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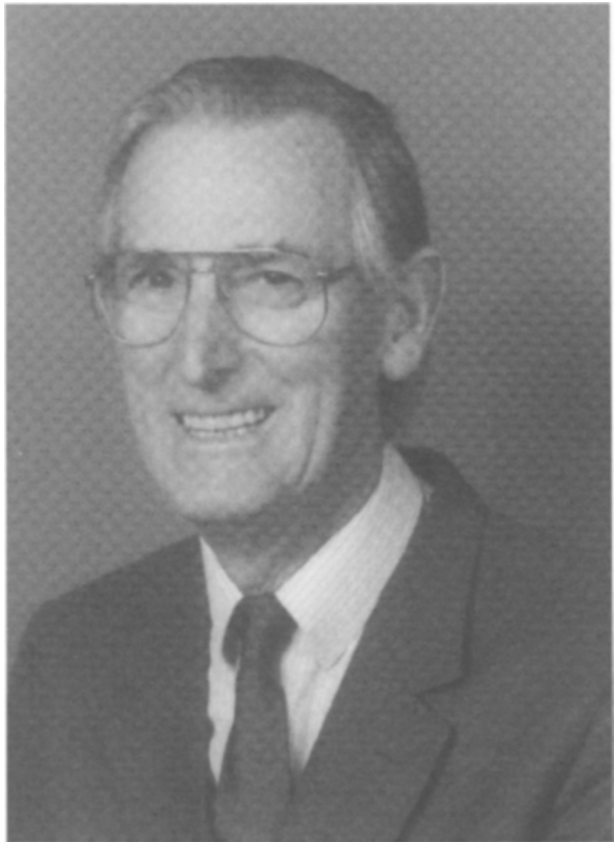

Ainsley Iggo

BORN:

Napier, New Zealand
August 2, 1924

EDUCATION:

University of New Zealand, M.Agr.Sc. (1947)
University of Otago, B.Sc. (1950)
University of Aberdeen, Ph.D. (1954)
University of Edinburgh, D.Sc. (1962)

APPOINTMENTS:

University of Otago (1948)
University of Edinburgh (1952)
Locke Research Fellow, Royal Society (1960)
University of Edinburgh (1962)
Dean, Faculty of Veterinary Medicine (1974–1977, 1986–1990)
Professor Emeritus, Edinburgh University (1990)

HONORS AND AWARDS:

Fellow of the Royal Society of Edinburgh (1963)
Fellow of the Royal Society (1978)
Fellow, Royal College of Physicians Edinburgh (1985)
Member, Academia Europaea (1991)
Bicentenary Medal, Royal Society of Edinburgh (1997)

Ainsley Iggo is an electrophysiologist who pioneered the study of sensory cutaneous receptors and afferents, the organization of the dorsal horn, and the physiology of ascending tracts within the spinal cord. He provided the first classification system for C fibers, classified mechanoreceptors, and discovered thermoreceptors in the skin.

Ainsley Iggo

I was born Napier, New Zealand, not far from my mother's childhood home at Clive. At that time, New Zealand was still suffering from post-war economic collapse, to be made even worse by the Great Depression, that engulfed the world as it spread from the United States. My childhood was spent in its shadow, in a peripatetic home, with my parents ever searching for a livelihood. To quote my old colleague, A. S. Paintal, 'If England catches cold, India gets pneumonia' (substitute New Zealand). The early Methodist upbringing of my father seems to have been dissipated by his wartime experiences, but my mother sustained and was sustained by her Christian convictions. My parents were children of nineteenth-century emigrants to New Zealand—paternal from Newcastle-on-Tyne via Lancashire in 1875 and maternal from Scotland in 1865 and Norway in 1872—who settled in New Zealand and survived the early colonial lifestyle to raise large families. There is no evidence of any scholastic or academic inclinations or attainments on either side, though it has to be said that the opportunities must have been pretty limited.

Schooling began on the west coast of New Zealand, initially in Greymouth, but then I was transferred to a two-roomed country school further down the coast at Camerons. One surviving memory is of a roller chart on the classroom wall. It depicted a small bird sitting on a very large rock and the caption said 'Each morning the bird sharpened its beak on the mountain and when the mountain was worn away, only one day in eternity had passed'! Such were the subliminal influences of childhood. Maybe my later enthusiasm for exploring a world that extended beyond my childhood horizons was sparked by such experiences and aided no doubt by a copy of a children's encyclopedia at home. There were few traces of the past in New Zealand, a country settled about 1000 years before by Maoris, who arrived in canoes from remote Pacific islands. My time was otherwise spent in childhood bliss; I was lulled to sleep by the Tasman Sea crashing its great breakers on the beach. I also enjoyed trips in my father's car, which was fitted with a horn on the exhaust that made satisfying, if mysterious, booming sounds to warn oncoming traffic.

The next family move was to a house built speculatively by my grandfather in Invercargill, not far from his birthplace in the Bluff. One step from here was the South Pole; to the east was the immensity of the Pacific Ocean and 2000 kilometers away to the west was the next landfall, our

colonial neighbor, Australia. This I was soon to learn was 29.5 times the landmass of my homeland. In Invercargill I was enrolled in the rural class program of the Southland Technical College, a decision made by my father that was to determine my future. Here, I had the good fortune to have a class director, Kenneth McKinnon (of Scottish extraction). He took me under his wing and encouraged me to have academic aspirations. In 1941 I left secondary school for university with an Agriculture Bursary, a 4-year stipendiary scholarship.

Undergraduate Life, 1942–1949

Undergraduate life began at Otago University and continued at Canterbury Agricultural College, outside Christchurch. Again, I was fortunate. My degree tutor, M. M. (Malcolm) Burns, encouraged my academic efforts. After 5 years, I left in 1948 with a master's degree in agricultural science, an interest in physiology, some congenial friends, and the McMillan Brown Travelling Scholarship. It would be 2 years before the scholarship was vacant and so I searched an interim job. Professor Ian Coop, my M.Agr.Sc. supervisor, suggested that I go to Otago, where there was an internationally recognized physiology department. My way home by train from Christchurch to Invercargill took me through Dunedin. During a 20-minute refreshment break at Dunedin (there were no restaurant facilities on New Zealand trains), I made a telephone call from the railway station that was to change my life. I phoned Professor J. C. Eccles. More than 50 years later on the occasion of my retirement, he wrote to remind me of this, our first contact. He did not at the time seem unduly impressed with my suggestion that he hire me as a research assistant. Instead, he suggested that it would be not just better, but necessary, for me to learn some physiology first. I was penniless, having used my last penny on the telephone call. My cousin, Edward Iggo, a pharmacist, rescued me with a generous loan to cover an undergraduate year at Otago. There I spent a rakish year exposed to the brilliant teaching of 'Synaptic Jack' Eccles and, among others, neurophysiologist Archie McIntyre, biochemist Norman Edson, and neurologist Victor McFarlane. The next year I became an assistant lecturer, giving a course of lectures to Home Science and Diploma of Physical Education students while I was doing honors physiology.

Under the powerful influence of Eccles, I began, with his daughter Rose, an investigation of synaptic transmission in autonomic ganglia. Eccles was still promoting the electrical hypothesis of synaptic transmission, although this was challenged by the Dale School in England and former colleagues of his Sydney era, Bernard Katz and Stephen Kuffler. It was clear that peripheral synapses were influenced by acetylcholine. Rose and I excised superior cervical ganglia to record extracellularly *in vitro* to test

ganglion blocking drugs. Eccles suggested that the ciliary ganglia offered a particularly interesting model since both pre- and postganglionic transmissions were cholinergic. Attempts to isolate viable ciliary ganglia from experimental cats were unsuccessful. End of story. The seduction of overseas study and the new experiences it offered nullified J. C.'s blandishments to stay and enroll for a postgraduate degree. Would I do it again? Among later vivid recollections is a Physiological Society meeting in London in 1952. Eccles was about to present the experimental evidence that refuted his electrical hypothesis of synaptic transmission in the mammalian nervous system. His excitement was almost palpable.

Crossing the Line, 1950

With the McMillan Brown Agricultural postgraduate scholarship in my pocket, I looked to the United Kingdom. Who could advise me on a venue? One obvious choice was the ARC Physiological Institute at Babraham, near Cambridge, headed by Joseph Barcroft. Unfortunately, he died before I could take up the scholarship. Eccles was characteristically forthright about Barcroft's successor, de Burgh Daly, and persuaded me to seek a place with Andrew Phillipson, one of Barcroft's Babraham protégés, who had moved to another ARC-supported institute near Aberdeen. It has to be said that viewing one island from its antipodean pole on the other side of the world can lead to error. If Dunedin was remote, so too, for a poor student, was the Rowett Institute. I was committed and set off on my great adventure, shipping as a steward on the S. S. Mataroa. We steamed across the boundless waste of the Pacific, crossed the equator between Pitcairn Island and the Panama Canal, and arrived in the United Kingdom in August.

Rowett Research Institute, 1950–1952

Research in A. T. Phillipson's department concentrated on reflex regulation of ruminant gastric movements in sheep. The topic was important because of the potentially fatal problem of bloat. The first fruit of my stay at Rowett was a paper on the galvanotropic fractionation of rumen ciliates (Masson *et al.*, 1952). This was a diversion while I began to equip a physiological laboratory in a room being built in the attic. As a novitiate in electrophysiology in an institute in which soldering irons were high tech, I had many new tricks to learn. My salvation was the technical monograph *Electrophysiological Techniques* by C. J. Dickinson. Local advice at Aberdeen came from a marine engineer who built sonar equipment for the fishing industry; I persuaded him to make electronic equipment for me based on circuit diagrams in Dickinson's book. Eventually, I started experiments recording from afferent and efferent gastric fibers in the cervical

vagus of sheep. My plan was to follow the activity in single units, but they had thin axons and their impulse activity was hidden by the rhythmically active pulmonary inflation receptors. Such activity as I found quickly disappeared, as it turned out, for technical reasons. The preamplifiers that I made were poorly balanced and there was sufficient grid current flowing between the recording electrodes to kill my thin axonal preparations. A quotation from Dickinson is relevant: 'care should be taken to see that the bias is easily sufficient to prevent this flow (of grid current in the preamplifier circuit) which may have disastrous effect on delicate biological tissue.' As was the case. I sought sophisticated advice from A. E. Ritchie at St. Andrews and from David Whitteridge and Jock Austin in Edinburgh. During my 2-year stay at the Rowett I developed a preparation for the analysis of the central control of the movements of the reticulum and rumen (Iggo, 1956), the topic of my Ph.D. thesis.

Edinburgh Physiology Department, 1952–1960

In 1952, I married Betty McCurdy at St. Mary the Virgin in Oxford. She was a fellow New Zealander working in Oxford. Our honeymoon began at the International Congress of Biochemistry in Paris, a choice partly dictated by the need to get a foreign currency allowance (£50) for foreign expenditure. We settled in Edinburgh after I had taken up appointment to David Whitteridge's physiology department at the Edinburgh University Medical School. Again, I was teaching dental students, among others. Betty signed up for a Ph.D. in C. P. Stewart's Clinical Biochemistry Unit at the Royal Infirmary, thus continuing her interest in vitamin C begun in Hugh Sinclair's laboratory in Oxford. This she completed before the birth of our first son, Neil, in 1956.

While all this was going on, I needed to contain my frustration regarding the time it was taking to set up my laboratory and start experiments. Along with two other recruits to the Edinburgh team (Andrew Swan and Morrell Draper), we each laboriously built our equipment. Under the tutelage of Jock (W. T. S.) Austin, 'Jock Boxes' were hand-made from raw material, which included sheet metal, army surplus electronic gear, miles of tinned copper wire, and pounds of lead solder. These masterpieces were integrated electrophysiological recording units, key components of our future research laboratories. Once my box was working, and at David Whitteridge's suggestion, I began the analysis of electrical discharge in urinary bladder afferents. This was a prelude to a renewed attack on my thesis theme.

Those experiments (Iggo, 1955) established that many bladder receptors were 'in-series' tension receptors, excited by vesicular distension and by isometric contraction. Several other kinds of afferent were found, including 'flow' detectors in the wall of the urethra. All these entered the

spinal cord via the pelvic visceral nerves. Now that I had suitable techniques of nerve dissection, recording, and analysis, I turned to the gastric sensory receptors of the cat. There were two main kinds of sensory receptors (Iggo, 1957a,b): in-series tension receptors of the kind found in the wall of the bladder and more superficial receptors located in the mucosa, some of which were pH sensitive. Because conclusions were subject to doubt and confusion when based on recordings from multiunit preparations, I needed to be able to identify receptors as single afferent units. This almost mandatory requirement led to the developments of a 'collision' method for the electrophysiological identification of single fibers (Iggo, 1958). This technique greatly helped the otherwise extremely tedious task of isolating slowly conducting Aδ and C fibers as identifiable units.

The Search for Nonmyelinated (C) Afferents

Once the single-fiber technique was mastered, my attention turned to cutaneous sensory receptors. It soon became clear that many C units in the hairy skin of cats were excited easily by innocuous tactile stimuli. This was contrary to received wisdom. There were also other receptors with higher thresholds. My results were inconsistent with human studies in which differential block of the myelinated axons in cutaneous nerves abolished tactile sensibility. Light tactile stimuli were not felt after the myelinated axons were blocked. Only pain was experienced in response to severe mechanical and thermal stimuli. A Ciba Foundation Study Group meeting in 1959, at which Yngve Zotterman and Lord Adrian were active participants, discussed the issue. They were the old masters who had first discovered methods for investigating single afferent fibers in 1924 (the year of my birth!). For many years afterwards, Yngve had struggled with resources of the time. By 1939, he reported that stimulation of the skin could evoke low-amplitude unit activity in a peripheral nerve in cats (Zotterman, 1939). My single-unit results, reported to the Ciba meeting (Iggo, 1959), showed that several categories of C fiber afferent units existed. The whole size range of axons was accessible, with conduction velocities ranging from 0.5 to 60 m/sec, i.e., C and A fibers in Gasser's terminology. A diversity of sensitivities to mechanical, thermal, and chemical stimuli existed and, as a first step, I classified the C units in three classes as mechanoreceptor, thermoreceptor, and nociceptor. In 1959, I attributed putative nociceptor roles to the Aδ and C units. Activation thresholds for the so-called C heat receptors and for pain were similar. In addition, as found by Douglas and Ritchie (1957), many C mechanoreceptors were highly and selectively sensitive to innocuous tactile stimuli (Iggo, 1960), with thresholds not much higher than those of the A mechanoreceptors. The published literature left them without an obvious sensory function. Åke Vallbo *et al.*(1999) described sensitive

C mechanoreceptors in human hairy skin and had the same difficulty that I had faced. The sensitive C mechanoreceptors were at one end of a spectrum of C afferents. It has taken nearly 40 years for resolution of this controversy. The results of the single-unit analysis were consistent with the 'specificity' concept of sensation rather than the 'temporospatial pattern' hypothesis advocated by Graham Weddell or the 'nonspecific' hypothesis of Melzack and Wall.

Cutaneous Thermoreceptors

One open question in 1959 was the mechanism of cutaneous thermoreception. Herbert Hensel and Yngve Zotterman had found afferent units in the lingual nerve of cats with a well-defined and selective sensibility to tongue temperature. The skin mechanisms were in question. For example, Witt and Hensel (1959) found evidence for dual sensitivity in cat skin—receptors that were sensitive to both tactile and thermal stimuli. It was therefore easy for me in 1959 to accept an invitation to visit Hensel's laboratory, where we would test my preliminary conclusion that there were specific C thermoreceptors in hairy skin of the cat. Hensel's laboratory was well equipped for thermal studies, in which he specialized, and I contributed my single C fiber techniques. I well remember isolating C cold receptors and testing them properly with Hensel's equipment. Rigorous testing of C afferent fibers revealed some units with a classical temperature sensitivity curve of the kind found for lingual cold thermoreceptors. The skin cold receptors had a peak sensitivity of about 25°C, a temperature range of 15–36°C, and dynamic responses only to cooling the skin. Within the next few days we found 'warm receptors.' They had maximum sensitivity at about 42°C and a thermal range of 35–45°C. They responded as temperatures rose and were insensitive to mechanical stimuli. We had put specific cutaneous thermoreceptors with C afferent fibers on the map (Hensel *et al.*, 1960).

Australian National University, Canberra, 1959

I departed for my sabbatical leave to be spent in Eccle's laboratory at the Australian National University (ANU) in Canberra, Australia. Betty had preceded me with our two infant sons and I set off in good spirits to rejoin her, enlivened by the news from the high seas that once again she was 'enceinte.' Our two boys were going to be joined by a sibling in Canberra, adding an Australian to our New Zealand–Scottish family.

The sabbatical taken at ANU Canberra gave me the opportunity to learn new experimental skills that I could use on my return to Edinburgh. I became happily immersed in laboratory work once again with Rose Eccles. I still have the certificate 'in note-taking and tea-making' that was presented to me on my departure. These skills were essential for survival

during the long and grueling laboratory work needed to secure satisfactory results, and they were well exercised on my return to Edinburgh. Our brief in Canberra was to quantify recurrent inhibition of motor neurons by firing impulses along ventral roots while recording intracellularly from Renshaw cells. The experiments were successful, but the functional significance of the results was equivocal (Eccles *et al.*, 1961). As an aside, Rose and I examined the double twitch of the gracilis muscle reported by Buller and Eccles. We showed that the phenomenon was an artifact caused by the method of attaching the muscle to the myograph (Eccles and Iggo, 1961). The only real consequence was the opportunity for J. C. to amend a manuscript 'in proof' and delete a spurious rapidly contracting skeletal muscle from the literature.

Locke Research Fellowship, 1960–1962

On my return from sabbatical leave in 1960, I resumed active work on cutaneous sensory mechanisms with a Locke Research Fellowship of the Royal Society. My aim was to settle the controversy over 'temporospatial patterning' and 'modality specificity' by making a quantitative analysis of the morphofunctional characteristics of peripheral sensory receptors.

Species differences led to the use of monkeys as models for primates (Iggo, 1963). There was already strong histological evidence for receptor specialization in glabrous skin, which is particularly well developed in primates. Primate skin had mechanoreceptors similar to those in nonprimate species. The cold receptors, however, differed in that they had myelinated afferent fibers (Iggo, 1962). I brought the preliminary conclusions of my search for peripheral sensory receptors together for a University Federation for Animal Welfare (UFAW) symposium, The Assessment of Pain in Man and Animals, which was organized by C. A. Keele and M. Smith in 1963. By this time, my studies had extended from the viscera to skeletal muscle and skin. On the one hand, the large-diameter inflow had roles as tactile (skin) and reflexogenic (muscle) systems. On the other hand, nonmyelinated and small myelinated axons, until then relegated to the role of 'pain' fibers, had turned out to comprise a mixed bag. Many visceral receptors in the gastrointestinal tract and urinary bladder were in-series tension receptors unable to discriminate between passive distension and active contraction of the viscus. Others (e.g., in the gastric mucosa) were excited by fluids of low pH. Muscle nociceptors had high thresholds for mechanical stimulation similar to those in human tendons that evoked pain. Curiously, an extremely painful maneuver, contraction of an ischemic muscle, did not elicit high frequencies of discharge in C fibers. The results from my hard-won single C units were tabulated for the UFAW meeting into four categories: mechanoreceptor (44%), nociceptor (mechano 24%, thermo 25%), and thermoreceptor

(10%). The use of putative chemalgogens of the kind then available gave equivocal results when used in an attempt to identify cutaneous nociceptors.

Mechanoreceptor Specificity

In 1961, Nancy Armitage (Fjällbrant) and I, while testing the action of noxious chemicals on cutaneous receptors, found differences in the adaptation rate of myelinated mechanoreceptors. Three classes were made: (i) PC, Pacinian corpuscles, with a very rapidly adapting discharge, already well-known from the work of John Gray and later intensively studied by Loewenstein; (ii) hair follicle mechanoreceptor of several subtypes (T, G, and D); and (iii) slowly adapting mechanoreceptors. A combined structural and physiological examination with Alan Muir led to the discovery of touch spots (as it turned out, the rediscovery of the Pinkus *haarscheibe*). These are small circular elevations of the epidermis. Each is innervated by a myelinated axon that branches to end as Merkel discs, associated with Merkel cells. Alan Brown, who was intercalating a B.Sc. in his medical studies, and I examined the function of Merkel cells. To do this, we cut or crushed the saphenous nerve in the thigh and followed the progress of the nerve and receptor during recovery. The regrowing nerve showed Tinel's sign, which is a brief discharge of impulses when the nerve tip is tapped. Not until the axon had grown back into a touch spot and the Merkel cell complex had reformed did the normal slowly adapting response recover (Brown and Iggo, 1963). These touch spot afferent units were subsequently named SAI (slowly adapting type I) mechanoreceptor to distinguish them from the SAII (slowly adapting type II). It was becoming evident that cutaneous sensibility was served in the periphery by distinctive sets of sensory receptors. These had ranges of properties sufficient to justify the conclusion of modality specificity based on the morphofunctional characteristics, and that cutaneous sensation did not depend on a temporospatial pattern code in afferent fibers.

The events during regeneration of a peripheral nerve were again examined at Monash University in 1995 (Proske *et al.*, 1995). We followed the regeneration of cut skin and muscle nerves into cuffs made of synthetic material. There was evidence that substances transported down the nerves accumulated at the growing tips to give mechanical sensitivity. The development of ongoing discharge and stretch responses of the growing nerves revealed differences between the skin and muscle afferent fibers. Some regenerating muscle afferents had a resting discharge and responded to stretch. In contrast, the skin afferent fibers were silent and those that responded to stretch were active only during the dynamic component of stretch. this was another hint that the SAI skin receptors required reformation of the receptor complex in the skin for slow adaptation.

Veterinary Physiology, 1962–1990

In 1962, the university appointed me to the newly created chair of veterinary physiology in the nascent veterinary faculty. The 130-year-old Dick Veterinary College was in a state of flux following its incorporation into the university in 1953. It began to develop a field station and relocate some departments to it. One consequence was that vacant space became available at Summerhall, which I could turn into research laboratories and technical workshops with funds from the university and the Agricultural Research Council (ARC). I was imbued with the idea of promoting science in veterinary medicine and not just in the undergraduate course. Some of these objectives were spelled out in my inaugural lecture, delivered in 1962. I wanted to develop both practical and theoretical principles in the undergraduate course and to offer more advanced neuroscience courses. On a rereading, the lecture seems full of pious platitudes as my aspirations were spelled out. What strikes me, nearly 40 years later, is the extent to which those aspirations were realized. Two of the consequences of the move to the 'Dick' were a resumption of work on ruminant gastric mechanisms, for which I was fortunate to recruit Dr. Barry Leek, and an extension of somatasensory studies.

Ruminant Gastroenterology

Ruminant digestion relies on the continuous mixing of ingesta and the eructation of gaseous waste products. This is brought about by coordinated sequences of contraction and relaxation of the reticulum and rumen. They are integrated by a reticuloruminal center in the medulla oblongata (Iggo, 1956). The ARC equipped a laboratory for the analysis of reflex mechanisms using single-unit techniques to record from the afferent and efferent axons in the cervical vagus. The pattern of discharge in preganglionic efferents in the vagus had a temporal relationship to reticuloruminal contractions. Seven patterns of efferent unit activity were found (Iggo and Leek, 1967a). Four were directly correlated with, and preceded, reticular and ruminal contractions. In the absence of efferent discharge, or when the cervical vagus nerve was blocked, the stomach was quiescent. Reflex integration was investigated by manipulating the afferent inflow. Since we now knew that many vagal afferents were in-series tension receptors, the afferent inflow could be altered in several ways: by imposing isotonic or isometric conditions on the stomach, by blocking efferent action with parasympathetic drugs, or by changing the pH of the abomasal (ruminant fourth stomach) contents. We concluded that a tonic afferent inflow from in-series receptors during the inactive phase of the cycle provided a reflex drive to the medullary gastric centers (Iggo and Leek, 1967b). The sequence of subsequent afferent input during the reflexively elicited contractions then determined the rate and amplitude of gastric efferent

preganglionic discharge and thus the resulting movements. High levels of afferent inflow, as in an impacted rumen, were inhibitory. These studies ended when Barry moved to become the chair of veterinary physiology in Dublin.

The ARC laboratory was reinvigorated by David Cottrell. *Inter alia* there was an opportunity with Ralph Kitchell (on a research visit from UC Davis) to explore the sensory innervation of the ram's penis (Cottrell *et al.*, 1978). We attempted to correlate the well-known morphology of sensory receptors with the electrophysiological properties of afferent units. Both rapidly and slowly adapting mechanoreceptors had afferent fibers in the dorsal nerve of the penis. About 10% of the single units were thermoreceptive. We were not successful in making secure morphofunctional correlations.

My active participation in ruminant physiology experiments was concluded with a collaborative study with David Cottrell on the duodenum. We produced graphical models that could account for the properties of the different receptors, i.e., in-series tension receptors in the longitudinal muscle, parallel receptors in the serosa, and stretch receptors in the duodenum (Cottrell and Iggo, 1984). As in the stomach, sensory receptors in the duodenal mucosa adapted slowly to mechanical probing. A variety of drugs were excitatory, although refractoriness often developed quickly. Bolus injections of gastrointestinal polypeptides aroused or enhanced activity in the tension receptors. Analysis of the gustatory mechanisms was developed by David Cottrell and David Carr, who had arrived from New Zealand (Carr *et al.*, 1987). We extended an old interest in gustatory receptors to the exploration of the sensory receptors in facial skin of sheep and goats.

Somatosensory Mechanisms

My second and sustained interest was in somatasensory mechanisms. Alan Brown had joined the department after graduating from the medical school, and together we launched a vigorous assault on cutaneous sensory receptors. Simon Miller joined us briefly in an attempt to resolve the question of modality specificity. In particular, we wanted to compare the differences between results obtained by Weddell and Miller, who used microelectrodes as recording devices, and our results using the microdissection technique. The former method had restricted the systematic examination of receptive field properties to larger axons (>5μm, >40 m/sec) because of the limited survival of the more slowly conducting myelinated axons. In contrast, the microdissection method allowed the lengthy survival of even nonmyelinated fibers. Type D and G hair follicle units were present in our sample from the rabbit ear, but SAI and SAII as well as type T hair units typical of normal body skin were absent (Brown *et al.*, 1967). The sensory innervation of the rabbit's ear thus differs from the

general body skin, and conclusions about modality specificity cannot be justified on the basis of the rabbit ear alone. These results were not inconsistent with our overall view that there was modality specificity.

Alan and I then embarked on a systematic rigorous sampling exercise by combining the collision technique with precise synchronized control of time-locked mechanical stimuli (Brown and Iggo, 1967). We deliberately chose to work with nerve strands containing as many as 10 myelinated units in the electrically evoked compound action potentials. Up to 100% of fibers in multiunit samples were identified. Units were assigned to the classes of mechanoreceptor that our laboratory had established, namely, hair follicles type T, G, or D and SAI or SAII. The small number of unidentified units in our sample of more than 800 was attributed to myelinated nociceptors that our mechanical sampling intensities were not designed to test.

A parallel investigation with Margaret Chambers was aimed at the slowly adapting cutaneous mechanoreceptors, already subject to a vigorous and detailed intensity coding study by Werner and Mountcastle (1965). The 'touch corpuscles' that Alan Muir and I had shown to be SAI were now easy to recognize. However, the population of SA units often contained strangers that differed sufficiently for us to make a clear distinction between them and the SAI. In the literature, there had been no awareness of the existence of two kinds of SA mechanoreceptors. We named these novel receptors the SAII. The SAII, unlike the SAI, had no visible surface features, and to identify them we eventually had to mark the sensitive spot with fine stainless-steel wires. We collaborated with Karl Andres and Monika v. Düring in the histological examination of serially sectioned glutaraldehyde-fixed tissue. The results showed spindle-shaped nerve endings, oriented parallel to the skin surface, with large myelinated axons. The latter were of the size expected from conduction velocity measurements in anesthetized animals (Chambers *et al.*, 1972). The receptors had the typical structure of the Ruffini ending, the sense organs found by their eponymous discoverer in 1881.

The outcome of two decades of experiments and similar investigations in other laboratories on several species was that modality specificity could be assigned to specific structures in many situations. It was time to turn to the spinal mechanisms. Alan Brown was the first to take the plunge and became well-known for his masterly analysis of the spinocervical tract (SCT) in cats. One notable early success was his use of intracellular loading of cells with dyes to label afferent fibers and neurons. He could specify the cells physiologically (Brown *et al.*, 1977).

Spinal and Cerebral Somatasensory Mechanisms

Various aspects of somatasensory processing were explored. The ability to produce a nerve volley in a peripheral cutaneous nerve that can be

restricted to activation of only one class of afferent unit provides a powerful tool for analyzing spinal and cerebral mechanisms. Witness the record of John Eccles. The saphenous nerve of the rabbit has such a characteristic. Alan Brown had found that low-intensity electrical stimulation of the rabbit sural nerve excited only SAI axons. Using this information, R. L. Ramsey and I explored evoked potentials in the rabbit SI somatosensory cortex. We recorded a potent response to an input from the SAI mechanoreceptor afferents (Iggo and Ramsey, 1976). This suggested that these cutaneous receptors could have a sensory effect, as was so convincingly established in man by Hagbarth and successors in Sweden. Their experiments combined the percutaneous recording of single-unit afferent discharge with assessments of human sensation (Vallbo and Hagbarth, 1968).

SRC Somatosensory Research Group

The computing facilities of the group were originally at the University Computing Centre remote from the laboratory and serviced by a van. The first lab-based machine was a Biomac hard-wired bench computer (based on the ATLAS machine) and next a Cromenco, bought on the advice of the Computing Centre but soon superseded by DEC machines. My awareness of developments in laboratory computers made a quantum leap during a visit to Vernon Mountcastle's laboratory in Baltimore in 1966. He showed the ease with which, in a few minutes, he could complete an off-line interspike interval analysis using a LINC computer. It had taken me painful hours of manual measurement using photographs of oscilloscope traces to do the same, and I was quickly and completely converted. In 1969, I secured funding from the Science Research Council for a PDP 12A computer, which included enhancements in design embodied from the LINC.

Once the PDP 12 was operational and after Bob Ramsey and Doug Young had written some programs, it was used to collect and process the afferent data from sinus hair follicles. Karl Andres had already published a detailed description of the fine structure of sinus hair follicles, so we had a solid foundation for our electrophysiological experiments. Kay Gottschaldt constructed an ingenious 'angle stimulator' capable of moving the sinus hair in three axes. With it, we identified several kinds of sinus hair mechanoreceptors in maxillary and carpal hairs in the cat (Gottschaldt *et al.*, 1973). Two kinds of slowly adapting units were found. One of these, the STI, could confidently be assigned to the Merkel cell units based on earlier work. The other, STII, we assigned to the straight and branched lanceolate endings. There were also two kinds of rapidly adapting discharge. One of these could be attributed to Golgi–Mazzoni corpuscles in facial sinus hairs or to Pacinian corpuscles surrounding carpal sinus hairs. The others, the low-velocity rapidly adapting (RA) units, were left in limbo.

Spinal Actions

An invitation to join Manfred Zimmerman and Hermann Handwerker in Heidelberg provided an opportunity to examine the segmental spinal actions of the various kinds of cutaneous receptors. This visit also gave the Zimmerman and Iggo families the chance to enjoy Christmas and the new year skiing together in the Schwarzwald. In Heidelberg we set out to generate modality-selective afferent inputs using radiation to excite 'heat nociceptors' and brushing of the skin for mechanoreceptor inputs, etc. Two classes of dorsal horn neurons were described from the results (Handwerker *et al.*, 1975). Class 1 neurons were driven by sensitive mechanoreceptors and class 2 by noxious thermal and noxious mechanical receptors and by sensitive mechanoreceptors. Afferent volleys in C fibers powerfully excited the class 2 neurons. In spinal animals these latter excitatory actions were prominent but were often absent in intact preparations, evidence of potent supraspinal control of class 2 neurons. There was also evidence of a local segmental inhibition of nociceptor-evoked response by an interposed input from sensitive mechanoreceptors via large myelinated axons. A third category, class 3, was added in 1974 (Iggo, 1974). These were dorsal horn neurons in lamina 1 that were excited only by noxious thermal and/or mechanical stimuli. Differential cold block of a peripheral nerve (Franz and Iggo, 1968) made it possible to restrict the afferent inflow to unmyelinated fibers so that only an input in C fibers entered the spinal cord. In these conditions the class 3 receptors were still excited. They did not need an A afferent input to play against the C nociceptors so that 'gating' did not need to be invoked. These class 3 neurons were presumably the same as those that Christensen and Perl (1970) had excited with an Aδ afferent input.

International Association for the Study of Pain

The somatosensory group in 1973 turned its attention to nociception and pain. This decision was probably strongly influenced by the creation of the International Association for the Study of Pain (IASP). The concept of a worldwide pain society was discussed and agreed upon at an international meeting held in Issaquah, Washington, under the dynamic leadership of John Bonica. At that meeting, two far-reaching decisions were made: to set up IASP with a permanent secretariat and hold periodic international pain congresses and to found a journal for the dissemination of research in the broad field of pain. The inaugural board of editors comprised John Bonica, Bill Noordenbos, Pat Wall, and myself. Under Pat Wall's direction as editor-in-chief, the journal flourished and has become a thriving international periodical of distinction in the field of pain. Very successful world congresses on pain are held every 3 years at different locations throughout the world.

Somatosensory Research Group

The Edinburgh somatosensory research (SSR) group prospered, developing ever more sophisticated and complex technology to search for and identify neuronal activity in the spinal cord. Precise methods were used for the intracellular labeling of identified neurons and for the computer-aided collection and analysis of data. A gradual focusing on the electrophysiology and neuropharmacology of nociception and the supraspinal control of segmental mechanisms followed.

Several overlapping lines of interest were taken up, including ascending spinothalamic pathways and the descending control systems that play on the dorsal horn and contribute to the molding of its output. Fox, McMillan, and Mokha assessed the effects of electrical stimulation of the brain stem, with particular emphasis on the locus coeruleus and raphe magnus nuclei. Both had an inhibitory action on dorsal horn neurons, including the SCT, traveling by separate spinal pathways (Mokha *et al.*, 1985). Mokha and McMillan concentrated on the challenging problem of supraspinal control of the dorsal horn. They combined microelectrode recording in the dorsal horn with electrical stimulation of identified regions in the brain stem. Brain stem stimulation has widespread actions in the spinal cord and the analysis of the mechanisms is certainly not to be undertaken lightly (Mokha and Iggo, 1987).

Another topic was introduced by Sue Fleetwood-Walker, who joined the SSR group in 1982. She already had experience in exploring the descending catecholamine systems. Using pharmacological methods, she established that the major action was via α2-adrenergic receptors expressed on the processing of nociceptive input. Her funding came from the Wellcome Trust and her continuing interest is in the application of molecular biological techniques to the expression of mRNA in chronic inflammation and neuropathic pain. Arthur Duggan became the chair of veterinary pharmacology in 1988, bringing his special knowledge of neuropeptides in the spinal cord, and established an active research group.

Superficial Dorsal Horn

My major interest in the superficial dorsal horn developed gradually. The most superficial layer of neurons in the dorsal horn (Rexed's lamina 1) contains some relatively large cells (Waldeyer's marginal cells). Perl and colleagues had already reported that some neurons in this lamina could be excited only by nociceptors. An intensive search for nociceptor-driven dorsal horn cells was initiated as a natural follow-up from my experiments in Heidelberg on class 1 and 2 dorsal horn neurons. This was the start of a fruitful collaboration with Fernando Cervero and Hisashi Ogawa (Cervero *et al.*, 1976). We searched for lamina 1 neurons in anesthetized cats using pontamine-blue filled microelectrodes for recording and marking cell

locations. To assess the existence and potency of supraspinal control, we applied reversible cold block to the spinal cord. My earlier experiments with Handwerker and Zimmerman had shown the importance of using selective natural cutaneous stimuli (e.g., touch and radiant heat) as a way of evoking well-controlled nociceptor inputs. We could further restrict the afferent inflow to particular kinds of afferent fiber by local cooling of peripheral nerves.

The Waldeyer neurons in the marginal zone (lamina 1) included nociceptor-driven neurons; some were excited exclusively by Aδ-innervated mechanical nociceptors (class 3a) and others by noxious mechanical and noxious thermal receptors with Aδ and C fibers (class 3b). However, the zone was not exclusively populated by such cells. There were larger, more easily recorded cells of class 2, with a bimodal input. Light tactile stimuli, in contrast, provoked a powerful inhibition of nociceptor-induced discharges—an effect reminiscent of the relief of pain caused by gently rubbing a sore place. This potent inhibition was still effective when the spinal cord was blocked rostrally—an example of a local segmental interaction. The central projection of the class 3 dorsal horn cells was uncertain. Most of the cells were local neurons, but there was no doubt that a private pathway for nociception, such as the spinothalamic tract, exists.

Substantia Gelatinosa

The severe technical problems of gaining exact information about the origin of electrical activity that could be recorded led us to develop ever more sophisticated methods. These methods eventually led to the intracellular examination of substantia gelatinosa (SG) neurons. There is no doubt that much of the controversy surrounding the electrophysiology of the dorsal horn, and particularly its 'pain' components, arises from technical problems. Perseverance and access to excellent engineering and technical support from departmental staff played a part in enabling us to obtain precise information about the neurons that we analyzed. The cell bodies of the SG neurons are tiny (10–20 μm diameter). Special microelectrodes were developed (Ensor, 1979) to allow us to record intracellularly from the neurons and to mark them with dyes (Molony *et al.*, 1981). Inevitably, the yield of such neurons when adopting these stringent criteria was small. The prize was worthwhile. Intracellular records revealed that the SG neurons with excitatory noxious inputs had persistent background synaptic activity. The ongoing SG discharge could be regarded as being a simple renewal stochastic processes, with each spike being generated by the cumulative action of randomly occurring synaptic events (Steedman *et al.*, 1983).

One output path from the dorsal horn is Lissauer's tract (LT). It contains mostly unmyelinated axons, with a smattering (20%) of

thin myelinated axons. Up to one-half are dorsal root afferents, and the rest are axons of dorsal horn neurons. The tract thus contains incoming dorsal root afferent fibers and outgoing lamina I and II axons. Its role has attracted interest in part as an interconnecting pathway for the SG. We investigated this by electrical stimulation of the tract while recording intracellularly from SG neurons two to four segments distally. The functional types of neurons projecting through LT are diverse—there are both short- and long-range systems and the SG component is short range. The review by Cervero and Iggo (1980) is a comprehensive account of the anatomy and physiology of the SG, a topic not to be condensed into a few sentences.

Spinocervical Tract

Alternative pain pathways were also explored. Alan Brown and colleagues, working in an adjacent lab, were analyzing the spinocervical tract (SCT), which clearly was an important pathway from hair follicle afferents in cats. Together with Vince Molony, who had joined our team, we explored the possibility that the SCT might have a role in nociception. It was clear from Alan's lab that many centrally projecting SCT cells were driven by an input from cutaneous mechanoreceptors and nociceptors. This we quickly confirmed, in addition to a response to pure nociceptor inputs. Eighty-four percent of our sample of SCT cells were affected by noxious inputs; most were excited but a minority either were inhibited or gave a mixed response. Nearly all these SCT neurons were recorded in deeper laminae in agreement with Brown's intracellularly marked neurons, which were almost exclusively in lamina III. Significant from the viewpoint of nociception was that only one cell in our sample was excited exclusively by nociceptors. We concluded that the SCT in the cat is not a nociceptive 'private' line system (Cervero *et al.*, 1977a,b).

For more than a decade, the dorsal horn research team included F. Cervero, D. Ensor, H. Handwerker, V. Molony, H. Ogawa, R. L. Ramsey, and W. Steedman. Today, as I view the senior posts and honors that have come their way, I realize how fortunate I was to have enjoyed such congenial company in my personal research argosy through the dorsal horn. To work with this talented group was a far cry from the days in the 1950s when it was possible to make progress on one's own. Full credit is also due to the highly skilled technical staff on whom so much of the success of the research laboratories hangs. In 1988, my personal involvement with the dorsal horn ended.

These various investigations and their integration into the corpus of neurophysiology are charted in articles in *Brain* (Cervero and Iggo, 1980) and in a Royal Society symposium (Iggo *et al.*, 1985). Views on nociception current in 1988 were brought together at a NATO Advanced Science Institute symposium (Cervero *et al.*, 1989).

Cutaneous Sensory Receptors

While the somatosensory laboratory was busy, H. Ogawa and I continued studies on other sensory mechanisms (Iggo and Ogawa, 1977). We sought to identify the mechanoreceptors in glabrous skin of the cat's footpad using the combination of physiological and electron-microscopical techniques that had been developed for settling the SAI–SAII issue. Typical RA units with myelinated afferent fibers were found to have Krause corpuscles of cylindrical type as their sensory receptors. Their physiological responses distinguished them from PC and SA. The stratum corneum of the footpads, in which the receptors lay, clearly influenced their mechanical sensitivity and tuning curves. Again, this was further evidence for the morphofunctional specificity of cutaneous sensory receptors.

The transduction process in SAI mechanoreceptors engaged my attention, and that of several collaborators, for many years. Various procedures were used in attempts to resolve the role of the Merkel cell. In the 1960s, Alan Brown and I established that the reinnervation of Merkel cells, after denervation, was required for the reestablishment of the typical slowly adapting response of SAI to mechanical stimulation. Others tried procedures such as anoxia. It was not unusual to find that the osmiophilic granules in Merkel cells were fewer when the response of an SAI to a mechanical stimulus was absent. The cells subsequently recovered on reversal of the procedure that had caused the reduction. We were unable, however, to attribute the effects exclusively to changes in the Merkel cell since the expanded nerve ending (Merkel disk) was exposed simultaneously to the various procedures we tried (Findlater *et al.*, 1987).

By 1991, a new approach was called for. An invitation from Haru Ohmori provided the opportunity to spend several months at his research laboratory in Okazaki, Japan. Ohmori (1984) had developed techniques for the enzymatic isolation of cochlea hair cells. In his laboratory, I tried to measure changes in calcium ion concentrations in dissociated Merkel cells using fura–2. It was my intention, on returning to Edinburgh, to continue to use these cell isolation techniques. When Masakazu Tazaki arrived from Japan to spend a sabbatical in my laboratory in 1992, these experiments continued. He was skilled at dissecting SAI receptors from the buccal mucosa of cheek pouches of golden hamsters. Attempts to measure stimulus-induced changes in calcium ion levels in the isolated quinacrine-labeled Merkel cells were unsuccessful. We did, however, extend previous statistical analyses of the adapted afferent discharges of the SAI and concluded that the ISI distribution during a steadily maintained mechanical stimulus was the product of independent spike generators, namely, of the individual Merkel cell–neurite complexes (Tazaki and Iggo, 1995). Since his return to Japan, Masakazu has succeeded in measuring the activity of voltage-dependent Ca^{2+} channels in Merkel cells (Tazaki and Suzuki, 1998).

Chemalgia

My interest in chemalgia had lain dormant since the experiments with Nancy Fjällbrant in 1959. It were reawakened by Loris Chahl, an Australian pharmacologist (Chahl and Iggo, 1977). We tested potent algogens by exploring the effect of intraarterial injection of these drugs using a development of the technique used previously with Nancy Fjällbrant. Our interest had been aroused by emerging information on nonsteroidal inflammatory agents (NSAIDS) and the suggestion of Ferreira that prostaglandin could sensitize pain receptors. Bradykinin (BK) alone had little effect, but it became potent after a priming infusion of prostaglandin E1(PGE1) and vice versa. We concluded that the two agents, acting peripherally, had a mutually potentiating action on the nociceptor terminals.

This interest in neuropharmacology lapsed after Loris' return to Australia, but it was revived a decade later during a short sabbatical leave funded by a European Science Foundation Twinning grant. This gave an opportunity to live in two of Europe's most fascinating cities and engage in serious scientific work. Experiments began in Ulf Lindblom's department in Stockholm and continued in Gisele Guilbaud's laboratory in Paris. My interest had turned again to sensory receptors, in the company of experienced pharmacologists.

A type of arthritis, similar to human rheumatoid arthritis, can be induced in rats by the intradermal injection of complete Freund's adjuvant (a suspension of killed *Mycobacterium butyricum* in mineral oil). The activity of dorsal horn, thalamic, and cortical neurons can be changed dramatically by joint inflammation. We tested the peripheral effects by evaluating the responses of afferent fibers that innervated rat ankle joints. The joint nociceptors, normally silent, in inflamed joints now developed an ongoing discharge and were more easily excited by innocuous stimuli (Guilbaud *et al.*, 1985). The topical application of lysine acetylsalicylate (ASA) (a soluble aspirin) or paracetamol reversed the enhanced sensitivity but did not alter normal receptors. These actions were attributed to the irreversible blocking action of NSAIDS on cyclooxygenase, thus preventing the formation of prostaglandins. The experiments continued on my return to Edinburgh, under an Arthritic Research Council grant, with Danny McQueen and Blair Grubb. PGE_2, PGI_2, and prostacyclin (a stable analog of PGI_2) were injected retrogradely into the femoral artery of normal and inflamed ankle joints. PGE_2 had no obvious effect on the mechanical excitability of the receptors in either normal or arthritic rats. Nor was it able to restore excitability in arthritic rats after its reduction by ASA. It could, however, enhance the potency of BK. In contrast, PGI_2 and prostacyclin caused both sensitization to mechanical stimulation and excitation of a majority of the joint nociceptors in normal and arthritic

rats. These effects were consistent with the hypothesis that endogenous PGI_2 has a role in lowering nociceptive thresholds in the arthritic joint (Grubb *et al.*, 1991; Birrell *et al.*, 1991).

Electrosensory Cutaneous Receptors, 1984–1996

My interest in cutaneous sensory receptors took a new direction when Karl Andres in Bochum showed me his specimen of a platypus bill. This indigenous Australian monotreme is a cosurvivor, with the echidna, of the monotremata. These distantly related egg-laying mammals, along with marsupials, survived on the island continent of Australia after it had separated from the Asian landmass. They had therefore escaped predation by the eutherian mammals, including the carnivores. One distinctive feature of the platypus is its very richly innervated bill. This rich sensory nerve supply was first described in the late nineteenth century by E. B. Poulton, but it had remained a curiosity until Andres, an electron microscopist with an interest in brain development, became interested. With Monika von Düring, he described a complex array of sensory receptors in the skin of the bill. When I consulted him about sensory receptors in mammalian skin, he raised the question of the functional properties of the platypus bill receptors and suggested that we might mount a joint morphofunctional study of them. There was one small bureaucratic difficulty. Although not an endangered species, the platypus and echidna are protected and accorded a special role in Australian biology. This made it necessary to obtain the very restricted licenses from the relevant department of fisheries and wildlife before we could obtain specimens. By good fortune, Uwe Proske, a comparative physiologist at Monash University, Victoria, Australia, cooperated wholeheartedly with the project. To some extent, several visits to Monash assuaged my wanderlust. These visits were scientific expeditions that combined an element of open-air adventure (to capture the experimental animals) and laboratory-based electrophysiology. Platypuses are twilight animals and I remember the Southern Cross describe an arc around the South Pole while I attended to the net during my turn as night watchman.

The monotremes provided a surprise. Our first experiments in 1984 were on echidnas and gave results that confirmed and extended previous analyses of skin receptors in eutherian mammals (rather too well, as it turned out). The usual set of myelinated mechanoreceptors was confirmed with, in addition, an unusual thermoreceptor. This posed the question, 'Are there additional kinds of receptors unique to the monotreme?' Next came a report from Scheich *et al.* (1986), who found (i) that the platypus could detect weak electric dipoles and (ii) that evoked potentials appeared in the somatosensory cortex of the brain when the bill was exposed to weak electrical fields. They concluded that the receptor array of the platypus bill included electroreceptors. This indeed was news and, posthaste, we got licenses and did morphofunctional experiments on the platypus. Within a year we had

electrophysiological evidence for electroreceptors in the platypus bill. The receptors were associated with the ducts of the large mucus sensory gland (Gregory *et al.*, 1987). Each duct contained an assemblage of nerve terminals at its epidermal base. The platypus, however, had 'reinvented the wheel' because these electroreceptors were quite unlike those that have evolved in fish. The latter comprise a receptor cell and an associated sensory nerve terminal, whereas in the monotreme the electroreceptor is the structurally specialized terminal of a somatic afferent nerve fiber.

With this new evidence on electroreceptors, we again examined echidnas and found electroreceptors that were concentrated about the tip of the snout. This was where we had previously found 'thermoreceptors.' In light of the new results, they were probably electroreceptors. Behavioral experiments confirmed that the echidna could detect weak electric fields in water (Gregory *et al.*, 1989). Although it is a terrestrial animal, the possibility remains that it may use its electroreceptors when rooting around in damp soil with its long snout while seeking prey. An unsettled issue is the function of the vesicle chain receptors that lie at the core of the push rod in the monotremes. This is another complex receptor, found in both platypus and echidna. We made several attempts to mark the receptive fields of mechanoreceptors. The density of innervation of the bill/beak skin defeated all our attempts at a secure morphofunctional correlation. A detailed account of the anatomy and fine structure of the echidna snout by Andres *et al.* (1991) enabled us to put the sensory receptors into context. A review of these various investigations (Proske *et al.*, 1998) appeared in an issue of the *Philosophical Transactions of the Royal Society* that was devoted to the monotremes.

Retrospect

In addition to my multifarious departmental activities were the inevitable administrative duties that British universities required of their professors. More satisfying was service on the editorial boards of scientific periodicals, such as the *Journal of Physiology, Experimental Brain Research*, and *Pain*. Equally rewarding was the responsibility for initiating and organizing international research conferences and symposia, both in Britain and abroad. From 1972 to 1975, I was the inaugural chairman of the IUPS Somatosensory Commission, a committee that promoted periodic symposia and continues its work under successive chairmen to this day. As president-elect of IASP, I was responsible for the local organization of the Third World Congress on Pain held in Edinburgh in 1981.

International science, through scientific congresses and symposia, with the give-and-take of discussion that they generate, contributed to my research activities and, I hope, to the world's knowledge base. A particular pleasure of my lifestyle has been the way it has afforded me opportunities

to explore the world. In part, this has come from joint research interests with colleagues in other countries. The consequences of the research visits have been enduring friendships and new knowledge.

Coda

As a small boy I went fishing on my own on the bank of the Grey River in Greymouth. I used a hook fashioned from a bent pin attached to a string to catch cockabully (a small, freshwater fish). This was a favorite pastime. Once, the target fish was out of reach and, oe'r-stretched, I fell in and was being swept out to the Tasman Sea. My thoughts could hardly have been on the distant future when I was plucked from disaster downstream by a fisherman who caught me in his whitebait net. The plucking has continued throughout the ensuing 70 years. The tide that has carried me to my present retirement was of a different kind and there have been other fishermen. There is no doubt that their aid has been just a providential. Several people stand out—my tolerant parents first. At high school, K. E. McKinnon was a surrogate father whose counsel and judgment saw me through my teens and channeled my efforts into academic pursuits. Undergraduate years at Lincoln College were guided by M. M. Burns. He had ventured forth from New Zealand and knew the international academic world and served me as an early role model. Probably the most significant influence was that of J. C. Eccles, who took me, a raw agriculture graduate, and introduced me to the delights, mysteries, and challenges of neuroscience. He too had grown up in a rural antipodean community. At Oxford, he had been a tutor to David Whitteridge. I felt like a 'scientific grandson' when I was recruited by David, who was then a professor of physiology at Edinburgh. I was fortunate to join David's department when my skills and knowledge did not match the scientific goals that I had set for myself. He guided and supported my emergence as an electrophysiologist. Since 1962 when I was appointed to the chair of veterinary physiology, I have ploughed a more independent furrow, gradually building up research teams and a department whose work I am proud to recall. I let the record speak for itself as, more than 50 years later, I look back with gratitude on an active life spent in the service of my university and scientific discipline.

Mozart, gardening, and bee-keeping are now my chosen pursuits.

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