

# Primum non nocere: first do no harm

Linda Bryder

In 2010 following the publication of my book, *A History of the "Unfortunate Experiment" at National Women's Hospital*, there was an extended correspondence in the *New Zealand Medical Journal* which was drawn to a close by the editor who declared, "Any further letters published in the NZMJ on this topic must provide new insights into the issue, not just re-stating what an author previously said (or did not say)..."<sup>1</sup>

Important new information has now appeared. On 27 February 2018 the *British Medical Journal* published a systematic review and meta-analysis of the clinical course of untreated cervical intraepithelial neoplasia grade 2 (CIN2) under active surveillance. The study covering 3,160 women concluded, "Active surveillance of CIN2 rather than immediate intervention is justified, especially among younger women".<sup>2</sup> In other words, after conducting a meta-analysis and systematic review over the period 1973 to 2016, these authors support what Associate Professor Herbert Green suggested to the National Women's Hospital Medical Committee in 1966, ie, that young women diagnosed with carcinoma in situ by cytology should be given a punch biopsy and carefully monitored rather than immediately offered radical treatment.

Green's critics might say the new study only refers to CIN2, not CIN3 or 'carcinoma in situ', the focus of Green's management. But the BMJ study points to inter-observer variability between CIN2 and CIN3 and "misclassifications of lesions" at the present time, and this would have been even more pronounced in the 1960s and 1970s with less advanced technology. A 2007 publication by the International Agency for Research on Cancer referred to the "extremely poor inter- and intra-observer reproducibility in the differentiation of carcinoma in situ from dysplasia" in those earlier decades.<sup>3</sup>

Reflecting these continuing uncertainties, the WHO decided in 2014 to reclassify the dysplasias from three (CIN1- CIN3) to two groups (low grade and high grade) with the high grade group including both CIN2 and CIN3 (CIS).<sup>2</sup>

Thus the findings of the researchers in the BMJ study have direct relevance to the high grade cervical dysplasias. They found that, "Despite the observed heterogeneity and even bias resulting from possible misclassification of lesions, the rates of regression were still high in young women even at the most conservative estimates." They conclude: "The results of our analysis show higher rates of regression and lower rates of progression of histologically confirmed CIN2 lesions than previously reported, particularly in women aged less than 30. Conservative management with active surveillance, instead of immediate local excision, is therefore justified in selected women, especially if further pregnancies are considered and compliance with surveillance is likely to be high (*primum non nocere*). With increasing maternal age and increasing awareness that local treatment for CIN is associated with increased preterm birth and mid-trimester loss, treating only those with disease that has a true progressive potential is of utmost importance. In cases of disease that persists beyond two years, treatment is likely to be warranted."<sup>2</sup> When Green took his proposal for conservative treatment to National Women's Hospital Medical Committee in 1966 he specified, "If at any stage concern was felt for the safety of a patient, a cone biopsy would be performed."<sup>4</sup> As he later explained, "Clearly patients treated in this manner must be assessed and followed carefully, and if clinical, cytological or colposcopic evidence requires it, be subjected to more radical diagnosis and treatment."<sup>5</sup> The authors of the 2018 study, suggesting treatment if the disease persists beyond two years, would agree.

Professor Charlotte Paul critiqued Green's protocol in the *New Zealand Medical Journal* in 1990, responding to Dr Graeme Overton's statement that there was no group of 'untreated' patients at National Women's Hospital. Paul admitted that "most of these women did eventually receive treatment", but her concern was the absence of 'initial' treatment, which she and co-researchers claimed then, and in subsequent publications, caused harm.<sup>6</sup> Yet, as noted, the BMJ report suggests as good practice that, "In cases of disease that persists beyond two years, treatment is likely to be warranted."

The meta-analysis also acknowledges the influence of human papillomavirus. The study comments, "The risk of progression was particularly low in women negative for high risk human papillomavirus (HrHPV) or HPV16/18."<sup>2</sup> The 2007 IARC study referred to above also made this point, stating, "In general, cervical abnormalities persist longer and progress more quickly in women who have carcinogenic HPV infections than in

women who have noncarcinogenic infections or no HPV." HPV was first identified in the 1980s and was not something that Green and colleagues could have taken into account, but the failure of the subsequent long-term follow-up studies of patients from National Women's Hospital<sup>6</sup> to acknowledge this possible influence is a matter for concern.

The BMJ paper markedly contradicts the frequent claim that Green was a maverick and questions Judge Silvia Cartwright's assessment that he was attempting to prove a 'personal belief'.<sup>7</sup> The new systematic review identified no fewer than 250 studies around the world between 1973 and 2016 that addressed the same questions, reporting studies in which women with histologically proved CIN2 were not treated at diagnosis, but were monitored for three or more months (follow-ups varied from 3 to 60 months). Here is convincing evidence that many health professionals around the world have long grappled with the issue that Green raised—*primum non nocere*.

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**Competing interests:**

Nil.

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