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

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'chance favours the prepared mind'

Louis Pasteur

In 1808 Robert Willan described psoriasis as a clinical entity in his book " On Cutaneous Diseases(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.

Figure 1: Robert Willan (1757-1813)

Dithranol

Dithranol (anthralin) has been used as a treatment for psoriasis for over one hundred years. The first scientific reference to its use was by Balmanno Squire in 1876 (2)(3).It was originally derived from a natural product called Goa powder. A patient of his told him that he had used the powder to treat "ringed" psoriasis. The patient had mistook the psoriasis for ring worm. 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 anthralin was made in Germany and shown to be effective treatment for psoriasis by Galewsky in 1916 (4)

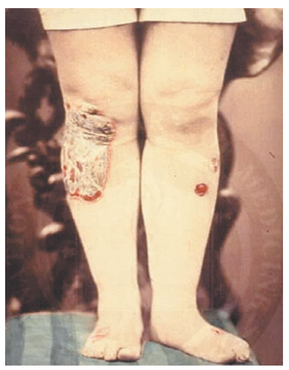

Figure 2: 'Squame' illustration from Balmanno Squire's Book 'Photographs of Diseases of the skin' published by John Churchill and Sons, London 1865. Balmanno Squire made the first scientific reference for the use of Goa powder (the forerunner of dithranol) as a treatment for psoriasis.

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. Morimoto and Kumahara in 1985 described a patient whose psoriasis was 'cured' by oral administration of 1 a, 25-dihydroxyvitamin D_3 (5).They describe a 81 year old man who had been referred for treatment for osteoporosis. He was also noted to have extensive large plaque psoriasis. He was given 0.75 mg/day of 1a-hydroxyvitamin D_3 orally. He was not receiving either topical or systemic treatments for psoriasis. Within 2 months his psoriasis had cleared. The same researchers published an open study in the British Journal of Dermatology a year later looking at the effects of oral and topical forms of vitamin D_3 on Psoriasis(6).

Figure 3: Wood engraving from Harper's Weekly 1879. Cuticura remedies have not been subject to clinical trials where as vitamin D analogues have.

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. Gubner et al in 1951 described a patient that was being treated with aminopterin (closely related to methotrexate) for rheumatoid arthritis, they observed a striking remission of the patient's psoriasis (7). Gubner then did a follow up study with 13 patients with psoriasis who all responded well to daily oral aminopterin, alhough all developed side effects (8). Subsequently Edmundson and Guy found methotrexate to be of value for psoriasis (9). The study had 24 patients treated with aminopterin and 13 treated with methotrexate. Excellent results were found in 75% of the patients and toxic effects were said to be rare.

Figure 4: Folic Acid studies in rats in a laboratory in Bethesda, Maryland, USA 1954.

Cyclosporin A

Sandoz Laboratories discovered and isolated cyclosporin A (CSA) from the soil fungi Trichoderma polysporum and cyclindrocarbon lucidum in 1973 (10). 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 (11). In a pilot study to investigate the effect of CSA in patients with rheumatoid arthritis, four patients with psoriatic arthritis were also treated (12). All four 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.

Figure 5: Joseph Stalin 1879-1953. Had Cyclosporin A been available to treat Stalin's psoriasis, would he have been such a homicidal maniac?

Retinoids:

Animals deprived of vitamin A were shown to have modifications of the epithelial structure with increased epidermal keratinisation and squamous metaplasia of the mucous membranes (13). In man, vitamin A deficiency manifests itself with dry skin and follicular hyperkeratosis (14). This observation led researchers to postulate a role for vitamin A in the pathogenesis of Darier's disease (15). In 1949, Studer and Frey (16) observed that sub-toxic doses of vitamin A could induce 'peeling' of the horny layer and it was then thought that it could be of use as a treatment for psoriasis. Initial therapeutic trials with megadoses of vitamin A were found to have a slight improvement in psoriasis but unfortunately the subjects developed Hypervitaminoses A syndrome with dryness of mucous membranes, desquamation of healthy skin and neurological problems (17). During the 1960's and 70's 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 that all- trans-retinoic acid and very encouraging clinical results were reported (18). 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

Other Treatments

Topical corticosteroids were developed in the 1950's 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 1960's topical corticosteroids were being used under occlusive dressings as a treatment for psoriasis (19). 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.

Figure 6: Use the supreme skin remedy, Sulphide of arsenicum, M Buffords sons 1876. Not all treatments for skin diseases have stood the test of time.

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 forefathers but to celebrate 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 !

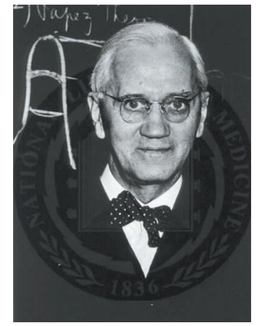

Figure 7: Alexander Fleming 1881-1955. Inspired Genius or dirty chemist?

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