

the north would be a useful first step toward the accumulation of capital, so vital for poor countries to achieve their economic take-off.

Poor countries in 2004 need to nurture their economies just as rich countries needed to do in the past when they were at a corresponding level of economic development. In fact, the QUAD (the United States, European Union, Japan and Canada) have protected their agricultural sectors enormously in the past 50 years, and still continue to do so.

Canada as an influential member of the QUAD can do much in the WTO to promote the phased elimination of tariff and nontariff barriers to exports from developing countries. To add to our credibility, we can initiate this measure within Canada. Fortunately our economy is strong enough to withstand a structural adjustment program of the type that has often been imposed on those countries, but without the devastating effects seen in them.

Health For All remains the elusive goal declared at Alma Ata. We can contribute something concrete toward its realization. Healthy, productive human beings with adequate incomes create trading partners that safeguard our security and our own economic well-being.

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## Who was S. Weir Mitchell?

A recent commentary by Paul W. Armstrong and Robert C. Welsh opens with a quotation attributed to S. Weir Mitchell, who is identified as an American novelist.<sup>1</sup>

Mitchell was also one of the most prominent physicians of the late 19th and early 20th centuries and is recognized as one of the most important neurologists in American medicine. In

the 1850s, Mitchell completed extensive experimentation in medical physiology, publishing 25 papers in the *Proceedings of the Academy of Natural Sciences of Philadelphia*. During the Civil War years 1862 to 1864, Mitchell worked as a contract surgeon in the Union Army. Of the many publications resulting from his Civil War work, the 2 most important were *Gun-*

*shot Wounds and Other Injuries of Nerves*, published in 1864 with coauthors G.R. Morehouse and W.W. Keen, and *Injuries of Nerves and Their Consequences*, a comprehensive work published in 1872. *Gunshot Wounds* immediately became the authoritative work on nerve injuries; it featured the first descriptions of phantom limb, ascending neuritis and causalgia (the

“burning pain”) and discussed various treatment methods. As recently as 1965, the American Academy of Neurology reprinted *Injuries of Nerves and Their Consequences*, referring to Mitchell as the “father of American neurology.”

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## More about hyperprolactinemia

In the comprehensive review of hyperprolactinemia by Omar Serri and associates<sup>1</sup> the answers to some important questions remain unclear.

Fig. 2 of the article recommends MRI of the pituitary if pathologic hyperprolactinemia is identified on repeat measurement of prolactin, but there is no definition of what constitutes pathologic hyperprolactinemia. It appears that the authors are suggesting MRI of the pituitary if the prolactin level remains elevated on repeat measurement, but what extent of elevation should lead to consideration of MRI? For example, should the physician perform imaging studies if the prolactin level is marginally elevated but still less than 100 µg/L? In clinical practice, patients with marginally elevated levels on 2 or 3 occasions often undergo imaging studies of the pituitary gland, but is this practice justified? Consideration of MRI of the pituitary is one of the most important clinical decision-making points in the management of hyperprolactinemia, so it would be helpful to have some guidance in this regard.

In addition, to what extent does nipple or breast stimulation cause elevation in prolactin levels, and how long should the patient avoid such stimulation be-

fore the repeat measurement of prolactin is performed?

Turning to the causes of this condition, Fig. 1 of the article lists anti-ulcer agents, specifically H<sub>2</sub> antagonists, as medications causing elevation of prolactin levels. However,<sup>2</sup> other medications, metoclopramide and domperidone<sup>3</sup> (motility agents commonly used in patients with gastroesophageal reflux), are dopamine antagonists and are more likely than H<sub>2</sub> antagonists to cause elevated prolactin levels. These drugs should be considered as causative agents and should be discontinued before further investigations are undertaken.

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#### References

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2. Camanni F, Genazzani AR, Massara F, La Rosa R, Cocchi D, Muller EE. Prolactin-releasing effect of domperidone in normoprolactinemic and hyperprolactinemic subjects. *Neuroendocrinology* 1980;30(1):2-6.

The recent review by Omar Serri and associates<sup>1</sup> on the diagnosis and management of hyperprolactinemia did not address the important issue of a potential link between hyperprolactinemia and increased risk of breast cancer. This omission is not unique; in fact, no recent review on the management of hyperprolactinemia mentions the issue.<sup>2,3</sup> However, concern about such an association is often raised by psychiatrists and their patients because hyperprolactinemia can be caused by certain atypical antipsychotic medications and selective serotonin release inhibitors.<sup>4</sup> A recent comprehensive review<sup>5</sup> reported that laboratory studies have shown definitively that prolactin stimulates both normal and cancerous breast tissue to grow and differentiate in culture. However, in the clinical setting there are too few data to allow conclusions either way. The sole large prospective trial cited in the review<sup>5</sup> did establish an association between hyper-

prolactinemia and increased risk of breast cancer among postmenopausal (but not premenopausal) women. Other epidemiological evidence reviewed by Clevenger and colleagues<sup>5</sup> suggested a strong link among breast cancer, oral contraceptive use and hyperprolactinemia.

There is a physiologic basis to explain why prolactin can stimulate breast cancer cells to grow and differentiate in culture but might not readily do so in vivo. When prolactin is elevated, the gonadotropins and sex steroids are normally suppressed. Thus, a potent and well-recognized stimulus for breast cancer growth (estradiol) is reduced at the same time that a likely weaker stimulus (prolactin) increases. This may explain why normal lactation (prolactin increased, estradiol reduced) has been associated with reduced risk of breast cancer in several studies.<sup>6,7</sup> Conversely, it may also explain the association, reported by Clevenger and colleagues,<sup>5</sup> between increased risk of breast cancer and the combination of oral contraceptive use and hyperprolactinemia (prolactin and synthetic estradiol-equivalent both increased).

The current standard of practice in the management of hyperprolactinemia is to leave asymptomatic patients untreated unless there is a lesion of the pituitary that needs control. However, many of my patients object to that approach because of uncertainty about whether hyperprolactinemia is truly benign to breast tissue, and many have opted for treatment of their asymptomatic hyperprolactinemia (or discontinuation of the causative medication).

We clearly lack the definitive data needed to reassure our patients about the long-term risks of hyperprolactinemia. Carefully controlled prospective studies are needed to determine the increase in risk of breast cancer (if any) for a woman with chronic hyperprolactinemia. In the meantime, it would be helpful if review articles on managing hyperprolactinemia addressed this issue. For example, algorithms for management (such as that on page 579 of the article by Serri and associates<sup>1</sup>