Dr Irvine H. Page, Neuroscience and Hypertension

To the Editor:

The 2000 Nobel Prize in Medicine goes in part to Dr Arvid Carlsson for his recognition of the role of dopamine not only in the brain but also in the periphery.1 This was further extended by his collaborator Dr Snider who recognized dopamine as a stress-released catecholamine2 and subsequently summarized it in relation to hypertension.3 This reminds us that in 1935, Dr Irvine H. Page, who is not well known for his contributions to the field of neuroscience, was the first to observe a very particular form of paroxysmal hypertension with sympathetic discharge in the absence of pheochromocytoma. He wisely observed that in contrast to the pheochromocytoma-related paleness, those patients had a “blush over the face, neck and trunk as well as nausea during the paroxysm.” He concluded that this resulted from irritation of sympathetic and parasympathetic centers in the diencephalon. The subsequent discovery of norepinephrine as a dominant sympathetic marker in the 1950s raised hope but failed to demonstrate a relationship to the above episodes.

Primarily, this was due to the fact that norepinephrine was not found elevated and would cause paleness rather than flushing due to norepinephrine-induced vasoconstriction. Facing this enigma, Dr. Page, reminded of Carlsson’s work, argued strongly in favor of dopamine. In his words, this “orphan catecholamine,” in its action, best fit his original clinical description of flushing and nausea (he later added polyuria).6 Further studies of these paroxysms, probably more common than in pheochromocytoma and summarized under the “pseudopheochromocytoma” heading,7 have shown a multiplicity of underlying syndromes that may more likely be associated with hypertensive dopamine surges while norepinephrine remains normal. Nevertheless, the causes of these episodes remained unexplained in approximately one half of the 63 patients.8 Patients of this unexplained subgroup usually did not report emotional distress. Careful psychosocial interviewing revealed, however, a relationship to emotions that patients had not been sensitized to, and, therefore, were unable to report.7 This is again consistent with Page’s conceptualization as “hypertensive attacks brought on by excitement.”4 Reports confirming dopamine increase during hypertensive attacks are rare.7 This is not surprising, because it is difficult to design a study where blood sampling has to be performed within 2 to 3 minutes following an unpredictable paroxysm of hypertension, while excluding, at the same time, dietary and drug contamination.

Dopamine infusions comparable to the level of dopamine surges indicated that dopamine is not responsible for hypertension.9 However, its elevation is a marker that distinguishes the paroxysm from the mostly norepinephrine-associated blood pressure surges in pheochromocytoma. In addition, dopamine may not only hold the key to understanding flushing and nausea but also the panic reactions occasionally associated with these hypertensive paroxysms. Such panic attacks may be due to “a spontaneous diencephalic discharge influencing autonomic outflow from the brain,” as Page speculated 65 years ago.4

Otto Kuchel
Emeritus Professor
University of Montréal

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Otto Kuchel;

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