 Clinical Medicine 2009, Vol 9, No 6: 588–94

Dermatology: the last 30 years – a rollercoaster ride

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I entered dermatology by default, having previously flirted with cardiology (too competitive), psychiatry (I lacked the patience) and paediatrics (interviewing committee members didn't appreciate my finer qualities). My dermatology career began inauspiciously in 1962, when, as a medical registrar, I presented a patient with temporal arteritis to the section of dermatology of the Royal Society of Medicine. I don't think my presentation was very good, since unlike most of the other physicians, I read from a script. But I was impressed by some of the discussants who had a substantial knowledge of internal medicine as well as the skin, and of their ability to integrate the two, so I made dermatology my career. That it spanned a period encompassing dramatic advances in biomedical sciences applied to skin diseases, with increasing understanding of their pathogenesis, diagnosis and treatment, has been my good fortune.

The molecular era of skin research

In the early 1960s dermatology crossed the threshold from a mainly descriptive to a science-based specialty. Post-1945 medical research had already entered the molecular era. Inflammatory diseases were deemed to be driven by molecular mediators. Molecular regulators of epithelial growth – relevant to psoriasis prompted attempts to recover 'chalone' from pig skin. Chalone was a natural inhibitor of cell proliferation, possibly deficient in the skin of psoriasis. These experimental approaches suffered from the limitations of the available technology and had little impact. But they demonstrated the potential of the skin as a medium for basic pathophysiological research.

Molecular biology and genetics

In 1953, Watson and Crick published the double-helical structure of DNA elucidating how information encoded in genomic DNA was translated into structural protein. The International Human Genome Sequencing Consortium published the sequencing of the human genome in 2001.[1] The new genetics enabled identification of mutant genes causing Mendelian dominant and recessive disorders. In the early 1990s progress was dramatic in the hereditary mechanobullous disorders and ichthyoses. The dominant genodermatosis epidermolysis bullosa simplex was due to mutations in one of two keratin genes *K5* and *K14* whereas the gene defect in autosomal dominant bullous ichthyosiform erythroderma proved to reside in *K1* and *K10*.[2,3] However patients with common diseases, such as psoriasis and eczema, involving genetic polymorphisms accounting for disease susceptibility have yet to benefit significantly from the genetic 'revolution'.

Psoriasis is a heritable disease but identification of a single gene abnormality has not proved possible. For psoriasis to develop, a complex combination of multiple psoriasis susceptibility genes, such as PSORS 1, and environmental factors need to interact.[4] Susceptibility to atopic eczema has recently been associated with a mutation of the gene that encodes for filaggrin, a major structural component of keratin of the stratum corneum, causing impairment of barrier function.[5] This leads to early exposure to multiple epicutaneous allergens causing a predominant Th2 response associated with other features of the atopic state.

Pharmacogenomics

Expression of specific genes or single nucleotide polymorphisms may reveal susceptibility to a drug in terms of efficacy or toxicity. Recently in Singapore General Hospital I frequently had to deal with severe drug-induced toxic epidermal necrolysis (TEN) in Chinese. The mortality approached 30% and allopurinol or carbamazepine were the usual culprits. In 2004 Taiwanese workers showed a very strong concordance between *HLA-B*1502* and carbamazepine-evoked TEN in Han Chinese and between *HLA-B* 5801* and allopurinol-evoked severe adverse cutaneous drug reactions.[6,7] I foresee genotyping for common drug susceptibility genotypes becoming routine in neonates.

Advent of monoclonal antibodies

I was on the Medical Research Council Cell Board when Milstein described bulk production of monoclonal antibodies using myeloma cells and a hybridoma technique, for which he subsequently shared a Nobel Prize with Kohler.[8] Milstein initially intended monoclonal antibodies to be used for accurate identification of specific cell types. In dermatological tissue diagnosis they are used routinely to identify specific cell surface antigens.

Monoclonal antibodies as immunobiologics in dermatology

Advances in treatment during my career include photochemotherapy with psoralens and ultraviolet A (PUVA), systemic and topical retinoids and topical calcineurin inhibitors. But the most dramatic in terms of high efficacy and minimal toxicity are the immunobiologics for psoriasis. These are designed molecules that modify specific lymphocytes or cytokines that are involved in defined pathogenetic pathways in

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inflammatory or neoplastic diseases. In the 1960s and 1970s, psoriasis was considered a primary epidermal disease with an inflammatory component. Van Scott and Ekel reported eight-fold shortening of the epidermal cell cycle, prompting research into intracellular regulatory mechanisms presumed to be deranged causing disordered epidermal cell growth.[9] Cyclic adenosine monophosphate was suggested to be the elusive chalone referred to above.[10] In the 1980s interest shifted towards the dermis and the inflammatory nature of psoriasis. Abnormal levels of eicosanoids, including leukotrienes, were demonstrated in psoriasis by several groups including my laboratory.[11] Concurrently immunopathological studies highlighted the key role of T lymphocytes, epidermal hyperproliferation and disordered differentiaton being a consequence of products of activated T lymphocytes.[12] Cyclosporin, a selective T cell inhibitor, is effective in psoriasis although toxicity limits its utility.[13] Discovery of a monoclonal antibody conjugate, denileukin diftitox, selectively inhibitory against T cells expressing IL-2, and highly effective in psoriasis (albeit with unacceptable side effects) was a landmark,[14] followed by reports that Crohn's disease patients treated by the tumour necrosis factor (TNF)-α monoclonal antibody infliximab experienced dramatic resolution of concurrent psoriasis.[15] Immunobiologics with specific activity against different components of the T cell activation pathway in psoriasis are now in routine use, or soon will be – the most recent, and as yet unlicensed, being a monoclonal antibody against a p40 subunit common to IL-23 and IL-12.[16]

Evidence-based dermatology

These therapeutic advances became available because they had been subjected to rigorous evaluation for efficacy quality and safety by controlled trials which were demanded by regulatory authorities prior to licensing. This was not always the case, and in the earlier days of my career treatment modalities for skin diseases were deemed effective largely on grounds of long historic usage, expert opinion and publications of uncontrolled series. In the 1960s and 1970s randomised controlled trials were performed in dermatology but the results were not used systematically. Due to the efforts of Cochrane and Sackett the importance of an evidence-based approach became accepted and applied routinely to scrutiny of strength of evidence for efficacy and safety.[17,18]

Significance of quality of life and its measurement in skin disease

That personal and social impairment due to skin disease may be devastating has only recently been recognised.[19] An effective treatment does not merely reduce the area of skin involvement or itching intensity, but should also help the patient to function better in their occupational, social and familial environments. For evaluation of investigational new drugs for licensing purposes, data on quality of life (QoL) is now mandatory. Chronic skin diseases tend to be at the end of the queue when it comes to resource allocation for research or clinical care facilities. My own experience in chronic urticaria, illustrates this point. Until we demonstrated using a QoL instrument, the Nottingham Health Profile, that QoL impairment equalled that of patients with severe coronary heart disease,[20] and it was almost impossible to prioritise healthcare resources for these handicapped patients. The advent of the dermatology-specific QoL questionnaire – the Dermatology Life Quality Index (DLQI) has had a major impact since it can be used for almost any skin disease.[21]

Environmental dermatology

In my recent work in the Far East, it was clear that skin cancer was rare except in expatriates. Subsequently in an NHS dermatology clinic in Poole the large number of patients with actinic skin cancer or photoageing has been a revelation. Reasons include affluence, recreational aspirations and (possibly) global warming. The 21st-century dermatologist has to work closely with the plastic surgeon and oncologist, and have expertise in skin surgery. Environmental dermatology is not just about actinic damage. The burden of occupational skin disease is now widely recognised and is increasing.[22] Occupations most prejudicial to skin health include hairdressing, machine tool operation and printing. The cost of absenteeism due to occupational skin disease is increasing, and medico-legal issues arising from compensation claims are a regular feature of the contemporary dermatologist's work.

Infections

During my early years, infections were considered a diminishing problem due to the advent of potent antibiotics and antivirals. That this complacency was misplaced became obvious in 1981 when a new viral infection, AIDS, emerged in the USA and rapidly became a worldwide problem, especially in Africa. AIDS has had a major impact on dermatological practice. The disease presents in the skin as seborrhoeic dermatitis, eosinophilic folliculitis, pruritus, severe adverse drug reactions, opportunistic infections and exacerbations of psoriasis, constituting a diagnostic and therapeutic challenge. New serious infections are still appearing as I found to my cost. In Singapore General Hospital in 2003 I became heavily embroiled in the severe acute respiratory syndrome (SARS) epidemic and there were several deaths among the medical staff before the infection was controlled.[23] I deplore the recent tendency in the UK and other developed countries for the practice of medical dermatology (by which I mean care of sick patients with skin problems) to become less popular among trainees, many of whom are tempted by less demanding and far more lucrative 'aesthetic' dermatology. It only takes an hour or two to learn how to inject botox for facial lines, but it takes considerable experience and hard work to evolve and enact a management plan for an 80-year-old with diabetes, chronic renal impairment, generalised pruritus and recurrent cellulitis.

Postgraduate education in dermatology

When I arrived at St John's Institute of Dermatology in 1975, my predecessors, Charles Calnan and Robert Meara, had already set up, mainly for overseas medical graduates, a University of London one-year diploma course in dermatology. Later on as dean of the institute I had an opportunity to expand and develop the postgraduate training programme, including an additional University of London masters course in dermatology. It is now hard to find a country in the world devoid of St John's alumni, and in most countries I have worked in or visited they form a sizeable proportion of accredited dermatology specialists. Accordingly British dermatology enjoys a high reputation worldwide. Many of the developing countries are setting up their own specialist training programmes. I have been privileged to be involved in establishing one such Universiti Kebangsaan Malaysia advanced masters course in Kuala Lumpur, which has already produced its first batches of graduates, and to actively participate in strengthening specialist training in Singapore over several years. This trend will eventually impact on the St John's and other postgraduate UK courses which will need to be flexible and offer alternative more specialised training in specific fields such as dermatopathology, photobiology, dermatological surgery and others, with correspondingly reduced emphasis on general dermatology training.

Conclusion

During my career, advances in biomedical sciences in dermatology have enabled it to become established as a leading science-based clinical discipline. The better understanding of aetiology and pathogenesis of skin diseases, as well as an increase in the scope of investigation, prognosis and treatment – and opportunities for research – has made dermatology a high profile and immensely satisfying specialty for the ambitious and aspiring clinician. This happy state of affairs could be jeopardised by trivialisation of the specialty due to increased involvement in cosmetic dermatology. My anxiety is that this will be seen as an opportunity for encroachment by other specialties which have seen their own clinical bases diminish in recent years. I hope my successors will guard against this.

References

1 International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. *Nature* 2001;409:860–921.
2 Bonifas JM, Rothman AL, Epstein EH. Evidence in two families for keratin gene abnormalities. *Science* 1991;254:1202–5.
3 McLean WHI, Eady RAJ, Dopping-Hepenstal PJC *et al.* Mutations in the rod 1a domain of keratins 1 and 10 in bullous congenital ichthyosiform erythroderma. *J Invest Dermatol* 1994;102:24–30.
4 Trembath RC, Clough RL, Rosbotham JL *et al.* Identification of a major susceptibility locus on chromosome 6p and evidence for further disease loci revealed by a two-stage genome-wide search in psoriasis. *Hum Mol Genet* 1997;6:813–20.
5 Morar N, Cookson WO, Harper JL, Moffatt MF. Filaggrin mutations in children with atopic dermatitis. *J Invest Dermatol* 2007;127:1667–72.
6 Chung W-H, Hung S-I, Hong H-S *et al.* Medical genetics: a marker for Stevens–Johnson syndrome. *Nature* 2004;428:486–9.
7 Hung S-I, Chung W-H, Hong H-S *et al.* HLA-B* 5801 allele as a genetic marker for severe adverse cutaneous reactions cause by allopurinol. *Proc Natl Acad Sci* 2005;102:4134–9.
8 Kohler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* 1975;256:495–7.
9 Van Scott EJ, Ekel TM. Kinetics of hyperplasia in psoriasis. *Arch Dermatol* 1963;88:373–81.
10 Voorhees JJ, Duell EA. Psoriasis as a possible defect in the adenylate cyclase-cyclic AMP cascade: a defective chalone mechanism. *Arch Dermatol* 1971;104:352–8.
11 Barr RM, Wong E, Mallet AI *et al.* The analysis of arachidonic acid metabolites in normal uninvolved and lesional psoriatic skin. *Prostaglandins* 1984;28:57–65.
12 Valdimarsson H, Baker BS, Jonsdottir I, Fry L. Psoriasis: a disease of abnormal keratinocyte proliferation induced by T lymphocytes. *Imunol Today* 1986;7:276–9.
13 Griffiths CEM, Powles AV, Leonard JM *et al.* Clearance of psoriasis with low dose cyclosporine. *BMJ* 1986;293:731–2.
14 Gottlieb SL, Gilleaudeau P, Johnson R *et al.* Response of psoriasis to a lymphocyte selective toxin (DAB 389 IL-2) suggests a primary immune but not keratinocyte pathogenetic basis. *Nat Med* 1995;1:442–7.
15 Oh CJ, Das KM, Gottlieb AB. Treatment with anti-tumour necrosis factor –α (TNF-α) monoclonal antibody dramatically decreases the clinical activity of psoriasis lesions. *J Amer Acad Dermatol* 2000;45:829–30.
16 Kimball AB, Gordon KB, Langley RG *et al.* Safety and efficacy of ABT-874, a fully human interleukin 12/23 monoclonal antibody in the treatmentof moderate to severe chronic plaque psoriasis: results of a randomised placebo controlled double – blind phase 2 trial. *Arch Dermatol* 2008;144:200–7.
17 Cochrane A. *Effectiveness and efficiency. Random reflections on health services.* London: Nuffield Provincial Hospital Trust, 1972.
18 Sackett DL. *Clinical epidemiology: a basic science for clinical medicine.* Boston: Little, Brown, 1991.
19 Finlay AY, Kelly SE. Psoriasis: an index of disability. *Clin Exp Dermatol* 1987;12:8–11.
20 O'Donnell BF, Lawlor F, Simpson J *et al.* The impact of chronic urticaria on quality of life. *Br J Dermatol* 1997;136:197–201.
21 Finlay AY, Khan GK. Dermatology Qualty of Life Index (DLQI): a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994;19:210–6.
22 Cherry N, Meyer JD, Adisesh A *et al.* Surveillance on occupational skin disease: EPIDERM and OPRA. *Brit J Dermatol* 2000;142:1128–34.
23 Greaves MW. Coping with SARS: a day in the life of a United Kingdom dermatologist in Singapore General Hospital. *J Amer Acad Dermatol* 2004;50:e2–4.

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