SKIN PIGMENTATION, A RARE SIDE EFFECT OF CHLORPROMAZINE*

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Introduction

In 1961 at the Verdun Protestant Hospital we first investigated some patients with slate-blue pigmentation of the face and the extensor surface of the forearm following upon chlorpromazine administration. When this medication was first given at this Hospital (1953), the only light-related side effect observed was that patients developed hypersensitivity to sunlight and in general had to be protected from ultra-violet radiation. No peculiar pigmentation whatever was noted before 1958 in any patients receiving chlorpromazine (10).

In this paper we will discuss our findings with respect to our study of a group of patients on chlorpromazine therapy who revealed this discolouration and the controls set up to verify these findings. On their basis, it would seem that prolonged administration of chlorpromazine in high dosage increases the melanin-forming activity of the melanocytes in the epidermis, resulting at a certain point in their exhaustion and the appearance of the overt permanent skin pigmentation. We will discuss its nature and development, attempt to integrate our findings with other experimental results and suggest means of preventing such skin pigmentation. Finally, a hypothesis will be developed with respect to one of the mechanisms involved.

It is of interest to note here that when this slate-blue colouration was first observed in 1961, a skin biopsy was taken from the affected area in one of the patients—a 30-year-old mentally defective female who was simultaneously on chlorpromazine, prochlorperazine and trihexyphenidyl therapy. According to the pathology report, the epidermis was normal; the sole abnormality being the presence of pigment-loaded macrophages localized around the blood vessels in the dermis. The pigment which did not stain iron or copper, was described as resembling melanin and the condition was diagnosed as a pigmentary disturbance of the skin compatible with Riehl's melanosis. The latter is a metabolic disease due to a vitamin B insufficiency occurring simultaneously with exposure to sunlight. However, there is also an inflammatory infiltrate present during pigmentation in this disease which was not present in our patients.

Review of the Literature

Only two articles were found related to this particular topic. The first paper was published in a dermatological journal in 1962 (19). In it Perrot and Bourjala briefly discuss a diagnostic problem of a 'purple' face (*un visage mauve*) that developed in a 48-year-old schizophrenic female who received chlorpromazine and thereafter thioridazine treatment for several years. The condition was diagnosed as toxidermia.

The second paper was published in the Canadian Medical Association Journal in 1964 (10). Its authors, Greiner and Berry, described their observations on 70 patients since 1959. According to them, the characteristic chlorpromazine skin pigmentation develops only in females and in 80% of them it is connected with amenorrhea. It develops in the sun-exposed areas of the face, neck, upper chest, dorsum of hand and light-exposed lower legs, and after a minimum of three years of chlorpromazine administration in a daily average dosage of 500-1,500 mg. These two papers will be discussed at greater length under the appropriate headings.

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TABLE I

BASIC INFORMATION ON THE FIFTEEN (15) PIGMENTED PATIENTS IN THE EXPERIMENTAL GROUP.

Patient No.	Age	Sex	Diagnosis	Duration of phenothiazine treatment	Chlorpromazine average daily dose	Additional medication
1	36	F	Schizophrenia	8 years	1000 mg.	prochlorperazine
2	44	F	Schizophrenia	8 years	600 mg.	prochlorperazine
3	31	F	Schizophrenia	2 years	1500 mg.	
4	33	F	Mental retardation	8 years	600 mg.	
5	48	F	Schizophrenia	8 years	400 mg.	prochlorperazine
6	35	F	Schizophrenia	3 years	900 mg.	prochlorperazine perphenazine
7	55	F	Schizophrenia	9 years	400 mg.	prochlorperazine
8	35	F	Schizophrenia	7 years	300 mg.	
9	29	F	Schizophrenia	6 years	800 mg.	prochlorperazine perphenazine
10	24	F	Schizophrenia	3 years	1000 mg.	
11	24	M	Epilepsy	8 years	400 mg.	diphenylhydantoin phenobarbitone
12	36	M	Schizophrenia	6 years	600 mg.	
13	23	M	Schizophrenia	3 years	1000 mg.	prochlorperazine
14	38	M	Schizophrenia	7 years	1000 mg.	perphenazine prochlorperazine
15	24	M	Schizophrenia	7 years	300 mg.	perphenazine

Median age: 33 years
Mean age: 34.3 years

Median duration of treatment: 7 years
Average duration of treatment: 6.2 years

Median daily dosage: 600 mg.
Mean daily dosage: 720 mg.

Method and Procedure

The Verdun Protestant Hospital, a 1,500-bed mental hospital, was surveyed and 15 patients with the typical skin pigmentation were found. This experimental group (Table I) was matched to the closest approximation with respect to age, sex, diagnosis, duration of phenothiazine treatment and the average daily dosage of chlorpromazine, with 15 non-pigmented patients to form the first control group. A second similarly matched control group was chosen consisting of 10 patients on phenothiazine, but not on chlorpromazine, and a third of 10 chronically hospitalized psychiatric patients on psychotropic but not phenothiazine medication. Our fourth control group was comprised of five normal volunteers selected from the staff of the Verdun Protestant Hospital who were not receiving any drugs.

All subjects in the experimental and control groups were given a complete dermatological and ophthalmological examination by specialists in these respective fields. A photosensitivity test was done and skin biopsies for histochemical reactions were taken from a representative sample.

Discussion of the Experimental Group

Table I presents details of the 15 pigmented patients in the experimental group with respect to age, sex, diagnosis, duration and type of treatment and daily dosage.

It is to be noted that 10 of the 15 cases received other medication in addition to chlorpromazine and only one patient received a non-phenothiazine medication (No. 11). In the latter case the diagnosis was that of epilepsy and he was on anticonvulsant medication and chlorpromazine.

As in the case of the article by Greiner and Berry referred to (10), all our pa-

tients with the characteristic skin pigmentation had also received without exception chlorpromazine in a fairly high dosage for a considerable length of time. On the other hand, we had patients who received it for less than three years (two years) and others who received it in a lower average dosage than 500 to 1,500 mg. a day (two patients 300 mg. and three patients 400 mg. average daily dosage).

However, a relationship between the absolute mean of chlorpromazine received and the skin pigmentation was indicated by the fact that the only patient who received the drug for a period of just two years before the pigmentation occurred, was taking the medication in a relatively high daily dosage (1,500 mg.) and the patients who developed it while on a lower dosage were taking it for a relatively long time (two for seven years, two for eight years and one for nine years). Furthermore, there were five males in our experimental group and no characteristic amenorrhea was revealed in the 10 female cases. These latter findings were incongruent with Greiner's.

Dermatological Findings

The first dermatological description by Perrot and Bourjala to which we have also referred, described the pigmentation as an erythema with a violet hue of the face (forehead, nose and cheeks) and with symmetrical manifestations on both hands and leucokeratosis of the intrabuccal mucous membrane (19). Greiner and Berry (10) found the skin manifestations only on sun-exposed areas. According to them the discolouration of the face varies 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.

Dermatological examination of all the patients in the experimental and control groups included skin, hair, nails, and mucous membranes and in all cases, with the exception of skin pigmentation, findings were normal. In addition, the effect of vitropression in the affected areas was investigated and it was noted that discolouration did not disappear—in contrast to the superimposed erythema present in some of the patients.

The discolouration of our sample appeared in three degrees of severity and can be described as follows:

First degree (mild)—Slate grey colouring (Picture 1).

Second degree (moderate)—Superficial complexity of violet, grey, brown, blue and yellow, which we labelled 'purple'.

Third degree (marked)—Same as the second above but a more marked and intense variation (Picture 2).

These degrees were observed on the face, neck, shoulder, upper part of the chest, dorsal surface of the hands, extensor surface of the arms and, in general, in the light exposed areas. Table II reveals that the degree of manifestation was directly proportional to the degree of exposure to ultra-violet radiation. Thus on the more exposed face, six of the pigmented group presented third degree and six second degree and only three first degree discolouration. With respect to the hands, no third degree discolouration is described. Table II also indicates that the thorough dermatological examination revealed that seven patients of the first control group manifested first degree discolouration of the face and only two (same group) showed a mild pigmentation of the hands.

Our findings were in accordance with Greiner's and differed from Perrot's, whose case presented a lesion of the intrabuccal mucous membrane.

Photosensitivity Test Results

Since among the dermatological complications with chlorpromazine, i.e. contact sensitivity, generalized eruptions, photosensitivity, the latter occurs the most commonly, a test was designed to study the photosensitivity in our patients in all experimental groups (2).

TABLE II

THE NUMBER OF SUBJECTS ON WHOM PIGMENTATION OCCURRED AND THE DEGREE OF PIGMENTATION IN THE EXPERIMENTAL AND CONTROL GROUPS.

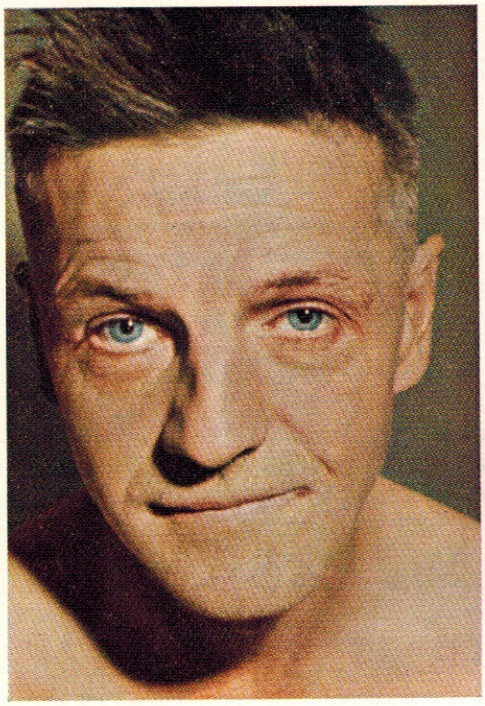
		Pigmented Group	Matched Chlor-promazine Control Group	Phenothiazine Control Group	Non-Pheno-thiazine Control Group	Normal Control Group
FACE	No pigmentation	0	8	10	9	5
	First degree (mild pig-mentation)	3	7	0	0	0
	Second degree (moderate pig-mentation)	6	0	0	0	0
	Third degree (marked pig-mentation)	6	0	0	0	0
	Total	15	15	10	9	5
HANDS	No pigmentation	2	13	10	9	5
	First degree (mild pig-mentation)	7	2	0	0	0
	Second degree (moderate pig-mentation)	6	0	0	0	0
	Third degree (marked pig-mentation)	0	0	0	0	0
	Total	15	15	10	9	5

One minute after the exposure to an ultra-violet light source all the patients from the experimental group with two exceptions showed photosensitive reaction and all but five from the chlorpromazine, not pigmented, matched control pairs. On the other hand, only one patient had a mild positive reaction after one minute from the phenothiazine, non-chlorpromazine and from the non-phenothiazine groups. In the experimental and the first control group, besides minor alterations no major change occurred at the six-hour checking point. On the other hand four more positive reactions were seen at that time in the second and two more positive reactions in the third control group, suggesting that other phenothiazines or other miscellaneous psychotropic drugs may also produce photosensitivity.

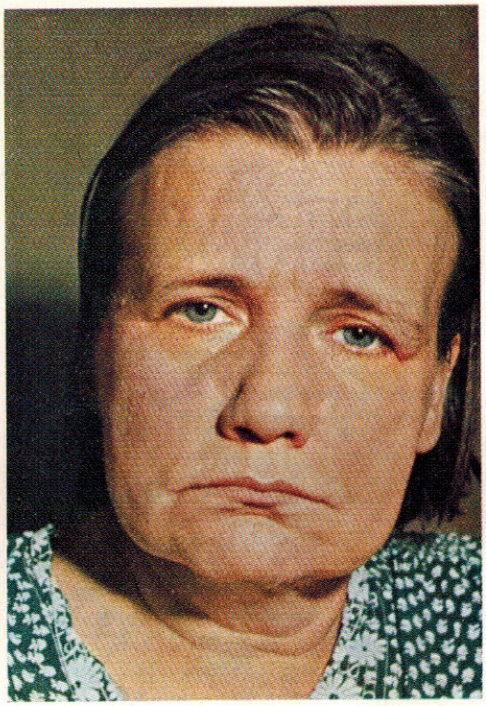
Ophthalmological Findings

The first ocular findings related to phenothiazine administration in animals were described by Whitten and Filmer (1947) and by Clare (1947). This was keratitis in young cattle. Similar keratitis could not be produced in sheep. The sulfoxide metabolite of the phenothiazine was thought to be the inciting cause of the condition since this was identified from the blood and aqueous humor of cattle but not of sheep.

Ocular manifestations were found in 12 of Greiner's severely pigmented cases. This was described as a peculiar hazy brown pigmentation of the exposed sclera



Picture 1
First degree skin pigmentation, slate grey colouring.



Picture 2
Third degree skin pigmentation, complexity of violet, grey, brown, blue and yellow.

and cornea. Ophthalmoscopic examination revealed a dark brown irregular, stellate or cocklebur-shaped opacity of the lenses with a dense central area and radiating branches. On slit lamp examination, discrete yellow-white dots became visible, which were concentrated at the centre with radiating arms in the anterior subcapsular pole. Under the same conditions, the corneal lesion was described as yellowish-white granules, mainly in the posterior half of the cornea, less dense peripherally than centrally. The granules were localized in the stroma.

The experimental and control groups with the exception of five cases, were exposed to an ophthalmological examination which included general external examination, fundoscopic examination, vision testing (multiple pin holes which give corrected visual acuity), refraction (under cycloplegia) and slit lamp examination.

Conjunctival, corneal and lens pathology was found in all of the experimental subjects but one, who had an intact cornea and conjunctiva. No conjunctival pathology was found in the chlorpromazine control group, while pathological findings simultaneously on the iens and cornea were revealed in eight cases. All the patients in the other control groups had normal conjunctiva, cornea and lenses. There was no evidence that a greater number of patients had impaired vision in the experimental than in the control groups.

It was the ophthalmologist's impression that there is a high correlation between the abnormal ocular findings and the consumption of chlorpromazine; that the abnormal findings occur with higher incidence in those patients with skin pigmentation and also in a higher degree of severity; that patients on chlorpromazine without skin pigmentation show no con-

junctival changes, but they are not exempt from corneal and lens pathology, and that sunlight would appear to bear some relationship to the corneal and conjunctival superficial changes.

Histochemical Findings

The pathology report of our first pigmented case in 1961 found the epidermis normal and revealed pigment-loaded macrophages around the blood vessels in the dermis. It was suggested by the pathologist that the pigment may be melanin in this case.

In Greiner's series (10) histochemical examinations were done on biopsies from pigmented skin areas and from non-pigmented skin areas of pigmented patients and also from unaffected patients on prolonged high doses of chlorpromazine medication.

In the affected skin areas a golden brown finely granular pigment was found superficially in the dermis in plump cells mainly around the capillaries. Occasionally there was an absence of melanin in the basal layers of the epidermis overlying the pigment in the dermis. The different histochemical methods (hematoxylin-eosin stain and periodic acid Schiff stain) stained the pigment golden-brown. While the pigment gave negative iron reaction with Gömöri's method, it gave a strongly positive (dark black) reaction with Fontana's method.

Similar mildly abnormal findings were found in biopsies from the unaffected areas of pigmented patients while no abnormalities were found in unaffected subjects.

In our experiment, skin biopsies were taken from eight patients, three from the experimental group, three from the chlorpromazine matched controls and one from each of the second and third control groups.

The excised material was exposed to a battery of histochemical procedures. This included tests for external crystalline pigment and also for pigments which are the result of liver impairment. It also included tests for the three most commonly occurring pigments which are haem-pigments, lipid-pigments and tyrosin-tryptophane-pigments. For the latter pigments, the dopa reaction and Fontana-Masson's stain were used. All but the latter two tests were found negative, which indicated that the pigment belongs to the tyrosin-tryptophane group (melanin).

On Table III the different characteristics of the two reactions as seen in the epidermis and in the dermis are presented for the different groups.

It can be seen that the dopa reaction (Bloch 1927) which indicates the capacity for melanin formation in the basal layer of the epidermis is strongly positive in the chlorpromazine control group, indicating that pigment formation is markedly increased, contrary to the pigmented group where it is decreased. The Fontana reaction, a simple silver nitrate procedure which indicates pigment storage, behaves similarly to the dopa reaction in the epidermis, while in the dermis it is increased slightly in the non-pigmented first control group and markedly in the representative cases from the experimental group.

In patients from the second and third control groups normal dopa and Fontana reactions were found.

On the basis of these findings (Table III) it seems that chlorpromazine in high dosage with prolonged administration increases the melanin-forming activity of the melanocytes in the epidermis and there is also a concomitant increase in melanin storage of the melanophores in the same epidermal layer. However, beyond a certain point, simultaneously with the appearance of overt skin pigmentation, the pigment formation and storage in the epidermis decreases while a marked increase of descended melanin is found in the dermis.

Differential Diagnosis

Any coloured material in the skin is called a pigment. The colour of the pigment is dependent upon the absorption of light rays by the pigment-forming sub-