Restricting resident work hours: The good, the bad, and the ugly

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Objectives: Inadequate sleep and long work hours are long-standing traditions in the medical profession, and work schedules are especially intense in resident physicians. However, it has been increasingly recognized that the extreme hours commonly worked by residents may have substantial occupational and patient safety consequences. Largely because of these concerns, new regulations related to resident work hours came into effect July 2011, in the United States. Residents in their first year of training are now restricted to a maximum shift length of 16 hrs, with residents in subsequent years restricted to a maximum of 24 hrs. The purpose of this review is to summarize the literature regarding resident work hours in the intensive care unit, focusing on the potential positive and negative impacts of work hour limits.

Data Sources: The authors electronically searched MEDLINE, manually searched reference lists from retrieved articles, and reviewed their own personal databases for articles relevant to resident work hour limits.

Methods and Main Results: To function well, humans, including physicians, require adequate sleep. Resident work hour limits will likely reduce the incidence of fatigue-related medical errors and improve resident safety and quality of life. However, a reduction in work hours may not represent the panacea for patient safety given the potential for increased errors because of discontinuity. Furthermore, there may be other substantial negative impacts, including reduced clinical exposure, erosion of professionalism, and inadequate preparation for independent practice. Costs of implementation are likely to be substantial.

Conclusion: Currently, there is fairly limited evidence available, and a more in-depth understanding of this complex topic is required to design a residency experience that will provide the next generation of physicians the best compromise between education, experience, and quality patient care. In the end, the primary goal of the postgraduate medical education system must be to ensure the creation of healthy physicians who can provide excellent clinical care in this complex interdisciplinary medical industry and who will have long fulfilling careers providing this outstanding care to their patients. (Crit Care Med 2012; 40: 960–966)

Key Words: education; graduate fatigue; medical error; resident work hours; sleep deprivation

T here is an evolving paradigm shift in how residents in North America are being trained. Specifically, it has been increasingly recognized that the extreme hours commonly worked by residents in training programs may have substantial occupational and patient safety consequences (1). Because of these concerns, the Accreditation Council for Graduate Medical Education (ACGME) enacted new regulations related to the work hours of residents that came into effect July 1, 2011 (2). Residents in their first year of training are now restricted to a maximum shift length of 16 hrs, with residents in subsequent years restricted to a maximum of 24 hrs. These regulations differ substantially from those in 2003, when shifts up to 30 hrs in length (24 hrs of continuous care followed by up to 6 hrs for transition of care) were endorsed (3). Not unexpectedly, these changes have been associated with significant controversy focused mainly on the extent of changes to residency required to provide the appropriate balance of education, experience, and quality patient care (4).

The purpose of this article is to offer a balanced review of this complex topic. We begin with a brief review of relevant sleep physiology and then describe current work hour limitations in other high-risk industries and for resident physicians in other countries. We focus on the current state of the evidence surrounding work hour limitations, highlighting both positive and negative potential consequences. Finally, we discuss potential future directions for research in the rapidly evolving context of postgraduate medical education. Because a recent article in Critical Care Medicine reviewed the potential options available to address workforce shortages in the intensive care unit (ICU) that may occur as a result of the new regulations (5), we will not revisit that issue in this review.

Sleep Physiology. Sleep is an essential biological process that is integral in maintaining health and cognitive function (6). Sleepiness may be quantified subjectively, when subjects are asked how sleepy they are currently (e.g., Stanford Sleepiness Scale) or have been in the past month (e.g., Epworth Sleepiness Scale Score). Sleepiness may also be quantified objectively, by recording the time for EEG measured sleep to occur during daytime nap opportunities (e.g., multiple sleep latency testing), although it must be noted that this test may be affected by motivation (88). The impact of sleepiness may also be assessed by measuring the impact on cognitive tests. Without adequate sleep, subjects in the laboratory experience significant deterioration in many of the skills and attributes that physicians require to function effectively, including attention, memory, decision-making, mood, ability to accurately self-assess, and motor skills (7–9). There are four major physiologic factors that con-
Contribute to fatigue and sleepiness in resident physicians.

Acute total sleep loss (sustained wakefulness) continues to occur frequently during residency training in North America, despite work hour restrictions. In general, as an individual stays awake longer, the pressure to sleep increases and alertness deteriorates. For example, after 24 hrs of continuous wakefulness, performance of cognitive tasks is similar to that when blood alcohol concentrations are 100 mg/dL, a level considered above the legal limit for driving (10). Even after 17 hrs of wakefulness, performance was similar to a blood alcohol concentration of 50 mg/dL. Residents also experience decrements in clinical performance caring for simulated critically ill patients after 26 hrs of wakefulness (11).

Chronic partial sleep deprivation occurs when a person consistently obtains less (but not zero) sleep than would normally occur if sleep was not curtailed. Chronic curtailment of sleep is associated with a decrease in cognitive performance similar to that seen with acute total sleep loss. For instance, staying in bed <6 hrs per night for 2 wks resulted in cognitive function similar to 1 night of total sleep deprivation (12).

The third contributor, sleep inertia, represents the phenomenon of reduced neurocognitive performance on awakening (13). Its effect is most prominent during the initial 10–15 mins after awakening, but it may take hours to dissipate (14). Sleep inertia effects can be substantial, with an acute effect similar to that of 26 hrs of total sleep deprivation (15). This is of particular relevance for on-call residents in the ICU who may be awoken suddenly to provide care to a critically ill patient.

The fourth contributor is from the circadian pacemaker, or the body's internal clock. The circadian pacemaker is located in the hypothalamus and stimulates wakefulness during the day and a nadir in the early morning hours (3:00 AM–5:00 AM) (16). This pattern enables sustained performance and alertness throughout the daytime and an ability to consolidate nocturnal sleep. Performance and vigilance deteriorate substantially when attempting to function at an adverse circadian phase (i.e., when working night shifts) (17, 18).

It is also important to note that these four factors may act in a synergistic fashion. For instance, the impact of sleep inertia is worse when individuals are awoken at an adverse circadian phase (19). It is therefore to be expected that the traditional “on-call” schedule when residents work in excess of 24 hrs every third to fourth night would substantially impact performance, especially in the middle of the night. This type of schedule results in acute total sleep deprivation given the long lengths of shifts and chronic sleep loss given that residents are on-call frequently. Residents are often unable to make up for the sleep loss between the on-call shifts. Sleep inertia occurs given that they are often awakened in the middle of the night to provide care to critically ill patients, and circadian effects occur given that residents must also function in the middle of the night (during the nadir of circadian performance). Of note, these types of schedules would be different from standard night shifts commonly worked in North America, because workers on these night shifts will typically start much later (e.g., 7:00 PM–11:00 PM) with nap opportunities during the day and are thus not exposed to the effects of acute and chronic sleep loss to the degree experienced by residents. Sixteen-hour shift limits could predominately mitigate the impacts of acute and chronic sleep loss, although sleep inertia and circadian effects would still be of concern.

One must also understand that there is substantial inter-individual variation in the susceptibility of subjects to sleep deprivation in terms of cognitive performance (90, 91). Some variability may be related to inherent subject factors (e.g., age, gender, genetics), but some may be related to modifiable factors such as training and motivation. To our knowledge, formal assessment of sleep deprivation susceptibility has not been part of selection procedures for medical school or residency programs; however, it is certainly possible that residents with resilience to sleep loss may choose to enter more intense specialties. In this vein, a recent survey study compared responses to a Sleep Deprivation Impact Scale of surgery and internal medicine residents (91). Surgery residents scored significantly lower on this scale (45.2 vs. 51.5), suggesting less perceived impact to sleep loss. Whether this represents a true resilience to sleep loss or false optimism is open to debate (93). Of note, we know that sleep deprivation may impair the ability to accurately gauge one’s performance (92), and that there is no significant correlation between resident perception of their susceptibility to sleep deprivation and actual deterioration in clinical performance in simulated critical care cases after sleep loss (11).

Although attempts to counteract the effects of inadequate sleep with pharmacologic stimulants such as caffeine, scheduled napping or exercise have shown some promise; the optimal strategy for minimizing the negative consequences of sleep-deprivation is to prevent it from developing in the first place (20, 21). This is fundamentally the rationale behind the implementation of work hour restrictions for residents.

**Work Hour Limits in Other Industries and Countries.** Based on an understanding of the potential adverse safety impacts of long work hours, and fuelled by major industrial disasters that have been at least partially attributed to the actions of sleepy workers (such as the Exxon-Valdez oil spill (22)), work hour limits exist for pilots, marine operators, and truck drivers. For example, pilots who have flown >8 consecutive hours must be given at least 16 hrs of rest before being assigned any further duties, and work hours may not exceed 100 hrs per month when working for domestic air carriers (23).

In general, the healthcare system has been much slower than these other high-risk industries to adopt work hour restrictions. For example, the aviation industry began placing limitations on the number of hours pilots could work nearly 75 yrs ago (24). However, over the past two decades, significant changes to resident work hour limitations have occurred in different parts of the world, but there remains significant variability in the number of hours resident physicians can work (Table 1).

We provide an overview of the literature relevant to resident work hour limitations, highlighting potential positive consequences (the good), negative consequences (the bad), and areas of uncertainty (the ugly).

**The Good**

*Positive Impact on Patient Care.* One of the major driving forces behind the implementation of work hour limitations has been patient safety concerns, with an assumption that reducing work hours will lead to less medical errors attributable to fatigue (25). In general, results reported in the literature have been somewhat mixed, with some studies suggesting a substantial positive impact on
Table 1. Work hour limits for residents in selected countries (25)

<table>
<thead>
<tr>
<th>Location</th>
<th>Maximum Hours of Work Per Week</th>
<th>Maximum Consecutive Hours of Work</th>
<th>Minimum Hours of Rest Between Shifts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>37</td>
<td>13–16</td>
<td>11</td>
</tr>
<tr>
<td>European Union</td>
<td>48</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>France</td>
<td>48</td>
<td>10</td>
<td>NA</td>
</tr>
<tr>
<td>New Zealand</td>
<td>72</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>El Salvador</td>
<td>Unrestricted</td>
<td>36</td>
<td>NA</td>
</tr>
<tr>
<td>United States</td>
<td>80</td>
<td>16–24</td>
<td>8</td>
</tr>
<tr>
<td>Canada</td>
<td>80</td>
<td>16–28</td>
<td>8</td>
</tr>
</tbody>
</table>

NA, not available.

patient safety with work hours restriction and others finding no change (1, 26–29).

The best available evidence comes from one crossover randomized trial in which 20 interns working in critical care units were randomized to a traditional schedule (i.e., 1 in 3 nights on call, with shift lengths of ≥24 hrs) or an intervention schedule with a maximum shift length of 16 hrs (30). Amount of sleep was significantly greater during the intervention arm compared to the traditional schedule (7.4 vs. 6.6 hrs per day; p < .001). The incidence of medical errors was increased during the traditional schedule, with interns committing 35.9% more serious medical errors, 57% more nonintercepted serious errors, and 5.6-times as many serious diagnostic errors. However, the rate of medical errors with adverse events was not significantly different (21 vs. 16.5 per 1000 patient days; p = .21).

Although this was a landmark study, there are a number of factors that could limit generalizability of the results. First, the study was modest in scope. Instituting substantial changes in policy based on a single-center study of 20 participants may be premature. Second, only intern schedules were modified; supervising senior residents still worked ≥24-hr shifts. If the supervising residents also worked a shift schedule, then there may have been an increase in discontinuity-related errors that could have counterbalanced the decrease in fatigue-related errors.

Only a few other authors have examined the effect of reduced work hours on ICU outcomes. In a time series study, Aessa et al evaluated patient outcomes during 16 wks of a traditional one-in-four schedule and 5 wks of a 14-hr shift work model (31). They found no difference between the two schedules with respect to ICU mortality, hospital mortality, or ICU length of stay. Prasad et al reviewed >230,000 ICU admissions in 40 hospitals before and after the 2003 ACGME restrictions were introduced (32). They found no significant difference in risk-adjusted mortality between ICUs with residents and those without residents, thereby concluding that work hour restrictions had no measurable impact on major patient outcomes. However, when interpreting these results, it is important to remember the 2003 recommendations still allowed shifts up to 30 hrs in length and compliance with the recommendations may have been suboptimal (33). Furthermore, if attending physicians were working more when the work hours of their residents or fellows were restricted, then this may have been a substantial confounder that may have affected the results of these observational cohort studies (29, 32).

Therefore, although extremely limited, the best evidence currently available would suggest that patient-related outcomes may be improved and are unlikely to be worsened after initiation of work hour limits. Of note, long-term comparative efficacy trials in this area have not yet been performed but should be considered.

As mentioned, the recent ACGME regulations have restricted the hours of postgraduate year 1 residents to 16 consecutive hrs, but more senior residents are limited to 24 hrs. One could argue that the impact of sleep loss on cognition would be unlikely to differ in senior and junior residents, and that all residents should have shifts restricted to 16 hrs. However, the ACGME believed that the increased shift lengths in senior residents could be justified based on the concept of “progressive liberalization of the duty hour standards as the resident demonstrates the competency to be delegated greater degrees of conditional independence in the care of patients” (95); it was felt that this may also better-prepare residents for the rigors of unsupervised practice at the completion of residency.

Improved Resident Quality of Life and Health. In general, studies have found a positive impact on resident quality of life when the length of on-call shifts has been reduced. The findings include lower levels of stress (34), decreased burnout (35), lower depression scores (36), less emotional exhaustion (37), improved availability for responsibilities outside of medicine (38, 39), improved motivation to work (37), and decreased subjective fatigue (34). Parthasarathy et al (89) examined the impact of the 2003 work hour restrictions on sleep and quality of life in 34 residents and ten fellows in the ICU. Overall, there were modest improvements in sleep time, subjective sleepiness, and some measures of quality of life. In residents, time spent reading increased from 9 to 16 hrs per week but did not increase significantly in fellows. Interestingly, objective sleepiness as measured by mean sleep latency testing was not improved by work hours restriction, with substantial sleepiness still present in both groups (89). However, one must note that shift lengths were still in excess of 24 hrs after reduction, and the impact likely would be much greater if shifts were restricted to 16 consecutive hrs.

It is also possible that a reduction in work hours may improve the health of physicians in the long-term. In epidemiologic studies, chronic sleep loss has been associated with the development of hypertension, coronary artery disease, diabetes, and obesity (6, 40). Residents completing extended on-call shifts have impairment in vascular function, significantly increased serum levels of inflammatory markers (a risk factor for atherosclerosis), and development of markers of metabolic stress (41, 42).

Decreased Risk of Resident Personal Harm. Driving is a complex action that requires vigilance, and sleepiness (regardless of the cause) increases crash risk (43, 44). It is therefore not surprising that residents after call are at increased risk for crashes. In a prospective cohort study of >2500 U.S. interns followed-up for 1 yr, rates of motor vehicle collisions were significantly greater when driving home after an extended (>24 hrs) compared with a nonextended shift (odds ratio, 2.3) (45). The impact of these crashes endangers the safety of not only residents but also the public. This was highlighted by the case of Heather Brewster, a woman who experienced a severe disabling brain...
The Bad

Discontinuity of Care. A reduction in shift lengths will necessarily lead to more transitions of patient care responsibility from one physician to another. This lack of continuity can result in physicians being responsible for patients for whom they do not have complete clinical information and with whom they lack an ongoing relationship (48). Not surprisingly, it also can be associated with adverse events.

In a study of 3146 patients admitted to a general medical service, patients who experienced a preventable adverse event were more likely than control patients to be covered by a physician from a team other than the primary care team at the time of the event (26% compared with 12%; odds ratio 3.5; p = .01) (49). In a multivariate analysis, cross-coverage persisted as a strong predictor of a preventable adverse event (odds ratio 6.1; 95% confidence interval 1.4–26.7). Given the requirement for 24-hr coverage, the complexity of patients, the dynamic nature of management plans, and the involvement of multiple interdisciplinary teams, preserving continuity of care in critically ill patients is challenging (50). Although there are methods to improve hand-offs of patient care using standardized signouts and other techniques (51), there remains little evidence assessing their impact on patient outcomes (52).

In the trial by Landrigan et al (30), despite the significant reduction in errors associated with the shift work schedule, some participants felt that increased hand-overs sometimes handicapped the incoming team, because the night-call intern was often unaware of significant historical details of patients admitted by the day-call team (53). This emphasizes the importance of addressing the issue of hand-overs, perhaps by instituting formal evening rounds for the entire team coupled with the use of innovative electronic sign-out systems (54).

Impact on Attending Physicians. The potential ripple effect that work limits may have on other healthcare professionals has not been well-studied. Some surveys report that attending physicians have had a significant increase in clinical workload because of reduced resident presence on the wards (37, 55–57). As a result, they then have less time for teaching and research and describe a significant reduction in their overall career satisfaction (56, 58–61).

Impact on Professionalism and Perceptions of the Profession. Concerns regarding the negative impact that limiting residents’ work hours will have on their development as a professional have been long-standing (62–65). However, because of the lack of consensus on what defines “professionalism” within the field of medicine (66, 67), rigorous evaluations of this construct over time have not been possible. As a result, we are limited to studies that have mainly reported the subjective impressions of key stakeholders.

Numerous surveys have reported attending physicians’ concerns regarding the level of work ethic, sense of responsibility, and patient ownership of current trainees (37, 57, 68). Program directors (n = 464) have echoed these concerns, with 65% believing residents’ professionalism will decrease as a result of implementing the new ACGME duty hour regulations (69). A frequent underlying theme is that the traditional patient-focused culture in medicine is being eroded by a “shift worker” mentality in residents (37), although one could argue that these are largely unproven opinions.

Interestingly, a telephone survey of 1200 members of the public found that only 1% approved of shifts lasting ≥24 hrs, and 81% believed residents have an obligation to inform their patients if they have been working for that length of time (70). These results would suggest that the general public’s impression of residents as professionals would not be negatively impacted by a reduction in work hours alone. That being said, there is far more to what makes a professional than simply the number of hours worked.

Lack of Preparation for Independent Practice. Both attending physicians and residents have expressed concern regarding the disconnect between the work hours experienced during residency and those typically encountered in real-world practice (71, 72). For example, on completion of residency, there are no limits to the number of consecutive or cumulative hours that the majority of attending physicians in North America may work. To our knowledge, no investigations have assessed the effect that different call schedules during residency have on facilitating the transition into independent practice, but both residents and attendings have mentioned it as a potential concern (65, 73).

Educational Opportunities. Another objection raised over the reduction of resident work hours is the potential negative impact on resident education because of reduced clinical exposure (74). Several residents who served as subjects in the study by Landrigan et al (33) believed that their learning was compromised by the shift work schedule. A study by Bismilla et al (94) showed that institution of modest work shift limits in Ontario (from 28 to 24 consecutive hours) did not result in less time with documentation (i.e., papework) but did result in less time spent in direct supervision, less time in direct patient care, and reductions in numbers of new patients admitted or discharged. Further reduction in these types of activities with more substantial work hour limits could significantly impact education. Attending physicians have also raised concerns that a reduction in clinical experience from work hour limitations is at least partially responsible for the lower than expected levels of clinical judgment, technical skills, and efficiency that they have observed in current residents (37, 57, 68).

However, many others have argued that resident exhaustion leads to an impaired ability to learn (75), especially given that sleep is important in memory consolidation (9, 76). In addition, the majority of studies have found that there has been no measurable negative impact on the educational opportunities for residents as a result of work hour restrictions or on examination scores used for certification (1, 27, 77).

Perhaps the discrepancy between the clinical observations of attending physicians and the findings in the literature are attributable to recall bias and cynicism from burnout. That is, attending physicians may feel that their experience during residency was more intense than that of the current trainees, even though
this may or may not have been the case. Alternatively, attending physicians’ assessments of residents’ clinical competence may be correct. Repeated assessments in the hospital over time may provide a more accurate assessment of their true clinical performance than surrogates such as written examination scores or number of operative cases performed (78–80). For example, a comparison between senior surgical residents trained in the Netherlands (mean 55 hrs/wk) and Canada (mean 84 hrs/wk) found no difference in medical knowledge or technical skills (81). However, Canadian candidates scored significantly higher than Dutch candidates when required to integrate assessment and management skills in the setting of complex patient scenarios (Patient Assessment and Management Examination). The authors hypothesized that the additional time in training (approximately 7000 hrs or >2 yrs of residency) and experiences encountered during that time could be partly responsible for the difference, although other factors also may contribute.

If the shift work paradigm is embraced fully, then the way we educate and evaluate postgraduate trainees will need to adapt. There will be a need to provide greater opportunities for teaching and evaluation of residents. This may include use of more structured direct observation or simulation-based technologies.

Economic Impact. Implementing work hour restrictions for residents will have significant economic ramifications. Initial estimates for implementing all of the 2008 Institute of Medicine recommendations in the United States were in the range of 1.6 billion U.S. dollars per year (82). For the ACGME regulations that were put in place in July 2011, cost estimates are lower, but still substantial, ranging from $820 million to $1.64 billion (U.S. dollars) per year depending on the strategy used to address the predicted workforce shortage the restrictions will create (83). These up-front and ongoing costs potentially could be lessened if the new regulations result in a significant reduction in preventable adverse events; one analysis predicted preventable adverse events would need to decrease by 7.2%–25.8% for net costs to be zero for major teaching hospitals across the United States (83). Whether this degree of reduction of adverse events would be expected with a work hours intervention is unclear and might be optimistic based on current data (29, 30, 32).

The Ugly

The “ugly” aspect of resident work hour restrictions, in our opinion, is our current inadequate scientific understanding of this extremely complex issue. This statement in no way diminishes the outstanding contributions that countless researchers, scholars, clinicians, and their respective teams have made to the literature over the past 10 yrs. Instead, it is meant only to highlight how far we still have to go.

For example, we need to continue to build on fundamental aspects such as: creating explicit conceptual frameworks for research in the area of work hour restrictions that would enable researchers and scholars to build on each other’s work in a more programmatic and efficient way (84); optimizing knowledge translation from the extensive existing body of literature in other relevant disciplines such as sleep medicine, cognitive psychology, and other high-risk industries to help our understanding of the issues at hand and design interventions; exploring exactly which aspects of resident performance in the clinical environment are negatively impacted by sleep deprivation on a day-to-day basis over time and using this information to develop rational duty schedules; systematically investigating different options for length and timing of shifts that provide the best compromise between optimal sleep hygiene, resident performance, costs, educational experience, and provision of care; exploring the inter-individual variation in susceptibility to the effects of sleep deprivation and the impact this trait may have on the ability of the residents to tolerate different work hour restrictions (85, 86) (it will also be important to recognize this as a potential confounder when designing future investigations); defining the most relevant short-term and long-term outcome variables and how to measure them (for example, determining how to measure the long-term impact of these changes (78) on not only the level of competence residents achieve by the end of training but also, more importantly, their performance once in clinical practice); and to better-understand the competing balance between fatigue-related errors and discontinuity-related errors. One major focus would be to comprehensively study measures to reduce discontinuity related errors in the setting of reduced shift lengths through better use of information and communication technology, standardized sign-outs, and other methods.

CONCLUSION

“Mens sana in corpore sano” (87); this classic quote from the poet Juvenal translates as, “A sound mind in a sound body.” Similarly, one cannot expect the mind to function well if the body and brain have been deprived of sleep. Work hour restrictions during residency have been implemented in an attempt to minimize the occurrence of sleep deprivation and the very serious consequences that may arise as a result. However, a reduction in resident work hours may not represent the panacea for patient safety and may be associated with substantial negative impacts, including increased discontinuity errors and costs.

In the end, the primary goal of the postgraduate medical education system is to ensure the creation of competent and caring physicians who will be able to and will also want to have a long career providing outstanding care to their patients. Therefore, given the limited evidence currently available, we require a more in-depth understanding of this complex topic to provide the next generation of physicians a residency experience that is the best compromise between education, experience, and quality patient care while still preserving a reasonable quality of life.

REFERENCES


29. Levin JE, Adusumilli J, Landrigan CP: Effects of reducing or eliminating resident work shifts over 16 hours: A systematic review. *Sleep* 2010; 33:1043–1053


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58. Winslow ER, Berger L, Klingensmith ME: Has the 80-hour work week increased faculty hours? *Carr Surg* 2004; 61:602–608
64. Camins MB, Sutton BH, Daly JM: How will work hour restrictions affect medicine? *Bull Am Coll Surg* 2004; 89:12–16
78. ten Cate O: Trust, competence, and the supervisor’s role in postgraduate training. *BMJ* 2006; 333:748–751