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

Aniruddh Chhabra, University of Liverpool

Introduction

In his landmark book *The Structure of Scientific Revolutions*[1], the American scientist Thomas Kuhn challenged the deep-rooted view – as typified by the traditional 'scientific method' – that scientific knowledge advances through the gradual accumulation of "new truths to the stock of old truths". Instead, he asserted that scientific knowledge develops due to periods of revolutionary, conceptual breakthroughs being interspersed between phases of steady, cumulative progress[2]. If one subscribes to this view, then such paradigm shifts, as they have become known since, can clearly be identified as having occurred with spectacular frequency within biomedical science in the last 25 years. From the sequencing of the human genome and the discovery of recombinant DNA to major improvements in epidemiological and surgical practices, such feats have left virtually no facet of medicine untouched by their capacity to prevent death and suffering. The actual examples are legion – the introduction of imatinib as truly targeted therapy for chronic myelogenous leukaemia[3], the percutaneous coronary intervention revolution in managing obstructive coronary artery disease[4] and the establishment of total mesorectal excision in colorectal cancer surgery[5], just to mention a few. The situation in dermatology has been no different. Indeed, a nomination list for the honorific prize of '*the* most important advance' would be easily saturated with countless remarkable discoveries and developments in diagnostics and therapeutics, in parallel with improvements in the understanding of various skin diseases. I believe, however, that the

single most important advance in dermatology in the last 25 years has not been an isolated development or leap in understanding but rather the collective *rediscovery* of something which has been embedded in dermatology since the specialty began in earnest in the nineteenth century – the rediscovery of a philosophy.

"Variability is the law of life", said Sir William Osler, "and as no two faces are the same, so no two bodies are alike and no two individuals react alike and behave alike under the abnormal conditions which we know as disease". The truth of this sage observation arguably resonates most deeply with dermatology, a specialty which – perhaps more so than others – can reasonably proclaim that no two patients are ever the same. This is not just a consequence of the high visibility and accessibility of dermatoses, which arouse a range of complex, patient-specific emotional responses, but also the highly variable ways in which skin disease, with its potentially protean cutaneous and systemic manifestations, can intermingle with a patient's psychosocial background and expectations. This naturally confers a great responsibility on the dermatologist's shoulder, namely the need to always adopt an intrinsically tailored and individualised approach towards all aspects of patient management. In theory, achieving this may not appear too difficult, especially as the detailed study of skin disease is made easily amenable – uniquely in all of medicine – by its visibility and its position at the interface between our dynamic internal and external environments. However, this privilege has been historically juxtaposed alongside the overtly descriptive, empirical and conservative nature of dermatology, which has suppressed the extent to which such personalised care can be delivered in practice[6]. Nevertheless, several notable events which have punctuated the course of the specialty in the last 25 years have together served to reinvigorate and bring this philosophy to the fore. This essay will discuss how such events have restored this philosophy as an emblem of contemporary dermatology, and how this most important of advances may pave the way for the next 25 years and more.

The road to personalisation: advancement in the modern molecular genetics era

The time around the turn of the 21st century heralded rapid progress in our understanding of the genetic and molecular basis of disease, peaking with the sequencing of the entire human genome and the introduction of 'massively parallel' sequencing techniques. One of the ultimate aims in this burgeoning field since has been the attainment of personalised, gene-based therapies for various diseases. Although touted by some experts, including dermatologists[7], as being too unrealistic and nebulous an objective to achieve within the next few decades, the journey to 'personalised medicine' has been an impressive catalyst for delivering more patient-focused care within dermatology. For example, individual genetic variation has long been recognised to play a key role in producing variability in the efficacy and toxicity of various drugs. As such, dermatology has fostered a close alliance in the last 25 years with pharmacogenetics — the study of how single gene variations affect the metabolism and action of drugs — in order to shift the treatment paradigm for skin disorders from one employing empirical, 'trial-and-error' approaches to more optimal, *relatively more* personalised therapies[8]. This has directly benefited patients by maximising the therapeutic benefit conferred and reducing the risk of unpleasant side-effects. For example, although azathioprine would represent a cost-effective corticosteroid-sparing agent for treating generalised bullous pemphigoid in an elderly man, its use in this setting may be significantly limited by concerns about potentially fatal myelotoxicity[9]. However, it is known that the haematopoietic toxicity is inversely related to the level of activity of thiopurine methyltransferase (TPMT), an important metabolising enzyme. Since genetic polymorphisms result in a spectrum of TPMT expression, its levels can now routinely be measured by dermatologists and used to optimise azathioprine doses for individual patients and guard against adverse effects[10].

The elucidation of pathological events at the molecular level is also helping to reshape the classification and treatment of various skin diseases, including melanoma, the

deadliest cancer of the skin in which up to one-fifth of patients progress to metastatic disease[11]. Advanced melanoma has a poor prognosis given its resistance to conventional, 'one-size-fits-all' chemotherapeutics, and this has paved the way for more selective alternatives in the last two decades. For example, using high-throughput sequencing technology to study melanomagenesis, it was recognised that half of all melanomas harbour a specific mutation in the *BRAF*-gene, mainly at codon 600, which is associated with a poorer prognosis[12]. This is usually an early event in tumorigenesis and results in constitutive activation of the oncogenic MAPK-pathway and vemurafenib — an inhibitor of mutant BRAF — was soon shown to dramatically improve survival in patients with mutation-positive advanced disease[13,14]. The development of rationally targeted therapies has also been a key feature in the management of a number of dermatoses, especially psoriasis. Although several effective treatments were available for this chronic disease 25 years ago, finding one which achieved an acceptable balance between disease 'clearance' and side-effects was a frustrating endeavour, particularly due to interindividual variability in treatment response, something which demanded better understanding of the underlying pathophysiology[15]. Fortunately, our understanding of psoriasis over the last 25 years has been completely transformed: originally seen as a tango between some unknown immune mediators, it is now understood to be a troupe of dozens of cell types (mast cells, neutrophils, dendritic cells, etc) and cytokines, choreographed chiefly by interleukin-17 producing CD4+ T-helper cells[16]. As a result, the emergence of novel agents – biologics such as ustekinumab – targeting various cytokines have revolutionised the management of patients with extensive psoriasis and psoriatic arthritis, with most patients showing a significant improvement in disease severity[17]. These developments have also stimulated research into the use of specific molecular markers to select the 'right' patients for the 'right' drugs in psoriasis. Numerous genetic polymorphisms have been investigated as predictive biomarkers of efficacy and toxicity for methotrexate therapy, which remains a common

first-line systemic oral treatment given the much higher expense of the biologics[18]. Although no single polymorphism has shown a clinically reproducible association, it is likely that several may exert a collective influence on methotrexate safety and efficacy, providing an opportunity to develop a multivariate model which allows better identification of those individuals who are likely to benefit most from methotrexate therapy (as has been attempted for its use in rheumatoid arthritis)[19].

Refining a time-tested method: surgery for skin cancer

Dermatologic treatment is unique in that it is required not only to rectify the underlying pathological aberrations but also to remove all visible remnants of disease, a process specific to each patient. For example, the age-old first-line treatment offered to most individuals with skin cancer is surgical excision[20]; however, the exact protocol used has been refined the last 25 years and is now guided by a multitude of patient-specific factors, including cancer location, type and stage, and patient preference. In essence, this approach minimises the risk of recurrence while improving cosmetic outcomes. For example, Mohs' micrographic surgery was developed in the 1930s and can be used for tumours with aggressive histologic features or those located in cosmetically or functionally critical sites and boasts favourable cure rates[21]. Importantly, this indication has become established as the most patient-specific approach as a result of studies which have repeatedly questioned this technique, in a bid to continually improve best dermatological practice. This technique, used for basal and squamous cell carcinomas involves stage-by-stage excision of the lesion with frozen-section examination of peripheral and deep margins at each stage, thereby permitting maximal tissue conservation and lessening scar formation. The latter has been recognised in the last 25 years to represent a formidable emotional burden for patients in their long-term recovery[22]. Indeed, scarring is another aspect of therapy which is amenable to a tailored philosophy; for instance, the skilled dermatological surgeon can utilise a

patient's unique geometry of skin tension lines to make incisions which result in a more optimal alignment of scars, markedly reducing disfigurement[23].

Skin disease and psychosocial distress: the 'chicken or the egg?' conundrum unravelled

As touched upon earlier, a diagnosis in dermatology is rarely just skin deep. It encompasses not just the specific pathology (or pathologies) involved but also intimately considers a plethora of patient-specific demographic, emotional, psychosocial and environmental variables and determinants. For instance, rosacea – *in vacuo* – is a chronic inflammatory condition which typically manifests as erythematous flushing, telangiectasias, papules and pustules affecting the central face, an area which is central to human communication. As such, it sets the scene for profound physical and psychological discomfort, the latter being particularly incessant in the current age of digitalised beauty ideals. Of course, this can only be understood by furnishing one's clinical assessment through a careful patient-centred appraisal of the effects of the disease. Patient surveys on this topic in the bygone decades have repeatedly shown a detrimental impact of rosacea on the self-esteem, confidence and life satisfaction of sufferers[24,25]. In turn, these often snowball over time into negative sequelae with respect to an individual's relationships, occupation and social role, independent of any negative ramifications arising from other individuals' perception and responses (both conscious and subconscious) towards rosacea patients[26].

Although research in the last 25 years has solidified our understanding of the psychosocial burden of chronic skin disease, one cannot claim that these findings are entirely new or unforeseen. The crucial development, however, has been the relatively recent foray into elucidating the precise bidirectional relationship between skin disease and a patient's psychosocial traits and dimensions. This point can again be illustrated using the example of rosacea, in which emotional psychological stressors are known to function as precipitants of disease exacerbation through complex, albeit poorly understood,

psychoneurocutaneous cascades[27]. Thus, the question which arises spontaneously is akin to the 'chicken or the egg' causality dilemma: does a skin disease such as rosacea first cause a psychological stressor (which in turn acts to propagate it) or do a set of highly innate psychosocial factors somehow initiate the disease process? Although the answer probably lies somewhere in the middle, the importance *itself* of seeking the answer has been increasingly recognised in the last 25 years as it holds the promise of providing insights into how to effectively break the relentless stress mediated exacerbation cycle which characterises so many skin diseases. Thankfully, much progress has been made in these endeavours. In the case of atopic dermatitis, for instance, the detrimental effect of psychological stress on the barrier function of skin has been well documented[28]. The impairment in the stratum corneum integrity and cohesion has also been demonstrated in human subjects, using peripheral glucocorticoid administration as a surrogate for the activation of the hypothalamic-pituitary-adrenal axis by psychological stress[29]. In addition, animal studies examining the pharmacological blockade of peripheral glucocorticoid action have yielded encouraging results, suggesting that blunting the stress response in conditions like atopic eczema may decrease the susceptibility to progressive skin barrier dysfunction and bacterial infection[30]. Such findings clearly offer some very tantalising therapeutic prospects and have sparked further research in this field in the last 25 years. This has been and will continue to be instrumental in laying the foundation for an approach which appreciates the psychosocial consequences of skin disease far beyond what even the most caring and least pressed-for-time dermatologist could have hoped to achieve decades earlier.

Conclusion – back to the future: the next 25 years

Dermatology is a specialty distinguished by the variability of the diseases it studies and the patients it cares for. "If it were not for the great variability among individuals", said Sir

William Osler, “medicine might as well be a science, not an art”. If Sir Osler were alive today, he would no doubt comment on the unique remit of dermatology as an art *and* a science, due in no small part to the progress made over the last 25 years. This progress has been fascinating, propelled by remarkable bench and translational research advances which have delivered direct benefit to the whole spectrum of patients with skin disease. Although this has made dermatology more personal and holistic than ever, I suspect history will continue to repeat itself by posing stern new challenges and daring dermatologists to venture into unchartered territories in order to make the diagnosis and management of skin diseases even more patient-specific. In the case of advanced melanoma, for instance, encouraging results from the use of individualised therapies such as vemurafenib and trametinib (an inhibitor of MEK1 and MEK2 proteins, which are constitutionally activated by RAF kinases in melanoma) have been mitigated by the emergence of potent drug resistance within 6-8 months of commencing therapy[31]. Efforts to decipher the precise mechanisms of such resistance and at overcoming or delaying it are underway, utilising and building on the advances which occurred decades earlier (e.g. trialling the combination of immunotherapy agents with BRAF-inhibitors[32]), and it is probable that more effective targeted therapies will emerge and complement the existing armamentarium in the next few decades. Such targeted therapies are also likely to become established for other skin conditions. For example, epidermal growth factor receptor (EGFR) inhibitors have the potential to be of considerable value in patients with non-melanoma skin cancers in which EGFR signalling represents a dominant driver for tumour progression[33]. However, for all skin diseases, such developments will be increasingly contingent on overcoming the challenge of gaining an even more detailed understanding of the pathophysiological mechanisms involved (e.g. association between EGFR overexpression and response to EGFR inhibitors in the case of non-melanoma skin cancers[34]). Still, given the precedent that has been set over the last 25 years, dermatologists everywhere can prepare to face these

challenges with undiminished confidence and optimism, armed with the philosophy which has been their hallmark for decades.

Word count: 2500 words (excluding citation numbers and references)

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