeping sickness. Perhaps a similar technique could be used to identify the plant hosts of migrating aphids and thus the source of overwintering virus. Neither immunology as then practiced nor plant phenolics, both of which offered a potential fingerprint, proved applicable because they are not transported in measurable quantities in the phloem vessels of plant that are tapped by aphids. But all was not lost in this venture for in the process of dissecting countless winged aphids I found that those that had fed on sugar beet or other members of its family, the *Chenopodiaceae*, were pot-bellied; their guts were stuffed with an insoluble mass whereas those from cabbage, for example, had mere traces of solid material in their crop. This observation in itself raised interesting questions that are still to be addressed for phloem is thought to transport only small soluble molecules such as sugars and amino acids. Standard agricultural practice was to store harvested sugarbeets through the winter in "clamps" (earth-covered piles in the field), and these clamps provided refuge for aphids. It was thus important to know how many aphids among the spring migrants had come from this virus reservoir. (This was the nearest I ever got to clamping studies.)

A byproduct of my experience with aphids was the demonstration that their defense mechanism against parasites was based on the release of supercooled liquid wax that is stored within the body in special cells (oenocytes). When extruded it instantaneously solidifies on contact with a solid surface thus enveloping a would-be parasite (Edwards, 1966; Chen and Edwards, 1972).

To the New World

Further field testing with spring migrant aphids and the nature of their gut contents were left unresolved when the opportunity to work in the United States arose during a sabbatical visit of Howard Schneiderman from Cornell to Wigglesworth's lab. His ferocious enthusiasm was infectious and the added prospect of working with Tom Eisner on chemical ecology led to plans for a move to Cornell. I had secured a National Institutes of Health (NIH) post doc on the limited New Zealand quota that was generally reserved for MDs, when news came from Schneiderman that he was moving to Western Reserve University in Cleveland along with Marcus Singer, to head the Biology and Anatomy Departments respectively and to found a Developmental Biology Center. I was given the option of going to Cleveland or to Cornell. The decision was difficult. It was tempting to pursue some aspect of chemical ecology with Tom Eisner at a renowned university and continue the theme of insect venoms, but I opted for the unknown Western Reserve University whereupon Schneiderman advised me to get immigration visas for the family in case the Developmental Biology Center should

prove attractive as a faculty position. An ecological and climbing expedition to North East Greenland and then the usual bureaucratic wait for immigration visas ensued and we were finally on board the *Queen Mary* to arrive in a bedecked New York on March 2, 1962, where we were happy to share the tickertape festivities for John Glenn on his return from orbit.

The renaissance of Biology at Western Reserve proved to be an exciting process. Schneiderman had attracted able new faculty, including Boris Ephrussi, Bob Josephson, and Michael Locke. Singer had brought Ted Voneida to the Anatomy Department. I met him through Colwyn Trevarthen, a friend since undergrad days who had been with Ted in Roger Sperry's lab at Cal Tech. That meeting proved to be providential for although I had intended to join the frenzied search for the identity of the insect juvenile hormone in which Schneiderman was a front runner I had doubts about being a late arrival in what Schneiderman himself described as "a mighty crowded frontier." In the end the prize for that race went elsewhere but by then I had read Singer's papers on amphibian neural regeneration (Singer, 1965), Ted had shown me Sperry's seminal paper on neural specificity (Sperry, 1963), and I knew where I wanted to go. Growth and regeneration of insect nervous systems has been a preoccupation ever since.

Adventures with the Insect Nervous System

I had found an empty frontier—almost. Dietrich Bodenstern had looked *en passant* at regenerating insect nerves and Hans Nuesch had published his beautiful studies showing the trophic necessity for motor nerves in the development of adult muscles during metamorphosis of giant silk moths, but the issue of specificity had not been directly examined. Given the difference between vertebrates and arthropods in the origin and organization of sensory neurons it seemed that insects could provide a simpler system for the analysis of sensory regeneration. I started out with the so-called American cockroach *Periplaneta americana* (in fact an import in slave ships from Africa). They regenerate appendages well during immature stages but their development was too slow for my impatience and when, by chance, a marketing sample of house crickets sent from Fluker's Cricket Farm in Louisiana, as potential teaching material, arrived in the lab I found my animal. They proved easy to keep, they bred prolifically, they developed relatively rapidly, and they regenerated lost appendages vigorously during immature stages. Franz Huber in Cologne had already shown the value of crickets in his pioneering brain stimulation studies. And further, unlike cockroaches and assassin bugs, which elicit responses of disgust and fear from colleagues, no one objected to the pastoral song emanating from the garbage cans where the crickets lived happily on a diet of cat chow.

Crickets and their orthopteroid relatives have abdominal cerci, sensory appendages that project from the posterior end of the abdomen. The many mechanosensory hairs on their surface function as warning systems for impending predatory or parasitic attack; they are in effect antennae *a posteriori*. The mechanosensory neurons arise during embryonic and postembryonic development from a monolayer of epidermal cells that underlie the cuticle. They both transduce the mechanical stimulus and project to the central nervous system (CNS) where they synapse with a small population of giant interneurons. Their giant axons traverse the abdominal ventral nerve cord to synapse with motor systems in the thorax and in the brain. They elicit rapid evasive movements, the so-called startle reflex made famous by Kenneth Roeder's studies of the cockroach nervous system (Roeder, 1967). The cercal startle system is widespread among orthopteroid insects and their evolutionary ancestors such as silverfish and bristle tails gave the potential for comparative and phylogenetic studies. Cricket cerci can be simply amputated with a flick of fine forceps. During immature stages (but not in adults) the cerci regenerate from epidermal cells, becoming more complete through successive molts. The new sensory neurons, associated with each sensory hair, are derived from epidermal cells. They grow to the CNS where they reestablish central connections with arborizations of the giant interneurons. They fully restore the startle reflex behavior even, as I later showed with John Palka, after prolonged absence of regenerates (Edwards and Palka, 1971). Then, with post doc fellow Tara Sahota we tried transferring a cercal regenerate to a leg stump, thus testing whether an ectopic cercus could regenerate functional central connections in different central territory. We asked, in the context of Sperry's chemospecificity hypothesis and Singer's ideas about amphibian neural generation, whether the transplanted cercal sensory axons, now far from their familiar territory in the terminal ganglion, could find their targets. Our criteria were crude by present day standards, but we did show that the ectopic cerci elicited characteristic giant interneuron spikes in response to airpuffs, as in normal animals. We concluded that the ingrowing axons had found their target cells at a site far removed from normal (Edwards and Sahota, 1967). This was, I believe the first exploration of specificity in an invertebrate system. The crudity of those experiments is laughable by present day standards; it surely illustrates the extraordinary technical advances since then. Later work by Rod Murphey and his students greatly refined this experiment, but the general finding held. I returned later, with colleagues, to the problem of sensory input from ectopic appendages using a homeotic mutant of *Drosophila* and homeotic regenerates in a stick insect *Carausius* and concluded that the pathway to the center is specific for a given ganglion, so that *antennapedia* "legs on heads," both as mutants and as regenerants, obey the same guidance rules that are intrinsic to the segment, irrespective of sensory modality. At about

that time, two other approaches to neural regeneration and growth were getting underway in my lab. To look at the capacity for central neurons to regenerate I chose another "white rat" of insect labs that was already in use in the Schneiderman lab for hormone assays: *Galleria mellonella*, the wax moth larva. It has a rugged larval stage that can take a lot of abuse. I severed the ventral nerve cord in larvae that were ready to undergo a molt to the pupal stage. To my surprise segments anterior to the cut, wherever it was made along the length of the larva, resulted in a tonic contraction of body wall musculature anterior to the cut while the posterior segments relaxed and expanded. I found no evidence for central neural regeneration, but, again to my surprise, these larvae never made the molt to the pupal stage. They remained alive, slowly metabolizing themselves away long after the controls had completed metamorphosis to the adult. Cuts to the CNS made well clear of any possible damage to the endocrine glands that regulate molting, prevented the molt, while small control epidermal incisions that did not sever the cord had no significant effect on the timing of the molt. It seemed possible that a proprioceptive input was involved in the release of the molt cycle. There seemed to be a parallel with the demonstration by Wigglesworth (1934) that proprioceptive input in response to the stretching of the integument by a blood feed activated the neuroendocrine release of the molting sequence in *Rhodnius*. Accordingly I developed a straitjacket technique using adhesive tape to constrict various regions of the body. Such animals did not pupate until they were released from constraint (Edwards, 1966). My conclusion from these experiments that proprioceptive input was one parameter, among others such as adequate nutrition and time of day, that must signal "go" to release the brain hormone and the subsequent train of endocrine events that induce the molt, was supported in later experiments with Frantisek Sehnal, a visitor from Prague (Sehnal and Edwards, 1969).

Another point of departure in setting out on neural developmental studies concerned brain changes during neural metamorphosis, the pattern of profound changes that accompany the transformation of a rudimentary larval brain to a large and complex adult structure. The chosen animal for these studies was the Monarch butterfly *Danaida plexippus*, a favorite animal of mine since childhood in New Zealand, that was common in the milkweed fields of Ohio where the larva, a vegetative feeding machine, contrasted with the long-lived migratory adult. My first graduate student, Ruth Nordlander, took on the Herculean task of sequential tritiated thymidine labeling animals throughout postembryonic development and by means of radioautography to trace the events of cell proliferation and migration. Brain metamorphosis had been described in broad outline in work from the late 19th and early 20th century but the cellular events were then unknown. The series of papers that came from that study (Nordlander and Edwards, 1968a, 1968b, 1969a, 1969b, 1970) became classics of insect

development. At the same time a Master's student, Anne Gymer, looked at glial cell growth during postembryonic development of the house cricket. We showed for the first time that, although the number of neurons in ganglia of the CNS remains constant throughout postembryonic development, increasing only in volume, the glial cell population increases twentyfold, in synchrony with the molt cycle (Gymer and Edwards, 1967). Glial cells hear the signals to epidermal cells to divide, but neurons do not.

Cleveland at that time was an exciting place, not only for biology but also for music. The Cleveland Orchestra was brilliant under the baton of George Szell, the Cleveland and Guanieri String Quartets were starting out on their illustrious careers, and James Levine was emerging as a prodigy. As well the Cleveland Museum of Art's magnificent collections, especially of Asian art, were a treasured resource for wet weekends. All of us who were in Biology at Western Reserve during the late 1960s remember it as a time of intense and buoyant intellectual ferment. It was the crucible in which I learned to do science the American way. Growth was the flavor, grant money flowed, and faculty numbers swelled in the post-sputnik boom. It felt good to be part of it but it was not to last. There were unsettling tensions within the Biology Department, and I became aware that my eclectic proclivities might stand in the way of tenure. Echoes of undergraduate admonitions about diffusivity of effort returned, but thanks to Boris Ephrussi, who "adopted" me and who insisted that I concentrate my efforts and publish, tenure came shortly before my move West.

Summer expeditions to the Teton Range and winter climbs in New England's White Mountains kept a love of mountains alive and the call of the Cascades became irresistible when the University of Washington advertised for Zoology faculty. I visited, gave a seminar, we liked each other, and their offer was airdropped to me in Base Camp during the first winter ascent of Denali (Mt. McKinley, Alaska) (Davidson, 1986). So, later in 1967, now with four small boys, we traveled west to Seattle.

Across the Cascades to Seattle

Although I was sorry to be leaving such wonderful colleagues as Ted Voneida, Bob Josephson, and Jim Weston, I can only write with enthusiasm about my years in Zoology (now Biology) at the University of Washington. The collegiality, open doors, and broad coverage of population, organismal and later molecular biology achieved by unusual disciplinary altruism made it a great environment for such as myself with eclectic interests that could not be ignored and with tenure in hand. I had picked up on my cercal regeneration work when John Palka joined the faculty. We began a rewarding collaboration that lasted many years with NIH support, the last 7 of them on a Javits Award. John brought the electrophysiology and I the developmental background to an analysis of neural regeneration

in the cricket. We worked on decoding the rulebook for postembryonic regeneration (Edwards and Palka, 1974; Palka and Edwards, 1974; Edwards, 1980, 1988). I like to think that our demonstration of the potential of the cricket cercal system attracted others such as Rod Murphey and his students who took the system to higher levels of refinement.

A Year in Basel

In 1973 a sabbatical leave supported by a John Simon Guggenheim Fellowship took the family to Basel and the Zoologisches Institut, then co-directed by Hans Nuesch who was my host there. My room at the Institute overlooking the Rhine was said to be where Miescher first isolated nucleic acids from sperm of migrating salmon netted from the river below and may also have housed Paracelsus, a 16th century father of modern medicine. Research in progress there was not exactly cutting edge, but Nuesch and his wife were wonderful hosts and Basel remains a magical place to all the family. And for frontier science a short walk across town took me to the Biozentrum where big things were happening. My objective in Basel was to get to know the embryo of the house cricket. I first needed to become familiar with the timeline of developmental events and learn the microsurgery that would enable me to remove embryonic cerci before they had neural connections with the CNS. I further hoped to resurrect the ultraviolet (UV) lesion equipment that Geigy had used in Basel for his embryo studies but that did not prove practicable. However, an hour away by autobahn in Freiburg was Klaus Sander and his Institute devoted to mechanisms of insect embryogenesis. I found a welcome there and by extraordinary good fortune Klaus Kalthoff was using a focussed UV beam for his lesion studies and was willing to let me use his equipment. I hoped to remove the embryonic cercus rudiment before it sent afferent fibers to the CNS, then later challenge the “naïve” ganglion with a transplanted cercal regenerate. Simple surgery having failed to yield cleanly deafferented embryos, I hoped that the UV beam would work. Many attempts later I concluded that, at least in my hands, the lesions were not localized enough to be useful. Success would await later laser studies described later. A delicious memory of those visits to Freiburg is of eating spargel with excellent Riesling in the town square after days at the microscope.

Cricket: Embryos Again and Responses to Deafferentation

Back in Seattle I set about refining, with my long-suffering electron microscope technician SuWan Chen, the timeline of neural development in the cricket egg (Edwards and Chen, 1979). We were slow to realize what the montages of embryonic cerci at successive stages were telling us, and we

had just concluded that there must be a set of initial axons that reach the embryonic CNS before the circus elongates and that these provide the pathway for the functional sensory afferents that grow to the center later in embryogenesis when Michael Bate published his elegant paper showing the role of pioneer fibers in locust embryos (Bate, 1976). It became clear that this was a general mechanism by which the periphery makes contact with the center. It was also immediately clear that the relatively large locust embryo, where axons could be seen in the light microscope, was the material of choice for studies of neurogenesis and in the hands of Corey Goodman, David Bentley, and their students the locust embryo became the object of ground-breaking studies of sensory, motor, and CNS development.

It remained to be shown that pioneer fibers were indeed necessary and sufficient for the orderly development of the functional nervous system. Our earlier attempts to prevent the formation of pioneer fibers by mechanical and UV lesions not having been productive, we did at last achieve success in collaboration with Michael Berns at Irvine, using his laser beam microlesion system (Edwards, Chen, and Berns, 1981). We were able to show that after ablation of the source of pioneer fibers in the apex of the cercal rudiment, the later developing functional afferents grew in a disorganized looping fashion. We concluded that in the cricket cercus, the dorsal and ventral pioneers are essential to normal development and that after detaching from the epidermis they fuse to form the pathway to the center for the late-developing sensory axons. The successive additions of new axons in each instar between molts follow this pathway to the center by contact guidance.

Along with embryo studies we were also pursuing questions of metabolic effects of deafferentation. We had made a start in Cleveland at looking at the cricket terminal ganglion as a potential model for the analysis of trophic processes in showing the presence of three membrane-bound acetylcholinesterases (Edwards and Gomez, 1966), but it was Mark Meyer's neurochemical know-how that enabled a targeted approach to the effects of deafferentation on the metabolism of the terminal ganglion. First he showed that the ganglion had high levels of muscarinic binding sites, in contrast to the generally reported nicotinic binding sites in insects (Meyer and Edwards, 1979), and we went on to show with quantitative radioautography that the suppression of growth in target giant interneurons deprived of their cercal sensory input was reflected in depressed uptake and incorporation of tritiated leucine after chronic deafferentation, although not in short-term deafferentation (Meyer and Edwards, 1982). That led to an analysis of the effects of deafferentation on the density of cholinergic binding sites and acetylcholinesterase (Meyer, Reddy, and Edwards, 1986) in which we showed changes in the turnover of three macromolecules associated with cholinergic transmission in the cercal sensory-giant fiber system. We thus demonstrated trans-synaptic effects on the synthesis and turnover of specific molecules.

Franz Huber and Huberhaus at Seewiesen

In 1980 a Humboldt Award enabled the entire family to take a year in Germany thanks to Franz Huber, whose section at the Max Planck Institute for Behavioral Physiology at Seewiesen centered on the neuroethology of crickets. Seewiesen is famed for the ethologists led by Konrad Lorenz, who set it in the idyllic landscape of Bavaria near Munich. Later members included Dietrich Schneider whose group broke new ground with anatomical and experimental studies of insect olfaction and Franz Huber. Among the first scientists to cross the Atlantic at the close of World War II, Franz had worked with Ted Bullock and he maintained an international perspective both in his research and his hospitality at Cologne and then at Seewiesen. That visit was a wonderful time for the family, a year to savor the rich history of the area and to live on the beautiful Starnbergersee, half way between the music of Munich and the snows of the German Alps. My research plan was to explore the cercal system of primitively wingless insects, silver fish, and firebrats with the aim of extending the comparative and evolutionary history of the cercal system. I posted a note in my most polite German on the Institute notice board requesting silverfish or firebrats. The meager result was an occasional anonymous specimen in a vial left on my desk. When I commented to Franz on the paucity and anonymity of the offerings Franz replied, "Oh, no German housewife would ever let it be known that there were insects in their home!" I felt that I should distribute Karl von Frisch's beautiful book *Twelve Little House Friends* that gives a lyrical account of our insect cohabitants. I did get enough material to get to know the neuroanatomy and something of their development. That work laid the foundation for later studies in Seattle. A memorable feature of life at Seewiesen was the seminars from visitors or sometimes from a resident in rapid-fire German only intermittently intelligible to me. Questions after the seminar would begin with technical details and end, sometimes hours later, with discussions by that time dealing with such things as "What is life?" I recall also abstaining from the massive farmers' lunches served in the mensa, conducive only to a prolonged but reluctant afternoon nap. Instead I took bread and cheese on crosscountry skis, sometimes with Ali Steinbrecht, through the local countryside (which I likened to frozen Schubert), to lunch on a viewpoint where we talked science.

On one of those forays I noticed snowfleas, so named because these minute wingless members of the insect order Mecoptera can make flea-like leaps even at near-freezing temperatures on the snow surface as a predator evasion tactic. Here began another tangent: I found that the length of their long-jumps was independent of temperature over quite a wide range and that the power for the jump came from energy stored in an elastic protein, resilin, derived from a wing hinge that was distorted by muscular action then rapidly released. The detailed microanatomy proved to be indeed a prototype of the resilin-powered jump of the true fleas and this finding

added data to the view that the true fleas were derived in phylogeny from Mecoptera rather than the true flies (Diptera). This project remains a work in progress and has become yet another project waiting in the files for further high speed movies of the jump.

Another tangent: I had to admit that I knew nothing about Alexander von Humboldt when I received my Award from the Humboldt Foundation. Who was he? What did he do? The more I read of his life the more I became intrigued by his extraordinary accomplishments. His name is everywhere, an ocean current, a glacier, a county, a college, but his science has been lost to all but historians. His was the last great sweeping view of the Cosmos as a great piece of eternal clockwork before Darwin swept the world of Biology and Geology with a dynamic evolutionary view of life on earth. Ironically it was Humboldt's writings on his South American journey that persuaded Darwin to join the *Beagle*. But a different facet of Humboldt's impact led me on another quest that stemmed from my interest in the history of landscape painting. Humboldt's writings were greatly admired by painters of the Hudson River School, and one of their leaders, Frederick Church, followed Humboldt's exhortation to go to the tropics and paint the tropical scenery, so well described by Humboldt, for all to see. Church's epic landscapes from the Andes were a sensation and I believe that there is a causal pathway to be traced from those paintings and those of contemporaries such as Bierstadt to the political will to create the first national parks and thence the modern conservation movement (Edwards, 1999). I had the opportunity to present these ideas at a symposium held in connection with a major show of Hudson River paintings at the Metropolitan Museum in 1989. I have yet to commit a detailed study to scholarly print.

Firebrats and Flights of Fancy

On my return from Seewiesen to Seattle I resumed work with firebrats and invited a visiting post doc, Rajarami Reddy, to work with me on the project. We found that, as with the silverfish I had worked on at Seewiesen, the central projection of the median terminal appendage split to left and right halves, joining the neighboring cercal nerves. The central projections of these combined nerves closely resembled that of the cricket, the cockroach and other orthopteroid insects. And, as judged by segmental position and detailed pattern of arborization, the giant interneurons of the firebrat appeared to be directly homologous with those of the cricket (Edwards and Reddy, 1986). Later work with the most primitive living insects, the bristle tails, revealed the same general pattern and this led me to some speculations (flights of fancy, as one reviewer said) on the origin of insect flight. Arguably one of the major innovations in evolutionary history with profound consequences for terrestrial life (not to mention human ecology), the evolutionary origin of insect wings and the pressures that led to flight,

have been debated ever since Darwin. The dominant theory through most of the 20th century was based on the development of lateral extensions of the thoracic segments that would act as passive gliding wings when the proto-flier jumped out of trees. Some of the sparse fossil material then available, analogous to ideas about *Archeopteryx*, and later a nice biomechanical analysis (Kingsolver and Koehl, 1985) lent support to the gliding hypothesis. But the rival view, that the wing originated as an active structure, gained support from newer fossil discoveries (Kukalova-Peck, 1990) and the finding in *Drosophila* that the embryonic origin of the wing was from a leg-base rudiment, called for an alternate view of the selection pressure that led to active flight. Our work with the ancient startle reflex comes in here. It is known that various arachnids, some of them now extinct, colonized the land at the same time as the first insects. It must have been a jungle back there. That those early insects devoted about 30% of the volume of their abdominal nervous system to their mechanosensory predator evasion system based on the startle reflex surely reflects the predation pressure for which running then jumping served as the escape. A jump requires symmetrical motor patterns, as does flight. Any palaeoneuroethological reconstruction is just a story but the known facts seem to fall into place and become a plausible hypothesis. The first land-dwelling insects faced diverse predators. Startle mechanisms arose, based on abdominal giant interneurons, that responded to the air movements made by incipient predators. The response of prey was to run, then to leap away from danger. Extensions from basal leg segments found in early fossils provided stabilizing glide surfaces, then active flight. Flight then opened up new adaptive space, allowing exploitation of a spatiotemporally patchy environment and that in turn led to their unparalleled diversification of species and ecological function (Edwards and Palka, 1991). We concluded that an important operating principle in insect neural evolution seems more like a fugue than that of an opera. Richness of variety has been generated by the combination and recombination of a small number of themes rather than the invention of new melodies to suit the appearance and disappearance of characters as the plot evolves. At the same time we were learning that the insect nervous system is by no means a rigid hardwired device in its development and the behavior that it mediates.

Are Insects Relevant?

Relevant to *what*? The late 1960s through the 1980s was a time when the long-held notion that insect (and other invertebrate) behavior was rigidly stereotyped and that their nervous systems were parsimonious and hardwired, inflexible, and therefore ultimately irrelevant to most of mammalian/human neurobiology on which research support was focused. As Greenspan (1981) commented: "Insects may be tolerated in neurobiology,

but they are rarely admired. More often they are disdained by students of higher organisms for their lack of relatedness to mammals.” There were those who discounted invertebrates, such as Roger Sperry and Pasko Rakic. There were also public defenders of invertebrate work, Graham Hoyle militantly so, others less provocatively, such as Rod Murphey (1986) and Ian Meinertzhagen (2001) among many others. Times have changed. Increasingly, even before genomic studies began to emphasize similarities rather than differences, invertebrate studies found plasticity and modulatory systems and that endowed them with more respectability. At that time also interest was growing in the developmental and modulatory role of glia and we began to address the question of insect glial diversity in the house cricket *Acheta*. My long-time colleague Mark Meyer, a man of infinite resource, made a series of monoclonal antibodies to preparations of cricket glia (Meyer, Reddy, and Edwards, 1987). The set of glial types that emerged from that immunohistological study, proved to fit remarkably well with the glial classification made by Wigglesworth (1959) on the basis of light microscopy, and subsequent work with *Drosophila* also conforms to the same general pattern. One of our monoclonal antibodies, 5B12, recognized a high molecular weight glycoprotein associated with central and peripheral glial cells that we named glionexin. Its expression proved to be developmentally and spatially modulated. It was widely expressed on the basal lamina of embryonic epithelia along which developing neurons grow (Meyer, Brunner, and Edwards, 1988) but is later confined to the glial lacunar system surrounding ganglionic neuropile. In the periphery of postembryonic and adult crickets it is retained in sensory nerves at much higher levels in mechanoreceptor sensilla than elsewhere (Field, Meyer, and Edwards, 1994). Thus, a transient embryonic adhesive component involved in guidance serves in the adult in a role that is consistent with ion homeostasis.

Bergen

Seattle is the sister-city of Bergen, Norway, and the University of Washington has a sister relationship with the University of Bergen. The long-running faculty exchange program provided me with the opportunity in 1989 to visit the place where Fridtjof Nansen, the famous explorer and statesman began his career. A hero since boyhood for his stories of Arctic exploration, I had been incredulous at finding in the newly published Bullock and Horridge (1965) a reference to Nansen's PhD thesis on the structure of the invertebrate nervous system. A beautiful study, illustrated with his own lithographs, he reached the plainly stated conclusion, on the basis of comparative studies of numerous invertebrates, that nerve cells touch each other but *do not fuse*. In this he clearly presaged Ramon y Cajal's famous formulation of the Neuron Doctrine. I found no relics of

Nansen's time in Bergen, but my continuing interest in his work led to contact with Nansen's latest biographer, Roland Huntford (1997), with whom we reached the conclusion that Cajal must have been aware of Nansen's work but chose to ignore it, Nansen having left for his remarkable first crossing of Greenland immediately after defending his dissertation, never to return to neuroscience (Edwards and Huntford, 1998). Our idols are not lightly dethroned and Nansen's neuroscience will surely remain an obscure footnote to Cajal's fame.

A Return to Cambridge

In 1990, thanks to another sabbatical leave and a Visiting Fellowship from my old college, Gonville and Caius, I had a sparkling year back again in Cambridge where I lived in Stephen Hawking's delightful little rowhouse overlooking the garden of Little St. Marys, its vertical structure being no longer accessible to the great cosmologist. I often had the opportunity to lunch with Sir Vincent Wigglesworth who was then 91 and still engaged in research. He commented on one occasion: "I am working on difficult problems now because I don't feel the pressure to publish." It is telling that he was asked to give up his lab shortly after my visit and he died within months. My research interests having turned again to glial cells, I had planned to work with John Treherne and his Agricultural Research Council Unit on glial regeneration. But to my dismay and profound sorrow John died of a heart attack just days before I arrived. I was there in time to attend his funeral in Downing College Chapel where, following a moving service, there were floods of tears when, following his request his favorite jazz band struck up "The World is Waiting for the Sunrise" as his coffin left the classical portico of the chapel. John's group was left in utter disarray and rather than intrude into their mourning I was able to join Michael Bate's group with whom I had also hoped to work during my time in Cambridge. Mike had done pioneer (literally) work with locust embryos but was now a drosophilist. So once again a sabbatical offered another opportunity for a change of course. I was soon immersed in his dynamic group with Helen Skaer and others working on neural development in *Drosophila*. I found myself in a whirlwind learning process. Questions in the back of my mind since Cleveland days concerning the source and diversity of glia had floated to the front on reading Treherne's (Treherne, Smith, and Howes, 1988) remarkable series of papers showing that excitability was lost in cockroach ventral nerve cords after chemical lesions to the surrounding glial sheath cells. The action proved to be reversible; glia grew back to replace the lost cells and conduction in the cord was restored. The beauty of these experiments using the cockroach ventral nerve cord is that the cell bodies of all neurons are distant from the lesion sites so that the integrity of axons is not affected. There were questions, however, about

the identity and terminology of the cell layers that enclose the nerve cords. Discussions with Mike and Helen raised the possibility that the identity of the cell layers surrounding the nerve cord might be determined using mutant *Drosophila*. Nancy Lane had used electron-opaque lanthanum ions to explore the establishment of the blood–brain barrier in blowfly (Lane and Swales, 1978) and this approach seemed feasible with mutant *Drosophila* embryos. The mutant *twist* is an embryonic lethal in which no mesodermal structures form but the CNS that is derived from ventral ectoderm does develop. After learning the fine art of embryo dissection, 20-hour embryos of wild type and *twist* were opened and exposed to saline containing lanthanum. With the help of Lesley Swales' superb microscopy we were able to show that the overlying neural lamella and its formative cells were absent in *twist* mutants, but as in wild type embryos the CNS was impermeable to lanthanum due to the formation of a superficial layer of glial cells, the perineurial glia that in Treherne's work had provided the permeability barrier and which were killed with chemical lesion. In contrast, similar experiments with Delta mutant embryos in which neuroblasts excessively proliferate, an outer perineurial layer was formed, but both it and the underlying glial sheath occurred as discontinuous islands, having been forced apart by neurogenic cells, and the core of the neural mass was in this case permeable to lanthanum (Edwards, Swales, and Bate, 1993). This work resolved continuing ambiguity concerning the investing layers of the insect CNS and vindicated the work of Berta Scharrer (1939), whose intuition based on light microscopy recognized the distinction between the mesodermal sheath forming cells and the underlying glial layer. It became clear too that there are striking parallels between neural repair and gliogenesis in insects (Smith, Shepherd, and Edwards, 1991). Later I was delighted to have the opportunity to join with Leslie Tolbert, who has done magnificent work on the role of glia in the development of the olfactory lobe in the moth *Manduca*, to write a review of the diversity and classification of insect glia (Edwards and Tolbert, 1998).

One of the joys of High Table at Caius College was the opportunity to meet people from different disciplines. During the year I got to know Bob Butcher, a physicist and agile rock climber, and with him I finished the sabbatical year devoted to glia on a high point literally by climbing all of the peaks of the High Atlas Mountains of Morocco where we shared the experience of standing on summit snow and looking down to the sands of the Sahara.

National Science Foundation

A year at the National Science Foundation (NSF) as Program Director for Developmental Neuroscience in 1996 stands out as perhaps the busiest, but certainly one of my happiest, years in science. The workload was

enormous, especially for a new recruit (a second year would have been a piece of cake) but the insights into the currents of neural development and the attractions of Washington D.C., galleries, museums, and great music too, gave little chance for down time. As for so many other transient directors in the neuroscience fields, staffer Christopher Platt made it all endurable with his guidance and support especially during the rapid learning phase. I was there during the infamous shut-down of Congress when the budgetary standoff reached its climax thanks to Newt Gingrich and government departments closed down. Orders came to leave the NSF building in Balston within 10 minutes, taking only personal effects. Attempts to re-enter the building during the crisis would be a federal offense we were told. Like some other program officers who were worried about delays in informing anxious applicants, I smuggled out my awards book and made "anonymous" calls from my apartment to those for whom such things as tenure or set-up hung on the news. During the year I became aware that Neuroscience was no darling of Mary Clutter, Assistant Director for Biological Sciences at NSF, who saw it as a province of NIH. My exit interview with her was one long argument for the place of Developmental Neuroscience at NSF, recounting the track record of innovative studies, especially those on invertebrates that would not have prospered at NIH, at least at the outset. I doubt that my argument carried much weight, but I felt good for having tried.

Full Circle

Much as I admired the world of *Drosophila* and enjoyed my brief encounter with it in Cambridge, I did not feel the urge to join the ranks on its crowded frontier. So I returned full circle to my dissertation work, acquired a colony of assassin bugs, found that my immune system seemed to have forgotten them (or that I had learned to be more careful), and joined with my colleague Mark Meyer in a new assault on the neurotoxic mechanism. Starch gel in 1956 had yielded six proteins, polyacrylamide revealed at least 14 bands. Enzyme activities were confirmed but the exciting step forward came when we found that the neurotoxic component of the saliva survived 3 minutes at 100°C, a treatment that denatured and precipitated all the hydrolytic enzymes. A neurotoxic peptide was isolated from the supernatant. At that stage we sought the advice of Michael Adams, a spider-venom specialist at Riverside. We have since collaborated on a work in progress. We know that the peptide(s) rapidly depolarize muscle and nerve cells die after a brief volley of spikes. The simplest explanation is that the venom knocks holes in cell membranes, rather like the blood-borne antibacterial agents in most insects that knock holes in bacterial membranes. The precise mode of action proves to be a difficult problem for which I am glad that I no longer feel the pressure to publish but I expect

to solve the challenge. The peptide led *en route* to brief flirtation with a big-time biotech company. It led nowhere but it did provide a glimpse of a facet of modern biology with which I am glad not to tangle.

The Other Side of the Mountain

It may seem out of place in the context of neuroscience history to write of volcano ecology, but it has loomed large in my activities in recent decades. The pursuit grew from a hobby to a professional activity when Mount St. Helens blew up in 1980. I had for years been fascinated by the life of invertebrates at high altitudes and latitudes, a seeming paradox in habitats where homeotherms were better equipped against the cold. But arthropods and other heterotherms thrive in these arid places, variously using tricks such as antifreeze and/or behavioral ways of coping with extremes. With students I had looked at the biology of one of the northwest's insect treasures, grylloblattids, a rare group, some of which live high on such mountains as Mt. Rainier. They spend their lives in a thermal window close to 0°C. They go into heat convulsion above about 12°C, and they freeze lethally at about -6°C, lacking antifreeze. Their giant interneurons respond with spikes to stimulation of their abdominal cerci down to about -5.8°C, just above their lethal temperature (Morrissey and Edwards, 1979). Their behavior patterns are such that they never need see lethal cold for they are sheltered in rock fissures, where they are insulated by deep snow during winter extremes.

So much for their thermal biology, but what do these alpine dwellers eat in a habitat devoid of plants? The answer we found, to quote Bob Dylan, is "blowin' in the wind." We measured the quantity of organic fallout, composed mainly of derelict arthropods carried from productive lowlands on the winds, and showed that it was the source of sustenance for the diverse alpine invertebrate fauna and was also significant for alpine birds that rely on arthropod derelicts laid out on the white tablecloth of the snow as their principal protein source in the breeding season. In the context of years of study of arthropod fallout on snowfields around the world, the eruption of Mount St. Helens, just 25 years ago as I write, proved to be an irresistible temptation. Here was a naked mountain cooked to several hundred degrees, a moon landscape only 3 hours drive from Seattle. NSF recognized the opportunity to follow the biological events following the eruption and supported a multidisciplinary approach. Here we had the opportunity to observe Act 1, Scene 1 of the succession play, at first by helicopter visits, and later on reconstructed roads. Just as we predicted, the standard story of primary succession was turned upside down. Most ecology texts give plants the pioneer role on bare land, followed by herbivores, and then the scavengers and predators. But on Mount St. Helens, and we suspect on most

other such newly devastated sites, the pioneers are predatory and scavenging insects, specialists in exploiting the ubiquitous windborne organic fallout (Edwards, 2005).

Teaching

Some are born teachers, some have teaching thrust upon them, and some should never teach. I started my teaching career somewhere between the latter two. I know that my early attempts must have been as pathetic as they were excruciating. It is painful to remember and I pity those early students. But I worked at the art over the years and I found that two things, conviction and enthusiasm, were paramount and outweighed all the psychobabble and technology that professional pedagogues love to promote. My most challenging but exciting teaching was a bold attempt at Case Western Reserve in 1967 to team up for a Comparative Neurobiology of the Animal Kingdom, with Bob Josephson and Ted Voneida. Bob did the squishies (to use Graham Hoyle's terminology), I did the crunchies, and Ted the bonies. From sponges, coelenterates, and mollusks (Bob) to arthropods (JSE), we had the help of the newly published Bullock and Horridge (1965) volumes and we learned what a storehouse of information they were. The course was well received and could have become a staple had not I left right away for Seattle, Bob a little later for Irvine, and Ted to help found a new medical school in North East Ohio. I taught the wonders of insect biology with emphasis on their physiology, development, and ecology for many years at the University of Washington and enjoyed it, having become reasonably skilled in the later decades. I have been energized over the years by the sheer fascination of insect life and by a sense of the value of an organismal biology perspective in these reductionist times. I like to quote E.O. Wilson to the effect that if primates were suddenly removed from the globe, terrestrial ecosystems would revert to prehomimid conditions within a relatively short time, whereas if the insects were to be abolished all terrestrial ecosystems would quickly subside into chaos.

A stint as Director of the Biology Program at the University of Washington during the 1980s involved putting together Introductory Biology courses that were taught by faculty gleaned from the separate Departments of Biochemistry, Botany, Genetics, and Zoology. It held little joy, with struggles for shares of declining budgets, and the constitutive resistance of faculty to change anything, especially course content and sequence. In contrast I gained great satisfaction from directing the University Honors Program during the 1990s. Small classes of highly able undergrads who were eager to learn and to be challenged made the chore of persuading chairs to release their best faculty for Honors courses a worthwhile if strenuous exercise in diplomacy. I looked forward each year to teach in the Honors core a course that I called Human Ecology, a subject that

comes in many flavors, but which I used to impart some general biological literacy to nonmajors, many of whom entered the course wary of science and suspicious of its implications. I hope it left some future leaders among the incipient lawyers, business people, teachers, and legislators with a more rational perspective on the place of *Homo sapiens* on Planet Earth. At least they know what the Laws of Thermodynamics tell them about sport utility vehicles (SUVs) and compost heaps, and that the gas bubbles in their beer are the same stuff that leaves the SUV tailpipe to warm the globe.

Family

I met my future wife, Ola Shreeves, when we were undergraduates on a student expedition with the Auckland University Field Club to Mayor Island, an offshore island near the coast of the North Island, one of many extinct volcanoes. We shared a strong interest in field ecology, her interests centering on Botany and mine on Zoology. We were engaged in New Zealand and married in Cambridge, England in 1957 where she taught high school biology while I struggled with my thesis work. Summer vacations were spent traveling Europe on a heavily laden Lambretta scooter and midwinter took us to icy Scottish mountains with fellow grad students Hugh Rowell and Thelma Giles. Two boys, Richard and Duncan, were born in Cambridge, the latter only weeks before we left for Cleveland. Two more boys, Marten and Andrew, were born in Cleveland. All of them have accompanied their parents on mountain forays, sometime as willing (more or less) field assistants. One of them, Marten, has followed in my footsteps and is now a mosquito molecular biologist at Muhlenberg College. Richard is immersed in the world of computer programming far beyond my level of comprehension. Duncan is a jet aircraft engineer in Fairbanks who, with his family, lives the Alaska life to the fullest. The youngest, Andrew (Zack) works with a government archives office in Seattle. By the time the boys reached adulthood, our marriage, which had worked pretty well for 30 or so years, was no longer sustainable and in 1987 we divorced. Later, at a Society for Neuroscience meeting, Ruth Nordlander and I met over lunch and in the course of conversation we compared loss by divorce with bereavement by death, her husband, an organic chemist turned Dean, having died of cancer. That led in due course to our marriage in 1999, after which Ruth left her faculty position in the School of Dentistry at Ohio State University, where she worked on spinal cord development in *Xenopus*, and moved to Seattle where she expected to continue her *Xenopus* research and we talked of returning to the insect neural development work that had been so fascinating back in Cleveland long ago. The prospect of our sharing research and travel into retirement was however taken from us with the realization that Ruth, then aged 62, had early symptoms of Alzheimer's disease. It is hard to put on paper how our hopes were dashed

when that new reality intervened. After several years during which I cared for her at home, Ruth is now in an excellent Adult Family Home that specializes in the care of advanced Alzheimer's victims. Retirement now gives me the opportunity to re-open old files of variously unfinished manuscripts (finding that what was obvious 10 years ago is now a challenge to decipher). I have time to study harpsichord; to travel, especially to enjoy European music festivals with my antipodean brother, Graeme; and to collect more mountain ranges, from Siberia to Tasmania. Carpe diem.

Acknowledgments

I recall Don Kennedy saying at a Snowmass Winter Brain Research Conference many years ago: "When I say I, I mean we and when I say we I mean they." I have used the same code in this chapter. I thank all the students, graduate and undergraduate, who helped make the science in this chapter and made life in the lab and in the field so full of adventure and fun. I especially thank my enduring colleague John Palka and my long-time loyal technician Su-Wan Chen, for their tolerance of my inability to stay on target, and Mark Meyer whose try-anything spirit propelled much of our work together. A scientist by day and a serious, accomplished graphic artist by night, I could never figure out when Mark slept. Of course, most of the neuroscience could not have been done without some 35 years of support from NIH. I am restricting my thanks here to my partners in neuroscience, but we all know that it would not have been possible without the forbearance and support of family and friends. Finally, thanks to my sister-in-law Roberta Abbey for untangling the computer problems that dogged my work on this chapter.

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