The Effects of Oral Melatonin on Skin Color and on the Release of Pituitary Hormones

JAMES J. NORDLUND AND AARON B. LERNER

Department of Dermatology, Yale University School of Medicine, New Haven, Connecticut 06510

ABSTRACT. We studied the effects of prolonged ingestion of melatonin, 1 g per day, on skin color and the serum levels of pituitary hormones in 5 human subjects with hyperpigmented skin. Melatonin lightened hyperpigmented skin of one patient with untreated adrenogenital syndrome, but had no effect on three patients' skin with idiopathic hyperpigmentation and one patient with treated Addison's disease. Melatonin appeared to depress the level of luteinizing hormone (LH) in serum and may have inhibited in some patients the release of growth hormone from the pituitary gland after stimulation by stress or L-dopa. The subjects all noted increased drowsiness but thorough studies on the eyes, liver, kidneys, and bone marrow revealed no other evidence of toxicity. (*J Clin Endocrinol Metab* **45**: 768, 1977)

MELATONIN in some mammals inhibits the release of melanocyte stimulating hormone-like peptides (MSH-Pep)[1] (1,2), luteinizing hormone (3–6) and growth hormone (7). In rodents it can suppress thyroid function (8,9). Little is known about the function of melatonin in human beings. The compound and its derivatives are found in human urine (15) and cerebrospinal fluid (11). The urinary excretion of melatonin exhibits a diurnal variation (12). Peak excretion of melatonin occurs during the night, from 2300 to 0700 h, possibly in response to darkness. Melatonin administered iv to normal human volunteers produces sleepiness and changes in the electroencephalogram, mainly an increase of alpha waves (13,14). Melatonin can inhibit or stimulate the release of growth hormone in response to insulin hypoglycemia (15), possibly by competitive inhibition of serotonin receptor sites (16). There are few other studies on the effects of melatonin administered to humans. We have completed a preliminary study in human subjects on the effects of melatonin on serum levels of GH, FSH, LH, skin color, and on its toxicity, for the liver, kidney and hematopoietic system.

Received October 25, 1976.

Reprint requests to: Dr. Nordlund, Department of Dermatology, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510.

[1] MSH-Pep indicates pituitary peptides with capacity to induce pigmentation of the skin.

Materials and Methods

Five Caucasian patients with hyperpigmented skin from various causes were invited to participate in the study (Table 1). Approval for use of melatonin as an experimental drug was obtained from the Food and Drug Administration (IND 7737) and from the Human Investigations Committee at the Yale-New Haven Hospital. Each patient was carefully studied to determine the etiology of his hyperpigmentation (Table 1). Patient 2 had developed primary myxedema and idiopathic Addison's disease six years prior to admission at our hospital and was receiving full replacement therapy with hydrocortisone acetate 37.5 mg to 50 mg, fludrocortisone acetate (Florinef acetate), and levothyroxine (Synthroid) before and during the melatonin study. Her skin, which became deeply pigmented during the evolution of her Addison's disease, never returned to normal color even with replacement therapy. Patient 3 was a 19 year old male with adrenogenital syndrome (21-hydroxylase deficiency) that had not been recognized before. He received no steroid therapy prior to or during administration of melatonin. Patients 1, 4 and 5 had idiopathic forms of hyperpigmentation.

The patients were admitted to the hospital for baseline studies of skin color, and of their endocrine, hepatic, hematopoietic, and renal sys-

TABLE 1. Patients receiving melatonin

Patient	Sex	Age (Yrs)	Cause of hyperpigmentation	Other diseases noted	Medication during trial of melatonin
1	F	41	Idiopathic hyperpigmentation	Monoclonal gammopathy Benign thyroid nodule	None
2	F	36	Addison's disease	Primary myxedema	Cortisol 37.5 mg qd Florinef 0.1 mg qd Synthroid® 300 μgm qd
3	M	19	Adrenogenital syndrome 21-Hydroxylase deficiency	None	None
4	F	48	Idiopathic hyperpigmentation	Thyroid nodule	Cytomel® 100 μg qd
5	F	29	Idiopathic hyperpigmentation	None	Ovral-28®

tems prior to receiving melatonin. Eye examinations were performed before and after the administration of melatonin. Electrocardiograms, liver function tests, routine blood and urinalyses and blood urea nitrogen, calcium, phosphorus, uric acid and total proteins were obtained before and weekly during the administration of melatonin.

Specific tests

Skin color. The color of the skin was evaluated by clinical examination and by measurements of reflectance with a Photovolt reflectometer (17).

Growth hormone. The levels of growth hormone were determined in the Clinical Chemistry Laboratory of the Yale-New Haven Hospital by radioimmunoassay (18).

Growth hormone in patient 2 was studied after an iv infusion of arginine (300 ml R-Gene 10, Cutter Laboratories) beginning at 0800 h before and during the administration of melatonin. In patients 1, 3, 4 and 5 growth hormone was measured at rest, 15 min after a standard exercise stress test, (rapidly climbing 5 floors) and 0.5 h after breakfast. On separate days patients 1, 3 and 5 also received 500 mg L-dopa by mouth at 0800 h to stimulate the release of growth hormone. Sera were obtained 0.5 and 1 h before and intermittently for 2 h after the administration of L-dopa.

Luteinizing hormone (LH) and follicle stimulating hormones (FSH). Serum concentration of LH and FSH were determined by radioimmune assay at Bioscience laboratories, Van Nuys, California (Bioscience Handbook). Patient 1 and 2 had regular monthly menses. LH and FSH levels were measured in these patients on the same day of the menstrual cycle (day 1 is the first day of menses). Patient 3 was a male; patient 4 was post-menopausal; and patient 5 was receiving birth control pills (Ovral-28®).

Thyroxine. Serum thyroxine (T_4) levels were measured in the clinical laboratories by competitive protein binding.

Plasma and urinary steroids. Blood was obtained for the determination of cortisol at 0800 and 1600 h before and during melatonin trials. Serum cortisol was assayed by a fluorometric method. Twenty-four hour collections of urine were assayed in the hospital laboratory for 17-keto steroids by the Zimmerman reaction and for 17-hydroxycorticosteroids by the Porter-Silber method.

Administration of melatonin

Crystalline melatonin, a gift of the Regis Chemical Company, was dissolved in 95% ethanol (250 mg per 5 ml). Patients received 250 mg melatonin by mouth at 0000, 0600, 1200, and

TABLE 2. The effect of melatonin on the serum concentration of growth hormone stimulated by exercise, L-dopa and arginine

	GH					
	Pre-melatonin			During melatonin		
Patient	Fasting	Post-exercise	Post-prandial	Fasting	Post-exercise	Post-prandial
1	0	0	0	0	0	0
2	3	25	4	0	0	0
3		5	2	0	0	0
4	5	0	0	2	10	2
5	1	12	2	1	2	1

	L-dopa					
	Minutes from baseline			Minutes from baseline		
	0	30	60	0	30	60
1	4.5	9.3	14	4.7	15	15
2	ND			ND		
3	4	3	9	3	0	0
4	ND			ND		
5	1	10	15	0	3	5

	Arginine infusion					
	Minutes from baseline			Minutes from baseline		
	0	45	60	0	45	60
2	2.5	15	15	0	7	4

1800 h. All patients received the drug for 25–30 days. Patient 1 took melatonin during two separate trials that were approximately 2 years apart. During the first study, she received crystalline melatonin, 250 mg, in gelatin capsules every 6 h, and during the second she was given melatonin in ethanol. No differences were noted in the two trials.

Results

Growth hormone

Blood for the determination of the baseline levels of growth hormone always was drawn 2 h (at 0800 h) after a dose of melatonin (250 mg) dissolved in 5 ml of ethanol and 100 ml of water (given at 0600 h). Patient 2 received an infusion of arginine (30 g) beginning at 0800 h before and during the time she received melatonin. The increased concentration of growth hormone from the infusion of arginine fell substantially during the time that melatonin was given (Table 2).

In two patients receiving 500 mg L-dopa by mouth, the increment of serum growth hormone above the baseline was less after melatonin in ethanol.

In all 5 patients growth hormone was measured at rest, 15 min after a standard exercise test and 30 min after breakfast. Patients 2, 3, 5 had lower levels of serum growth hormone while on melatonin (Table 2). Growth hormone secretion in response to exercise was not depressed by melatonin in patient 4. The effect of ethanol alone on growth hormone levels was not tested.

LH and FSH

Two patients, 1 and 2, had normal menses before and during the time that they received melatonin. Serum from patient 1 obtained on day 14 of the menstrual cycle. The

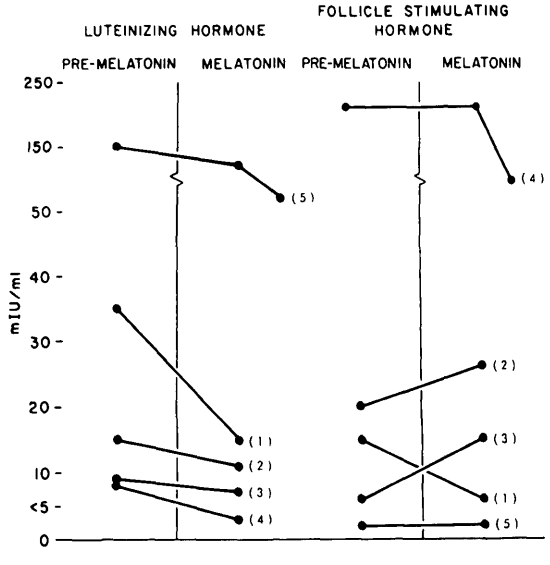

FIG. 1. Serum levels of LH (mIU/ml) and FSH (mIU/ml) before and during ingestion of melatonin. The serum concentration of LH was consistently depressed by melatonin. The concentration of FSH did not follow any pattern. The number in parenthesis refers to the patient (Table 1).

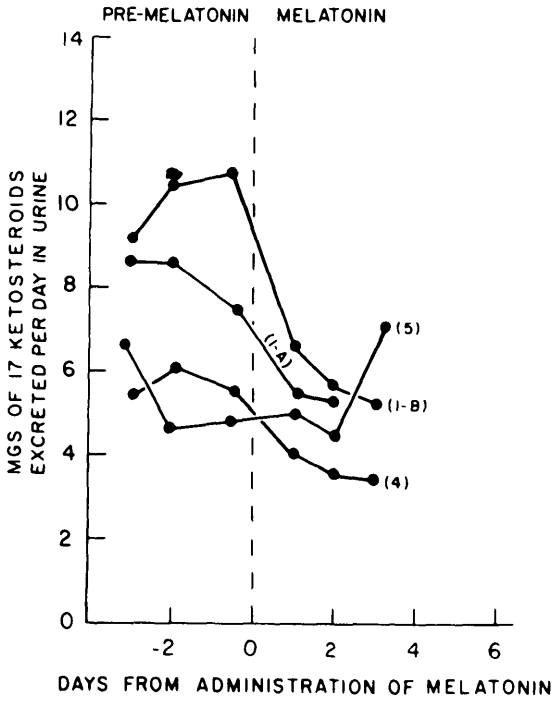

FIG. 2. Twenty-four hour urinary 17-ketosteroids were measured in patients numbers 1, 4, and 5. Patient 1 was treated twice with melatonin, the first (1-A) with melatonin in gelatin capsules, and the second (1-B) with melatonin dissolved in ethanol. The daily excretion of 17-ketosteroids fell during the administration of melatonin for patients 1-A, 1-B and 4 but rose for patient 5.

abrupt drop in LH and FSH (Fig. 1) while she was on melatonin could be attributed to either the suppressive effect of melatonin or to a sampling error because the concentration of gonadotropins in the serum changes rapidly at the time of ovulation. Serum from patient 2 was obtained at day 21 before and while taking melatonin. LH was lower and FSH higher. For patients 3, 4, 5 endogenous menstrual cycles were not involved. In these four patients, serum LH decreased. In patient 4, who was post-menopausal, LH levels fell from 150 mIU/ml to 112 mIU/ml and later to 60 mIU/ml (Fig. 1).

No consistent change was observed in serum levels of FSH. Patients 1 and 2 noted no change in the onset, duration or character of their menses while on melatonin.

Adrenal function

Blood for cortisol determinations was obtained at 0800 and 1600 h in three patients before and 7 days after initiation of melatonin therapy. Plasma cortisols and urinary 17-hydroxycorticosteroids were unaffected. Patients 1 and 4 showed a consistent abrupt drop in the excretion of total 17-ketosteroids following the ingestion of melatonin (Fig. 2). The drop in excretion of 17-ketosteroids occurred on both occasions patient 1 was studied.

Thyroid function

Patients 2 and 4 were on thyroid replacement during the studies and serum thyroxine levels were not evaluated. In the other 3 patients no changes were noted in the serum levels of thyroxine. An I^{131} uptake test performed on patient 1 was normal and did

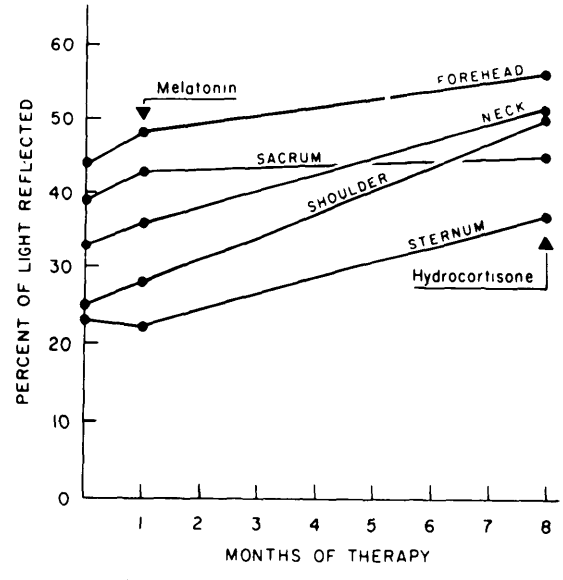

FIG. 3. Reflectometer measurements on skin color of patient 3, a Caucasian, who had hyperpigmented skin due to untreated adrenogenital syndrome. Five areas were observed, the forehead, neck, sacrum, sternum and shoulder. After one month of receiving melatonin indicated by the arrow, the forehead, neck, sacrum and shoulder were clinically and measurably (3–4%) lighter, although the sternum showed little change in color. After 7 months of replacement therapy with 37.5 mg hydrocortisone acetate per day, the patients skin showed further loss of pigment.

not change with the administration of melatonin.

Skin color

Melatonin had no effect on the color of patients 1, 2, 4, and 5. But patient 3 who had untreated adrenogenital syndrome, received melatonin during the summer and became yet lighter as determined clinically and by reflectometer measurements. His exposure to sunlight was not consciously altered. Six months later on replacement therapy with hydrocortisone acetate his skin was even less dark.

Central nervous system

Melatonin given iv induces sleep. On the electroencephalogram it produces slow rhythms and increased alpha and theta wave activity (13,14). All of our patients reported drowsiness during the trial. This symptom was most marked at the onset and became less pronounced as the study progressed. Patient 1 who received melatonin in gelatin capsules and later melatonin dissolved in ethanol noted the same soporofic effect from either mode of administration. Electroencephalogram in patient 2 showed a few bursts of theta activity not noted on baseline recordings. Otherwise, no changes were noted in the function of the central nervous system.

General toxicity

All subjects were watched carefully for signs of toxicity. Slit lamp examinations, direct and indirect fundoscopy, visual acuity, and visual fields showed no evidence of retinal toxicity. Blood pressure and pulse rate were unchanged. Electrocardiograms were not affected. All hematologic tests including white blood cell counts, hemoglobin, hematocrit, platelet count, reticulocyte count, differential white counts were normal throughout the trials. All of the blood chemistry tests including urea nitrogen creatinine, uric acid, calcium, phosphorus, SGOT (serum glutamic oxalacetic transaminase), LDH (lactic dehydrogenase), bilirubin, total proteins and albumin, were normal. Urinalyses were normal.

Discussion

We had three main goals in this study. We wanted to determine the effects of pharmacologic doses of melatonin on skin color, to find out if the secretion of any pituitary hormones was affected by melatonin, and to study the toxicity of this compound.

The amount of melatonin normally found in the urine is measured in pg per day (18). In comparison, the amount of melatonin we gave to our patients, 1 g per day, was enormous. That some of the effects we noted were in response to the pharmacologic dose of drug or the large quantities of metabolites circulating in the blood remains a possibility. These large amounts administered for one month produced no apparent toxicity other than drowsiness in any of the subjects. Others have noted the non-toxicity of melatonin (19,20).

In human beings melatonin is released from the pineal in a diurnal pattern, the major load excreted in the urine from 2300 to 0700 h (12,21). In most studies, melatonin seems to induce sleep (13). All of our patients complained of persistent sleepiness most marked during the first week of receiving melatonin.

We observed no significant changes in the wave pattern on EEG in our patients. Others have noted melatonin produced an increase in alpha waves (13,14). In many of these studies, melatonin, dissolved in alcohol, was given iv. Whether the different results obtained by EEG noted on our study are due to differences in dose, route, or solvent employed, or some other factor is not known.

In rodents melatonin has been shown to depress the thyroid hormone secretion rate (8,22) and the uptake of I^{131} by the thyroid (9). Others found that in rats the pineal gland had no effect on the pituitary thyroid axis (23). In our human subjects melatonin did

not affect serum levels of thyroxine during the time period studied. The responses to melatonin may be species dependent.

Melatonin can suppress the release of luteinizing hormone from the pituitaries of rats and sheep (3–6) by inhibition of the secretion of releasing factors (LRF) from the hypothalamus (3–6) or in neonates by blocking the action of luteinizing hormone releasing factor on the pituitary (6,24). Serum concentrations of melatonin fluctuates during the menstrual cycle of normal women (25). The concentration of melatonin in the blood is highest during the menstrual bleeding when the level of LH is lowest. During ovulation serum levels of melatonin are at their nadir when LH is highest. In only one other study in human beings has the effect of melatonin on luteinizing hormone been examined. Small quantities of melatonin, 10 mg, given im did not depress serum LH in post-menopausal women or normal men (26). Our data are consistent with the many studies on other animal species in which pharmacologic doses of melatonin depressed the concentration of LH in the blood. Rapid metabolism of melatonin may be responsible for the lack of effect of the small doses noted in one study (26).

FSH levels were not affected in humans or in rats. No changes were observed in the menstrual cycle. The persistence of menstrual cycles in our patients after melatonin does not necessarily indicate a lack of effect of the drug. The monthly pattern of release of LH from the pituitary may not be altered by melatonin although the peak levels of LH could be lowered.

Melatonin can also block the release of growth hormone due to many stimuli in humans and other animals (15,16). Our study suggests that melatonin may block the release of GH stimulated by L-dopa, stress, and in one patient, by an infusion of arginine. Our data combined with the previous studies would suggest that melatonin may block both dopaminergic and serotonergic receptors. Alternatively, melatonin may act directly on the end organ, *i.e.*, the GH secretory cells of the pituitary gland by blocking their ability to respond to any stimulus. We favor this latter hypothesis because melatonin administered systemically is preferentially taken up and concentrated in the pituitary (27).

Melanin in the epidermis is formed in the melanocytes and transferred to keratinocytes where it remains until sloughed off at the surface of the skin approximately 28 days later. In four of our five patients there was no change in the color of skin over a period of 28 days. Melatonin may not directly affect the epidermal pigment cells. Patient 3 with untreated adrenogenital syndrome became lighter after melatonin ingestion. Patients with adrenal insufficiency have elevated serum levels of MSH-Pep. The lightening effect of melatonin in this patient could be due to suppression of MSH-Pep or related peptides from the pituitary gland (1).

Melatonin appeared to affect the adrenal gland. In 3 of 4 trials, 17-ketosteroid excretion dropped abruptly by about 40% during the administration of melatonin. In the fourth patient who was on Ovral-28® it increased slightly. Patient 2 and 3 had adrenal disease and could not be evaluated. There were no clear cut effects on 17-hydroxycorticosteroid excretion in the urine of any patient or on diurnal variation of plasma steroids.

The results of our study are preliminary and do not permit definitive conclusions about the physiologic or pharmacologic effects of melatonin in humans. They suggest, however, that melatonin may affect pituitary release of LH, and GH in human subjects. It may lighten the skin color of patients with certain pigmentary disorders. Our finding in human subjects are consistent with most published studies in which rodents were utilized. The single exception is the lack of effect in humans of melatonin on serum thyroxine or I^{131} uptake. Equally important as these suggestive results are the data which indicates that

melatonin may be relatively safe in adult human subjects.

References

1. Rust, C. C., and R. K. Meyer, Hair color, molt, and testis size in male, short-tailed weasels treated with melatonin, *Science* **165**: 921, 1969.
2. Kastin, A. J., S. Viosca, R. M. G. Nair, A. V. Schally, and M. D. Miller, Interactions between pineal, hypothalamus and pituitary involving melatonin, MSH release-inhibiting factor and MSH, *Endocrinology* **91**: 1323, 1972.
3. Fraschini, F., B. Mess, and L. Martini, Pineal gland and the control of luteinizing hormone secretion, *Endocrinology* **82**: 919, 1968.
4. Kamberi, I. A., R. S. Mical, and J. C. Porter, Effect of anterior pituitary perfusion and intraventricular injection of catecholamines and indoleamines on LH release, *Endocrinology* **87**: 1, 1970.
5. Domanski, E., F. Przekop, B. Skubisewski, and W. Wolinska, The effect and site of action of indoleamines on the hypothalamic centers involved in the control of LH release and ovulation in sheep, *Neuroendocrinolog* **17**: 265, 1975.
6. Moguilevsky, J. A., P. Scacchi, R. Deis, and N. O. Siseles, Effect of melatonin on the luteinizing hormone release induced by Clomiphene and luteinizing hormone-releasing hormone, *Proc Soc Exp Biol Med* **151**: 663, 1976.
7. Smythe, G. A., and L. Lazarus, Growth hormone regulation by melatonin and serotonin, *Nature* **224**: 230, 1973.
8. Singh, D. V., and C. W. Turner, Effect of melatonin upon thyroid hormone secretion rate in female hamsters and male rats, *Acta Endocrinol (Kbh)* **69**: 35, 1972.
9. Reiter, R. J., R. A. Hoffman, and R. J. Hester, Inhibition of ^{131}I uptake by thyroid glands of male rats treated with melatonin and pineal extracts, *Am Zool* **5**: 472, 1965.
10. Barchas, J. D., and A. B. Lerner, Localization of melatonin in the nervous system, *J Neurochem* **11**: 489, 1964.
11. Smith, I., P. E. Mullen, R. E. Silman, W. Snedden, and B. W. Wilson, Absolute identification of melatonin in human plasma and cerebrospinal fluid, *Nature* **260**: 718, 1976.
12. Lynch, H. J., R. J. Wurtman, M. A. Moskowitz, M. C. Archer, and M. H. Ho, Daily rhythm in human urinary melatonin, *Science* **187**: 169, 1975.
13. Cramer, H., J. Rudolph, U. Consbruch, and K. Kendel, On the effects of melatonin on sleep and behavior in man, *Adv Biochem Psychopharmacol* **11**: 187, 1974.
14. Anton-Tay, F., Melatonin: Effects on brain function, *Adv Biochem Psychopharmacol* **11**: 315, 1974.
15. Smythe, G. A., and L. Lazarus, Suppression of human growth hormone secretion by melatonin and cyproheptadine, *J Clin Invest* **54**: 116, 1974.
16. Smythe, G. A., and L. Lazarus, Growth hormone responses to melatonin in man, *Science* **184**: 1373, 1974.
17. Lerner, A. B., and J. S. Mcguire, Effect of alpha- and beta-melanocyte stimulating hormones on the skin colour of man, *Nature* **189**: 176, 1961.
18. Rosselin, G., R. Assan, R. S. Yalow, and S. Berson, Separation of antibody-bound and unbound peptide hormones labelled with iodine-by talcum powder and precipitated silica, *Nature* **212**: 355, 1966.
19. Reiter, R. J., *In* Altschule, M. D. (ed.), Frontiers of Pineal Physiology, The MIT Press, Cambridge, Mass., 1975, p. 54.
20. Burns, J. K., Administration of melatonin to nonhuman primates and to women with breast carcinoma. *J Physiol (Lond)* **229**: 38, 1973.
21. Axelrod, J., The pineal gland: A neurochemical transducer, *Science* **184**: 1341, 1974.
22. Singh, D. V., G. D. Narang, and C. W. Turner, Effect of melatonin and its withdrawal on thyroid hormone secretion rate of female rats, *J Endocrinol* **43**: 489, 1969.
23. Rowe, J. W., J. R. Richert, D. C. Klein, and S. Reichlin, Relation of the pineal gland and environmental lighting to thyroid function in the rat, *Neuroendocrinology* **6**: 247, 1970.
24. Martin, J. E., and D. C. Klein, Melatonin inhibition of the neonatal pituitary response to luteinizing hormone-releasing factor, *Science* **191**: 301, 1976.
25. Wetterberg, L., J. Arendt, L. Paunier, P. C. Sizonenko, W. Van Donselaar, and T. Heyden, Human serum melatonin changes during the menstrual cycle, *J Clin Endocrinol Metab* **42**: 185, 1976.
26. Fideleff, H., N. J. Aparicio, A. Guitelman, L. Debeljuk, A. Mancini, and C. Cramer, Effect of melatonin on the basal and stimulated gonadotropin levels in normal men and postmenopausal women, *J Clin Endocrinol Metab* **42**: 1014, 1976.
27. Wurtman, R. J., J. Axelrod, and L. T. Potter, the uptake of H-melatonin in endocrine and nervous tissues and the effects of constant light exposure, *J Pharmacol Exp Ther* **143**: 314, 1964.