primordium of the limbs appears, also induces anomalies. For this fact, we are at present not able to give a definite conclusion—that is, the possibility that this chemical affects the cells of the earlier stage than the primordium or that its action continues in the embryo for many days could not be decided. There are many chemical agents, which induce teratogenic effects mainly on the skeletal system, such as nitrogen mustard (*4*), ethylurethan (*5*), 8-azaguanine (*6*), 2,3-dimercaptopropanol (BAL) (*7*). But it is peculiar to the case of nicotine treatment that the critical period for anomalies in limbs is so long and that malformations so often occur in the various joints.

It may be concluded that we confirmed that nicotine has a lethal effect upon embryos of mice and also has a powerful teratogenic effect on their skeletal system when it is administered during pregnancy.

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Effects of 8-Methoxypsoralen and Ultraviolet Light in Human Skin

Extracts of *Ammi majus* (Linn.) have been used by the Egyptians as pigmenting agents for centuries (*1*). Recently one of the active ingredients of this plant (8-methoxypsoralen) has been publicized by magazines and newspapers as the "sun-tan pill." This substance has been used in the treatment of vitiligo, a disease of human skin in which circumscribed spots of the skin stop forming pigment. 8-Methoxypsoralen has been shown to be a photosensitizer (*2*) but, paradoxically, many individuals have reported that the ingestion of this substance protects them against sunburn (*3*).

The following experiment (*4*) was performed to clarify the mechanism by which 8-methoxypsoralen and sunlight alter the physiological reactions of human skin. The subject (blond, blue-eyed, healthy, 33-year-old white male) exposed an area of the left thigh to ultraviolet irradiation with a mercury vapor lamp at 30 inches distance and with exposure times of 1, 3, 5, 5, 5, 5, 10, 10, 15, 15, 15, 15, 15, and 15 minutes on successive days. Afterward a similar area of the right thigh was exposed in the same manner, but in this second series of irradiations, 20 mg of 8-methoxypsoralen was taken by mouth 2 hours before each exposure. The ultraviolet irradiation was of low intensity, and no clinical redness was produced at any time. Specimens of skin for microscopic examination were removed from the irradiated areas of both thighs on the 7th and 14th days of the irradiation series.

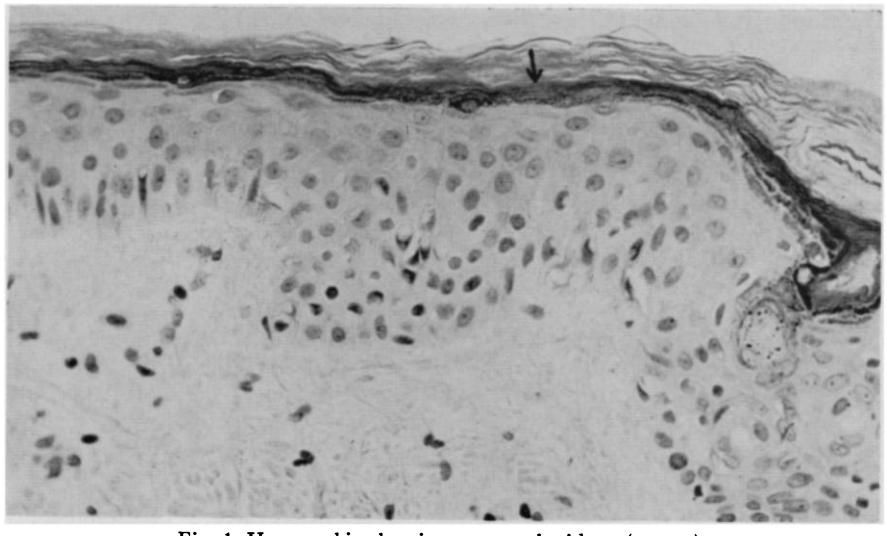

Fig. 1. Human skin showing stratum lucidum (arrow).

After 14 days of irradiation, the threshold erythema dose of ultraviolet light in the treated area of the left thigh was 25 minutes; 50 minutes of irradiation to the corresponding area of the right thigh produced no redness. Microscopic examination of the specimens of skin revealed that the most prominent change occurred in the horny layer. The horny layer had thickened in both treated areas, but the specimen from the right thigh also revealed the formation of a stratum lucidum. Normally, a stratum lucidum is seen only in areas where the epidermis develops a thick horny layer —for example, on palms and soles. Physiologically, it is never seen in the skin of the thigh. The thickening of the stratum corneum and formation of a stratum lucidum appears to represent the initial reaction of the skin in response to 8-methoxypsoralen and sunlight. There was no melanin present in the stratum corneum in these specimens, so the increased tolerance to ultraviolet light was due solely to the alteration in the horny layer. Miescher (*5*) has shown that ultraviolet irradiation produces thickening of the horny layer; such thickening constitutes the primary protective mechanism of the skin against ultraviolet irradiation. Microscopic examination of skin from the back of an individual who had been using 8-methoxypsoralen and sunlight for 2 months revealed a prominent stratum lucidum (Fig. 1.).

The combination of ultraviolet light and 8-methoxypsoralen resulted in more new pigment formation in the treated area of the right thigh than in the corresponding control area of the left thigh. The quantity of newly formed pigment was not great. Examination of the skin from the individual who had used 8-methoxypsoralen for 2 months revealed an abnormally large amount of pigment in both the basal cell layer and the horny layer. The pigment-forming cells and their dendritic processes were not filled with melanin. The absence of pigment in the dendritic processes would indicate that no great amount of pigment was being formed at the time the specimen of skin was removed. It appears from these findings that, while 8-methoxypsoralen increases the pigmenting effect of ultraviolet light, the development of the psoralen tan is due primarily to retention of pigment in the skin. The psoralen tan has a curious quality (*6*), and this may be due to the large amount of melanin retained in the altered horny layer.

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