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5 YEARS' EXPERIENCE OF 5-S-CYSTEINYLDOPA IN MELANOMA DIAGNOSIS

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Abstract. Determinations of the urinary excretion of 5-S-cysteinyldopa were performed in 571 patients previously treated by surgery for melanoma or melanoma metastasis. 90% of the 161 patients with metastases showed values exceeding 0.15 mg/24 h, and 9% of the 410 patients without metastases had such values. The increase in 5-S-cysteinyldopa excretion was generally more pronounced in men with metastases than in women, 98% of the men and 77% of the women with metastases showing values exceeding 0.15 mg/24 h. High levels of 5-S-cysteinyldopa are of grave prognostic significance; of patients with metastases and 5-S-cysteinyldopa excretion exceeding 5 mg/24 h 44% died within one month, and only 3% survived for more than a year. In Sweden, determination of 5-S-cysteinyldopa in patients operated on for melanoma gives maximum information in the winter (October–March), when sun exposure does not influence the excretion levels.

Key words: Melanoma; Cysteinyldopa; Amino acids; Catechol

During the past few years considerable progress has been achieved in the biochemistry of melanin. The definition of phaeomelanin formation (21) has led to the detection of several new substances excreted from the melanocytes, namely, 5-S-, 2-S-, 6-S-cysteinyldopa, 2,5-S,S-dicysteinyldopa, and four different *O*-methylated cysteinyldopas (4, 6, 7, 22).

All these compounds are catechol derivatives or their metabolites. They were first detected in the urine of patients with melanoma metastases, but with the development of more sensitive methods several have been demonstrated in the urine of healthy individuals, and also in serum where the concentrations are lower than in the urine (3, 18).

Cysteinyldopas were first described as precursors in the formation of phaeomelanins. Our studies have demonstrated that these substances are products formed and excreted by all active melanocytes, and our recent findings indicate that cysteinyldopas are building-stones of eumelanins. Among the new substances defined as melanocyte metabolites 5-S-cysteinyldopa has attracted most attention, as it is quantitatively the most important and most specific excretion product of the melanin-forming cells so far known. Several methods have been developed for its detection. Ion-exchange chromatography, amino acid analysis, fluorimetry, gas chromatography–mass spectrometry, and high-performance liquid chromatography in combination with electrochemical detection have been used at our laboratories, and ion-exchange chromatography in combination with colorimetry of reaction products at others (11, 12, 13).

A fluorimetric method for quantitation of 5-S-cysteinyldopa has been extensively used for studies on normal and pathological pigment metabolism (24). Several reports have appeared on the increased 5-S-cysteinyldopa urinary excretion in malignant melanoma (1, 2, 10, 14, 15). In some cases 5-S-cysteinyldopa excretion may reach pathological levels before the appearance of clinical or laboratory signs of metastasizing disease (2, 19).

The fact that exposure to sunlight leads to increased excretion of 5-S-cysteinyldopa in the urine (20, 23) illustrates the sensitivity of 5-S-cysteinyldopa determination in defining the functional state of melanocytes, but limits to some extent the usefulness of 5-S-cysteinyldopa determination as a predictor of metastasis (20, 23).

There is an increasing demand for tests capable of predicting metastasizing melanoma and thus guide therapy, and in spite of its limitations the determination of urinary 5-S-cysteinyldopa excretion seems to be the most helpful method available. We have been using this test for 5 years in patients operated on for primary melanoma or melanoma metastases, and this report summarizes our experience.

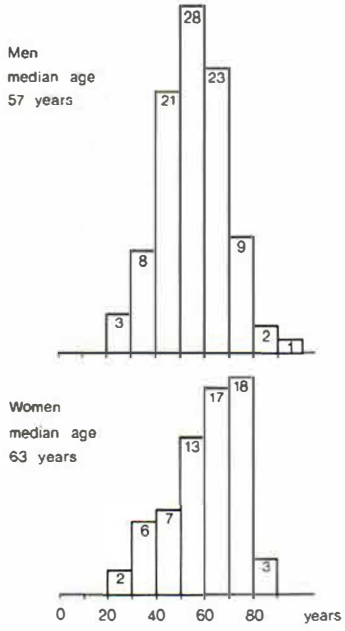

Fig. 1. Age of the patients with melanoma metastases.

MATERIAL AND METHODS

The investigation was started in October 1973 and the 571 patients, 243 men and 328 women, were followed until October 1978. They had previously been operated on for melanoma of the skin, eye, or mucosa or for a melanoma metastasis from an undiagnosed primary tumour. 95 men and 66 women exhibited metastases during the observation period—39% of the men and 20% of the women (Table I). The age distribution of the patients with metastases is given in Fig. 1.

Most of the patients were examined at the departments of oncology or surgery at the hospitals in Lund and Malmö, but others from many centres all over Sweden are included in this report. In Lund and Malmö, patients are seen at intervals of 3–4 months during the first 2 years after surgery, and subsequently twice yearly for a further 5–10 years. At every visit the entire skin surface and all superficial lymph nodes are examined. A liver scintigram is performed within a year of operation, and the lungs are X-rayed each year. Estimation of urinary 5-S-cysteinyldopa was performed from the beginning of September to the end of April every year. During the months May–August, urine sampling was only performed for special investigative purposes, and no such determinations are included in this report.

Table I. *571 patients operated on for melanoma and investigated with regard to 5-S-cysteinyldopa excretion*

	No metastases	Metastases
Men	148	95 (39%)
Women	262	66 (20%)

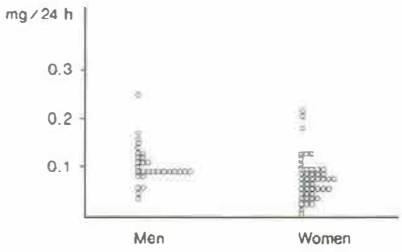

Fig. 2. Excretion of 5-S-cysteinyldopa in the urine of healthy subjects. 30 men and 46 women.

24-hour specimens of urine were collected in plastic bottles containing 50 ml acetic acid and 1 g sodium metabisulphite. A fluorimetric method was used for determination of 5-S-cysteinyldopa (24). In many patients more than one determination was performed. In these patients the highest value obtained is reported, except in Tables VI, VII and VIII. In Table VI the 5-S-cysteinyldopa values obtained at the time when the metastases were first detected are given. Table VII shows the first elevated values giving rise to investigations leading to the detection of metastases. Table VIII contains the first pathological 5-S-cysteinyldopa values which confirmed the diagnosis of melanoma metastasis.

RESULTS AND DISCUSSION

In the evaluation of 5-S-cysteinyldopa values obtained from the urine of melanoma patients we have been guided by our accumulated experience of 5-S-cysteinyldopa excretion under normal and pathological conditions. In a normal series (3) of Swedish men and women a mean value of 0.10 mg/24 h in men and 0.08 mg/24 h in women was noted (Fig. 2). The values did not show a Gaussian distribution.

From studies on negroes it is evident that genetically dark-skinned subjects may show a greater

Table II. *Distribution of 5-S-cysteinyldopa excretion values in patients with and without metastases*

5-S-cysteinyldopa (mg/24 h)	Metastasis: Yes M	Yes F	No M	No F
Pathological >0.4	63	32	3	3
Borderline 0.15–0.4	30	19	15	6
Normal <0.15	2	15	130	253

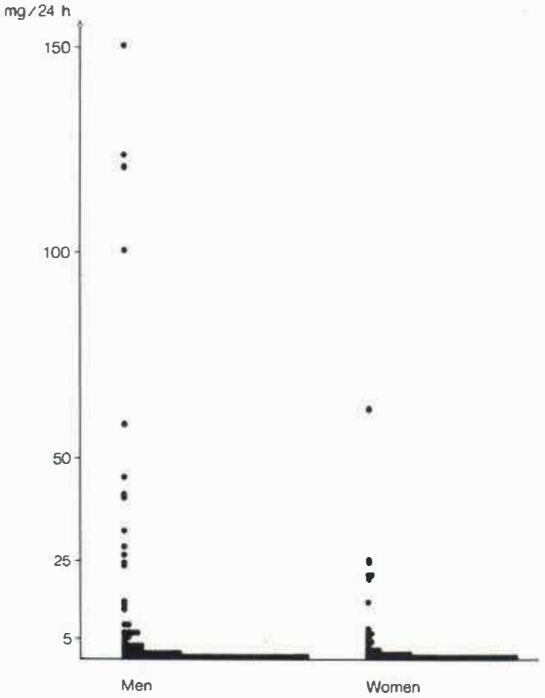

Fig. 3. 5-S-cysteinyldopa in the urine of 161 patients with melanoma metastases. 95 men and 66 women.

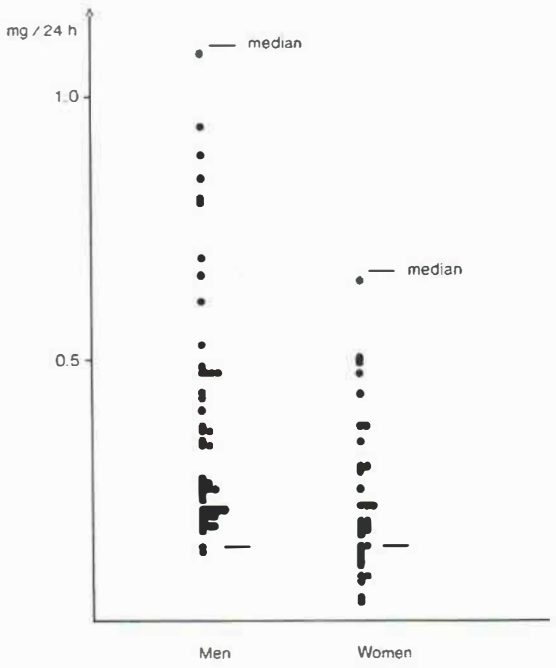

Fig. 4. 5-S-cysteinyldopa in the urine of the 47 men and 33 women with melanoma metastases having cysteinyldopa excretion below the median values. The medians and the arbitrarily chosen normal level at 0.15 are indicated.

normal variation of 5-S-cysteinyldopa excretion than Swedes (5). Furthermore, a low excretion rate of 5-S-cysteinyldopa has been recorded in negroes (unpublished observation). Other studies have shown that exposure to UV-light can increase the 5-S-cysteinyl-dopa excretion (8, 20, 23).

For practical purposes we regard figures for 5-S-cysteinyldopa excretion below 0.15 mg/24 h as normal, between 0.15 and 0.40 mg/24 h as borderline, and above 0.40 mg/24 h as pathological, provided the patients have not been exposed to sunlight for several weeks prior to the examination.

The distribution of 5-S-cysteinyldopa values in the different groups is evident from Table II. It is seen that most of the patients with metastases had values over 0.40 mg/24 h, but that many showed borderline values between 0.15 and 0.40 mg/24 h. There were 15 women with metastases and normal values below 0.15 mg/24 h, but only 2 men. The number of false-negatives was thus small in men but greater in women. There were 6 false-positives (3 men and 3 women), and 21 patients (15 men, 6 women) in whom no metastases were found belonged to the borderline group.

In patients with clinically evident metastases, therefore, 60% had pathological 5-S-cysteinyldopa excretion, 30% had borderline values, and 10% normal excretion. In the patients with no apparent metastases 91% had normal excretion. 7% had borderline values, and less than 2% pathological excretion.

Fig. 3 shows the distribution of urinary 5-S-cysteinyldopa values in the patients showing metastasis. Note that on the lowest line most of the values are >0.40 mg/24 h. It is clear that the excretion reaches higher values in men with metastasis than in women. This is also a striking finding in Fig. 4, which shows the values below the median. The difference between men and women is even more remarkable when the mean values for excretion are compared (Table III).

Since 5-S-cysteinyldopa is the most important compound in the formation of phaeomelanin it might be suspected that the highest values are to be found among patients with red hair. Table IV shows, however, that only 3 of the patients with the highest values had red hair. This tallies with the number of red-haired patients (33%) in the group

Table III. *Median and mean values of 5-S-cysteinyldopa excretion in 95 men and 66 women with melanoma metastasis*

	5-S-cysteinyldopa (mg/24 h)	
	Median	Mean
Men	1.16	10.3
Women	0.66	3.9

with melanoma metastasis (Table V), in whom the hair colours were known.

19 patients had metastases but showed normal excretion, and are of course of great interest, since this group illustrates the limitations of the method. Table VI shows the sites of the metastases in these patients. Two of the 19 patients subsequently developed borderline values when the metastases progressed.

The normal excretion of 5-S-cysteinyldopa observed in the presence of metastases in 19 patients did not have any single explanation. Some metastases were amelanotic or weakly pigmented, some were solitary and/or small, but normal values were observed in some cases with pigmented numerous metastases. Normal 5-S-cysteinyldopa excretion was found in some patients with metastases to many different organs. The findings reported in Table VI demonstrate that normal 5-S-cysteinyldopa excretion cannot preclude metastatic melanoma disease.

When assessing the sensitivity of a method for diagnosis of melanoma, a classification according to stage is often used. It has already been shown that melanoma stage I, i.e. melanoma without signs of metastasis, cannot be diagnosed by increased excretion of 5-S-cysteinyldopa (1). In this series many patients with signs of regional metastasis and raised excretion of 5-S-cysteinyldopa have shown a return to normal levels after removal of the metastasis, yet excretion levels often remain high. In such cases the clinical impression of melanoma stage II has proved false.

In 23 patients, 12 men and 11 women, operated on for primary melanoma or lymph node metastasis, the 5-S-cysteinyldopa excretion was found to be raised although there were no symptoms or signs of metastasis. Owing to the elevated 5-S-cysteinyldopa values, however, further investigations were performed and metastases were found within 1/2 to 14 months (Table VII). In 12 of

Table IV. *Ranking of 10 patients with melanoma metastasis and the highest values of 5-S-cysteinyldopa in the urine*

Age (y.)	Sex	Red hair	5-S-cysteinyldopa (mg/24 h)
45	M	–	150
41	M	+	124
26	M	–	121
54	M	–	100
60	F	–	62
47	M	+	58
51	M	–	45
42	M	+	42
33	M	–	40
44	M	–	32

Table V. *Number of redheads among 99 patients with melanoma metastasis*

Red hair	Men	Women	Total
+	21	12	33
–	39	27	66

Table VI. *Site of metastasis in 19 patients with melanoma and normal urinary 5-S-cysteinyldopa values*

Age	Sex	Site of metastasis	5-S-cysteinyldopa (mg/24 h)
42	F	Widespread amelanotic	0.04
47	F	Brain, amelanotic	0.04
58	F	Regional lymph node	0.05
64	M	Lymph nodes faintly pigmented	0.05
69	F	Skin, amelanotic	0.06
84	F	Skin, amelanotic	0.07
78	F	Lymph nodes faintly pigmented	0.07
72	F	Lymph nodes, lungs pigmented	0.08
63	F	Lungs	0.09
66	F	Skin, site of primary melanoma	0.09
32	M	Brain	0.09
34	F	Brain	0.10
36	F	Regional lymph node	0.11
66	F	Regional lymph node	0.12
70	F	Widespread amelanotic	0.13
52	F	Widespread amelanotic	0.13
62	F	Lymph node	0.14
45	M	Skin, weakly pigmented lungs	0.14
78	F	Skin, site of primary melanoma	0.15

Table VII. *23 patients with no clinical signs but with elevated urinary 5-S-cysteinyldopa values*

The interval between the 5-S-cysteinyldopa determination and the detection of metastases is indicated

Age	Sex	5-S-cysteinyl-dopa (mg/24 h)	Time interval (months)	Site of metastasis
61	M	0.16	6	Lymph nodes
51	M	0.19	0.5	Lymph node
27	F	0.19	1	Lymph node
45	M	0.20	6	Skeleton
69	F	0.20	2	Brain
60	F	0.22	4	Lymph nodes
66	M	0.24	4	Lymph nodes
72	F	0.25	2	Brain
76	M	0.27	5	Liver
54	M	0.27	12	Pleural
61	F	0.32	1	Brain
69	M	0.36	14	Lungs
63	F	0.43	4	Regional lymph node
46	M	0.49	2	Lungs, liver
79	F	0.58	1	Lymph nodes
59	F	0.65	1	Pancreas
53	M	0.70	7	Liver
80	M	0.72	1	Lymph node
63	M	0.86	10	Intestine
47	F	0.89	1	Lymph nodes
28	F	1.8	14	Liver
48	M	2.0	3	Liver
39	F	5.9	5	Liver

the 23 patients the 5-S-cysteinyldopa values were only slightly raised (borderline). The fact that such borderline values prompted investigations leading to the diagnosis of metastasis in 12 of the patients illustrates the significance of even a minor increase in 5-S-cysteinyldopa excretion.

In 5 of these 12 patients the urinary 5-S-cysteinyldopa returned to normal after removal of the metastases. The 23 patients constituted 14% of the whole group with metastasis.

In another 14% (16 men and 6 women), history and clinical signs motivated 5-S-cysteinyldopa determination and the results confirmed or gave the diagnosis of metastasis (Table VIII). It should be noted that in 7 of the patients in Table VIII there was no history of a primary melanoma. In 2 of these patients, removal of metastases, in one case a cutaneous tumour and in the other a cerebellar tumour, was followed by return of the 5-S-cysteinyldopa excretion to normal.

Table IX illustrates the value of 5-S-cysteinyldopa excretion in predicting the prognosis in patients with metastasis. The survival figures indicate that

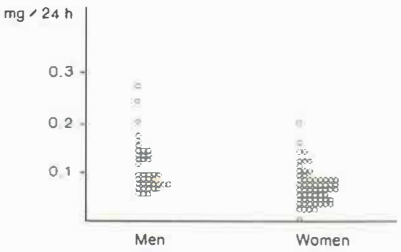

Fig. 5. Urinary excretion of 5-S-cysteinyldopa in 102 patients, 40 men and 62 women, operated on for primary melanoma, who did not develop metastases during the 2 years following the cysteinyldopa determinations.

in most cases the disease is disseminated when strongly pathological figures are obtained. Only one patient with a very high 5-S-cysteinyldopa excretion value has survived for more than 2 years. This patient had a testicular metastasis treated by surgery.

Borderline excretion values in certain melanoma patients with no clinical signs of metastasis may nevertheless indicate spreading of the disease, even though this becomes clinically evident only much later. Values in patients with long survival times should to a greater extent be strictly normal. This actually proved to be the case. In patients with no clinical signs of metastasis followed up for 2 years the urinary excretion of 5-S-cysteinyldopa during the months October–March was similar to that in normal subjects (Fig. 5). Addition of September and April excretion values elicited several borderline cases, thus illustrating the effect of even slight sun exposure.

The subject of chemical diagnosis of malignant melanoma has been reviewed extensively (16, 17). Many different methods for determination of catechol derivatives or indoles have been recommended, but none so far seems to be ideal for the detection of the spread of melanoma. We have not compared the 5-S-cysteinyldopa test with other methods for detection of melanoma metastasis, but it seems to compare well with the best of them. The fact that 5-S-cysteinyldopa excretion increases after even moderate sun exposure implies certain limitations in the clinical usefulness of the test in sunny countries. Even in Sweden it is most reliable in the dark months October–March. On the other hand, no other method for the chemical diagnosis of melanoma has been reported to reflect such slight changes as sun tanning. As long as 5-S-cysteinyldo-

Table VIII. *Symptoms and signs in 22 patients under observation for metastasis, in whom 5-S-cysteinyldopa confirmed the diagnosis melanoma metastasis*

Age	Sex	Site of primary melanoma	Symptoms and signs	5-S-cysteinyl-dopa (mg/24 h)	Site of melanoma metastasis
57	M	Unknown	Skin tumours, histology malignant	0.18	Skin
71	M	Skin	Facial paresis	0.21	Brain
33	M	Unknown	Subcutaneous tumours	0.32	Skin
45	M	Unknown	Ataxia, vertigo	0.33	Cerebellum
48	M	Unknown	Anaemia, haematemesis	0.40	Intestine
33	M	Skin	X-ray & scan skeletal tumour?	0.60	Skeleton
45	M	Skin	Headache, dizziness	0.73	Brain
80	F	Eye	Hepatomegaly	0.81	Liver
56	M	Unknown	Loss of weight, apathy	0.84	Brain
44	M	Eye	X-ray, skeletal tumours?	0.97	Skeleton
66	F	Skin	Pulmonary oedema	1.0	Lungs
62	F	Eye	X-ray & scan skeletal tumour	1.2	Skelcton
68	M	Eye	Cachexia	1.5	Widespread
63	M	Skin	Suspected local recurrence	1.5	Skin
52	F	Unknown	Non-pigmented metastases	1.6	Skin, lungs
61	M	Skin	Weight loss, confusion	2.9	Widespread
74	F	Unknown	Cutaneous tumours unspecified carcinoma	4.7	Widespread
71	M	Eye	Jaundice	5.4	Liver
47	M	Skin	Lumbago	6.9	Skeleton
74	F	Skin	Lymph node metastasis	9.3	Lymph nodes, liver
52	M	Skin	Pathological liver scan	13	Liver, skin
73	M	Eye	Huge abdominal tumour	28	Mesentery

pa is the only substance known to be increased by slight pathological changes in the melanocytes, we consider this method to be the best available for the detection of grave pathological changes in the melanocytes, such as those in metastasizing melanoma.

The diagnosis of melanoma metastasis is so serious that we have been anxious to avoid false-positive results. With the arbitrary pathological limit at 0.40 mg/24 h, fewer than 2% of patients under observation for melanoma show a positive test in the absence of signs of melanoma, and a further 7% have values in the borderline range without evident metastasis. Findings in the borderline range should prompt further investigation, since 30% of patients with metastases belong to this group.

It might be tempting to set the limit between the normal and the pathological at 0.15 mg/24 h, in which case the test would detect 90% of patients with melanoma metastases. However, the grave implication of a 'positive' result in the 7% of patients in whom melanoma metastasis could not be detected has motivated our practice of setting all values between 0.15 and 0.40 mg/24 h as borderline values, calling for further investigation. If a lower value is found on reinvestigation, the subsequent clinical investigation need not be so comprehensive. 12 of our 13 patients with metastasizing melanoma of the eye gave positive 5-S-cysteinyldopa values. In one this was borderline, possibly owing to special metabolic conditions in these particular cells. Duchoň has also reported that his method for Tormählen positive melanogens is more often positive in ocular than in cutaneous melanomas. In disseminated ocular melanoma metastasis he found 27 out of 27 tests positive (16).

A finding of great biological interest is the fact that 5-S-cysteinyl-dopa excretion values are higher in men than in women with metastasis. The excretion of 5-S-cysteinyldopa is greater in normal men than in normal women, but this difference is exag-

Table IX. *Survival time in 154 patients with metastases at different 5-S-cysteinyldopa excretion levels*

5-S-cysteinyldopa (mg/24 h)	>1 month (%)	>1 year (%)
<0.15	94	50
0.15-0.4	91	42
0.4–1	84	16
1–5	76	9
>5	56	3

gerated in the presence of melanoma metastases. The biochemical background for this sex difference is not known, but it is tempting to speculate that the same factors that make melanoma less malignant in women may also be of importance in regulating 5-S-cysteinyldopa production and excretion.

It is now firmly established that 5-S-cysteinyldopa is formed not only in melanocytes of people with red hair but also in those with other hair colours. It was therefore no surprise that determination of 5-S-cysteinyldopa excretion was equally useful in patients of all hair colours. The highest values were no commoner in patients with metastases and with red hair than in other patients with metastases. When analysing these findings it was found that no fewer than 33 % of our patients with metastases had red hair, which is a very high figure, considering the fact that only 7 % of schoolchildren in the south of Sweden are red-heads (9).

5-S-cysteinyldopa examination may be of prognostic value in the presence of metastasis. In a group of patients with normal excretion of 5-S-cysteinyldopa, 50% survived for more than 1 year, whereas only a few per cent of the patients with high 5-S-cysteinyldopa excretion survived for 1 year.

Determination of 5-S-cysteinyldopa has become the most popular method of studying the biochemistry of normal and pathological melanocytes. This study shows, however, that in spite of its great sensitivity and specificity, it is not absolutely reliable in diagnosing metastatic melanoma, even in the advanced stage. Nevertheless, it is a method that in combination with clinical examination probably provides more information than any other diagnostic procedure.

ACKNOWLEDGEMENTS

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