Adventures in physiology: The times and life of Autar S Paintal (1925–2004)

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1. Introduction

"In a sheaf of photographs on a table is one of an elderly man, clad only in his trousers, the lean muscles standing out in his swimmer's back as he bends over a complicated apparatus garnished with oscilloscopes, recorders, and a massive camera that once formed part of a World War II surveillance aeroplane. In many ways it is a classical record of classical science, the scientist in his laboratory at the dead of the night, immune to the passing of time and the fact that he is semi-nude. The progress of the experiment is independent of the minor constraint of the motion of the earth on its axis, and the shirt is off for what better way than this to beat the Delhi heat." (*Patriot*, July 1982) (figure 1). Autar Paintal, determinedly at work in his laboratory: having recently been through the most trying years of his life, which were replete with expressions of academic disharmony. Finding an enormous gulf between their achievements and his, some of the faculty – not much younger than him – were trying to shut down his laboratory. His election in 1981 to the fellowship of the Royal Society of London (1981) seemed to have intensified their effort in this direction. Had a passionate involvement with scientific activity not been the fulcrum of his life, and had not his well wishers and admirers at home and abroad stood by him, he would have certainly succumbed to the pressure and closed his laboratory, so tenacious was the exercise to do so.

For Autar Paintal, the terrain underfoot was always rough in whatever he chose to study or pursue, but he managed some how to infuse great excitement into it; this made me borrow the title from Sir Henry Dale's book by the same name (which is a selection of the latter's scientific publications).

Paintal was born on September 24th, 1925 in Mogok, a town in northern Burma (Myanmar). His father, Man Singh, was one of the few members of the family who survived the great plague epidemic of 1903. He went to live with an uncle in Burma where he studied at Rangoon Medical College and obtained a licentiate degree to practise medicine. Thereafter he worked for the British Medical Service. But, not unusually for those times, Dr Man Singh found himself in the grip of the movement for independence. His political views were inflected towards socialist ideology and he was fiercely combative with his British employers especially when it came to upholding the rights of the underdog. In his own words, he was "Always in disagreement with his seniors".

2. Early days

As a youngster Autar Paintal spent a lot of time hanging around the hospital and surgery where his father worked – occasions, which the latter utilized to tutor him in many matters. It is possible that his upright and unbending attitude in issues of right and wrong took root during these exchanges.

He had to change schools every few years, as after every confrontation with the British, his father was posted out, at times to remote mosquito-infested towns as "punishment postings". He at first attended St Paul's School in Rangoon and then when the family moved to Mandalay, he went to St Peter's. Here football was his great passion (on our visit to this school in 2003, a year before he passed away, he was pleasantly surprised to find that the goal posts still stood where they used to). He never lost an opportunity to play truant and go fishing with his friends in the moat that surrounded Mandalay Palace. He recalled that invariably he was caught and caned, as was the practice in those days; he took to wearing two pairs of shorts at the same time to lessen the pain. This may have been an early instance of his devising something simple to overcome a problem, a quality that persisted right until his last days. The extra pockets also allowed him to stow away any unfancied part of his lunch.

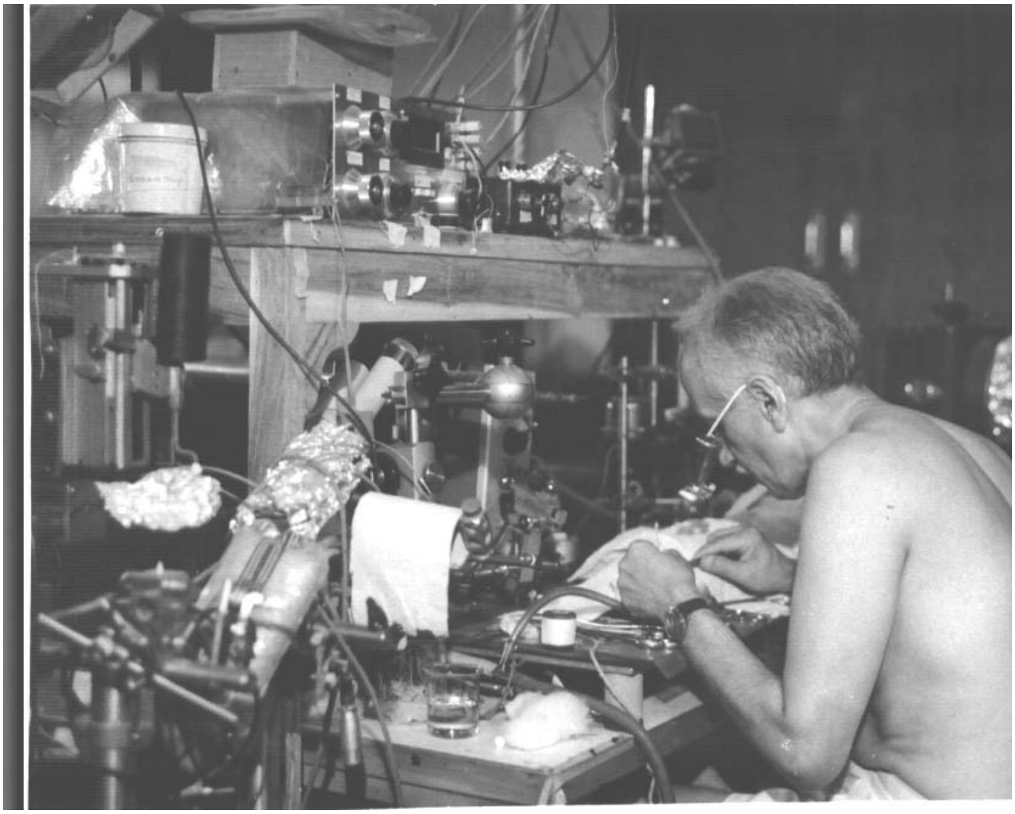


Figure 1. In his laboratory in Delhi – getting the vagal nerve fibres ready to record from.

From Mandalay the family moved to Kalaw, a picturesque hill station in the southern Shan States where he went to Kingswood school. He was ten years old and left in the school's residence when the family returned to Rangoon. In 1939 when war was imminent and a Japanese occupation likely, he was sent to an aunt in Lahore ahead of the rest of the family to finish his matriculation. He was fourteen years old, studied in the Khalsa High School and worked hard at his lessons without help from anyone. His cousins went to a fancy school and generated a lot of peer-pressure, which he countered by excelling at studies and amusing them with his fund of limericks. Along with them, he also learnt to row the large country boats that were used for ferrying villagers across the river Ravi. Rowing became a favourite pastime and was to remain a way to relax, a form of exercise and a getaway. Much later, in January 1986, when he found his name in the President's list of honours, he bade us pack a picnic and spend the entire day on the river Yamuna, rowing and spotting birds on the water's edge. Sundown made us go back when he had to answer the phone calls from which he could not escape any more.

In Lahore, Paintal attended Forman's Christian College and wrote the Intermediate Examination of Punjab University (1943) after which he joined the family in Lucknow, where his father had chosen to settle down.

3. Medicine and early research

He read medicine at King George's Medical College in Lucknow in 1943, where he was supported by the Burmese government as he was an evacuee from that country. He had to sign a bond to serve Burma after completion of his medical studies but was unable to do so because the conditions prevailing at the time prevented him from travelling there. The years at King George's Medical College (1943–1948) were marked by distinctions, honours and awards, finished off by winning the coveted Hewitt Gold Medal for obtaining the highest marks in the final MBBS examination. For the ultimate quiet that he sought for concentrating on his lessons, he often found himself studying under the bright lights in the grounds of the Lucknow Residency. On other occasions he extended this by holding together a few of his friends in a discussion group in the coffee house in Hazartganj or the "high street" in Lucknow. Leisure time was spent rowing on the river Gomti with friends, and as amateurs the group became skilled enough to win awards in the annually held Regattas of Lucknow University.

One does not know what drove him to the research bench with such intensity after having obtained a degree in medicine, which he did in 1948 with many honours. His enviable performance as a medical student meant that he was expected to take up clinical medicine and make a success of it in more than one way. Clearly, what did take him away from pursuing clinical medicine as a career was the 'duplicity' as he often put it, that he began to encounter in the profession. After the first false report that he was made to sign by his senior, he all but made up his mind not to pursue medicine as his career. His attitude towards such tendencies hardened with time. Later, it was to result in his spearheading the movement for ethical values in the conduct of science; by 1986 he had helped found the Society for Scientific Values – the first of its kind in the world.

Paintal started to work for an MD degree in psychophysiology whilst a lecturer in the Physiology department of his medical college. His thesis was entitled "Electrical resistance of the skin in normals and psychotics". He chose the problem himself and worked on his own. Building apparatus and handling it with great dexterity, he collected extraordinary data and devised an index which came to be referred to as the 'Paintal Index' Since the index was independent of basal skin resistance, it assumed considerable value till more advanced methods were available to psychiatrists to diagnose psychosis (Paintal 1951).

In 1950, having acquired a post-graduate degree in physiology and brimming with ideas, he applied to the Rockfellar Foundation for a Fellowship to work on a problem which was largely of his own choosing. He arrived in Edinburgh in November of that year to work for a PhD, just three months ahead of Professor David Whitteridge, who was to introduce him to visceral sensory physiology. At that time the department of physiology at the medical school had a reasonable library and workshop but nothing in the way of a well-equipped electrophysiological research laboratory. With help and advice from Jock Austin, an electronics engineer who was his technical assistant, the Professor built up an excellent infrastructure for research and teaching in electrophysiology, and supplemented these efforts with lectures in electronics to students and junior colleagues. Like the other new students, Paintal too was encouraged to spend the first six months building equipment (figure 2) from parts obtained from World War II disposal or surplus equipment. He had become quite skilful at rigging up electrical circuits during his MD studies at Lucknow.

Life for him was quite simple till July 1951 when he decided that it was impossible to record the electrical activity of single nerve fibres using the old "steam box". In those days the entire experimental animal, which was a cat, was kept inside a box in which steam was generated continuously. This was done in order to prevent the dissected-out nerve from which electrical recordings had to be made, from drying up. But a dripping condensate made it impossible to see the nerve fibres through the microscope; dissecting them so finely as to provide identifiable components of the compound action potential was unthinkable. Instead, Paintal thought of doing away with the box and immersing the nerve under study in liquid paraffin, to prevent it from drying. He told the Professor his plan, saying that otherwise it was going to be impossible to dissect out single live nerve fibres from the vagus nerve and measure their individual conduction velocities. This was the object of his study and was necessary for studying the properties of nerve fibres innervating the heart and lungs, which are carried in the vagus nerve. Whitteridge warned him that others before him had tried to dissect and record from single fibres from peripheral nerves under paraffin, but had given it up as a failure. But he persisted. Jock was aghast, warning him, "You are throwing away the Professor's box, you know! I hope you have a return ticket on the ship to Bombay." Finally, Paintal did succeed in dissecting nerve fibres under paraffin and recording the electrical activity not only from pulmonary stretch receptor fibres (the ones that respond when lungs are inflated) but also from nerve fibres originating from baroreceptors in the heart (sensory receptors that are sensitive to stretch of the heart muscle). However, it was not until he had recorded from nerve fibres coming from the lung vasculature that the Professor himself worked on, measured their conduction velocity and 'proved' it with some more new tricks, that the latter finally got excited.

This technique came to stay and is utilized even today by neurophysiologists in laboratories all around the world. By fearlessly opening the chest and prodding about the heart and lungs with a glass rod, he also succeeded in short-circuiting the Professor's rather elaborate and indirect ways of localizing cardiac and pulmonary vagal afferent nerve endings (Paintal 1954).

4. Single active nerve fibres — identification and properties

During the years that he worked for his PhD, besides developing the technique of single nerve fibre dissection and measuring their conduction velocities, he utilized other electrophysiological techniques (concentrating on the vagus nerve of the cat) and succeeded in relating the conduction velocities of the two kinds of afferent (the ones that go from the periphery to the brain) nerve fibres i.e. the myelinated ones with large diameters ranging from 1 to 10 μm (conduction velocity, 2.5 to 59 m/s) and the non-myelinated ones with diameters ranging from 0.4 to 1.2 μm (conduction velocity, 2.5 m/s or less). The technical task of isolating and recording from single live nerve fibres, especially non-myelinated ones of small diameter, i.e. thin and delicate ones, is an exasperating exercise. Only those who have undertaken it know how the exercise can fail repeatedly, leaving not a single fibre to record from at the

Figure 2. Edinburgh days: Some lighter moments in the lab, and his own joy on unrolling the filmed records of the experiment of the night before.

end of the day. He overcame this problem somewhat, by isolating the activity of a single active fibre from a multi-fibre preparation. With this technique he was able to study the various characteristics and functions of nerve fibres that run in the vagus nerve. Subsequently he was to show that all myelinated nerve fibres were blocked at about the same temperature, 7°C. This was an advance, because it made it possible to identify the reflexes originating from non-myelinated fibres after lowering the nerve temperature to this level. He also showed that there existed a transition between the properties of the myelinated and non-myelinated fibres and that the spike duration and rise time of the impulse vary with the diameter of the nerve fibre and were not constant for all nerve fibres as was believed till then (Paintal 1953c, 1965a,b, 1966a,b, 1967). These findings were utilized in studying demyelinating peripheral neuropathies (e.g. as seen in diabetes mellitus). Much later he was to write an authoritative review on the properties of mammalian nerve fibres (Paintal 1978).

He became adventurous after submitting a PhD thesis and decided to find out where in the lungs the pulmonary vascular receptors that Whitteridge had been studying were located**.** To his utter surprise and horror he found them in the left and right atria (i.e. in the heart and not in the lungs). He knew the Professor would be shocked and did not know how to break the news to him. More data was required which he succeeded in obtaining. After a couple of weeks, Whitteridge accepted the finding and said that he was delighted to have been corrected. This gave Paintal instant fame and notoriety, and also inaugurated a new phase in his career. But at that time he did not realise the importance of the finding, certainly not till he had communicated it to the subsequent Physiological Society meeting, where Whitteridge got up and gave an appreciation of what he called Paintal's "heroic experiments" (opening the chest of the cat for localizing the receptor with a single active fibre on the electrode). He found this rather embarrassing but enlightening at the same time. When the paper was published in the *Journal of Physiology,* it had only Paintal's name on it (Paintal1953a). The Professor had shown him the rules of the game. These were, to give credit unhesitatingly where it was due, and to restrict the authorship of papers to those who actually took part in the study. The rules remained with him throughout his life but he found that his insistence on them were a source of great irritation to several of his colleagues in the institutions that he worked in, in India. For him, a legitimate author was one who, finding a pack of slides suddenly thrust into his hand, could give a sensible talk about the paper under discussion, and additionally be able to answer all questions asked.

Thus the first of his significant findings was showing that the "pulmonary vascular fibres" which Whitteridge had reportedly discovered, did not exist. The techniques that he introduced and the sensory receptors that he discovered and described have become the building stones of our present knowledge of visceral physiology. Amongst the cardiac receptors that he discovered, are the type B atrial receptors which signal the amount of atrial filling and the ventricular pressure receptors which cause a reflex fall in blood pressure when pressure inside the ventricles rises (Paintal 1955b); the work came to be included in the Benchmark Series, as one of the classical papers in cardiovascular physiology. Other discoveries were the gastric stretch receptors, mucosal mechanoreceptors of the intestines, pressure-pain receptors of muscles and contributions to the understanding of chemoreception in the peripheral (arterial) chemoreceptors.

From the very beginning of his career, Paintal had to make do with meagre resources. He not only taught himself "mathematics for technical students" and "physics for biologists" but also the German language — a fair number of the classical papers in physiology that he wished to read were written in German. He made several electronic circuits in his laboratory in Delhi and was able to repair his Beckman and Grass preamplifiers and stimulators most of the time. David Whitteridge remarked once that Paintal was probably the only Director in the world who wields a soldering iron. According to him, his laboratory in Delhi took form as a result of friendships with the electronics technicians in all the laboratories that he had worked in. After Jock in Edinburgh came Harry Feintuch at the University of Utah. In 1958, as he was about to leave the US for India, he received a telegram from Professor Kurt Krämer, the Director of the Physiologisches Institut, Göttingen, inviting him to spend some time there as a Guest Professor, and to demonstrate to the Germans too, his newly discovered neuro-physiological techniques that had been fascinating laboratories all around. The equipment which he wished to use had been built in the university's workshop in Utah and was lying in a ship in Genoa destined for Bombay. So he went to Genoa, got it out of the hold and brought it to Göttingen where with the help of the electrical, mechanical and electronic workshops he built some more bits and got the experimental set-up going.

Throughout his life, holidays and weekends saw him either repairing his own or a student's equipment or getting it ready for the next experiment. He remained in admiration of electrical engineers, who he said "are priceless people, they are like neurologists in tracking down the site of lesions". When computerized equipments took over physiology laboratories, he looked upon them with disinterest – not being able to calibrate them and not being able to identify the source of the problem when they stopped to function. Indeed, more so because colleagues started to talk in terms of "cleaning up their data" with the help of computers.

5. Lung deflation receptors (juxtapulmonary-capillary receptors)

From Edinburgh he went to work in Kanpur (1952–1954) at the Technical Development Establishment Laboratories (TDE) of the Ministry of Defence, after seeing the post of a Technical Officer advertised by the Union Public Service Commission. The agreement with the Rockefeller Foundation had demanded that he return to an institution where he would also teach, but the hiring criteria at his parent institution in Lucknow showed scant interest in his scientific achievements or capabilities. After a harrowing exchange of letters between the Lucknow University, the Foundation and himself he was freed to take up this assignment. By contrast, the Superintendent of the TDE laboratories, Dr T S Subramaniam, showed great generosity and allowed him to carry out the work begun in Edinburgh, outside normal working hours and on holidays. His main assignment was to develop suitable clothing keeping in mind the equipment that the armed forces worked with and the extremes of temperatures that it was carried out at. Here he discovered the gastric stretch receptors (the ones which are responsible for the immediate satiation of hunger and thirst; Paintal 1953d). With this he opened up the study of electrophysiology of sensory mechanisms of the gastro-intestinal tract. But to him the finding did not appear to be glamorous enough, and yet it seemed to have given him the momentum that culminated in subsequent discoveries. By the end of two years he began to despair in the academic wilderness that he had got into. After making sure that such a thing would not happen at the Vallabhbhai Patel Chest Institute, Delhi University, he accepted the position of an Assistant Director there (1954–1956). He had been in pursuit of a vagal sensory receptor that he first encountered in the Edinburgh days. It was late one night (or early in the morning) in 1954 that a thin nerve fibre responded with a volley of impulses within 2.5 s to a right atrial injection of phenyl diguanide (pdg), an amidine derivative which produces the cardiovascular and respiratory reflexes that he had begun to study in Edinburgh. A further study and its identification (see below) marked the important discovery of a lung sensory receptor, which later was to be named the juxta-pulmonary capillary or J receptor (Paintal 1955a).

This was the first great discovery in the field of medicine in independent India; there had not been one of comparable impact since Ronald Ross's finding of the role of the mosquito in the life cycle of the malarial parasite. Paintal had wished to preserve for posterity the bit of lung from which he had just recorded, but unfortunately it had to be thrown away: at the time, the rules of the Institute did not allow him to issue out formalin from the stores. Later, as Director of the Institute (1964–1990), he tried to streamline its functioning by keeping the interest of the research investigator foremost.

When he first reported the existence of these nerve endings that were stimulated by injections of pdg into the right atrium and by pulmonary congestion, he called them deflation receptors. This was because they were also stimulated by deflating the lungs and reflexly produced slowing of the heart (bradycardia), a fall in systemic blood pressure (hypotension) and an acceleration of breathing (tachypnoea). But what was their physiological stimulus? He proposed that it should be pulmonary congestion — even transient and in a limited sense, not necessarily frank pulmonary oedema but enough to produce an increase in pulmonary capillary pressure by as little as 2 mm Hg. This would be adequate and, according to him, significant physiologically – although not be thought so by the pathologists in whose domain pulmonary oedema normally lies. He came to this conclusion not by any theoretical calculations nor by serendipity but by a series of experiments. First of all he knew that the endings could not be stimulated by deflation in the normal cat in its daily life. Furthermore, he had concluded that they would be located near the lung (pulmonary) capillaries, because of the short duration during which they were stimulated when chemicals were injected into the pulmonary circulation. However, he was not absolutely certain about their location.

Fourteen years after first describing them, he published a third paper (Paintal 1969) on these receptors and suggested that they were primarily responsible for producing reflex respiratory acceleration (rapid shallow breathing) and that they also took part in reflex bradycardia (slowing of the heart) following injections of the drugs used in these investigations. He also proved that the endings must be located in the interstitial tissue in juxtaposition to pulmonary capillaries and the alveoli. He therefore called them juxta-pulmonary capillary receptors or type J receptors (currently, J receptors). The location of these nerve endings was suggested by the short latency with which they were stimulated by the introduction of volatile anaesthetics into the lungs. This is best illustrated by the following schematic diagram (figure 3).

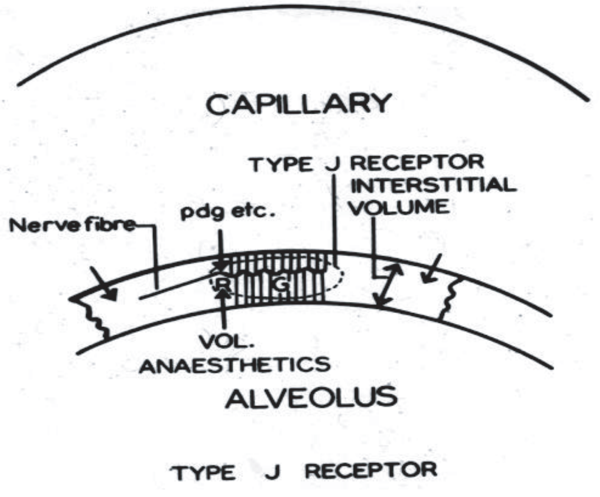


Figure 3. Schematic diagram of the location of a J receptor.

Figure 4. Getting ready to get a capsaicin shot from Abe Guz.

However, the most notable part of this work consisted of new observations on the responses of these endings during pulmonary congestion. He showed that no matter how the congestion was produced, whether by increase in back pressure in the pulmonary circulation or by a combination of increase in pulmonary capillary pressure and increased permeability of the capillary wall, the result was the same, i.e. an increase in the activity of the endings. As a result of these observations he postulated that the endings must be located in the collagen tissue in the interstitium and that the receptors become excited by the swelling of this collagen due to an increase in the outflow of fluid as a consequence of increase in pulmonary capillary pressure. The turning point in the life of the J receptors came at the Ciba Symposium held in London in 1969 to celebrate the centenary of the Hering Breuer Reflex.

There he met Abraham Guz, a Professor of Medicine at Charing Cross Hospital, London. Guz was able to persuade his colleague Lynn Reid to undertake an electron microscope examination of the lungs to find out if the receptors existed in the location that he had predicted. In return, Paintal volunteered to be a subject for Abe Guz's next investigation which was studying respiratory sensations of intravenously injected capsaicin (figure 4). Capsacin is the pungent principle present in capsicum; injecting it intravenously makes the face, hands and much else burn and go red.

Reid found evidence of their existence in the rat in the predicted location. Others found it in the mouse and in man.

6. What do the J receptors do?

6.1 *The J reflex*

In 1969, Paintal postulated that if the J receptors were indeed stimulated by a rise in pulmonary capillary pressure, which muscular exercise produces, some mechanism must exist to lower it reflexly (to provide cardiovascular adjustments). In view of the absence of any known mechanisms, since these receptors would be stimulated during exercise under normal condition (particularly when exercise is done at high altitudes, e.g. at 3,000 metres), and since no reflex cardiovascular adjustments were known that could reflexly reduce the activity of the receptors, he concluded that stimulation of these receptors must lead to reflex termination of exercise so that the muscle pump is shut off in the exercising limbs. This would provide a protective reflex to humans and animals against excessive pulmonary pressures and prevent the occurrence of pulmonary oedema. Thus if pulmonary capillary pressure rises with exercise there must be a natural way of reducing it (Paintal 1969).

Once, just before he left town, he asked Sharad Deshpande and Marcus Devanandan, two of his colleagues at the Vallabhbhai Patel Chest Institute, to examine the monosynaptic reflexes of both flexor and extensor muscles of the hind-limb of the cat in response to injecting phenyldiguanide (pdg), the chemical used for stimulating J receptors. Two days later when he returned, he found them pacing the corridor restlessly. He thought that their equipment had broken down and that they were waiting for him to return and repair it. Instead the duo told him that they had got a marked inhibition of the reflex each time they had injected pdg. He left them in the dark for a while about the possible reason, but asked them to repeat it in many more cats; which they did and came up with the same result each time. This reflex inhibition, conveniently called the J reflex, is a postsynaptic inhibition and the inhibitory impulses to the motoneurons are carried in the spinal cord. They also showed that unlike the respiratory and cardiovascular reflexes of the J receptors, the J reflex was abolished by decerebration, indicating that higher centres were involved. This was established soon afterwards by Madhu Kalia. Subsequently, in experiments with Koepchen in Berlin, Kalia also demonstrated this in conscious, freely-moving cats, by injecting pdg intravenously via a long indwelling catheter -- the cats were seen to stop suddenly.

7. The prey and the predator?

The reflex termination of exercise was described as one of the most important functions of these receptors. However, at the August Krogh Centenary symposium that Paintal organized as a satellite of the 26th International Congress of Physiology in 1974 at Srinagar, Dan Cunningham (Physiological Laboratory, Oxford), an unrepentant teleologist, posed an intriguing question. What would be the role of the reflex in animals like the rabbit and hare, which were prey for carnivorous predators? He could understand that if the predators ran into a pulmonary hazard (as described here), they would stop their activity. To the prey on the other hand, lying down till they recover is not of any use, as they would be eaten up. The possible answer to this is that the “protective J reflex” is overridden from higher centres of the brain when an emergency arises, i.e. in life-threatening situations. In the prey it would be seen as resetting of the inhibitory reflex with the J reflex being overridden by increased down-going neural inputs from supra cortical centres so that the run could continue. In animals the resetting of the reflex can occur from ‘arousal’, based on fear, with the perceived benefit overridng the reflex at the cost of impending doom (see below). In normal humans this can be illustrated by considering the case of elite athletes who can overcome this reflex that stops physical activity and increases breathlessness, by keeping the award at the end of the run foremost in their minds, and but who by the end of this severe exercise, may have blood-stained sputum due to rupture of pulmonary capillaries caused by raised pulmonary capillary pressure (which the reflex was supposed to prevent).

7.1 *Breathlessness*

“But even more remarkable, was his breathing, quick as a bird’s and noisy, in out, in out, in out all the time, tick tick tick, brittle as a clock with the same sense of urgency and no time to waste, no time for anything else”. (William Golding, *Free fall,* Chapter 1.)

In animals the stimulation of J receptors by a rise in the interstitial fluid volume and increase in pulmonary blood flow had already been demonstrated to give rise to an increase in the breathing rate (or breathlessness). In 1980, their activity was shown to be stimulated significantly in response to increasing cardiac output by two-fold, which moderate exercise produces (Anand and Paintal 1980). In healthy people breathlessness is well known with heavy exercise but in patients with lung or heart disease, it is seen with modest exercise or even while sitting or lying down and its ‘awareness’ in them is called dyspnoea.

Soon afterwards, observations were also made about respiratory sensations that accompany breathlessness and these could be related to increased impulses from J receptors. This was done by comparing (in man) the sensations produced by injecting lobeline intravenously (undertaken with Dr Hans Raj) with those produced by natural stimulation of J receptors during pulmonary oedema at high altitude. To carry out the latter one had to study subjects with pulmonary oedema either at Delhi or at high altitude. Since there was no way of studying a large number of them at either place, Paintal obtained special permission from the Director-General of Armed Forces, Medical Health, to peruse the medical records (from MI-1, or first Medical Investigation Report, onwards), of soldiers who had had high-altitude pulmonary oedema. This meant going well stocked with sandwiches and a flask of tea and spending about eight hours daily poring over stacks of records in their Delhi headquarters for several weeks in the record room. At the end of this he had a poster ready for the next Congress of Physiology at Sydney (1983). The finding that similar sensations were produced in the upper respiratory areas with high altitude pulmonary oedema (gradual stimulation of J receptors) and by injecting lobeline (sudden stimulation) was startling and at the centre of much discussion. He was invited to write up a review for the *News in Physiological Sciences* (Paintal 1995).

That the sensations produced by lobeline in normal human subjects are due entirely to stimulation of J receptors, was eventually established by correlating the responses of the three groups of pulmonary receptors and the J receptors in cats, to injections of lobeline with the sequence of events relating to the sensations produced by lobeline in man (Raj *et al* 1995). Normally such a vast study would have been distributed among 2–3 papers, but he insisted that all the data must be put inside the same covers and the story made complete from all angles. The publication triggered great interest among those studying respiratory sensations (in cardiorespiratory disease and in exercise), prompting Simon Gandevia in Sydney to investigate it in recipients of lung and heart-lung transplants (Butler *et al* 2001). Early on after surgery, the sensory receptors in the lungs of such patients are without their original vagal innervation and injecting lobeline into them at that interval should not produce any of the respiratory sensations that are known to be associated with it; and it did not. This reaffirmed the origin of the lobeline-induced sensations, to be J receptors.

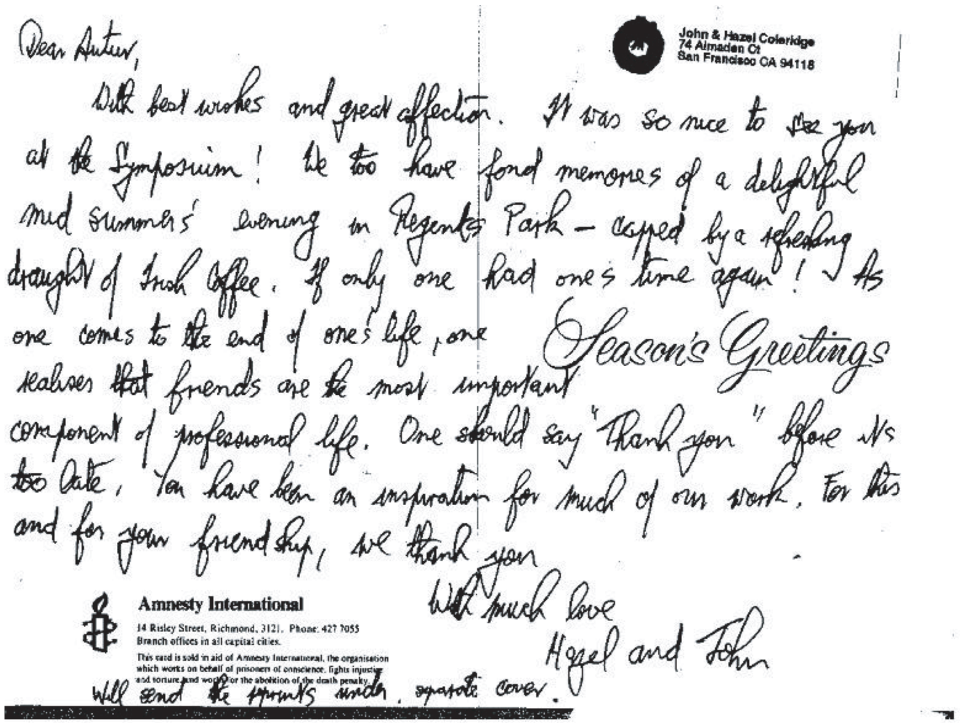
Natural stimulation of J receptors produces dry cough in addition to respiratory sensations in the throat and upper chest (Dehghani *et al* 2004). This finding has assumed significance clinically in people experiencing dry cough (as it indicates underlying interstitial oedema and heart disease), especially since it has been established that lobeline-induced cough is a reflex (from J receptors) and can be evoked in anaesthetized as well as in unconscious patients (Raj *et al* 2005).

J receptors were also shown to be stimulated by increasing the permeability of the pulmonary capillaries, an event that would have increased the pressure in the interstitial spaces (i.e. their natural stimulus). This was demonstrated not only as an enhanced response to pdg but also while using other chemical excitants such as nicotine and capsaicin (Anand *et al* 1993). Changes in permeability were brought about by using phosgene, as our interest in permeability oedema had been aroused by the leak of methyl-isocyanate gas (MIC) from the Union Carbide plant in Bhopal in 1984. MIC had produced pulmonary oedema and muscle weakness (reduced physical capability) in the affected persons.

The last few studies that Paintal was involved in were to demonstrate the application of the above knowledge for reducing the disabling consequences of exertion or exercise in patients with cardio respiratory disease. In this regard we were to seek further insight into the role of J receptors in termination of exercise (exhaustion or fatigue).

8. Commandeering discoveries by changing terminology

At the August Krogh Centenary symposium held at Srinagar during the 26th International Congress of Physiology in 1974, John and Hazel Coleridge presented evidence showing that J receptors were stimulated by a rise in left atrial pressure and that the degree of this stimulation was related to the degree of pulmonary congestion or oedema. This was clearly an advance. However, at the end of the morning's session, John Coleridge got up and said, "When we go out now for coffee, let us dig a hole six feet deep and bury the J receptors for ever". "Henceforth, these receptors will be known as pulmonary C fibres". A majority (80%) of the nerve fibres associated with J receptors have conduction velocities of 2.5 m/s (slowly-conducting) and should according to Gasser's definition, which is used for all nerve fibres be classified as non myelinated or 'C' fibres. However, about 20% of the population (a significant fraction) has conduction velocities above 2.5 m/s (fast-conducting). According to the classifying criteria the latter fall into the category of myelinated or A delta fibres. Besides others, the Coleridges' too found and reported that these sensory cells were innervated with both kinds of fibres. Yet they insisted that the entire population of these receptors be referred to as 'C' fibres and not as J receptors any more. At that time the Coleridges headed one of the most well-known laboratories in cardio-respiratory research, the Cardiovascular Research Institute in San Francisco. They were on the Editorial Boards of major Respiratory and Physiology journals and held important positions in Cardio-Respiratory research funding agencies (NIH, American Heart Association). Thereafter, all journals in North America forbade the use of the word J receptors and insisted that if manuscripts had to pass muster with referees, the receptors had to be referred to as C-fibres. This nomenclature was to be followed for research proposals being sent up for funding as well. Here, I should point out that it is customary to name sensory receptors either after the stimulus to which they are sensitive, to their function, or to their location. They have never been named after the type of nerve fibre that innervates them (i.e. 'C' or A delta). But the



John & Hazel Coleridge
74 Almaden Ct
San Francisco CA 94118

Dear Autar,

With best wishes and great affection. It was so nice to see you at the Symposium! We too have fond memories of a delightful mid summers' evening in Regents Park – capped by a refreshing draught of Irish Coffee. If only one had ones time again! As one comes to the end of one's life, one realises that friends are the most important component of professional life. One should say "Thank you" before it's too late. You have been an inspiration for much of our work. For this and for your friendship, we thank you

Season's Greetings

With much love
Hazel and John

Amnesty International
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This card is sold in aid of Amnesty International, the organisation which works on behalf of prisoners of conscience, fights injustice and torture and works for the abolition of the death penalty.

Will send the reprints under separate cover.

Figure 5. Not many knew that John and Hazel Coleridge had swept away their contentious issues with Autar Paintal.

Coleridges' view held sway. Paintal must have been amused by this but not unduly perturbed. Once earlier too he had encountered this with another one of the receptors that he had discovered, the type B atrial receptor, whose name Ron Linden and Tissa Kappagoda, had attempted to change.

One never saw him deterred by such displays of one-upmanship. He always looked forward to opportunities to be able to justify his convictions and argue about his disagreements in a friendly and forward-looking manner. He kept his analytical perceptions and sense of humour handy during these times. In his later years, while talking about his journey in science, he recalled such instances with his usual panache as the "romance and rivalry in science". Not many knew, but John Coleridge eventually acknowledged Paintal's leadership in the field (see figure 5 and Coleridge and Coleridge 1995).

9. The person

In most matters of life Paintal was painfully naive and quite incompetent at guessing what was expected of him. On this being pointed out, he would remark that his training as a scientist had rendered him incapable of such "psychic attributes". He was at the same time full of fun and dare and had a sense of humour, which navigated him through life. At committees and meetings his eyes would blaze with anger at the first hint of dissembling, but would sparkle with mischief as he made light of other serious moments with jokes and limericks.

He was an unaffected man who would make tea for all visitors to his lab and wash up later. The Vice-Chancellor's office in Delhi University was always amused to find him telephoning them directly and answering their calls without an assistant. Summer or winter, it was not unusual for him to walk across to the University for a meeting, the relevant files tucked under his arm. He was happy to have the Director's office double up as his laboratory, which was especially convenient if an experiment was on; the experiments could easily go well past midnight. He was not even a Professor of Physiology at the Chest Institute -- just the Director doing his own research.

Paintal pursued scientific activity for science's sake, which required him to sacrifice social success and personal security. He found that leading such a life was full of excitement and freedom. He was part of a large family and his playing fields extended to Europe and North America. He admitted that life for a scientist in India was almost an impossibility; "One had to spend 12 to 14 hours daily in the laboratory and that left little time for observing the innumerable ceremonies, festivals, fastings and relatives; the latter had to be received, entertained and seen off often enough".

His pleasures were simple. Disappointments with failed experiments were overcome by going off for a walk or bird watching if the weather was cold, and for a swim if

Figure 6. Savouring the last of the wintry sun after a day's rowing on the river Yamuna.

it was warm. When writing to his friends about his good and bad experiments and where they were leading, there would always be a paragraph devoted to such activities. To Richard Riley, an old colleague, while describing our newer experiments that were still holding up the model of carotid body chemoreception that he had proposed earlier, he wrote "We made it to the Wazirabad bridge thrice (!) this year. This was entirely because of 'foreign aid'. We had Richard Iggo, Ainsley 's son (Ainsley Iggo was *a collaborator from Edinburgh*) with us and he is an expert punter. So with us rowing and him punting we made it with great ease. It was also amazing that two years later we should see the white-breasted kingfisher precisely in the same location, on a branch sticking out from the eucalyptus grove (figure 6)."

10. Conduct and goals of scientific activity

He put in as much effort as he could to highlight, nationally and internationally, India's contribution in his field. To him, organizing a meeting or a symposium seemed appropriate only when there were advances to be talked about and taken advantage of; the three symposia that he organized in his lifetime were just such occasions. He published slowly and with care and recommended that the best journals be sought if findings were not to be lost from view. He was, however, appalled to find that the number of citations that a publication received was being used as a criterion of achievement in science. "This has had an adverse effect by reducing discoveries and advances. Many scientists do not have goals relating to making of discoveries or making inventions or trying to apply science for social needs. One gets the impression that scientists are not unhappy on account of not having made an important discovery. They are happy because their papers are being cited in peer-reviewed journals. Citations can be considered as being equivalent to the ovation given to performing artists such as musicians. Can the intensity of such ovations (i.e. number of people clapping) be considered as the brilliance of the music composition itself?"

His obsession with maintaining standards and ethics in science was well known and he never minced words while talking about it, either privately or publicly. After having served for a spell as the convener of the Biological Sciences Panel, he wrote to the Chairman of the University Grants Commission, "I have got the firm impression that the members of the Panel and other referees to whom some proposals have been sent, do not go through the proposals carefully. Most of the proposals themselves are poorly written up. They do not begin from a particular point in existing knowledge and as a result they do not seek definite answers. In my opinion they are not useful to our country and it is quite easy for me to see that only an appearance of applied research has been given. Although I have painted for you a logical picture, let me assure you that the Biological Sciences Panel is in a far superior to the situation to the one that prevails in the field of medical sciences e.g. Physiology. The main purpose of these research projects is to expand one's research empire, have large laboratories full of equipment, carry out mundane work and produce large numbers of papers that the publishers are only too happy to publish for the sake of their own existence."…. "I have been searching very hard for the past 8 years for the means by which we should improve the scientific standards of work done by our scientists. I have even tried to set an example, but I do not suppose it (the example) has been given enough for others to follow. Doing my own experiments, analysing my own results, repairing my own instruments and cleaning up my own apparatus, is not an example that has been followed. In the field of biology it has been demonstrated for over 100 years that the best research was done by the biologist himself with the help of a collaborator. It is therefore not surprising, that the quality of biological research is not high because nearly all investigators get their work done entirely by research fellows ranging from 4 to 20 or even more".

He advocated international scientific collaboration (especially as the Director-General of the Indian Council of Medical Research), but not AID. Not surprisingly, he always talked fearlessly about intellectual independence. After one such occasion in 1988, where told the graduates of the University of North Bengal 'think for themselves and not be dependent on others', the Ambassador of the United States asked him to desist from making such statements adding, by way of threat, "It will be bad for you".

11. Society for Scientific Values

In about the mid-1970's several instances of scientific misconduct in India began to be written about in science magazines the world over, he became concerned about the declining standards of scientific ethics in the country and started to speak about this and about the lack of goals and absence of accountability in Indian research activity. In 1986, after having conducted many rounds of informal discussions, he and several others who were similarly distressed by the situation sent out a circular to a large number of scientists in the country, explaining the necessity of founding a society to be called the 'Society for Scientific Values'. An excerpt from the circular reads as follows. "After independence, India has made considerable investment for the development of science and technology. There are many scientific and technical institutions, some of which have been very well equipped. However, the scientific contributions have not been commensurate with the investment. In fact, hardly any discoveries, innovations and technologies have originated in the country in recent decades. There are several reasons for this, e.g. inadequate salaries and other needs such as housing, transport, schooling, medical facilities and so on. But these are not the main reasons, as these facilities were not better before independence when some outstanding contributions of great importance were made in science in India. It is the lack of healthy scientific environment which has been throttling the creative potential of Indian scientists and technologists". According to him a healthy scientific environment was one that was free from prejudices, bureaucratic formalisms, dishonesty, propaganda of unsubstantiated research claims, suppression of dissent, showmanship, sycophancy, political manipulation, manoeuvring, and so on. He further advocated that it was of "utmost importance to promote, by personal and collective efforts, the ethics and norms of science not only for the progress of science and technology in the country but also for building its national character".

This society was the first of its kind in the world and though not immediately, its creation made the International Council of Scientific Unions aware of the necessity to direct all constituent scientific academies of the world to create similar sections in their organizations which would set down guidelines and be seen pursuing them (for information about the aims and activities of the Society for Scientific Values, see *www.scientificvalues.org*).

In his professional lifetime he had seen the advent of newer techniques and approaches, with molecular biology heading the list. Did he feel that the days of integrative systems physiology were numbered, especially when he saw the younger generation of physiologists and biologists in India referring to his science as "old fashioned". I think not. For most of the time he found that they did not have questions to answer and appeared only to be following the fashions of the day.

Acknowledgements

A few portions have been reproduced here from the "*Biographical Memoir Fellowship",* Indian National Science Academy, New Delhi 29, pp 145 –168.

References

Anand A and Paintal A S 1980 Reflex effects following selective stimulation of J receptors in the cat; *J. Physiol*. **299** 553–572

Anand A, Paintal A S and Whitteridge D 1993 Mechanisms underlying enhanced responses of J receptors of cats to excitants in pulmonary oedema; *J. Physiol*. **471** 553–547

Butler J E, Anand A, Crawford M R, Glanville A R, McKenzie D K, Paintal A S., Taylor J L and Gandevia S C 2001 Changes in respiratory sensations induced by lobeline after human bilateral lung transplantation; *J. Physiol*. **534** 583–593

Coleridge H M and Coleridge J C G 1995 *Control of the cardiovascular and respiratory systems in health and disease* (eds) T Kappagoda and M Kaufman (New York: Plenum Press) pp 199–206

Dehghani GA, Parvizi M R, Sharif-Kazemi M B, Raj H, Anand A and Paintal A S 2004 Presence of lobeline-like sensation in exercising patients with LVD; *Respir. Physiol. Neurobiol*. **143** 9–20

Paintal A S 1951 A comparison of the galvanic skin responses of normals and psychotics; *J. Exp. Psychol*. **41** 425–428

Paintal A S 1953a A study of right and left atrial receptors; *J. Physiol*. **120** 596–610

Paintal A S 1953b The response of pulmonary and cardiovascular vagal receptors to certain drugs; *J. Physiol*. **121** 182–190

Paintal A S 1953c The conduction velocities of respiratory and cardiovascular afferent fibres in the vagus nerve; *J. Physiol*. **121** 341–359

Paintal A S 1953d Impulses in vagal afferent fibres form stretch receptors in the stomach and their role in the peripheral mechanism of hunger; *Nature (London)* **172** 1194–1195

Paintal A S 1954 A method of locating the receptors of visceral afferent fibres; *J. Physiol.* **124** 166–172

Paintal A S 1955a Impulses in vagal afferent fibres form specific pulmonary deflation receptors. The response of these receptors to phenyl diguanide, potato, starch, 5-hydroxytryptamine and nicotine, and their role in respiratory and cardiovascular reflexes; *Q. J. Exp. Physiol*. **40** 89–111

Paintal A S 1955b A study of ventricular pressure receptors and their role in the Bezold reflex; *Q. J. Exp. Physiol*. **40** 348–363

Paintal A S 1965a Block of conduction in mammalian myelinated nerve fibres by low temperatures; *J. Physiol*. **180** 1–19

Paintal A S 1965b Effects of temperature on conduction in single vagal and saphenous myelinated nerve fibres of the cat; *J. Physiol*. **180** 20–49

Paintal A S 1966a The influence of diameter of medullated nerve fibres of cats on the rising and falling phases of the spike and its recovery; *J. Physiol*. **184** 791–811

Paintal A S 1966b Re-evaluation of respiratory reflexes; *Q. J. Exp. Physiol*. **51** 151–163

Paintal A S and Riley R L 1966 Responses of aortic chemoreceptors; *J. Appl. Physiol.* **51** 151–163

Paintal A S 1967 A comparison of the nerve impulses of mammalian non-medullated nerve fibres with those of the smallest diameter medullated fibres; *J. Physiol*. **193** 523–533

Paintal A S 1969 Mechanisms of stimulation of J receptors; *J. Physiol.* **203** 511–532

Paintal A S 1978 Conduction properties of normal peripheral mammalian axons; in *Physiology and pathobiology of axons* (ed.) S G Waxman (New York : Raven Press) pp 131–144

Paintal A S 1983 Localization of the sensations produced by J. receptors (J Area); *Proc. Int. Union Physiol. Sci*. **25** 245

Paintal A S 1995 Sensations form J receptors; *News Physiol. Sci*. **10** 238–243

Raj H, Bakshi G S, Tiwari R R, Anand A and Paintal A S 2005 How does lobeline injected intravenously produce a cough?; *Respir. Physiol. Neurobiol.* **145** 79–90

Raj H, Singh V K, Anand A and Paintal A S 1995 Sensory origin of lobeline induced sensations : A correlative study in man and cat; *J. Physiol*. **482** 235–246

*e*Publication: 11 October 2006