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A multinational study of the relationships between nighttime urinary melatonin production, age, gender, body size, and latitude

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Abstract Overnight urines were collected each month for 12–16 months from 321 normal subjects at 19 medical centers in 14 countries distributed on 5 continents at latitudes from 31 01 South to 77 00 North. Mean melatonin concentration was found to negatively correlate with age, weight, and height. When the sexes were considered separately melatonin only correlated with age for female and with age and weight for males. A weak correlation with latitude, but not longitude, was also found.

Key words Melatonin · Urine · Age · Sex · Height · Weight · Urine volume · Latitude · Longitude.

Introduction

The nightly periodic production of melatonin by all mammals, and its consequences for the seasonal reproduction of some, has long attracted the interest of science (Moore et al. 1967). Over recent years the mechanisms by which this periodic rhythm is obtained and maintained as well the mechanism by which it is coupled to the daily light-dark cycle have been the subject of intensive physiological and biochemical studies and at least the general outlines have been elucidated. Recently, non-ocular light stimulation (Campbell and Murphy 1998) as well as weak electro-magnetic fields (Repacholi 1998) and biometeorological factors (Hardeland 1997), have also been implicated as regulators of melatonin formation in humans. The melatonin rhythm has also been of clinical interest as well because of periodicity in drug metabolism, the periodic nature of some diseases and the linkage between behavior, reproduction, and melatonin in seasonal breeders. This has led to examination of the status of the melatonin system in depression (Claustrat et al. 1984; Brown et al. 1985; Jimersen et al. 1977; Miles and Philbrick 1988; Wetterberg et al. 1979; Wirtz-Justice and Richter 1979; Mendlewics et al. 1980; Beck-Friis et al. 1984; Nair et al. 1984; McIntyre et al. 1986), seasonal affective disorder (Kevan 1980; Eastwood and Stiasny 1978; Rosenthal et al. 1986; Thalén et al. 1995 and 1997), premenstrual syndrome (Wirtz-Justice and Arendt 1979; Hariharasubramanian et al. 1984; Wetterberg et al. 1976; Webley and Leidenberger 1986; Parry et al. 1997), degenerative diseases of the elderly (Sharma et al. 1989; Skene et al. 1990; Sandyk et al. 1991), childhood autism (Nir et al. 1995), vascular diseases (Monroe and Watts 1998), and sleep (Sack et al. 1997; Palm et al. 1997; Duffy et al. 1999).

Recent reports that melatonin modulates immune responses (Maestroni and Conti 1996; Nelson and Demas 1997), inhibits growth of some tumors (Cos et al. 1996; Bartsch et al. 1997); and is a physiologically important antioxidant (Reiter and Leppaluoto 1997) have also attracted the news media and has resulted in a flood of lay periodicals and monographs extolling its virtues. In some countries melatonin is promoted by the health food industry and is apparently in wide public use, despite inadequate reference data on melatonin and the factors influencing it. There is nearly complete absence of data regarding the consequences of its long term use in adults, much less prepuberal children, despite the known effects of melatonin on gonadal maturation and reproduction in some species (Turek 1997).

A worldwide study on nighttime melatonin production provides unique data derived from a global estimate of normal nighttime urinary melatonin concentration in urine sampled before the time period with wide use of melatonin in the population. This study, on circumannual mela-

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tonin rhythmicity, examined monthly nocturnal melatonin production by normal subjects of varying ethnicity living in widely different climatic, dietary, social, and geographic circumstances. It was carried out at 19 centers in 14 countries distributed on 5 continents at latitudes from 31 01 South to 77 00 North. The present paper presents reference data. Some of this material was presented at a symposium on light and melatonin (Wetterberg et al. 1993) and in an analysis of individuals with low and high melatonin production (Wetterberg et al. 1999).

Methods

Subjects

Subjects were healthy volunteer university students and faculty members at 19 medical centers throughout the world. Urine samples were obtained from 361 subjects. Complete information on sex, age, height, weight, urine volume and urinary melatonin concentration was available on 321 of these subjects, 165 men and 156 women, between the ages of 18–62 years. All subjects were medically and psychiatrically screened to exclude somatic or mental disease. Those on medication were excluded except that oral contraceptives were permitted if used consistently throughout the study period. Informed consent was obtained from all subjects.

Sample collection

Urine samples were collected on the first Wednesday of each month (± one day) for 12–16 months. Subjects were provided with graduated plastic beakers to measure urine volume and plastic vials for storage. The collection procedures consisted of emptying the bladder at bedtime (10–11 pm) on the night of the collection period, discarding the urine, and recording the exact time of voiding. The measuring beaker was then placed on the toilet and thereafter the total urine produced during the night, including the first morning urination (at about 7 am), was collected into the graduated plastic beaker. The time of collection, the total urine volume and time of any nocturnal voiding was recorded. A portion of the total urine was poured into the plastic bottle and taken in the morning to a collection point where it was frozen and stored at –20 °C. Samples were not collected from subjects traveling more than 300 miles (500 km) north or south of their residence during the month preceding sampling. At the end of the study, all urine samples were transported to Stockholm, Sweden on dry ice, where they arrived in frozen condition and were stored at –20 °C until assayed. Previous studies have shown that urinary melatonin is stable under these conditions of storage and transfer (Wetterberg et al., 1978) and that urinary melatonin concentration in samples collected in this manner correlates highly with the 2 am peak value of serum melatonin ($N = 64$; $r = 0.8$; $p < 0.001$; Almay et al. 1987). Since melatonin production occurs mainly at night, and melatonin concentration is in equilibrium with blood concentration, overnight urinary melatonin concentration provides an integrated value for melatonin production.

Analytical procedure

Urine was analyzed for melatonin using a specific radioimmunoassay developed for use with urine and blood samples (Wetterberg et al. 1978). The assay had a sensitivity of 10 pmol/l. Interassay variability was 4.8% for melatonin levels above 150 pmol/l ($N = 60$). Melatonin values were expressed as concentration in pmol/l. Melatonin was extracted from the urine samples and the cross-reactivity of the melatonin antiserum to possible related structures was less than 1 : 1000 (Wetterberg et al. 1978).

Data handling and statistics

One or more urine samples were obtained from the 321 subjects on whom all demographic data were available and a yearly mean cal-

Table 1 Demographic data for the 19 centersparticipating in the study

Center location	Latitude ∅/min	N	Age years	Height cm	Weight kg	Uvol ml	Melatonin pmol/l
1 Svalbard Norway	77 00N	19	38 ± 07	175 ± 10	72 ± 14	343 ± 162	328 ± 087
2 Tromso Norway	69 40N	19	42 ± 10	174 ± 08	72 ± 12	459 ± 153	273 ± 140
3 Pajala Sweden	67 11N	20	39 ± 10	168 ± 09	69 ± 13	413 ± 128	387 ± 095
4 Umea Sweden	63 50N	20	44 ± 08	170 ± 08	65 ± 11	379 ± 149	282 ± 108
5 Stockholm Sweden	59 20N	25	36 ± 08	173 ± 08	71 ± 13	410 ± 141	337 ± 214
6 Visby Sweden	57 05N	10	33 ± 07	177 ± 08	77 ± 17	429 ± 115	271 ± 109
7 Malmo Sweden	55 36N	20	34 ± 09	171 ± 08	66 ± 13	387 ± 129	272 ± 126
8 London England	51 30N	13	38 ± 11	170 ± 13	69 ± 14	455 ± 144	165 ± 098
9 Basel Switzerland	47 38N	20	31 ± 07	172 ± 10	64 ± 09	398 ± 144	333 ± 111
10 Genoa Italy	44 25N	15	30 ± 05	176 ± 06	70 ± 13	379 ± 116	218 ± 196
11 Bethesda USA	38 54N	09	35 ± 10	174 ± 06	69 ± 10	405 ± 218	201 ± 128
12 Athens Greece	37 58N	22	34 ± 05	170 ± 12	68 ± 12	308 ± 102	271 ± 124
13 Osaka Japan	34 40N	10	32 ± 03	172 ± 08	65 ± 11	380 ± 161	274 ± 088
14 Los Angeles USA	34 04N	19	39 ± 10	174 ± 12	72 ± 13	388 ± 135	261 ± 143
15 Harare Zimbabwe	17 15S	17	42 ± 10	175 ± 09	74 ± 12	521 ± 123	144 ± 063
16 Johannesburg S. Africa	25 10S	17	28 ± 06	170 ± 09	66 ± 12	338 ± 087	338 ± 123
17 Buenos Aires Argentina	34 37S	21	34 ± 09	169 ± 10	69 ± 12	380 ± 160	263 ± 097
18 Melbourne Australia	37 45S	19	32 ± 10	173 ± 08	68 ± 12	454 ± 169	257 ± 115
19 Mar de Plata Argentina	38 01S	6	37 ± 08	160 ± 07	61 ± 15	399 ± 138	150 ± 073
All		321	36 ± 09	172 ± 09	69 ± 12	398 ± 142	274 ± 120

Values are means ± S.E. Abbreviations are: ∅/min = degrees and minutes of latitude, N = number of subjects and uvol = urine volume.

culated for each individual. Group means for the total population in the 19 centers, for those in the 14 centers in the northern hemisphere, the 5 centers in the southern hemisphere, the 8 centers above latitude 51 north, and the 6 centers between the equator and latitude 51 north were calculated from the individual means. Correlations and estimates of the statistical significance of correlations for normal data and seasonal variations were computed using the BMDP programs 1D, 6D, 1R, and 2R, while 2V was used for the analysis of gender difference covaried for age. The log of urinary melatonin concentration was also used for some statistical computations of the normal reference data because the log was more normally distributed than the raw data.

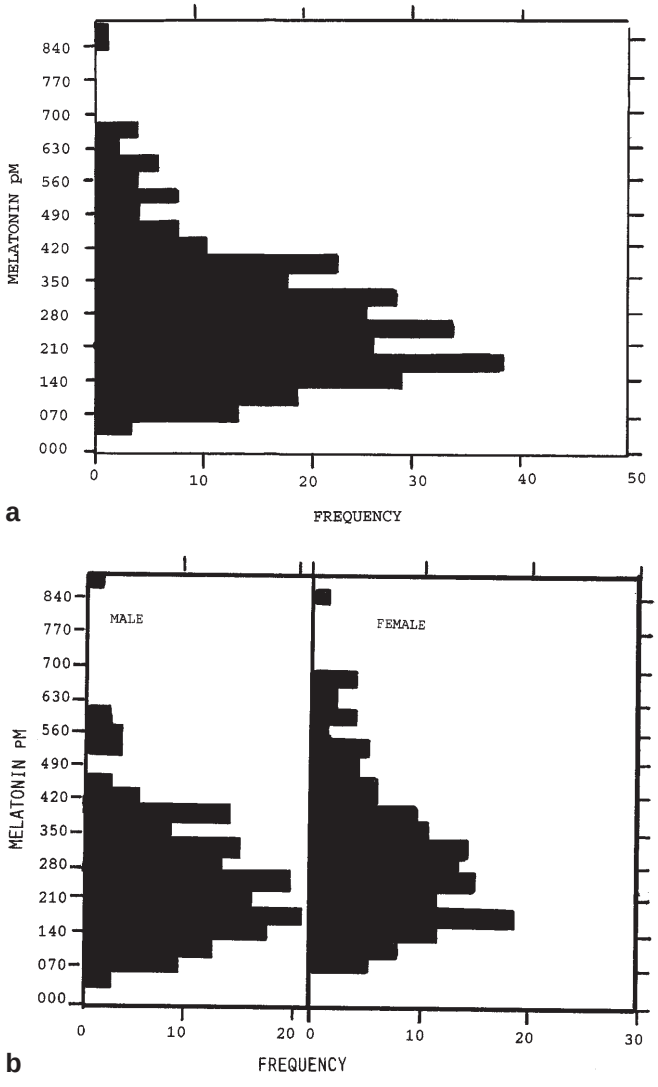

Fig. 1 **A** Distribution of 12 month mean of overnight urinary melatonin values for all subjects in the study. The ordinate is melatonin in pM, the axis, frequency. The mean ± S.D. for the 321 subjects 274 ± 120. The maximun value was 860 and the minimum 24. **B** Distribution of 12 month mean of overnight urinary melatonin concentration of males and females in the study. The ordinate is melatonin in pM, the axis, frequency. The mean ± S.D. for the 165 males was 250 ± 129 with a maximun value of 860 and a minimum of 24. For the 156 women, the values were 300 ± 151 for the mean ± S.D. while the maximun value was 850 and the minimum 55 pmol/l

Results

Table 1 presents demographic data on the subjects at the 19 centers. Mean ages ranged from 30 (Genoa) to 44 (Umea). Subjects at the most southerly site, Mar De Plata Argentina consisting of 1 male and 5 females, were the shortest (mean ht = 160 cm) and lightest (61 kg) while those at Visby Sweden, consisting of 4 males and 6 females, were the tallest (177 cm) and heaviest (77 kg).

Fig. 1 shows the distribution of melatonin concentration for the whole group and for males and females separately.

The correlations between age and melatonin at each center are shown in Table 2 while Fig. 2 shows the distribution of values and their correlation. Overall, the correlation coefficient was 0.19 for males, females, and both groups combined ($p < 0.001$ in each case). Correlation coefficients between age and melatonin at individual sites were negative in 15 and positive in 4 of the cases. The number of subjects at each center was small (6–25), positive correlations were generally small (0.02, 0.04, 0.08, and 0.23) and negative correlations were generally more robust. Four of the negative correlations were statistically significant.

Although values for melatonin at each center showed considerable variation (Table 3) there was a statistically

Table 2 Correlation between age and melatonin for the 19 centers participating in the study

Center No.	Male	Female	n	R
1	12	7	19	–0.22
2	11	8	19	–0.32
3	8	12	20	+0.23
4	5	15	20	–0.14
5	14	11	25	–0.40*
6	4	6	10	–0.03
7	7	13	20	+0.08
8	7	6	13	–0.60*
9	11	9	20	–0.16
10	12	3	15	–0.51*
11	3	6	9	+0.04
12	12	10	22	–0.11
13	9	1	10	–0.44
14	11	8	19	–0.40
15	9	8	17	–0.56*
16	8	9	17	–0.24
17	13	8	21	–0.03
18	8	11	19	+0.02
19	1	5	6	–0.21
Men	165			–0.19**
Women	156			–0.19**
Both	321			–0.19**

Abbreviations are: For identification of Center numbers see Table 1. N = number of subjects, R = Pearson correlation coefficient; * = $p < 0.05$; ** = $p < 0.001$

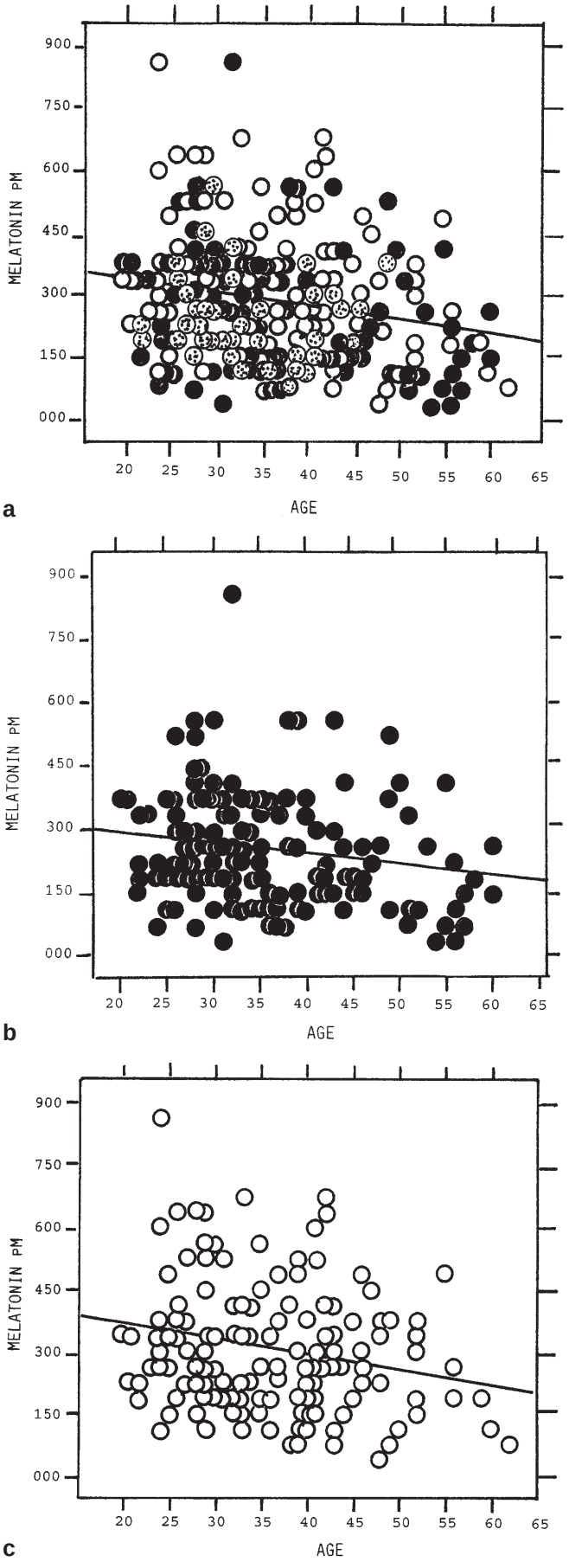

Fig. 2 **A** The correlation between age (years) and melatonin values (pM) for both males and females. Values for males are designated by closed circles, values for females by open circles and values where both coincide by stippled circles. The line is that of the regression equation. The correlation coefficient between melatonin and age for the 321 subjects was 0.188; $p < 0.001$. The regression equation was: Melatonin = 0.37726 - 0.0028 (age). **B** The correlation between age and melatonin values (pM) for males. Values for males are designated by closed circles. The line is that of the regression equation. The correlation coefficient between melatonin and age for the 165 males was 0.193; $p < 0.013$. The regression equation was: Melatonin = 0.34417 - 0.0026 (age). **C** The correlation between age (years) and melatonin values (pM) for females. Values for males are designated by open circles. The line is that of the regression equation. The correlation coefficient between melatonin and age for the 156 female subjects was 0.190; $p < 0.017$. The regression equation was: Melatonin = 0.31296 - 0.0031 (age)

Table 3 Correlations between melatonin concentration and height, weight, urine volume, latitude, and longitude

	Male (N = 165)	Female (N = 156)	Total (N = 321)
Melatonin vs:	R (p)	R (p)	R (p)
Height	–0.004 (ns)	–0.018 (ns)	–0.114 (< 0.04)
Weight	–0.166 (0.03)	–0.143 (ns)	–0.230 (< 0.001)
Urine V	–0.234 (0.002)	–0.239 (0.003)	–0.246 (< 0.001)
Latitude	–		0.202 (< 0.001)
Longitude	– –		–0.068 (ns)

R = correlation coefficient, p = probability, ns = not significant

Table 4 Correlations between age and melatonin concentration and content, height, weight, and urine volume

	Male (N = 165)	Female (N = 156)	Total (N = 321)
Age vs:	R (p)	R (p)	R (p)
Melatonin (pM)	–0.193 (0.01)	–0.190 (0.02)	–0.188 (< 0.001)
Log melatonin (pM)	–0.245 (< 0.001)	–0.237 (0.001)	–0.245 (< 0.001)
Melatonin (pM)/kg wt	–0.240 (0.002)	–0.212 (0.008)	–0.204 (< 0.001)
Log melatonin (pM)/kg wt	–0.177 (0.023)	–0.186 (0.02)	–0.178 (< 0.001)
Melatonin (pmoles)	–0.149 (0.06)	+0.040 (ns)	–0.55 (ns)
Height	–0.075 (ns)	–0.097 (ns)	–0.061 (ns)
Weight	–0.243 (< 0.01)	–0.147 (ns)	–0.147 (0.01)
Urine V	–0.145 (ns)	–0.335 (< 0.001)	–0.237 (< 0.001)

R = Correlation coefficient, p = probability, ns = not statistically significant

significant relationship between latitude and melatonin for the whole sample ($R = 0.202$, $p < 0.001$) and for subjects in the northern hemisphere alone ($N = 241$, $R = 0.157$, $p = 0.015$). There was a similar, but nonsignficant, correlation for subjects in the Southern hemisphere ($N = 80$, $R = 0.197$, $p = 0.81$). Melatonin and longitude were not significantly related ($R = –0.07$; NS).

Also shown in Table 3 are the correlations between melatonin and height, weight and urine volume. Height was not significantly correlated with melatonin ($r = –0.004$, $–0.018$ respectively) for males or females sepa-

Table 5 Gender differences in melatonin, body height and weight, and in urine volume

	Male (N = 165) mean ± S.E	Female (N = 156) mean ± S.E	F	Df	p
Height (cm)	178 ± 7	165 ± 7	298	1,319	< 0.0001
Weight (kg)	77 ± 10	60 ± 9	257	1,319	< 0.0001
Melatonin (pmol/l)	250 ± 129	300 ± 151	10	1,319	0.0016
Urine volume (ml)	409 ± 139	386 ± 145	2	1,319	0.2 ns

rately but was significantly correlated for the whole population (–0.114; $p < 0.04$). Male body weight ($R = –0.17$ $p = 0.03$), but not female body weight (–0.14; NS), correlated with melatonin while weight and melatonin were correlated for the entire group ($r = –0.23$ $p < 0.001$).

Correlations between age and the other variables are shown in Table 4. The correlation between log melatonin and age was even better than that between melatonin and age probably because log melatonin is more normally distributed than the raw data. Normalizing melatonin to body weight did not materially alter the relationship between melatonin concentration and age or between log melatonin and age. Melatonin content in the urine of males correlated with age but not in the urine of females or the melatonin content for both groups combined. As expected, urine volume was negatively correlated with melatonin concentration for males ($R = –0.23$ $p = 0.002$), females ($R = –0.24$, $p < 0.003$) and both groups together ($R = –0.246$, $p < 0.001$) (Table 3).

The data in Table 5 show the gender differences in these variables. As might be expected, the sexes differ in height and weight.They also differ in melatonin concentration. For this reason an analysis of variance with sex as covariate was carried out confirming the effect of age on melatonin (Df = 1,318, F = 12, $p = 0.0006$) with age adjusted mean melatonin concentrations of 250 ± 129 for males and 300 ± 150 pmol/l for females.

Discussion

In agreement with other reports (Lang et al. 1981, Coetzee et al. 1989, Graham et al. 1998), inter-individual melatonin concentrations varied greatly while intra-individual variance was small. The highest mean yearly value observed, 870 pmol/l was nearly forty times as great as the lowest value, 23 pmol/l, and more than three times the mean for the entire population, 278. On the other hand standards deviations of individual means varied from 7 to 293 or from 8 to 155% of the individual means over the year.

The negative correlation between age and nighttime urinary melatonin concentration in this study is consistent with other reports in the literature (Touitou et al. 1985; Iguchi et al. 1982; Beck-Friis et al. 1984; Nair et al. 1986; Sack et al. 1986; Grinevich and Lebunetz 1986; Sharma et al. 1989; Reiter et al. 1981; Pang et al. 1990; Wetterberg et al. 1992; Watson 1997; Waldhauser et al. 1998) and is derived from a much larger and diverse population than previously reported. The magnitude of the correlation coefficient in this study, however, is considerably smaller than the value of 0.47 calculated by Sack et al. (1986) from measurement of urinary 6-hydroxymelatonin or the 0.38 found by Sharma et al. (1989) using the acrophase of the blood melatonin rhythm. These quantitative differences in the magnitude of the correlation might reflect how well these various measures of melatonin track its true daily variation. As seen in Table 1 the magnitude of the age-melatonin correlation varied considerably between centers and correlations between age and melatonin concentration in these small populations only reached statistical significance in 4 of the 19 participating centers (Stockholm, London, Genoa and Harare), It approached significance in two others (Los Angeles and Osaka).

The negative correlation between body height and urinary melatonin found in this study corresponds to the correlation found by Beck-Friis et al. (1984) between height and plasma melatonin and by Sack et al. (1986), between height and urinary 6-hydroxymelatonin. However, it was much weaker and was only seen for the whole population but not for males or females alone.

The inverse relationship between melatonin concentration and overnight urine volume was expected as a natural consequence of the free passage of melatonin from blood into the renal tubule. Since blood melatonin peaks around 2 am, urine passing into the bladder at this time is also high and concentration is diluted by urine collecting before and after that period in accordance with the lowered blood levels at those times.

In agreement with Ferrier et al. (1982) and Arendt et al. (1982), we found a significant correlation between melatonin and weight. However, normalizing melatonin to body weight did not materially affect the correlation of melatonin with age indicating that the correlation between melatonin and age is not a simple reflection of age-related changes.

Our finding of a gender difference in urinary melatonin production which persisted after age correction, supports and extends the observation by Touitou et al. (1985) of higher blood melatonin in aged women than in aged men. This does not appear to be accounted for by gender differences in body mass.

The mechanism accounting for the relationship between age and melatonin is not clear. Age-linked losses of noradrenergic neurones (Bondareff et al., 1981), decreases in catecholamine metabolism (Finch, 1973) or a fall in the pineal enzyme, hydroxy-O-methyltransferase,which con-

verts N-acetylserotonin to melatonin (Axelrod and Weissbach, 1960; Klein et al., 1971) could each contribute to the relationship. A more practical issue is that of evaluating the contributions of sex, age, height, and weight to the results of studies on the clinical significance of melatonin production. While we find a consistent and statistically significant relationships between melatonin and age, the magnitude of the relationship for the normal population studied here is small, accounting for only 5% of the variance leaving 95% to other factors. We (Almay et al. 1987, Wetterberg et al. 1992) and others (Arendt et al. 1982, Touitou et al. 1985, Bartsch et al. 1997, Webb et al. 1997) have previously shown that among these factors is clinical status. Given the meager contribution of age towards melatonin production, it is not surprising, that the magnitude of the correlation between age and melatonin, or indeed, even evidence of that relationship, varies between populations in various studies. This can even be seen in Table 2 of this study where, given small number of subjects, the direction of the correlation in four centers differs from that in the others. Further, the magnitude of the effects of age on melatonin production is sufficiently small that it is unlikely to contribute much to reported abnormalities in melatonin production by clinical populations unless the pathologies themselves alter the effects of age on melatonin production. Whether this proviso is true, however, needs to be established.

Similar considerations apply to assessing the influence of gender on studies of melatonin. Females do have significantly higher urinary melatonin concentrations than males after age correction but again the differences are relatively small so that incomplete sex matching of experimental and control populations is unlikely to result in significant population differences when N's are small but may lead to statistically significant, but physiologically trivial differences when N's are large. Obviously good experimental design requires close matching for both age and sex.

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