In Memory of Thomas Bernhard Fitzpatrick

Madhu A. Pathak

Harvard Medical School and Massachusetts General Hospital, Boston, Massachusetts, USA

My long association with T.B. Fitzpatrick (TBF) at Portland, Oregon and Boston, Massachusetts covers a span of 47 years—from 1956 to 2003. This essay fulfills one of Fitzpatrick’s quotations by Oliver Wendell Holmes: “Historic continuity with the past is not a duty, it is only a necessity”.

In 1980 TBF told me, “The Department is built on the strength and dedicated efforts of its faculty, residents, fellows and staff of both clinical and basic research. No stronger foundations can exist than that of trust, respect, and desire shared by these parties working for advances in the basic sciences and clinical areas and for the excellent care of patients”. He inspired me to work in my research laboratories and generate additional funds for the science of skin diseases.

In 1956, after careful evaluation and strong recommendations from his trusted friend Dr Soli Hakim (Oxford University), TBF invited me to work in his research unit at the University of Oregon Medical School in Portland, where he was the chairman and Professor of Dermatology. Fitzpatrick was fascinated with the melanogenic and sun-tan stimulating action of 8-methoxypsoralen (8-MOP), isolated by chemists from an Egyptian plant (Ammi majus Lin). TBF was using 8-MOP for repigmenting the amelanotic and disfiguring skin of vitiligo patients and for treating the hypopigmented skin of fair-skinned Caucasians. The research unit at Portland included: Dr Howard Mason, a professor of Biochemistry working on tyrosinase and tyrosine and its hydroxylation and subsequent oxidation to melanin; Dr W.L. Fowlkes, an organic chemist interested in photochemical interaction of UV radiation and biological substrates, including the inhibition of mitochondrial enzymes and photosensitized lethal inhibition of bacterial growth; Dr A. Kukita, a dermatologist from the University of Tokyo Medical School working on melanin pigmentation of human hair with radio-labeled tyrosine; Dr George Szabo, an anatomist studying the population density of melanocytes of all ethnic varieties of human skin in different regions of the body.

Having a background in biochemistry and pharmaceutical and medicinal chemistry, with two postgraduate degrees from Bombay University, I was assigned to work on furocoumarins (psoralens and isopsoralens) and enrolled as a PhD student in biochemistry and biophysics on the skin photosensitizing action and augmentation of melanin pigmentation. We established that linearly annulated tricyclic furocoumarins (e.g., 8-MOP, 5-MOP, 4,5,8 trimethyl-psoralen, TMP) and a few other psoralens (over 10) were uniquely photoactive, inducing phototoxicity and increased melanin pigmentation of mammalian skin.

Professor M. Seiji of Sendai, Japan collaborated with TBF at Oregon in 1958, and subsequently in the UK generated the identity of melanosomes that constituted the end product of melanocytes and melanin pigmentation of skin. Dr Seiji and I became close friends when we both came to Boston in 1960 to work at MGH.

Since 1959 the use of psoralens and UVA radiation have been the subject of at least six (or perhaps more) dermatologic conferences actively encouraged by Fitzpatrick and other interested investigators in photobiology to permit the exchange of information among scientists and clinicians. Fitzpatrick encouraged all of us to work with total intellectual freedom to acquire new knowledge and to probe in depth the beneficial or adverse reactions to psoralens by living organisms (bacteria, plants, laboratory animals, and informed human subjects with skin problems). Fitzpatrick promoted an international meeting to allow scientists and clinicians to evolve an avenue for better treatment of skin diseases with pigmentary problems. He strongly postulated that oral psoralens would constitute a better prophylactic approach to ward off and reduce actinic damage to fair-skinned individuals.

Since the dramatic effectiveness of psoralen phototherapy (PUVA) in the treatment of many different heterogenous diseases of the skin was observed, there was a resurgence of worldwide interest in photobiology and UVA radiation. Dermatology initiated a new era in “photomedicine” for the treatment of various skin diseases. TBF’s book, *Therapeutic Photomedicine*, edited by H. Honigsmann and G. Stingl, provides a comprehensive review of therapeutc photomedicine involving psoralens and UVA radiation, as well as detailed information on the current clinical and experimental developments in the field of photomedicine in the treatment of psoriasis, cutaneous T cell lymphoma, vitiligo and photodermatoses, with well-documented sources of original papers and references. By 1988, the psoralens and high intensity UVA radiation sources were widely used in the USA, Europe, Japan and the rest of the world.

The use of retinoids given concurrently with PUVA increased the efficacy of psoralens in the treatment of severe psoriasis and other skin diseases. The Sixth International symposium entitled “Les Psoralenes” was held at Brussels in 1991. This symposium included several leading researchers on psoralens from France, Germany, UK, USA and some countries of Africa and Asia. It emphasized the need for photoprotection and photomedicine protection of human “white skin” against sun-induced skin cancer from increased UVB radiation as a result of
stratospheric ozone depletion. Unlike the US experience, the carcinogenic risk of PUVA therapy was less emphasized and reported in patients receiving PUVA therapy with TMP or 5-MOP. Besides the beneficial effects of 8-MOP and UVA photochemotherapy on psoriasis and other skin diseases, the use of 5-MOP (Bergapten) in France was shown to be equally as good or even better for treatment of psoriasis and severe cases of vitiligo in India and Africa. 5-MOP was found to be less nauseating and induced no pruritus or skin photosensitization in patients, compared to 8-MOP.

Fitzpatrick will be remembered as a world-leading dermatologist-scientist for his basic and clinical research contributions. With the help of his associates, TBF contributed to the treatment of vitiligo using either 8-MOP, 5-MOP, or TMP in over 600 patients with well regulated sunlight exposure doses for people of poor countries, where high intensity UVA emitting lamps are not readily available for providing PUVA therapy as practiced in the USA and Europe. Other dermatologists may not like this approach, but TBF strongly emphasized the precautions necessary to prevent phototoxic skin reactions and eye problems in patients receiving either 8-MOP, 5-MOP or TMP plus solar UV exposure.

TBF’s contributions to decreasing skin hyperpigmentation in patients with melasma and his use of 2–3% hydroquinine with 0.05% retinoic acid and the topical use of broad-spectrum, high SPF sunscreens is highly recommended and used by physicians all over the world to treat patients with melasma. His contributions to treating total depigmentation of skin in patients with disfiguring, generalized vitiligo with 20% monobenzyl ether of hydroquinone (Benoquin) have been recognized for achieving “one tone skin color” in children and adults. He in fact did not recommend the use of 4-isoprophyl catechol (4-IPC), a more effective and potent depigmenting agent than Benoquin. 4-IPC was found to cause delayed skin sensitization reactions not only at the site of application but also at other distal sites. He often recommended and even initiated and conducted well-controlled clinical trials on the effectiveness of sunscreens for protecting the skin of fair-skinned individuals against actinic damage.

In this regard, I still recall the outdoor sunscreen study in Brisbane, Australia in 1972 where TBF tested Australian, European, and US sunscreens using paid Australian volunteers with the approval of a regional hospital in Brisbane. He did not hesitate to comment to the Australian Press reporters on the poor photoprotection results of Australian sunscreens. He learned from the results of this study to classify skin responses of fair-skinned Australians who participated in his study of midday sun exposure into three main sun reactive categories: Skin Phototype I: those who burn easily and do not tan at all; Skin Phototype II: those who burn easily and tan with difficulty (freckled and often red-haired individuals); and Skin Phototype III: those who burn moderately, show immediate pigment darkening reactions and tan moderately after about 60 minutes of midday sun exposure. These classifications were very helpful back in Boston in regulating and administering UV doses for PUVA therapy in patients with psoriasis. Fitzpatrick’s skin phototypes I, II, III, and IV became well accepted and popular in dermatology for phototherapy of skin diseases and SPF evaluation of sunscreens. In 1972, the US FDA adopted this classification for the evaluation of SPF values of sunscreens.

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