BIOGRAPHICAL MEMOIRS

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Geoffrey Raisman

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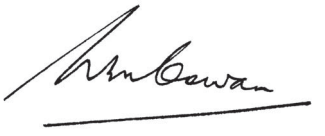

WILLIAM MAXWELL COWAN

27 September 1931 — 30 June 2002

Elected FRS 1982

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William Maxwell Cowan ('Max') was born in 1931 in Johannesburg. His father was a former Glasgow shipyard engineer driven by the imminent closure of the Clyde shipyards to seek employment in the mining industry in South Africa. Max's parents had intended him to be a real-estate lawyer. However, after taking the initial courses in languages, economics and history at Witwatersrand University, a short vacation work period as a trainee nurse in a psychiatric hospital had aroused what was to be his lifelong interest in the workings of the brain. Max decided he wanted to transfer to medical school.

During his preclinical training at Witwatersrand University Max had the good fortune to meet a number of interesting, stimulating and brilliant people, perhaps the most eminent being the future Nobel Prize winner, Sydney Brenner (FRS 1965), with whom Max formed an enduring friendship. Through the enthusiastic neurophysiology teaching of Michael Wright, Max conceived the ambition to take a year out of the medical course to study for a BSc in the anatomy of the nervous system. He would probably not have realized it then, but his life's course was now set.

The Oxford years

Professor Raymond Dart, the head of the Anatomy Department in Johannesburg, was also a noted anthropologist, responsible for the concept of the australopithecine human ancestor, the first fossil evidence of the long-sought 'missing link' between apes and humans. This interest was shared with Sir Wilfrid Le Gros Clark FRS, head of the Department of Human Anatomy in Oxford. In 1953 Le Gros Clark had asked Dart whether he had a promising young man to recommend for a junior faculty position in neuroanatomy in Oxford. Michael Wright would have been the obvious choice, but for reasons Max never knew, Dart recommended Max, who

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now left South Africa to join Le Gros Clark's department in Oxford. The first stage in Max's wanderings had begun.

In the Department of Human Anatomy at that time, Le Gros Clark was examining the brain of a patient who had died 24 days after having most of the cerebral cortex removed on one side. It had long been known that the cortex was divided into many specialized regions, each with a distinctive tissue architecture, and each with a different function—vision, hearing, speech, and so on. Le Gros Clark was interested in finding how the nerve fibres carrying these different messages were sorted out so as to reach these different areas of the cortex. This required pinpointing the location of the different groups of nerve cells ('neurons') that sent their fibres to the various cortical areas. Overall, these cells were known to be grouped into an intermediate relay station called the thalamus. So the aim of the investigation was to find how the different cell groups making up the thalamus were mapped onto the surface of the cerebral cortex.

After removal of parts of the cortex, the thalamic nerve cells that give rise to the nerve fibres ('axons') projecting to the lost cortical areas die. This response was known as 'retrograde degeneration' (because it goes in the opposite direction to the nerve impulses that originate at the cell body and pass down the nerve fibre). By comparison with the normal, unoperated side of the brain, the histological analysis of the pattern of loss of neurons in the thalamus on the damaged side of the brain would identify which nerve cells had fibres projecting to the cortex, and thus a map of the origin and termination of the thalamo-cortical projections could be constructed. Le Gros Clark had entrusted this analysis to Tom Powell (FRS 1978), a former trainee neurosurgeon, and after Max had arrived in Oxford, Le Gros Clark asked him to join the project. Thus began the highly productive working relationship of the Cowan–Powell team that lasted 13 years, until Max left Oxford.

The first major observation to come from the study of retrograde degeneration was the unexpected finding that a group of neurons lying in the midline of the thalamus and in the laminae of tissue between the major thalamic cell groupings showed few or no degenerative changes after the cortical removal (1)*. The research performed by Cowan and Powell now showed that this was because the major fibre projection from the midline and intralaminar thalamic neurons was to the striatum, a part of the brain that had remained intact when the cortex was removed. The characterization of the thalamo-striate system was due largely to this work and was supported by parallel studies in primates (4), and also in the avian thalamus (5), which was particularly suited to this investigation because the major part of the forebrain in birds consists of striatum rather than cortex.

The problem of understanding how the wiring connections of the brain were organized was rather like trying to unravel an extraordinarily complicated haystack. By simply staining nerve fibres in normal material, the complex courses, and the interweaving and branching of long and short fibre pathways, made it impossible to say which was connecting—or as neuroanatomists like to say, projecting—to which. Experimental methods were needed to 'label' individual fibre pathways so that their origin, their course through the brain, and their final destination could be traced.

Le Gros Clark had been one of the major champions of the need for experimental methods to trace fibre connections. At the time when Max arrived in Oxford, the mapping of patterns of retrograde degeneration after injury had long been the main experimental technique for tracing

* Numbers in this form refer to the bibliography at the end of the text.

fibre pathways. There were as yet few reliable techniques for tracing fibres in the 'orthograde' direction (so named because it was the direction taken by the impulses originating in the nerve-cell body and travelling away from the nerve-cell body and down the nerve fibres). Like the retrograde tracing technique, the earliest orthograde tracing techniques were also based on making localized areas of damage ('lesions') that destroyed the nerve cells giving rise to specific projections. The destruction of the body of the nerve cell was followed by the break-up of the nerve fibre that originated from it. By tracing the trail of degenerating axonal debris leading from the area of damage it was possible to map the pathway.

Some of the first and ill-fated investigations in which Le Gros Clark experimented with the orthograde degeneration technique were based on the Glees technique, an attempt to use silver staining to identify degenerating axons and their terminals. It had long been known that the nerve cells of the cerebral cortex send fibres down to the parts of the brain and spinal cord concerned with the control of movement. However, in addition there was an idea that the cerebral cortex also had a direct influence on the hypothalamus, the part of the brain concerned with the control of the unconscious, visceral and endocrine functions of the body. In collaboration with Paul Glees and Margaret Meyer, Le Gros Clark had reported orthograde degeneration in the hypothalamus after damage to the cerebral cortex. This would imply that there was a direct connection from the cortex to the hypothalamus.

Unfortunately it was to turn out that these observations were based on a staining artefact. With the caution that characterizes great scientists, Le Gros Clark encouraged Max and Tom Powell to look again at the same material. Their suspicions were aroused when they found that there was no relationship between the extent of the cortical lesions and the distribution of the degeneration. Then, when examining sections from a control brain with no damage to the cortex, they found that the hypothalamus presented the same appearance (3). Le Gros Clark at once withdrew the incorrect conclusion. This example of scientific integrity made a deep impression on Max, who never forgot the limitations and frustrations of these early attempts at orthograde axon labelling. Over the years to come, Max and his students were to develop ever more sophisticated methods of both retrograde and orthograde labelling of pathways.

In the mid 1950s an important advance in the study of fibre connections was provided by Walle Nauta's development of a much improved orthograde degeneration technique (Nauta 1954). This was based on the photographic principle of selective reduction of a carefully adjusted silver nitrate solution, which resulted in the deposition of a microscopically accurate metallic silver image of the degenerating nerve fibre particles on the tissue sections. The technique was extremely delicate to use, and capricious. It depended on modifying the affinity of the silver ions in solution by complexing them with the charged nitrogen of aromatic molecules such as pyridine or collidine so as to make the fine distinction between the chemical composition of normal nerve fibres and that of the fragments of nerve fibres undergoing degeneration as a result of the lesion.

Max was keen to explore the potential of the new Nauta silver staining technique. With Tom Powell he used this to show that the avian retina received a 'centrifugal' input from a group of cells in the brain, the isthmo-optic nucleus (10). Later, in collaboration with John Dowling in Baltimore, Max showed with the electron microscope that these centrifugal fibres terminated on a specialized cell type in the retina, the amacrine cells (11). The existence of fibre projections from the brain to the sense organs was an important anatomical confirmation of the fact that sensations are not objectively determined by the sensory inputs from the environment, but that the performance of the sense organs is also controlled by signals originating

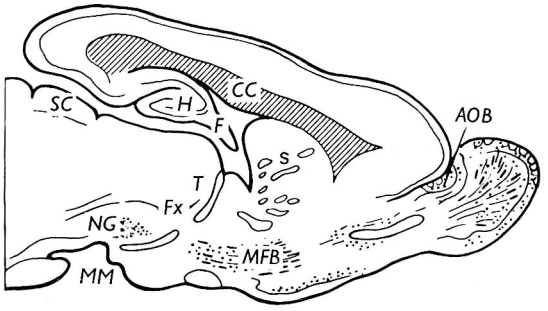

Figure 1. An example of the kind of drawings using a template based on hand-traced outlines of the main brain areas to illustrate the patterns of axonal degeneration caused by a lesion of the olfactory bulb (OB). AOB, accessory olfactory bulb; CC, corpus callosum; F, fimbria; Fx, fornix; H, hippocampus; MFB, medial forebrain bundle; MM, medial mamillary nucleus; NG, nuclei gemini; S, striatum; SC, superior colliculus; T, thalamus. Modified from Fig. 7 in (7).

in the brain and running outwards, in this case to the retina, to set a level of subjective bias on how visual inputs are dealt with.

After two years' research and teaching in anatomy, Max entered the clinical course at the Radcliffe Infirmary in Oxford. Max said he agreed to do this only because his parents had told Le Gros Clark that they had always hoped their son would become a 'real' doctor. So now, at the same time as conducting and publishing his neuroanatomical researches, and carrying a full teaching load of preclinical students, Max completed his own clinical course studies in Oxford qualifying in medicine (BM, BCh) in 1958, a career he was not to take up.

This was the time when I started as a preclinical medical student. My first encounter with Max was in his capacity as tutor in anatomy at Pembroke College. The work load of those days was extraordinary. In addition to the one-to-one tutoring of students in gross anatomy, histology and embryology, Max also taught for several days in the dissection room. In addition, out of financial necessity, he also took on students from several other colleges, who paid him piecemeal by the hour, like a wage slave. And yet, in our tutorials, either sitting knee to knee in the cramped space of the tiny student library at Osler House or walking round the lush water meadows in summer sunshine where the University Parks came down to the river Cherwell, Max never lost his enthusiasm for teaching, and had all the time in the world for his student, and for explaining his excitement at the attempt to unravel the mysteries of the connections of the brain (figure 1).

For me all of this was a magical experience. After my first degree, and before proceeding to the clinical course, I was thrilled to be invited to become Max's first PhD student (his only one in Oxford). After Le Gros Clark's studies of the thalamic connections of the cortex, there remained one cortical region that was still mysterious—the hippocampus—and my assignment was to use the Nauta technique to study the pattern of its fibre connections (9).

The hippocampus is, from an evolutionary point of view, the oldest part of the cortex. During evolution the cortical surface of the brain becomes ever larger and more convoluted, and as a result the hippocampus comes to lie hidden under the lower edge of the expanded cortical mantle. The nerve fibres originating from the cells of the hippocampus project to several areas, including the septum and the mamillary bodies, which in turn project to a special group of nuclei in the anterior part of the thalamus, and these in turn project to the most medial (cingulate) strip of the cortex. Whereas other cortical areas receive their fibre input from the

thalamus, the hippocampus receives its input not from the thalamus but from the adjacent entorhinal cortex.

The whole arrangement of the hippocampal connections was quite unlike any other cortical area, and at that time clinical observations of Korsakow's syndrome (confabulation associated with mamillary body degeneration in chronic alcoholism) and loss of recent memory (in patient H.M., in whom both hippocampi had been removed to control epilepsy) were providing the first indications of the crucial role of the hippocampus in memory.

One of the puzzling observations coming from the retrograde degeneration method for tracing connections came from experiments in which the fimbria (the fibre pathway running between the hippocampus and the septum) was cut. In work with Powell, H. M. Daitz, a South African student who had also come to Oxford from Johannesburg a few years before Max (and who died tragically young), had used the retrograde degeneration method to show that although the hippocampus was known to send fibres through the fimbria to the septum, the hippocampal nerve cells showed no retrograde degenerative changes when the fimbria was cut (Daitz & Powell 1954). This was attributed to the presence of 'sustaining' collateral branches that were emitted before the fibres entered the fimbria and were therefore spared. In contrast, a quite unexpected observation was that nerve cells in the septum underwent severe shrinkage (6). This was the first demonstration that there was a fibre projection in the reverse direction—in other words, not only did the hippocampus project to the septum, but the septum sent a hitherto undiscovered reciprocal projection back to the hippocampus (8).

The early 1960s saw important new technical developments for the fixation of nervous tissue by the use of glutaraldehyde perfusion and osmium tetroxide postfixation, new polymerized resins for embedding, and the development of ultramicrotomes with glass and diamond knives. The introduction of stains based on heavy metals such as lead and uranium afforded such fine preservation of histological structure that brain tissue could now be studied at the magnifications achieved under the 80 kV or 100 kV beam in the vacuum tube of the electron microscope. Electron microscopy permitted an increase in magnification of a thousandfold over the most powerful light-microscope lenses. In the study of nervous connections, the existence of synapses, the minute gaps between nerve cells, had long been predicted from electrophysiological and other studies. This was crucial to the theory that the brain was made up of a network of individual cells called neurons (the 'Neuron Theory'). Now, in a pioneering study taking advantage of the new, millionfold magnification of the electron microscope, Palay (1958) was able to demonstrate the physical existence of the synaptic cleft, the discontinuity that occurs at the point where nerve fibres make synaptic connections with their neuronal targets.

Max was fascinated by the possibilities of this new technology to reveal new levels of precision of neural connections, and it soon became apparent that, when observed at the electron microscopic level of magnification, orthograde degeneration techniques could be used to identify the synaptic terminals of severed nerve fibres with a degree of precision hitherto unobtainable. Max gave me every encouragement to adopt this new technology.

However, things were changing at the Department of Human Anatomy in Oxford. After the retirement of Le Gros Clark, the new head of department was Geoffrey Harris FRS, and the departmental focus, and its resources, shifted to neuroendocrinology. This marked a crucial turning point in Max's career, and in 1965 he took a year's sabbatical leave in the Department of Anatomy at Washington University Medical School in St Louis, Missouri. During his absence I pressed ahead with applying electron microscopy to the hippocampo-septal

projection that I had previously been studying with the Nauta technique during my PhD work with Max. It struck me that the use of the electron microscopic degeneration approach yielded data of an essentially digital nature: synapses could be counted and divided into degenerating and non-degenerating. The characterization of the pathways could become quantitative.

On Max's brief return to Oxford in 1966–67 I discussed my data with him, and particularly the curious postsynaptic specializations ('vacated thickenings') that remained in the septum after it had been deprived of its fibre input from the hippocampus. A suggestion from Max (which had occurred to him while examining the PhD thesis of Les Westrum) led to the totally heretical speculation that perhaps, after injury, new connections might re-form spontaneously in the adult brain. Later, I was to develop this idea, which I referred to as plasticity (Raisman 1969), and it has led me to a very fulfilling lifetime study of how to turn this information to advantage in developing a method for repairing human brain and spinal cord injuries. Looking forward in our story to an occasion many years later, I mentioned to Max, my old mentor, that I hoped one day he would be proud of me. I was referring to the hope of discovering a method for helping patients with these injuries. Alas, things have not yet reached that point, and if they do, it will be a great regret that I cannot see the hoped-for approval of someone who played such a large part in my life.

The sabbatical year of 1965 that Max spent at Washington University was the beginning of the end of his work in Oxford. Pembroke College tried to retain him: 'If you stay you can have a mediaeval room in college', he was told. 'Yes,' he retorted, 'but in America I can have my own electron microscope.' Max had never really fitted into the self-admiring, donnish Oxford of those times. He never lost sight of the real world beyond the ivied quadrangles, the bitter struggles of his working-class parents, and the terrible conditions of the African blacks under the apartheid system. 'I swore', he said, 'I would never go back to South Africa while that system continued.'

So Max did not succumb, as did his equally working-class colleague, Tom Powell, to the seductions of being admitted into that begowned and privileged elite who enjoyed the traditional college life of Oxford. He liked to quote a book called *These ruins are inhabited* by an American sabbatical visitor in Oxford. When, after a long and somewhat agonized discussion, a slender majority of the conclave of the Pembroke governing body (colleges were then unisexual) came to the decision that wives might be granted the occasional privilege of attending a festive dinner at high table, Max capped the debate by saying, 'How do you know that the wives would want to attend?' And when I announced my intention to break the college rules about scholars and get married, it was only Max's forceful support for me that prevented the governing body from voting to expel me. Later he commented, 'Those guys were very bright. But lazy.' Like Aesop's fox and the grapes, Max always showed great facility in rationalizing his decisions.

Max was neglectful of things that did not relate to his science. He had an old car in Oxford, and he was proud to tell me that it had never been washed. More surprisingly, for a neuroanatomist who was utterly at home in the intricacies of brain networks in many different species, I discovered that after more than 10 years in Oxford, he did not know his way about the streets even close to his home.

Max returned from Washington University to Oxford for a year, and then, after two years at the University of Wisconsin in Madison, was invited back to Washington University to become Chairman of Anatomy, a post he held from 1968 to 1980 when he moved to the Salk Institute, San Diego, California, where he became Vice President in 1982. In 1986 he returned

to Washington University as Provost, but finding that the administrative aspects of this position prevented him from concentrating on neuroscience, in 1988 he accepted the position of Vice President and Chief Scientific Officer of the Howard Hughes Medical Institute, in which role he continued for 13 years until his retirement in 2001.

Madison and St Louis

With Max's move from Oxford to the USA he emerged from the shadow of Le Gros Clark and his association with Tom Powell. Max had seen the exciting advances in knowledge that followed each advance in practical techniques for studying neuronal connections, and the development of new neuroanatomical techniques would be something of a *leitmotif* for the rest of his research life. Always aware of the limitations of the degeneration techniques, Max was one of the first to espouse the newly found method of introducing into the brain tracer substances to be carried along intact nerve fibres to distant destinations in both orthograde and retrograde directions (14).

From now he started to accumulate around him, and to train, a quite stellar group of young researchers, who contributed to the landmark publications establishing the definitive methodology for using radioactive amino acids or non-radioactive substances as orthograde tracers, and enzymes such as horseradish peroxidase and multiple fluorescent coloured dyes as retrograde tracers. Another of Max's achievements at Washington University was the recruitment of Richard and Mary Bunge. This brought tissue culture into the department, and Gary Banker was later to develop a tissue-culture method for growing isolated hippocampal neurons (21) and making some of the seminal discoveries on how axons and dendrites are formed.

One of the problems of using degeneration techniques for orthograde tracing of nervous connections was that although it gave a clear picture of the termination of a fibre projection, it was less effective at demonstrating its exact origin. This was because lesions not only destroy the nerve cells of a particular region of the brain, they also destroy nerve fibres passing through that region but arising from nerve cells located in other parts of the brain that had not themselves been directly damaged. Max called this the 'fibres of passage problem'. It was to turn out that some of the conclusions from my own work with Max on the origin of the hippocampal projection to the mamillary bodies had been affected by this problem.

During the early 1960s it was becoming understood that not only do nerve fibres convey impulses from one nerve cell to another, but they also contain cytoplasm ('axoplasm') and have an active bi-directional transport system that conveys material both in the orthograde direction (that is, from the cell body down the axon to the nerve terminals) and in the retrograde direction (from the terminals up along the axon to the parent cell body). Bernice Grafstein (Grafstein 1971) and others had shown that the proteins formed in the cell body can be labelled by uptake of radioactively labelled amino acids, and their orthograde progress down the axons can be followed by autoradiography of histological sections.

With Anita Hendrickson (17) and his newly recruited consortium of students Max was involved in studies showing that after the deposition of small amounts of radioactive amino acids localized to specific cell groups in the brain, autoradiographic tracing of labelled molecules introduced into the axoplasmic flow could be used for tracing axonal projections. The slides carrying the histological sections were dipped in photographic emulsion, and the 'signal' to detect the presence of the radioactive molecules was the deposition of silver grains in

the irradiated emulsion. This lent itself to digital counting techniques, and Max was among the first neuroanatomists to exploit the potential of computerized analytical techniques to provide an objective quantitative assessment of neuroanatomical data (18), avoiding the subjective element that had always plagued earlier neuroanatomical studies.

One of the findings that Larry Swanson, one of his first graduate students in America, and Max drew from the autoradiographic method was that the degeneration I had seen in the mamillary bodies after lesions of the hippocampus was actually a casualty of the 'fibres of passage' problem (19). The degeneration was not due to damage to fibres arising in the hippocampus proper, but to damage to fibres that arose from nerve cells lying behind the hippocampus in the subiculum. The hippocampal lesions I had used to produce the degeneration had damaged these subicular fibres as they passed forwards over the hippocampus.

Another interesting observation to arise from the improved orthograde tracing techniques was the description of the retinal projection to the suprachiasmatic nuclei (17), which provided the basis for understanding how the diurnal variations in the timing of environmental light are fed into the central generator of circadian rhythm. Shortly afterwards, Bernice Grafstein made the seminal observation that some of the transported radioactive label was released at the synapses and taken up 'transneuronally' by the next neurons in the chain. LeVay, Hubel and Wiesel (LeVay *et al*. 1980) took advantage of this to map the ocular dominance columns in the visual cortex, a study that was a significant component of the Nobel Prize-winning work of Hubel and Wiesel.

Encouraged by the success of the new non-degenerative techniques for orthograde tracing, Max now turned his attention to developing a retrograde tracing method that similarly would not require lesions to be made. It had been a major disadvantage inherent in the use of retrograde degeneration for fibre tracing that it depended on the cells of origin of a pathway degenerating after a lesion of the region in which the nerve fibres terminated. The problem was exemplified by Cowan and Powell's earlier study of the thalamo-striate system (12). Whereas retrograde degeneration had identified the midline and intralaminar thalamic nuclei as the location of neurons projecting to the striatum, it had failed to reveal that there was also a projection from the neurons of the same thalamic nuclei to the cerebral cortex. Although the main destination of the nerve fibres arising from the thalamic nuclei was indeed the striatum, the thalamo-striate fibres also had a minor projection to the cortex. After cortical lesions that left the striatum intact, the retrograde degenerative changes in the thalamus had been too slight because the thalamic neurons had been sustained by their much larger intact projections to the striatum (figure 2).

As with the use of axoplasmic flow for orthograde tracing, the new retrograde tracing method was based on the fact that axonal components are also transported in both the retrograde and orthograde directions. A tracer substance was applied to the region in which nerve fibres terminated and was carried backwards by retrograde axonal transport to label the cells of origin of the pathway. Retrograde tracing had already been clearly demonstrated in a Swedish study of motoneurons whose cell bodies lie in the spinal cord and project through peripheral nerves to muscles in distant positions in the limbs. Max encouraged Jennifer LaVail (LaVail & LaVail 1972) to develop the use of the retrograde tracer horseradish peroxidase, which was to become one of the founder substances for the most robust and widely used methods for retrograde tracing in the central nervous system.

Later, while at the Salk Institute, Max continued his interest in developing improved neuroanatomical tracing technology. One drawback of the radioactive orthograde tracing technique

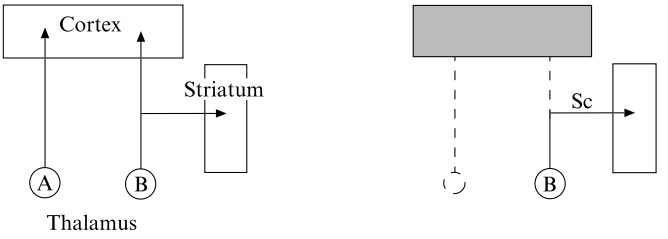

Figure 2. Sustaining collaterals. Two thalamic neurons, A and B, project to the cortex. However, B also has a collateral branch to the striatum. When the cortex is destroyed, A degenerates and dies, but B is sustained by its collateral (Sc) and survives. This simple anatomical observation seeded a train of ideas that wound through Max's life. That the survival of nerve cells is dependent on something produced by their targets would lead to the concept of nerve growth factors and the idea that the circuitry of the nervous system is not fixed genetically, but is moulded by external influences, adapting it to the environmental conditions of the individual.

was that, as a result of the scatter of radioactive particles from even a low-energy emitter such as tritium, the distribution of silver grains gave only a poor picture of the morphology and branching of individual nerve fibres and made it difficult to identify individual synaptic terminals. C. R. Gerfen and P. E. Sawchenko, in Max's division at the Salk Institute, showed that a non-radioactive lectin tracer derived from *Phaseolus* agglutinin could be applied by ionophoresis with pinpoint precision and gave an accurate picture of an entire nerve fibre, with all its branches and presynaptic terminals (Gerfen & Sawchenko 1985).

Max also continued to encourage work with new retrograde tracers. Whereas existing tracers, such as horseradish peroxidase, could be used to label single-axon pathways, they could not distinguish whether individual nerve cells sent branches to two different regions, or whether there were two types of adjacent nerve cell, one projecting to one region, and one to the other. In Rotterdam, Hans Kuypers and his colleagues had demonstrated (Kuypers *et al*. 1980) that several molecules that fluoresced at different wavelengths under ultraviolet radiation could be used as tracers that were transported retrogradely from the terminal regions of axons back to the cells of origin, where they persisted for long periods. By applying a retrograde tracer of one colour ('Nuclear Yellow') to one terminal area and a second tracer of another colour ('True Blue') to the other terminal area, individual cells could be doubly labelled. Double labelling of an individual cell would indicate that the two projections did not arise from different neurons but that fibres arising from the same neuron divided and gave divergent branches that projected to both terminal zones (22). One benefit of this sort of information was that it could demonstrate the presence of 'sustaining' collaterals whose unrecognized existence had been the reason for some of the puzzling results of retrograde degeneration studies. Max and his colleagues now applied this new experimental tool to a study of the competitive and pruning processes that occur during the normal development of neuronal connections.

Max's persistence in encouraging the development and application of tracing techniques contributed significantly to establishing what are still the valid standards of accuracy and reliability. Max himself later came to disparage somewhat the use of these approaches simply as a way to work out the patterns of neuronal connections in the brain—something he wryly described, by analogy with the diagrams popular in neuroanatomy textbooks, as the 'black arrow school of neuroanatomy'. Max foresaw that accurate tracing techniques would open the way to discovering how neuronal connections developed in the embryo, and how genetic and environmental factors interacted in determining the final pattern of connections in any individual.

Development of the nervous system

Throughout his career Max had a voracious appetite for neuroscience and an unerring instinct for identifying, and interacting with, the cutting edge research that would provide the conceptual advances into the future. While at Washington University Medical School in St Louis, Max became fascinated by the work of Viktor Hamburger and Rita Levi-Montalcini (ForMemRS 1995) (Hamburger & Levi-Montalcini 1949), the later Nobel Prize winner, co-discoverers of the first nerve growth factor.

Since the nineteenth century, the basic tenet of the Neuron Theory was that the nervous system consists of immense numbers of separate, independent nerve cells that send impulses down their fibres and signal to each other across the synaptic gaps. One of the pieces of evidence on which this theory was based was that when a nerve cell is damaged it degenerates, but the adjacent nerve cells remain intact, thus proving that the synapse is a barrier to degeneration and that individual neurons are independently viable cellular entities. Two of the observations from Max's own research experience did not fit into this simple pattern.

The first was that degeneration occurred where the Neuron Theory would not have predicted it to occur. Thus, it was known that the mamillary bodies send fibres to the anterior thalamus, and that the anterior thalamus sends fibres to the cingulate cortex. When the cingulate cortex is damaged, the anterior thalamic nerve cells degenerate. This fits with the Neuron Theory: the cells are dying because their fibres have been cut, leading to retrograde cell degeneration. However, what Max and Tom Powell had found is that the cells in the mamillary nuclei also degenerate, even though they have not been directly damaged (2). The degeneration had crossed the synapse from the damaged nerve cell to the undamaged nerve cell with which it was in synaptic contact—retrograde transneuronal degeneration. Later, with Jennifer Hart (later LaVail), Max confirmed von Gudden's nineteenth-century report (von Gudden 1870) that degeneration passed even one more synapse back, to the ventral tegmental nucleus.

The second discrepant observation was that degeneration did not occur in situations in which the Neuron Theory would have predicted it ought to occur. Thus, when the fibres projecting from the septal neurons to the hippocampus were cut, the septal cells of origin degenerated (as would be predicted by the Neuron Theory), but when fibres from the hippocampal neurons to the septum were cut, the hippocampal cells of origin did not degenerate. It was assumed that the presence of surviving collateral branches had somehow spared the cells from degeneration. Max later confirmed this sustaining effect of collaterals in work with F. J. Fry on the mamillothalamic and mamillotegmental tracts (15).

Hamburger and Levi-Montalcini's concept that neuronal survival and development was regulated by growth, or 'trophic', factors offered a key to understanding the mechanism of these discrepancies. The observations could be explained if the communication between nerve cells involved not only the transmission of impulses but also the transmission of trophic, or survival, factors. If the survival of a nerve cell depended on the availability of a protein produced by another nerve cell (or by other targets, such as muscle or gland cells) with which it was in synaptic contact, this would explain how degeneration could cross a synapse, because the loss of one neuron in a chain could deprive the next neuron in the chain from access to the growth factors needed for its survival. It could also explain how surviving collaterals, by maintaining access to growth factors, could save a cell from degeneration.

Viktor Hamburger recommended his student Eleanor Wenger to work with Max on demonstrating the role of trophic factors in development. Working with chick embryos, Cowan

and Wenger demonstrated retrograde cell degeneration in the developing visual system when the targets of the neurons of the trochlear nucleus, the ciliary ganglion, and the isthmo-optic nucleus were removed, thus demonstrating that the principle of trophic dependence on target-derived factors applied during development (13).

A study by G. M. Innocenti had shown that the development of the adult pattern of fibre connections also proceeds via the formation of a larger than normal number of 'exuberant' fibre projections, which are subsequently pruned down to the final mature adult pattern (Innocenti 1981). Max and his co-workers confirmed the occurrence of pruning of collaterals during development (20). Using quantitative autoradiography in the dentate gyrus, they also showed that one reason for this pruning was competition by the developing nerve fibres for a limited quantity of growth factors in the terminal areas (16), so that survival of a fibre projection depended on a temporal, first-come-first-served basis. Such observations were laying down some of the most fundamental principles behind our present understanding of how the complex pattern of connections of the adult nervous system is put together.

Whereas both adult and—even more so—embryonic nerve cells and fibres degenerate when damaged, during normal development there is a major loss of nerve cells and nerve fibres that is not a result of damage (23). The picture emerged of a developing nervous system in which there is both an initial excess of neurons and also a premature exuberance of axonal connections, which are later pruned by developmental events to give the adult pattern. The widespread occurrence of cell death and axonal pruning is a very important principle: sculpting the adult nervous system from a larger model has an adaptive value. Work in Max's department at the Salk Institute with James Fawcett, Dennis O'Leary and others showed that these refinements of connections in the nervous system can be driven and modified by impulse activity (24). This links the remodelling of connections with the patterns of stimuli specific to the environment in which an individual finds itself.

In retrospect we can see that this work also provided the germ of an idea that would challenge one of the most entrenched concepts of the nervous system: they showed that the brain does not consist of a predetermined and stable network of interconnected elements, but depends on continuous maintenance. The brain was beginning to be seen not as a glorified telephone exchange but as a living, modifiable structure.

Molecular biology and Howard Hughes

Apart from the impetus to his research made possible by the greater human and material resources available to him in the USA, Max's transatlantic move heralded a major change in his lifestyle and his method of working. In Oxford, Max had carried a very heavy load of first-hand teaching in gross anatomy (what he called 'kitchen anatomy'), histology, embryology and neuroanatomy, as well as being involved at bench level in all aspects of his research. Although in practical terms he and those working with him were perhaps more relaxed when he left delicate histological operations to others, the realms of photography and microscopy he made his own. 'Dust', he liked to say, 'is the enemy of photography.' However, now the extent of Max's increasing administrative and editorial roles made it difficult for him to find time for personal involvement in research. More and more he became confined to an advisory role in recruiting, planning, discussing results, and writing up. 'I miss that close family atmosphere of the laboratory', he once told me.

At the same time, however, he was increasingly in a position to indulge his lifelong fascination in what one might call the wheels of history. His venue now was increasingly the boardroom and the corridors of power. The student walk in the water meadows of the Oxford University Parks was not forgotten but was relegated to a nostalgic memory. From his early student study of Renaissance history in Johannesburg, Max had always been interested in the question of how ideas developed, how they changed society, and, particularly, the Machiavellian role that key individuals can play in this historic process.

Once Max was satisfied he had achieved his objectives in building up his own department in Washington University, he turned his attention to the wider field of neuroanatomy, and neuroscience as a whole. Following Kuffler's use of the term Neurobiology for his department in Harvard, Max used the term Anatomy and Neurobiology for his department in Washington University. This acknowledged that it was only through combining the techniques of the separate disciplines that major advances in conceptual understanding of the nervous system could be made. To this end he proposed to unite his anatomical department with Cuy Hunt's Department of Physiology, amalgamating the two often warring disciplines into which traditional neuroscience teaching and research had formerly been split.

However, the major new discipline now on the horizon, and the one that was to dominate future research, was the discovery of the DNA structure of genes, the genetic regulation of protein synthesis, and its role in development and in the adult phenotype. Max was captivated by the new science of molecular biology and by its novel and powerful technology. This interest received a major impetus from a visit to the first neuroscience course at Cold Spring Harbor in 1972, where he met Jim Watson (ForMemRS 1981). Later, at the Salk Institute, Max's thinking was honed and stimulated by his contact with other eminent founders of molecular biology, such as Francis Crick FRS and Sydney Brenner. During his years at the Salk Institute, Max played an important role in shaping the scientific strategy and the recruitment of the faculty who would set the scene for the Salk's future in molecular biology.

Max was one of the earliest and foremost of the neurobiologists of his time to realize that molecular biology would have a leading role in the development of neuroscience, and particularly in the neuroscience of development. He described the human genome mapping project as the scientific equivalent of Columbus, Magellan and the great global circumnavigators and explorers discovering new worlds. In 1988 Max was appointed Vice President and Chief Scientific Officer of the Howard Hughes Medical Institute, in which roles he continued for 13 years until 2001. This put him in a commanding position to exert his leadership skills and opinion-forming roles in publication, grant-giving and public understanding, and to support and encourage the integration of molecular biology with existing neuroanatomical technology.

This was a time of transition for the Howard Hughes Medical Institute. Max's guiding principle in supporting research was the identification of individuals of exceptional talent. Having done that, he gave them complete independence in deciding what to do and how to do it, and it was entirely up to them if their interest led them into a quite different field. Max believed that research stemmed from an innate curiosity in the human spirit that could not be directed or commissioned. He had faith in human genius. There are perhaps no other funding bodies then or now that venture to take such daring responsibility in making decisions, in not requiring the investigators to follow a fashionable topic, nor to spell out the numbers of rats they will use, nor the numbers of months or years it will take to reach this or that particular milestone. Max would probably have agreed that if the research could be planned in such detail it was prob-

ably blinkered to doing nothing more than decorating a foregone conclusion. Although peer review (by competitors) is the best firewall to absolve bureaucrats of the need to defend their policies, it is by its nature a conservative process, innately hostile to unconventional ideas, and reducing assessment to the lowest common denominator. As Churchill might have said of democracy, it is both the worst and the best of all possible methods.

Max had the courage to believe in liberating the human spirit, not in fettering it, and in doing so he accepted that those exercising the power to make decisions must also accept responsibility for them. I think he realized how he was setting his face against the overwhelming tide of stifling regulations inflicted on us by today's back-watching bureaucracy. His policy was to select a limited number of excellent individuals, fund them generously and insist on the highest levels of achievement. Under his guidance the Howard Hughes Medical Institute focused on bringing forward some of the best young scientists of the day, particularly in the burgeoning field of molecular developmental biology. Their success is a testament to his policy. But without a genius making the decisions, how does one avoid cronyism and the insidious corrupting effect of power?

Archival work

Max was always dedicated to education, and over and above their scientific training, he took a keen and sympathetic interest in helping his protégés face the challenges and problems of their lives. Throughout his career he recruited and trained a galaxy of highly talented young people, virtually all of whom went on to outstanding careers of their own. Max's interests and knowledge spread far beyond neuroanatomy, and this enhanced his effectiveness as a communicator. At one conference where we were together I discovered that Max slept as little as three hours a night, and often read a whole book in the remaining dark hours. The sustained enthusiasm, the tireless energy and the incisive thought he brought to the fabric of scientific communication and to the development of the scientific community were outstanding, at least matching the impact of his own personal research.

In 1969, following the suggestion of Jerzy Rose, Max had taken over the editorship of the *Journal of Comparative Neurology*, raising it from obscurity to the one of the foremost neuroscience journals of its time, and relinquishing the post only when, after 11 years, the press decided to abolish its not-for-profit status. Max played a key role in the development of the American Society for Neuroscience, which brought together all disciplines working in neuroscience. He was President of the Society (1977–78), and Founding Editor and Editor-in-Chief (1980–87) of the *Journal of Neuroscience*, the flagship of the society.

Over the last 10 years or more of his life, I saw Max only two or three times. At 8 o'clock one morning, as I was joining the throng of many tens of thousands converging from their various hotels onto the immense meeting of the American Neuroscience Society, we coincided. He seemed both pleased and unhurried, and we started to chat.

'I hate these huge meetings', I said.

'So do I', said Max. 'Coffee?'

The coffee lasted until midday.

In 1978 Max, together with Eric Kandel, Zach Hall and Richard Thompson, launched *Annual Review of Neuroscience*. Max served as an editor for 25 years. Until his death in 2002 he was active in identifying larger topics of historical importance, many of which involved

compiling research and individual contributions into definitive articles that had never before been made accessible. In 1993 he became co-chairman, with Jim Watson, of the Dana Alliance, which formulated the objectives of the Decade of the Brain and which has subsequently been active in promoting public understanding of the importance of brain research, including through Max's vice-chairmanship of EDAB, the European Dana Alliance for the Brain.

One of the key conceptual advances in which Max was a leader was the realization that the separate ways of studying the nervous system—anatomy, physiology, psychology and development—could not adequately be advanced as isolated disciplines. Max was one of the most effective proponents of the new, inclusive discipline called neuroscience, or neurobiology. Possibly his outstanding contribution during his period at the Howard Hughes Medical Institute was to integrate the newly burgeoning molecular biological approach with the existing, older disciplines already included in neuroscience. Over several successive years Max's annual reports to the Howard Hughes Medical Institute were among the most authoritative summaries of advance in an extraordinarily wide field of biological research, and a testimony to the remarkable breadth and depth of his grasp of science.

Overview

As a person Max was slight, his manner was self-effacing and sometimes teasingly softly spoken. Yet in any gathering where he was present his personal charisma ensured that everyone was aware of his presence. His character was somewhat enigmatic. He had enormous and totally genuine personal warmth. He thought of his team, and his past students, as a family. He delighted in company and conversation, and it was clear to me that he felt the loneliness of his later eminent positions. There was always something about him of the schoolboy seeking approval. He could be dismissive of those he considered not up to standard, and his junior colleagues sometimes referred to him as 'The Godfather'. He sought out the great, enjoyed their company and thoughts, forgave them their trespasses, and himself was talked about as 'a very special person'—an epithet that, although flattering, in itself exemplified the difficulty in classifying this complex and fascinating man.

Max was concerned about the public understanding of science and about its consequence, the public support of science. He regarded communication not as an extra but as an important responsibility. When I was still a student I recall him saying, 'If you read something carefully and do not understand it, it is probably because the writer did not understand it.' Max did not associate with industry or profit-making ventures, showed no interest in patenting, and, despite his earlier clinical training, did not particularly interact with clinical research. He was fascinated by the basic principles of scientific knowledge, and he used his influence to support or fund only those he judged as first class. He did miss things. Once, he dismissed the discovery of adult neurogenesis, characterizing the discoverer as 'an ass'. Max could have a sharp tongue, and revelled in cleverly phrased, if cruel, pejoratives.

Max was proud to acknowledge his debt to Le Gros Clark, his mentor, but less so to Oxford's Regius Professor of Medicine, who visited St Louis while Max was Chairman of Anatomy. US medicine was dominated by many and expensive laboratory tests. The Regius wanted to show the superiority of Old World wisdom and personal judgement. So, after hobbling into the ward round, flanked by acolytes, like a cantankerous and bristly whiskered grandee, he told the assembled students how he made a diagnosis by how the patient walked,

and came to a treatment decision the moment he entered the room, by the time he had reached the foot of the bed.

'What did the students say?' I asked Max.

'They thought he was mad.'

But Max was above all a member of the neuroscience community. He will be recalled for his many brilliant students and influential interactions, including David Amaral, Anita Hendrickson, Gary Banker, Josh Sanes, Jeff Lichtman, James Schwob, Ted Jones, Richard and Mary Bunge, Dale Purves, Larry Swanson, Paul Sawchenko, Charles Gerfen, James Fawcett, Dennis O'Leary, Brent Stanfield, Richard Anderson and Greg Lemke, among many others, whose names are now a roll call of current leaders in the field, as well as senior colleagues with established status, such as Viktor Hamburger, Rita Levi-Montalcini, Gerry Edelman, Sydney Brenner, Eric Kandel, Steve Kuffler ForMemRS and Francis Crick.

Max Cowan was one of the most outstanding neuroanatomists of his day; he trained some of the most important scientists of the next generation, and he made a virtually unparalleled contribution to the recruitment and dissemination of the study of the brain. Because of the influential posts he held, Max was in a position to make many important decisions, not only in his own research and in the recruitment of his team, but on a wider stage in the guidance of his field through his untiring work on advisory boards, societies and journals, in the distribution of major funds, and in his co-authorship of books. In these positive roles I know of no case in which he did not choose well, and in which his actions were not of benefit to the field of neuroscience to which he dedicated his all.

Max was keen to encourage the recording of definitive passages in neuroscience, and for this reason he edited several books and review articles that were intended not, as so often now, to gain another item on a curriculum vitae, but as historical records. In a minor way he asked me to write a review of the scientific contribution of Geoffrey Harris for the volume of *Annual Review of Neuroscience* that he was editing.

Knowing how reluctant I would be to take on this diversion from my own research, Max wrote to me, 'I hate to ask a friend to do this…'.

How could I refuse?

And once I had reconciled myself to the time involved, I enjoyed the writing (Raisman 1997), but even more the chance to spend a couple of days with him at the Howard Hughes Medical Institute in Bethesda. To my surprise, Max met me in a no doubt very expensive and fashionable small sports car, which seemed quite out of character for him, but in the back was thrown some very advanced looking photographic tackle, which did not. He showed me into the overwhelming new buildings of the Howard Hughes Institute, of which he was obviously immensely proud, and I spent my time in his private library, carefully stocked with beautifully bound volumes, including his own works. Throughout the silent corridors immaculately furnished in expensive, gleaming new wood, I saw no one else. A magnificent colour photograph of some commanding bird of prey, every feather pin sharp, looked down on me. 'A holiday in the Rockies', Max said. Expecting him to be busy, I tried not to intrude on his time, but he seemed to want to do nothing more than chat with me. He hung my coat solicitously in the wardrobe, showed me round the executive loo, the canteen whose chef was—in Max's opinion—very good, and the bijou lecture theatre in whose plush seats a country's president might sink with dignity. I formed the impression of a bird in a gilded cage.

The last time I saw him was at a function of the European Dana Alliance for the Brain at which he was, as had now become usual, the guest of honour. I was surprised to find him there,

and even more surprised when he made his way through an eminent company towards me, and to my immense pride spent most of the evening at the hotel bar, talking in his customary soft voice, almost inaudible in the evening hubbub of the small crowded room. Our conversation ranged over our past acquaintances in Oxford. Finally he said, 'Well, Geoff, I think we have been over all the people we knew.' He was tired, and he knew he was dying. It was my last conversation with him, and he had not hurried it.

Once he knew he had lost his battle with cancer, Max expended his remaining energy on a last and very characteristic task. With no diminution of his customary rigorous standards, he compiled a scientific autobiography. It was not so much an account of his own achievements but, like a photograph in which the subject was defocused and which brought forward the background, he presented a series of wonderful and warm personal sketches of the people, some famous, some obscure, who had guided the course his life had taken. To the end Max had been consistent in his dedication to leaving a record of what had happened, so that those who come next could benefit—as he so strongly felt that he had done—from what had gone before.

Max died when he was still at the height of his intellectual vigour. He not only had an uncanny prescience of where his field was going, but he had sought and held the positions of power and influence that enabled his opinions to contribute to the advancement of the field to which he dedicated his life. Coming from a strict low-church background, Max never lost his religious faith. It was the only area in which I found him to be resistant to scientific argument. To the end, he was frugal, and a populist. 'I have to do something to justify this ridiculous salary they pay me', he said. He disapproved of expensive things, and derided ostentation. Once, when we left the dissection room together he took off his white coat with the comment, 'Now I can stop looking like a baker's boy.' Shirt sleeves and hairy chest was his ideal of a scientist.

Max had no retirement, which spared him the horrors of looking after a garden. 'Blooming nuisance, a garden,' he said. 'I would prefer to live in an apartment.' Nor did he taste the sweet sadness of decline. Throughout his life Max did not ski at ski meetings. He indulged in no sports, nor games, no golf, no bridge. Not for him gentlemanly pursuits in some comfortable country seat, spending his dotage fondly observing his growing grandchildren, no padded leather armchair in a study lined with certificates and diplomas. Instead, he left us in the full flow. Max's life and his career were co-extensive and the same, an enigmatic character, at the same time both frail and immensely strong. But I cannot think of something he left that was not of benefit to his field, and a great deal more lasting than most.

William Maxwell Cowan was elected a Foreign Associate of the US National Academy of Sciences in 1981, and Fellow of the Royal Society in 1982.

Margaret Cowan writes:

> In spite of his great achievements in science, Max was a warm and loving husband for 47 years. Always an avid reader, we also enjoyed his time away from work walking, bird watching and taking photographs, which were long-standing hobbies shared with our children. He was a loving and supportive father and grandfather to our two grandsons. Max did his best to keep his home as a retreat and separate from his work situations. Though he had loved the California climate as it reminded him of his childhood in South Africa, he often talked of retiring back to England; it seemed an old cottage in a picturesque village where no cars were needed and everyone knew everyone else would be his ideal habitat.
>
> When Max and I heard the news of his illness, he said, 'I want to be at home with my family.' I was the only nurse he would allow and our children, Ruth, Stephen and David, came to help

as often as they were able. We were all with him, including our grandchildren, at our home in Maryland when he died.

We loved him dearly and miss him greatly. He was an extraordinary man.

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