

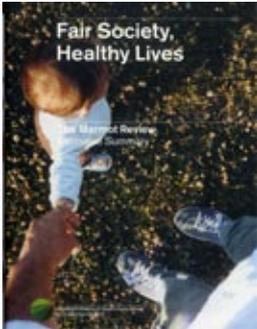
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# EDITORIALS

## Getting to grips with health inequalities at last?

Marmot review calls for renewed action to create a fairer society



ANALYSIS, p 346

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The World Health Organization's Commission on Social Determinants of Health published its hard hitting and well received report in mid-2008 with the stark message that "social injustice is killing people on a grand scale."<sup>1,2</sup> The commission's chair, Michael Marmot, was promptly invited by the UK prime minister and then health secretary for England to consider the implications for health inequalities in England, with a view to informing the government's post-2010 strategy for tackling them. Fresh thinking and renewed momentum were needed in the face of mounting evidence that the 2010 inequalities targets would not be met.<sup>3</sup> The government's national equality panel has since concluded that inequalities in earnings and incomes are high in the United Kingdom compared with other industrialised countries.<sup>4</sup> Economic advantage and disadvantage reinforce themselves across the life cycle.

The Marmot review team submitted its final report to ministers in December, marking the end of a frenetic period of activity involving nine task groups, three working committees, and two interim reports.<sup>5</sup> The timing has eerie echoes of the groundbreaking 1980 Black report.<sup>6</sup> Although the review chaired by Sir Douglas Black was set in motion by a Labour government, it reported to a Conservative one that was distinctly cool on the subject of health inequalities.

The Marmot report may avoid a similar fate: an election is some months away and all political parties have affirmed a commitment to tackling health inequalities. Nevertheless, as politicians of all hues become increasingly preoccupied with securing electoral advantage, it is questionable whether this important report will receive the careful and considered attention it deserves. There are few votes in health inequalities, and although the report is at pains to point out, as others have, that we are all adversely affected and our lives diminished by the growing health gap,<sup>7</sup> this message could easily get lost. More public debate about the sort of society we want to live in might, however, provide a context for greater political courage.

The review advocates two aims: to improve health and wellbeing for all and to reduce health inequalities. To achieve these it wants social justice, health, and sustainability to be at the heart of all policies (box). The report is critical of the poor record of policy success in tackling health inequalities and places an emphasis on delivery systems and leadership. Its attempt to draw lessons from past experience is welcome. Public health experts and academics are adept at producing descriptions of the problem, as are policy makers at developing strategic responses. But the processes of delivering system-wide changes invariably receive less attention.

We believe that three reasons for the lack of progress

stand out.<sup>8</sup> The first is the phenomenon of "lifestyle drift," whereby governments start with a commitment to dealing with the wider social determinants of health but end up instigating narrow lifestyle interventions on individual behaviours, even where action at a governmental level may offer the greater chance of success. The response to the Marmot report must avoid this drift at all costs.

The second—a deep seated inability to join up policy and delivery across government, both horizontally at central and local levels and vertically—is evidence of how fossilised our institutional structures have become and how incapable they are of providing effective solutions to the complex problems we face.<sup>9,10</sup> The response to Marmot's recommendations must not mirror the inadequate and simplistic lifestyle oriented solutions to the complex problems of obesity and alcohol misuse.

Merely to do more of what we have always done is not an option. A paradigm shift in thinking is needed. The report singles out the importance of leadership and new approaches to partnership working to deliver change. Conceivably, initiatives like Total Place (a "whole area" approach to providing public services) could herald a new approach to governance and to managing policies and services locally that departs from the tribalism that too often scuppers attempts to work across professional and organisational boundaries.<sup>10</sup>

The third reason for policy failure lies in the realm of politics. Rhetoric and glossy policy statements aside, is there sufficient genuine and sustainable political will to tackle health inequalities? With the economic outlook bleak and an election looming, the temptation will be for politicians to say that we can't afford to deal with health inequalities

### Six policy recommendations to reduce health inequalities

- Give every child the best start in life: increase the proportion of overall expenditure allocated to the early years and ensure it is focused progressively across the gradient
- Enable all children, young people, and adults to maximise their capabilities and have control over their lives: reduce the social gradient in skills and qualifications
- Create fair employment and good work for all: improve quality of jobs across the social gradient
- Ensure a healthy standard of living for all: reduce the social gradient through progressive taxation and other fiscal policies
- Create and develop healthy and sustainable places and communities
- Strengthen the role and effect of the prevention of ill health: prioritise investment across government to reduce the social gradient

just yet. The imperative is to show that we can't afford not to. This will be the Marmot report's sternest test.

The policy changes needed for Marmot's recommendations to succeed can occur only if these three obstacles to progress are confronted. A focus on individual lifestyle must not be allowed to obscure the need for appropriate government action. This action should go hand in hand with a more radical shift in implementation that will require new forms of adaptive leadership<sup>11</sup> and looser partnership structures that allow for flexible solutions tailored to local contexts,<sup>12</sup> and which provide genuine space for community empowerment. Underpinning these must be a real political commitment at all levels, because a fairer society will benefit all. The Marmot report, aware that its timing is less than auspicious, says inaction is not affordable. Both this government and its successor should heed the warning, for the journey will be both long and arduous.

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## Interaction of serotonin reuptake inhibitors with tamoxifen

### Avoid coprescribing paroxetine and tamoxifen in women with breast cancer

RESEARCH, p 355

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Tamoxifen has an established role in the treatment of hormone receptor positive invasive breast cancer.<sup>1</sup> Evidence has emerged in recent years that the main pharmacological effects of tamoxifen are not mediated by the parent drug itself but by an active metabolite called endoxifen (4-hydroxy-*N*-desmethyltamoxifen).<sup>2</sup> The bioactivation of tamoxifen to endoxifen is mainly catalysed by the cytochrome P450 isoenzyme 2D6 (CYP2D6).<sup>2</sup> Certain drugs inhibit the activity of CYP2D6, and this results in decreased plasma concentrations of endoxifen.<sup>2,3</sup>

In the linked observational study, Kelly and colleagues show that the risk of breast cancer related death is higher in women taking tamoxifen plus the selective serotonin reuptake inhibitor (SSRI) paroxetine. The authors suggest that this is explained by inhibition of CYP2D6.<sup>4</sup>

SSRIs are prescribed for women with breast cancer who are taking tamoxifen for two main reasons. Firstly, to treat depression or anxiety, and, secondly, to reduce hot flushes, which are a common side effect of tamoxifen. Some SSRIs such as paroxetine are strong inhibitors of CYP2D6. It is reasonable to suggest that concomitant use of these drugs attenuates the clinical effectiveness of tamoxifen, but observational data supporting this hypothesis were lacking until now.

Kelly and colleagues used data from a healthcare record database in Ontario, Canada, to evaluate the clinical consequences for women with breast cancer who were treated with both tamoxifen and an SSRI. They selected a cohort of women who were at least 66 years old, who were newly treated with

tamoxifen for breast cancer between 1993 and 2005, and who received a single SSRI during tamoxifen treatment. They found that the risk of death from breast cancer increased with the length of concomitant treatment with paroxetine, but not with other SSRIs. For example, if women used paroxetine for 41% of the time that they took tamoxifen, one additional death from breast cancer occurred within five years of stopping tamoxifen for every 19.7 (95% confidence interval 12.5 to 46.3) women treated.

This finding is in accordance with what might be expected because of the strong CYP2D6 inhibiting properties of paroxetine, and it provides the first evidence of a clinical effect of long term CYP2D6 inhibition during tamoxifen treatment. Previous observational studies that looked for an increased risk of the recurrence of breast cancer after the concomitant use of CYP2D6 inhibitors and tamoxifen failed to identify increased risks, but they were limited by low statistical power,<sup>5-7</sup> or they focused on a weaker CYP2D6 inhibitor.<sup>8</sup>

How should clinicians treat depression or hot flushes in women who take tamoxifen in the light of these findings? The straightforward answer is to avoid prescribing strong CYP2D6 inhibiting SSRIs (such as paroxetine or fluoxetine) for women with breast cancer who are prescribed tamoxifen, and to consider instead drugs with low potential to inhibit CYP2D6 (such as citalopram or venlafaxine).<sup>9</sup> A switch to an antidepressant with low or no CYP2D6 inhibitory activity should be considered in patients who are already treated with tamoxifen and paroxetine or fluoxetine. In the rare case that



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the patient cannot tolerate other SSRIs or did not respond to them in the past, switching tamoxifen to an aromatase inhibitor might be an option in postmenopausal women.<sup>9</sup> Importantly, however, Kelly and colleagues' study does not justify abrupt discontinuation of the antidepressants fluoxetine or paroxetine. The potential longer term benefits of discontinuing their use do not yet clearly outweigh the potential adverse effects of immediate withdrawal of effective SSRI treatment (such as recurrence of severe depression).<sup>10</sup>

The clinical effects of CYP2D6 related drug interactions with tamoxifen need further study. Two yet unpublished cohort studies on the risk of breast cancer recurrence that were presented at the 2009 meeting of the American Society of Clinical Oncology (ASCO) showed conflicting results. One study from the Netherlands reported no increased risk of recurrence with concomitant CYP2D6 inhibitor use,<sup>11</sup> whereas an American study found that the risk of breast cancer recurrence roughly doubled in two years if CYP2D6 inhibitors were used together with tamoxifen.<sup>12</sup> The reasons for the different findings should be evaluated after full publication.

In Kelly and colleagues' study, concurrent use of the strong CYP2D6 inhibitor fluoxetine was not associated with increased risk of death from breast cancer.<sup>4</sup> The authors speculate that this might result from the low number of women exposed to fluoxetine in their cohort, which suggests that the effects of concomitant use of fluoxetine and tamoxifen need to be studied further. Their findings also need to be reproduced in other populations because residual confounding from other drugs, disease severity, or comorbidity cannot be reliably excluded. For safety reasons, coprescription of fluoxetine and tamoxifen in women with breast cancer should be avoided until additional evidence becomes available.

At present, information contained in different summaries of product characteristics of tamoxifen and paroxetine is not consistent. According to the electronic Medicines Compendium, three manufacturers in the United Kingdom are currently marketing products that contain tamoxifen. Two of them list the possibility of reduced tamoxifen efficacy caused by concurrent use of CYP2D6 inhibitors, whereas one does not. In Germany, 13 companies make tamoxifen, and nine of them report a potential interaction via CYP2D6, whereas four do not. Similarly, the summary of product characteristics for

most products that contain paroxetine in the UK and Germany do not yet mention explicitly an interaction with tamoxifen, even though a pharmacokinetic study showed the interaction in 2003.<sup>3</sup> Promotion of the paroxetine-tamoxifen drug interaction among doctors and pharmacists and harmonisation of the summary of product characteristics are needed.

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## Higher hospital volume and specialisation

Outcomes are better in hospitals that do more procedures

The association between surgical volume and patient outcomes for total joint replacement and other surgical procedures has been examined extensively.<sup>1-5</sup> The reasons why surgeons who perform a higher volume of cases have better outcomes are intuitive. Surgeons who have more experience with a procedure tend to deliver better outcomes—after all, “practice makes perfect,” even beyond the learning curve.

What is less well understood is why a hospital procedural volume-outcome association persists even after adjusting for surgeon volume. Patients operated on by lower volume surgeons in high volume hospitals still have better outcomes than those operated on by similar volume surgeons in lower

volume hospitals. This effect is thought to result from improved care processes in higher volume hospitals.

In the linked study, Hagen and colleagues examine one possible explanation for this hospital volume-outcome association.<sup>6</sup> They show that hospitals that specialise in orthopaedic surgery have better patient outcomes for total joint replacement than do less specialised hospitals. They define specialisation in orthopaedics using the proportion of all patients admitted to the hospital who were admitted for a musculoskeletal condition. Specialisation in this context may be a proxy for the amorphous process of care improvements at higher volume hospitals. Previous analyses by the same research group evaluated the

### RESEARCH, p 351

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outcome effect of highly specialised private hospitals, which have been criticised for “cherry picking” younger healthier patients to maximise profits by minimising complications and associated costs.<sup>7,8</sup> In that research, they showed that patients were younger and healthier than at other hospitals, but that outcomes were significantly better even after adjusting for age, comorbidities, and surgical volume. Building on this research, Hagen and colleagues now investigate the effect of specialisation beyond private specialty hospitals to investigate whether specialisation can improve outcomes.

They show that the advantage conferred by specialisation follows a classic dose-response association. Patients undergoing elective unilateral total joint replacement in hospitals that are incrementally more specialised in musculoskeletal care were less likely to die and had fewer complications than those in less specialised hospitals. After adjusting for patient characteristics and hospital volume, the most highly specialised hospitals had an odds ratio of 0.56 (95% confidence interval 0.51 to 0.62) for 90 day mortality and 0.62 (0.58 to 0.67) for risk of complications after joint replacement compared with the least specialised hospitals.

Although these reductions seem impressive, the validity and generalisability of the results should be considered. The research used Medicare claims data, which are restricted mostly to patients aged 65 or older. According to 2005 estimates from the Healthcare Utilization Project National Inpatient Sample (HCUP-NIS), patients under 65 accounted for 44% of total hip and 40% of total knee replacements. This current analysis has no information on these younger patients or their outcomes. Younger patients may be more likely to seek joint replacement in specialty hospitals and also tend to have a lower rate of complications and lower mortality.<sup>9,10</sup> Excluding these patients from the analyses probably biases the results against increased specialisation.

In contrast, two other factors may bias Hagen and col-

leagues’ results in favour of increased specialisation. The total joint replacement procedures evaluated in this analysis were elective, so patients undergoing joint replacement for trauma and those undergoing bilateral procedures during a single admission were excluded. However, highly specialised hospitals are more likely to perform bilateral procedures and to be affiliated with trauma centres, so that they perform more joint replacements for trauma related conditions.

Although these concerns warrant further research into the effects of specialisation, it is worth looking at the bigger picture. It seems clear from this and other research that outcomes are influenced by surgical specialisation,<sup>1-5,11,12</sup> whether defined by volume or degree of specialisation. However, this creates a conundrum. Not all hospitals can achieve higher surgical volumes, and any attempt to increase specialisation in one practice area results in a decline in specialisation in another.

Fortunately, a more promising avenue for exploration and potential improvement in patient outcomes exists. This is to examine the process of care elements that result in improved outcomes in higher volume or more specialised hospitals and identify ways to transfer these improvements from centres of excellence to other hospitals. If successful, this would ensure continued access to specialty care at local hospitals and improve outcomes throughout the medical system by closing the outcome gap.

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ANTONIA REEVE/SP/L

Joint replacements done in specialty hospitals have lower mortality and complication rates.

## Venlafaxine and cardiovascular toxicity

Risk seems no greater than for selective serotonin reuptake inhibitors



CRISTINA PEDRAZZINI/SPL

### RESEARCH, p 352

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People with depression have a higher incidence of cardiovascular disease and mortality from cardiovascular disease than people without depression.<sup>1</sup> Ideally, the use of antidepressants should not add to this risk. Depression may also provoke suicide, so toxicity in overdose is a crucial consideration when choosing an antidepressant.

Older tricyclic antidepressants may increase mortality from cardiovascular disease when used therapeutically and are often fatally toxic in overdose, whereas selective serotonin reuptake inhibitors (SSRIs) show little if any cardiotoxicity at any dose, although, their antiplatelet effect has potential for harm.<sup>2</sup> The serotonin-noradrenaline reuptake inhibitor venlafaxine has been thought to show cardiovascular toxicity somewhere between that of tricyclics and SSRIs, so its use has been restricted in some countries. In the linked case-control study, however, Martinez and colleagues challenge the notion that venlafaxine is more cardiotoxic than SSRIs.<sup>3</sup>

In their study using data from the general practice research database in the United Kingdom, which looked at 207 384 first time users of antidepressants, venlafaxine was not associated with an increased risk of sudden cardiac death or near-death compared with fluoxetine, citalopram, or (generally low dose) dosulepin. Risk was lower for venlafaxine than for other drugs examined, and confidence intervals effectively excluded any clinically important increased risk for venlafaxine. If considered in isolation, this study strongly suggests that the therapeutic use of venlafaxine is as safe as use of the two SSRIs and low dose dosulepin. Because SSRIs are considered to have minimal cardiovascular toxicity, the same might now be assumed for venlafaxine.

Evidence suggesting that venlafaxine is cardiotoxic is limited and is derived from diverse sources. Two studies in animals have shown that venlafaxine can inhibit cardiac ion channels,<sup>4,5</sup> but the concentrations of venlafaxine associated with inhibition were much greater than those seen in humans taking therapeutic doses. Studies of overdoses in humans suggest that venlafaxine has a much higher fatal toxicity index than SSRIs,<sup>6</sup> and that prolongation of QRS and QTc intervals (electrocardiographic indicators of inhibition of potassium and sodium channels) are often seen in overdose.<sup>7,8</sup> Therapeutic doses of venlafaxine also increase blood pressure to a small extent.<sup>2</sup>

Against this is a substantial body of evidence suggesting that venlafaxine has minimal arrhythmogenicity even in overdose. In an analysis of 5510 overdoses where venlafaxine alone was ingested, only 12 (0.22%) were fatal, and cardiac conduction defects were seen in fewer than 2% of all cases.<sup>9</sup> Even in the two studies noting changes on electrocardiography in venlafaxine overdoses, serious arrhythmias did not occur in one (51 overdoses observed) and were rare (3/235 overdoses), benign, and transient in the other.<sup>7,8</sup> In addition, the drug's relatively high fatal toxicity index may be related to non-cardiac toxicity (seizures, for example<sup>7</sup>) or its prescription to people who are more likely to attempt suicide.<sup>10</sup> Moreover, the fatal toxicity index is probably a poor measure of inherent toxicity—the index has been reported to be as low as 5.5 and as high as 53.6 for the antidepressant nortriptyline, effectively making it both one of the least toxic and most toxic antidepressants available.<sup>11</sup>

Lastly, as discussed by Martinez and colleagues,<sup>3</sup> formal pre-marketing and postmarketing observations of venlafaxine did not suggest a significant potential for cardiotoxicity.

Regulatory authorities, particularly in the UK, have been inconsistent with their advice on the safe prescribing of venlafaxine. Its use was at first severely restricted in the UK because of “concerns about cardiotoxicity and toxicity in overdose,” although many (but not all) of the original restrictions were later lifted after the Medicines and Healthcare Products Regulatory Agency (MHRA) conceded that “available data do not point towards an increased risk of cardiotoxicity for venlafaxine versus SSRIs.”<sup>12</sup> A key aspect to regulatory deliberations seems to have been the high fatality rate in venlafaxine overdoses, with the MHRA citing the case fatality rate of single overdoses in the UK adverse drug reactions online information tracking (ADROIT) database to be around 27%.<sup>12</sup> This fatality rate is very different from that described in more robust observational studies, and it probably represents extensive reporting bias, as the MHRA seemed ultimately to conclude.

So, therapeutic use of venlafaxine seems not to increase risk of sudden death or near death compared with SSRIs, and venlafaxine causes arrhythmia only rarely in overdose. Its toxicity in overdose may be higher than that for SSRIs, but this is not clearly substantiated and toxicity in overdose is not linked to any cardiovascular effects of the drug. Evidence suggesting any arrhythmogenic potential for venlafaxine is weak, especially where normal therapeutic use is concerned. Future research should centre on meaningful outcomes (arrhythmia, cardiac mortality) in humans, rather than surrogates of toxicity in animals. For now, continued restriction on the use of venlafaxine on the grounds of cardiovascular toxicity seems inappropriate.

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# Chronic fatigue syndrome

Defeatism among clinicians is undermining evidence that it can be treated



REX FEATURES

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The recent acquittal of Kay Gilderdale, who had been charged with the attempted murder of her 31 year old daughter Lynn, has led to blanket press coverage. She was given a one year suspended sentence for the lesser charge of aiding and abetting suicide, to which she had earlier entered a guilty plea. The debate in the media has focused on the rights and wrongs of assisted suicide, the wisdom of bringing a prosecution for attempted murder, and whether the law needs to be changed.

Yet perhaps the most striking aspect of the case from the clinician's point of view is the largely uncontested media portrayal of a condition referred to as chronic fatigue syndrome or myalgic encephalomyelitis (now commonly if unsatisfactorily called CFS/ME) as a progressive, paralysing, and commonly fatal illness. Little has been said in the media about the uncertainties and controversies that this diagnosis has always attracted. The details of the Gilderdale case and the coroner's inquest and postmortem are not available to us, so it would be inappropriate to comment on this specific case, and as in any criminal case, the matter is best decided by judge and jury. However, general points are raised that merit comment, not least for professionals who will almost certainly have to manage similar challenges in the future.

The first and most obvious point is that severe presentations such as that of Lynn Gilderdale are fortunately unusual in CFS/ME, and clinicians should consider alternative diagnoses that would better explain the symptoms. But assuming that these alternatives have been ruled out, what is the excess mortality associated with CFS/ME? Data clearly show that mortality is not increased in patients diagnosed with this condition and that the greatest risk to life is likely to be suicide.<sup>1</sup> Many studies have shown that suicide is associated with depression, and that depression is associated with CFS/ME. People with a history of depression are more likely to get CFS/ME,<sup>2</sup> and vice versa.<sup>3,4</sup> Whatever the direction of causality, nobody would dispute that depression can be treated, whether it occurs alongside life limiting cancer, motor neurone disease, or a diagnosis of CFS/ME.<sup>5</sup> Any patient with CFS/ME who openly talks about suicide should be reviewed by a psychiatrist because 90% of suicides are associated with a psychiatric diagnosis.<sup>6</sup> If a diagnosis of depression is made, treatment should be comprehensive, involving pharmacotherapy and appropriate psychotherapies, and patients should be monitored for response.

Treatments such as cognitive behavioural therapy and graded exercise therapy have been shown to work in CFS/ME in adults<sup>7</sup> and children<sup>8</sup> (for whom the outcome is generally more optimistic) and they are recommended for both groups by the National Institute for Health and Clinical Excellence (NICE).<sup>9</sup> The data are admittedly less robust for patients at the extreme end of the spectrum, although NICE guidelines assert that management of these patients may incorporate the principles of cognitive behavioural therapy and graded exercise therapy, and some evidence supports this.<sup>10</sup> Clinical experience indicates that in patients with severe CFS/ME such programmes may need to be adapted and prolonged, but that they can be the trigger for improvements and sometimes

dramatic recovery. In contrast, the alternative to treatment is often no treatment, and this can have a disastrous effect on the patient, who may feel that the medical profession has given up on them as a hopeless case.

Unfortunately, an air of defeatism exists within the medical profession about this condition, particularly for those who are severely affected, and this is in danger of becoming a self fulfilling prophecy. Doctors are uncertain about what they are dealing with, they are generally reluctant to get involved, and perhaps inevitably a breakdown of trust between doctors and the patients and their families often occurs. The profession is often reluctant to engage in debate because, as Mr Justin Simon has observed, there is, "A perception that this is an area of medicine where contrary views are not to be voiced, and where scientific enquiry is to be limited, [that] is damaging to science and harmful to patients."<sup>11</sup> There is even a view that emphasising the incurable and even fatal nature of CFS/ME is the only way to persuade the medical profession that it is a real illness.

Undoubtedly our current treatments could be improved, recovery may not be complete in many cases, and access to services for those too disabled to attend hospital clinics needs to be improved. Physiotherapy, psychology services, community support, and dietetic advice may all have a part to play in the management of severe CFS/ME, and support for the family may be necessary, particularly when children are affected. The influence of the internet in shaping suicidal behaviour in young people is a new danger for families and clinicians.<sup>12</sup> The medical profession must continue to go with the evidence in choosing treatments, in what can be a fraught clinical situation. We owe it to our patients and to our professionalism to do what we can to help those with this potentially treatable condition because, notwithstanding the difficulties, this is our primary duty.

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