Advances in dermatology

Christopher EM Griffiths* speaks to Alisa Crisp, Commissioning Editor: Christopher EM Griffiths gained a first class BSc degree in Anatomy and qualified in Medicine from St Thomas' Hospital Medical School, London University (London, UK). He trained in Dermatology at St Mary's Hospital (London, UK), and at the University of Michigan (USA), where he was also on the Faculty for 4 years. He was appointed as the Foundation Chair in Dermatology at the University of Manchester (UK) in 1994 and is an honorary consultant dermatologist at Salford Royal NHS Foundation Trust (Salford, UK). Professor Griffiths developed the 'hub-and-spoke' model of dermatology services for Greater Manchester and introduced a multidisciplinary clinic for severe psoriasis – the Manchester Psoriasis Service – awarded Hospital Doctor Dermatology Team of the Year in 2002. At the University of Manchester he has served in various roles as: Head of Medicine and Neuroscience, Head of the School of Translational Medicine, Research Dean and Director of the Manchester Academic Health Science Centre. Professor Griffiths' named lectureships include: Sydney Watson Smith (2006); Parkes Weber (2007); Von Zumbusch, Munich (2008) and Hellerstrom, Stockholm (2010). He is cofounder of the International Psoriasis Council and is its President-Elect. He received the psoriasis lifetime achievement award of the American Skin Association in 2009. *The Times of London* named him as one of the UK's Top 200 doctors in 2010 and in 2011 he was appointed as an NIHR Senior Investigator and elected to Fellowship of the Academy of Medical Sciences. Professor Griffiths has been President of the British Association of Dermatologists (2004–2005); European Dermatology Forum (2010–2011) and British Society for Investigative Dermatology (1997–2000). He serves on the editorial boards of eight scientific journals and is an Associate Editor of the *Journal of Investigative Dermatology*. He has published 451 PubMed cited articles in scientific journals and has an H-Index of 73. Professor Griffiths is coeditor of *Rook's Textbook of Dermatology* and his research interests cover all aspects of psoriasis.

Q How much has the field of dermatology changed throughout your career?

I have been in dermatology for close to 30 years. The major change has been the growth of what is called procedural dermatology, which ranges from dermatological surgery for skin cancers, to what most people call cosmetic dermatology, which is the use of fillers and botulinum toxin and peels

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that are used for aesthetic reasons, mainly anti-ageing. There has also been the introduction of lasers, which are now used to treat a variety of different conditions: from port-wine stains – vascular birth-marks on people's faces – to cancers and the signs of aging. There is the the development of better systemic therapies: two major breakthroughs have been biologic therapies for the treatment of psoriasis and the introduction of vitamin A products, retinoids, for the treatment of acne and psoriasis

Finally, there have been major changes within the workforce – certainly in the UK – where we have seen the empowerment of nurses to take on a lot more of the physician's role. This includes running clinics for patients on systemic therapies for psoriasis, performing minor surgery, laser treatments and managing more outpatient referrals. The acceptance and empowerment of nurses means that they are now working alongside, rather than for, doctors. I believe in dermatology we have been able to take this forward better than some other specialties, so nurses are viewed very much as part of the team.

Q What is the achievement that you are most proud of to date?

One achievement is being involved in the big changes in the treatment of psoriasis. When I started in dermatology, I was in the team that carried out some of the first work to show that psoriasis is an immune-mediated disease. I have been able to observe how that concept has developed over the ensuing 30 years, from initial skepticism to the use of the targeted biological therapies for patients with severe psoriasis. I am proud to have been involved with this the whole way through – in other words, from discovery through to care.

I am most proud of our achievements in Manchester (UK). I trained in dermatology at St Mary's Hospital (London, UK) and then in the USA – at the University of Michigan. I have been in Manchester for 19 years. I was appointed as the first professor of dermatology in Manchester where there was originally no academic department; I am proud that Manchester is now one of the leading dermatology centers in Europe.

Q Is there anything or anyone in particular that has helped you in achieving this?

In most things in life you have mentors, and there have been two influential people, outside my immediate family. The first is Professor Lionel Fry who was the consultant dermatologist I worked with at St Mary's Hospital in London and who not only was an excellent clinician, but also was a very good researcher. I learnt a lot from him about research. At the University of Michigan, the Chairman there was Professor John Voorhees, who not only taught me about research, but also how to run the department as a business.

Q You mentioned the idea of immunology as the mechanism in psoriasis – would you say that the biological causes of this have been completely identified, or is there still more that we need to know?

We have made a lot of progress in our understanding of psoriasis over the past quarter of a century; there is no doubt about that. We do know that genetics and genetic predisposition play an important role, but how that really determines psoriasis is still not well understood. We do know that several genes are involved in the development of psoriasis. However, the disease is a consequence of a genetic predisposition and an environmental trigger. Thus one can have the gene for psoriasis but never develop the disease, which is unlike diseases, such as cystic fibrosis, where if one has the gene for cystic fibrosis one will get cystic fibrosis. With psoriasis, you need to have an environmental trigger. A classical example is having a Streptococcal infection, such as tonsillitis or pharyngitis, which leads to an acute presentation of psoriasis. Stress can also trigger the first presentation and so the disease needs to have that confluence of genetics and environment. We understand a lot more about the immunological pathways that are involved in psoriasis, and that knowledge is expanding month by month. There is a lot of interest in that area, particularly as this is identifying new attractive targets for therapies. This is a good example of how academia and industry are collaborating to a common goal.

Q In your opinion, are we likely to find an answer for this soon?

As we surmised some time ago, psoriasis is more than one disease; with the power of molecular genetics and immunology, we will be able to ascertain that it is several similar conditions. That in itself will allow us to stratify the disease, in the sense that you can say if you have psoriasis type X, that will respond best to drug A rather than drug B. This is the concept of stratified medicine so that one can align the best possible therapies for that individual patient. However, I do not think that we are going to have a definitive answer. Obviously the ideal would be to be able to prevent it, and/or cure it. At the moment we are unable to do either.

Q So your current work is looking at trying to treat the disease?

We are trying to treat it. But, the other thing that we have learnt is that we have to practice much more of a biopsychosocial model for the management of patients who we have just ascertained as having a chronic, incurable disease. So we are now managing the whole patient for three reasons. One is that we have these very powerful new treatments, which can manage the skin. Secondly, these patients also have significant psychosocial difficulties, which come with having a disease that carries a stigma, as a lot of skin diseases do. The patients have to adjust to that and some people cannot; this can then lead to significant depression and suicidal ideation. Third, there is emerging evidence that psoriasis, particularly severe forms, is associated with cardiovascular disease. Thus, patients are at a higher risk of dying early from ischemic heart disease, stroke and hypertension. What we are trying to ascertain is whether psoriasis itself causes those problems, and therefore if one manages the psoriasis and treats it early on, one might be able to prevent these. Alternatively it could be that psoriasis is linked to other genes and risk factors that dictate that you get those diseases? Arthritis has a similar association with cardiovascular disease and there is evidence that if you treat arthritis early, you may be able to reduce the incidence of heart attack.

Q Do we have any ideas about the mechanisms that would be causing this at the moment?

One of the main theories is that it is inflammation in the skin that drive atherosclerosis. Therefore, if inflammation is reduced, it may reduce the development of those other problems.

Q Is there one treatment that you yourself find to be most useful for treating patients with psoriasis?

I think that is a very difficult question. For the vast majority of patients, 80% or more have psoriasis of a fairly limited extent, and can be managed in primary care. The best treatment in primary care, the one that has made the most difference in recent years, is the use of topical vitamin D-containing drugs. They have made a huge difference to the way that we can manage psoriasis of limited extent. We still use these drugs in secondary care, it is just that we don't see many patients that only require topical vitamin D therapy. As a class, and after the advances that we have made, I think the answer returns to biological therapies. As a class, they are the most useful as they are filling a previously unmet need.

Q How important has the development of these biological therapies been in the management of this disease?

It is a very important step forward and is one of the best examples across the whole of medical translational research, whereby discoveries are taken rapidly into patient care. Obviously, the use of these powerful immunosuppressive drugs produces concern about side effects; some of these drugs have been used in arthritis but there might be different risks when using them for psoriasis. One way that we are trying to identify the true risks of using these biologics is that all patients in the UK and Ireland have the opportunity, when they start biological therapy, to be enrolled into the British Association of Dermatologists' Biologic Interventions Registry (BADBIR). This then means that such patients are followed-up over a number of years, and we are ascertaining whether they develop any adverse events that would not have been

picked up in clinical trials and are reflective of real-life use. When you use drugs in real life, the patients do not have the same profile as those in clinical trials – they have other concomitant medication or they have other diseases, and so there may be risks that were not revealed in the trials themselves. Other European countries have also set up such registers.

Q Can you explain a little more about BADBIR?

The idea came from discussions I had in 2005 with Dr Anthony Ormerod, who is a dermatologist at the University of Aberdeen (UK). We could see that the biologics were about to become an increasingly important part of our armamentarium and we needed to have a better understanding of the risk of using these drugs in dermatology, as well as a way of monitoring side effects. It is based on the success of a very similar registry in rheumatology, the British Society for Rheumatology Biologics Registry, which runs in Manchester. This being the main reason for BADBIR being run from Manchester. I am the chief investigator for BADBIR. The idea also came from the pharmaceutical companies because, when their drugs are licensed, they are asked to ensure that there are adequate pharmacovigilance arrangements in place. We, in Manchester, are a step removed from the companies; the companies interact with the British Association of Dermatologists, who then interact with us here in Manchester to keep the lines clear.

Q What potential treatments currently being tested in clinical trials are you most excited about?

Of potential treatments, there are two that are the most exciting. One is a form of biological therapy targeting IL-17. Three companies have anti-IL-17 antibodies in clinical trials, the results from those are very impressive. More patients in these trials are achieving complete clearance of their psoriasis – that is 100% improvement – compared with what we have seen with other biologic therapies, so these are an exciting new avenue for management of patients with severe disease. The other exciting area involves what are called small molecules, which target other components of inter- and intra-cellular signaling and the immune system. These are taken orally, so are tablets rather than injections – all biologic therapies are injections. The exciting thing is that there are a lot of new drugs coming down the pipeline, so we are not out of ideas yet by a long way.

Q You're credited with introducing the idea of multidisciplinary treatment teams for psoriasis in Manchester. In your opinion, how important is the idea of multidisciplinary treatments for this disease?

I think it is absolutely vital to manage the whole patient; as alluded to early on. In general, nurses are much better at educating patients than doctors are. Nurses are probably also better at the routine follow-up of patients. We also have psychologists as part of the team, because as I mentioned before, the psychological elements of psoriasis have previously been underestimated. You do need to have that ability to interrogate and further understand the impairment of quality of life, and to understand when the patient needs to be referred for psychological help because they are overtly depressed or anxious. I think that in general practice, or even in the specialist psoriasis clinic, where we think that we are experts, we perhaps under-recognize depression and anxiety and, even if we do recognize it, we don't always refer on or interrogate as deeply as we should do because of time constraints. We are very much in favor of managing the whole patient. We need to understand why they have come for treatment now and what treatment is going to work best for them, and not just manage the disease. The other thing that we have introduced is managing a patient's lifestyle. We are running large studies at the moment to see if actively promoting a healthier lifestyle (i.e., more exercise, losing weight – these patients as a general rule tend to be overweight – stopping smoking and reducing alcohol consumption – both of which are higher in patients with psoriasis) actually improves outcomes for the psoriasis patient.

Q Can you explain the 'hub-and-spoke' model?

In Greater Manchester, the dermatology center is based at Salford Royal Hospital with 32 consultant dermatologists working there. We also have a number of other hospitals around Greater Manchester, which those consultants will either visit or have as their base and then come into Salford to run specialist clinics. This means the conurbation of Greater Manchester, which has a population of close to 3 million people, is served by one department. We also have a 'hub-and-spoke' training system in place for trainee dermatologists, where for the first year of a 4-year program, they will not be based in any of the district general hospitals that are linked to us, but in a hospital outside that service element, so maybe out as far as Blackburn, Burnley, Macclesfield or Blackpool. This means the specialist registrars get exposure to different dermatologists and different teaching and much more general dermatology. Then they come into the Salford center for the subsequent 3 years for the more specialized training. So there are two hub-and-spoke systems in place: service and training.

Q How do you see the treatment of psoriasis changing in the next 5–10 years?

I think there will be the further development of new targeted therapies, based on the better understanding of the disease; for example, there are going to be other biologics, other cytokines that will be targeted and other drugs that will target small molecules. I hope that there will be a greater understanding of psoriasis by primary care practitioners, and thus better management of psoriasis and other skin diseases in primary care. I think this is very important, so that only the patients that really need to be referred to secondary care centers are referred. I also hope that there will be a better understanding of psoriasis by the general public; psoriasis still carries with it that stigma, the so-called 'leper complex', which causes significant problems for these patients. I think increasing public awareness is important. There is a requirement to promote the holistic approach to the management of psoriasis, in effect, treating the whole person beyond the skin.

Q For the field of dermatology in general, how do you see it changing in the future?

It is impossible to say, as obviously by working in the National Health Service you are dictated by changes higher upstream. My view is that dermatology will continue, of course, but there will be more dermatologists working out in the community, so-called office dermatologists. I am not talking about general practitioners who have a specialist interest. I am talking about dermatologists themselves being based out in the community, out in primary care, not working in hospitals but linked via a slightly different format, to a center such as ours here in Manchester. Thus, the center would be dealing with the really high-end, much more complex cases. There would therefore be more dermatological conditions managed out in the community, and that makes sense. If you look around the world, that is what happens in Europe and in the USA and there is no reason why that should be any different here in the UK. There will be a rise in aesthetic medicine – that is true across the world and there is no reason why the UK should be any different. But I think we will start to see a regulation of that; maybe on the back of the Poly Implant Prothèse breast implant scandal, there may be better regulation of who can actually use those therapies. The management of skin cancer could bring some interesting developments over the next 15–20 years; at present skin cancer is still managed predominantly by surgical excision. However, if you look across the spectrum of cancer management, a lot of cancers that have been managed entirely by surgery in the past are managed by minimal surgery and by oncological and drug approaches, and I think that we might start to see this creeping into the way that we manage skin cancer patients. I think that it will make a big difference.

Q What projects will you be working on in the next year/are you working on at the moment?

I suppose I am working on all the things that we have been talking about. So we are working on what is called the brain–skin axis, which is looking at how the brain and

skin communicate with each other; how psoriasis itself may cause depression, but also how stress can trigger and/or exacerbate psoriasis. That is pertinent, not just to psoriasis, but probably other skin diseases, such as eczema and acne – we just know about psoriasis.

We are also working on the cardiovascular disease and psychological associations with psoriasis, and how we can better identify and manage those. We are researching how one can improve management of psoriasis in primary care. We also have research ongoing on the genetics and immunology of the disease, in addition to clinical trials and new therapies as they come forward for psoriasis. So we have a lot of things going on; indeed, we have a very active psoriasis research program, probably one of the most comprehensive in the world I would guess.

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