Eur J Cancer Clin Oncol, Vol. 23, No. 7, pp. 949–957, 1987.
Printed in Great Britain

0277–5379/87$3.00+0.00

The Clinical Significance of Melatonin Serum Determination in Oncological Patients and its Correlations with GH and PRL Blood Levels

P. LISSONI,* A. BASTONE,* R. SALA,* R. MAURI,* F. ROVELLI,* S. VIVIANI,† E. BAJETTA,† D. ESPOSTI,‡ G. ESPOSTI,§ L. DI BELLA‖ and F. FRASCHINI§

**Ospedale S. Gerardo-Monza, Milano, Italy, †Istituto Nazionale Tumori, Milano, Italy, ‡Istituto Fisiologia Umana II, Università di Milano, Italy, §Cattedra di Chemioterapia, Dipartimento di Farmacologia, Università di Milano, Italy, ‖Cattedra di Fisiologia Umana, Università di Modena, Italy*

Abstract—*In order to investigate the pineal function and its relation with the hypophysis in human neoplasms, melatonin and GH serum levels were determined in 63 patients, 42 affected by solid tumours and 21 by lymphoma or leukaemia.*

In women with breast cancer PRL was also measured. Melatonin, GH and PRL were evaluated in 52 healthy subjects acting as controls.

The oncological patients showed significantly higher mean melatonin serum levels than the control subjects. Mean melatonin values were lower in patients with solid tumours who had metastases, than in cases without metastases.

Chemotherapy caused an evident decrease in melatonin levels. Surgery was followed by a fall in melatonin in patients without metastases. Mean GH serum levels observed in oncological patients were similar to those in control subjects and were not influenced by therapy. PRL levels were within the normal range in women suffering from breast cancer.

INTRODUCTION

IT HAS been known for several years that the pineal gland may exert an antineoplastic activity. Pinealectomy stimulates tumour growth [1], whereas the administration of melatonin, the most investigated pineal hormone, inhibits neoplastic development [2].

It is supposed that the pineal gland may regulate tumour growth through several mechanisms, including a direct antimitotic action [3], an influence on neuroendocrine systems [4], a regulation of polyamine synthesis [5] or pteridine metabolism [6] and a regulation of the immune system [7, 8].

Moreover, it has been shown that there is a diurnal rhythm of sensitivity in the response of some tumours to melatonin antineoplastic action [9].

The pineal gland could be considered as a research model for a possible psychoneuroendocrine control mechanism on tumour growth [10] because of its relationship with other hormones, such as the growth hormone (GH) and prolactin (PRL), which seem to be involved in the regulation of tumour development too. GH levels are inversely proportional to the pineal weight in patients suffering from cancer [11]; moreover, the effects of melatonin on tumour growth seems to depend upon GH blood levels [12]. PRL has been shown to be important in the development of mammary tumours [13].

Since a chronic administration of melatonin reduces PRL secretion [14], it has been suggested that melatonin may inhibit the development of tumours by means of a suppression of PRL release.

In human neoplasias morpholgical, biochemical and physiological changes have been shown in the pineal gland. The pineal glands from patients dying of malignant neoplasms have been found to be larger in both size and weight than those of patients who died from non-malignant diseases [15]. Moreover, they also showed degenerative changes [16]. However, only a few studies have been carried out in order to evaluate melatonin secretion in oncological patients and their results are rather contradictory, since normal [17], low [18, 19] and high [20–23] melatonin levels have been referred to in cancer patients by the various authors.

Accepted 18 December 1986.

Table 1. *Clinical data and hormonal serum levels of oncological patients*

Cases	Sex	Age (years)	Tumour	Clinical stage	Melatonin (pg/ml)	GH (ng/ml)
				Solid tumours		
			Breast cancer			
1	F	34		T3N1bM1	76	4.2
2	F	23		T3N1bMo	158	3.9
3	F	38		T2aN1bMo	135	2.7
4	F	40		T4bN1bMo	113	3.8
5	F	44		T1aN1aMo	161	2.2
6	F	40		T2aN1aMo	139	1.7
7	F	33		T2aN1bMo	142	2.3
8	F	42		T2aN1aMo	118	2.1
9	F	26		T1aNoMo	118	1.8
10	F	44		T1aN1aMo	168	1.7
11	F	34		T1aNoMo	147	3.5
12	F	32		T4N3M1	81	4.9
13	F	37		T3N3Mo	129	2.2
14	F	64		T2aN1aMo	122	2.9
15	F	57		T2aN1bMo	194	1.4
16	F	35		T1aN1aNo	128	4.3
17	F	61		T3N1bMo	146	2.1
18	F	44		T4N3M1	58	4.7
			Lung carcinoma			
19	M	46		T3N2M1	69	4.8
20	M	23		T3N2M1	56	4.3
21	M	44		T3N2M1	60	2.8
22	F	54		T3N2M1	68	3.4
23	M	45		T3N2M1	73	2.3
			Stomach cancer			
24	M	43		T3N3Mo	125	2.0
25	M	52		T4N2M1	68	4.9
26	M	49		T3N2Mo	181	3.1
27	F	51		T3N3M1	76	3.8
28	M	56		T3N2M1	60	4.5
			Colorectal cancer			
29	M	50		T4N4M1	53	4.9
30	M	38		T3N1Mo	184	1.5
31	F	54		T3N1Mo	152	1.6
32	M	71		T4N4M1	63	1.8
33	M	49		T4N4M1	79	1.3
34	F	52		T3N1Mo	143	2.4
35	M	53		T2N1Mo	180	1.1
36	F	56		T2N1Mo	131	1.9
37	M	51		T4N3M1	70	1.4
38	F	49		T3N3Mo	148	1.6
39	F	55		T3N2Mo	140	2.4
			Lyposarcoma			
40	M	39		T2NoMo	169	3.4
41	M	31		T2NoMo	118	4.1
42	F	36		T3NoMo	149	2.6

The evidence of high melatonin blood levels in oncological patients seems to be in accordance with the observations of Kerenyi *et al.* [24], who described an enhanced activity of HIOMT, the enzyme converting *N*-acetylserotonin into melatonin, in the pineals of cancer patients.

It has to be pointed out that in most clinical studies on melatonin in cases of human neoplasias the physiological light/dark rhythm typical of the pineal hormone activity was not taken into account, as determinations of melatonin levels were performed only once during the 24 hr cycle. The investi-

Table 1. *continued*

Cases	Sex	Age (years)	Tumour	Clinical stage	Melatonin (pg/ml)	GH (ng/ml)
				Haemolymphopoietic tumors		
			Hodgkin's disease			
43	M	20		I_A	148	2.3
44	M	28		II_A	165	1.9
45	F	23		II_A	169	0.8
46	F	25		IV_B	51	1.4
47	F	24		IV_B	63	3.4
48	F	24		II_A	177	1.2
49	F	28		II_A	150	1.8
50	F	23		IV_B	56	4.2
51	F	25		II_B	146	2.4
52	F	15		II_A	139	3.2
53	M	44		II_B	148	3.0
54	F	22		III_A	62	3.1
			Non-Hodgkin's lymphoma			
55	M	24		II_{EA}	115	2.4
56	M	57		IV_A	98	3.1
57	F	48		IV_A	88	3.7
58	M	28		II_A	135	3.1
59	M	35		III_A	78	2.4
			Leukaemia			
60	M	35	Acute myelomonoblastic leukaemia		14	3.8
61	M	26	Acute myeloblastic leukaemia		29	2.9
62	F	24	Acute myeloblastic leukaemia		38	3.1
63	M	31	Acute myeloblastic leukaemia		33	2.2

gations carried out to analyse the circadian rhythm of melatonin in malignancies revealed the existence of a decreased melatonin nocturnal rise in women affected by oestrogen receptor positive breast cancer [25] and in cases of Hodgkin's disease [21].

Longitudinal studies performed to investigate changes in circulating levels of melatonin with the progress of neoplastic diseases and to evaluate melatonin variations following the various antineoplastic therapies have never been properly carried out. Therefore, the clinical significance of melatonin blood level measurements in the prognosis of human neoplastic diseases is still unclear and has still to be established. Preliminary observations, however, seem to show that melatonin secretion changes in relation with the tumour mass, since a marked decrease in its levels has been reported after surgery in women with breast cancer [23] and in a group of oncological patients after chemotherapy [21].

In order to evaluate the pineal function and its relation to GH and PRL secretion in neoplastic diseases, and to establish if its activity may be influenced by the various antineoplastic therapies, melatonin, GH and PRL serum levels were measured in a group of oncological patients both in basal conditions as well as after surgery or chemotherapy.

MATERIALS AND METHODS

From January 1985 to April 1985, 63 patients (26 males and 37 females) with histological evidence of neoplastic disease, aged between 15 and 71 years (mean age 39 years), were evaluated. The TNM classification [26] was employed in patients with solid tumours, and the Ann Arbor [27] classification was employed in cases where a diagnosis of lymphoma was made. Breast cancer and Hodgkin's disease were the neoplasms most frequently occurring in our patients. Table 1 shows a histologic classification and the clinical stage of the various neoplasms considered. The patients were observed during hospitalization. They showed a normal sleeping–waking daily rhythm. Lights were turned off from 9.00 p.m. to 7.00 a.m., thus the light/dark cycle was 14/10 hrs. At the time of the study, none of the patients had undergone surgery, radiotherapy or chemotherapy. Fifty-two healthy volunteers of both sexes (22 males and 30 females), aged between 13 and 44 years (mean age 34 years), were included in the study as controls. Patients and controls had not been taking any medication for at least 7 days prior to study. Venous blood samples were collected during the maximum light period (hr 10–12) after overnight fasting. Three venous blood samples were

drawn from each subject or patient at 5-min intervals, and the mean basal hormonal concentrations were obtained by averaging the three concentrations determined. Venous blood samples were collected in plastic tubes. Serum samples were obtained by centrifugation and stored at −20° C until assayed. In each serum sample melatonin and GH were measured; in women affected by breast cancer, PRL levels were also determined.

In 29 surgically treated patients melatonin and GH serum levels were assayed before as well as 5 days after surgical removal of the tumour. Moreover, in 10 patients treated with chemotherapy, melatonin and GH were measured before as well as 21 days after the first chemotherapeutic regimen cycle. In one woman with breast cancer only the hormonal determinations were made both after surgery as well as after chemotherapy. PRL and GH serum levels were measured with the double antibody RIA method using commercially available kits (Sclavo-Milano, Italy). Melatonin serum levels were determined according to the RIA method described by Wetterberg *et al.* [28], using commercial kits (WHB-Stockholm, Sweden). Melatonin was extracted with methylene chloride, and melatonin was determined in the extract using tritium-labelled melatonin as a tracer and rabbit melatonin antiserum. The antigen–antibody complex was precipitated with saturated ammonium sulphate. The precipitate was dissolved and the tritium content was determined in a liquid scintillation system. The intraassay and interassay coefficients of variation were 9% and 12%, respectively.

The data were analysed by Student's t test and the results are reported as mean values ± SD.

RESULTS

The individual melatonin and GH serum levels observed in oncological patients are listed in Table 1.

The untreated cancer patients showed significantly higher mean melatonin serum levels than healthy subjects ($P < 0.001$). Melatonin serum levels were within the normal range in 3 patients only. No differences in mean melatonin serum levels were seen between patients with solid tumours and those with haemolymphopoietic neoplasias. Among the patients affected by solid tumours, those with distant organ metastases had significantly lower mean melatonin serum levels than the subjects who showed no distant metastases ($P < 0.01$). On the contrary, in cases without distant organ metastases no significant differences could be seen between patients with and without regional lymph node involvement. Patients suffering from leukaemia had lower melatonin levels in comparison with those affected by lymphoma ($P < 0.001$). Mean melatonin serum levels between patients with Hodgkin's disease and those affected by non-Hodgkin's lymphoma did not differ. Among the cases with Hodgkin's disease, patients at clinical stage I–II showed statistically higher mean melatonin levels than patients at stage III–IV ($P < 0.01$), while no significant differences were noticed between patients who presented systemic symptoms and those who did not.

GH serum values were within the normal range in all patients, and mean GH serum levels observed in oncological patients were not statistically different in comparison with those seen in control subjects. There was no significant correlation between GH and melatonin serum concentrations. Mean GH serum levels showed no differences between patients suffering from solid tumours and those affected by haemolymphopoietic neoplasias. Mean GH serum levels were higher in patients with metastases than in cases not showing metastases, without, however, statistically significant differences. Mean melatonin and GH serum levels observed in normal subjects and in oncological patients are reported in Table 2. Table 3 shows mean melatonin and GH serum concentrations observed in 29 surgical patients affected by solid tumours both before and after surgery. In patients who had no metastases, mean melatonin serum levels were significantly higher before than after surgery ($P < 0.1$). Surgery was followed by a melatonin fall higher than 50% in 16 of the 23 surgical patients who did not show metastases (69%). On the contrary, in patients with metastases there were no significant differences in mean melatonin serum levels before and after surgery, and in no patients could a decrease in melatonin levels higher than 50% be observed.

Table 4 shows the effects of chemotherapy on melatonin serum levels. Regardless of the type of regimen, chemotherapy caused a melatonin fall higher than 50% in 7 out of 10 patients (70%), and the mean melatonin serum levels observed after chemotherapy were significantly lower ($P < 0.1$) than those recorded before therapy. In one woman with breast cancer (case No. 2), who underwent surgery as well as chemotherapy, melatonin decreased after both therapies.

In contrast to the effects of antineoplastic therapies on melatonin secretion, neither surgery nor chemotherapy significantly influenced GH secretion, and mean GH serum concentrations after both therapies were comparable with those recorded before.

As far as the evaluation of PRL secretion in women suffering from breast cancer is concerned, it was considered as normal in all patients, and no differences in mean PRL serum levels could be determined between controls and patients with mammary carcinomas (see Table 5). In patients in

Table 2. Melatonin and GH serum levels (mean ± SD) in healthy subjects and in oncological patients

Cases	Melatonin (pg/ml)	GH (ng/ml)	PRL (ng/ml)
Healthy subjects (n = 52)	18 ± 7 (range 6–30)	2.1 ± 0.8 (range 0.7–5.1)	7.2 ± 1.4 (range 5.6–16.3)
Oncological patients (n = 63)	111 ± 46	2.8 ± 1.1	
Solid tumours (n = 42)	118 ± 42	2.9 ± 1.2	
Patients without distant metastases (n = 27)	146 ± 22	2.4 ± 0.9	
Patients with distant metastases (n = 15)	67 ± 9	3.6 ± 1.3	
Haemopoietic tumours (n = 21)	101 ± 53	2.6 ± 0.9	
Lymphomas (n = 17)	117 ± 43	2.5 ± 0.9	
Hodgkin's disease (n = 12)	123 ± 49	2.5 ± 0.9	
Stage I–II (n = 8)	155 ± 13	2.1 ± 0.8	
Stage III–IV (n = 4)	58 ± 5	3.0 ± 1.2	
Patients with systemic symptoms (n = 5)	93 ± 50	2.9 ± 1.0	
Patients without systemic symptoms (n = 7)	144 ± 39	2.0 ± 0.9	
Non-Hodgkin's lymphoma (n = 5)	103 ± 23	2.9 ± 0.6	
Leukaemias (n = 4)	29 ± 10	2.9 ± 0.5	

whom surgery was followed by a melatonin decrease higher than 50%, mean PRL serum levels were significantly higher after surgery than those observed before surgical treatment ($P < 0.01$) (see Table 6), and an increase of PRL higher than 50% was seen in 7 of the 10 patients considered. On the contrary, chemotherapy did not seem to influence PRL secretion (see Table 7).

DISCUSSION

This study shows that melatonin blood levels are altered in oncological patients, and that they change in relation to tumour growth. According to the data previously referred by Raikhlin *et al.* [20] and by ourselves [21], this study shows that patients suffering from cancer, regardless of the type of tumour and its localization, present higher mean melatonin serum levels during the day compared to those observed in normal subjects. This pineal response could actually be a phenomenon secondary to an altered endocrine–metabolic balance caused by an increased demand of the developing tumour. As an alternative the enhanced melatonin secretion might be considered as a compensatory mechanism because of its antimitotic action and interpreted as an effort to secrete substances capable of regulating neoplastic growth. The biological activity of melatonin, however, depends not only on its circulating levels, but also on the sensitivity of its specific receptors. High melatonin blood levels during the day could determine a hyposensitivity of melatonin receptors through a down regulation mechanism [29]. Therefore, despite its enhanced secretion, melatonin might lack biological activity in oncological patients. It would be very interesting to establish whether the anomalous melatonin secretion precedes or if it is due to tumour development. In fact, if there is no doubt that melatonin regulates cancer growth, some experimental observations seem to demonstrate that, on the other hand, the tumour may also affect pineal function. This conclusion is supported by the fact that a carcinogenetic process is generally associated with changes in the activity of the hypothalamus and of the pineal gland [10, 30]. Finally, it has been observed that melatonin levels in rat pineal gland decrease accordingly with progressive tumour growth [31]. The possible effects of tumour development on melatonin secretion could be due to metabolic changes induced by the presence of the neoplasia or, alternatively, they might depend on a direct action at pineal site by means of various factors capable of influencing melatonin biosynthesis and release. In fact, an abnormal α_1-acid glycoprotein, which can bind pterins thus affecting their metabolism, has been found in oncological patients' blood [32]. Since pterins are involved in the regulation of melatonin synthesis and release [33], an alteration of its metabolism could determine an anomalous secretion of the pineal hormone.

On the basis of the evidence that patients with solid tumours without metastases showed higher mean melatonin serum levels than those observed in patients with metastases, it seems that melatonin secretion decreases progressively with tumour development. The same conclusion could be drawn about Hodgkin's disease, where patients at clinical stage I–II had higher mean melatonin levels than those at stage III–IV.

These clinical results are in agreement with the data found in animal studies, which revealed the

Table 3. Melatonin and GH serum levels before and after surgery in a group of 29 patients affected by solid tumour

	Melatonin (pg/ml)			GH (ng/ml)	
	Before	After	% variation	Before	After
Patients without metastases (n = 23)					
2	158	78	−50.1	3.9	2.9
3	135	51	−62.1	2.7	2.4
5	161	76	−52.9	2.2	2.3
6	139	31	−76.5	1.7	1.5
7	142	29	−79.8	2.3	1.8
8	118	41	−65.1	2.1	2.9
9	118	90	−23.5	1.8	2.2
10	168	139	−17.4	1.7	2.1
11	147	62	−57.6	3.5	3.8
14	122	43	−64.8	2.9	2.0
15	194	87	−55.1	1.4	1.6
16	128	62	−51.5	4.3	2.1
17	146	154	+5.4	2.1	2.2
24	125	57	−54.2	2.0	1.4
26	181	62	−65.7	3.1	2.7
30	184	64	−65.0	1.5	1.8
31	152	154	+1.2	1.6	1.5
34	143	95	−33.5	2.4	2.2
35	180	57	−67.9	1.1	0.7
36	131	69	−47.8	1.9	2.5
38	148	53	−64.1	1.6	2.2
39	140	59	−58.0	2.4	2.1
40	169	135	−20.2	3.4	3.0
$\bar{X}$	149	76		2.3	2.2
±SD	22	37		0.8	0.6
Patients with metastases (n = 6)					
18	57	67	+16.3	4.7	3.2
25	68	90	+31.8	4.9	4.3
29	53	48	−9.2	4.9	4.3
32	63	60	−5.2	1.8	1.6
33	79	82	+3.0	1.3	0.9
37	69	63	−10.0	1.4	1.5
$\bar{X}$	65	68		3.2	2.6
±SD	9	15		1.8	1.5
All patients (n = 29)					
$\bar{X}$	131	70		2.5	2.3
±SD		33		1.2	0.9

existence of an inverse relationship between tumour growth and pineal melatonin content [31]. Moreover, they also seem to be in agreement with the low melatonin levels observed by Pico *et al.* [18] in patients suffering from disseminated carcinomas.

As far as the relationship between surgery or chemotherapy and the pineal function is concerned, the results of this study demonstrate that antineoplastic therapies are generally followed by a melatonin decrease which tend to return within the normal range. The change in melatonin concentrations induced by antineoplastic therapies is difficult to be explained. It has been demonstrated that the abnormal α_1-acid glycoprotein observed in the blood of oncological patients becomes undetectable after effective antineoplastic therapy [32] with a normalization of pterin metabolism. This finding could at least in part explain why melatonin secretion tends to return within the normal range after effective antineoplastic therapy. Other studies, however, will be needed to clarify a possible relation between melatonin secretion and the altered metabolism of pterins in human neoplasias.

At present, it is not yet possible to evaluate the clinical significance of melatonin decrease after surgery of chemotherapy in oncological patients, and to establish if it should be regarded as an undesirable effect or simply as a marker for the effectiveness of the treatment. On the basis of the fact that melatonin is able to exert an oncostatic

Table 4. Melatonin and GH serum levels before and after chemotherapy in a group of 10 oncological patients

Cases	Chemotherapy*	Melatonin (pg/ml) Before	After	% variation	GH (ng/ml) Before	After
1	CNF	76	84	+9.7	4.2	4.8
2	CMF	78	26	−67.3	2.9	3.6
4	IMI-58	113	27	−70.0	3.8	4.6
12	IMI-58	81	62	−23.0	4.9	4.6
13	IMI-58	129	28	−78.4	2.2	2.5
19	CAV	69	21	−69.3	4.8	3.2
20	CAV	56	50	−10.0	4.3	4.7
45	ABVD	169	44	−73.8	0.8	1.2
55	CHOP	115	35	−69.7	2.4	2.9
58	CHOP	135	42	−69.2	3.1	3.0
$\bar{X}$		102	42		3.3	3.5
±SD		36	19		1.3	1.2

*CMF: cyclophosphamide, methotrexate, fluorouracil; IMI-58: deoxydoxorubicin; CAV: cyclophosphamide, adriamycin, vincristine; ABVD: adriamycin, bleomycin, vinblastine, dacarbazine; CHOP: cyclophosphamide, adriamycin, vincristine, prednisone.

Table 5. Individual and mean serum levels of melatonin and PRL in 18 women affected by breast cancer before and after therapy

Cases	Therapy	Before therapy Melatonin (pg/ml)	PRL (ng/ml)	After therapy Melatonin (pg/ml)	PRL (ng/ml)
1	Chemotherapy	76	7.2	84	7.9
2	Surgery	158	5.4	78	9.2
3	Surgery	135	6.6	51	7.4
4	Chemotherapy	113	7.8	27	8.2
5	Surgery	161	7.2	76	9.1
6	Surgery	139	5.3	32	14.8
7	Surgery	142	5.2	29	12.4
8	Surgery	118	7.2	41	11.9
9	Surgery	118	7.2	90	6.8
10	Surgery	168	8.4	139	9.2
11	Surgery	147	8.2	62	7.5
12	Chemotherapy	81	7.5	62	7.1
13	Chemotherapy	129	6.2	28	8.4
14	Surgery	122	5.2	43	11.3
15	Surgery	191	5.6	87	15.7
16	Surgery	128	6.1	62	11.2
17	Surgery	146	7.4	154	7.9
18	Surgery	58	8.2	67	7.6
$\bar{X}$		130	6.7	67	9.6
±SD		34	1.0	36	2.7

activity, its decrease after antineoplastic therapies could represent an undesirable response. Nevertheless, since high melatonin levels can induce a persistent down regulation of its receptors, a normalization of melatonin blood concentrations could recover the sensitivity and responsiveness of biological systems to melatonin. Therefore, melatonin decrease after antineoplastic therapy might be followed by a reappearance of its biological activity. On the other hand if further studies indicate that a fall in melatonin with antineoplastic therapy should be rather considered as a side effect, melatonin treatment could be associated with surgical removal of the tumour or with chemotherapy.

As far as GH secretion in oncological patients is concerned, our results do not allow us to confirm the observations of Starr [12], who described low GH serum levels in patients suffering from certain

Table 6. PRL levels before and after therapy in 10 women with breast cancer, in whom surgery caused a melatonin fall higher than 50%

Cases	Melatonin (pg/ml) Before	After	% decrease	PRL (ng/ml) Before	After	% increase
2	158	78	50.1	5.4	9.2	70.4
3	135	51	62.1	6.6	7.4	12.1
5	161	75	52.9	7.2	9.1	26.4
6	139	32	90.1	5.3	14.8	179.2
7	142	29	79.8	5.2	12.4	138.5
8	118	41	88.3	7.2	11.9	65.3
11	147	62	57.6	7.2	7.5	4.2
14	122	43	64.8	5.2	11.3	117.3
15	194	87	55.1	5.6	15.7	180.3
16	128	62	51.5	6.1	11.2	83.6
$\bar{X}$	144	56	65.2	6.1	11.1	87.7
±SD	22	20	15.3	0.9	2.8	64.7

Table 7. PRL and melatonin serum levels (mean ± SD) in women with breast cancer before and after surgery or chemotherapy

	Melatonin (pg/ml) Before	After	PRL (ng/ml) Before	After
Surgery ($n = 14$)	138 ± 31	62 ± 32	6.6 ± 1.1	10.1 ± 2.9
Chemotherapy ($n = 5$)	95 ± 24	45 ± 26	7.6 ± 1.1	8.2 ± 0.9

tumours, particularly breast carcinoma and melanoma, and high GH levels in patients with sarcoma.

Therefore, our study seems to exclude the idea that the effects of melatonin on cancer growth may be mediated by a modulation of GH release, since there was no significant correlation between GH and melatonin levels; moreover, our study reveals that GH blood levels are not affected by antineoplastic therapy. PRL secretion on the contrary seems to be involved in breast cancer and changes after tumour removal in an opposite way if compared with melatonin levels.

In conclusion, this study shows that melatonin secretion is abnormally high in patients affected by cancer, and that it changes with antineoplastic therapies. Longitudinal studies, however, will be needed to clarify the role of melatonin in influencing the prognosis of neoplastic diseases. Moreover, other investigations are required to establish if the pineal hormone could be a marker of early stages of solid tumours, particularly because of the relief of high melatonin levels in several clinical disorders different from neoplastic diseases.

REFERENCES

1. Rodin AE. The growth and spread of Walker 256 carcinoma in pinealectomised rats. *Cancer Res* 1963, **23**, 1545–1548.
2. El-Domeiri AAH, Das Gupta TK. Reversal by melatonin of the effect of pinealectomy on tumour growth. *Cancer Res* 1973, **3**, 2830–283.
3. Banerjee S, Margulis L. Mitotic arrest by melatonin. *Exp Cell Res* 1973, **78**, 314–318.
4. Lapin V. Pineal gland and malignancy. *Oster Z Onkol* 1976, **3**, 51–60.
5. Fraschini F, Ferioli ME, Nebuloni R, Scalabrino G. Pineal gland and polyamines. *J Neural Trans* 1980, **48**, 209–221.
6. Ebels I. A survey of the location, isolation and identification on indoles, pteridines and some unknown active substances in sheep pineals. The possible significance of pteridines for the neuroendocrine control of neoplastic growth. *J Neural Trans* 1980, **49**, 87–105.
7. Jankovic BD, Isakovic K, Petrovic S. Effect of pinealectomy on immune reactions in the rat. *Immunology* 1970, **18**, 1–6.
8. Lissoni P, Marelli O, Mauri R *et al.* Chronomodulatory sequence of stimulation and inhibition of human NK cell activity by melatonin given in the afternoon to nocturnally

resting subjects. *Proceedings 2nd Int Cong. Medico-Social Aspects of Chronobiology*, Florence, 2 October 1984.
9. Bartsch H, Bartsch C. Effect of melatonin on experimental tumours under different photoperiods and times of administration. *J Neural Trans* 1981, **52**, 269–279.
10. Lapin V, Ebels I. The role of the pineal gland in neuroendocrine control mechanisms of neoplastic growth. *J Neural Trans* 1981, **50**, 275–282.
11. Tapp E. The human pineal gland in malignancy. *J Neural Trans* 1980, **48**, 119–130.
12. Starr KW. Growth and new growth, environmental carcinogens in the process of human ontogeny. *Prog Clin Cancer* 1970, **4**, 1–29.
13. Welsch CW, Nagasawa H. Prolactin and murine mammary tumorigenesis: a review. *Cancer Res* 1977, **37**, 951–963.
14. Leadem CA, Blask DE. Evidence for an inhibitory influence of the pineal on prolactin in the female rat. *Neuroendocrinology* 1981, **3**, 268–275.
15. Rodin AE, Overall J. Statistical relationship of weight of the human pineal to age and malignancy. *Cancer* 1967, **20**, 1203–1214.
16. Hajdu SI, Porro RS, Lieberman PH, Foote FW Jr. Degeneration of the pineal gland of patients with cancer. *Cancer* 1972, **29**, 706–709.
17. Tapp E, Skinner RG, Phillips V. Radioimmunoassay for melatonin. *J Neural Trans* 1980, **48**, 137–141.
18. Pico JL, Mathe G, Young IM, Leone RM, Hooper J, Silman RE. Role of hormones in the etiology of human cancer. Pineal indole hormones and cancer. *Cancer Treat Rep* 1979, **63**, 1204.
19. Bartsch C, Bartsch H, Jain AK, Laumas KR, Wetterberg L. Urinary melatonin levels in human breast cancer patients. *J Neural Trans* 1981, **52**, 281–294.
20. Raikhlin NT, Kvetnoy IM, Tyurin ES. Melatonin in the blood serum of oncological patients. *Klin Med (Moscow)* 1980, **58**, 77–79.
21. Lissoni P, Viviani S, Bajetta E *et al.* A clinical study of pineal gland activity in oncological patients. *Cancer* 1986, **57**, 145–150.
22. Schloot W, Dubbels R, Birau N. Genetics of melatonin. In: Birau N and Schloot W, eds. *Melatonin. Current Status and Perspectives*. New York, Pergamon Press, 1981, 269–284.
23. Mori W. Melatonin in non-endocrinological pathology. In: Birau N and Schloot W, eds. *International Symposium on Melatonin*. Bremen, 28–30 September, 1980.
24. Kerenyi Na, Sotonyi P, Vacek K. HIOMT activity in the pineal in different disease groups. *Am J Clin Pathol* 1977, **68**, 105–106.
25. Tamarkin L, Danforth D, Lichter A *et al.* Decreased nocturnal plasma melatonin peak in patients with estrogen receptor positive breast cancer. *Science* 1982, **216**, 1003–1005.
26. Unione Internazionale contre le Cancer (UICC). *TNM, Classification of Malignant Tumours*. Geneva, Harmer 1978.
27. Kaplam HS. *Hodgkin's Disease*. Cambridge, Harvard University Press, 1980.
28. Wetterberg L, Eriksson O, Friberg Y, Vangbo B. A simplified radioimmunoassay for melatonin and its application to biological fluids. Preliminary observations on the half-life of plasma melatonin in man. *Clin Chim Acta* 1978, **86**, 169–177.
29. Tamarkin L, Westrom WK, Hamill AI, Goldman BD. Effects of melatonin on the reproductive systems of male and female Syrian hamsters. A diurnal rhythm in sensitivity to melatonin. *Endocrinology* 1976, **99**, 1534–1541.
30. Tapp E. Pineal gland in rats suffering from malignancy. *J Neural Trans* 1980, **48**, 131–135.
31. Lapin V, Frowein A. Effects of growing tumours on pineal melatonin levels in male rats. *J Neural Trans* 1981, **52**, 123–136.
32. Fink M, Ziegler I, Maier K, Wilmanns W. Blood levels of a pteridine-binding α_1-acid glycoprotein in cancer patients. *Cancer Res* 1981, **42**, 1574–1578.
33. Ebels I, Baleman MGM, Van Benthem J, Noteborn HPOM, De Morée A. Pteridines in the pineal and effects of these substances on the indole metabolism of this organ. In: Axelrod J, Fraschini F, Velo GP, eds. *The Pineal Gland and its Endocrine Role*. New York, Plenum Press 1983, 220–236.