LETTER TO THE EDITOR

Sergio Henrique Ferreira (1934–2016)

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Received 18 October 2016; **Revised** 23 November 2016; **Accepted** 27 November 2016

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Dear Editor,

Many members of the Society will be saddened to hear of the recent death of Sergio Ferreira, a Brazilian pharmacologist who had a scientifically fruitful and therapeutically significant collaboration and a long friendship with many British pharmacologists and the BPS.

During his PhD project, supervised by another famous Brazilian pharmacologist Rocha e Silva who had been the first

to describe bradykinin and its generation *in vivo* by the venom of the Brazilian viper, *Bothrops jararaca*, Sergio isolated from the same venom, a bradykinin potentiating factor (BPF), which did not generate bradykinin but appeared to prevent its enzymic inactivation. It was this BPF that Sergio brought with him on his first visit to the UK to work with John Vane at the Department of Pharmacology at the Royal College of Surgeons (RCS) in London. Here, his skill and insight into bioassay was soon made obvious, as he joined enthusiastically and successfully in Vane's research programme using the 'blood bathed organ technique' that was developed in the Department.

He did not have the opportunity to investigate further the activities of his BPF and it was left to another young researcher, Y.S. Bakhle, to show that BPF would also inhibit the conversion of angiotensin I to angiotensin II by the enzyme ACE. This observation encouraged Sergio, in collaboration with an American biochemist, Lewis Greene, then at Brookhaven National Laboratory, to isolate several of the constituent peptides of BPF and to sequence two of them, a pentapeptide BPP5 and a nonapeptide BPP9.

All these peptides were potent inhibitors of ACE, *in vitro* and *in vivo*. These were the results that started the process, which culminated in Squibb (now Bristol-Myers Squibb) introducing the first synthetic ACE inhibitor (captopril) into clinical use, as a new type of anti-hypertensive agent, in 1981. Now ACE inhibitors are used routinely and successfully in many other clinical settings, including heart failure, post-infarct treatment, protection against diabetic kidney damage and failure or for diabetic retinopathy. The success of the ACE inhibitors stimulated the eventually successful search for angiotensin receptor blockers (ARBs). Together, the ACE inhibitors and ARBs have totally changed the practice of cardiovascular medicine and for the better.

On his second visit to John Vane's lab, this time accompanied by his wife and two sons (their third child, a daughter, was to be born in London), Sergio was involved in

a new area, the prostaglandins. One of his significant findings was that PGE₂ injected subdermally was not, as were histamine or bradykinin, directly painful, but that it potentiated the painful effect of a stimulus such as pressure, an effect referred to as hyperalgesia. It was during this time that Vane demonstrated the mechanism of action of aspirin and the other non-steroidal anti-inflammatory drugs in a, now classical, set of papers in *Nature*, one of which was co-authored by Sergio and another, newly arrived, addition to John Vane's team, Salvador Moncada.

Sergio's interest in the mechanisms of pain was to continue for the rest of his research life and he was to make several important contributions to this area. When John Vane left the RCS to become Research Director of Wellcome in Kent in 1973, he took with him several research staff from the Department, including Rod Flower and Salvador Moncada, and asked Sergio to head up a new group at the Beckenham Laboratories of Wellcome. During the years that he led the 'Department of Prostaglandin Research' as it was called, Sergio had a major impact on the strategy of the group. Initially, he pursued his work on prostaglandins as mediators of pain as well as inflammation, and one of his first projects was to develop an anti-PGE₂ antiserum, which was patented by the company as an anti-inflammatory and analgesic agent. Although it was never developed further, it anticipated by many years similar projects by other pharmaceutical companies.

He also developed a novel hypothesis postulating the existence of peripheral opiate receptors, which ran counter to the prevailing dogma. Nevertheless, Sergio was able to show clearly that morphine and its congeners had a peripheral site of action, quite distinct from those known to be in the CNS. This finding had two important consequences. First, morphine could exert biological effects without crossing the blood-brain barrier, which relieved the synthetic chemists of one restriction on the structure of possible morphine mimetics. Second, such mimetics, if designed to be excluded from the CNS, should not exhibit two of morphine's major side-effects, respiratory depression and potential for addiction, both known to be mediated centrally. Indeed, it is activity at opioid receptors in the gut that has led to the success of drugs like lomotil and loperamide. Although the treatment and relief of diarrhoea makes less attractive headlines than recovery from myocardial infarction, for the patient, the outcomes are equivalently welcome.

Sergio gave up his consultancy at Wellcome in 1975 and returned to Brazil, to pursue his analysis of pain mechanisms involving the interleukins and the NO-cGMP system, but still in collaboration with British pharmacologists. One was Terry Smith who had been a member of Kosterlitz's team during the discovery of enkephalin, had later worked with Sergio at Wellcome and now was with the British Technology Group. The other important collaborator was Steve Poole who had a particular expertise in cytokines. This collaboration progressed as far as demonstrating the anti-nociceptive effects of small peptides that inhibited IL-1-induced hyperalgesia, but these were not considered to be commercially viable. This collaboration continued until Sergio's retirement from the Department of Pharmacology at Ribeirao Preto in 2009. However, Sergio's novel ideas on pain are still being pursued by his colleagues at Ribeirao Preto.

Over the years, the significance and importance of Sergio's work received international recognition by the award

of the Ciba Prize for Hypertension (1983) for his work on ACE inhibition and, in 2002, election to the National Academy of Sciences in the US. In 2005, he was awarded the Trieste Science Prize and an Award from the IASP for pain research; in 2008, he received the Prince Mahidol Award from Thailand. He was a councillor in the International Union of Basic and Clinical Pharmacology (IUPHAR) from 2006 to 2010. In Brazil, he was elected to the Brazilian Academy of Sciences in 1984 and served as President of the Brazilian Pharmacological Society (SBFTE) for two terms of office, in 1986 and again in 1988. He was also the recipient of several prizes and awards from scientific bodies and the Government.

Perhaps Sergio's greatest scientific strength was his willingness to follow unlikely leads; the more unusual and unexpected the results, the more enthusiasm they generated. In this, he could be said to be following John Wilkins, one of the originators of the Royal Society and its first Secretary, who maintained that '*that the Strangeness of this opinion is no sufficient reason why it should be rejected; because other certain truths have been formerly esteemed as ridiculous, and great Absurdities entertained by Common Consent*'. It is relevant to note that the possibility that ACE inhibition could be of clinical benefit to any but a handful of high renin hypertensives was, in its time, strongly discounted by the hypertension experts and the idea that opioids could have significant peripheral effects was similarly dismissed, because 'everyone knew' that morphine exerted its effects on the CNS; strange opinions, indeed.

On a personal level, Sergio was immensely likeable with a strong sense of humour, which often manifested itself in strange uses of the English language. His sometimes erratic and often hilarious grasp of English syntax and grammar did not prevent him from being an enthusiastic and prolific participant in BPS meetings (member since 1968), then held about four times a year at University Departments. John Hughes remembers going with Sergio in his (fairly decrepit) van from London to a BPS meeting in Dundee, a trip he describes as being both life-threatening and a formative experience. During the sessions and in the bar afterwards (where so much good Pharmacology is planned), he always brought a new perspective to the discussion. As a scientist, he was highly intelligent, innovative and inventive, often irreverent in his approach to the establishment and established ideas and totally intolerant of needless bureaucracy. Another characteristic, which might well be considered strange these days, was his belief in bioassay as an essential, perhaps the only essential, technique for pharmacological discovery. Bioassay brought him many scientific successes, but it too has been largely ignored by modern molecular pharmacologists. In 2009, on the 50th Anniversary of IUPHAR, he wrote a strong defence of bioassay for the IUPHAR Journal.

For many members of the BPS, he was a role model, a mentor and a friend and they will treasure their memories of Sergio. His legacy as a man and a scientist will endure, not just among his friends, colleagues and collaborators but in the lives of the many patients who have benefitted from his work on the inhibition of ACE.

Yours sincerely

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