

## Junior doctors' working hours and the circadian rhythm of hormones

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*How poor are they that have not patience!  
What wound did ever heal but by degrees?  
Thou know'st we work by wit, and not by witchcraft;  
And wit depends on dilatory time.*

(*Othello*, II, iii, 376–9)

Junior doctors' working hours have been debated ever since evidence emerged that continuous on-call commitments, with no or some disrupted sleep, can potentially affect the efficiency and safety of medical care delivery. The problem of overworked junior doctors is two-fold, affecting the health of the young doctors but also potentially their patients.

A recent American study revealed that attention span and cognitive performance after a heavy call rotation are more significantly impaired than after alcohol ingestion with a blood alcohol level of 0.04–0.05 g% (per 100ml of blood).<sup>1</sup> In the USA, working hours for junior doctors of over 100 hours a week were considered routine and even by some as a mandatory rite of passage. Others warned, however, that continuously overworked junior doctors may represent a problem spiralling out of control, exacerbated by the increasing demands of rapidly developing medical technology. In 2003, the Accreditation Council for Graduate Medical Education reduced working time for US interns and residents to no more than 80 hours per week and limited continuous on-call commitments to 30 hours, but this is still a considerable workload. In the UK, this problem was addressed by the introduction of the New Deal in 1991 which aimed to reduce working hours to 56 hours per week by 1996. Adherence to the new policy, however, was variable. The European Working Time Directive (EWTD), introduced in the UK in 2004, aims to restrict working hours to 48 hours per week and impose a limit of 13 hours of continuous on-call commitment by 2009. The potential consequences of this change on doctor's quality of life and the standard of patient care are discussed below.

Recent systematic reviews investigating the impact of junior doctors' working hours claimed that studies (mainly in the USA) are hampered by suboptimal design and use of non-validated test instruments.<sup>2,3</sup> In this issue, Smith *et al* report on a cross-sectional

study carried out on South Yorkshire-based junior doctors whose working hours accorded with the EWTD.<sup>4</sup> By assessing health-related quality of life in relation to different working patterns and by measuring serum cortisol and testosterone levels, the study highlighted two important points: firstly, the significance of the diurnal secretion of hormones for maintaining the day–night rhythm and improving the quality of sleep; and secondly, the crucial role of hormones in the physiological stress response. In the context of junior doctors, shift work will obviously affect diurnal rhythms and while this disruption already represents a source of stress, a doctor on-call will continue to encounter stressful situations.

Melatonin plays a pivotal role in maintaining the sleep–wake cycle. Its synthesis from serotonin in the pineal gland is readily inhibited by light leading to maximum secretion in the early hours of the morning. The highest levels are achieved during the first three years of life; young adults have 20 times lower levels. With ongoing ageing, melatonin secretion declines and the nightly peak level occurs 1–2 hours earlier.<sup>5</sup> It has also recently been suggested that age-related insomnia may be improved by melatonin which is thought to have a sleep-inducing effect.<sup>6</sup> The main physiological function of melatonin is the regulation of the diurnal rhythm, and seminal work has demonstrated that melatonin administration can restore this balance in blind people with free-running day–night cycles<sup>7,8</sup> and also in individuals suffering from jet lag.<sup>9</sup> Rotas involving frequent shift changes and night-time work are most likely to disrupt the rhythm of melatonin secretion.

Adrenal steroid hormones play a major role in the endocrine response to stress. Cortisol, the major glucocorticoid, is of crucial importance and its secretion rapidly increases following the onset of stress. Cortisol is secreted at a similar rate over a lifetime but displays a distinct diurnal rhythm with an increase during the early morning, peak levels in the late morning, and a decline to minimum levels around midnight. Patients with adrenal insufficiency can rapidly deteriorate and suffer from adrenal crisis if they do not increase their glucocorticoid replacement during periods of increased stress or illness.<sup>10</sup> Their daily glucocorticoid dose is usually distributed

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over the day to mimic the diurnal rhythm. It is of key importance, however, that this is adjusted to the actual hours awake in patients doing shift work. In those with chronic stress or major depression, serum cortisol is often continuously elevated, resulting in a loss of the diurnal secretion rhythm. Smith *et al* sampled baseline bloods in the morning but, as highlighted in their discussion, this does not take into account the 24-hour secretion of cortisol; the decreased cortisol levels after a night shift may well represent a consequence of adjustment to the changed wake–sleep rhythm. Further investigations of 24-hour urinary collections or salivary cortisol day profiles would certainly be of interest.

Another adrenal hormone with a central role in the stress response is the sex steroid precursor, dehydroepiandrosterone (DHEA).<sup>11</sup> DHEA and its sulphate ester, DHEAS, are the most abundant steroids in human circulation. In contrast to the two other major adrenal steroids, cortisol and aldosterone, DHEA secretion exhibits a characteristic, age-associated pattern.<sup>10,11</sup> Immediately after birth, circulating DHEAS levels are high due to its synthesis by the fetal adrenal glands. Serum DHEAS concentrations rapidly drop, however, and only start to rise again between the sixth and tenth year – a phenomenon referred to as ‘adrenarche’. Its regulation has so far remained elusive. After reaching the intra-individual maximum levels during the third decade of life, serum DHEAS steadily declines to 10–20% of levels seen in young adults. This decline has been termed ‘adrenopause’ in spite of the fact that cortisol secretion does not change considerably with age.<sup>12</sup> Adrenarche and adrenopause are unique phenomena observed in humans and some non-human higher primates. While serum DHEAS concentrations do not vary throughout the day, DHEA secretion follows a diurnal rhythm similar to that of cortisol. Also, like cortisol, DHEA responds acutely to adrenocorticotrophic hormone stimulation and stress with an increase in secretion. DHEA mainly exerts indirect action following downstream conversion to other steroids, mainly sex steroids. Importantly, it also has neurosteroidal properties resulting in anti-depressant action and DHEA replacement in patients with adrenal failure has been shown to enhance health-related quality of life and mood.<sup>13,14</sup> In addition, there is accumulating evidence that DHEA and DHEAS have direct immune modulatory properties, which appear to be partly synergistic and partly antagonistic to the immune effects of cortisol.<sup>15</sup> Tissue-specific activation of DHEA may be enhanced with ageing<sup>16</sup> and also as a consequence of inflammatory stress. Similarly, the generation of active cortisol from inactive cortisone by the enzyme 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ -HSD1), an important regulator of tissue-specific glucocorticoid availability,<sup>17</sup> can be upregulated by inflammatory cytokines in various tissues<sup>18,19</sup> including immune cells.<sup>20,21</sup> It is obvious that disruption of the diurnal rhythm of adrenal steroid secretion by phase shift and acute and chronic stress will have an impact on this system.

Another endocrine system that is likely to be affected by acute or chronic stress is the hypothalamus–pituitary–gonadal (HPG) axis. It is well established that chronic stress, acute disease and also excessive exercise will lead to a decrease in gonadal sex

steroid production with subsequent amenorrhea in women. However, as observed in the study by Smith *et al*,<sup>4</sup> interest in sex may well decline in response to stress without concurrent changes in circulating sex steroids. Another hormone important in this context is the milk hormone prolactin that is released from the pituitary in response to stress at an increased rate in both sexes. Chronic hyperprolactinaemia leads to a down-regulation of the HPG axis and can subsequently lead to loss of libido and, in women, to oligorrhea or amenorrhea.

Vitamin D, 1,25-dihydroxyvitamin D<sub>3</sub> (1,25(OH)<sub>2</sub>D<sub>3</sub>), a pluripotent steroid hormone, has properties that extend well beyond its established role in calcium homeostasis<sup>22–24</sup> with recent work highlighting its important role in the immune system.<sup>22,25</sup> Sufficient bioavailability of active vitamin D is dependent on dietary intake and regular exposure to light. The elderly, especially those living in nursing homes, have insufficient vitamin D levels. Extended working hours and night shift work are also associated with lack of sunlight and often unhealthy diets and have a similarly negative impact on the vitamin D balance.

Taken together, the impact of working hours and rotas on our hormonal system is an important topic to be addressed by the medical community. The implementation of the EWTD may represent a unique opportunity to initiate research projects with a longitudinal design. The impact of workload and work conditions on the health and training of junior doctors and the quality of care they provide for patients certainly deserves close attention. Clinical research should address this now and combat the criticism of recent systematic reviews.<sup>2,3</sup> A successful approach is exemplified by the extensive literature on the effects of working conditions on flight crews, who face a similar situation to doctors, being responsible not only for their own well-being but also for those under their care.

Despite all the criticism, the UK is in a good position compared to several other European countries which still ignore the policy outlined in the EWTD. The effects of changes in rotas on medical ethos and professionalism should be monitored. An earlier study from the USA documented that consultants perceived the development of a ‘shift mentality’ in junior doctors after the introduction of a shift system which aimed to reduce working hours, a view that was not shared by the junior doctors themselves.<sup>26</sup> It remains to be seen whether new working times will have an impact, and this may be a good opportunity to revive the medical professionalism debate – being a doctor certainly does not end with the shift.

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