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Design and Serendipity in the Path to Prostaglandins

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Abstract

Leon Wolfe was a brilliant scientist who was gifted with curiosity and drive. This personal account touches on salient events in a rewarding collaboration and lifelong friendship, starting from the original identification of prostaglandin as a natural neurohumoral agent and progressing with the unpredictable developments of this research beyond the brain. Design and serendipity are the leitmotifs in an exciting story unfolding over the years.

Index Entries: Prostaglandins; ductus arteriosus; oxygen; endothelin; fever mechanism; fetal and neonatal physiology.

Introduction

In a volume dedicated to Leon Wolfe, it is appropriate to recall the circumstances leading to our collaboration and lifelong friendship and to reflect, coincidentally, on how drastically a fortuitous event may change one's direction of research.

Finding Prostaglandins

My encounter with Wolfe dates back to 1963. At that time, I was a postdoctoral fellow in Herbert Jasper's laboratory at the Montreal Neurological Institute working toward a career in neurophysiology. Jasper was studying (among other things) the conditions governing the release of acetylcholine from the cerebral cortex *(1)*; because of my doctoral work in Italy dealing with the cerebellar physiology *(2)*, it was decided that I should comparatively examine the cerebellar cortex. Then, Wolfe came into the picture. The project entailed the use of a biological assay; despite our lack of experience with isolated organs, the rat stomach fundus *(3)* was chosen, rather than the conventional frog rectus abdominis preparation, which, incidentally, was already available in the laboratory. In pursuing this outwardly foolish course, Wolfe's rationale was to simultaneously measure acetylcholine and 5-hydroxytryptamine in cerebellar superfusates, whereas my motivation was to address the question of the identity of the active substance known at the time as the

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"cerebellar factor of Crossland" *(4)*. As it turned out, this choice was most fortunate. In fact, few experiments were required to note the presence in the superfusates of a spasmogenic principle with unique biological and physico-chemical properties.

Wolfe was quite adamant when first faced with my data: it must be a prostaglandin! This meant the neurophysiologist of the team would have to start sifting through chemistry papers, extolling the unique virtues of gas chromatographic/mass spectrometric analytical procedures. In any case, it was prostaglandin *(5)*. By sheer chance, we had selected for the assay an organ that for many of the following years would be the preparation of choice for the measurement of prostaglandins *(6)*. Hence, a new line of activity started for both of us that was totally absorbing and ever rewarding.

The demonstration of the natural occurrence of prostaglandins in the central nervous system, to which contributed our studies as well as studies from other laboratories *(7)*, had an impact. There was a great deal of interest in these substances within the broad field of the neurosciences (an interest that remains vibrant to this day) because they afforded a new dimension in the study of humoral mechanisms.

The original choice of the rat stomach fundus proved to be fortunate in another respect. After returning to Italy, but still in association with Wolfe, work with this preparation demonstrated that the spasmogenic response to prostaglandins is critically, and quite uniquely, dependent on the presence of oxygen *(8)*. This observation, coupled with the notion (acquired almost in the same period) that the synthesis of prostaglandins is also conditioned by oxygen *(9,10)*, later formed the premise for the idea of these compounds as messengers of the oxygen constriction in the ductus arteriosus and, hence, being responsible for closure of the vessel at birth *(11)*. Regretfully, this appealing concept did not pass the test of the laboratory—a common destiny for "beautiful hypotheses when being confronted with ugly facts" (T. H. Huxley). However, prostaglandins, specifically PGE_2, were found important in maintaining patency of the ductus prior to birth *(12)*. A scheme diametrically opposite to that conceived from our original premise but still quite rewarding for its conceptual and practical implications *(12)*.

This circuitous path for prostaglandin research does not end there. Subsequent studies, still aiming to the elucidation of the mechanism of ductus closure, provided convincing evidence for a role of endothelin in the constrictor action of oxygen *(13)*. This was confirmed through the use of mutant mice lacking the ET_A receptor subtype of endothelin *(14)*. However, similarly to any wild-type animal, the same mutants close their duct at birth *(14)*. The key to explain this paradox again is linked to the prostaglandins. As shown by us and others *(15,16)*, blood levels of PGE_2, which are quite high in the fetus, fall abruptly at the time of birth. Hence, coincidentally with birth, there is the withdrawal of a potent relaxant influence on the ductus *(17)*. Under normal circumstances, this event may simply contribute to the closure process. However, when the contractile drive is missing, as may happen with the ET_A mutant, it can become the determining factor for closure.

After all, 30 yr later, a role was found for prostaglandins in ductus closure, although their mode of action turned out to be opposite of that perceived at the start of the investigation—so much for design and serendipity.

There are other aspects of my work that are ideally linked with Wolfe. After a period of research on the mode of action of prostaglandins on individual neurons *(18)*, much effort was invested in the verification of the role of PGE_2 as an intermediary agent for pyrogens in causing fever. Eventually, following a vigorous debate involving our laboratory as well as the laboratories of others *(19)*, this scheme gained wide acceptance. Recent studies with mice lacking distinct components of the PGE_2 system have not only firmly established this concept but have also charted the way to new therapeutic tools *(20–22)*.

The premise of this article began many years ago with Leon Wolfe. Memory holds him as a brilliant, yet unassuming person and, first and

foremost, a person with great enthusiasm and drive. Besides honoring him with a fitting tribute, this article highlights, individually and collectively, a special season of life that has influenced our work ever since.

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