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Ocular Pigmentation, Extrapyramidal Symptoms and Phenothiazine Dosage

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Oculo-cutaneous pigmentation has often been reported (*Brit. med. J.*, 1967) in patients receiving heavy doses of phenothiazines. This paper sets out to investigate, (*a*) the incidence of ocular pigmentation in such patients; (*b*) whether the measures suggested by Valentine and Jardine (1966) for minimizing this complication are effective; (*c*) the relationship of ocular pigmentation to extrapyramidal symptoms (and hence whether the pigmentation can be regarded as a sign of brain damage).

Patients and Method

A hundred patients who had had heavy or prolonged phenothiazine medication or who were showing extrapyramidal symptoms were examined ophthalmologically. Of these 97 were co-operative enough to include in the final series.

The method of examination in every case was as follows: external examination was carried out by naked eye, corneal loupe and slit lamp. Visual fields were tested by confrontation and any abnormal case was checked by perimetry. A detailed examination of the lens and fundus was carried out after mydriasis. A refraction was performed and glasses prescribed where necessary. The pressure was assessed digitally before and after mydriasis. Two suspected cases of glaucoma were found and subsequently investigated.

Chlorpromazine was the main drug recorded in 93 cases: other phenothiazines given were converted to chlorpromazine equivalents by a potency factor.

Results

1. *Pigmentation*

(*a*) *Occurrence.* Abnormal pigmentation was not seen in the *skin* of the face, eyelids or hands, but was observed in the *eyes* of 22 out of the 97 cases in the following sites (in eight cases only unilaterally):

Retina only	1
Lens only	7
Lens and cornea	12
Lens and conjunctiva	1
Lens, cornea and conjunctiva	1
	22

(*b*) *Appearances.* In the two cases with conjunctival pigmentation there were yellow granules scattered over the bulbar conjunctiva, mainly in the area of the palpebral fissure. Corneal pigmentation was only observed in the posterior part of the stroma, Descemet's membrane and endothelium; this was yellow or golden brown and appeared granular. Pigment in the lens was confined to the anterior lens capsule, being particularly dense in the central (pupillary) area. The retinal pigmentation appeared stippled and was only seen in the equatorial region of the fundus.

A fairly high degree of slit lamp magnification was essential for the accurate observation of the conjunctival, corneal and lenticular deposits. Pigmentation of the conjunctiva and retina was found to be rare. This may well be due to the difficulty in the differential diagnosis between normal pigmentation and the early stages of pigmentation due to chlorpromazine.

(*c*) *Age.* Pigmentation occurred significantly more often in patients over sixty than in those below that age.

(*d*) *Vision.* No visual impairment was found to be associated with pigmentation.

2. Phenothiazine Dosage

The *occurrence* of pigmentation was considered against phenothiazine dosage in four respects.

(*a*) *Total dose of drug prescribed.* On the whole pigmentation occurred more with increasing dosage, though the trend did not reach statistical significance. Thus, with a total dose of over 600 gm. chlorpromazine pigmentation was twice as common as with dosage below this figure. A third of the patients who had received over 600 gm. of drug had some pigmentation. The trend suggested that pigmentation can be expected in half the patients who have had 1,000 gm. or more of drug.

(*b*) *Highest daily dose of drug ever prescribed.* In this sample over a third of the patients who had had a highest-ever daily dose of over 600 mg. per day showed pigmentation, differing significantly from those who had had under 600 mg. per day.

(*c*) *Number of years on drugs.* Only two of the 22 patients showing pigmentation had had their drugs for less than three years but this proportion was no different from that in the patients showing none.

(*d*) *Largest total dose prescribed in any one year.* More than a third of those patients receiving in any one year over 200 gm. of drug showed pigmentation, the difference between them and those receiving under 200 gm. being significant.

The degree of pigmentation showed no relationship to drug dosage as measured above, but it should be remarked that the degree of pigmentation in this sample did not reach the severer degrees described in such heavy-dosage series as that of Barsa *et al* (1965).

3. Protective factors during drug treatment

Valentine and Jardine (1966) suggest the following factors as possibly protective against ocular complications during phenothiazine therapy:

(1) Avoidance of continuous high dosage and reduction of medication at all times to the minimum required for control of symptoms.
(2) Change from one phenothiazine to another.
(3) Use of combinations of preparations.
(4) Intervals of treatment by non-phenothiazine preparations.

We could not find evidence that the last three measures reduced pigmentation. There was a trend (not significant) showing that if the dose was halved once in each year pigmentation was less, which supports their first suggestion.

4. Brain Damage

A quarter of the patients examined showed extrapyramidal symptoms such as Parkinsonism, akathisia, oral dyskinesia and (in two cases) persistent grosser dyskinesias extending beyond the mouth, tongue and face. The two patients mentioned showed no pigmentation, and in general no association was found between extrapyramidal symptoms and pigmentation. Only at the extremes of dosage was any relationship seen between the total dosage of drug prescribed and the occurrence of extrapyramidal symptoms.

No statistical association was found between leucotomy and pigmentation or extrapyramidal symptoms but one patient, who had received only a small total dose of trifluoperazine and who had had a surgically too drastic leucotomy, had heavy ocular pigmentation and some oral dyskinesia.

Discussion

1. Critical Dosage for Ocular Pigmentation

The bare relationship between drug administration and pigmentation was established in reports of patients on really heavy dosage, e.g. Greiner and Berry (1964), Zelickson and Zeller (1964), Wetterholm, Snow and Winter (1965), and in Britain, by Cairns, Capoore and Gregory (1965). The incidence of pigmentation has varied between 20 to 39 per cent. in different series (*Brit. med. J.*, 1967). Large surveys have shown the degree of pigmentation to be proportional to the drug/years, e.g. Barsa, Newton and Saunders (1965), and to total dosage and maximum daily dosage (Barnes and Cameron, 1966).

Siddall (1965) gave the critical dose of chlorpromazine for causing choroidoretinopathy as 2,400 mg. per day for 24 months, and for causing ocular pigmentation as 800 mg. per day for 20 months. Moderate dosage schedules do

not touch these levels and with such schedules there are always some patients who resist pigmentation (Bock and Swain, 1963), even at the higher dosage levels (Galbraith, Gibson, Crock and Pearce, 1966). At the other end of the scale, DeLong, Poley and McFarlane (1965) considered that patients taking less than 500 mg. a day escaped pigmentation. This is now found not to be true (Barsa *et al.*, 1965; Galbraith *et al.*, 1966; Barnes and Cameron, 1966): some patients are found to have pigmentation after quite small doses or only a year or two of treatment. Clinicians using levels of dosage customary in Britain will not generally be concerned with critical figures for pigmentation at the highest levels of drug dosage, nor with figures like Siddall's involving a time factor of less than a couple of years, because they will often be wanting to continue phenothiazines with reasonable safety almost indefinitely until better remedies are found.

Surveys of patients treated on moderate-dose schedules produce less clear cut relationships between drug dose and pigmentation than the heavy-dose surveys. Thus, Mathalone, in the only large British survey published (1965, 1967), could only say "there is some indication that patients who have had a large amount of drug are more likely to be affected". Our findings confirm his. Thus, he found that of his patients taking 300 mg. chlorpromazine per day for more than two years 36 per cent. had pigmentation; we found 29 per cent. Of those taking less than 300 mg. per day for over two years he found 14 per cent.; we found 15 per cent. Most of the affected patients in both series had been on the drug for several years. The 15 patients of Valentine and Jardine (1966) had been on necessarily heavy phenothiazine dosage (all over 600 gm. total; median nearly 1,000 gm.); only one had pigmentation. It is not clear whether they consider that any of their four possibly protective factors did actually reduce the incidence of pigmentation in their cases or whether they were merely offering them as suggestions to be tested. Margolis and Goble (1965) consider that all the phenothiazines have a cumulative effect and that changes and combinations are therefore not protective. This view is consistent with our findings. Everyone agrees that minimizing the dose of drugs reduces pigmentation.

2. Pigmentation and Harm

Most authors so far find little or no evidence of visual damage from the ocular effects of the drug, so that it can be said (*Brit. med. J.*, 1967) that in this respect "the benefits of treatment outweigh its disadvantages", though the possibility of phenothiazines causing death (or damage) by deposition in internal organs has not yet been fully evaluated. Margolis and Goble (1965) in fact used as one criterion of selection of the 31 patients they examined (in eight of whom there was pigmentation) their judgment that the drugs were being vital in maintaining a social remission.

Our own failure to show any correlation between pigmentation and extrapyramidal symptoms, so far as any negative finding can go, suggests that the ocular pigmentation is not a special sign of brain damage from these drugs.

Summary

Ninety-seven patients, many of whom had extrapyramidal symptoms, and most of whom had received phenothiazines in large doses over several years, were examined for ocular pigmentation, which was found in 22 patients. The incidence was roughly in proportion to the amount of drug received so that about a third showed pigmentation who had, (*a*) received a total 600 gm. of chlorpromazine or equivalent, or (*b*) ever had a daily dose of 600 mg. or (*c*) had a total of 200 gm. in any one year.

Little confirmation was found of the efficacy of the methods which have been suggested for protecting patients on phenothiazines from pigmentation, apart from keeping down the dose.

No link was shown between ocular pigmentation and extrapyramidal symptoms generally or dyskinesia in particular. This study does not therefore offer its indirect support to the idea that drug-induced cerebral damage is due to pigment deposits in the brain. Nor does it seem that routine ophthalmological examination would help to warn of impending cerebral damage by phenothiazines.

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