

# WHAT IS THE MOST IMPORTANT ADVANCE IN DERMATOLOGY IN THE LAST 25 YEARS?

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## **What is the most important advance in dermatology in the last 25 years?**

### **Introduction**

The capacity of the skin and its associated conditions to incite an intrinsic fascination seems limitless. With around 2000 estimated diagnoses, dermatology boasts an unmatched abundance of clinical variety. From the neonate afflicted by a genodermatosis to the elderly patient with skin cancer, the scope of dermatology is broad and tremendously varied, and progression within this specialty has the potential to significantly enhance all aspects of patient care.

The last 25 years have seen the exciting hallmarks of dermatological advancements come in many forms. Genetic and therapeutic innovation has accelerated our understanding of the mechanisms underlying cutaneous disease and broadened treatment options, whilst evolution of the sub-specialty psychodermatology is addressing the demand for holistic management, and the combined feat of continued education, research and public awareness continues to raise the profile of the dermatological discipline. Collectively, these developments are paramount to the success of the unique medico-surgical specialty we behold today.

### **Lasers**

Significant advances in the development and use of lasers has revolutionised their application in the practice of modern dermatology. The destructive potential of the laser (*light amplification by stimulated emission of radiation*), its role first established in skin by Goldman *et al* in their treatment of tattoos,<sup>1</sup> has since been harnessed, focused and refined to produce a versatile tool currently at the forefront of management for many

dermatological conditions. The need for improved laser technology was realised with the unacceptably high rate of scar formation and suboptimal results in the treatment of port wine stains (PWS).<sup>2</sup> The continuous energy delivered by the argon laser, an early instrument in dermatological laser innovation, dispersed into neighbouring dermis producing non-selective thermal damage.<sup>3</sup> The science of 'selective photothermolysis' (SPTL) was thus introduced:<sup>4</sup> specific destruction of chromophores (light-absorbing molecules) via intense pulses of light at a preferential wavelength, allowing better localisation of thermal energy and minimisation of damage to surrounding tissues.<sup>5</sup> This theory was the key to modern laser dermatology and the basis for an abundance of novel therapeutic instruments, namely pulsed lasers.

With the possibility of choosing treatments based on wavelength and pulse duration, this rapidly expanding therapy led to and continues to inspire a surge of contemporary applications for pulsed lasers. The millisecond pulsed dye laser is the first example of any such instrument to be created exclusively for the purpose of medical intervention. In fact, it remains the treatment of choice for neonatal and childhood PWS,<sup>6</sup> a microvascular malformation that left untreated may cause significant psychological burden for child and parent alike.<sup>7</sup> Owing to advancements in technology, pigmented skin structures containing melanin or carbon can also be successfully treated by Q-switched lasers, a further example of the radical pulsed laser. This includes the removal of tattoos once limited by the likelihood of scarring, and treatment other disorders of cutaneous pigmentation such as nevus of Ota, café-au-lait macules, solar lentigines, melasma and post-inflammatory skin changes.<sup>8</sup>

New concepts in laser technology further extend to encompass the successful treatment of photoaged skin and removal of unwanted hair. The notion of epidermal sparing for improved skin rejuvenation commanded the use of fractional photothermolysis, a non-selective counterpart of SPTL.<sup>9</sup> The first laser treatment to accurately control the depth and width of skin treated, inducing vertical columns of dermal thermal wounds via thousands of focused laser micro-beams,<sup>10</sup> this innovation evaded the epidermal damage associated with earlier ablative techniques, and is a highly effective strategy for skin resurfacing and the treatment of fine lines.

### **Melanoma genetics and targeted therapies**

Of the cutaneous malignancies, melanoma possesses the greatest potential for metastasis. Not only is it aggressive, but it is becoming increasingly common: it is the fifth most frequent and second fastest rising cancer in the UK.<sup>11</sup> Although early diagnosis and surgical resection of the primary tumour is still the best opportunity for cure,<sup>12</sup> metastatic melanoma has historically portended a poor prognosis.<sup>13</sup> Limited treatment options for advanced disease, punctuated by an intrinsic resistance to chemotherapy and a tendency for rapid progression,<sup>14</sup> makes the escalating number of cases especially troubling. With this in mind, the landmark discovery of activating mutations in the BRAF oncogene, present in up to half of all malignant melanomas,<sup>15</sup> offered renewed hope in the battle against metastatic and recurring melanomas; it provided an opportunity for tumour genotypes to be translated into clinically effective targeted therapies.

The treatment landscape for late-stage melanoma has thus been revolutionised. Aberrant components of the mitogen-activated protein kinase (MAPK) pathway, in which BRAF is a key constituent, are responsible for unrestrained cellular proliferation in more than 90% of

melanomas.<sup>16</sup> The advent of several targeted therapies specifically directed at suppressing this mode of tumour growth have begun to challenge the notion that melanoma is one of the most treatment resistant malignancies. UK approved BRAF inhibitors, Vemurafenib and Dabrafenib, both confer a survival advantage over the traditional chemotherapy regimens utilised in advanced melanoma.<sup>17,18</sup> Additional developments in immunotherapy have also provided much promise for melanoma treatment. Ipilimumab, a monoclonal antibody employed to exploit the innate capacity of the immune system, also offers improved overall survival outcomes compared with conventional therapeutics.<sup>19</sup> Advances in the understanding of the genetics driving malignant melanoma have undoubtedly paved the way for remarkable progression in the development of novel strategies for melanoma treatment and will continue to do so.

## **Biologics**

The emergence of biologic agents has transformed the management of many autoimmune diseases, including those of a cutaneous nature. Since the advent of the first UK approved biologic in 2004, they have become a particularly prominent tool in the treatment of psoriasis.<sup>20</sup> A debilitating skin condition characterised by chronic inflammatory lesions, this hyperproliferative disorder of the epidermis is a highly visible disease. As with any disorder that elicits a discernible difference, the potentially disfiguring appearance of psoriasis carries enormous implications for a patient's psychological wellbeing<sup>21</sup> and patients are often additionally burdened by its associated symptoms; continual shedding, itching and tenderness<sup>22</sup> can be particularly troublesome and have a significant bearing on the quality of life of those affected by it.<sup>23</sup> It is therefore unsurprising that an opportunity for effective

control of the underlying inflammatory processes was greeted with great enthusiasm and overwhelming expectation.

Whilst traditional treatment modalities for psoriasis are well established and continue to play a major role in its management, studies have indicated a high degree of patient dissatisfaction with the effectiveness and safety of these conventional therapies.<sup>24</sup> A requirement for therapeutic options with increased tolerability, convenience in usage and lasting remissions was remedied by the arrival of biologics. Agents that target specific pathogenic events in the psoriatic inflammatory cascade,<sup>25</sup> these biological therapies offer a more direct approach to impeding the underlying disease process, improving symptom control and reducing associated co-morbidities.<sup>20</sup>

There are currently four biologic agents available for use in moderate-to-severe psoriasis, which fall into two distinct classes; Tumour Necrosis Factor- $\alpha$  antagonists (Infliximab, Etanercept and Adalimumab), and the newer Interleukin-12/23 monoclonal antibodies (Ustekinumab).<sup>26</sup> A plethora of randomised controlled trials (RCTs) have demonstrated good efficacy and benefit/risk profiles for these therapies in the first year of psoriasis treatment.<sup>27-32</sup> Although evaluation of long-term safety outcomes is still ongoing and the costly nature<sup>33</sup> of the drugs currently presents somewhat of an obstacle to prescribing, biologics undoubtedly provide a much sought after addition to the management of many conditions in both dermatology and other branches of medicine.

### **Psychodermatology**

Dermatologists and patients alike have long been aware of the complex interplay between mind and skin. Cutaneous disease has not only the potential to considerably influence one's

mental and emotional wellbeing, but may also be stimulated by the detrimental effects of various negative psychological states itself. In response to a vast and continually expanding body of research highlighting this interactive relationship, the field of psychodermatology has gained significant ground in recent years.<sup>34,35</sup> Psychodermatology encapsulates the very interaction between skin and the psyche. It addresses the psychosocial factors involved in the cycle between dermatological disease and mental health,<sup>36</sup> and in doing so provides a strong source of support for patients.

Research indicates that up to 40% of dermatology outpatients possess an underlying psychiatric disorder that either contributes to or is caused by a skin complaint,<sup>37</sup> and in depth studies of skin biology are consistent in reporting the link between compromised epidermal barrier function and psychological stressors.<sup>38,39</sup> With this in mind, it is clear that the needs of the psychodermatologic patient are complex and require attention that can only be provided by specialised clinics. The management of such patients in dedicated psychodermatology clinics promotes higher levels of service-user satisfaction; negative perceptions of isolated psychiatric consultations often results in nonattendance or rebuttal of referral.<sup>40</sup>

In support of the Government's pledge to improve quality of life in patients with chronic disease,<sup>41</sup> the UK Psychodermatology Working Party proposed a set of minimum standards for the provision of psychodermatology services in the UK.<sup>42</sup> This consensus statement is a fundamental first step in providing highly sought after psychological and psychiatric care for dermatology patients. Although provision of these services has previously been limited, the recognition of a necessity for integration of care is an important drive toward a more holistic approach to the patient.

## Genetic skin disease

Discoveries in cutaneous genetics have been driven by important progression in sequencing technologies and genome wide association studies. In 2006, after 20 years of complex genetic analysis, the underlying genetic component of atopic dermatitis (AD) was finally unravelled.<sup>43</sup> The identification of 2 common polymorphisms associated with AD signifies the single most significant breakthrough in understanding the genetic aspects involved in the complex aetiology of this very common disease.

Null mutations in the implicated filaggrin (*filament-aggregating protein*) gene lead to epidermal barrier dysfunction. Assisting in the formation of a cornified cell envelope during terminal epidermal differentiation,<sup>44</sup> filaggrin plays a key role in maintaining the mechanical integrity of the skin, providing a permeability barrier to water and allergens, and imparting natural cutaneous hydration.<sup>45</sup> Its deficiency, at least in part, helps to explain the dryness and inflammation characteristic of AD.

In fact, the post-Human Genome project era has been witness to a whole host of remarkable developments in the genodermatoses. The loss-of-function mutation in filaggrin is also central to the pathogenesis of ichthyosis vulgaris, the most commonly inherited disorder of keratinisation, which is highly prevalent and typified by excessively dry skin and an associated fine white scale.<sup>46</sup> Identification of the genes underlying several monogenic conditions have similarly provided a unique insight into the biology of a number of disease processes, including the ABCA12 gene mutation in harlequin ichthyosis,<sup>47</sup> abnormalities in the TRPV3 gene in Olmsted syndrome<sup>48</sup> and changes to the cystatin A gene in exfoliative ichthyosis.<sup>49</sup> The implications of these discoveries are vast; they offer an opportunity to

translate these findings into therapies that will undoubtedly improve patient care and afford those afflicted a better quality of life.

### **Raising awareness in dermatology**

Efforts to raise the profile of the dermatological discipline, a field often regarded as a 'Cinderella specialty'<sup>50</sup> by those who commission services, have been propelled by the continued education and training of physicians, increased public awareness of skin disease, and the charitable funding of essential research.

With over 2000 recognised skin disorders, accurate diagnosis and successful treatment are grounded in the proficiencies of the consulting general practitioner (GP) and their ability to appropriately refer to secondary care if deemed necessary. Whilst there is certainly room for improvement in diagnostic accuracy amongst GPs,<sup>51</sup> the relatively new remit of GPs with a special interest (GPwSI) in dermatology has enabled primary care clinicians to take a more active role in dermatological patient care at an expert level. There are few effective alternatives to consultant-led dermatology department consultations for patients with skin disease, and it has been shown that dedicated GPwSI clinics do not represent a solution to prolonged waiting times for secondary care appointments.<sup>52</sup> Nevertheless, access to those physicians best informed about individual patient care provides a faster, more convenient option to those with mild to moderate skin disease fortunate enough to have a GPwSI at their local practice. A formal training session given to GPs in Italy increased accurate diagnosis of suspected melanomas from 55% to 73% after only 4 hours of tuition,<sup>53</sup> highlighting the importance of continued education for GPs, which is slowly improving.<sup>54</sup> A commitment to lifelong learning (and teaching!) is paramount to both personal progression and continued growth of the discipline.

Similarly, education has also been imperative in raising public awareness of skin disease. In particular, it is national skin campaigns<sup>55,56</sup> that have been the key force in fostering an understanding about the dangers of excessive UV exposure and importance of early detection. Skin cancer is the most commonly diagnosed malignancy in the UK, was the cause of 2,633 deaths in the UK in 2009<sup>11</sup> and had a total financial cost that exceeded £240 million in the same year.<sup>57</sup> Through the medium of educational posters and leaflets, roadshows, and TV and magazine advertisement, campaigns have sought to reduce the year-on-year escalation in incidence of skin cancer. Although skin cancer rates have failed to decline, studies have shown that since their advent in 2003, campaigns such as SunSmart and Sun Awareness have been largely successful in their mission to increase levels of skin cancer awareness.<sup>58</sup>

The funding of research essential to aiding our understanding of dermatological disease has been facilitated by a number of charities. The British Skin Foundation is one of a handful of such bodies that awards money specifically for skin disease research,<sup>59</sup> and in doing so works to actively promote the plight of those with cutaneous conditions, improving public recognition of the field and advancing the science behind it.

## **Conclusion**

Each of these exciting advancements have been pivotal to the continued progression of dermatology and it is their union that makes this diverse branch of medicine the discipline it is today. Dermatology has exploited landmark developments in genetics, pharmacology and laser technology to forge improved patient management; it has established the subspecialty of psychodermatology to enhance patient support; and it has raised awareness amongst

physicians and patients alike to address the wider social implications of skin disease. These milestones significantly guide patient care and serve to benefit everyone involved.

Nevertheless, it is those aspects of progression that are beyond the remit of the laboratory that have perhaps had the biggest impact. From the cultivation of an increased awareness of dermatology and its diseases to the offerings of a sub-specialty that honours the values of patient-centred care and a holistic approach, these contributions to the discipline are far-reaching and serve to expand and humanise the sphere of the dermatological field.

Whilst it is hoped that the next 25 years will bestow a similar wealth of advancements, cautious optimism is warranted: in the current climate of political upheaval and ongoing changes to the NHS, there are forces at work that may be detrimental to the services provided by dermatology departments throughout the UK. During these times we must consider the remarkable achievements of the dermatological discipline and reflect on just how fruitful the last quarter of a century has been for this constantly evolving speciality.

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