OCULAR MELANOSIS WITH SPECIAL REFERENCE TO CHLORPROMAZINE*†

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Causes of Melanosis other than Chlorpromazine

THE pathological deposition of melanin is rarely seen in the tissues of the eye. Normally, small collections of melanin are sometimes seen in the eyes of Caucasians where the ciliary vessels pierce the sclera near the limbus. Larger collections of melanocytes form a benign naevus which may invade the cornea, or there may be multiple collections of melanocytes scattered throughout the conjunctiva forming the condition termed by Reese (1951) "precancerous melanosis". Melanin deposits around the limbus can also be seen in Addison's disease.

Deposits of melanin derived from the iris and ciliary body and transmitted by convection currents in the anterior and posterior chambers are commonly seen on the endothelial surface of the cornea in old age, in cases of diabetes, and after eye operations. Here they adhere to the lower part of the corneal endothelium, usually in a characteristic shape (Krukenberg's spindle).

Brown lines on the lower corneal surface, which would appear to be due to melanin but which are in fact due to haemosiderin, are found in many normal middle-aged and elderly persons (Hudson-Stähli line). They are also noticed in association with corneal scars and at the head of pterygia. Similar brownish-olive lines in the lower half of the cornea have been described as a toxic manifestation of chloroquine therapy (Smith, 1962); it is not known if this is related to melanin deposition. In an autopsy case, it was reported that the basal layer of the corneal epithelium was hyperplastic and contained leptochromatic nuclei with a prominent basal membrane, but melanocytes were not mentioned (Lloyd and Hiltz, 1965).

A brown olive-green deposit of copper in the deeper corneal layers, resembling an arcus senilis, is seen in hepato-lenticular degeneration (Wilson's disease) and following the retention of copper fragments in the eye after injury, *e.g.* from an exploding percussion cap (Kayser-Fleischer ring). In both these conditions the copper may also be deposited on the anterior capsule of the lens behind the pupil where it forms a 3–4 mm. central green opacity with radiating arms resembling a flower. Such an opacity is commonly described as a sunflower cataract, but, while it may resemble a sunflower, it is not strictly a cataract. A similar-shaped deposit of melanin in the anterior capsule and cortex of the lens will be presently described as an early manifestation of chlorpromazine toxicity. Here, however, the corneal deposits do not resemble the Kayser-Fleischer ring or the pigmentation produced by chloroquine toxicity, but consist of granules of melanin scattered diffusely through the cornea and closely associated with Descemet's membrane.

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Two other rare forms of pigmentation of the sclera may be mentioned. In alkaptonuria there is an accumulation of homogentisic acid in the tissues, shown clinically in the eye in the form of slatey-blue wedge-shaped areas in the sclera close to the limbus in the interpalpebral line.

In Gaucher's disease also wedge-shaped pigmented areas may be present near the limbus in the interpalpebral line, but the pigment is brown and not slatey-blue as in alkaptonuria. In this respect it resembles the conjunctival pigmentation which will presently be described as occurring sometimes in chlorpromazine toxicity.

The combination of skin pigmentation, corneal deposits, and retinal pigmentation is now known to result from excessive dosage by the antimalarial drugs mepacrine (atebrin, quinacrine) and chloroquine. The first reports, which appeared in 1946, referred to a darkening of the skin produced by mepacrine which had been used for some years as a malarial suppressant (Lutterloh and Shallenberger, 1946; Sugar and Waddell, 1946). Later reports refer to the corneal and retinal changes and skin pigmentation produced by prolonged dosage with chloroquine (Lloyd and Hiltz, 1965). This drug, which was used as an antimalarial in the second world war is now used for the long-term treatment of systemic lupus erythematosus and rheumatoid arthritis. The pigmentation following chloroquine described by Tuffanelli, Abraham, and Dubois (1963), was not restricted to the outside skin (*e.g.* face and legs) but was also mucosal (palatal and subungual). There was also de-pigmentation of the roots of the hair and eyebrows. Histologically these authors found the pigmentation to be due to the deposition of yellowish dark-brown granules in the cells of the deeper layers of the dermis.

The corneal changes, which are reversible, are seen as thin brown olive-green lines. They are sub-epithelial and are found in the lower half of the cornea. Under high slit-lamp magnification they have a finely granular crystalline appearance. Since they resemble the Hudson-Stähli line which commonly occurs in the normal corneae of middle-aged and elderly persons, it is well for patients who are about to undergo prolonged chloroquine therapy to have their corneae carefully examined beforehand by an ophthalmologist.

The retinal changes produced by chloroquine are severe and irreversible. Characteristic pigmentation of the macula produces the so-called bull's eye appearance and is responsible for the decreased visual acuity and central and para-central scotomata. Equatorial pigmentation and narrowing of the retinal vessels produce the later constriction of the peripheral fields (Hobbs, Eadie, and Somerville (1961).

In 1952, a precursor of chlorpromazine, piper-chlorphenazine (NP-207), was used in the psychiatric department of Basel University (Baumann, 1957); of the fifteen patients examined the majority were found to have abnormal adaptation, six showed some abnormality in the fields of vision, and in one the vision was very much reduced because of extensive macular pigmentation.

Chlorpromazine Melanosis

Thus, when chlorpromazine (Largactil) was introduced to the Basel University Psychiatric Clinic early in 1953, a very careful watch was kept for eye complications. Baumann (1957) examined 35 co-operative schizophrenic patients. The examination

included central vision (near and distance), dark adaptation, quantitative light perimetry using the Goldmann perimeter, central colour vision, ophthalmoscopic appearance of the fundus after mydriasis, keratometer readings, tests for paracentral scotomata, convergence, corneal sensitivity, slit-lamp examination of the media, tonometry, and pupillary reactions. The duration of chlorpromazine therapy in these cases ranged from 6 months to 2½ years and the total dosage from 25 to 248 g. However, in no case could Baumann find unequivocal evidence of chlorpromazine toxicity. Bock and Swain (1963) observed what we now know to be typical chlorpromazine lens changes but did not attach any special significance to them. They examined 27 patients in whom the total dose of chlorpromazine ranged from 153·7 to 815·3 g., and found no ocular abnormalities; in one patient they saw powdery white spots on the anterior capsule of the lens in the central pupillary area, but missed their significance.

Chlorpromazine early found use as a vermicide in sheep and cattle and as an insecticide against the codlin moth which attacks apples. In 1940 photosensitive and phototoxic skin reactions were reported in orchard workers (Rees, 1962), with a growing list of general toxic reactions which included circulatory disturbances, tachycardia, drowsiness, nystagmus, facial pareses, amenorrhoea, impotence, polyuria, constipation, dryness of the mouth, icterus, agranulocytosis, and extra-pyramidal reactions. In comparison with the value of the drug, however, these were thought to be of minor significance. Ayd (1963) confidently stated that "on the basis of 10 years' world-wide clinical experience with chlorpromazine given to millions of patients it can be forthrightly stated that this psycho-pharmaceutical drug has passed the test of time".

However, all was not as rosy as Ayd thought, and in March of the following year Greiner and Berry (1964) (Essondale, B.C., lat. 49° 11' N) described for the first time the oculo-cutaneous changes produced by chlorpromazine therapy. The corneal changes consisted of yellow-white granules lying in the posterior half of the cornea, and less densely concentrated in the periphery than in the centre. The lens opacity appeared as a dark-brown irregular stellate or cocklebur-shaped opacity with a dense central area and radiating branches and was situated in the anterior sub-capsular pole. It is of interest that these authors did not note any ocular changes in any male patient or in any non-pigmented female patient.

A little later in the same year Greiner and Nicolson (1964) showed, in twelve patients who died unexpectedly while taking chlorpromazine, that there was widespread deposition of melanin in many internal organs, including the liver, heart, intestines, lung, kidney, thyroid, adrenal, pituitary, spleen, and lymph nodes. Brown pigment deposition in the cornea and lens was noticed in two patients.

Both pigmentation of the peripheral retina and depigmentation at the macula were noticed by Zelickson and Zeller (1964) (Minneapolis, lat. 44° 58' N) in three of eight facially-pigmented female psychiatric patients. In one who wore glasses constantly, they noticed that the facial skin behind the rim was not pigmented. They concluded therefore that at least ultra-violet wavelengths greater than 3,200 Å must be involved. They did not comment on any corneal or lens changes.

Fine dust-like corneal deposits near Descemet's membrane were described by Feldman and Frierson (1964) (Topeka, Kansas, lat. 39° N) in one patient. There

was skin pigmentation in the exposed areas but no anterior capsular lens deposits.

Cairns, Capoor, and Gregory (1965) (Bexley, England, lat. $51^{\circ} 28' N$) reported skin and ocular changes, similar to those observed by Greiner and Berry, in four female patients from the Bexley Mental Hospital in whom the total dosage of chlorpromazine ranged from 1,102 to 2,427 g.

A report from Philadelphia (lat. $39^{\circ} 50' N$) by DeLong, Poley, and McFarlane (1965) concerns 49 patients in the Norristown State Mental Hospital who were found to have typical lens changes; 24 had corneal changes and in most cases there was a strong correlation between the signs of toxicity and the total dosage. The latter is also obviously related to the duration of therapy and the daily dose. Thus 45 of their patients had received a daily dose of at least 500 mg. chlorpromazine for 3 years.

Clinical Material

The following report concerns nineteen female and nine male patients with either lens or lens and corneal changes which could reasonably be ascribed to chlorpromazine toxicity. They do not represent the total number of patients affected in the 2,000 bed Brisbane Special Mental Hospital, but only those that could be conveniently examined. The predominance of female patients is arbitrary, as more females than males were initially examined for eye changes.

The patients were divided into three groups according to the density of corneal and lens pigmentation. The most heavily affected (six females) had signs in both cornea and lens which were easily recognizable macroscopically with side illumination by a bright pencil torch. The moderately affected group (nine females, five males) had in general less well marked corneal and lens changes. The third group (four females, four males) had minimal lens changes which could be seen macroscopically only by very careful observation. No patient was observed with corneal changes only, although many were seen with lens changes only.

Conjunctival Pigmentation

This was seen only in those patients with the heaviest skin pigmentation; it consisted of brown triangular areas in the interpalpebral line, the bases of the triangles being situated at the limbus (Fig. 1). The pigmentation resembled that seen in conjunctival naevi and was fairly evenly distributed over the triangular area.

FIG. 1.—Conjunctival pigmentation due to chlorpromazine.

Corneal Pigmentation

This was found only in the first two groups and under the slit lamp ($\times 40$) was seen to consist of myriads of minute, discrete, brown spots, mainly restricted to Descemet's membrane (Fig. 2a). In the more severely affected patients, however, there were also larger, white flocculent particles in Bowman's membrane, with a sparse distribution in the corneal stroma. The peripheral cornea was not as densely affected as the central area and there was a noticeable lack of pigmentation in the cornea above where it is normally covered by the upper lid. When viewed by strong side light, the cornea of the most heavily affected patients presented the appearance of a fine snow storm. In those patients in whom the corneal pigmentation was less dense, slit-lamp observation was necessary to render it visible.

Even in those patients with marked conjunctival and corneal pigmentation, no photo-allergic symptoms were seen. The eyes were quiet with no lacrimation, photophobia, or injection. Indeed, no visual complaints of any sort were volunteered by any of the more intelligent patients.

This is in contrast to veterinary experience, where phenothiazine has been used as an anthelmintic since 1941; in that year in New Zealand (Wallaceville, lat. $41^{\circ} 06' S$) severe keratitis was reported to occur in young cattle 36 hours after dosing with phenothiazine. It was associated with exposure to bright light and was not seen if the eyes were occluded. Recovery took place spontaneously after one week, but in the severer cases there was residual corneal scarring and vascularization. A similar reaction after phenothiazine therapy has been reported in swine, sheep, goats, and pheasants (Enzie and Whitmore, 1953).

FIG. 2(a).—Artist's impression of the corneal and lens changes due to chlorpromazine in slit-lamp section and in surface view. In the slit lamp the corneal opacities appear dark brown and grey and the lens opacities white (line medium).

FIG. 2(b).—Photograph of a chlorpromazine-induced lens opacity (retouched).

Lens Pigmentation (Fig. 2b)

This was present in every patient and in the more prominent cases was seen as a white star-shaped area restricted to the pupillary area. In the less affected cases it was difficult to see macroscopically and was either circular or had small projections resembling a cockle-burr.

Mydriasis allowed the star to be studied in greater detail with the slit lamp. In the majority of cases it consisted of four to six radiating spokes often connected by a denser central circular spot. Sometimes there were two central spots and occasionally the spot was eccentrically placed and irregular in shape. Even in cases with faint lens opacities, a central denser spot could often be seen.

The spokes themselves were seen to have a denser central axis which often branched into two at the end. Occasionally the appearance resembled that of mild traumatic cataract with long, pale, feathery spokes.

The high power of the slit lamp showed that the star consisted of minute, discreet, white particles which were more densely accumulated in the central axes. The deposits were seen by optical section to be restricted to the anterior lens capsule, epithelium, and superficial cortex, except in the central axis where they dipped slightly into the deeper lens substance. The pigment is thus seen to have been deposited mainly in the superficial cortical sutures of the lens.

Other Changes

Lid Pigmentation.—This was found only in association with generalized skin pigmentation (Fig. 3a) and showed the same dusky slate-blue colour (Fig. 3b).

FIG. 3(a).—Generalized skin pigmentation in a severely-affected case.

FIG. 3(b).—Facial pigmentation in the patient illustrated in Fig. 3(a).

Pupils.—These were of normal diameter and shape and contracted briskly to light and accommodation. However, patients with dense corneal and lens pigmentation showed poor mydriasis even with 2 per cent. cyclopentolate.

Visual Acuity.—Unfortunately, the patients with the most marked lens opacities had the most severe mental changes and were not amenable to subjective refraction. Six of the

FIG. 4.—Conjunctival biopsy, showing pigment in the basal cells and in macrophages near the subconjunctival vessels. Haematoxylin and eosin. $\times 266$.

remaining cases with moderate and minimal lens changes were chosen arbitrarily and refracted. In each case no difficulty was experienced in bringing their corrected vision to normal or better for both distance and near.

Congenital cases of sutural cataract, where the Y sutures of the foetal nucleus are densely affected by the deposition of an abnormal substance, do not show any reduction in visual acuity due to this cause. Also, in the present series, the deposition of pigment is well anterior to the nodal point, so that any reduction in vision is made more unlikely.

Fundi.—No change in blood vessels, disc, retina, or macula were seen.

Pathology.—None of the cases in this series has come to autopsy. A conjunctival biopsy of a pigmented area revealed changes similar to those in the skin. Pigment was present in the basal cells and in macrophages which were often clustered around the subconjunctival vessels (Fig. 4).

The eye changes described above were found in some patients who had ceased chlorpromazine therapy 6 years ago.

Photosensitivity

A wide variety of substances is known to produce photosensitive reactions, amongst which may be mentioned porphyrins, sulphonamides, antihistamines, griseofulvin, and thiazines. These substances fluoresce in ultraviolet light; *i.e.* they absorb a quantum of light energy for a relatively long time (10^{-7} sec.) and emit a different wavelength. The captured energy stimulates tyrosinase activity and hence ultimately melanin production. Spectrophotometric measurements have demonstrated another pigment in the skin of affected patients (Satanove, 1965). This may be responsible for the purplish discoloration and is possibly a derivative of chlorpromazine.

The phototoxic skin pigmentation was first noticed in the summer months in high latitudes and is most likely related to the increased ultraviolet content of the atmosphere at this time. Thus the first oculo-cutaneous changes were reported from Essondale, British Columbia (lat. $49^{\circ} 12' N$), followed by Minneapolis (lat. $44^{\circ} 58' N$) and Bexley, England (lat. $57^{\circ} 28' N$). If ultraviolet light is regarded as the photosensitizing agent, one would have expected the first reports to have come from tropical cities. Certainly in Brisbane (lat. $27^{\circ} 30' S$) there are many patients with oculo-cutaneous pigmentation, but they have been overlooked and this may be the explanation for the lack of reports from other tropical cities.

The fact that skin and eye changes can occur at high latitudes suggests that it is the

longer ultraviolet wavelength that is responsible. One patient who had worn glasses constantly was reported with pigmentation of the face behind the glasses (Zelickson and Zeller, 1964). Since spectacle crown glass cuts off light below 3,200 Å, wavelengths higher than this must be effective in producing skin changes.

TABLE I
CORNEAL AND LENS ABSORPTION OF
ULTRAVIOLET LIGHT IN THE RABBIT EYE
(KINSEY, 1948)

Wavelength(Å)	Percentage Absorption	
	Cornea	Lens
2,900	100	—
3,200	40	95
3,500	30	95
3,700	25	85
4,000	20	30

Only those wavelengths of light which are absorbed can exert any affect (Grotthus-Draper law). At 3,700 Å, the lens absorbs 85 per cent. of the light falling on it (approx. 75 per cent. of the incident light) but at 4,000 Å only 30 per cent. Since the lens is often affected alone whereas corneal changes always occur in association with lens changes, it would appear that 3,700 Å represents the upper limit of the ultraviolet light responsible for the ocular effects (Table I).

The greater frequency of lens changes is no doubt related to the greater percentage of absorption of ultraviolet light by the lens of wavelengths up to 3,700 Å. (Wavelengths as short as 2,900 Å are found only at high altitudes at the equator.)

Significant amounts of ultraviolet light of this order filter through to the earth on cloudless days at high latitudes. At lat. 50° N, the sun is at an altitude of 40° for 150 days of the year, and although the increased air mass does restrict ultraviolet radiation, this effect is exerted mainly on those wavelengths below 3,200 Å (Koller, 1952).

The reported absence of retinal lesions may be explained by the fact that very little light below 3,700 Å reaches the retina. Since the iris absorbs most of the light falling on it, the lighter irides at least would be expected to show colour change, but this was not observed. Perhaps even in the blue iris the natural pigment is sufficient to mask any further increase.

It finally remains to attempt to explain the occurrence of the pigmentation in Descemet's membrane and the anterior lens capsule.

Although light from the sun (which subtends a small angle) may be focused on the retina and may produce a macular burn such as eclipse blindness, that from the sky (which subtends a large angle) is focused on the anterior part of the eye. In doing so it may be concentrated in the pupillary region several million times (Duke-Elder, 1954) (Fig. 5a, b, opposite).

The ultraviolet light because of its short wavelengths is refracted most and hence the anterior lens capsule rather than the posterior capsule is predominantly affected. The concentration of light falling on the cornea is seen to be only a fraction of that falling on the anterior lens capsule. When, in addition, the decreased absorption of ultraviolet light by the cornea is taken into account, it is easy to see why the lens changes are a sensitive sign of chlorpromazine toxicity.

FIG. 5(a).—A small point light source is focused on the retina.

FIG. 5(b).—A light source subtending a large angle is concentrated on the anterior segment, especially the lens.

Relationship of Lens and Corneal Changes to Chlorpromazine Dose

In trying to assess any relationship between lens and corneal changes and total chlorpromazine dosage, it must be remembered that the latter is but one factor to be considered. Assuming absorption and distribution of the drug to be the same in all cases, the other important factor is the time of exposure to the relevant ultraviolet rays. This is probably greater amongst the men, who work more often outside in the yards where they are exposed to both direct and indirect ultraviolet light. Even here there would be individual differences due to different types of head-gear, etc. Some of the women spend much time out of doors in both winter and summer, and even while sitting on a covered verandah, significant amounts of ultraviolet light can be received from indirect radiation. It is assumed in the analysis that follows that both men and women were exposed to similar amounts of ultraviolet light.

Greater numbers of women than men were examined since there was less easy access to the male wards.

Most patients had also received other phenothiazine derivations or related compounds, either concomitantly with chlorpromazine or separately, *e.g.* thioridazine, trifluoperazine, triflupromazine, amitriptyline, and imipramine. However, in those patients examined, chlorpromazine was the only drug constantly used and much more of it had been taken than of any other compound. One therefore feels justified in concluding that the signs observed are most likely due to chlorpromazine alone.

The overall eye changes were graded: marked (3), moderate (2), minimal (1), and nil, and varied with the severity or otherwise of the accompanying lens and corneal changes. The lens changes were graded similarly, since it was easy to separate them into four groups by slit-lamp observation. The corneal changes could be classified only as marked, moderate, and nil, since there was not the same degree of gradation as with the lens changes. By this method the grading was arrived at which is described on p. 304

Six women had grade 3 lens and corneal changes and hence overall grade 3 eye changes. Five men and nine women in the overall grade 2 eye change group had

mainly moderate lens and corneal changes, but some had moderate lens changes and no corneal changes while others had minimal changes in both lens and cornea. Four men and four women with minimal lens changes and no corneal changes were placed in overall grade 1. Finally there were 45 women on doses from 1.2 to 1,152 g. with neither lens nor corneal changes.

Results

(1) Effect of Total Dosage on Overall Grading

Here, the mean of the total dosage for Grade 1 is significantly lower than that for Grades 2 and 3 ($P = 0.0001$). However, as pointed out above, the effectivity of the total dosage may be modified by other factors, especially the total exposure to ultra-violet light.

(2) Effect of Total Dosage on Lens Changes (Table II)

Since the greatest total dose of chlorpromazine used was 1,500 g., 750 g. was chosen as a suitable division between high and low dosage. Because of the small numbers in the four groups, the no change and minimal, and the moderate and marked, were combined.

TABLE II
TOTAL DOSAGE AND SEVERITY OF LENS CHANGES

Total Dosage (g.)	Nil and Minimal	Moderate and Marked	Total
Below 750	1	9	10
Above 750	57	7	64
Total	58	16	74

On testing the non-association hypothesis, the probability of obtaining the above and less likely configurations is 9×10^{-7} , i.e. extremely small.

As expected, an extremely high association was found between total dosage and lens change. One female patient showed moderate lens changes with a total dose of only 99 g. chlorpromazine (equivalent to 150 mg./day for almost 2 years).

(3) Effect of Total Dose on Lens and Corneal Changes (Table III)

Again a high association was found between total dosage and ocular changes.

TABLE III
TOTAL DOSAGE AND SEVERITY OF LENS AND CORNEAL CHANGES

Total Dosage (g.)	Nil and Minimal	Moderate and Marked	Total
Below 750	3	8	11
Above 750	54	8	62
Total	57	16	73

On the hypothesis of no-association between the total dose and lens and corneal change, the probability of this and less likely configurations is $P = 0.000018$, which is again an extremely high association.

Summary

- (1) Ocular melanosis in general, and that due to chlorpromazine, is discussed.
- (2) Lens changes were found with smaller total doses of chlorpromazine than previously described.

- (3) It is thought that ultraviolet rays of wavelength 3,200–3,700 Å are responsible for the skin and eye pigmentation.
- (4) Eye changes were found to be present in some patients who had ceased chlorpromazine therapy 6 years before.
- (5) Men and women (including aboriginals) were affected equally.
- (6) There was an extremely high association between eye changes and the total dosage of chlorpromazine.

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REFERENCES

- AYD, F. J. (1963). *J. Amer. med. Ass.*, **184**, 51.
 BAUMANN, H. (1957). *Klin. Mbl. Augenheilk.*, **130**, 769.
 BOCK, R., and SWAIN, J. (1963). *Amer. J. Ophthalm.*, **56**, 808.
 CAIRNS, R. J., CAPOORE, H. S., and GREGORY, I. D. R. (1965). *Lancet*, **1**, 239.
 DELONG, S. L., POLEY, B. J., and MCFARLANE, J. R. (1965). *Arch. Ophthalm. (Chicago)*, **73**, 611.
 DUKE-ELDER, S. (1954). "Text-book of Ophthalmology", vol. 6, p. 6463. Kimpton, London.
 ENZIE, F. D., and WHITMORE, G. E. (1953). *J. Amer. vet. med. Ass.*, **123**, 237.
 FELDMAN, P. E., and FRIERSON, B. D. (1964). *Amer. J. Psychiat.*, **121**, 187.
 GREINER, A. C., and BERRY, K. (1964). *Canad. med. Ass. J.*, **90**, 663.
 ——— and NICOLSON, G. A. (1964). *Ibid.*, **91**, 627.
 HOBBS, H. E., EADIE, S. P., and SOMERVILLE, F. (1961). *Brit. J. Ophthalm.*, **45**, 284.
 KINSEY, V. E. (1948). *Arch. Ophthalm. (Chicago)*, **39**, 508.
 KOLLER, L. R. (1952). "Ultraviolet Radiation", p. 111. Wiley, New York.
 LLOYD, L. A., and HILTZ, J. W. (1965). *Canad. med. Ass. J.*, **92**, 508.
 LUTTERLOH, C. H., and SHALLENBERGER, P. L. (1946). *Arch. Derm. Syph. (Chicago)*, **53**, 349.
 REES, R. B. (1962). "Dermatoses due to Environmental and Physical Factors". Thomas, Springfield, Ill.
 REESE, A. B. (1951). "Tumors of the Eye", 1st ed., chap. 7, p. 198; pp. 330–341. Hoeber, New York.
 SATANOVE, A. (1965). *J. Amer. med. Ass.*, **191**, 263.
 SMITH, J. L. (1962). *Arch. Ophthalm. (Chicago)*, **68**, 186.
 SUGAR, H. S., and WADDELL, W. W. (1946). *Ill. med. J.*, **89**, 234.
 TUFFANELLI, D., ABRAHAM, R. K., and DUBOIS, E. I. (1963). *Arch. Derm. (Chicago)*, **88**, 419.
 ZELICKSON, A. S., and ZELLER, H. C. (1964). *J. Amer. med. Ass.*, **188**, 394.

APPENDIX

GENERIC NAMES	TRADE NAMES
chlorpromazine	Largactil
perphenazine	Trilafon
prochlorperazine	Stemetil
thioridazine	Melleril
trifluoperazine	Stelazine
amitriptyline	Tryptanol
imipramine	Tofranil
triflupromazine	Siquil

Neuro-ophthalmology. (Third Symposium of the University of Miami and the Bascom Palmer Eye Institute). Edited by J. L. SMITH. 1967. Pp. 349, 200 figs, refs. Mosby, St. Louis; Kimpton, London. (£9 7s. 6d.)

This book is based on the contributions to the third symposium held at Miami Beach and upholds the standards set by the first symposium.

The theme reflects the current vogue in paediatric ophthalmology and this has resulted in some excellent chapters, among which is a stimulating exposition of current thought on the diffuse scleroses with a classification of the various forms of this condition. Apart from the paediatric aspect there are contributions on the extra-ocular muscles, pituitary ablation in diabetic retinopathy, and a first class anatomical and radiological study of the "sphenoid strut".

In the preface it is stated that there is no overlap with previous symposia. This is a claim that cannot be sustained with the inclusion of articles on Schiötz *versus* applanation tonometry, ocular clues to stroke mechanisms, and the inevitable chapters on syphilis.

Nevertheless this is an excellent book, with first class illustrations. The latter no doubt contribute to the price, and if this is so it seems a shame that there are reproductions of two radiographs of cases of absence of the corpus callosum, especially as there is no discussion of the clinical features of this condition and of recent experimental work about it. Despite the price of the book, the cost per page is less than last year, being just over 6d.

Trachoma: Prevention and Treatment. By G. BIETTI and G. H. WERNER. 1967. Pp. 227, 13 figs, 16 tables, refs. Thomas, Springfield, Ill. (\$11.50)

This monograph, written by a well-known ophthalmologist and an equally eminent virologist, is a survey of modern conceptions on trachoma. The first part deals with the bacteriology of the TRIC agents and their immunology. These have now been cultured in many laboratories throughout the world and it is generally agreed that a very similar or the same agent causes trachoma and inclusion conjunctivitis. The second part of the book describes the prophylaxis and treatment of trachoma. The hygienic methods of prophylaxis receive due attention and the difficulties of treatment by chemotherapeutic or antibiotic agents are fully discussed; it is concluded that the most effective plan is to combine long-acting oral sulphonamides with the administration of topical antibiotics, particularly the tetracyclines or erythromycin. Even when this treatment is practised with enthusiasm, however, a cure does not always follow owing to recurrent relapses and the existence of resistant cases. The value of vaccines can only yet be guessed; several types have now been tried but the period of observation has been short. Bietti advises that they could be recommended for healthy individuals particularly exposed to infection, to aid chemotherapeutic and antibiotic treatment, to prevent relapses in highly endemic areas, and as a prophylactic measure in young children in such areas. It can hardly be claimed that this advice is yet fully justified.

NOTES

VII YUGOSLAV CONGRESS OF OPHTHALMOLOGY

Vrnjačka Banja, October 2 to 5, 1967

The chief topics are the Causes of Blindness in Yugoslavia (main subject) and all problems regarding the cornea, uvea, and retinal ablation; there will also be free papers.

For accommodation apply to "Putnik" Travel Agency, Vrnjačka Banja (Congress fee: 100 new dinars).

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CORRIGENDUM

In the article by M. E. Cameron which appeared in the May issue (*Brit. J. Ophthalm.*, 1967, 51, 295), on p. 297, l. 14, please read:

Phenothiazine was first used as a vermicide in sheep and cattle, etc.