CORRESPONDENCE

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BLUISH COLORATION IN LEPROMATOUS LESIONS DURING TREATMENT WITH AMODIAQUIN

To the Editor:

Some time ago Dr. J. A. Doull published [The Journal **27** (1959) 385] an interesting letter under the above title, calling attention to a matter in which I have been interested ([1–4]). I would suggest that the condition he described may be explained as a fixed drug eruption characterized by a nonspecific hypermelanosis due to amodiaquin (Camoquin) administered in a daily dosage of 0.2 gm.

Skin pigmentation with Camoquin used as a malarial suppressive has been reported by Campbell ([5]) in the nailbeds of fingers and toes, the nose, and "other parts of the face, lips and palate." The pigmentation was discrete in localized macules, or diffuse and extensive. Photosensitivity may have been a factor in its production. With a suppressive dose of 0.6 gm. of amodiaquin weekly, the minimum period elapsing before the appearance of the hyperpigmentation was about 12 months; i.e., the total dose administered would be about twice the amount given in Doull's cases in 10 weeks.

If the quantities of amodiaquin actually employed in Doull's series were standard minimal or optimal therapeutic or prophylactic doses, the usefulness of the drug would be limited because of the high proportion of persons affected by the cutaneous pigmentation, just as Nirvanol (phenylethyl hydantoin), used for a time in chorea and epilepsy, had to be abandoned for similar reasons ([8]).

These observations on hyperpigmentation following the administration of an antimalarial drug are to be considered in relation to similar reports in respect of mepacrine (references in ([2])), and chloroquine ([6]); and to findings with sulfones and sulfonamides recently reported by me.

In the case of mepacrine, cutaneous rashes (including facial hypermelanosis and diffuse blueness) developed in 0.2 per cent of subjects after taking the drug from 1 to 11 months; when the suppressive daily dose exceeded 0.1 gm., the incident of rashes was higher and their appearance was accelerated.

The clinical picture in those cases, conforming to the pattern seen by Doull, is that of a discrete macular or diffuse hypermelanosis of postinflammatory type. Histologically, there is a deposition of finely granular melanin, chiefly extracellular, in the papillary and reticular layers of the dermis.

In one well-defined group of cases observed in which the hyper-

melanosis followed sulfone therapy ([2]), the lesions on the face occurred in areas reminiscent of that of chloasma uterinum ([9]), i.e., in the butterfly (or bat's-wing) area; in the peripheral parts of the forehead, cheeks and chin; on the central forehead and the most prominent parts of the nose, cheeks and chin; or in ill-defined macules scattered over the face. In some patients the hyperpigmentation fortuitously occurred near lepromatous lesions on the face. Hypermelanosis may be confined to the face, in which case the areas involved are usually affected diffusely; more often, discrete and well-defined macules occur elsewhere. It may be observed in the mucosae (nasal, buccal, labial, urethral), and the conjunctivae, as well as the skin and nails.

A most interesting observation is that while the areas of sulfone-induced hypermelanosis usually react like the well-known fixed drug eruptions of phenolphthalein, phenacetin, phenazone, etc., becoming inflamed on each subsequent administration of the incriminated drug, in some cases further ingestion of the drug causes no local exacerbation.

According to Wise and Sulzberger ([10]), in the case of phenolphthalein-induced fixed drug eruptions, it is not the epidermis itself that is sensitized, since full-thickness skin taken from a normal area and grafted on to the affected area will react to subsequent administration of phenolphthalein, whereas skin from the affected area transplanted to a normal area will not so react (Naegeli's transplantation); i.e., the mechanism may be nervous.

I have observed a few instances of parallergic sensitization: some patients sensitive to dapsone are also sensitive to sulfoxide, and even rarely to diphenylthiourea and to Etisul, reacting with a diffuse facial hypermelanosis or with focal exacerbation of existing hypermelanotic macules.

The blue color observed by Doull is optically similar in origin to the blue of blue nevi and of Mongolian spots, i.e., it is due to light from fine particles in the dermis passing through the collagen—the so-called "scattering phenomenon," or Tyndall effect. Particulate matter, whatever its nature or color, will in this situation appear blue. The degree of blueness depends principally on the fineness of the particles, and also on their disposition and depth in the dermis. It is not necessary to posit the transformation of amodiaquin into a blue compound to account for the observed blueness.

The actual shade of blueness seen in any given subject depends not only on the factors enumerated, but also on the existing skin pigmentation. Thus, if the pigment-bearing cells of the epidermis are lost by desquamation, the blue will appear unchanged. In neighboring areas, however, where the epithelium is intact, a similar basic degree of blueness will be modified by the existing normal cutaneous pigmentation and appear as slate-gray, blue-gray or purplish-black, depending on the actual amount of melanin present superficially.

The localization of the hypermelanosis is of much interest, but the mechanism is obscure. It is tempting to speculate that the fixed and nonfixed eruptions may find a parallel in the polar forms of leprosy, in which an apparently similar agent may either induce a marked allergic response in skin and nerves, or multiply unstrainedly in the cells of the reticuloendothelial system.

The localization of the hypermelanosis on the face may possibly be mediated by a pituitary hormone, as may chloasma uterinum.

The concentration of the blueness near lepromatous lesions of the face seen in Doull's cases may be compared with the hypermelanosis frequently observed in these situations in cases under treatment with the sulfones. It would be interesting to learn if similar bluish coloration is present elsewhere on the body, and if so whether it is confined to the vicinity of lepromatous lesions.

The fact that white mice show no lesions when given amodiaquin is consistent with the supposition that the condition observed is a hypermelanosis; *white* mice cannot respond by hypermelanosis. Similarly, white mice do not develop blue macules when given Sulphetrone, nor do cows when treated by intramammary injection of dapsone (DDS) for streptococcal mastitis.

The presence of pigment giving the reactions of iron would be of crucial value if constant, but it would appear to be fortuitous. Biopsies should be made for the purpose of elucidating this point, and of determining if the pigment gives the histo-reactions of a melanin, being bleached by hydrogen peroxide.

Another observation that may be of interest in this connection is the therapeutic effect of the antimalarials, mepacrine and chloroquine, in lupus erythematosus, a collagenosis of uncertain etiology occurring frequently in a region of great dermatologic and neurologic significance.

I hope that these observations may resolve some of the questions raised by Doull's letter, and stimulate further discussion of some of the interesting problems he has indicated.

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