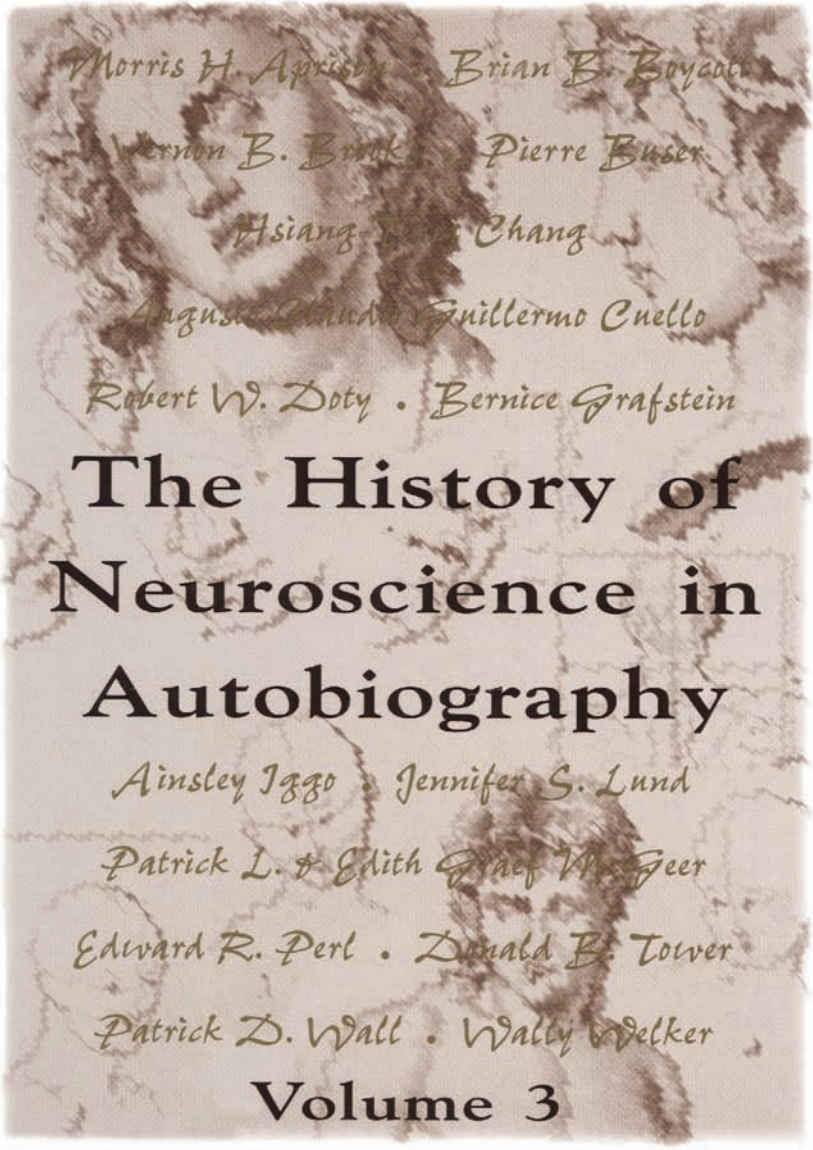

Edited by Larry R. Squire

The History of Neuroscience in Autobiography

VOLUME 3

Edited by Larry R. Squire

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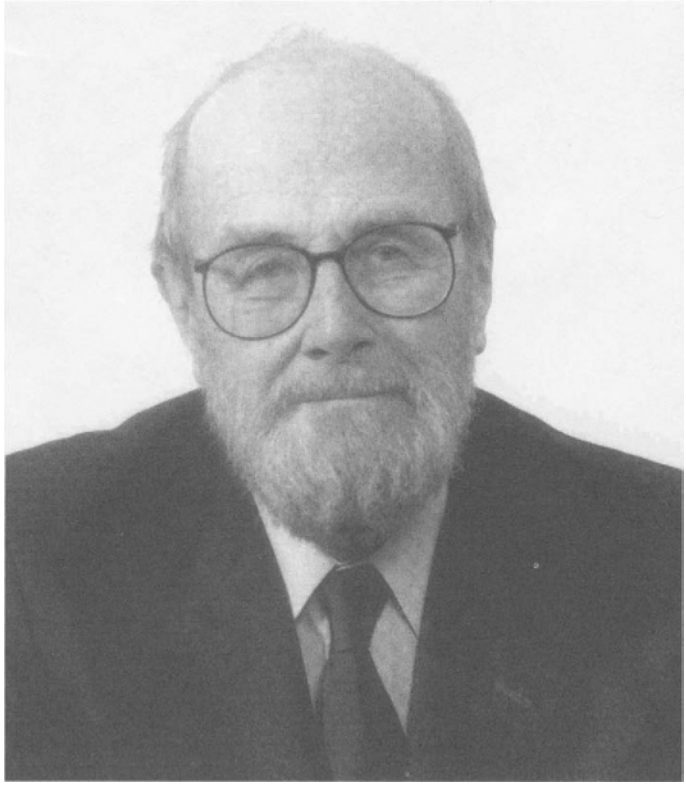

Patrick D. Wall

BORN:

Nottingham, England
April 5, 1925

EDUCATION:

Oxford University, M.A. (1947)
Oxford University, B.M., B.C.H. (1948)
Oxford University, D.M. (1959)

APPOINTMENTS:

Yale University (1948)
University of Chicago (1950)
Harvard University (1953)
Massachusetts Institute of Technology (1953)
University College London (1967)
Hebrew University of Jerusalem (1972)
King's, Guy's and St. Thomas' Hospital Group (1992)

HONORS AND AWARDS (SELECTED)

Fellow Royal College of Physicians (1984)
Sherrington Medal, Royal Society of Medicine (1987)
MD Hon Siena (1987)
Fellow Royal Society (1989)
Fellow Royal College of Anaesthetists (1992)
MD Hon Debrecen (1993)
Congress of International Association for the Study of Pain honoring P. D. Wall (1999)

Patrick Wall worked throughout his career on the physiology of sensory systems, particularly in the periphery and spinal cord. He is best known for his research and theory concerning the nature of pain mechanisms, for his early studies of plasticity, and for the concept of 'silent synapses' that can be unmasked by deafferentation.

Patrick D. Wall

Childhood

I was brought up in a family full of adventure. My father's extrovert character effectively submerged my mother's covert Puritanism. My older brother's obsession with cars and airplanes so successfully distracted my parents that I grew up in a wonderful calm. Three watersheds punctuated my childhood. At age 8, a teacher told us in class that cotton grew in Lancashire. Deeply puzzled, I scuttled home to ask my parents, who told me that Lancashire was famous for spinning and weaving cotton but that none grew there. I was shattered by the revelation that some grown-ups in authority did not know what they were talking about, and I settled into a lifetime of doubting authoritarian pronouncements. At age 10, I had an emergency operation for a strangulated hernia and was so impressed by the drama of it all that I decided that a career in medicine was for me. At age 13, since my parents were dedicated agnostics (thank God!), my opportunity for juvenile revolt was to turn to religion. I was so impressed by the apparently profound difference between the organic and inorganic world that I decided that there must a God to organize it. Then, Penguin New Science published a picture of crystalline tobacco mosaic virus. My religious world collapsed on itself and I settled into doubting divisions based on faith.

Teachers

Almost everyone can identify a teacher who had a profound effect on them. I was lucky enough to have two.

S. A. Barnett

In 1508, Colet founded St. Paul's School, which had settled into a rigorous traditional routine when I entered as one of the 158 scholarship boys. With the outbreak of war, everything changed. We were evacuated into the country 20 miles west of London, billeted in very strange houses (I was in a doctor's house in the major criminal lunatic prison), many masters went off to the war, and the courses were reorganized. Into this mess, Tony Barnett, fresh from obtaining his Ph.D. in zoology at Oxford, was directed

to teach since his health prevented his army call-up. He knew nothing of teaching, deplored discipline, and decided to use his very considerable intelligence to reason with us. The order in which we had been drilled evaporated in favor of first names only, smoking was almost compulsory, and any hangover of discipline was impossible with his younger brother James in the class. We argued, debated, objected, worked twice as hard, and did brilliantly. We were praised for thought and doubt and quickly formed a distinct group separate from our schoolmates, who continued to plough their traditional furrows in subjects such as Latin and Greek.

Not surprisingly, we all became socialists except for a few who kept very quiet. It is a cliché to speak of a socialist phase as a temporary aberration of youth in revolt. The times were revolutionary. The Red Army was smashing the German army to bits. It is easily forgotten that, in May 1945, the great majority of the population voted against Churchill and the conservatives and installed a socialist government. At Oxford, I became chairman of the socialist club and then migrated to the communists. They were the warmest, brightest, most active, caring people I had met. However, my distaste for discipline and authority soon had me on my way to the Left past Trotsky to Plekhanov to Proudhon. The urgent practical issue for us at the time was the introduction of the National Health Service. The British Medical Association (BMA) was of course opposed and realized that the students were in favor. In their confusion, the BMA helped us to organize the medical students and I founded my first journal, *The British Medical Students Journal*, which of course was dedicated to promoting the change. I have not changed my mind about the need for social change since those heady days. A half century of promises by the likes of Reagan and Thatcher that private enterprise would generate such wealth that social economic problems would cure themselves have failed. Thirty percent of our children still attempt to grow up below the poverty line. If one visited a large city hospital emergency room, one would find a mass of confused, impoverished, alienated people similar to those who haunted such places 50 years ago.

Paul Glees

The chance for an undergraduate to develop as an individual remains a severe problem. The best bet is the company of fellow undergraduates. Undergraduate teaching retains the ambition of mass production and many students succeed in diagnosing precisely what is the approved end product. The events of 1968 and the various student revolts accelerated the pace of successful mass production. University faculties used to retreat from teaching to concentrate on research. The process is now reversed and great ingenuity is used to force-feed their charges. The problem of individual development is slightly ameliorated by programs of elective courses, seminars, tutorials, and special projects but always at the grudging expense of time taken from research by the faculty. I had the remarkable

opportunity for contact with faculty when an uncle arranged for me to be a laboratory assistant with Alexander Fleming during vacations. This led to the bizarre situation of being taught pathology by Howard Florey and E. B. Chain in term time and working for Fleming in the vacations while the whole story of penicillin was flowering. Oxford and Cambridge are slightly better than other universities in having limited numbers of undergraduates, each of whom has a personal tutor who receives an essay each week. Even this luxurious arrangement leaves the mass of students as anonymous units left somehow to organize their own development. I was hugely fortunate that Paul Glees was a teacher in the anatomy department at Oxford. He, who was not a Jew, had moved from Germany in order to protect his Jewish wife, Eva. He went to Amsterdam to continue his neuroanatomy in Kapper's Brain Institute. With the fall of Holland, they escaped to Oxford. He was the opposite of the familiar German stereotype; he was warm, soft, generous, welcoming, and uncertain. He and Eva formed a salon for medical students as though it was the most natural event in the world. A transient coterie of students were made to feel individually welcome and special. A generation of students were marked by the experience and we left with our heads a little higher. This gang of Glees included Oliver Sacks, neurologist and author. In 1943, Glees developed a silver stain that allowed one to see the irregular outline and blobs of degenerating terminal arborizations. It was a huge advance on the previous degeneration methods, which were diffuse and limited mainly to myelinated fibers. It was rapidly overtaken by the method of Nauta that permitted clear staining, limited to the degenerating axons. The last phase of this development of staining degeneration up to terminal boutons was the method of Heimer, who had joined Nauta at MIT. The first paper with this new method (Heimer and Wall, 1968) showed that unmyelinated afferents terminated in the substantia gelatinosa, a fact vigorously denied at the time but which was to lead me and many others to concentrate on this fascinating structure. The whole study of degenerating terminals moved from light to electron microscopy while transport methods of marker molecules such as HRP took over the analysis of connection to be followed in turn by the contemporary colorful rainbows.

Glees invited me to join him in the laboratory to help confirm the difficult identification of the areas of degenerating fibers. The first target of our work was the centromedial nucleus of the thalamus and the subthalamic nucleus (Glees and Wall, 1946), regions that remain of considerable interest. The electrolytic lesion method is unsatisfactory with regard to its limit on shape, and I therefore invented a spring steel knife held within a hypodermic needle and extruded and rotated within the brain to cut tracts (Glees *et al.* 1947). This method was used extensively by the Szentagothai group in their hypothalamic studies and in my own work (Glees and Wall, 1948; Wall *et al.*, 1951; Wall and Davis, 1951). As a result of the generosity

of Glees, I was involved in enthralling research from the age of 19, and although I went on to complete my medical degree I was set to resume research as soon as possible.

Chiefs

The role of head of department has evolved radically. The traditional function was that of patriarch and remains so in some benighted countries and universities. The appointed role of these grand patrons was to control everything—appointments, budget, and research plan. Very rarely, these monolithic organizations are wonderfully successful, as in the case of the Molecular Biology Laboratory in Cambridge run by a cooperative of Nobel prize winners. More often, they are the scene of steady degeneration as the geheimrat ages. A revolution began in the 1950s, first in the United States and then in some other countries, when it became possible and then obligatory for junior research workers to apply for their own funds. This smashed the monopoly power of department chairmen and liberated a generation of scientists. It led to a great period of fertility. Needless to say, it generated a counterreaction where funds assigned to freewheeling individuals were anathema to central planners. We see now the reestablishment of 'centers of excellence,' 'institutes,' and 'units' with grand plans to which young scientists must commit themselves. I flourished in the period of liberation.

I have previously written about my doubts about authority which have been the leitmotif of my life. These doubts incorporated my own justification for authority and I therefore avoided ever being a department chairman. My background gave me the confidence that I was unlikely to starve to death. I therefore followed passions and obsessions without a feeling of a need to belong to one of the great mafias. While this entertained me, it did not amuse the leaders of the existing powerful mafias. Since I refused the role of big boss, being a small boss needed careful consideration. I did not relish the role of master. I chose students and especially postdoctoral fellows who had a clear air of independence. I started each with a single joint experiment with the student as apprentice, after which they became associates with shared responsibility. This has produced a group of very different and highly productive individuals who retain a shared fondness and mutual respect (Dubner, 1999). I therefore advise a very open-eyed analysis of the chief and illustrate this with sketches of the five in whose departments I worked and who epitomize the changes of neuroscience over the past 50 years.

John Fulton

In the 1920s, John Fulton went as a Rhodes scholar to Sherrington's Laboratory of Physiology at Oxford. He remained there, working mainly

on cortex and motor systems with many distinguished students, including J. C. Eccles and David Lloyd. In the 1930s, Yale medical school had fallen into decrepitude and was revived by Winternitz, who summoned Fulton back to build a physiology department. Over the years, he appointed a series of first-rate research workers, including Barron, Brobeck, de Barenne, Lloyd, Chang, McCulloch, Lamport, and Gelfan. The place became a mecca for young scientists and clinicians, especially neurosurgeons. Satellites were established such as the new medical school in Seattle, which was staffed by a mass migration from Yale of T. C. Ruch, H. Patton, and A. A. Ward. In 1938, he founded the *Journal of Neurophysiology*, published the first of three editions of *The Physiology of the Nervous System*, took on Howell's *Textbook of Physiology*, and began what was to become the best library of the history of medicine.

Fulton was the gentlest, kindest, most enthusiastic, and encouraging of men. As such, he disliked controversy. One can see this in his early work, in which he had to weave his way around the accepted dictum that lesions of the pyramidal tract produced spastic paralysis, whereas contemporary work revealed a flaccid paralysis. A striking example occurred in the first volume of the *Journal of Neurophysiology*, in which he published a paper by Nachmansohn proclaiming that nerve impulses were propagated along the axon by the release of a trail of acetylcholine. Inspection of the second volume shows that over half the editors, including Lorente de No and Gerard, had resigned over the publication of this preposterous paper. Ten years later, I was present at a lavish dinner in honor of Lorente de No, who had finally agreed to meet Fulton. Well-lubricated speeches of reconciliation were made until Lorente stood up and ended his speech with 'But, John, you were a fool.' The dinner party broke up into two camps and the two never spoke again. On one occasion, a long manuscript arrived from Denny-Brown on the effect of cortical lesions. Fulton asked him to shorten it on the grounds that 'this manuscript is longer than the combined works of Matthew, Mark, Luke, and John.' Denny-Brown refused, commenting that 'the works of the cited authors have not been confirmed.'

In 1934, Fulton and Carlyle Jacobsen operated on two chimpanzees, Becky and Lucy. They had carried out a two-stage removal of the frontal lobes and noted that the animals became calm without temper tantrums when frustrated. In 1935, these results were reported at a meeting at which Egas Moniz was present. On the basis of this experiment, the world pandemic of bilateral frontal lobotomy was launched with the intention of emptying the world's mental hospitals. In 1948, Fulton wrote,

> I would make an ernest plea for caution on the part of the neurosurgeon, lest in the absence of basic physiological data, he unwittingly do irremediable harm to human beings who

> might be benefited by a far less radical operation than is now being performed.

Fulton therefore set up his last scientific effort in an attempt to provide 'the basic physiological data.' This Yale Frontal Lobe Project included Pribram and Maclean (whose autobiographies appear in this series) and Kaada, Scoville, Delgado, and myself. We were a group of enthusiastic amateurs, and I do not recall a single critical intellectual discussion but I saw neuromythology flourish.

In this merry gang, there were two serious neuroscientists. I am indebted to H. T. Chang for introducing me to electrophysiology. He learned his trade with Woolsey and with Lloyd and soon moved to the Rockefeller and then defected to China, where he set up the Academy Institute of Physiology in Shanghai. The other was Alex Mauro, trained in physics and electrical engineering and with ebullient intelligence and hilarious mockery of the standards of our science. We realized that there was little chance of exploring the true physiology of the central nervous system if our first act in preparing to observe was to anesthetize the animal. Mauro knew how to make miniature radio receivers, which would allow us to stimulate the brain in local areas. He set about making the receivers and the transmitters from which we could transmit stimulating pulses by way of loop antennae placed on the skin. I encased the receivers in medical polythene and sutured them subcutaneously with the stimulating electrode on the cortex of monkeys (Mauro *et al.*, 1950). We measured the effects of long-term, low-level stimulation and of drugs on epileptic threshold. We had to interrupt these experiments since Mauro went to the Rockefeller and I to the University of Chicago. He developed the idea into cardiac pacemakers. Twenty years later, we reunited so that I could use the technique on humans as a test of the gate control theory (Wall and Sweet, 1967), which later grew into transcutaneous electrical nerve stimulation (TENS) and dorsal column stimulation. It took me another long period to complete the other related ambition, which was to record single units in a freely moving animal. This too required cooperation with a technical master, John Freeman, who showed that the incorporation of a field-effect transistor eliminated movement artifacts (Wall *et al.*, 1967). This advance was then used by many, particularly John O'Keefe in the hippocampus.

Peter de Bruyn

Thanks to Warren McCulloch, I was appointed assistant professor to teach neuroanatomy at the University of Chicago with the actual intent of allowing me to work with Jerry Lettvin at Manteno State Hospital (see Lettvin's autobiography in this series). The department was run by a cozy triumvirate of professors plus de Bruyn. It was immediately apparent that here

was the opposite of the social atmosphere of Yale. I had an interview, was shown very briefly around the department, and was then submitted to an evening's carouse to test my alcohol solubility and was informed the next morning that I had the job. I enquired, some time later, about this method of appointment. I was told that they knew nothing about my subject and had decided that at least they could appoint a good drinking companion. This was typical of de Bruyn, who was the greatest master I have ever met in organizing the world for his personal comfort. An example was his war service, which began with his call-up as a doctor into the Dutch army in April 1940. Within a day, he was sitting with tens of thousands of others in a German prisoner of war camp. Seeing a long stretch ahead, he wondered what might persuade the Germans to let him go. He smuggled a letter to friends asking them to arrange an unpaid job for him in the Public Health Department of Amsterdam. When the appointment was announced, the Germans were sufficiently impressed with the dire consequences of the absence of de Bruyn from public health control in Amsterdam that he was released. Taking up his nonexistent job, he proposed the idea that disease might be spreading on poorly washed glasses in bars and spent his days ordering drinks at the town's expense and taking swabs from the rims of the glasses after they were emptied. He then smuggled another letter to friends at the University of Chicago appointing him to another nonexistent job. Armed with this, he persuaded the Germans that they would improve their relations with the then neutral United States by permitting the emigration of someone they needed. Again, it worked and he and his family traveled across occupied Europe to Lisbon and Chicago. He was a great fount of aphorisms, one of which was 'Never sit on a committee unless it deals with money and serves a meal.' I have tried since to follow at least the first part of this advice. The department faculty had all promoted themselves to full professorship with the exception of two assistant professors. I was one and was happy to be ignored, especially in the company of equally ignored emeritus professors, Bensley for cytology, Poliak for the retina, and Kluver for the cortex and behavior. The other assistant professor was Roger Sperry, who had already made all the basic discoveries that were to lead to his Nobel prize. By manipulation of peripheral nerves and central nervous system in amphibia and fish, he had specified the ways in which nerve fibers are labeled and locate their targets and, as an extreme of manipulation, had isolated right from left brains in cats. The professors knew nothing of this remarkable work and cared less. They only knew that Sperry had come to them from Paul Weiss, whom they loathed. Sperry was nearing the end of his second term as assistant professor, and since there was a rule of promotion or dismissal, and since they had no intention of promotion, he was summarily dismissed. Many years later, I met one of the professor who said to me, 'When you were in the department, there was a fellow

working here called Sperry. Is that the same Sperry one hears about from Cal Tech?' It was no great struggle for me to protest and resign my faculty job the next year and move to a temporary job with the astonishing group at MIT.

Warren McCulloch

Warren McCulloch came from a distinguished old American family of farmers, lawyers, and pioneers. The family had owned a farm outside Washington called Chevy Chase, and his grandfather had defended John Wilkes-Booth, at least that is what McCulloch said. He poured out a continuous stream of stories, ideas, and opinions and I soon gave up trying to differentiate fact from fiction because they were all great. He collected people by the bushel and all his geese were swans. Some, such as Lettvin and Pitts, were indeed swans who deserved the gold crown around their necks. Some were ducks who did their best to live up to the master's nomination as swan. He succored the entourage with extraordinary care and generosity. There could be jealousies among the group of equals. McCulloch once declared, 'That Marvin Minsky has a mind like a steel trap,' to which Pitts replied, 'Yes. Always clanging shut on nothing.'

He had completed medical school and spent a brief amount of time in psychiatry at Bellevue and a period of physiology with Dusser de Barenne at Yale, after which he set up the Illinois Neuropsychiatic Institute. I first met him in 1950 when I approached him with some trepidation with results that criticized the basis of strychnine neuronography which he had developed with Dusser de Barrenne. This was a physiological method of establishing connectivity in the brain. It depended on the fact that strychnine applied to neurons provoked a synchronous explosion of activity that could be detected as a compound action potential in the axons leading from the neurons. It was believed that the wave was desynchronized by synaptic transmission. I had found that some synaptic areas could transmit the wave without desynchronization and that some neurons failed to generate a wave at all (Wall and Horwitz, 1951). Far from being phased, he said I must work with Lettvin, which he then arranged, and for his generosity I am deeply indebted. I saw this ability to handle criticism again when his major discovery of suppressor strips in the cortex was shown by Wade Marshall to be an evocation of the spreading depression of Leao. He wrote a series of brilliant decisive essays critical of contemporary psychiatry. After the revolutionary paper coauthored with Pitts on the computational possibility of the formal neuron, it was natural that he should join the extraordinary group whose names are associated with cybernetics: Wiener, von Neumann, Rosenblueth, von Foerster, von Bonin, *et al.* Pitts was already with Wiener at MIT, and it seemed natural that McCulloch and Lettvin and I should migrate to MIT. As Lettvin has written in his autobiography in this series, our arrival at MIT coincided with a violent

denunciation of McCulloch by Wiener. This was caused by the very generosity and hospitality that was characteristic of McCulloch. Pitts was mortally wounded, but the rest of us carried on protected by Jerome Wiesner. The general scientific atmosphere was to lead to an episode that marked me for years. I reported on our first results at the international physiological congress in Montreal (Howland *et al.*, 1955). After my presentation, I was asked to visit the office of Penfield and was there confronted by Penfield, Adrian, Eccles, and Jasper. They asked me to summarize what I had said and I showed them the first source-sink analysis of spinal cord activity from which we had concluded that there was a presynaptic control of impulse transmission. They then assured me that this heresy was undoubtedly an artifact caused by dorsal root stimulation. Furthermore, they said I was the right type with my Oxford and Yale background but that I should realize that I had fallen on bad company and that there was still time to mend my ways. Their fatherly advice was a declaration of war for me. There was a little solace when Eccles adopted the main idea as his own 5 years later.

Jerome B. Wiesner

Jerome B. Wiesner was an electrical engineer who had been deeply involved in the successful development of radar during World War II. He launched the Research Laboratory of Electronics at MIT and went on to be science adviser to President Kennedy and then to be president of MIT. The end of the war brought no relief for those developing the new military technologies—distant early warning radar lines, nuclear weapons, missiles and countermissiles, and their associated gadgetry. These projects remained isolated with their staff in secret establishments. Wiesner and a group of close colleagues in physics, mathematics, and electrical engineering realized that there were general problems behind the specific technical problems and that an exploration of these would flourish in an atmosphere free of secrecy. Norbert Wiener, for example, had moved from his experience of mechanical design to a general theory of stability and movement that applied as much to the brain as to an anti-aircraft gun. MIT had a policy against the formation of new departments but formed cooperative centers in which combined skills would have free rein without the necessary rigidity of academic departments, whose teaching requirements concentrated them on single subjects. Furthermore, Wiesner and his group realized that the armed forces and some industry could easily afford to finance such a free-running establishment for their own long-term interests. Under the innocently named Research Laboratory of Electronics umbrella, they collected an extraordinary collection of talent. Claude Shannon arrived from Bell Telephone Laboratories with information theory. Chomsky and Halle came to start their work on linguistics since this too was a key to communication. Kiang worked on the auditory

system. Pattern recognition was a key problem and grew into what is now called artificial intelligence. It was therefore not so bizarre that we should work on how the spinal cord analyzed its input and transmitted signals. It was never intended that this extraordinary mix should be permanent, and so none of us had permanent jobs. The ideas were born and weaned, and then individuals returned to the core MIT departments or to industry or they set up their own centers. Wiesner and his friends, such as Zacharias and Weisskopf, had the general idea, found the finances, and directed with an almost invisible hand. He was a unique chief. We worked very hard, talked endlessly, and tried to look like scientists when troupes of mystified admirals, generals, and company presidents made brief visits to be assured that their money was being well spent.

Irwin Sizer

Irwin Sizer was a biochemist and chairman of the biology department at MIT. In the late 1950s, there was a palace revolt and the governors of MIT fired the arrogant F. O. Schmidt, who was a classical patriarchal head of department. In his place, they appointed a surprisingly humble member of the department. No one, especially Irwin Sizer himself, would have labeled him as a brilliant scientist. He was a quiet Yankee with modest dignity. He set out to recruit brilliant scientists who towered above him intellectually but not as human beings. His recruits included Leventhal, Rich, and Luria, and the department he generated has produced three Nobel prize winners. He asked me to be his executive officer. Leventhal said it was obvious that I would eventually become a full professor, so they might as well get it over with. I include Sizer in my list of chiefs because he was such a rare paragon who chose well and then selflessly devoted himself to making a productive environment.

John Z. Young

John Z. Young was a zoologist, anatomist, and philosopher. As I wrote in his obituary (Wall, 1997), he was perhaps the last of the classical heads of department. He was a man of huge intelligence, inventiveness, and curiosity. He was descended from the Young of Young's modulus and of the Young–Helmholtz theory of color vision and who deciphered the Rosetta stone. His mother was the granddaughter of the Howard who showed that it was possible to identify plant species by the microscopic shape of their pollen and, more important, classified the clouds with the names we now use, such as cirrus, cumulus, stratus, and nimbus. Young studied zoology at Oxford and in 1928 went to Naples and began his lifelong study of the cephalopods. Early work included the identification of the giant nerve fibers of the squid, previously mistaken for blood vessels. He showed that they were indeed electrically excitable nerve fibers, established the rules for the relation of conduction velocity to fiber diameter, and showed that

they delivered action potentials to the mantle muscle, which generated the synchronous contraction allowing fast-forward motion. This discovery permitted Hodgkin and Huxley to describe the ionic nature of the nerve impulse because they could place electrodes within and without the conducting membrane. As a wartime project, Young investigated nerve degeneration, regeneration, and repair. After the war, he returned to Naples and the octopus whose lively behavior allowed his group to discover that these animals had the ability to recognize and remember targets by both vision and touch. With the world's cephalopod experts joining him and with his precise knowledge of cephalopod loculated brains, it was possible to trace the structures involved in these tasks by making small lesions in the various cell groups.

In 1946, he became the first person in Britain to head a department of anatomy without a medical degree. He revolutionized anatomy as a study of the relation of structure to function. Over the next 30 years, he created a large, lively research and teaching department that fostered such diverse characters as George Gray, whose electron microscopy classified the synapses, Semir Zeki (the visual system), and John O'Keefe (the hippocampus). Widely admired and imitated and budding off students to fill chairs of anatomy all over the world, it may have been the last department of its type. J. Z. Young was intellectually involved with all those projects. He hammered every member of the department for news of progress with vigorous comments, often wrong, but always with awesome intelligence. As faculty members become more independent, I think modern chairmen should be cautious in following the example of J. Z. Young. He created a new concept of an anatomy department, chose the faculty, and directed them. In 1967, he invited me to take over a failing research unit, and I accepted with gratitude since it was time for me to leave the United States. I was becoming far too much a member of the establishment. Old loyalties and aging parents made sense of my return. I was frightened to leave the luxury of MIT and the United States but thanks to the encouragement and support of J. Z. Young and new friends the move worked well.

Laboratory Assistants

I feel I must write about this vanishing tribe before they disappear completely. The most famous was Faraday, son of a blacksmith, apprentice book-binder, lab assistant to Sir Humphrey Davey, grudgingly recognized late in life. Karl Zeiss followed one route to recognition as a lab assistant in physics at Jena by setting up a company. In the 1920s, Alexander Forbes at Harvard made the measurement of the EEG feasible and his lab assistant, Albert Grass, created the equipment and also the company that manufactured the bulk of the world's EEG machines. The majority of these

workers never appeared in public and yet were crucial, especially in the development of neuroscience. The best of them were technical masters who understood problems and invented solutions. Without degrees, society placed them in the lower ranks where some built a creative niche. Now that society makes degrees more easy to obtain, most technicians are promoted into the general mass, but a few define and develop their special role. They have disappeared from most labs and are replaced by temporary amateurs or graduate students who are used as slave labor. For most chiefs, the intellectual life of ideas, schemes, and plans is paramount and technique is trivial. Sol Snyder proudly writes in his autobiography that he has never carried out an experiment in his life but is very good at giving ideas to others. It is true that in some endeavors, the technique is so precisely defined that the equipment is best bought off the shelf. I am saddened by the number of chiefs I know who have never thought to invent methods and are therefore stuck in endless repetition of small variations of the same experiment. A particularly bad contemporary example is brain imaging, where doctors who do not understand the technique hand the data over to computer experts who do not understand the questions. In my career, I was persistently faced with inadequate research methods that did not quite answer my questions and I therefore turned to technicians in genuine partnership. I mention four of them. Frank Kerby, a farm boy from Oxfordshire, had been extracted from Sherrington's lab to set up physiology at Yale by Fulton. He had appointed himself to the permanent rank of sergeant to keep us second lieutenants in line. In those opulent days, he and I would start the day and decerebrate six cats so that the medical students could do the experiments laid out in Liddell and Sherrington's laboratory handbook. When I was working on a long experiment, he would walk through my lab and announce, 'That cat's dead, doc.' I finally discovered that he had noticed that the last function to go in a cat is the muscle contraction on the hairs in the tail so that they stand out at right angles. The second was Bernard Turskey, electronic technician, union organizer, dedicated Trotskyite, and brilliant. He was a sculptor of electronic circuits who, once a purpose was defined, could weave components and wires together to fulfill the goal. He left us for a more challenging lab and somehow ended up as professor of sociology. Diane Major, histologist, was enthralled to master to perfection any new technique. When I left MIT for London, she moved to Nauta to run his lab. Finally, Alan Ainsworth, with his wife Penney, is a master of materials. From a poor background, with no degree, apprenticed to a specimen supplier, he is left wing, former union organizer, widely read, and a highly original thinker. An example of his creativity is the multiple microelectrode manipulator, sufficiently light and rugged to be used to record single units in the hippocampus of freely moving rats by John O'Keefe. He retired to the country where he supplies the world with perfectly made glass-covered,

tungsten and platinum-tipped microelectrodes of the type designed by Merrill and by Lettvin. I hope these are not the last of their line and that research chiefs will rediscover a respect for technique.

Associates

From school days to the present, I have strongly preferred the company of people who were witty, world wise, opinionated, argumentative, iconoclastic, intolerant of fools, and original to the level of eccentricity. In short, they are smart asses. The people with whom I chose to work were mainly noble examples of the type: Basbaum, Devor, Fetz, Fields, Gutnick, Hillman, Lettvin, Mauro, McMahon, Pitts, Werman, Woolf, and Yaksh. They are not everyone's cup of tea, but they are for me. Ronald Melzack, with whom my name is often associated, is the opposite. He is warm, friendly, hates confrontation, and presents ideas in an innocent fashion that is not my style. However, I suspect that deep below his social exterior of bonhommie there lies a secret covert smart ass.

Research

Synaptic Transmission

Currently, synaptic transmission is extraordinarily well understood at the membrane and molecular level. However, if one wishes to describe even the simplest examples of synaptic transmission in action, more understanding is needed to procure a complete picture of the event as a whole. That complete picture would include the rest state of the membranes before the arrival of the afferent volley and then the complete spatial and temporal sequence of events in the whole cell assembly after the arrival. Despite the massive search from the time of Lloyd to that of Jankowska, a satisfactory circuit diagram is still not available even for the monosynaptic reflex. An overall flow diagram of the flexion reflex remains vague and is represented by a crude diagram with cells shown as spheres and axons as lines. Egger made a valiant attempt to define the pathway of the plantar reflex after our work (Egger and Wall, 1971).

This problem is not limited to spinal cord so that the precise origin of the receptive fields of visual cells in area 17 remains speculative. To make a start on this problem, Lettvin and Pitts invented the method of microelectrode source-sink mapping in the dorsal horn (Howland *et al.*, 1955). This involved two stages of prolonged calculation by hand: First, it was necessary to interpolate between recording points since the flexibility of the microelectrodes did not permit recording at a regular grid of points. Second, the second differential of voltage between neighboring points was

calculated to measure the source or sink of current at each point. This provides a precise localization of activity at each instant. The method was largely ignored by physiologists, who understood nothing of field theory and for whom voltage amplitude satisfactorily identified the location of activity. Only now, 40 years later, with an improved understanding of physics by physiologists and with computers capable of doing the calculations almost online, have source-sink analysis papers begun to reappear and they are startling.

The results of our work revealed two new phenomena, both of which were declared heretical by the establishment. One was that interaction between systems began in the terminal arbor, presynaptically. The other was that part of the interaction involved the blockade of impulse transmission in axons. To provide direct evidence for such blockade in terminals was beyond the ability of direct observation in mammals at the time but was obvious in invertebrates. It was proposed by many but difficult to differentiate from the more favored explanation that there was variation in the amount of chemicals emitted at the synapse. The opportunity for direct observation arose when Werman and I found that myelinated afferents on entering the spinal cord divided and sent a descending branch over many segments (Wall and Werman, 1976). Since these axons extend into an area in which it is impossible to record postsynaptic effects of the afferent impulses, these axons were candidates for failing to transmit impulses. We therefore carried out a series of experiments on the anatomy and physiology of impulse conduction in these long-range descending afferents (Wall and Shortland, 1991; Shortland and Wall, 1992; Wall and McMahon, 1994; Wall, 1994a,b; Wall and Bennett, 1995). The outcome reviewed in Wall (1995) is that impulse transmission may be blocked even in myelinated fibers and that one mechanism for this blockade is the opening of calcium channels by GABA.

Presynaptic Focus

The creation by Lettvin of sharpened metal microelectrodes permitted their use for stimulation as well as recording. We used them first to establish the anatomical distribution of terminal aborizations of the pyramidal tracts and various types of afferent fiber (Wall *et al.*, 1955). We then confirmed, as Lloyd had proposed, that posttetanic potentiation of the 1A monosynaptic reflex was associated with hyperpolarization of the terminals as measured by recording the antidromic volley produced by stimulation of their terminals (Wall and Johnson, 1958). I thought it possible that one could detect the passage of impulses in one terminal arborization by carefully measuring the threshold in a passive neighboring arbor as can be done in peripheral nerves. I found instead that there was a gigantic decrease of threshold, which was later labeled primary afferent

depolarization (PAD) by Eccles (Wall, 1958). This depolarization is very strong in cutaneous afferents and weak in muscle afferents. It is clearly the internal origin of the large negative dorsal root potential and is associated with presynaptic inhibition. Its major source is the release of GABA, with serotonin as a minor source (Thompson and Wall, 1996). While early work examined only the acute provoked PAD set off by the arrival of an afferent volley, it later became apparent that there was a tonic phase controlled by descending impulses from the brain stem (Wall and Bennett, 1995) and a marked oscillatory generator in spinal animals (Lidierth and Wall, 1996).

It was then time to seek the cells that were the source of this control of the effectiveness of the sensory input. Eccles and, later, Rudomin and Jankowska concentrated on the weak presynaptic control of muscle afferents and believed they have identified a few cells deep in the dorsal horn. I concentrated on the source of the massive negative dorsal root potential of cutaneous origin and found dense activity associated with it in the substantia gelatinosa (Wall, 1962). Furthermore, the disturbance spread from one segment to the next by way of the Lissauer tract and could be evoked by stimulation of that tract without activation of afferents (Wall and Yaksh, 1978). The receptive fields of substantia gelatinosa are certainly not limited to nociceptive stimuli but usually respond to a wide variety of stimuli (McMahon and Wall, 1983). The same cells also respond to descending volleys from brain stem and cortex (Wall and Lidierth, 1997). There is a precise cross-correlation between the spontaneous firing of these cells and the spontaneous oscillatory dorsal root potential (Lidierth and Wall, 1998). There is no evidence that these cells are the direct source of sensation but rather are involved in a positive feedback controlling deeper cells (McMahon and Wall, 1988, 1989). Finally, activity in the cells is shown to be correlated with marked changes of response in deeper cells (Wall *et al.*, 1999).

Despite this mass of evidence that substantia gelatinosa is a zone through which all afferent activity must pass and which is capable of modulating the effect of the sensory input dependent on its own activity and on its setting by descending controls, many still opt to ignore the evidence. Despite this evidence, the myth persists that lamina I contains the cells responsible for the sensation of pain. It is true that the substantia gelatinosa is the major destination of unmyelinated afferents, which classical theory had assigned the role of 'pain' fibers. It is also true that a small minority of cells in the region respond only to noxious stimuli, but those who label these as pain cells have to ignore their selective search, the depth of anesthesia, the instability of their properties (Cook *et al.*, 1987), and the lack of any evidence that their activity produces pain (McMahon and Wall, 1989). I find it sad that many skilled workers writing in the latest textbook (Wall and Melzack, 1999)

still choose the simplistic conclusion that pain results from a dedicated line-labeled system.

The Organization of Interneurons

By the end of the 1950s, electronic advances permitted a search of the properties of single units. I determined to give cells the widest opportunity to express their potentiality by examining them in as many situations as was practical: anesthetized or unanesthetized, acute or chronic decerebrates, or spinalized with a surgical lesion or with a cold block, and finally freely moving (Wall *et al.*, 1967). I began with the large cells in laminae III—IV and later added the smaller cells of laminae I and II as I have just written. It was clear that the cells were organized in clear laminae (Wall, 1967) and that there were cells dominated by low-threshold cutaneous afferents and by low-threshold proprioceptive afferents. However, almost all of the cells responding to noxious stimuli also responded to innocuous stimuli (Wall, 1960) and were later named wide dynamic range cells. I looked for the origin of repetitive discharge (Wall, 1959), the effects of vibration (Wall and Cronly-Dillon, 1960), the effects of pairs of stimuli (Wall, 1964), and confirmed that similar cells existed in the trigeminal nucleus (Wall and Taub, 1962). The most dramatic changes of property were observed with competing pairs of stimuli and when manipulating descending control (Wall, 1967; Hillman and Wall, 1969), where the sensory modality of a cell could be changed.

In discussion with Melzack, we proposed that the separate modalities of sensation could just as well be achieved in the brain by a temporospatial code rather than by the classical dedicated pathways (Melzack and Wall, 1962; Wall and Melzack, 1965). Since these papers produced no reaction, we decided to simplify the issue and propose our views concentrating on pain (Melzack and Wall, 1965). This time the message penetrated to the cardinals of the establishment and produced public denunciation of the type I had experienced in private in Penfield's office. Curates of the cardinals published proclamations of heresy. Fortunately, support came from the surprising source of clinicians such as W. K. Livingstone and W. Noordenbos, who were thoroughly dissatisfied with the ability of the classical specific pain pathway theory to explain clinical phenomena. This support was greatly enhanced when Sweet and I published the predicted effects of large fiber stimulation on pain in humans (Wall and Sweet, 1967). This led to the rapid expansion of TENS, nerve stimulation, and dorsal column stimulation. There were clinicians who welcomed the descending control arm of the gate control, and the anesthetists were particularly welcoming. The traditional physiologists maintained their critical barrage but, slowly, as they began to repeat the experiments, they incorporated parts of our scheme into their own thinking, of course without attribution. Unfortunately, the theory was confused by Melzack and

Casey (1969), who published a proposal without evidence that sensation and affect were produced by distinct input pathways. However, general support by working scientists grew to the level where some form of gate control became accepted. The work of Basbaum and Fields greatly strengthened the idea, whereas the identification of a narcotic-dependent control by Yaksh added a specific mechanism and led to the widespread use of epidural and intrathecal narcotic therapy. Some of the criticisms of the original paper were correct, even if grossly exaggerated. I therefore published a reexamination with two modifications (Wall, 1978). For simplicity, I had included only presynaptic controls in the original diagram, but it rapidly became evident that postsynaptic controls were also in operation. Again for simplicity, I had proposed that the only control was by way of more or less inhibition, but it became apparent that there were distinct facilitatory mechanisms as well as inhibitory ones.

While some version of a gate control is now generally accepted and a great deal is known about the pharmacology, I am still not happy with what has been accepted (Wall, 1999, 2000). Most still write of the spinal gate as an elaborate gain control system affecting a one-way, input–output, pain-producing mechanism. I think of it as the tip of a distributed and integrated feedback mechanism, one of whose functions is to produce pain as an output state.

Slow Plasticity of Connection

I was drilled in the classical view that the working mechanism of sensory systems was laid down in an immutable fashion during development and that no substantial functional changes could occur in the adult. A single experiment changed my views and led to new pastures. I had been puzzled for some time about why the somatosensory system split into two—the dorsal horn relay system and the dorsal column medial lemniscus system (Wall, 1961)—only to recombine in thalamus and cortex. To investigate this, I mapped VPL in rat thalamus and then removed nucleus gracilis and remapped the entire nucleus. Immediately after the removal, the leg area of VPL was empty of cells responding to brush and touch on the leg. I thought back to the experience of my teacher at Yale, H. T. Chang, who had repeated an Eccles experiment, which showed that the repetitive firing of cells in VPL after the arrival of an afferent volley ceased if the sensory cortex to which VPL projected was removed. This experiment is used as evidence for the existence of a thalamocortical reverberating circuit. Chang thought it wise to give the system a chance to recover from the general effects of a major lesion and showed that the repetitive discharge reappeared after some hours and therefore that there was no evidence for a reverberating thalamocortical circuit. I thought it reasonable to do the same for VPL after excision of the nucleus gracilis, given my general rule that one should examine cells in as wide a variety of conditions as was

practicable. We found that as the days passed after the lesion, the arm area of the nucleus grossly expanded into the former leg area so that cells that had previously had receptive fields limited to the leg now responded to stimuli on the arm (Egger and Wall, 1971). A similar expansion of the arm area was observed in the sensory cortex. This type of experimentally induced plasticity was later carried out in various species and situations by the Merzenic group. I decided to pursue this phenomenon in the spinal cord in territory with which I was much more familiar and whose input could be easily manipulated. Therefore, Basbaum and I examined the organization of dorsal horn after chronic dorsal root section and observed grossly expanded and bizarre receptive fields (Basbaum and Wall, 1974, 1976). We also observed in nucleus gracilis that gross shifts of receptive fields could be observed immediately after the major input was cold blocked (Dostrovsky *et al.*, 1976). The classical view was that receptive fields were created uniquely by the presence of anatomically intact input pathways, and therefore the appearance of novel receptive fields could be produced only by the anatomical sprouting of new inputs. I maintained that the observed facts fitted much better the proposal that the novel inputs had been anatomically present all along but were held suppressed by physiological mechanisms. This led to the idea that there were ineffective or silent synapses whose presence could be unmasked by deafferentation (Wall, 1977).

I was stimulated by examining casualties during and after the Yom Kippur war to realize that while beautiful chronic anatomy of sectioned axons had been presented since Cajal, there was no plausible physiology. Gutnick and I found immediately that sprouting myelinated axons took on new properties; they became spontaneously active and mechanosensitive and were stimulated by adrenaline (Wall and Gutnick 1974a,b). Thus, we reexamined the injury discharge (Wall *et al.*, 1974). We noticed that rats would attack the anesthetic area some weeks after peripheral nerve section, autotomy (Wall *et al.*, 1979a,b). Devor and his team in Jerusalem carried out very extensive studies on these phenomena. Since the Hebrew University of Jerusalem proved to be a fertile ground, I set up there the Centre for Research on Pain, which continues to flourish. We found that the changes at the peripheral cut ends of axons spread centrally and involved the dorsal root ganglion cells (Wall and Devor, 1983). This too has been further studied by many groups and we have found that changes occur within 15 hours in dorsal root ganglion cells when the spinal nerve immediately lateral to the ganglion is cut (Liu *et al.*, 2000).

Since changes sweep centrally after peripheral nerve damage, we decided to look for changes within the spinal cord. Receptive fields reorganize (Devor and Wall, 1978, 1981a,b) dorsal root potentials change (Wall and Devor, 1981), inhibitions change (Woolf and Wall, 1982), and cord substance P changes (Barbut *et al.*, 1981). Perfusion of the cut end of the

nerve with nerve growth factor prevented most of these changes (Fitzgerald *et al.*, 1985), whereas chronic blockade with tetrodotoxin did not induce the central changes (Wall *et al.*, 1982). We then examined the central role of unmyelinated fibers in forming receptive fields and inhibitions. For this, we used both neonatal capsaicin to destroy most unmyelinated afferents and single adult nerve capsaicin to disable C fibers in single nerves. The results summarized in Wall *et al.* (1982) show that the C fibers maintain a chronic control of somatotopic organization both in the spinal cord and in the trigeminal system. Since the most precise somatotopic organization known is that of the whisker afferents in the mouse, we examined the effect of capsaicin both neonatally and applied only to the infraorbital nerve of the adult and found that both these treatments defocused the normally exact barrel fields in mouse cortex (Nussbaumer and Wall, 1985). This initial body of work has led to an industry in which the molecular components of the changes have been identified by many groups. The changes proceed for at least 30 days after the initial lesion. Some, such as the late central sprouting of the neighbors of lesioned afferents, are so delayed that they do not seem to play a role in the sensory changes associated with deafferentation.

Fast Plasticity of Connections

For many people, the only way in which connectivity in the nervous system could plausibly change would be by the anatomical growth of new connections. In the examples previously given, I had repeatedly failed to find evidence for new anatomical connections and therefore favored the idea that physiological changes could unmask ineffective synapses (Wall, 1977). However, the suspicion remained that some microscopic anatomical shift of synapses was occurring beyond the resolution of our detection methods. I therefore returned to examine a shift of excitability first observed by Mendell and called by him 'wind up.' We had observed that repetitive stimulation of unmyelinated afferents resulted in a slow, prolonged buildup of the excitability of dorsal horn cells (Mendell and Wall, 1965). Furthermore, we had observed large shifts of receptive fields in dorsal column nuclei that occurred within seconds after deafferentation and that were exaggerated in chronic states (Dostrovsky *et al.*, 1976; McMahon and Wall, 1983). Fortunately, Clifford Woolf set about investigating the long-lasting hyperexcitability of cord cells that follows the arrival of volleys of impulses in unmyelinated afferents. He developed a rugged preparation in which large increases of excitability were apparent in seconds with a duration of hours. I joined him in some of the early exploration of this phenomenon in which we found that C fibers of muscle origin were far more effective than skin fibers (Woolf and Wall, 1986) and that there was a preemptive effect of narcotics. Most striking, we showed that a brief input from C fibers would not only grossly expand the receptive

fields of lamina 1 cells but also shift a nociceptive specific cell to one which responded to light touch (Cook *et al.*, 1987). The work of Woolf's group has extended to define the chemistry of the synaptic changes associated with hyperexcitability. The clinical implications provide an understanding of the ongoing pain and tenderness associated with tissue injury and inflammation.

These studies open the way to a new field of analgesic pharmacology. In terms of the old story of specific pain afferents, it sounds the death knell for specificity theory in favor of a plastic mechanism that can shift from one state to another.

Applications

It might be said that I followed the advice of C. Judson Herrick, who said, 'To succeed in science, choose a subject no one else is working on, write a book about it, and start a journal.' He chose to examine the brain of the tiger salamander, wrote wonderfully on it, and started *The Journal of Comparative Neurology*. The plan needs careful thought. To advise a contemporary young scientist to find a topic 'no one else is working on' is an invitation to scientific suicide. We live with an intellectual, financial, and political establishment that has published plans and routes to achieve the required answers. If you are unwise enough to follow your intellectual curiosity and submit a grant application or manuscript outside 'the plan,' it is returned to you by the person who opens the mail in the office. It is true that I switched research topics four times in favor of neglected subjects and then left them when the area became so crowded that I was redundant. I did not choose the new fields simply because they were empty but took two precautions.

The first was to follow my socialist thinking and to opt for fields with social relevance. I realize how unfashionable this has become in a post-Reagan–Thatcher era in which they proclaimed that society had been replaced by free individuals seeking self-interest. Their idea is not new since Rousseau said, 'We no longer have a citizen among us.' Using my shift to a study of pain mechanisms as an example, I realized more than 50 years ago when I first began as a medical student to see patients in pain that the explanations given to them and to me by my teachers were overt rubbish. The fantasy explanations often depended on mechanical disorders for which there was no evidence, such as trapped nerves, extra ribs, strained muscles, or floating kidneys. If those failed to convince even the doctors, there was a leap to using as an explanation the supposed inadequate personalities of the patients: neurosis, hypochondria, hysteria, and malingering. Pain was not a busy field of study because the establishment was entirely satisfied with the classical specificity theory of pain fibers, tracts, and a pain center despite its complete sterility in explaining pains

or in helping patients in pain. I was happy to challenge and later mock the establishment because I counted on the support of real people beyond the authorities of the day. Those hidden allies turned out to be crucial.

The second precaution was not to leap into a new field but to explore quietly over long periods. That involved stealing time from funded projects. Many of these pilot experiments were simply wrong. Some, such as the production of small brain lesions with ultrasound (Wall and Horwitz, 1951), I took on and quickly left to others. Even the failures were educational, but some of these 'muck-about' evening and weekend experiments eventually led to substantial results. I am sorry that the days of these quasi-random scouting expeditions are almost finished in this current period of high-pressure, efficient planning. On grant committees, I have too often seen applications summarily dismissed as 'fishing expeditions.' I shudder in sympathy for the research team when I walk into a chief's office and see a giant squared plan on the wall with everyone's research schedule for the year. I fantasize that somewhere among the gleaming laboratories there is a secret room in which they are just mucking about. My fantasy evaporates when I listen in to private conversations at international conferences at which the topic is either minutiae or house mortgages.

Finally, socialism has affected my research in a more fundamental way. There is no doubt that reductionism dominates scientific research today for good reason. Physics is reductionist, hugely successful, and a model of the scientific method. A phenomenon can be reduced to a sequence of unique one-to-one events. The rare occurrence of indeterminacy does not weaken the power of reductionism. A reductionist physiology of pain would define the consequences of a unique set of nerve impulses arriving on a unique set of cells. A reductionist pharmacology would go further by defining the neurotransmitter and receptor molecules. An alternative to reductionism is dialectical materialism, which deals with the organization of populations and is not as formally advanced as reductionism. It is possible to give a reductionist analysis of how a football team scored a particular goal with defined players. It is not possible in reductionist terms to define the organization of the team that permits repeated goal scoring in the same terms as the analysis of one goal. An automatic pilot has inputs and outputs whose function can be and must be defined in reductionist terms. However, inside the box, the components achieve a goal by way of a distributed feedback and feedforward cybernetic control in which no one component has a uniquely definable action. I think of central neural circuits in this fashion and not as determinist chains with prescribable functions. The need for simplicity and a quick answer still means that the medical–industrial complex searches for a pain pathway made up of unique single links with amplification controls along the line (Wall, 2000). They will never achieve an explanation of how such a system falls

into stable pathological states, is immune to chemical and surgical lesions, oscillates spontaneously, shows a variable location of activity between individuals, and shows an ability to coordinate activity over long distances. That requires a distributed, widespread, interconnected population of cells with its own population abilities and deficiencies.

Since I wished to study systems and yet my research was necessarily limited to components, I thought it essential to study patients where one could observe and listen to disordered systems as a whole and could witness transitions from one state to another. I examined the action of the autonomic system above and below midthoracic spinal lesions, autonomic changes during frontal lobe surgery, amputees and peripheral nerve lesions, spinal cord injury, and the sensory effects of narcotics. Since itch and pain are so closely related, Greaves and I set up an itch clinic. Also, navicular disease in racehorses was shown to be a variety of human complex regional pain syndrome. Some of this led to publications; we examined the sensory state of a sample of all Israeli amputees after the Yom Kippur war (Carlen *et al.*, 1978), and the same men were examined 15 years later with depressingly similar results. Noordenbos and I examined the effect of excision and grafting following partial nerve section (Noordenbos and Wall, 1981). We followed the pain state of patients from immediately after injury for a day (Melzack *et al.*, 1982). After the discovery of endogenous opiates, we showed that opiate antagonists had no effect on normal subjects (El-Sobky *et al.*, 1976). Noordenbos and I examined the sensory effects of gross but partial spinal cord lesions (Wall and Noordenbos, 1978) and, in one case with three-fourths of the midthoracic cord cut, we reported on the sensory effects 1 week, 1 month, 1 year, and 15 years later (Danziger *et al.*, 1996). Recently, we examined the effect of capsaicin on kidney pain (Allan *et al.*, 1997). Practical results followed some of these studies. Sweet and I stimulated nerves to reduce pain with transcutaneous stimulation, with implanted stimulators, or with root stimulation (Wall and Sweet 1967). I took Yaksh's findings on the spinal effects of opiates to Magora in Jerusalem from which epidural morphine developed. We tried epidural medazolam on spastic spinal cord injury patients, intravenous xylocaine ameliorated postherpetic neuralgia, and I proposed preemptive analgesia (Wall, 1988) which works well in rats but not in humans.

It was time to try to pay back society for the privilege of support for years of research. Inspired by Kuffler, who was sad that neuroscientists in different nearby departments and universities did not speak to each other, I collected some money and, on my return to London, set up the Brain Research Association with the help of Rose, Evans, and Cragg. Determined to overcome the built-in inhibition of university buildings, we met regularly in the upstairs rooms in pubs. In 1968, Ed Perl and Louise Marshall were visiting London and I invited them to attend a meeting. Enchanted

by the informality and lively discussion, they returned to the United States and played a role in the birth of the North American Society for Neuroscience. In Britain, the idea spread to many cities and evolved into the British Neuroscience Association. Bonica, who had developed the concept of chronic pain and that of the pain clinic, was anxious to form an international organization to spread the word about advances in therapy and knowledge about pain. The International Association for the Study of Pain was formed. This gave the opportunity to start the journal *Pain* in 1975, which I edited for the next 25 years. It flourishes. In 1982, there was no comprehensive textbook on pain, and I approached Churchill-Livingstone with the proposal that they should publish one edited by Melzack and myself. It is an interesting sign of the times that their advisers turned down the idea on the grounds that pain was not a subject. I persisted, and the first edition was published in 1984. It succeeded because pain has become a respectable academic and clinical subject that moves rapidly so that four editions had been published by 1999. The expansion of study and the rationalization of therapy have been admirable, even though there are those inevitable rascals in the medical–industrial complex who discovered a new source of money to be mined in the old ignorance. I have done what I could to encourage those who are driving forward the advances of both research and therapy. The new thrusts are led by the anesthetists, but one should particularly applaud the new self-critical attitude of psychologists and physiotherapists. The focus of all research is the people who suffer and their companions. They begin to organize and all of them yearn for knowledge, understanding, comfort, and comradeship.

I have been enthralled by my progress of good luck and discovery, and my only regret has been the tedious dullness of the opposition.

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