TABLE III

PIGMENT FORMATION (DOPA REACTION) AND STORAGE (FONTANA REACTION) IN THE EPIDERMIS AND THE DERMIS IN A REPRESENTATIVE SAMPLE FROM THE EXPERIMENTAL AND 3 CONTROL GROUPS.

	Pt. No.	Epidermis		Dermis	
		Dopa	Fontana	Dopa	Fontana
Pigmented Group	1	—	—	O	+++
	2	++	++	O	++
	3	—	—	O	+++
Matched-Chlor-promazine Control Group.	1	N	N	O	+
	2	+++	+++	O	+
	3	+++	+++	O	+
Phenothiazine Control Group.	1	N	N	O	O
Non-Phenothiazine Control Group	1	N	N	O	O

O Absent or no reaction
— Decreased activity
N Normal activity
\+ Slightly increased activity
++ Moderately increased activity
+++ Markedly increased activity

stance. It depends also in what layer of the skin the substance is situated (13).

Brown and blue hyperpigmentation are generally distinguished. Brown pigmentation is the result of an increase in melanin-producing activity with little loss of the melanin formed. In brown hyperpigmentation the pigment is situated in the basal layer of the epidermis. This pigmentation is caused by photosensitisers, i.e. phenothiazines, hydantoins, sulfonamides, chlorothiazides, etc.

In blue hyperpigmentation the melanin is in the dermis in phagocytes or ectopic melanophores. This pigmentation is caused by chloroquine (7), chlorpromazine, etc. (3).

Chlorpromazine may produce photosensitivity and brown pigmentation, but the pigment revealed in our experimental group had bluish characteristics also.

On the basis of histochemical findings it was assumed that the pigment is melanin. The pigmentation could be differentiated from other conditions in which melanin hyperpigmentation is prominent (Addison's disease, ochronosis, incontinencia pigmentis, Riehl's melanosis). On clinical grounds it could also be established that this increased melanin formation is related to high dosage and prolonged chlorpromazine administration. Free melanin, however, could not be isolated from the excised skin sample.

What is the Pigment and the Mechanisms of Pigment Formation?

Although free melanin could not be isolated from the excised skin of pigmented patients, the strongly positive dopa and Fontana reactions in the epidermis during chronic high dosage chlorpromazine administration, indicated increased melanin formation in these cases and the strongly positive Fontana reaction in the dermis of the pigmented cases indicated increased melanin storage.

Melanin is formed in the melanoblasts (melanocytes) and stored in the melanophores. The dendritic melanoblast appears in the epidermis at the end of the third embryonic month (Boyd, 1949). These cells migrate from the neural crest and reach the skin along with the outgrowing sensory nerves (Masson, 1948). The melanoblasts are in the basal layer of the epidermis. Melanin is transferred from these by the penetration of

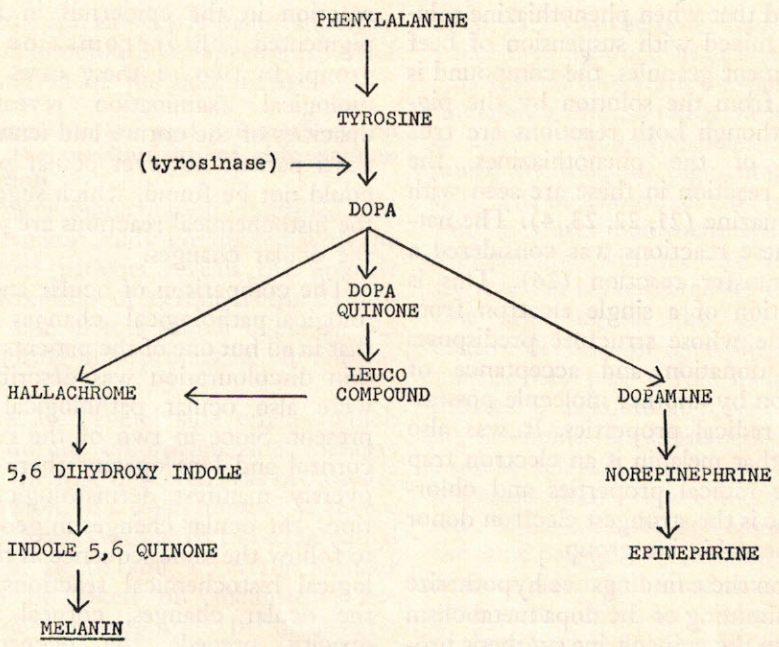

Figure 1
Phenylalanin metabolism and melanin formation.

dendritic processes into the basal melanophore cells (17, 27).

The formation of melanin pigment in the epidermal melanoblasts depends on the presence of melanin precursor substrate (tyrosine or di-oxy-phenylalanine), molecular oxygen and an enzyme (tyrosinase), a copper-protein complex (16). The reactions involved are presented in Figure 1.

As seen in Figure 1, melanin and epinephrine are derived from the same precursor: tyrosine. An enzyme, tyrosinase, catalyzes the oxydation of tyrosine to di-oxy-phenylalanine (dopa) and the produced dopa to melanin. The tyrosine-tyrosinase reaction, in reverse, is catalyzed by o-di-oxy-phenyl (dopa, etc.) compounds.

In 1917 Block and Löffler discovered that epinephrine and melanin are derived from the same precursor and they noted that if the adrenal glands do not utilize tyrosine for epinephrine synthesis it accumulates and is converted to melanin (16). The increased melanin formation (dopa reaction) in patients without pigmentation on high dosage chronic chlorpromazine administration indicates an activity similar to that which Block and Löffler described. It is suggested that as a result of this, a *relative* increase in melanin and a *relative* decrease of dopamine, epinephrine, and norepinephrine occurs, although it is realized that the absolute values of catecholamine excretion in patients treated with chlorpromazine are not consistently altered.

Since ultra-violet radiant energy catalyzes the tyrosine-tyrosinase reaction and thus catalyzes the oxydation of tyrosine to dopa decreasing the activity of the tyrosinase inhibitor sulfhydyl group, etc., this may explain why the pigmentation appears at first on the skin and on the eye, i.e. on the light exposed areas.

It has been found by using radioactive (labelled, tagged) compounds, that there is a selective accumulation of phenothiazines in the choroid and iris which is exclusively associated with the pigment present in these tissues. It has also been

established that when phenothiazine solutions are mixed with suspension of beef uveal pigment granules, the compound is removed from the solution by the pigment. Although both reactions are true for any of the phenothiazines, the strongest reaction in these are seen with chlorpromazine (21, 22, 23, 4). The nature of these reactions was considered a charge transfer reaction (26). This is the donation of a single electron from a molecule whose structure predisposes to such donation and acceptance of an electron by another molecule possessing free radical properties. It was also revealed that melanin is an electron trap with free radical properties and chlorpromazine is the strongest electron donor in the phenothiazine group.

Based on these findings we hypothesize that the shunting of the dopa metabolism away from the epinephrine synthesis produces increased melanin formation, which beyond a certain level (facilitated by light) may become exhausted and the *excess* melanin pigment which is 'dropped' from the epidermis into the dermis, may then form a complex with the *excess* of chlorpromazine. We suggest that this complex (melanin + chlorpromazine) is the pigment in our experimental group.

Correlation of data and the sequential development of skin pigmentation on high dosage chronic chlorpromazine administration

Findings of the dermatological and ophthalmological examinations and of the histochemical reactions were tabulated and the order of sequence of the skin pigmentation was reviewed.

The comparison of histochemical reactions and ocular pathological changes revealed that in all the six cases (three from the experimental and three from the first control group) on whom histochemical reactions were performed, pathological changes were found. This was manifested in a markedly positive Fontana reaction in the dermis in the pigmented experimental group, and in a markedly positive dopa and Fontana reaction in the epidermis in the non-pigmented chlorpromazine control group. In two of these cases ophthalmological examination revealed also opacities of the cornea and lenses. In the third patient however ocular pathology could not be found, which suggests that the histochemical reactions are preceding the ocular changes.

The comparison of ocular and dermatological-pathological changes revealed that in all but one of the patients in whom skin discolouration was described there were also ocular pathological changes present. Since in two of the cases with corneal and lens opacity there were no overtly manifest dermatological alterations, the ocular changes in general seem to follow the same sequence as the pathological histochemical reactions. Among the ocular changes, corneal and lens opacity precede the occurrence of greyish-brown conjunctival pigmentation. The latter was only present in the experimental group and never present without cornea or lens opacities.

The last step in the order of sequence is the overtly manifest intensive skin discolouration which occurs at first in areas more exposed to sun (face) and only thereafter in places which are less exposed to the light (hands). In seven cases was more skin discolouration found on the face than on the hands and in no patients was discolouration of the hands found without concomitant changes on the face.

Our findings suggest that the skin reaction seen in our experimental group begins with an increase of melanin synthesis in the melanocytes of the skin and of the eyes, as shown by the histochemical reactions. Thereafter, partly because ultra-violet light rays have a facilitating effect on melanin synthesis, and partly because certain parts of the eyes are relatively rich in melanocytes, the primary ocular changes occur (cornea, lens). Finally, the melanocytes become exhausted, the pigment drops or is carried into the dermis and reacts with chlor-

promazine and an overtly manifest permanent skin discolouration appears as well as pigmentation of the conjunctiva.

Skin pigmentation and a hypothesis on one of the mechanisms of chlorpromazine action

The skin pigmentation described and the systematic study conducted with the pigmented patients reveals the possible interrelatedness of certain formerly unrelated side effects which occur in patients during chlorpromazine administration.

There are several side effects which occur during chlorpromazine therapy. One of the first observed was orthostatic hypotension. In a small number of severe cases, this was considered to be the causal factor of death and a certain number had to be taken off medication because of this reaction. In orthostatic hypotension the systolic and diastolic blood pressures fall rapidly when the patient assumes an upright position. There is no compensatory tachycardia and the pooling of blood in the lower parts of the body does not excite vasoconstriction of the peripheral vessels. Luft and Von Euler (18) gave evidence that patients with this symptom have deficient epinephrine and norepinephrine release. Thus in the physiological balance (antagonism) between epinephrine and the vasodilator principle resembling histamine in its effect (Burn and Dale 1926), the latter outweighs the former (8).

Since chlorpromazine definitely produces orthostatic hypotension in a number of cases and since there is a decreased epinephrine, norepinephrine release in orthostatic hypotension (18), this suggests that the drug at a certain point may interfere with the tyrosine metabolism.

Photosensitivity is generally defined as a physiochemical phenomenon in which the radiant energy captured in the skin produces toxic effects which are manifested in a brisk and prolonged accentuation of the sunburn reaction (20). The immediately produced erythema (vasodilation) after cessation of exposure rapidly disappears. On the other hand, the ultraviolet rays produce an action which occurs several hours after exposure and in the case of intense radiation in the range of 2,800 - 3,200 Angstroms, this is followed by melanin pigmentation of the skin. The observed fact that chlorpromazine increases photosensitivity and the experimental evidence that the immediate reaction is facilitated by chlorpromazine also suggest that an immediate relative decrease of epinephrine-like substances may play a role in leading to a relative or absolute increase of vasodilating histamine-like substances. In the subsequent delayed reaction, in addition, an increased melanocytic activity is also present. Since melanin and epinephrine use the same precursor (tyrosine), this points again as a possible mechanism of chlorpromazine action to a relative decrease of epinephrine production and a resulting increase of melanin synthesis due to the shifted epinephrine-melanin balance.

Some of the most common side effects observed during phenothiazine administration are pathological extrapyramidal manifestations which resemble certain aspects of paralysis agitans.

It has been reported by a group of investigators that in Parkinson's disease the dopamine concentration in the basal ganglia — to which some of the manifestations of this condition are related — is usually low and also the urinary output of dopamine is below normal (25). These findings are not generally accepted and not confirmed in drug-induced Parkinsonism. On the other hand, some histochemical changes observed with fair regularity in these conditions are aggregates of melanin-containing neurons in the brain stem (1, 9).

The ocular changes and skin pigmentation follow a similar course of development. Melanin formation locally in the epidermal melanocytes depends on the presence of the melanin precursor aminic acid (tyrosine), molecular oxygen and an enzyme (tyrosinase). Furthermore, melanocytic activity is under endocrine in-

fluence. The melanocyte stimulating hormone (MSH) of the *pars intermedia* of the pituitary seems to be the primary regulator of melanin formation. There is an interaction between epinephrine, norepinephrine and the melanocyte stimulating hormone as the catecholamines have an inhibitory or negative feed-back effect on the secretion of the MSH (5, 6, 11, 14, 12, 15). This may explain at least partly why neuroleptic drugs in general darken the skin of frogs through increased action of MSH while monoamine - oxidase inhibitors suppress this reaction through increased action of the catecholamines (24).

All these observations suggest that it is a common characteristic of neuroleptic drugs to decrease epinephrine formation or the reactivity to it which in turn releases melanocytic activity, while it is characteristic of stimulants and antidepressants to inhibit the catabolism and elevate the level of epinephrine (a monoamine) which in turn restricts melanocytic activity. Chlorpromazine—a neuroleptic drug—has an anti-epinephrine effect and the increased MSH activity, which may be due to the decrease of epinephrine activity in some cases, becomes noticeable in the increased melanocytic activity revealed by the histochemical dopa reactions in the skin, as well as in visible ocular and skin pigmentation. Important factors which play a role in the skin pigmentation are:

1) among all the phenothiazines used in psychiatry chlorpromazine has been given for the longest period in the largest dosages;
2) chlorpromazine in clinically employed dosage produces the greatest melanin excess simultaneously with a possible excess of the drug;
3) among all the phenothiazines, chlorpromazine is the strongest electron donor which can go into a charge transfer reaction with the melanin, which having free radicals, is a strong electron trap (4, 26).

Besides the epinephrine-MSH balance, melatonin (a corpus pineale produced hormone, chemically close to serotonin) also plays a role in pigmentation. This substance is said to cause clustering of melanin granules about the nucleus of the melanocyte in the frog's skin, resulting in an apparent decrease in pigmentation (6, 15).

On these grounds it is suggested that orthostatic hypotension, extrapyramidal symptoms, ocular and skin pigmentation are not entirely unrelated phenomena during chlorpromazine administration, but common consequences of the action mechanism of the drug, which by interfering with dioxyphenylalanine metabolism decreases dopamine, epinephrine and norepinephrine synthesis. Thus a relatively reduced catecholamine level may lead to orthostatic hypotension, to increased MSH activity and to decreased melatonin synthesis. The latter in turn produce increased melanocytic activity in the eyes, in the skin (strongly positive dopa reaction in the epidermis) and in the brain stem. When massive doses of these drugs are given (and this is more likely with chlorpromazine), the melanocytes in the epidermis become exhausted, their pigment descends into the dermis and the excess of melanin with the excess of chlorpromazine forms a complex which clinically appears in the eye as conjunctival pigmentation and corneal and lens opacities, and in the skin as a bluish-brownish-grey discolouration.

Incidence, prognosis, prevention of chlorpromazine skin pigmentation

The first survey of pigmented cases in British Columbia reported 70 cases (10). The survey covered a 6,000-bed Provincial Mental Hospital at Essondale. At the Verdun Protestant Hospital (1,500 beds) the first survey collected 15 cases, but during our study seven additional cases with a milder degree of sustained pigmentation were found. This would indicate a little higher than 1% incidence of skin pigmentation in the

chronic mental hospital population. However, the fact that in some of the cases where there is no skin discolouration as yet ocular or the characteristic histochemical reactions are already present, would suggest that we may expect to see some rise in this incidence in future years.

Absorption from the dermis is difficult, which would explain why the skin pigmentation still prevailed in Greiner's cases six months after cessation of therapy (10). However, such re-absorption of melanin from the dermis is not impossible. The fact that the melanocytic activity in the skin in our photosensitivity test still could be stimulated, indicates that even if the absorption of the pigment complex in the dermis is delayed, further accumulation of pigment and deposits can be prevented. The same applies to the ocular changes which have not proved to lead to any changes of clinical importance in our series.

In reviewing institutions where patients with skin pigmentation were discovered and contrasting them with other mental hospitals, the only common denominator found was that in general chlorpromazine therapy, in the former, was more intensively carried out, i.e. more massive doses of the drug were administered for longer periods of time. Furthermore, we gained the impression that patients with a light complexion (with possibly weaker melanocytic activity) are more prone to develop this side effect.

The prevention of skin pigmentation lies in the adjustment of the therapeutic dosage of chlorpromazine. Small (needle) skin biopsies and slit lamp examinations at certain intervals, in patients exposed to high dose sustained chlorpromazine therapy, are suggested. Any pathological findings in the skin or eye of the type described would indicate that the drug is used in excess and in such dosage certain side effects due to excessive melanin production can be expected. With other phenothiazine drugs, the absence of pathological dermatological findings is attributed to the fact that they are used in lower dosages than chlorpromazine. The permanent pigmentation due to the combined effects of light and phenothiazines on the organism seems to be the result of a mass-action and the cumulative result of time of exposure and quantity of drug.

Summary

A greyish-brownish-bluish skin discolouration is described in patients who have received chlorpromazine in high dosages for a considerable length of time. Prior to the skin pigmentation an increased melanocytic activity with ocular manifestations appears, which beyond a certain point in some patients leads to exhaustion of melanocytic activity and to deposit of melanin in the dermis. The melanin/chlorpromazine complex is discussed and a hypothetical mechanism of chlorpromazine action is proposed which may lead to the described skin and ocular pathology.

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Résumé

Chez des malades ayant reçu de fortes doses de chlorpromazine, pour une durée très prolongée, une coloration gris-brun-bleue de la peau a été signalée.

Précédant la pigmentation cutanée apparaissent des manifestations oculaires ainsi qu'une augmentation de l'activité melanocytaire; ce qui entraîne au delà d'un certain point et chez certains malades un dépôt de mélanine dans le derme.

Le complex mélanine/chlorpromazine a été discuté, et une action hypothétique de la chlorpromazine entraînant les troubles déjà décrits, a été proposée.