Dithranol

In 1888 Robert Wilhelm described psoriasis as a clinical entity in his book, "On Cutaneous Diseas[1]. Most new treatments for psoriasis for more than 100 years have been discovered through serendipity and not through scientific design. We contest that the art of medicine is the prime innovator for radical new therapeutic approaches, whereas the science of medicine is responsible for slow incremental change.

Vitamin D Analogues

Topical Vitamin D analogues have been used for over a decade for psoriasis. The discovery of their usefulness as a treatment for psoriasis was by chance. Muramoto and Kumahara in 1973 described a patient whose psoriasis was “cured” by oral administration of 1, 25-dihydroxyvitamin D3. They describe a 90 year old man who had been referred for treatment for osteoporosis. He was also noted to have extensive large plaque psoriasis. He was given 5.75 µg/day of 1, 25-dihydroxyvitamin D3 orally. He was not receiving either topical or systemic treatments for psoriasis. Within 2 months his psoriasis had cleared. The same researchers published an article in the British Journal of Dermatology a year later looking at the effects of oral and topical forms of vitamin D2 or 25-hydroxyvitamin D3 on Psoriasis.[2]

Cyclosporin A

Sandor Laboratories discovered and isolated cyclosporin A (CSA) from the soil fungi Trichoderma polysporum and cyllindrocarbon lucidum in 1973.[3] Although CSA had only weak antibiotic activity it was found to have immunosuppressive properties. It was initially licensed for organ transplantation after successful trials in patients receiving renal allografts.[4] In a pilot study to investigate the effect of CSA in patients with rheumatoid arthritis, four patients with psoriatic arthritis were also treated. CO2, O2 for all patients had almost total clearance of their psoriasis within one week of CSA orally. The psoriatic lesions gradually returned in all patients to their previous severity about two weeks after stopping CSA. The study showed only a moderate effect of CSA when treating the patients with rheumatoid arthritis.

Retinoids:

Animals deprived of vitamin A were shown to have modifications of the epidermal structure with increased epidermal keratinisation and squamous metaplasia of the mucous membranes.[5] In man, vitamin A deficiency manifests itself with dry skin and follicular hyperkeratosis.[6] This observation led researchers to postulate a role for vitamin A in the pathogenesis of Darier’s disease.[7] In 1946, Studer and Frey[8] observed that sub- toxic doses of vitamin A could induce “peeling” of the horny layer and it was then thought that it could be used as a treatment for acne. Initial therapeutic trials with megadoses of vitamin A were found to have a slight improvement in psoriasis but unfortunately the subjects developed hyperkeratosis A syndrome with dryness of mucous membranes, desquamation of healthy skin and neurological problems.[9] During the 1980s and 70s new synthetic vitamin A analogues, such as isotretinoin, were found to be very effective treatment for acne. By 1975, a new aromatic retinoid, etretinate was tested in patients with psoriasis. This compound had a therapeutic index ten times more favourable than all-trans-retinoic acid and very encouraging clinical results were reported.[10] The use of retinoids and their development as a treatment for psoriasis is the only group that bucks the trend closer to science than serendipity.

Dithranol (antikrepsin) has been used as a treatment for psoriasis for over a hundred years. The first scientific reference to its use by Balmanno Squire of Cuticura Ltd, London, in 1870 is cited in a book on hair and scalp disorders. A patient of his told him that he had used the powder to treat “ringed” psoriasis. The patient had mistaken the psoriasis for ringworm. Goa powder had been used for centuries to treat fungal infections. Squire remarked on the skin irritation and skin staining. Goa powder was derived from the araroba tree which grew in the Bahia province in Brazil. The active ingredient in the powder was chrysarobine. The first related synthesised preparation arnoidrol was made in Germany and shown to be effective treatment for psoriasis by Galewsky in 1916.[11] The use of topical anthralin was described by Katter in 1932. He was also noted to have extensive large plaque psoriasis. He was given 0.75 mg/kg of 1, 25-dihydroxyvitamin D3 daily. He responded well to daily oral aminopterin, although all developed side effects (8). Excellent results were found in 75% of the patients and toxic effects were said to be rare.

Antimetabolites

Methotrexate has been used as a systemic treatment for psoriasis for about forty years. The discovery that folate antagonists were effective treatment for psoriasis was also made by chance. Gobiner et al in 1951 described a patient who was being treated with antifolates (closely related to methotrexate) for rheumatoid arthritis, they observed a striking remission of the patient’s psoriasis. The patient had a history of psoriasis of 22 years duration and all responded well to daily oral antifolates, although all developed side effects (8).

Subsequently Etminan and Guy[12] attempted to prove that chrysarobine to be of value for psoriasis. The study had 24 patients treated with antifolates and 13 treated with methotrexate. Excellent results were found in 70% of the patients and toxic effects were said to be rare.

Serendipity or science; historical evidence predicts future advances in psoriasis treatment.

Vitamin D3 analogues have been used for over a decade for psoriasis. The discovery of their usefulness as a treatment for psoriasis was by chance. Muramoto and Kumahara in 1973 described a patient whose psoriasis was “cured” by oral administration of 1, 25-dihydroxyvitamin D3. They describe a 90 year old man who had been referred for treatment for osteoporosis. He was also noted to have extensive large plaque psoriasis. He was given 5.75 µg/day of 1, 25-dihydroxyvitamin D3 orally. He was not receiving either topical or systemic treatments for psoriasis. Within 2 months his psoriasis had cleared.

Reinforcements:

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Other Treatments

Topical corticosteroids were developed in the 1950s and were tried as treatment for many different inflammatory dermatoses. Initial results were disappointing as the early preparations of topical corticosteroids were of a low potency. In the early 1950s topical corticosteroids were being used under occlusive dressings as a treatment for psoriasis.[11] The subsequent development of more potent topical steroids lessened the need for occlusion. The initial use of coal tar and ultraviolet light is hidden in the past but their use was surely serendipitous.

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Conclusions

Dermatology is not alone in its reliance on serendipity for advancement of treatments, this can broadly be said of all medical science. Surely the greatest advancement in medicine in the twentieth century was the discovery of antibiotics, that would not have occurred if Fleming had been more meticulous in laboratory cleanliness. That is not to underestimate the genius of many of medicine’s forerunners but to credit their exploitation of serendipity. In the future should we invest in specific drug development programs or just give the money to various scientists and clinicians to allow them to satisfy their own curiosity? History would suggest that the latter option may be more rewarding.

References

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