

the testing of hormones that do not trigger these mechanisms. For now, research should focus more on avoiding cardiovascular risk than finding benefit. Hormones for coronary disease prevention have come full circle.

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Death and dignity: dogma disputed

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For many people, death in modern advanced societies is inherently undignified. Terminally ill patients are connected to tubes and machines; they experience pain, shortness of breath, and other excruciating symptoms; they are unable to get out of bed, feed themselves, and even go to the bathroom alone; they are cared for in impersonal institutions. In such circumstances, there is no way to maintain dignity in the dying process.^{1–3} This loss of dignity is a major concern of dying patients and constitutes one of the main motivations behind efforts to improve palliative care and promote the goal of “a good death”.^{4–6} Yet one of the biggest hurdles in improving care at the end of life is the vagueness surrounding the concept of a good death.⁷

The first task for improving care at the end of life is to specify the components of a good death. The second task is to assess these components empirically, understand the frequency of problems, and identify barriers to improving the quality of the dying process. Only recently have investigators begun to spell out critically the notion of a good death, and design instruments to measure the more vague endpoints, such as dignity.^{8–11} Dignity is not a proxy measure along the way to a good death; it is one of the constitutive components of a good death.^{12,13} A primary reason to promote hospice and palliative care, dying at home rather than in the hospital, and improving symptoms at the end of life is the belief that these will promote dignity. Despite its centrality, few have attempted to study empirically dignity at the end of life.¹⁴

In *The Lancet* today, Harvey Chochinov and colleagues report the prevalence of indignity among patients at the end of life. Their study is a major contribution to understanding loss of dignity and elucidating those factors necessary to promote dignity. Importantly, not only did the investigators measure dignity but also used other well-established instruments to measure symptoms, quality of life, and independence in activities of daily living to determine associations with loss of dignity.

Their finding that 93% of patients in the study reported no loss of dignity is remarkable. In other words, only 7%, or just 16 of the 213 patients interviewed, reported having moderate or severe loss of dignity. Indeed, it appears that it was surprising even to the researchers, whose analysis emphasises the few patients who experienced substantial loss of dignity. Chochinov and colleagues use multivariate analysis to identify factors associated with a loss of dignity based on these patients. How meaningful is it to discuss predictors based on just 16 patients? The confidence intervals are wide, and with so few patients few predictors can be evaluated with any certainty. Indeed, with so few patients and so many variables, false-positive associations may arise because of the problem with multiple comparisons. With only 16 patients, only one or two variables should be evaluated in the multivariate model to avoid finding a result that is statistically significant by chance alone. Thus, the analysis looking at predictors of dignity should be interpreted with great caution or not at all.

Why did so many patients report maintaining a sense of dignity at the end of life? Perhaps the most plausible explanation is that end-of-life care is better than most people perceive. These data suggest that death and dying in the modern world are not inherently undignified. The tremendous emphasis over the past decade on improving care at the end of life may actually have produced real improvements in taking care of this population. Consequently, worries about terrible loss of dignity may be over-blown—an extrapolation from a few unrepresentative cases that are also out of date.

Other potential explanations for the surprising result relate to the methodology of this study. The instrument used to measure dignity may be flawed in two ways. First, Chochinov and colleagues could have the wrong concept of dignity. Second, dignity is much harder to measure than tumour responses or survival and a 7-item scale may be inadequate to capture the subtleties of how people define and experience dignity. Chochinov and colleagues say that their sample may be unrepresentative; because all the patients had cancer and were enrolled in a palliative care unit, they could have been receiving better care than the typical patient dying from cancer or heart failure who may experience more indignity. Chochinov's sample may well be unrepresentative, but the notion that patients in hospice or palliative care units receive better care is not supported by the available data.^{15,16} Of more concern is that many patients were excluded because of symptom distress as determined in screening by the research team and 28% of the patients who were eligible declined to participate. Consequently there may be bias if those excluded because of symptoms or those who declined to enter the study were more likely to experience a loss of dignity.

That the common perceptions about loss of dignity at the end of life are not supported by this empirical study is not unique to matters of dignity. For example, research studies evaluating quality of life, burden of care-giving and other endpoints do not show a benefit of hospice over conventional care which may seem counterintuitive.^{15–17} Similarly, the public perceives pain to be the most serious

symptom in the dying process. However, much of the data shows that pain is much less frequent than many people think, and more importantly, other symptoms, such as shortness of breath or depression are of more consequence to dying patients themselves.^{3,18,19} For most of the public the primary rationale for considering whether euthanasia or physician-assisted suicide should be permitted is relief of excruciating pain, yet the available data show that depression rather than pain is associated with a desire for euthanasia or physician-assisted suicide.²⁰ These results illustrate that common perceptions about the dying process are often wrong and misguided. These misperceptions probably arise because good deaths do not raise attention, while a few tragic cases reinforce natural fears about dying.

Clearly, the data on dignity reported by Chochinov and colleagues need to be confirmed by larger studies of diverse groups of dying patients. However, the data do suggest that the dying process may not be as bad as many people fear—at least as regards dignity. The results also emphasise the importance of educating the public about the dying process, so that unrepresentative horror stories do not lead to misguided policy-making about death and dying.

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Antimalarial cocktails—tropical flavours of the month

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Combining drugs to treat infections caused by mycobacteria and HIV is an effective strategy. How well does it work against drug-resistant *Plasmodium falciparum* malaria, for which artemisinin-based combinations have been particularly strongly advocated?¹ And which combinations should be used? Recently, two fixed-dose combinations have been brought to market: atovaquone-proguanil² and artemether-lumefantrine,³ and many other cocktails are being actively investigated.

In this issue of *The Lancet*, Grant Dorsey and colleagues examine three such combinations for childhood malaria in Uganda. Healthy children were randomly assigned one of three treatment regimens: sulfadoxine-pyrimethamine alone or the same combination with either amodiaquine or with artesunate (an artemisinin derivative). The children were then treated with the assigned combination when they contracted uncomplicated malaria in the following year. The regimen was maintained for subsequent infections, recrudescences notwithstanding. This design has the effect of amplifying differences in efficacy between treatment groups. Sulfadoxine-pyrimethamine combined with amodiaquine, which is one of the cheapest combinations, gave the best overall results when taking into account risk of recrudescence after 14 days. Sulfadoxine-pyrimethamine with amodiaquine reduced the rate of subsequent treatments for malaria by 54% compared with sulfadoxine-pyrimethamine monotherapy, and by 37% compared with artesunate combined with sulfadoxine-pyrimethamine.

So should artemisinins continue to be included in antimalarial combinations? In The Gambia, sulfadoxine-pyrimethamine combined with artesunate cured 98% of patients compared with 97% with sulfadoxine-pyrimethamine alone at day 14, making it difficult to demonstrate the added value of artesunate because of the pre-existing high efficacy of sulfadoxine-pyrimethamine used alone.⁴ Results with one combination partner for artemisinin may also be difficult to generalise to another. When efficacy against recrudescence guides choices, an artemisinin derivative is not a consistently advantageous addition. In Kenya, for example, artesunate increased cure rates to only 70% when given with amodiaquine (an antimalarial with a long half-life), which used by itself cured 41% of children 28 days after their episode of uncomplicated malaria. In Sénégal, artesunate failed to increase efficacy at all when combined with amodiaquine (82% vs 81%), whereas in Gabon the combination did improve efficacy (from 77% to 89%).⁵

There may be other reasons to include an artemisinin in antimalarial cocktails. Patients feel better more quickly, and parasitaemia disappears faster when artesunate (or indeed another rapidly acting antimalarial) is included in combination with a slower-acting antimalarial. Artemisinins may also decrease transmissibility of *P falciparum*. But in areas with high transmission of malarial parasites, as in tropical Africa, this advantage over other antimalarials could fade because rapidly reinfected individuals will continue to maintain a pool of transmissible parasites. Furthermore, 3 days of treatment with artesunate does not completely block maturation of immature gametocytes and their infectivity to mosquitoes.⁶ Another suggestion is that artemisinins slow down the emergence of resistance