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THE EFFECT OF CHLORPROMAZINE ON OCULOCUTANEOUS PIGMENTATION IN THE GUINEA PIG*

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In March, 1964, Greiner and Berry (1) described in detail their observations of 70 patients with abnormal oculocutaneous pigmentation following long-term, high dose chlorpromazine therapy. They first noted this phenomenon in 1958. Several common factors were found in most patients; the majority were Caucasians with very fair skin, and had histories of prolonged sunlight exposure. Most of the patients were females and all of these were amenorrheic. The principal neuropsychiatric disorders for which the drug was given were schizophrenia and mental deficiency. All patients had received very large, daily doses of chlorpromazine. Other authors have subsequently reported similar findings (2–7). The object of the present work was to attempt to reproduce the oculocutaneous pigmentation in the guinea pig. Once a suitable experimental technic was developed, it was hoped to elucidate the cause of the pigmentary defect and if possible the exact chemical nature of the pigment.

MATERIALS AND METHODS

Eighty-three mature guinea pigs were used and they were divided into groups as follows:

Group I consisted of 18 albino, 6 pure red and 6 pure black animals. Control skin biopsy specimens were taken from closely sheared areas on the anterior abdominal wall of each animal. The animals were then given 40 mg of chlorpromazine daily by mouth for 6 months. This dose was chosen since it closely approximated or exceeded per kilogram the daily dose of the drug given to humans. The closely sheared abdomen was exposed to ultraviolet light for twenty minutes daily using a technic described previously (8). A Sylvania forty watt fluorescent bulb with a peak output at 3,200 Å, placed thirty inches above each animal, was used as a light source. At the end of 3 and 6 months skin biopsy specimens were taken of the light exposed areas. All the biopsy specimens were fixed in 10% formal saline solution and imbedded in paraffin. Six micron thick vertical sections were cut, and unstained sections, sections stained with hematoxylin and eosin, and eosin alone were examined microscopically.† Three of the twelve pigmented animals; 2 red and 1 black were submitted to total autopsy examination. Sections of the liver, spleen and heart were examined microscopically.

Group II consisted of 12 male albino guinea pigs. Each animal was injected intradermally in four abdominal quadrants with a single dose—0.1 ml of an aqueous solution of pure chlorpromazine. 0.5 mgm/ml of chlorpromazine was chosen as a suitable dose for intradermal injections since larger concentrations had been found to be extremely irritating to the skin, often causing tissue necrosis. In order to study the combined local effect of chlorpromazine and ultraviolet light the injection sites of six of the animals were exposed to a light source of 3,200–3,600 Å each day for 10 days. One other animal was injected with chlorpromazine intradermally after the drug had been exposed to ultraviolet light for 20 minutes. At intervals varying from 7–11 days following the injection, skin biopsy specimens were taken and processed as described previously.

Group III consisted of thirty-six guinea pigs equally divided among males and females; red, black and albinos were used. Control skin biopsy specimens were taken from the closely sheared backs of each animal. All guinea pigs were then continuously exposed to an ultraviolet source placed 10 inches above their backs. It was decided to use a source of ultraviolet light which had a peak emanation frequency around 3600 Å since this frequency approximated the ultraviolet activation spectrum for the various forms of chlorpromazine. Because this part of the experiment was to extend over a prolonged period of time and it was desirable to have the minimum number of animal deaths from drug toxicity, the dose of chlorpromazine was reduced to 30 mgm/day. The drug was given for a 12 month period except for an interval of 2 weeks during the sixth month. The animals were sheared twice weekly to ensure that the dorsal skin was adequately exposed to the ultraviolet light source. Skin biopsy specimens were taken at 3, 6, 9 and 12 month intervals and processed as above.

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† Haag-Streit slit lamp examination of both eyes of the surviving animals were performed 1–3 months after cessation of the chlorpromazine therapy.

Group IV consisted of one albino, two red, and two black male guinea pigs. They were injected intraperitoneally with an aqueous solution of S^{35} labeled chlorpromazine having an activity of 4 microcuries per injection. Skin biopsy specimens were taken at one, three, fourteen and twenty-one days. Biopsy specimens also were taken of the liver, spleen and heart when the animals were sacrificed on the 21st day. Stained autoradiographs were made of 6 sections according to the procedure outlined by Joftes (9).

RESULTS

Group I

Macroscopic examination.—At the start of the experiment, erythema followed by scaling, without blister formation was evident on the U.V. light exposed areas in the albino and the very light red animals but tended to fade as the experiment progressed. Both the red and black animals showed a marked increase in pigmentation of the irradiated areas.‡

Microscopic examination.—In all the animals the stratum corneum was thickened. In the red and black animals the pigment was increased throughout the epidermis, but it was no greater than the increased melanin pigmentation which occurs after prolonged ultraviolet light exposure (8). No pigment was observed in the dermis, and no pigment deposits were noted in the visceral organs.

Group II

Macroscopic examination.—Each injection site of the chlorpromazine solution became erythematous and edematous but no ulceration occurred.

Microscopic examination.—All sections examined showed no evidence of dermal pigment deposits.

Group III

Macroscopic examination.—A marked increase in skin pigmentation was noted in the black and darker red animals within 1–2 weeks after initiation of ultraviolet exposure; the degree of pigmentation was similar to that found in the animals of group I.

All of the albino animals and several of the light red animals had severe erythema and blister formation on the skin of the backs and ears for the first seven days of the experiment. This reaction subsequently subsided without pigment formation. However, when the chlorpromazine therapy was resumed after two weeks cessation during the sixth month of treatment the skin reaction recurred.

Microscopic examination.—Thickening of the epidermis was evident in all the animals in this group. Increased epidermal pigment was observed in the red and black animals similar to that described in group 1. Again no dermal deposits of pigment were noted (Fig. 1).

Slit lamp examination.—At a magnification of ×16 the eyes of every animal were found to have lens opacities. The most frequent lesion was a veil-like opacity arranged in a geographic pattern (Fig. 2) and composed of small white dots. It was most commonly located in the anterior subcapsular area. The second most common site was the posterior cortex of the lens. No changes were observed in the nucleus, or associated with the suture lines of the lens. This lenticular lesion was not seen in any of the control animals of a similar age.

Group IV

S^{35} labeled chlorpromazine was not detected in any of the autoradiographic sections examined.

DISCUSSION

Chlorpromazine has been used (1) to alleviate the multiplicity of symptoms which are manifestations of mental disease; (2) as an antiemetic; and (3) to potentiate other central nervous system depressants. A large number of side effects have been attributed to the drug, yet none has been sufficiently severe or frequent enough to outweigh the therapeutic benefits derived from its use. Until Greiner and Berry described the pigmentary phenomena associated with chlorpromazine therapy, the only dermatological reactions recorded in the literature were of the photosensitivity type, both photoallergic and phototoxic. Exfoliative dermatitis had been reported infrequently.

Chlorpromazine pigmentation in the human subject gives a mild to pronounced, diffuse, purplish-grey metallic discoloration to the exposed skin surfaces. The exposed bulbar conjunctivae in patients with extensive skin pigmentation are usually brown in color. The

‡ We wish to thank Dr. Rufus Howard of the Department of Surgery, Yale University School of Medicine for examining the guinea-pig eyes.

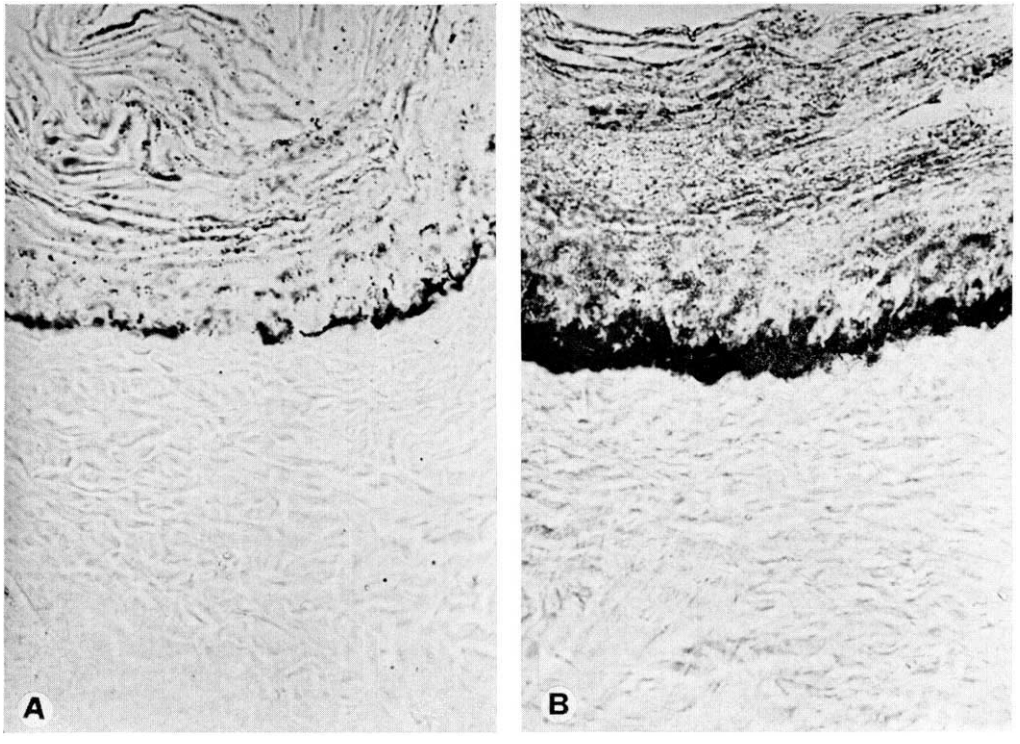

FIG. 1. Photomicrograph of vertical sections of dorsal skin of black mature male guinea pig (a) before treatment (b) after 12 months treatment with chlorpromazine and ultraviolet light. Shows a marked increase in the amount of melanin present in all layers of the epidermis especially in the basal layer. Note the complete absence of pigment in the dermis. No stain, × 150.

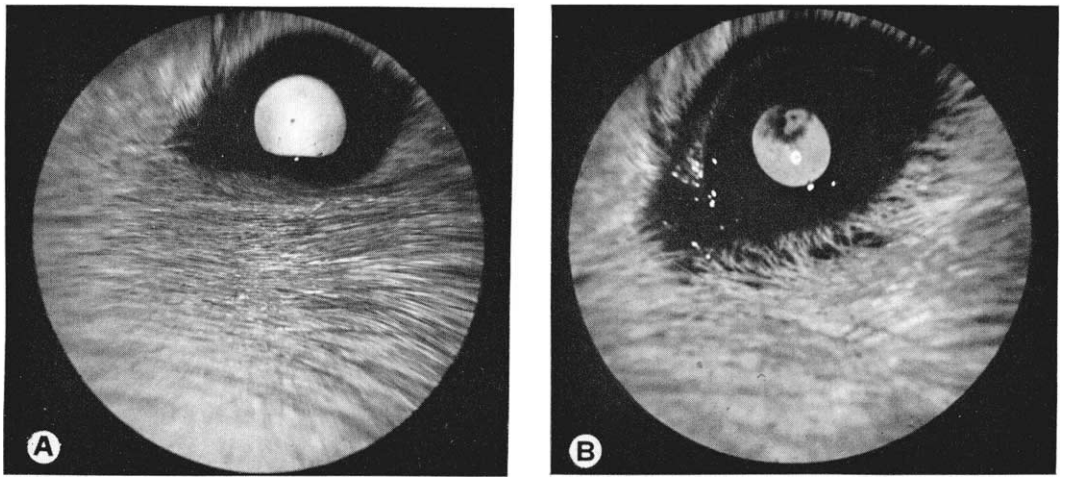

FIG. 2. Photograph of the eye of a red guinea pig. (a) no treatment (b) after 12 months treatment with chlorpromazine and ultraviolet light. Shows the veil-like lenticular opacity arranged in a geographic pattern.

difference in color of the pigment in the two regions is an apparent one and is due to the different optical properties of the tissue in which the pigment is located.

Histopathologically, the epidermis is normal. Extensive deposits of finely granular, golden brown pigment are seen in reticuloendothelial cells in the upper third of the dermis. The heavily laden cells usually lie in close proximity to capillaries. Silver stains of this material are strongly positive, peroxide bleaches out the pigment, and iron and fat stains have been consistently negative. As a result of the above reactions, Greiner and Berry and others felt strongly that the pigment is melanin (1, 5, 10). More recent studies by Zelickson and others have shown that the pigment does not have the same electron microscopic appearance as melanin (11). The intraocular manifestations are corneal opacities which are made up of a yellow-white granular material and central, stellate lenticular opacities composed of yellow-white granular material (12–14).

In the current experiments using the guinea pig, attempts were made to simulate conditions which were presumed necessary for the production of abnormal pigmentation in the human subject. Chlorpromazine was administered in large doses over a long period of time, and since cutaneous pigmentation only occurred on exposed surfaces, the shaved animals were subjected to continuous ultraviolet light. A mild toxic dermatitis was demonstrated when drug therapy was initiated and when it was resumed after an interval of two weeks during the sixth month of treatment but no dermal reaction was demonstrated. Although the drug was continued for a total period of 12 months in one group of animals it is possible that, in the guinea pig, chlorpromazine had to be administered for a longer period of time to produce recognizable skin changes. The ocular findings on the other hand, closely resembled those described previously in the human subject (12–14). Intraocular lesions are much more prevalent than skin findings in humans, and it is generally believed that ocular lesions precede the onset of skin lesions.

SUMMARY

(1) Large doses of chlorpromazine were administered to albino, red and black guinea pigs in an attempt to reproduce the abnormal oculocutaneous pigmentation reported in the human subject.

(2) After giving the drug for a period of 12 months and exposing the shaved animals continuously to ultraviolet light, no dermal deposits of pigment were demonstrated.

(3) Slit lamp examination of the guinea pig eyes following the drug treatment revealed lens opacities in all the animals. These were composed of small white dots located in the anterior subcapsular area and also in the posterior cortex of the lens. They were identical with those reported in the human subject.

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