THE PIGMENTATION OF CHRONIC RENAL FAILURE

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Abstract. Clinical and photometric observations have been made on the hyperpigmented skin of 31 patients in chronic renal failure and in control subjects. Histochecmical examination of skin biopsies indicates that the increased pigment observed clinically may not be melanin. A carotenoid or lipochrome substance could be involved.

Key words: Pigmentation; Melanin; Renal failure; Uraemia

Chronic renal failure is frequently accompanied by increased pigmentation of the skin. The sallow complexion of the uraemic patient has traditionally been attributed to the deposition in the skin of urochromes—the pigments which give urine its yellow tint—but without experimental proof. Regular haemodialysis does not usually correct the hyperpigmentation and in some patients the complexion darkens further; indeed one celebrated English patient was excluded from his local inn by a racially prejudiced landlord!

Tsaltas (3, 4) has studied the pigment in the plasma of normal and uraemic subjects and shown that the uraemic has a raised concentration of carotenoids and of larger molecular weight substances attached to lipoproteins which are referred to as lipochromes. One of the substances detectable only in uraemic plasma is probably an oxidation product of vitamin A produced by exposure to ultraviolet light, and is dark brown in colour. Tsaltas has shown that other lipochromes darken on exposure to ultraviolet light and has suggested that this is the mechanism of prolonged tanning after exposure to sunlight in chronic renal failure. However, he has not examined the skin histologically to see whether the pigment formed is indeed a “urochrome” or the more familiar melanin.

We have therefore studied pigmentation clinically and histologically in patients with renal failure and in control subjects. The patients were 16 men and 15 women with renal failure, most of whom were receiving regular haemodialysis and two of whom had had bilateral nephrectomy. Their average age was 42.4 years. The controls comprised 11 patients attending the Skin Clinic and 26 subjects studied at autopsy. None of the control subjects (19 male, 18 female) was suffering from renal disease or any pigmentary disorder. Their average age was 44.5 years.

All subjects, patients and control, were white Caucasians.

METHODS

Five millimetre (5 mm) punch biopsies were taken under local anaesthesia from the anterior aspect of the upper forearm or back and fixed in formaldehyde. Paraffin sections (5 µm) were stained with haematoxylin and eosin and parallel sections were stained by the Masson Fontana silver method (1) and a melanin bleach method (2). Pigment in the basal layer of epidermis giving a positive silver stain and removed by bleaching in potassium permanganate was regarded as melanin.

Sections from patients and controls were mixed and allotted code numbers at random by one of us (J. S. C). The sections were then examined blind by a single observer (T. A.) and, on the basis of the extent and intensity of silver staining in the basal epidermal layer, were assigned to one of five categories of pigmentation, viz. 0, +, ++, ++++, +++++. Very little silver staining was observed in dermal macrophages and this was ignored for the purpose of ranking sections.

In addition to histological evaluation of melanin deposition, clinical pigmentation was assessed clinically and also (in 16 of the renal patients and 24 controls) by using a reflectance photometer with a selenium cell as the sensor and a white enamel plate as standard. As with the histological investigation the sites examined (volar surface of upper forearm, upper scapular area of back) are not customarily light exposed, and these sites were chosen to avoid chance variations caused by casual exposure to sunlight.

RESULTS

A. Clinical pigmentation

There is a good correlation between visual assessment of the degree of pigmentation and the photo-
meter-readings (Fig. 1). The latter indicate significantly \( p < 0.02 \) greater pigmentation in the renal patients (mean \( 45.4 \pm 1.9 \) S.E.M.) than in the controls (mean \( 51.0 \pm 1.4 \) S.E.M.). Clinically, all the renal patients had increased skin pigmentation varying from yellowish to dark brown, and this was most obvious in light-exposed areas, but was also evident on the trunk and proximal limbs although, unlike Addisonian pigmentation, the areola of the breast, scars and skin creases were not especially picked out except in two subjects. None of the subjects, renal patients or controls, had significant pigmentation of mucous membranes.

B. Histological findings

The mean score for the controls was \( 1.57 \pm 0.15 \) (S.E.M.) and for the renal patient biopsies \( 1.84 \pm 0.15 \) (S.E.M.). This is not a significant difference \( (t = 1.26, p > 0.2) \) although the trend is similar to that seen clinically and on photometry.

Dr. John Hunter (personal communication, 1973) has reported on the electron microscopic appearances of skin biopsies from the renal failure patients as follows: There is definite hyperpigmentation and the average diameter of the melanosomes is about 0.17 \( \mu \). Roughly 60% of these are in singles whilst the rest are complexed but the melanosomes do not appear structurally abnormal.

DISCUSSION

The increased pigment observed clinically in the skin of the renal patients, assessed both visually and by reflectance photometry, is associated histologically with an increased amount of melanin. However, there is a wide scatter in the histochemical gradings for the latter observation and the difference between patients and controls does not achieve statistical significance. Nevertheless, both the hue of the chronic uraemic’s skin, and its deepening on exposure to light, suggest it to be melanin. However, as referred to above, Tsaltas [3, 4] has pointed out that lipochromes also darken on exposure to ultraviolet light. It is worth noting that these substances could be removed in the fixation and embedding process used for our histological studies.

Another explanation of our findings could be that the histological evaluation was insufficiently sensitive to detect slight differences. The chief difficulty is that the melanin is virtually confined to a single layer of cells in a highly heterogeneous tissue and that different specimens vary both in the amount of melanin (staining intensity) within pigmented cells, and in the proportion of basal cells that are pigmented. These factors rule out the use of more objective techniques such as point-counting. However, the most important of the objections to subjective assessment is overcome by the randomisation procedure we have adopted to study the sections. Nevertheless, the problem of assessing gradation of staining intensity with increasing amounts of melanin is a difficult one. It is worth noting that the reflectance photometer (and the clinicians’ eye) is assessing the average pigmentation of a relatively large area of skin (nearly 20 square mm in the case of a 5 mm punch biopsy) while the histological sections are 5 \( \mu \)m wide strips of skin. Sampling errors may also complicate the situation.

Observations on biopsies from light-exposed skin might be more likely to reveal differences in melanin deposition. However, it is not reasonable to request volunteers to permit biopsies to be taken from the face and back of hand. Furthermore, chance variation due to sunlight exposure would be much greater in such biopsy specimens.

On the basis of the present observations we suggest that an evaluation of the role of carotenoids and lipochromes should be made with regard to the hyperpigmentation of renal failure. Reflectance spectrophotometry would be a useful technique in such an investigation.

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REFERENCES

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