

Skin Pigmentation and Corneal and Lens Opacities with Prolonged Chlorpromazine Therapy

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SINCE the introduction of chlorpromazine in 1953 it has become one of the most prominent and widely used drugs in psychiatry. It was recently estimated¹ to have been the subject of some 10,000 publications and to have been used in 50,000,000 patients. In spite of its enthusiastic reception, the world medical literature contains many reports¹⁻¹¹ of its harmful side effects involving the cardiovascular, endocrine, secretory, dermatologic, renal, gastrointestinal, hematologic and central nervous systems.

The dermatologic complications which have been noted include generalized eruptions, photosensitivity and contact sensitivity. The skin manifestations reported herein do not resemble any of these and apparently have not been previously reported in the English literature.

In addition, a frequent associated finding of corneal and lens opacity was noted in the patients described in this study. While ocular complications of chlorpromazine therapy have not been previously reported, papilledema,¹² toxic amblyopia,¹³ retinitis¹⁴ and pigmentary retinopathy¹⁵ have all been observed with the use of related phenothiazines.

CLINICAL MATERIAL

Since 1954 many thousands of patients at the Crease Clinic and Provincial Mental Hospital have received large doses of chlorpromazine for the treatment of psychiatric illness of all forms.

Since 1959 a number of such patients have been noted to exhibit a peculiar pigmentation of exposed skin areas. This pigmentation was very marked in 21 patients and was present in varying degrees of lesser severity in another 49. Of the 21 markedly affected patients, 12 were noted to have grossly visible corneal and lens opacities which will be described further.

OBSERVATIONS

General

The two sets of complications to be described occurred in female patients only, 80% of whom were amenorrheic from the onset of their mental illness or from the onset of treatment with chlorpromazine, it being difficult to determine the exact date of onset in any of these cases. Their ages ranged from 25 to 62 years, averaging 43 years. All were of the Caucasian race.

ABSTRACT

Previously undescribed ocular and dermatologic complications of prolonged chlorpromazine therapy have been noted in 70 patients of a series of many thousands receiving similar therapy. All affected patients were women who had been receiving high doses of chlorpromazine, averaging 500 to 1500 mg. daily, for at least three to five years before the complications became apparent. Skin manifestations consisted of a peculiar purplish pigmentation of the skin of exposed areas of the face, neck and hands, characterized histologically by deposition of material with the staining properties of melanin in the superficial layers of the dermis, particularly in a perivascular distribution. Ocular complications consisted of granular opacity of the cornea and often of the lens as well, the latter producing a central stellate type of cataract.

All the affected patients had been receiving chlorpromazine for a minimum of three years prior to the onset of the skin discolouration and were on doses averaging 500 to 1500 mg. daily. Many of these patients were receiving other tranquilizers besides chlorpromazine but the findings to be described occurred only in patients receiving chlorpromazine, occurred in many patients who were receiving chlorpromazine alone, and did not seem to be related to any particular combination of chlorpromazine with any other drug.

Skin Manifestations

Pigmentation of the skin was found only on exposed areas of the face, neck and upper chest and occasionally on the dorsum of the hands and exposed parts of the lower legs. On the face it varied from a mild diffuse violaceous discolouration of the cheeks and nose in a butterfly distribution to a deep purplish-grey metallic colour of the entire face, with occasional sparing in facial wrinkles and in the deep cleft below the lower lip (Fig. 1). This colour was unlike a deep suntan and was quite distinctive. The discolouration often became first apparent in the summer but did not disappear in the winter, nor did it fade significantly upon cessation of drug treatment at least up to six months. There was no associated blistering of the skin nor were there any changes in skin texture.

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Skin biopsies were done in pigmented skin areas in six patients, in non-pigmented skin areas of pigmented patients in three cases, and in unaffected patients on prolonged high doses of chlorpromazine in three cases (one white male, one white female and one apparently unaffected Negro female).

In the affected skin areas the most pronounced finding was the presence of a marked accumulation of golden-brown finely granular pigment in plump cells situated mainly around capillaries in the superficial layers of the dermis. Occasionally they were also found lying free or in single cells in the superficial layers of the dermis just below the basal layer of the dermis (Fig. 2). The epidermis itself seemed unremarkable but there was an occasional suggestion of absence of the normal melanin in the basal layers of the epidermis overlying the most concentrated clumps of pigment in the dermis. With hematoxylin and eosin stain and with periodic acid-Schiff stain, the pigment was a golden-brown finely granular substance. It did not stain by the Gomori iron method. With Fontana's method for melanin the pigment was strongly positive, staining a dark black, and in fact it seemed more extensively present than with the routine stains. There was no inflammatory reaction.

In the affected patients, biopsies from clinically unaffected sites were also mildly abnormal and showed findings similar to those just described but not to the same degree.

No abnormalities were noted in biopsies from unaffected white females, the Negro female or the white male patient, all of whom had been on prolonged high doses of chlorpromazine.

Ocular Manifestations

In 12 of the severely pigmented 21 cases there was a peculiar hazy-brown pigmentation of the exposed sclera and cornea as well as a small central lens opacity. On ophthalmoscopic examination the



Fig. 1.—Note pigmentation of exposed areas of face, neck and dorsum of hands.

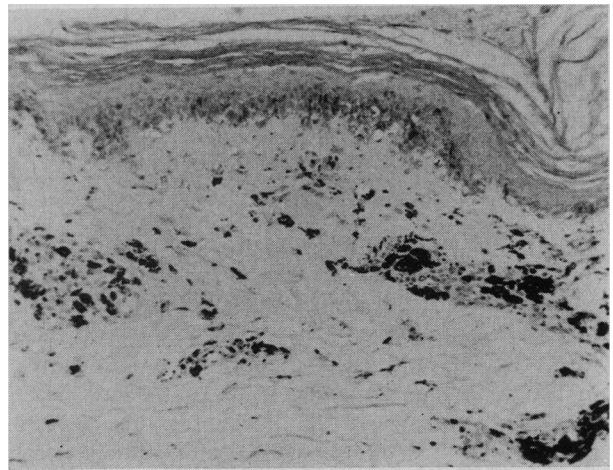


Fig. 2.—Skin from pigmented area of neck. Note deposits of pigment lying free in superficial dermis and more concentrated in perivascular aggregations. (Fontana stain, $\times 150$.)

lens opacity appeared as a dark brown, irregular, stellate or cocklebur-shaped opacity with a dense central area and radiating branches (Fig. 3).

Slit-lamp examination in two cases revealed the corneal lesion to be stromal in situation and to consist of yellowish-white granules mainly in the posterior one-half of the cornea, less densely concentrated in the peripheral cornea than in the centre. The lens opacity consisted of discrete yellow-white dots concentrated at the centre and having radiating arms, situated in the anterior subcapsular pole.

These changes have only recently been noted and it is too early to know the effect of drug withdrawal. These ocular changes were not noted in any of the non-pigmented female patients or in male patients on prolonged high doses of chlorpromazine.

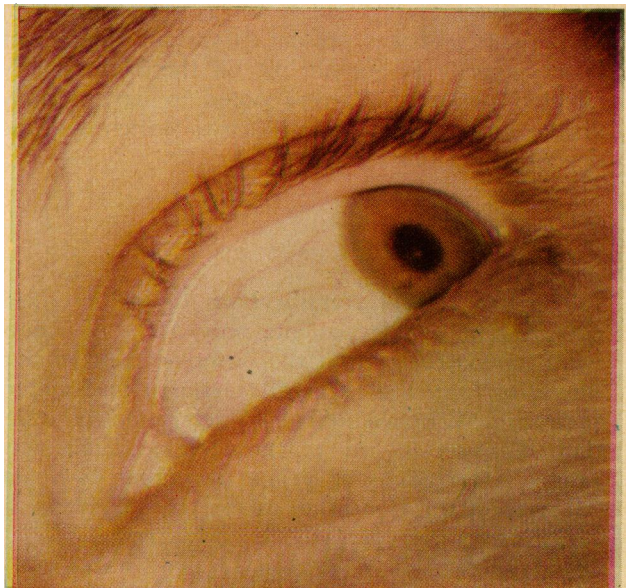


Fig. 3.—Note small central lens opacity.

DISCUSSION

The dermatologic and ocular signs herein described are apparently unique and seem most likely to be related to prolonged treatment with high doses of chlorpromazine. The presence of these findings in female patients only, as well as the fact that most of these women are amenorrhoeic, suggests that some endocrinologic factor may be partly responsible.

The distribution of the skin lesion clinically and its relation to exposure to sunlight suggest an element of photosensitivity, although the appearances are not characteristic.

The pigment seen on biopsy is probably melanin and is situated not in its normal basal epidermal situation but in the superficial dermis, and there is some suggestion that it may have dropped down from its normal position to be picked up by chromatophores in the dermis. The peculiar colour imparted to the skin by this deeply buried melanin is probably due to the fact that it must be seen through a greater thickness of tissue.¹⁶

The ocular complications of corneal and lens opacities are apparently also related to high doses of chlorpromazine over prolonged periods of time and also in some way to femaleness, as they have been found only in the group of patients described above. While cataracts are known to occur in certain metabolic conditions¹⁷ and as toxic reactions to the use of certain drugs,^{18, 19} they have not previously been reported with the use of chlorpromazine.

SUMMARY

A peculiar purplish-grey pigmentation of exposed areas of skin, often associated with corneal and lens

opacities, has been found in a number of female patients on prolonged high doses of chlorpromazine for various types of psychiatric illness. The skin pigmentation is probably due to the presence of perivascular deposits of melanin in the upper layers of the dermis. In the patients described, the use of this drug has apparently resulted in a disfiguring dermatosis and a threat to vision. It seems likely that these complications will become more common as the use of this drug increases.

We are grateful to Dr. F. G. Tucker, Clinical Director of the Crease Clinic and Provincial Mental Hospital, and his psychiatric staff for permitting us to examine their patients. We are particularly indebted to Miss Margaret Klassen for preparing the histologic material, to Drs. A. C. Johnston and G. Speakman for their help with the ophthalmologic studies and photographs, and to Dr. C. L. Dolman for the photomicrograph.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

GRADING OF NURSES

It is recommended that as rapidly as possible, city or county organizations and centres be brought into existence to be devoted to the specific purpose of supplying efficient nursing to middle-class families and to standardizing household nursing.

That a fully trained hospital graduate nurse be in charge of the details of such nursing in each centre under the supervision and direction of a representative board, as is the case in a small hospital serving a community, or a visiting nurse centre.

That a serious effort be made through organization to effect a better distribution of hospital graduate nurses and to secure the more general use of such nurses in acute cases, the ultimate aim to be to fit the nurse to the needs of the case, providing a graduate nurse where a high degree of skill is needed, and a less skilled and less expensive worker where such will fully meet the need.

A recognized minimum standard of instruction in practical nursing to be required of all who nurse for hire, so soon as local facilities for household nurses to acquire such instruction be provided.

That in each institution and training centre, a course of instruction in maternity nursing be provided for.

That active effort be made to secure the cooperation of the members of the medical profession and of public health officers, in establishing an efficient system of household nursing for families of moderate means in each community.

In order to secure this cooperation, the committee earnestly request physicians to forward answers to the following questions:

In your opinion, is it possible to meet the nursing needs of the average community in city, town and country, in the United States and Canada with graduate nurse service alone?

If, in your opinion, only graduate service should be used, will you kindly present an outline of a practical comprehensive programme for supplying graduate service to all classes needing continuous nursing?

If more than one grade of nurse is a necessity, will you please state how many grades you consider necessary? How would you classify nurses so as to include in your classification, all who nurse for hire?

If several grades seem to be necessary, how and where should the several grades be trained?

In view of the fact that many tuberculosis hospitals find it impossible to secure sufficient graduate nurses to care for their patients, what measures would you suggest for meeting the nursing needs in such institutions.

If training is given in a tuberculosis hospital, how long should the course be, and how would you classify those completing such a course?

Will you kindly suggest plans for improving the quality of home nursing now being received by those who cannot afford graduate nurses?—Report on the Grading of Nurses, American Hospital Association; *Canad. Med. Ass. J.*, 4: 251, 1914.