

PIGMENT DEPOSITS IN EYES AND LIGHT-EXPOSED SKIN DURING LONG-TERM METHACYCLINE THERAPY¹

Kjell Dyster-Aas, Holger Hansson, Gunnar Miörner, Halvor Möller and Alf Rausing

*From the Departments of Ophthalmology, Dermatology, Epidemiology and Pathology,
University of Lund, Malmö, Sweden*

Abstract. During long-term methacycline therapy for chronic respiratory disease, seven patients developed a greyish-black pigmentation of light-exposed skin, and a yellow-brown pigmentation of the exposed parts of the conjunctivae. The pigmentation should be considered phototoxic although not preceded by sunburn or other dermatitis. Light microscopy revealed a but slightly increased melanin content in epidermal and dermal cells, a profound actinic elastotic degeneration, and a granular pigment extracellularly in the elastotic fibres. This pigment has been examined with the electron microscope. Its nature is so far unknown; possibly, it is composed of a methacycline-melanin complex. The incidence of this drug side-effect is estimated to be 3% after administration of a total dose of 400-1600 g methacycline. The pigmentary disturbance apparently does not impair ocular or cutaneous function. Clinical and histological data have been compared with the hyperpigmentation occurring during therapy with chlorpromazine and amiodarone.

For several drug reactions in the skin, an interaction between ultraviolet radiation and the drug or its metabolites is required. The pathogenetic mechanism may be toxic or allergic and the clinical expression is that of an intense sunburn or a papulo-vesicular eczema. Remedies concerned usually belong to the sulfonamide and phenothiazine group, or, among the tetracyclines, demethylchlortetracycline.

Other drugs induce hyperpigmentation without or with minimal signs of a preceding dermatitis (17). When such pigment deposits are confined to light-exposed skin even the eyes may be involved. Examples of this are the dyschromias caused by chlorpromazine and related phenothiazines, by antimalarials, and, as recently reported (10), by amiodarone. In the following, a tetracycline preparation will be added to the list of drugs capable of inducing oculocutaneous hyperpigmentation.

CLINICAL AND LABORATORY EXAMINATION

Cutaneous findings. We report 7 Caucasian patients with a prolonged history of chronic bronchitis and/or bronchial asthma. The cases, 5 males and 2 females, are summarized in Table I. Insiduously, six of the patients have developed a hyperpigmentation on light-exposed skin as well as in the conjunctivae, the seventh patient in the conjunctivae only. The cutaneous pigmentation was first noticed by the patients during summer or fall while the ocular pigment was not noted prior to the clinical examination. Preceding symptoms of photo-dermatitis were absent or sparse. In cases 1-5 the skin areas usually involved by photogenic dermatoses, i.e. face and back of hands, were more or less intensely hyperpigmented with a dark-greyish or even black, homogeneous colour (Fig. 1). Over protruding parts of the face, such as cheekbones and lateral parts of forehead, the colour was in some cases enhanced. In patient 6 only the ventral parts of the legs were hyperpigmented; this patient used to wear shorts for several summer months each year. The dyschromia was absent in the wrinkles of the face, under the bows of spectacles (case 1), under the nose and chin, and in the palms in most patients (Fig. 1).

The texture of the coloured skin in most cases showed atrophy of actinic (senile) type but was otherwise normal. In some patients treated with corticosteroids (cases 1, 2 and 5) the skin of the forearms was atrophic with haemorrhages.

The nails were examined under Wood's light in 4 patients (cases 1, 2, 4 and 6). Within the first proximal millimetre there was a faint yellow-green fluorescence in cases 4 and 6 while it was intense in case 1. In all 4 patients the nail-plates distal to the lunula developed

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Table I. Clinical data on seven patients with oculocutaneous hyperpigmentation due to methacycline

	Case no.						
	1	2	3	4	5	6	7
Age, y.	67	66	64	60	56	45	55
Sex	♂	♂	♂	♂	♂	♂	♀
Diagnosis ^a	c.b.	c.b. + b.a.	c.b.	c.b.	b.a.	b.a.	b.-c.
<i>Skin pigment</i>							None
Age at start, yrs	66	63	63	60	56	43	—
Site	Face, back of hands	Face, back of hands and of forearms	Face	Face, neck	Face	Shins	—
<i>Ocular findings</i>							
<i>Pigment in</i>							
Conjunctiva	+	+	+	+	+	+	+
Cornea	+	—	—	+	—	—	—
Lens	—	+	+	—	—	+	—
Retina	—	—	—	—	—	—	—
Cataract	+	+	—	—	—	—	+
<i>Vision</i>							
RE	0.2	1/60	1.0	1.0	1.0	1.0	1.0
LE	0.1	0.1	1.0	1.0	1.0	1.0	1.0
<i>Laboratory tests</i>							
S-creatinine	2.2 mg %	S-creatinine 1.8 mg %	Normal	S-creatinine 1.5 mg %	Normal	S-bilirubin 1.3	Normal
<i>Drug therapy</i>							
Methacycline	4.5 y., 950 g	3 y., 600 g	5 y., 1 050 g	7 y., 1 260 g	7.5 y., 1 575 g	2 y., 420 g	7.5 y., 1 575 g
Other tetracyclines before methacycline	1.5 y., 480 g	—	10 months, 300 g	3 y., 700 g	2 y., intermittently	—	4 y., 850 g
Corticosteroids	+	+	Repeated short periods	—	+	+	—
ACTH	—	+	—	—	—	—	—

^a c.b. = chronic bronchitis; b.a. = bronchial asthma; b.-c. = bronchiectasies.

a spontaneous cyanotic appearance. One of them (case 6) was being treated with griseofulvin for a *T. rubrum* infection of hands and feet.

Ocular findings. Ophthalmoscopy and slit-lamp microscopy was performed in all 7 patients. The visual acuity was determined on Monoyer's tables. The visual fields were routinely examined by the Goldmann perimeter in all patients except case 2.

In all 7 patients there was a pigmentation of varying intensity in the bulbar conjunctiva within the palpebral fissure. The pigmentation, usually yellow-brown granules, was located just outside the cornea on both the nasal and temporal side, but often denser on the latter side of the eye. The pigmented granules were generally seen distinctly as separate granules, often distributed in a wedge shape. There were no pathological pigments in the palpebral part of the conjunctiva. In one patient (case 4) there was a dust-

fine pigmentation on the corneal endothelium. In another (case 1) there was a thin subepithelial line of pigment deposit resembling the Hudson-Stähli line. In 3 patients (cases 2, 3 and 6) a dust-fine deposit of pigment was found on the anterior lens capsule. The pigment was unevenly distributed but located mainly centrally. No pathological pigmentation was found in the retinae.

Patients 1 and 2 had bilateral cataracts of the senile type but no extraordinary pigmentation. There were opacities both in the posterior subcapsular part of the lens and in the nucleus. However, the cataracts were denser in the subcapsular area. In both cases an intracapsular cataract extraction was recently performed without complications. In case 7 there were fine opacities in the anterior and posterior subcortical areas of the right lens.

In the other cases there were no pathological

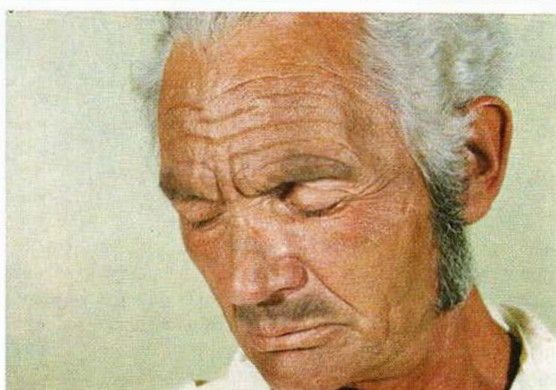
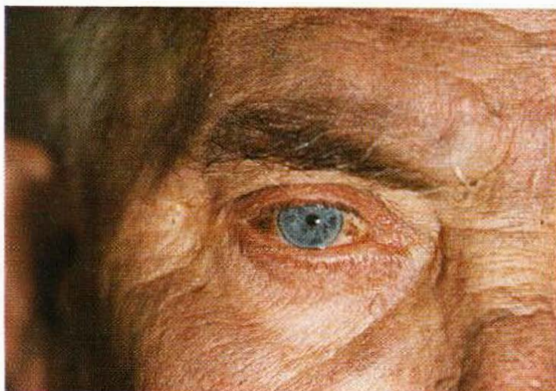
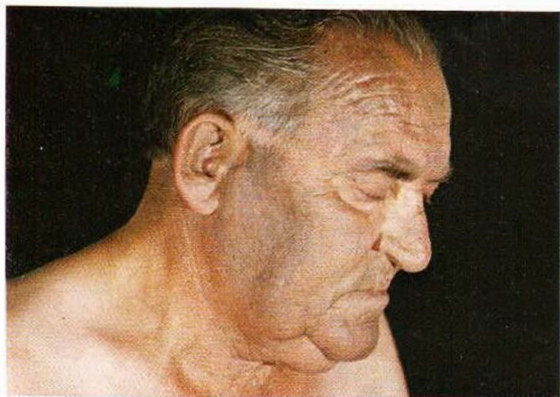


Fig. 1. Hyperpigmentation of skin and eyes with enhancement on areas of maximal light exposure (a, b, and c: case 1; d: case 3). Note sparing of skin under bows of spectacles (a).

in palm (c), and in wrinkles (d). Also note conjunctival pigment (b).

lenticular changes with the possible exception of the previously described fine pigmentation of the anterior lens capsule.

In all cases the ocular fundi were normal. The visual acuity was reduced in cases 1 and 2 due to cataract. In the other cases normal vision was found. The vision fields were normal.

Laboratory tests. The examinations included hemoglobin, white blood cell count, a liver profile (SGOT, SGPT, glutamyltranspeptidases (SGT), bilirubin, alkaline phosphatases), serum creatinine, urinary albumin and glucose. The liver tests were normal except for a slightly increased SGT in case 1. During methacycline therapy, at the time of developing hyperpigmentation, the serum creatinine was slightly pathologic, i.e. above the border value of 1.2 mg/100 ml, in 3 patients (1, 2 and 4). The S-bilirubin was slightly elevated in 1 patient (case 6). Other laboratory tests were normal.

Patients 1 and 5, while still on full-dose methacycline, were exposed to longwave ultraviolet light. The

dorsal skin, lacking signs of pigmentation and actinic elastosis, was irradiated daily for 5 days. One patient was exposed with two "black-light" tubes (Philips TL 40 W/05) emitting a continuous spectrum with a maximum at 360 nm; the skin-lamp distance was 20 cm, the exposure time 20 min. The other patient was irradiated with a Kromayer mercury lamp equipped with a filter for transmitting mainly 400 nm wavelengths; the light source was applied in immediate contact with the skin, the exposure time was 10 min. The ultraviolet light induced no phototoxic dermatitis or pigmentation.

MORPHOLOGICAL INVESTIGATIONS

Material and methods

Surgical biopsies from pigmented skin were examined by light microscopy from all the patients and by electron microscopy from all except case 4. The biopsy was taken from the forehead of patients 2, 3, 4 and 5. The biopsy from case 6 was taken from the lower leg and patient 1 was examined by biopsies from the wrist and neck. Non-pigmented skin from the abdomen was examined by light and electron

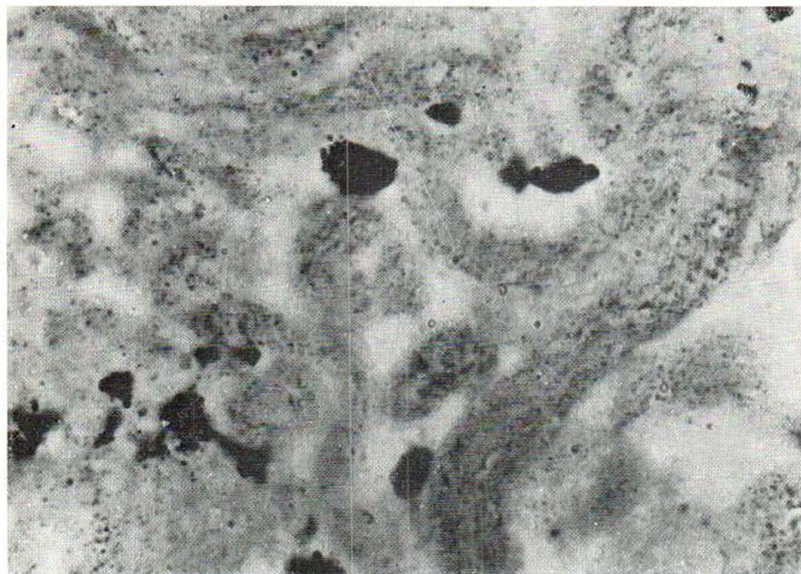


Fig. 2. Elastotic dermal connective tissue of patient 2. Heavily pigmented melanophages and finely granular pigment in elastotic fibres. Masson-Fontana, $\times 1150$.

microscopy from patients 2 and 5. Needle biopsies of the liver were examined by light and electron microscopy from patients 1, 3 and 5, and by light microscopy only from patient 4. The eye lenses of patients 1 and 2 were examined by light microscopy. A conjunctival biopsy from patient 1 was examined by light and electron microscopy.

Three surgical skin biopsies from the forehead of patients with actinic elastosis, not treated with tetracyclines, were used as controls for light microscopy. No control biopsy was available for electron microscopy. As a control, conjunctival tissue was taken at autopsy from a patient of about the same age as patient no. 1.

All tissues for light microscopy were fixed in formalin and embedded in paraffin according to standard procedures. Sections were stained with haematoxylin and eosin, PAS, toluidine blue, Prussian blue, Schmorl's ferricyanide, Weigert's elastic stain and with the methods of von Kóssa, Masson-Fontana and van Gieson, and with Alizarin red S. Deparaffinized, unstained sections were examined by fluorescence microscopy and in polarized light. Frozen sections were stained with Scarlet Red. Tissues for electron microscopy were immediately fixed in cold 3% glutaraldehyde in a phosphate buffer at pH 7.3. After post-fixation in 1% OsO_4 in the same buffer they were dehydrated in an ethanol series, passed through styrene and embedded in Vestopal W. Thin sections were stained in uranyl acetate (23) and lead citrate (19) or in a 5% aqueous solution of phosphotungstic acid at pH 6, or were examined without any staining. Furthermore, sections not treated with OsO_4 were also prepared. The photographs were taken in a Philips 300 electron microscope.

RESULTS

Light microscopy of skin. All the skin biopsies from hyperpigmented areas showed the same lesions. There was a moderate basal hyperpigmentation in

the epidermis, to all appearances melanin, staining black with Masson-Fontana and blue with Schmorl's ferricyanide method, which gave parallel results throughout. In the upper and intermediate dermis there was an intense elastotic degeneration of the connective tissue, positive in clastic tissue stain. Among the elastotic fibres there were moderate numbers of pigmented cells. The pigment was coarsely granular and stained variably positively with the Masson-Fontana method (Fig. 2) and to some extent also with the von Kóssa method. These cells had the appearance of melanophages. Patient 6 (leg skin) demonstrated less intense elastotic changes and more pigmented cells than the others but in principle the lesions were similar. In the pigmented dermal cells of this patient there was some positivity with the Prussian blue reaction for iron which gave negative results in all the other cases. Among the elastotic fibres there were occasional large, highly refractile bodies, similar to those in the conjunctival biopsy (*vide infra*). The elastotic fibres contained a very finely granular pigment which was seen as a brown dust in unstained sections. The granules were much smaller than those of the melanophages and did not fluoresce at any wavelength in the fixed, deparaffinized sections, whereas the elastotic fibres gave a bright autofluorescence. Neither did the granules light up in polarized light. They stained black in von Kóssa's stain, and with varying intensity in Masson-Fontana (Fig. 2). With toluidine blue the granules appeared blue-green, as did the pigment in the cells,

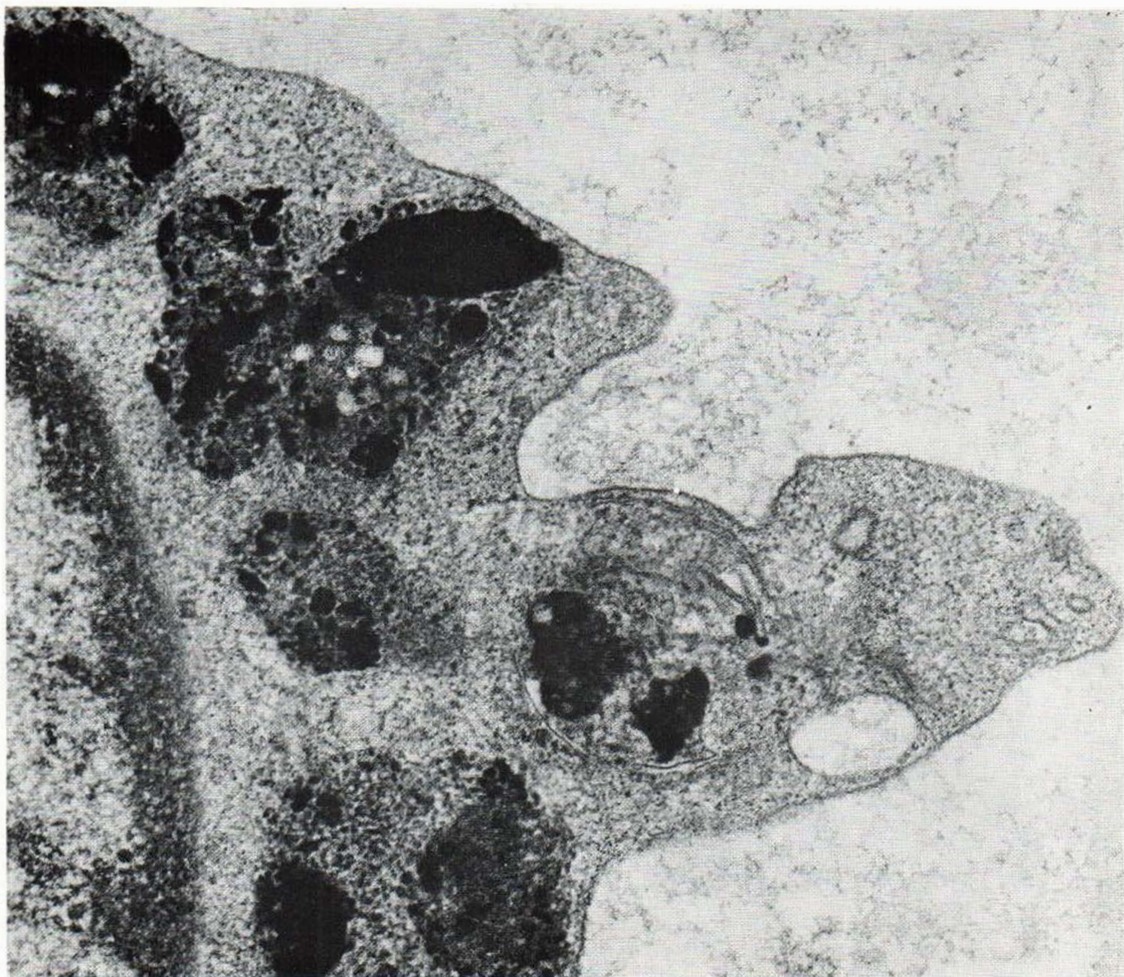


Fig. 3. Dermal pigment-containing cell of patient 3. Electron-micrograph showing characteristics of melanophages with melanin granules partly degraded within membrane-bound

structures. Part of nucleus to the left. Osmium fixation, uranyl acetate and lead citrate, $\times 50\,500$.

while they were negative in PAS and in Alizarin red S.

The staining for lipids demonstrated very fine droplets in some fibres and there was also some positivity intracellularly in the dermis. The skin of patients 2, 3 and 5 showed some insignificant perivascular lymphohistiocytic infiltrates but otherwise no signs of inflammatory lesions were detected.

In the control biopsies of abdominal skin there was neither abnormal pigmentation nor elastotic change. The biopsies from the control patients with actinic elastosis showed some granules in the elastotic fibres with the von Kóssa method but in the other stains no abnormal pigment was detected. The melano-

phages were appreciably fewer while the epidermal pigmentation did not differ noticeably.

Electron microscopy of skin. The epidermal pigment had the electron-microscopic characteristics of melanin (5). There was no apparent abnormality of the melanocytes. The pigmented cells in the dermal connective tissue contained structures very similar to the epidermal melanin granules, in various states of degradation, at least partly within membrane-limited structures (Fig. 3). The collagen fibres always seemed normal, though reduced in number and disorganized by the elastotic fibres. The elastic fibres showed few microfibrils and consisted of an amorphous substance of moderate electron density with all stains used. In

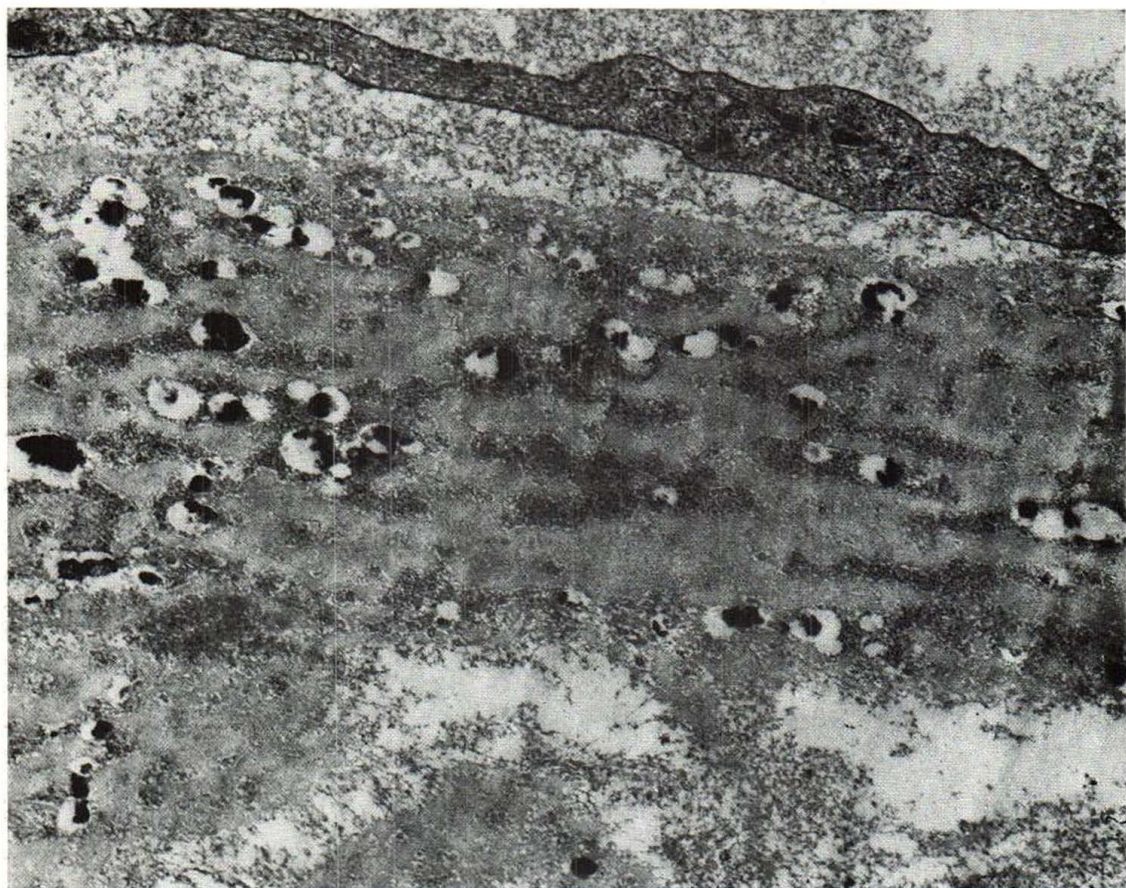


Fig. 4. Electronmicrograph of elastic fibre of patient 3. Electron-dense globules within light areas in fibre. Process

from connective tissue cell in upper part of picture. Osmium fixation, uranyl acetate and lead citrate, $\times 25\ 300$.

this substance there were streaks of osmiophilic, dark material, containing large numbers of irregularly shaped granules of great electron density (Fig. 4). They were easily seen in glutaraldehyde-fixed sections without treatment with osmium tetroxide or any other staining. They were often surrounded by a clear halo and had no discernible inner structure. Some fibres appeared as amorphous or finely granular debris containing large, irregular, dense bodies (Fig. 5). The vascular endothelium and basal membranes were normal.

Electron microscopy of abdominal skin from patients 2 and 5 disclosed no abnormality.

Conjunctival biopsy. Moderate basal epithelial pigmentation, probably melanin, staining black with Masson-Fontana. A similar degree of pigmentation was seen in the control specimen. More prominent changes were seen in the connective tissue than in the control. In the upper part of the lamina propria

there were many rounded foci of fibres with a coarse and fragmented appearance. They stained variably with elastic tissue stain and PAS, and negatively with van Gieson for collagen. Among the fibrils there were groups of large, irregular, refractile bodies which appeared brownish in unstained sections, as did the fibres. The larger bodies gave a weak auto-fluorescence but were invisible in polarized light. After staining with haematoxylin and eosin, the fibres were blue-brown, while the larger bodies were grey-blue. Both structures were negative in Alizarin red S and largely negative in Masson-Fontana, while their borders were intensely stained by von Kossa's method. Among the fibrils there were moderate numbers of cells of histiocytic appearance containing coarse granules staining more or less positively in Masson-Fontana. The face of the unstained paraffin tissue block was examined and photographed under incident illumination and the image was compared

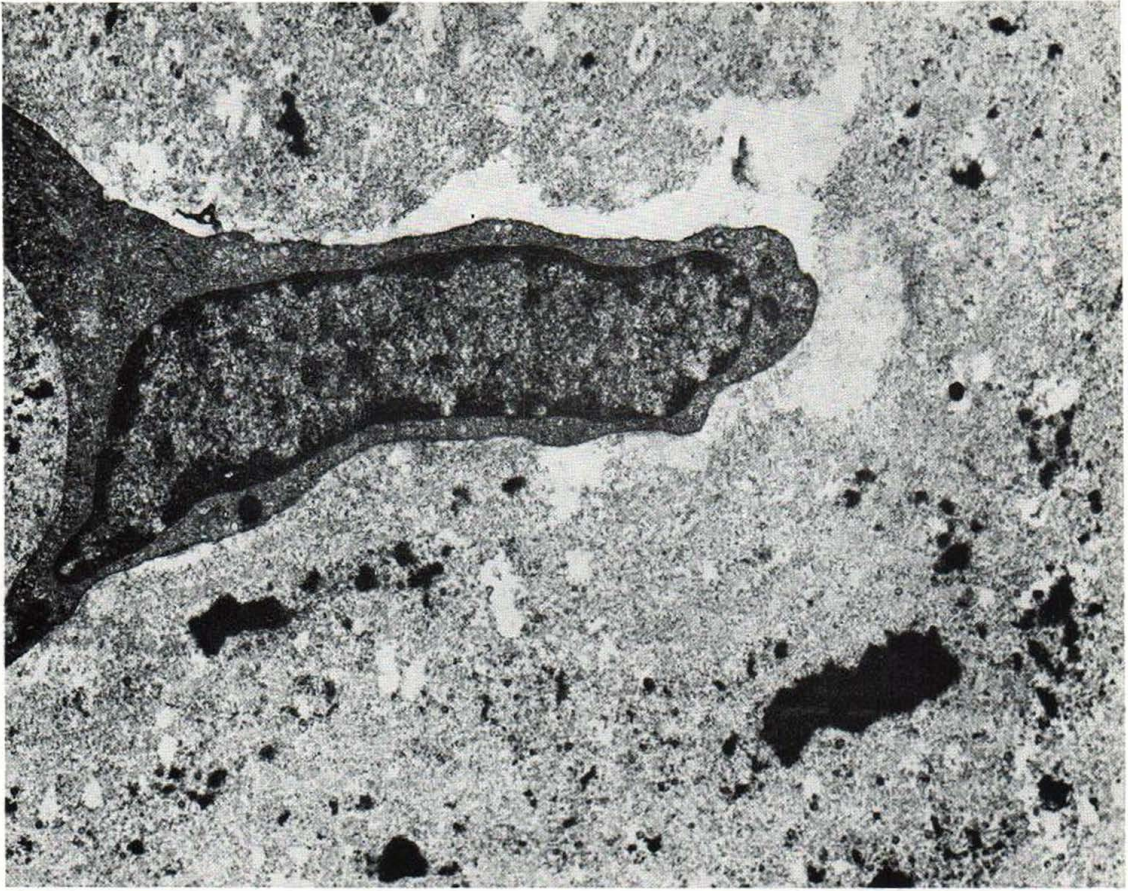


Fig. 5. Electronmicrograph of elastotic material in dermal connective tissue of patient 1. Granular degeneration with

electron dense bodies. Fibroblast in centre of picture. Osmium fixation, uranyl acetate and lead citrate, $\times 16\ 800$.

with sections stained according to von Kóssa, Masson-Fontana and with the other, above-mentioned stains. It was evident that the pigment in the unstained tissue corresponded exactly to the sites staining positively with von Kóssa's method, while the structures staining black with Masson-Fontana were inapparent in the unstained tissue (Fig. 7). The fibres and the homogenous bodies thus appeared to be the site of the pigmentation.

The electron-microscopic examination of the conjunctiva disclosed fibres of a homogeneous, moderate electron density after OsO_4 fixation and double staining. The fibres and the larger bodies appeared to be of the same nature and differed only in size and shape. Both kinds of structures had a narrow rim of material of high electron density (Fig. 6). An occasional dark body, probably lysosomal, was found in the connective tissue cells, but no structures

similar to melanosomes. The collagen fibrils appeared swollen and disintegrating.

The liver biopsies were essentially normal under the light microscope, though they showed quite a few lipofuscin granules, not exceeding what may be seen in normal subjects, however. Frozen sections were examined histochemically (Dr Inga Hägerstrand) but no abnormal activity of lysosomal enzymes could be detected. In the electron microscope the biopsies from patients 3 and 5 were quite normal. The hepatocytes and the Kupffer cells contained many lysosomes but probably within normal limits and of normal appearance.

One *eye lens* each from patients 1 and 2 was removed because of cataract. Under the light microscope they did not show any definite abnormality except such lesions as are usual in this disease.

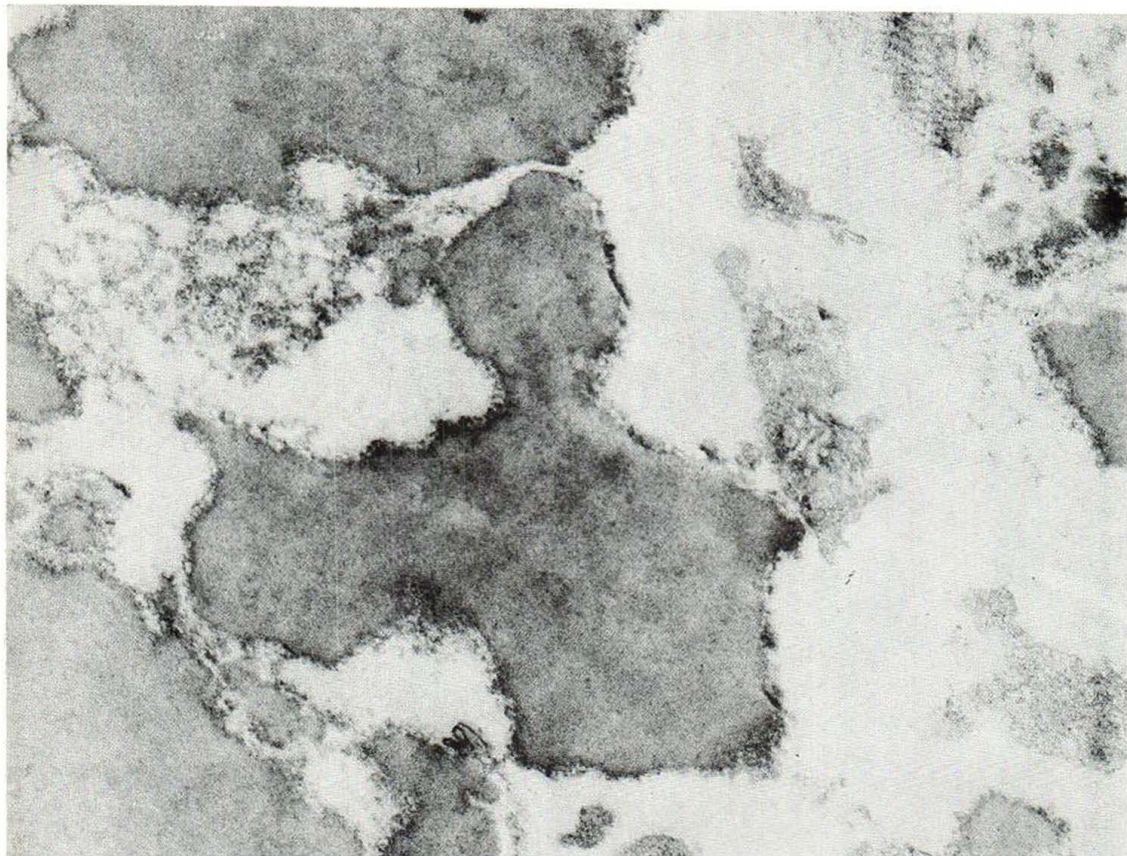


Fig. 6. Electronmicrograph of conjunctival biopsy. Irregular bodies similar to elastic fibres, with rim of dark material.

Collagen fibrils in upper right corner. Osmium fixation, uranyl acetate and lead citrate, $\times 36\,300$.

DRUG THERAPY

All patients had been treated with methacycline (Rondomycin®—Roerig S. A., Bruxelles, Belgium) 300 mg twice a day. In case 4 therapy was discontinued during 2 summer months each year; in the other 6 cases the drug was administered continuously. Hyperpigmentation of light-exposed skin appeared after 2–7.5 years of treatment. At that time the total amount of methacycline ingested was around 420–1 575 g.

All other therapy had been individually different. Thus, 4 of the patients had been treated with tetracyclines (oxytetracycline, lymecycline) for varying periods 10 years before the pigmentary disturbance. Low-dose corticosteroids had been given for long periods to 4 patients (cases 1, 2, 5 and 6), just sporadically to one (case 3). Only one patient (case 2) had regularly received ACTH for an appreciable period prior to methacycline therapy. Another patient (case

6) had been treated for the last 2 years, mainly after the start of hyperpigmentation, with griseofulvin for a *T. rubrum* infection of hands and feet.

DISCUSSION

It is apparent from the distribution of hyperpigmentation in the 7 cases reported that the effect of ultra-violet light has been of the utmost pathogenetic importance. Only light-exposed areas were involved; the maximal response was obtained on protruding surfaces of the face, e.g. overlying bony intumescences around the eyes, and dorsal aspects of hands, while the skin in facial wrinkles, under bows of spectacles, and in the palms, was spared. The ocular pigment deposits were confined to the part of the peripupillary conjunctiva that is maximally exposed to light through the palpebral rima. Such photogenic hyperpigmentation does not occur in connec-

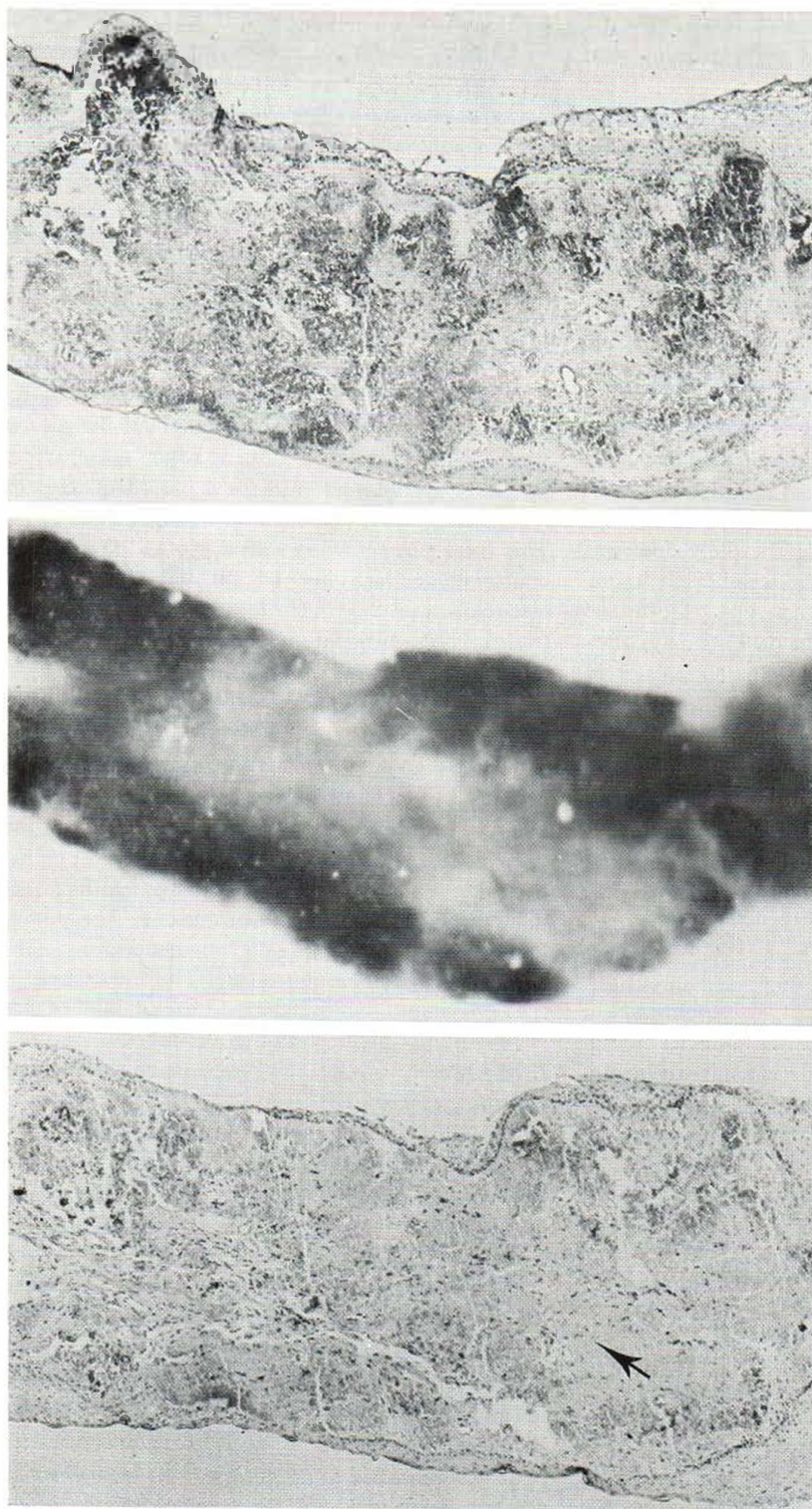


Fig. 7. Conjunctival biopsy. Picture in the centre shows face of sectioned, unstained tissue block. The biopsy is sectioned tangentially and there is epithelium on both sides but this is invisible in the unstained tissue. Upper picture shows section stained according to von Kóssa. Note positive reaction on the sites which are pigmented in unstained block. Lower picture is section of identical thickness stained according to Masson-Fontana. Small black dots are cells containing positive pigment (arrow). These are located in part not apparently pigmented in unstained tissue. All $\times 67$.

tion with pulmonary disease and there were no clinical or laboratory signs of other organic dysfunction.

An increased output of pituitary melanocyte stimulating hormone may induce a hyperpigmentation starting on light-exposed areas. However, it extends early to covered skin, includes palmar creases and mucosal membranes, neither of which was involved in the present cases. One of the patients had been treated for a period 3 years earlier with injection of porcine corticotropin (ACTH) which may give rise to an Addisonian melanosis. Such toxic reactions are rare and are usually caused by synthetic ACTH (13). This pathogenetic mechanism may also be ruled out because of the distribution of hyperpigmentation and lack of signs signifying hormonal dysfunction.

All the patients except 2 had been treated for years with oral corticosteroids. The daily dose was moderate and hyperpigmentation is not listed among known side-effects. Areas of cutaneous atrophy and purpura observed in some of the patients may, however, be explained on that basis. The corticosteroid therapy may also have contributed to the posterior cataract in 2 of the patients.

Thus, only methacycline remains as a common denominator to explain and cause the pigment deposits found in light-exposed skin and eyes. Tetracyclines are known to induce photogenic inflammation of the skin (18). A photoallergic dermatitis may occur very infrequently, whereas phototoxic reactions are common. When various tetracyclines are compared for phototoxic potency, demethylchlor-tetracycline is highly incriminated, doxycycline about ten times less so (3), and other tetracyclines practically not at all. Methacycline, in a clinical-experimental study (11), showed the same phototoxic potency as placebo. Photodermatoses induced by tetracyclines are acute or subacute sunburn dermatitides or eczemas which may leave a residual and intensified tan. Ocular deposits have not been reported. In some of our patients it is possible that a transient irritation or itching had preceded onset of hyperpigmentation but in no case a clear-cut photodermatitis.

It may thus be discussed if the photogenic hyperpigmentation should be considered primary or post-inflammatory. Drug-induced photodermatitis is generally mediated by long-wave ultraviolet (UV) light of 3 400–4 000 Å (12) which seems to hold true even in the present syndrome. Long-wave UV is transmitted through glass and this fact made ocular deposits possible in the 2 patients who wore

spectacles permanently. Furthermore, in the absence of a history of photodermatitis, a pigmentation may, however, develop "post-inflammatorily". If a long-wave psoralen dermatitis is provoked in human skin, even a subthreshold UV dose, not giving rise to clinical inflammation, may induce a late pigmentation (15).

Tetracyclines are taken up and stored in calcifying and degenerating structures (21) which may lead to discoloration of deciduous and permanent teeth (17). Pigmentation of ocular or cutaneous tissues during tetracycline therapy has not earlier been reported. The reason for this is probably a matter of dosage. Our 7 patients had all been maintained for several years on a methacycline dose at which tetracyclines generally are administered for a period of days or weeks only, exceptionally for a couple of months. This therapeutic scheme with a protracted full-dose course of methacycline has proved valuable and essentially non-toxic in chronic respiratory infections (6, 16). Photosensitization reactions or hyperpigmentation have not been observed.

For similar reasons the ocular pigment deposits can be attributed to the treatment with methacycline. Thus, the pigmentation very much resembles the one caused by phenothiazine derivatives, especially chlorpromazine. The main pigmentation in the present cases, however, is localized to the conjunctiva. The pigmented granules are generally larger than those caused by chlorpromazine. The pathological value of the dust-fine pigmentation on the corneal endothelium and on the anterior capsule of the lens might be questioned. In the higher age groups similar pigmentation quite frequently occurs. In the present group, however, one of the patients was only 45 years old.

The cataracts observed in 2 patients (cases 1 and 2), could be caused by several factors (8). The patients were 66 and 67 years old, i.e. in an age group where senile cataract is not uncommon. In both cases, the cataract was located mainly sub-capsularly in the posterior part of the lens. Prolonged medication with corticosteroids may also have caused the opacities, whereas in a third patient (case 7), in whom very fine cortical opacities were found in one eye, the possible effect of corticosteroids can be disregarded. There are no similarities to the lens opacities described after chlorpromazine, these usually consisting of an anterior stellate cataract.

From a histopathological point of view it is impossible to state anything with certainty concerning the

Table II. *Drug-induced oculocutaneous hyperpigmentation*

	Chlorpromazine	Amiodarone	Methacycline
Light-exposed skin	+	+	+
Preceding dermatitis	None	Slight	Questionable
Skin colour	Violaceous	Bluish-grey	Greyish-black
UV wavelength	> 3 200 Å	?	> 3 200 Å
<i>Light microscopy</i>			
Epidermis	Normal or melanosis	Normal or melanosis	Normal or melanosis
<i>Dermis:</i>			
Pigment	Perivascular, intracellular	Mainly intracellular	Intra- and extracellular
Inflammation	None	Some	None
Elastosis	?	Marked	Important
<i>Electron microscopy of pigment</i>			
	Lysosomal (melanin and other)	Lysosomal (melanin and lipofuscin)	Lysosomal (melanin) Non-lysosomal (other)
<i>Eyes</i>			
Corneal stroma	Opacities	Opacities	Normal
Conjunctiva	Pigment	Normal	Pigment
Lens	Cataracts/pigment	Normal	Pigment?
Total dose	500–1 000 g	200–300 g	400–1 600 g
Incidence	3–4 %	2 %	3 %

nature of the pigment. The epidermal pigment seems to be melanin but it is not sufficiently abundant to be, reasonably, the sole explanation of the intense pigmentation seen clinically. The macrophages of the dermal connective tissue are seen in greater numbers than in the control skin biopsies from patients with actinic elastosis. They contain a pigment which would also seem to be melanin but it is doubtful if their number and degree of pigmentation are sufficient as an explanation, even taken together with the epidermal pigmentation.

Therefore, we speculate that there is another pigment deposit, possibly related to the elastotic degeneration, which latter is probably not in itself an effect of the drug, but due to solar exposition. Viewed histologically, there is a granular pigment in the elastotic fibres. This is not visible in our control biopsies, which, admittedly, may be a question of degree rather than a qualitative difference. This pigment corresponds to the osmiophilic globules seen with the electron microscope, and also to the granules which stain positively for fat when viewed light microscopically. Globules staining positively for fat may be seen in any elastotically degenerating skin (22) but do not give rise to a blackish discoloration in other cases. The irregular electron-dense bodies probably correspond to such structures as

have been described by Banfield & Brindley (2) in actinic elastosis of the skin and by Klintworth (14) in actinic degeneration of the conjunctiva. They seem to correspond to the larger, refractile bodies seen in the light microscope.

The pigment in the skin and conjunctiva thus seems to be partly located in such structures as can occur in any patient with actinic degeneration of connective tissue structures. In patients not treated with methacycline these structures are, however, only faintly pigmented. Thus, there seems to be a coloured substance bound to them in molecular form. We have tried to characterize this substance histochemically. The staining reactions, however, are difficult to interpret.

The most consistently positive reaction on the pigmented sites is that of von Kóssa. This indicates the presence of phosphates, carbonates, urates or oxalates. These ions usually occur in the tissues together with calcium. It is well known that tetracyclines are deposited in degenerating tissues together with calcium (21). On the other hand the Alizarin red S reaction, said to be specific for calcium, is negative. This could possibly be explained by a chemical binding too tight for the stain to react with the calcium ion. A binding of a metabolite to lipid-containing structures could also be a possibility. The

Masson-Fontana reaction is variably positive which could be a result of variable amounts of melano-protein also being included in the complex. However, this reaction is certainly not specific for melanin but merely indicates the presence of a reducing substance. The absence of fluorescence in the granules seems to indicate that the tetracycline, if such there is, is in some way chemically altered.

Anyhow, we think that the methacycline, or some metabolite thereof, is bound to the degenerate connective tissue, possibly in conjunction with melanin, this complex being one cause of the hyperpigmentation. Here, a pertinent reference should be made to the recent finding of tetracycline affinity to melanin-holding structures (4). Also, epithelial melanin content will be increased since melanin formation can be stimulated by the presence of an alien pigment, as is the case with iron in hemochromatosis.

A comparison with similar drug-induced hyperpigmentations in eyes and light-exposed skin seems warranted (Table II). Both chlorpromazine and amiodarone dyschromias were first reported in the French literature, chlorpromazine causing a "visage mauve", and amiodarone different shades of blue and grey. (For extensive references, see 9, 10, 17.) For these two drugs, and for methacycline, the pathologic changes abound in upper dermis while epidermis appears essentially normal. Some inflammatory edema and cellular infiltration have been noticed in the amiodarone cases, though not with chlorpromazine and methacycline. This coincides with clinical evidence of photodermatitis. Information has not been found concerning elastotic degeneration with chlorpromazine; with amiodarone (10), and now methacycline, such change formed an important part of the histologic picture.

Light and electron microscopy after chlorpromazine and amiodarone revealed mainly intracellular pigment deposits. They were shown to be lysosomal and of a double nature: melanin and some other pigment, presumably a drug metabolite combination or lipofuscin. The pigment-holding cells were often clustered perivascularly which could be taken as evidence of a hematogenous source. In our methacycline cases the pathologic pigment was scattered extracellularly in close connection with the degenerated elastica. Here, the von Kossa stain suggested an affinity of the pigment to a calcium-containing tissue, a phenomenon well-known for tetracyclines.

With regard to ocular changes, corneal opacities in the stroma occurred with both chlorpromazine

and amiodarone, not so in our methacycline cases. Pigmentary deposits were seen in the exposed part of the bulbar conjunctiva after chlorpromazine therapy (7, 20), apparently very similar to the finding in our patients. This has not been reported with amiodarone. Lens abnormalities, mainly different types of cataracts, have been repeatedly noted during chlorpromazine therapy. The cataract occurring in 3 of our patients could not be ascribed to methacycline therapy. Finally, no retinal damage, as connected with antimalarial drugs, has been observed with any of the three drugs tabulated.

The daily methacycline dose in our 7 patients was 600 mg, with one exception given continuously for 2 to 7 years. This amounts to a total dose of 0.4–1.6 kilograms, i.e. roughly in the same order as the total dose required for the chlorpromazine pigmentation. The incidence of hyperpigmentation caused by chlorpromazine and related phenothiazines has been calculated to 3.4% during long-term therapy (1). The corresponding figure after amiodarone is probably 2% (10). The 7 methacycline patients belong to a material of about 250 patients similarly treated on the same indications, which leaves an approximate incidence of 3%.

It is difficult to evaluate the clinical importance of the pigment deposits in skin and eyes. At present, the pigmentation appears as a conspicuous cosmetic damage not violating ocular or cutaneous function. Because of the deep storage and adherence to the connective tissue of the pathologic pigment, it does not seem attainable for topical therapy and the prognosis with regard to healing should be guarded.

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H. Möller, M.D.
Department of Dermatology
Malmö General Hospital
S-214 01 Malmö
Sweden