Eur J Appl Physiol (1990) 60:288-292

European Journal of Applied Physiology and Occupational Physiology

Effect of shift work on the night-time secretory patterns of melatonin, prolactin, cortisol and testosterone

Y. Touitou[1], Y. Motohashi[2], A. Reinberg[2], C. Touitou[1], P. Bourdeleau[3], A. Bogdan[1], and A. Auzéby[1]

[1] Department of Biochemistry, Faculté de Médecine Pitié-Salpêtrière, 91 Boulevard de l'Hôpital, F-75634 Paris Cedex 13, France
[2] CNRS UA 581, Fondation A. de Rothschild, Paris, France
[3] Service Médical Shell Française, F-76650 Le Petit Couronne, France

Accepted October 20, 1989

Summary. In a study of the internal desynchronization of circadian rhythms in 12 shift workers, 4 of them, aged 25–34 years, agreed to be sampled every 2 h during their night shift (0000 hours to 0800 hours). They were oil refinery operators with a fast rotating shift system (every 3–4 days). We found marked changes in the secretory profiles of melatonin, prolactin and testosterone. Melatonin had higher peak-values resulting in a four-times higher amplitude than in controls. With respect to prolactin and testosterone, peak and trough times were erratic and the serum concentrations were significantly decreased in shift workers. Serum cortisol presented a decreased rhythm amplitude together with higher concentrations at 0000 hours in shift workers. This study clearly shows that fast rotating shift-work modifies peak or trough values and rhythm amplitudes of melatonin, prolactin, testosterone and cortisol without any apparent phase shift of these hormones. Whether the large rhythm amplitude of melatonin may be considered as a marker of tolerance to shift work, as reported for body temperature and hand grip strength, since it would help the subjects to maintain their internal synchronization, needs further investigation.

Key words: Shift work – Melatonin – Cortisol – Testosterone – Prolactin – Circadian rhythm

Introduction

A number of circumstances in the living conditions of normal man may result in differences in the circadian rhythm of biological variables. Among these circumstances which affect the chronological surroundings of humans, two are frequently encountered, transmeridian flight and shift work. Both may produce a desynchronization of the subjects with their external environment, requiring subsequent adaptation to the new conditions. This has been shown, for example, in isolation experiments (Aschoff and Wever 1981). A second feature to emphasize is that of the time required for each biological variable or function to adjust to the new external environment (synchronizers). It has been shown, after transmeridian flight (Carruthers et al. 1976), as well as in isolation experiments, that the speed of adjustment does indeed differ among biological variables, thus resulting in an internal desynchronization of the subjects.

Although the obvious difficulties in organizing such studies in work surroundings contribute to the small number of reports in the field of shift work, Chaumont et al. (1979) showed that in shift workers adjusting to weekly rotations there were quickly adjusting variables (mood, physical vigour, systolic blood pressure, urinary sodium excretion) and slowly adjusting variables (serotonin, heart rate, peak expiratory flow, oral temperature, grip strength, urinary volume, potassium, chloride, 17-hydroxy-corticosteroids and 17-ketosteroids).

The major complaints of many shift workers are usually associated with the morning shift (≈0500–1300 hours) e.g. increased feelings of fatigue, persisting sleep disturbances often accompanied by anxiety and gastrointestinal disorders (from simple troubles to peptic ulcers).

Few reports are available dealing with the temporal pattern of endocrine function in shift workers including night work. It is well established that some hormones, e.g. melatonin, are sensitive to photoperiodism (Klein 1979), some e.g. prolactin, are sensitive to the sleep-wakefulness cycle (Parker et al. 1973; Sassin et al. 1973) whereas others, e.g. cortisol, are considered as markers of the circadian temporal organization (Touitou et al. 1982, 1983). Therefore, we found it worth documenting the rhythmicity of the above-mentioned hormones as well as testosterone in volunteer shift workers.

Methods

Subjects. In a broad study on the internal desynchronization of circadian rhythms in 12 shift workers, 4 of them agreed to be sam-

Offprint requests to: Y. Touitou

pled every 2 h during their night shift in February. They were oil refinery operators, aged 25 to 34, with a rapid rotating shift system (every 3 or 4 days). The duration of this shift work situation had been for around 10 years. Their work involved using a cathode ray tube terminal in a dimly lit room (less than 200 lx). Two of the 4 shift workers were considered to have been non-tolerant of shift-work for a year according to clinical criteria (permanent fatigue, sleep disturbance, alteration of mood).

Experimental Protocol. Venous blood samples were drawn from each subject every 2 h while he was working from 0000 hours to 0800 hours. Six healthy men, aged 24–31, who were synchronized with lights turned on at 0700 hours ± 1 h and off at 2300 hours ± 1 h, were sampled at the same times and considered as controls. The secretory patterns of the six following hormones were studied using RIA methods: melatonin (Tecova), prolactin (International CIS), cortisol and testosterone (Travenol). Serum samples were kept frozen at −20° C until analysed. All the samples were assayed at the same time at the end of the protocol to avoid the variations between assays. The intra-assay variability was 9.5% at 38 $pg \cdot ml^{-1}$ of melatonin, 2.9% at 278 $mU \cdot ml^{-1}$ of prolactin, 3.2% at 11.6 $\mu g \cdot 100\ ml^{-1}$ of cortisol and 4.7% at 2.5 $pg \cdot ml^{-1}$ of testosterone. For each hormone, the overall 8-h means and the mean concentrations at the peak and trough times of shift workers and controls were compared using the Student *t*-test. The difference between the highest and lowest concentrations were expressed as percentage increases in trough values, i.e.

$$100 \times \frac{\text{peak value} - \text{trough value}}{\text{trough value}}.$$

Results

Melatonin

The secretory pattern of melatonin is depicted in Fig. 1. The patterns exhibited their typical physiological responses in 3 subjects out of 4 with a peak located at 0200 hours and a trough between 0600 hours and 0800 hours. Except for one intolerant worker (subject 2) who had low levels of serum melatonin at all times, the concentration of the hormone at the peak time (0200 hours) was elevated in shift-workers (range: 101–238 $pg \cdot ml^{-1}$) and significantly higher ($P < 0.02$) than that of controls (range: 25–78 $pg \cdot ml^{-1}$). The amplitude of the rhythm was therefore larger in shift workers than in controls (Table 1, Fig. 1). In addition, the general secretory profiles of melatonin were not the same in controls and shift-workers since there was a progressive decline of

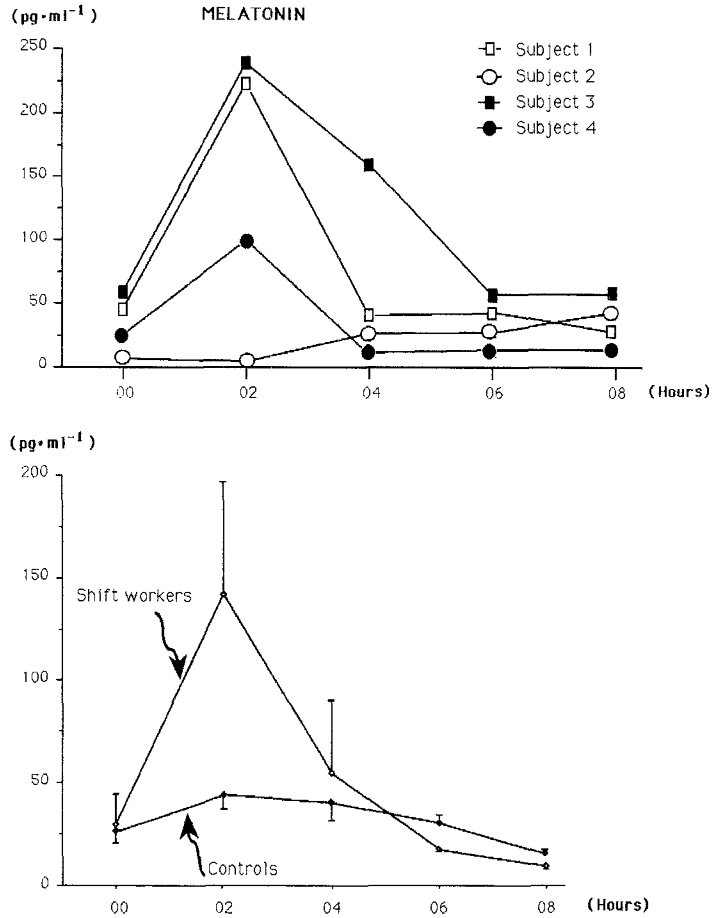

Fig. 1. Secretory profiles of serum melatonin in shift workers sampled during their night shift and in controls. Subjects 1 and 2 were non-tolerant to shift work. *Lower panel:* each time point represents the mean and SD value of the subjects

Table 1. Main characteristics of hormonal secretory profiles in shift-workers and controls

	Overall 8-h mean	Overall SD	Peak time (hours)	Peak mean value	Peak SD	Trough time (hours)	Trough mean value	Trough SD	Peak-trough difference in %
Melatonin ($pg \cdot ml^{-1}$)									
controls	32	16	0200	44	18	0800	15	4	195
shift workers	52	72	0200	187	75***	0800	14	3	914
Cortisol ($\mu g \cdot dl^{-1}$)									
controls	7.5	6.8	0800	17.6	3.3	0200	1.3	0.9	1253
shift workers	7.2	4.4	0800	14.8	2.2	0000	4.0	1.3**	270
Testosterone ($\mu g \cdot ml^{-1}$)									
controls	8.0	4.0	0400–0600	9.8	5.3	0000	6.5	2.6	51
shift workers	4.0	1.5***	0600	4.6	2.7	0200	3.7	1.0*	24
Prolactin ($\mu IU \cdot ml^{-1}$)									
controls	228	77	0200–0400	262	88	0000–0800	185	51	41
shift workers	148	46***	0200	164	29	0600	115	54	43

Values significantly different from the controls with: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

$$\frac{\text{peak-trough} \times 100}{\text{trough}}$$

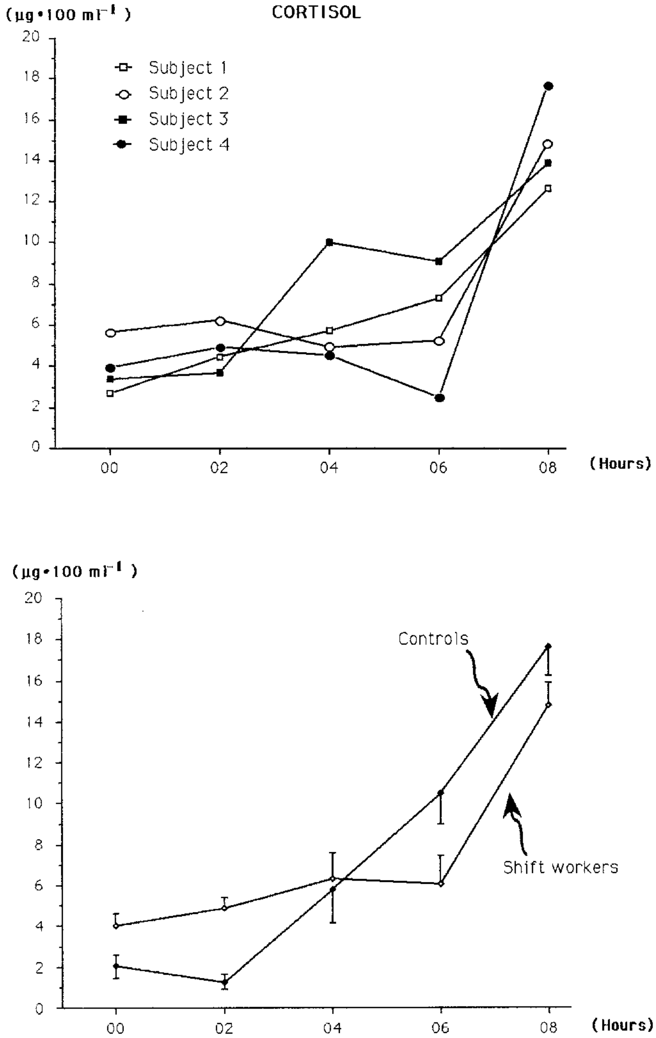

Fig. 2. Secretory profiles of serum cortisol in shift workers sampled during their night shift and in controls. Subjects 1 and 2 were non-tolerant to shift work. *Lower panel:* each time point represents the mean and SD value of the subjects

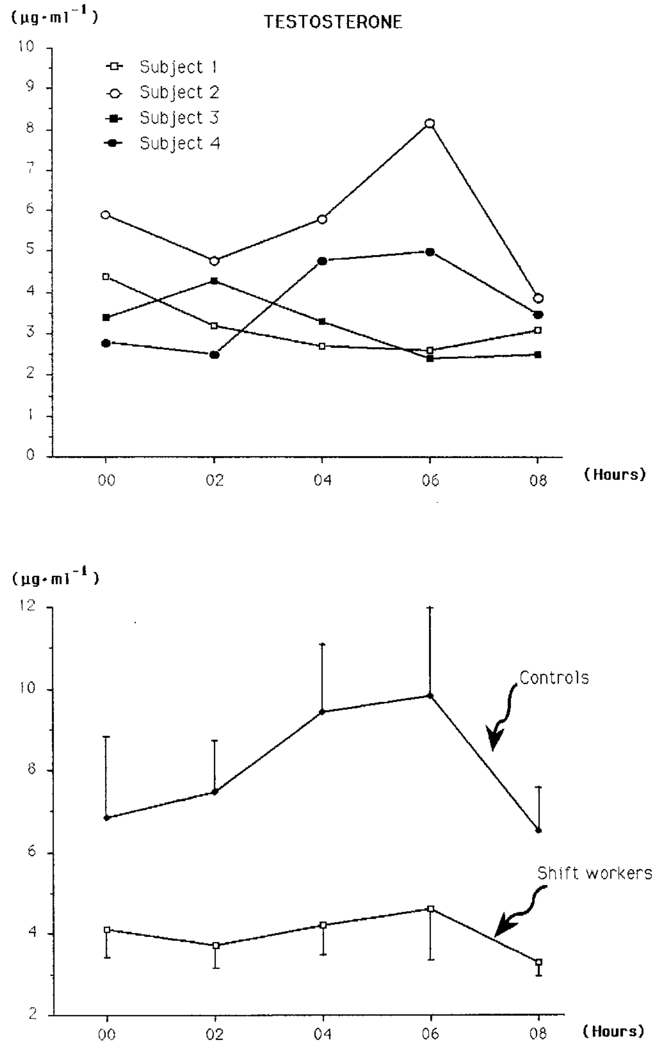

Fig. 3. Secretory profiles of serum testosterone in shift workers sampled during their night shift and in controls. Subjects 1 and 2 were non-tolerant to shift work. *Lower panel:* each time point represents the mean and SD value of the subjects

serum melatonin in the controls and a pronounced one 2 h after the peak time in the shift-workers (Fig. 1).

Cortisol

The patterns of response of plasma cortisol in shift workers and controls are depicted in Fig. 2. The peak time was always found at 0800 hours whereas the lowest levels occurred at 0000 hours–0200 hours. The mean concentrations of the hormone at the peak-time were not different in the two groups (Table 1). However, cortisol serum concentrations were significantly higher ($P<0.01$) in shift workers than in the controls at the presumably lower time-points of the nycthemere (0000 hours–0200 hours), which resulted in a lower amplitude of the rhythm in the shift workers (Table 1, Fig. 2). In addition, cortisol increased progressively from 0200 hours to 0800 hours in the controls but not in the shift workers.

Testosterone

The general secretory pattern of testosterone was different from one subject to another with respect to concentration of the hormone, peak and trough times as well as rhythm amplitudes (Fig. 3). Two subjects had a similar pattern with high concentrations at 0600 hours, then a 30%–50% reduction at 0800 hours (subjects 2 and 4), whereas the 2 others had quite different profiles (Fig. 3). The overall mean concentration of testosterone in shift workers (4.0 $mg \cdot ml^{-1}$, SD 1.5 was half that in the controls (8.0 $mg \cdot ml^{-1}$, SD 4.0). At the times of peak and trough the shift workers had lower levels of serum testosterone than the controls, which resulted in a decreased rhythm amplitude (Table 1, Fig. 3).

Prolactin

The overall 8-h mean of prolactin concentration in se-

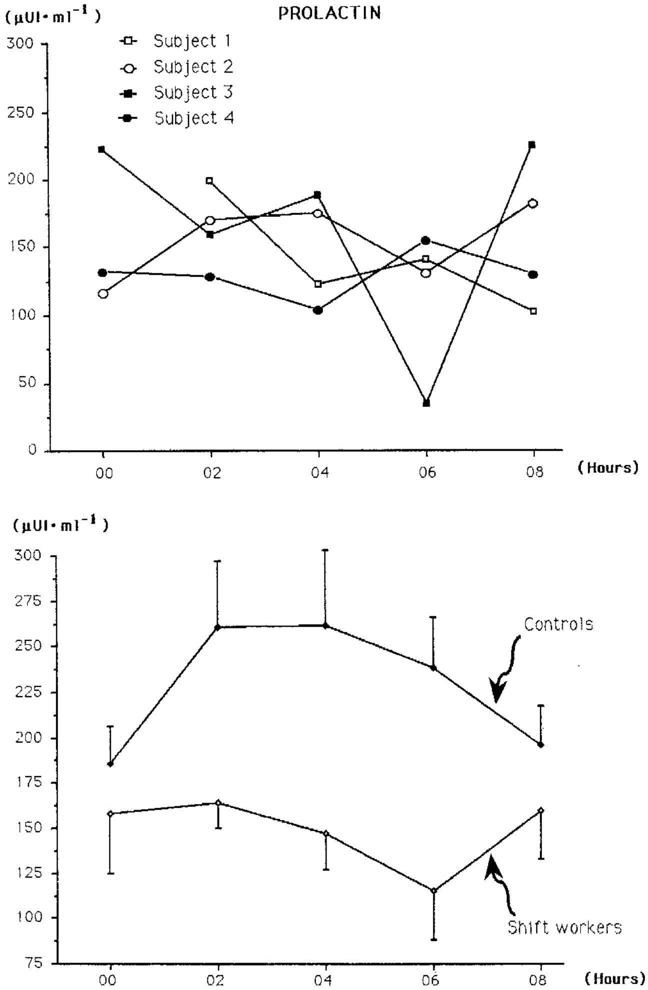

Fig. 4. Secretory profiles of serum prolactin in shift workers sampled during their night shift and in controls. Subjects 1 and 2 were non-tolerant to shift work. *Lower panel:* each time point represents the mean and SD value of the subjects

rum varied little from one shift worker to another (130–166 $mIU \cdot ml^{-1}$). However, the patterns of secretion were different between subjects as were the peak and trough times when compared to controls (Fig. 4). In addition, the shift workers had significantly lower levels of prolactin than the controls (Table 1).

Discussion

The tolerance of shift work is a fundamental problem in our civilization. Whereas a number of symptoms are apparent in nontolerant shift workers, the modification, if any, in the biology of such subjects is not clearly established. Besides the influence of season and geographic location, another variable to keep in mind is the kind of professional activity, since manual work as opposed to sedentary work might exert, per se, synchronizing effects of a possibly different nature. In addition, since the studies documenting hormonal circadian rhythms conventionally require repeated blood sampling, there are few dealing with shift-workers because of the understandable difficulties in organizing such protocols in work surroundings. In most of the studies performed so far circadian changes were documented from urinary excretions, e.g. 17-hydroxy-corticosteroids (17-OHCS), 17-ketosteroids, hydroxyindole acetic acid, catecholamines (vanilmandelic acid) among others (Reinberg et al. 1976). Our study is, to our knowledge, the only one that has reported the nocturnal fraction of the circadian rhythmicity of melatonin, prolactin and other hormones in shift workers. Blood sampling was performed during the 0000 hours–0800 hours span of working time since it includes the usual secretory peak times of melatonin and prolactin (0200 hours–0400 hours) or cortisol and testosterone (0600 hours–0800 hours).

Melatonin, prolactin and testosterone patterns underwent marked changes. In 3 out of 4 subjects, the apparent modification of melatonin rhythm was a dramatic increase of peak concentrations resulting in a very large amplitude of the rhythm. The nocturnal peak of melatonin is associated with darkness and even dim light in man. Large amounts of light (2500 lx) are needed to lower this nocturnal surge (Lewy 1980). Since workers of this study were working in dim light the results obtained fit with this experimental background. However, what was not expected was that the nocturnal peak height of melatonin, when occurring in 3 or 4 subjects, would be twice as large as that of day-active control subjects. A large amplitude circadian rhythm of variables such as body temperature and hand grip strength has been reported to occur in subjects with good tolerance to shift work (Reinberg et al. 1978). This could also be the case for melatonin, a large amplitude of this variable helping the subject to maintain his internal synchronization.

The profile of serum prolactin was different in shift workers with respect to the general secretory pattern, the peak and trough locations as well as the overall 8-h mean. Shift working also affected strikingly all the parameters of testosterone rhythmicity: peak and trough times were erratic, the serum mean level in this group of shift-workers was half that in the control group and the amplitude was also markedly decreased.

Lastly, this work showed that fast rotating shift work neither altered cortisol concentrations nor shifted the peak of hormone concentration. It is interesting to find this since data dealing with slower rotation has shown a phase shift of the circadian rhythm of 17-OHCS, the urinary metabolites of cortisol (Reinberg 1976). However, cortisol serum concentrations in our group of shift workers were higher at the presumably lower time-points of the nycthemere (0000 hours–0200 hours), resulting in a fivefold decrease in the rhythm amplitude of cortisol secretion when compared to the controls. These data are different from those obtained in another situation of desynchronization, i.e. after a Brussels-Chicago transmeridian flight. Indeed, it has been shown that the amplitude of the rhythm of melatonin decreased during jet lag but that it adjusted faster than that of cortisol (Fèvre-Montange et al. 1981).

In conclusion, our study has shown that fast rotating shift work in sedentary workers in a dimly lit environment clearly modifies some parameters (e.g. peak or trough values, amplitudes) of the rhythmicity of serum melatonin, prolactin, cortisol and testosterone. We could not find any precise relationship between intolerance to shift work and the secretory profiles of the hormones studied, at least for this particular group.

Acknowledgements. This work was supported by le Conseil Scientifique de l'Université P. et M. Curie (Formation recommandée par la Direction de la Recherche) and Caisse Nationale d'Assurance Maladie des Travailleurs Salariés. We wish to thank la Shell Française (le Petit Couronne) and the shift-workers who volunteered for this study.

References

Aschoff J, Wever R (1981) The circadian rhythm of man. In: Aschoff J (ed) Handbook of behavioral neurology, Vol. 4. Plenum, London, pp 311-331

Carruthers M, Arguelles AE, Mosowich A (1976) Man in transit: biochemical and physiological changes during intercontinental flights. Lancet i:977-980

Chaumont AJ, Laporte A, Nicolai A, Reinberg A (1979) Adjustment of shiftworkers to a weekly rotation. Chromobiologia [Suppl 1] 6:27-34

Fevre-Montange M, Van Cauter E, Refetoff S, Désir D, Tourniaire J, Copinschi G (1981) Effects of "jet lag" on hormonal patterns. II. Adaptation of melatonin circadian periodicity. J Clin Endocrinol Metab 52:642-649

Klein DC (1979) Circadian rhythms in the pineal gland. In: Krieger DT (ed) Endocrine rhythms. Raven Press, New-York, pp 203-223

Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, Markey SP (1980) Light suppresses melatonin secretion in humans. Science 210:1267-1269

Parker D, Rossman L, Vanderlaan E (1973) Sleep-related nycthemeral and briefly episodic variations in human plasma prolactin concentration. J Clin Endocrinol Metab 36:1119-1124

Reinberg A, Vieux N, Laporte A, Migraine C, Ghata J, Abulker C, Dupont J, Nicolai A (1976) Adjustement des rythmes circadiens physiologiques d'opérateurs d'une raffinerie, lors de changement d'horaires travail-repos tous les 3-4 jours. Arch Mal Prof Trav Sec Soc 37:479-494

Reinberg A, Vieux N, Ghata J, Chaumont AJ, Laporte A (1978) Is the rhythm amplitude related to the ability to phase-shift circadian rhythms of shift-workers? J Physiol (Paris) 74:405-409

Sassin J, Frantz A, Kapen S, Weitzman E (1973) The nocturnal rise of human prolactin is dependent on sleep. J Clin Endocrinol Metab 37:436-440

Touitou Y, Sulon J, Bogdan A, Touitou C, Reinberg A, Beck H, Sodoyez JC, Demey-Ponsart E, Van Cauwenberge H (1982) Adrenal circadian system in young and elderly human subjects: a comparative study. J Endocrinol 93:201-210

Touitou Y, Sulon J, Bogdan A, Reinberg A, Sodoyez JC, Demey-Ponsart E (1983) Adrenocortical hormones, ageing and mental condition: seasonal and circadian rhythms of plasma 18-hydroxy-11-deoxycorticosterone, total and free cortisol and urinary corticosteroids. J Endocrinol 96:53-64