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skin 'n' bones connection

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Dear Reader

Welcome to issue 53 of Skin 'n' Bones Connection.

You will find us in a reflective mood on page 2, where you will read about what PAPAA has achieved during the past few years. We are particularly pleased that some of our ambitions are beginning to prosper.

Part of our progress has been aided by those we've worked with and engaged, on behalf of all those affected by psoriasis and psoriatic arthritis.

Collaboration and the exchange of ideas are important elements of the work we do. On page 4 you can find out about an initiative we have joined to accelerate research into autoimmune conditions.

On page 5 there is a report about how other organisations are also seeing collaboration as a way to progress research.

Finally, we are grateful to Dr David Ashton, our senior medical advisor, for his numerous written contributions for this issue.

Managing editor

ANNOUNCEMENT:

We are sad to report that our trustee and treasurer Brian Lindsey died in March.
He was a loyal and dedicated member of the PAPAA team and he will be sadly missed.

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Collaboration – group of people with light bulb symbol by Rawpixel.com

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The origins of the Psoriasis and Psoriatic Arthritis Alliance (PAPAA) are in the early 1990s, with the current structure of PAPAA beginning in 2007. The aim of this new dawn was to establish the charity as the principal resource for information, support and help for people with psoriasis and psoriatic arthritis in the UK.

So, what has PAPAA achieved?

- The most comprehensive psoriatic-disease-specific website in the UK, with nearly 10,000 free-to-access items and pages.
- A range of 23 printed leaflets on the core aspects of psoriasis and psoriatic arthritis, with more than 200,000 distributed free in the last 10 years.
- More than 1,000 healthcare professionals provided with free patient support material.
- Supported 3,500 UK pharmacies to provide free patient resource at the point of medicine delivery.
- This biannual journal, regularly distributed since 1993 to patients and a wide range of healthcare providers.
- Engaged and represented your views with UK regulators, including NICE, SMC, AWMSG and the MHRA, to provide input into new drug appraisals and regulatory affairs.
- Actively engaged across the most popular social media channels, with around 10,000 interactions.
- We have gathered real stories via our engagement group and PAPAA surveys with more than 5,000 individual views and suggestions from lived-experience of psoriatic disease.
- Around three-quarters of a million pounds provided to support research and training initiatives in psoriatic disease.
- Regular updates provided via an eNewsletter to more than 1,300 people.
- Developed a multi-media online CPD-accredited programme called Psoriasis in Practice for multidisciplinary healthcare professionals, with numerous places provided at no cost.
- Provided anonymised access to peer support to those often desperate for someone to listen and hear their voice.

What's next?

We intend to continue to expand our activities, but will also be looking at how we can work with other groups and collaborate on projects that look beyond the skin and joint manifestation of psoriatic disease. Understanding the underlying common causes that may be part of a spectrum of different auto-immune conditions may begin to provide a wider view and contribute to awareness and ongoing debate. We will continue to advocate for people affected by psoriatic disease to access appropriate care, while being actively involved in the work and research to understand the causes and, ultimately, find a cure.

What can you do to help us?

All of the above needs to be resourced and to enable us to continue to provide it free of cost we need your help. Any donation, no matter how small, will help us to continue to produce and distribute more free leaflets to those that need them and to continue to fund research in the hope that one day a cure will be found for both psoriasis and psoriatic arthritis.

Your support will help us in our mission to make a real difference and change the view – and experience – of psoriatic disease forever.

For ideas of how you can support us, see page 19 or visit our website at: https://www.papaa.org/donate/

Connect Immune Research

PAPAA is pleased to announce that it has joined the Connect Immune Research initiative, which includes the type 1 diabetes charity JDRF, the MS Society, Versus Arthritis, Alopecia UK, and supporting partner, the British Society for Immunology.

The organisations will work together to accelerate research into autoimmune conditions, which see the body's immune system mistakenly attack healthy cells.

These conditions affect an estimated four million people in the UK – more than 6% of the population – but are currently incurable.

The Connect Immune Research initiative brings together researchers from across autoimmune condition specialisms to uncover the common threads in their work – meaning greater efficiency and, it is hoped, new treatments faster.

Autoimmune conditions

As well as accelerating research into new treatments for millions of people, the approach could also dramatically reduce costs. As a result, member charities believe this innovative approach could be key to helping the medical research sector adapt to the impact of the COVID-19 crisis.

Rachel Connor, director of research partnerships at the type 1 diabetes charity JDRF, said:

"The UK is a world leader in immunology research, but for too long teams have been working separately, focusing on specific conditions rather than the connections between them.

As more organisations join the Connect Immune Research initiative, bringing with them their experience and knowledge, we will come much closer to the research breakthroughs that will be transformational for people with autoimmune conditions."

We at PAPAA are very pleased to be part of this initiative. It is clear that there are common issues that affect many immune mediated diseases and working together with other, like-minded organisations makes good sense, not only for the groups involved, but more importantly for the patients we support and represent.

To learn more, visit:
https://jdrf.org.uk/connect-immune-research/

The University of Glasgow (UofG) has entered into a research collaboration with pharmaceutical company Eli Lilly and Company that aims to discover and validate the next generation of drug targets for immunological diseases.

The £4.6million research collaboration will work across four diseases – psoriatic arthritis, rheumatoid arthritis, fibrosis and vasculitis – and will be led by the University of Glasgow's Institute of Infection, Immunity and Inflammation.

The collaboration will allow scientists from UofG and Lilly to work together in order to drive the research forward – a move researchers hope will help enable the identification of first-in-class therapeutics for people suffering with these devastating and costly conditions. For instance, rheumatoid arthritis alone affects 0.3-1% of people across the globe and it is estimated that, within 10 years of diagnosis, 40% of those affected will be unable to stay in full-time work. This has major socio-economic repercussions. In the UK, this costs the NHS on average £700 million per year and indirectly costs the UK economy an estimated £8 billion per year.

The UofG team, led by Professor Carl Goodyear, includes Professor Stefan Siebert, Dr Mariola Kurowska-Stolarska, Dr Neal Millar, Dr Neil Basu and Dr Thomas Otto.

Professor Iain McInnes, vice principal and head of the College of Medical, Veterinary & Life Sciences at the University of Glasgow, said: *"In the current COVID environment, it is particularly important that our research continues to focus on discovering new ways to treat patients with other diseases that can and will affect people's quality of life.*

"We are thrilled to be partnering with Lilly in this extremely exciting collaboration. Strengthening links with industry is hugely important as we move to translate our research findings into clinical practice which benefits patients."

Professor Sir Anton Muscatelli, principal of the university, said: *"Glasgow's researchers have a vision to drive forward innovation, in order to tackle some of society's most urgent challenges. The Glasgow-Lilly collaboration is well positioned to be an inspiring example of this vision and of the exciting possibilities of industry and academia working together. I look forward to seeing this important partnership progress, advancing the next generation of first-in-class therapeutic agents and their alignment with precision medicine approaches."*

Ajay Nirula, M.D., Ph.D., vice president of immunology at Lilly, said: "Lilly's research efforts continue to expand beyond our own laboratories to include unique partnerships with top academic institutions such as the University of Glasgow.

"We look forward to collaborating closely with the scientific team at UofG to discover potential new therapies for immunological disorders."

Professor Carl Goodyear, professor of translational immunology at the University of Glasgow, added: "The collaboration represents a unique opportunity to combine Glasgow's world-class clinical and translational skills with Lilly's therapeutic capabilities and technology platforms for developing novel therapeutics.

"This is a highly unique collaboration that is aimed at harnessing not only cross-disease comparison but also intra-disease pathological comparison across different affected tissues. By providing this disease and tissue contextualisation, it will enable the identification and validation of unique therapeutic targets.

"We are delighted to be establishing this fantastic collaboration and we are confident that it will deliver the next generation of first-in-class therapeutic agents, which will fundamentally change the lives of people who are afflicted with devastating immunological disorders."

Source:
News Release
12 February 2021

The causes and triggers of psoriasis have long been studied and new discoveries continue to emerge. While no cure exists, the treatments that block inflammation are still not the complete answer. To improve treatment options, scientists need to better understand the dysregulation (not working correctly) of the immune system that leads to psoriasis lesions.

Using advanced computational genomic analysis of immune cells from mouse models, a researcher at the Pritzker School of Molecular Engineering (PME) at the University of Chicago and her collaborators discovered that, when exposed to a trigger, certain kinds of immune cells change their behaviour in unexpected ways to produce the protein signals that cause lesions.

The research, co-led by assistant professor Samantha Riesenfeld, reveals new pathways underlying immune responses and ultimately could lead to better treatment for the disease.

Understanding how immune cells behave

The researchers, including collaborators at Yale University and the Broad Institute of MIT and Harvard, set out to better understand innate lymphoid cells (ILCs), immune cells that reside in barrier tissues, such as the skin and lining of the gut. Though not as numerous as T-cells - which play a central role in the body's adaptive immune response - ILCs rapidly sense, integrate, respond to, and propagate signals, thereby modulating downstream immune responses (body's defense).

Previous studies observed a specific type of ILC in skin lesions and proposed their importance in driving psoriasis, but the origins of these ILCs and their role remained unclear. To find out what their role was, the group used a combination of advanced experimental and computational approaches.

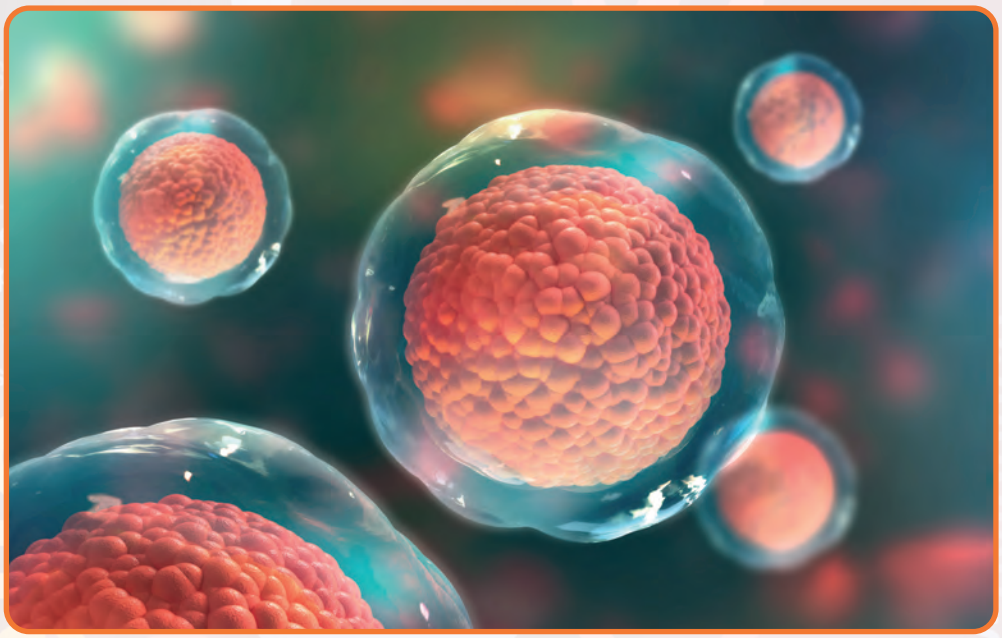
Experimentally, the researchers stimulated skin inflammation in models using interleukin-23 (IL-23) - a cytokine implicated in causing psoriatic lesions. Even in the skin model lacking all T-cells, ILCs could still drive psoriasis. The scientists isolated thousands of ILCs from the skin model over the course of disease induction and profiled the gene expression of these cells individually using single-cell RNA-sequencing.

Riesenfeld and her collaborators then used machine learning techniques on this high-dimensional gene expression data to quantitatively model the behaviour of ILCs before and in response to IL-23 treatment.

They found that ILCs were engaged in a spectrum of activities, unconstrained by previously identified roles. Their models suggest that ILCs across this spectrum have a plasticity that allows them to respond to IL-23 signalling by changing programmed actions, normally considered a stable part of their identities, to produce the pathogenic cytokines that induce skin lesions. The scientists experimentally validated these predictions.

"These findings tell us something new both about how psoriasis arises and about how an inflammatory trigger can change the behaviour of immune cells," Riesenfeld said. "We now think about the identities of ILC cells as more flexible and less predetermined than we used to. That is, cells that are predisposed

to play one role may do something very different under duress."



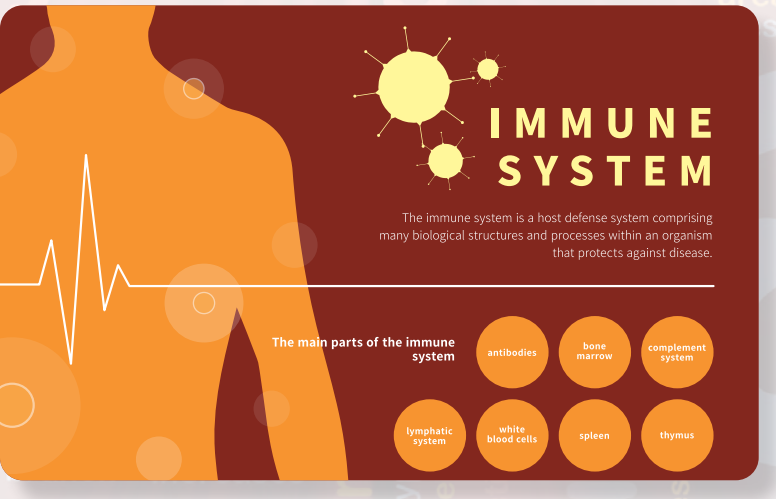
A new approach to understanding the immune system

The combined experimental and computational approach can be used to characterise not just one gene or protein, but whole transcriptional programs of individual immune cells, which can, with the appropriate analysis, offer valuable insights into immune response patterns.

"Understanding how heterogeneous cells integrate and are transformed by immune signals is central to addressing fundamental health-related questions, such as why one person responds to a stimulus with an inflammatory reaction, while another tolerates it," Riesenfeld said.

Delving into a basic understanding of how these cells work, this research suggests that better psoriasis treatment could ultimately involve blocking these early responder cells from becoming pathogenic.

The results were published recently in the journal *Nature*. "Skin-resident innate lymphoid cells converge on a pathogenic effector state," Bielecki, P., Riesenfeld, S.J., Hütter, JC et al. Nature, February 3, 2021. https://doi.org/10.1038/s41586-021-03188-w



Glossary:

Cytokine – messengers that carry biochemical signals to regulate local and systemic immune responses.

Plasticity – ability of certain solids to flow or to change shape.

Innate – existing naturally or by heredity rather than being learned through experience

Pathogenic – is a medical term that describes viruses, bacteria, and other types of germs that can cause some kind of disease.

Transcriptional – the process of constructing a messenger RNA molecule using a DNA molecule.

Heterogeneous – composed of parts of different kinds; having widely dissimilar elements or constituents.

Effector – one that causes or brings about something.

Source:

Eureka Alert

Virtual appointments

Why are psoriasis and psoriatic arthritis appointments being done virtually? Since the start of the COVID-19 pandemic, many people are being offered a non face-to-face (F2F) appointment or consultation. This may be via a standard telephone call and/or in an enhanced video setting, via such systems as Zoom or MS Teams.

It may appear that this is just a temporary process, but there is a view that this may be a good way to support people effectively in the future, according to the NHS Long-Term Plan:

'...by 2023/24 every patient in England will be able to access a digital first primary care offer. Access to primary care services via online consultations will be a key part of achieving that commitment.'

It's worth understanding what is likely to happen if you are offered a virtual consultation now or in the post-COVID healthcare world.

How will my appointment be made?

When you are offered an appointment, you will be asked if you have access to either a smartphone or a computer app so a video consultation can take place. If you don't, it can be done with a standard telephone call. You should make sure you have a quiet, private and comfortable place to take the call where you will not be disturbed.

You may be asked to send images of any areas of psoriasis that you have that are flaring or not responding to treatment. If so, you will need two photographs: one of the whole area or limb, and the other a close-up of the plaque. You will be sent a secure NHS transfer link where you can safely send the images.

You will also be asked to complete some questionnaires, which will be sent to you securely.

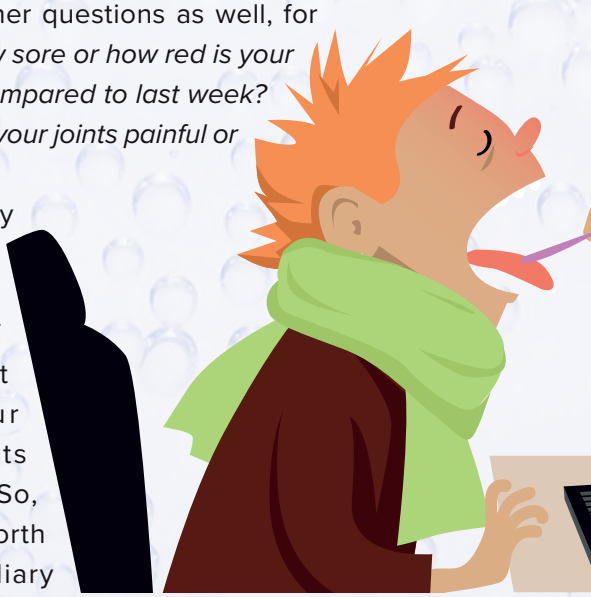
These will be:

- Psoriasis Area and Severity Index (PASI)
- Dermatology Life Quality Index questionnaire (DLQI)
- Psoriasis Epidemiology Screening Tool (PEST) questionnaire.

Once you have completed these questionnaires, they can all be returned via the same secure NHS transfer link as the images and they will be stored securely in your electronic record.

The start of the consultation

You should be reassured that the consultation will be similar to a standard face-to-face consultation and if at any time you feel uncomfortable, you can either stop the consultation or take a break. Before they make the call, the healthcare professional will have already looked at the images that you have sent, along with the completed questionnaires. You will probably be asked other questions as well, for example, *how sore or how red is your skin today compared to last week?* or *are any of your joints painful or feeling stiff?*



You may also be asked if you can think of anything that makes your skin or joints feel worse. So, it may be worth keeping a diary leading up to the consultation to see if there is anything that triggers a flare. You will be asked about any current treatments you are using and any that you may have used in the past. You will also be asked when and how you apply your treatments. You may find it useful to have any creams or medicines that you are using nearby so you can show them to your healthcare professional.

Working together

Your consultation should be a partnership between you and your healthcare provider, with a plan of care worked out jointly, which takes into account what treatments have worked in the past, and whether they are working now or need to be changed.

- You may wish for a family member to sit in for this part of the consultation, to help you understand the advice you are being given, and particularly if they are involved in your treatment regime such as applying creams to hard-to-reach places.

- You may also be given advice on general skin care and how to prevent possible flares. Make sure you fully understand what you are being told; if you are in any doubt, ask your healthcare provider to repeat anything you are not clear about.

- Sometimes it is easy to forget what you wanted to say, if you are feeling slightly overwhelmed or confused by information you are being given at the time. You may find it useful to prepare a list of questions as you think of them in advance – because this is the time in your appointment to ask them.

What happens next?

Once a treatment plan has been set out, you fully understand it and arrangements have been made for your prescription to be sent to your nominated pharmacy, a mutually agreed follow-up appointment will be made.

You may be asked to send in more images via the same secure link two days before your next appointment.

At this point your healthcare provider will ask if you have any final questions before they end the appointment. This is your final opportunity to clarify anything that you have not understood during the consultation.

Your feedback

Whether you have been offered a virtual consultation appointment or have already taken part in one, we would really value your feedback about the experience. We'd like to share your experiences – anonymously, of course - in order to help others who may be hesitant or unsure about the effectiveness of this style of care and interaction with a healthcare provider.

Please send your comments or views via the *share your story* online form, which you can do anonymously at https://www.papaa.org/coping/share-your-personal-journey/

You may also be interested to read the experiences of other people who have psoriasis and/or psoriatic arthritis via our *personal journeys* section: www.papaa.org/coping/personal-journeys/

We would love you to take part in the PAPAA survey, where we are gathering ongoing information that will help us to create the full picture of what it is like to live with psoriasis and psoriatic arthritis: https://www.papaa.org/get-involved/the-papaa-survey/

A brief history of psoriasis

This is the first of two articles on the history of psoriasis, with the second scheduled to appear in Issue 54.

Recognition and diagnosis

Psoriasis has probably been around for as long as modern man and has also been reported in non-human primates. Skin diseases were well known to the physicians (known as ašipu) of Ancient Mesopotamia more than 3,000 years ago. There is also a description of a skin condition called khusta in the religious Ayurvedic tradition in India, though this may have been leprosy rather than psoriasis. Astonishingly, it was not until the 19th century that psoriasis - as a disease in its own right – was finally recognised.

Ancient history

Although psoriasis is probably as old as mankind, the roots of the identification of psoriasis lie in Ancient Greece. The Greeks divided skin disease into the categories of psora, lepra and leichen. Psora referred to itch, while lepra was derived from the Greek words lopos (epidermis) and lepo (to scale). Hippocrates (460-377 BC), the Greek "Father of Medicine", is credited with writing some of the first descriptions of skin disorders. He used the word psora, which meant itch, and lopoi to describe the scaly, dry features of psoriasis and other inflammatory skin conditions, such as leprosy. At that time, skin conditions were lumped together, so that leprosy and psoriasis were frequently confused. This is obviously important, because lepers were generally excluded from normal society, because they were believed (wrongly) to be highly contagious.

Much later, the Roman nobleman Cornelius Celsus (25 BC- AD 50) provided a detailed clinical description of a skin condition which affected the limbs and nails. It was characterised by red skin covered with scales, which he called impetigo, but which was almost certainly psoriasis.

Galen (131-201 AD) of Pergamon was a Greek physician in the Roman Empire and was probably the first to have used the term "psoriasis". He described an itchy, scaly eruption of the eyelids and genitals, but this was likely to have been seborrheic dermatitis rather than psoriasis.

Overall, it seems that the great physicians of antiquity wrote rather little about skin diseases, which they did not regard as being of any particular importance. Therefore, no coherent or consistent description of psoriasis can be found in this period.

The Middle Ages

Following the demise of the Roman Empire, European history entered what is known as the Middle Ages, roughly the late 5th to the late 15th century.

Most literate men were in monastic orders and spent their days contemplating abstract theological questions, rather than medical or scientific problems. The random grouping together of all

inflammatory skin diseases led to stigmatisation of patients with psoriasis. For centuries, patients with psoriasis suffered the same cruel fate as lepers. They were outcasts, who were required to carry a bell or clapper to announce their approach and who could only mix with other "lepers". In 1313, Phillip the Fair of France ordered that they be burned at the stake. If you were unfortunate enough to have psoriasis during this period, you would have been well-advised to stay out of the way.

The Renaissance

The Renaissance, a cultural movement that spanned the 14th to the 17th centuries, began in Florence and later spread to the rest of Europe. During this period, by far the most important work on skin disease – *De Morbis Cutaneis* (Diseases of the Skin) – was written by Girolamo Mercuriale (1530-1606). In this book, widely regarded as the first scientific treatise on skin conditions, he divided

cutaneous diseases into those of the scalp and those of the body, referring to psoriasis under the name of lepra grecorum. Another Italian, Bernardo Ramazzini (1633-1714), is undoubtedly the father of modern occupational medicine. His original work – *De Morbis Artificum Diatribe* (Diseases of Workers) – includes basic descriptions of some skin conditions, such as eczema, dermatitis and psoriasis.

The 18th and 19th century

Although several important figures in the 18th century, such as Daniel Turner, Charles Lorry and Joseph von Plenck, wrote in general terms about skin diseases, none paid specific attention to psoriasis. Indeed, it was not until 1809 that an English doctor named Robert Willan (1757-1812) developed a simple classification of skin diseases, which allowed a more rational approach to diagnosis. Willan was essentially the founder of dermatology as a medical speciality and was the first to offer a clear description of different types of psoriasis, including guttate (small red, dotty patches), scalp and palmar lesions. He also observed that the disease began on the knees and elbows but could also attack the finger and toenails. This was a huge step forward in the recognition of psoriasis as a separate disease entity. Unfortunately, he used the term lepra vulgaris rather than psoriasis, which again perpetuated the confusion between psoriasis and leprosy.

One of the great figures in 19th century dermatology was Ferdinand von Hebra (1816-1880), an Austrian physician working at the Vienna General Hospital. He founded the Vienna School of Dermatology and, while still a young man, wrote one of the most influential books on skin diseases of all time – *Atlas der Hautkrankeiten* (Atlas of Skin Diseases). This was widely regarded throughout Europe, as much for its wonderful illustrations, as for its scientific and medical content.

Von Hebra is rightly regarded as the father of modern dermatology, in that he was the first to apply modern research methods to the study of skin disorders. He was also a great teacher and students from all over the world came to study with him in Vienna. Importantly for our story, is the fact that it was Von Hebra who permanently shed the term “lepra” from the description of psoriasis, finally separating the two diseases from one another once and for all.

Another 19th century milestone was the recognition of the association between psoriasis and a particular form of arthritis. Although this was first discovered by the French dermatologist, Jean Louis Alibert, in 1818, it was not until 1860 that Ernest Bazin (another Frenchman) coined the term “psoriasis arthritique” or “arthritic psoriasis”. A detailed characterisation of the condition was provided by Charles Bourdillon in his doctoral thesis, Psoriasis Arthropathies (1888).

Further refinements in the description of the various forms of psoriasis continued throughout the 19th century. In addition, some authors described signs that might be useful in the diagnosis of the disease. Heinrich Auspitz (1835-1886), one of Hebra’s students, noted that when scale is scraped from psoriatic plaques, tiny bleeding points occur – called the Auspitz sign. It is not, however, specific to psoriasis and is no longer regarded as a reliable diagnostic tool.

Heinrich Köbner (1838-1904) noted that some people with psoriasis developed lesions in areas in which the skin had been traumatised. This could be from a cut, a bruise, or a burn, but lesions may also develop on parts of the body where the skin is irritated by a waistband, or belt buckle. In all these cases, the psoriatic lesions occurred in areas outside those normally affected by psoriasis – called an isomorphic response. Although the Köbner phenomenon is a well-known aspect of psoriasis, it is not completely understood even today.

Finally, in 1898, an Australian dermatologist called William J. Munro described micro-abscess formation in the epidermal layers of the skin of psoriatic patients. Subsequent studies – as recently as 2011 – show that micro-abscess formation is highly specific for the diagnosis of psoriasis vulgaris – the most common form of the disease.

The 20th century

The start of the 20th century ushered in further, detailed descriptions of the various types and sub-types of psoriasis. In 1910, Leo von Zumbusch first described generalised pustular psoriasis. This is a serious - though fortunately rare – condition, characterised by widespread areas of reddening or the skin, which becomes painful and tender. Within hours, tiny pustules appear, many of which will consolidate into larger blisters. There is accompanying fatigue and fever.

Note that von Zumbach's generalised pustular psoriasis is not the same as the more common form of localised pustular psoriasis, affecting the palms of the hands and soles of the feet, called palmoplantar pustulosis (PPP).

In 1926, Dr D. L. Woronoff, a dermatologist at the clinic for skin diseases of Moscow University, described a pale (hypopigmented) zone of skin which appeared around healing psoriasis lesions. This pale "halo" became known as "Woronoff's ring". Until recently, the cause of this phenomenon was a mystery, but it has now been attributed to the effects of various inflammatory molecules, reducing the melanin content of the skin cells surrounding the healing psoriatic lesion.

The recognition of the Auspitz sign, Köbner's phenomenon, Munro's abscesses, generalised pustular psoriasis and the Woronoff ring provided important diagnostic tools which allowed physicians to be more confident in diagnosing psoriasis.

Another landmark event came in 1973, with the publication of a paper by John M. Moll and Verna Wright from Leeds, in the UK, on psoriatic arthritis, which proved to be a milestone in the history of psoriasis. Of course, as we have seen earlier, the association between psoriasis and arthritis had already been observed (by Alibert and Bazin), but what Moll and Wright did was show that the arthritis associated with psoriasis is unique to that disease and quite different from rheumatoid arthritis.

21st century

Today, psoriasis is no longer regarded simply as a skin condition, but as a chronic autoimmune disease, characterised by systemic inflammation. This inflammatory process affects not just the skin, but also joints and other bodily systems. Over the last decade, developments in molecular science and genetics have provided a deeper scientific understanding of the disease mechanisms involved, leading to exciting new treatments. This will be the subject of Part 2 of this history.

Nevertheless, we are by no means at the end of the journey and there is still a great deal about psoriasis that is completely baffling. As the distinguished American dermatologist, Paul E. Bechet, wrote in 1936: "Psoriasis is an antidote for dermatologists' ego".

Author:
Dr WD Ashton MD PhD

Part 2 will appear in the next issue of this journal.

There is a well described association between psoriasis and several other diseases, including obesity, arthritis, diabetes, osteoporosis, depression, inflammatory bowel disease and cardiovascular diseases. More recently, psoriasis has also been linked to several endocrine diseases and this article will discuss the most important of these.

The endocrine system

The endocrine system consists of a group of eight glands in different locations throughout the body, including the thyroid, pituitary and adrenal glands and pancreas. They secrete various hormones which act as chemical messengers to control and regulate various processes, including growth and development, metabolism, sexual function and mood.

Disorders of the endocrine system involve production of either too little hormone (called 'hypo' function) or too much ('hyper' function). Thus, an overactive thyroid is called hyperthyroidism (too much hormone) and an underactive thyroid is called hypothyroidism (too little hormone).

The association between psoriasis and diabetes is well known, but psoriasis has also been linked to an increased risk of several less common endocrine disorders, including Addison's disease, thyroid disease and Cushing's syndrome (also referred to as Cushing's disease). This short article discusses the strength of the associations for these three conditions and the implications for individuals with psoriasis.

Some clues

A good place to begin if we want to evaluate the risk of endocrine diseases in patients with psoriasis is to look at the prevalence of these conditions in large epidemiological surveys. The problem is that there are very few such surveys, so evidence is limited.

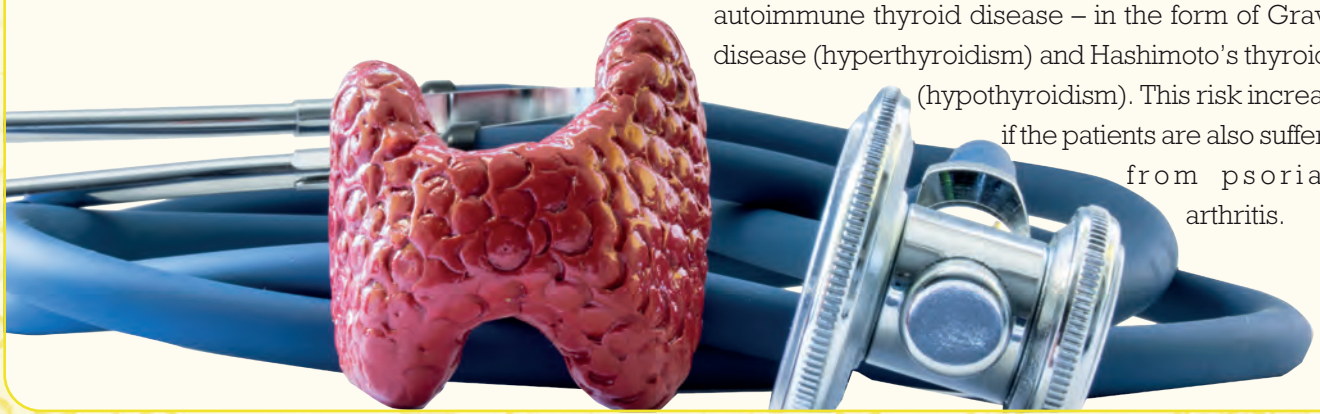
An interesting exception is a study carried out in Israel, which evaluated the prevalence of endocrine disorders in 3,161 patients with psoriatic arthritis (PsA), compared with 31,610 healthy controls.[1] Compared with control patients, significantly more patients with PsA had hypothyroidism (12.7% vs 8.6%) and Cushing's syndrome (0.3% vs 0.1%). Both osteoporosis and diabetes were significantly more common in patients with PsA than in control groups. However, the prevalence of a range of other endocrine diseases, including hyperthyroidism, acromegaly (excess growth hormone) and diabetes insipidus, was similar in both groups.

This study did not show an increased risk for Addison's disease in the psoriasis group, but (as discussed below) other research suggests that there is an increased risk for this disease in patients with psoriasis.

Psoriasis and thyroid disease

The possible link between psoriasis and thyroid disease has been explored in several studies, but the results have been contradictory. In the study quoted earlier, investigators found an association with hypothyroidism, but not for other thyroid diseases.[1] However, a recent study from Taiwan assessed the risk of thyroid diseases in patients with psoriasis and psoriatic arthritis in a large, national cohort.[2] The study included 149,576 patients with psoriasis alone and 13,266 also with psoriatic arthritis, as well as 162,842 matched controls without psoriasis. The mean age in all groups ranged from 43 to 45 years and roughly 40% were female.

Results clearly showed that patients suffering from psoriasis have an increased risk of developing autoimmune thyroid disease – in the form of Graves' disease (hyperthyroidism) and Hashimoto's thyroiditis (hypothyroidism). This risk increases if the patients are also suffering from psoriatic arthritis.



In one sense, the link between psoriasis and thyroid diseases is unsurprising, given that both are autoimmune diseases. Hence the researchers themselves speculate that the association may be explained by cell-mediated inflammation, which is involved in both types of diseases. An additional factor could be that both diseases share the same genetic predisposition. Either way, the connection between psoriasis and an increased risk of thyroid disease is relevant and even more important because most thyroid disorders are eminently treatable.

Addison's disease

Addison's disease, also called primary adrenal insufficiency (PAI), is a rare disease of the adrenal glands in which they cannot produce normal quantities of the adrenal hormones cortisol and aldosterone.

In the study referred to earlier, there was no increased risk observed for Addison's disease in patients with psoriasis compared with healthy controls.[1] However, a recent review from Denmark clearly suggests otherwise.[3] The study population was based on the Danish National Patient Register, from which the researchers included[1],199 individuals with PAI and 5,995 matched controls, 65% of whom were female and with an average age of 52.8 years. The data was then interrogated for cases of psoriasis and psoriatic arthritis (PsA).

In this population-based study, PAI was significantly associated with psoriatic arthritis, but not psoriasis alone, when compared with matched controls. As to the question of which came first – psoriasis or PAI – the investigators showed that it was most likely that psoriasis preceded the PAI.

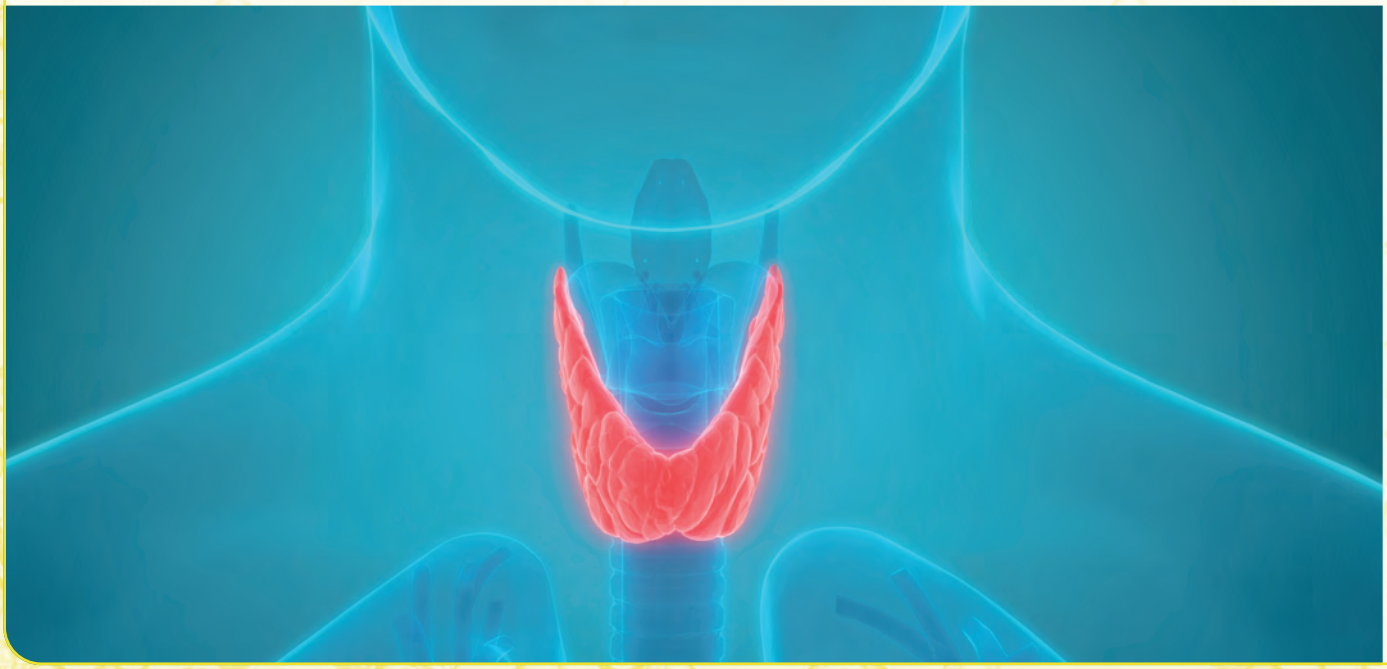
The explanation for the link is not clear, but - as with thyroid disease – is likely to be related to the underlying autoimmune response, characteristic of both diseases.

Although the link between the two diseases is significant, it is important to remember that Addison's disease is exceedingly rare. In the UK, the rate is 39 cases per 1 million (3.9/100k) of population, whereas in Denmark, the figure is 60 cases per 1 million (6.0/100k) of population.

Cushing's syndrome

Cushing's disease is a condition in which the body produces an excess of cortisol from the adrenal glands, which are small triangular structures located on top of each kidney. It is a rare disease – just 13 cases per 1 million – and is caused by a benign tumour, either of the pituitary gland (in the brain) or in the adrenal glands.

In the study referred to earlier, there was a threefold increase in risk of Cushing's disease in patients with psoriatic arthritis compared with healthy controls.[1] However, this was just 0.3% versus 0.1%, so still an extremely low risk. Importantly, this association



has not been found anywhere else in the scientific literature and the authors are not sure whether this association is real; it could be simply due to biases in the study. So overall, this is probably not a significant finding.

There is another form of Cushing's disease worth mentioning: the iatrogenic form. Iatrogenic disease happens when the treatment prescribed by a doctor produces unwanted effects (the word derives from the Greek iatros, which means healer). In the case of psoriasis, Cushing's syndrome can be due to long-term, high-dose steroids, usually prescribed orally. However, there are also cases in which prolonged topical use may also result in the features of Cushing's disease: weight gain, moon face, bruising etc.[4] Nowadays, however, this is likely to be an extremely uncommon complication.

Discussion

Diabetes and osteoporosis can both be regarded as endocrine disorders, each of which is strongly linked to psoriasis. In this article, however, the main concern has been the much less common endocrine diseases which may be linked to psoriasis. Based on the available evidence, we have identified three conditions:

1. Addison's disease is characterised by weight loss, fatigue, low blood sugar, nausea, depression and abdominal pain. While there is an increased risk for this disease in psoriatic arthritis, in absolute terms this is an exceedingly small excess risk. Symptoms such as abdominal pain, depression and fatigue are much more likely to be due to other much more common causes than Addison's disease, which only occurs in roughly 1 in 25,000 people. In this sense it is clinically relevant, but not practically relevant.

2. Cushing's syndrome is an even rarer condition than Addison's disease and there is no clearly demonstrated association with psoriasis. There is an iatrogenic form due to excessive use of steroids but, again, this is rare and so not something seen in practice.

3. There is an increased risk of thyroid disease in psoriasis and this has genuine practical implications. It may present as (a) an overactive thyroid (Graves' disease or hyperthyroidism) – with weight loss, anxiety, tremor of hands and/or fingers and an enlarged thyroid gland, or (b) an underactive thyroid (Hashimoto's thyroiditis or hypothyroidism – with fatigue, constipation, depression and weight gain.

Practice points

Cushing's disease, Addison's disease and various thyroid disorders have all been associated with psoriasis. However, only thyroid diseases are relevant in clinical practice. Family doctors should bear this in mind when managing patients with psoriasis and should arrange for suitable investigations in the event of relevant symptoms becoming apparent.

Dr David Ashton MD PhD

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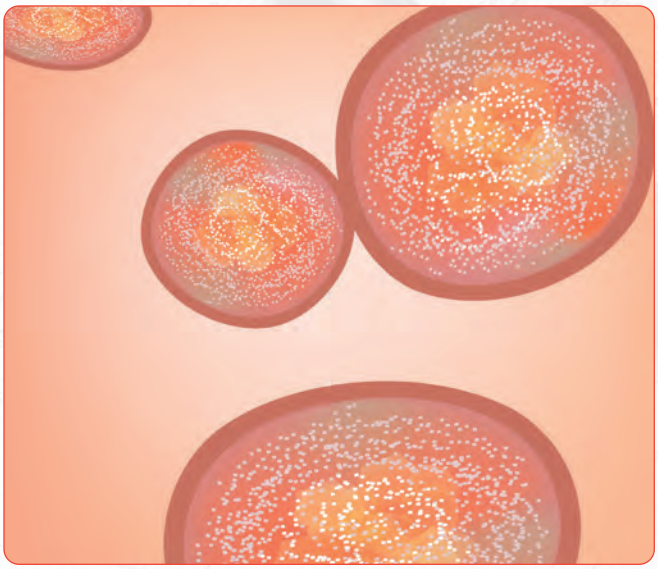
New horizons in treatment

Anyone struggling with a chronic disease wants to know when there is going to be a cure and people living with psoriasis are no exception. Unfortunately, psoriasis is an extremely complex disease and so a cure is still some way off. In the meantime, there is an extraordinary amount of exciting research work going on around the world. Here is a quick digest of some of the most interesting areas currently being investigated – not all of them high-tech!

1. Inflammatory protein targets

Inflammation is the body's natural defence and repair system. If you have an infection or cut yourself, your immune system triggers an inflammatory response, via a special group of proteins called cytokines. Cytokines are special signalling molecules – or 'immunomodulating agents' - which regulate the immune response and inflammation. In psoriasis, this inflammatory response takes on a life of its own and is directed against the body's skin cells, pushing them into overdrive (sometimes referred to as a cytokine storm). In fact, skin cells are made at a rate up to seven times faster than normal, resulting in the plaques, scaling and itching typical of psoriasis.

Examples of pro-inflammatory cytokines include tumour necrosis factor alpha (TNF-alpha) and various interleukins, including IL-8, IL-12, IL-17 and IL-23. Unsurprisingly, drugs which block the actions of these cytokines – biologics - have been therapeutic targets identified by pharma companies for many years.



A drug called ustekinumab (Stelara) has been used to treat psoriasis since 2009. It blocks the effects of two cytokine proteins, IL-12 and IL-23. However, scientists now believe that IL-12 may actually protect skin cells from a different inflammatory protein, IL-17. Attacking IL-12 may therefore not be such a good idea and better results may come from focusing on IL-17 and IL-23 inhibitors. This is where the most recent research has been directed - and the results are very promising.

IL-17 and IL-23 inhibitors

A new injectable drug that blocks the activity of IL-17 proteins was approved in 2016. Ixekizumab (Taltz) was given the green light for treatment of moderate to severe psoriasis after the experience of 80% of people in clinical trials improved when taking it. The drug cleared symptoms for almost half the people who tried it, a success rate which few other psoriasis drugs have been able to match. It joins another IL-17 inhibitor, secukinumab (Cosentyx), which was approved to treat psoriasis in 2015.

Three other drugs on the horizon target IL-23. The injectable IL-23 blocker, guselkumab (Tremfya) improved psoriasis better than the more traditional biologics, such as the TNF-alpha inhibitor adalimumab (Humira). Similar results are expected for the other two IL-23 blockers: risankizumab (Skyrizi) and tildrakizumab (Ilumya).

2. Gene-based gels

TNF-alpha, as we saw above, is one of the important inflammatory cytokines and a key driver of psoriasis. It has traditionally been a target for several drugs used in the management of psoriasis.

Now a different approach has been developed, based on three-dimensional spherical nucleic acid (SNA™) particles. These are essentially microscopic spheres of genetic material (nucleic acid) which prevent the body making TNF-alpha. What is innovative is that the new drug – known as AST-005 - is formulated and applied in the form of a topical gel.

A small trial in Germany, involving 25 patients with chronic plaque psoriasis, evaluated the safety, and tolerability of the gel and found no serious adverse events in any patient.

While larger studies are obviously needed, this is an exciting and innovative approach to delivering biologic agents which can directly target inflammatory cytokines in the skin. An obvious potential advantage is that there are usually fewer and less severe side effects with topically applied treatments, compared with oral medications.

3. Healing genes

Researchers from the University of California have discovered one of the key underlying genetic factors involved in repairing the skin lesions of psoriasis.[1] A gene called grainyhead-like-3 (GRHL3), originally discovered in fruit flies and which is known to be important in wound healing, also helps the body to heal psoriasis skin-lesions.

In support of this, they found that deletion of this gene in mice increased the severity and longevity of the psoriasis-like patches. Researchers are now studying whether people with psoriasis have a genetic change that weakens GRHL3's effects and, if so, whether there is a way to boost its healing powers.

The GRHL3 pathway represents an exciting new target for pharmaceutical products designed to enhance the natural mechanisms of skin healing in psoriasis patients.

4. Healing protein

Researchers at the Stanford University School of Medicine have identified a new molecular target - Rac1 - for potential therapies for psoriasis.

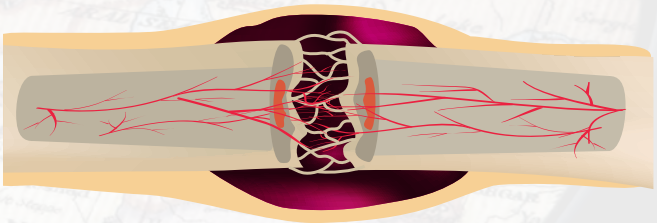
Rac1 is a small protein in the skin which is involved in wound repair. It is also linked to well-known environmental triggers of the disease – such as streptococcal sore throat – which are associated with disease flare-ups. When activated, Rac1 is believed to promote the proliferation of cells in the epidermis, as well as send signals to activate the immune system. Usually this is a necessary and graded response, to promote healing after an injury. But over-proliferation and over-inflammation could have detrimental effects.

Researchers consistently found that Rac1 was highly activated in biopsies of psoriatic skin from 20 people with the condition. When they artificially activated Rac1 in the skin of laboratory mice, the animals exhibited similar symptoms as human patients. They also found that blocking the activity of Rac1 in patches of psoriatic human skin that had been transplanted onto the backs of mice reversed the skin lesions and reduced the concentration of cytokines in the transplanted patch.

As a result, scientists think "switching off" Rac1 may help fight flare-ups. This could lead to treatments that are easier on the immune system than today's biologic drugs.

5. Bone preservation

There is good evidence that patients with psoriasis and psoriatic arthritis have an increased risk of osteoporosis and metabolic bone fracture.[2] The likely mechanism involved is high levels of cytokines, such as TNF-alpha, IL-6 and IL-17. These inflammatory molecules appear to increase bone loss.



A recent study was designed to investigate whether treatment with biologic agents, which inhibit inflammatory cytokines, could help to preserve bone density.[3] This study, which was conducted by researchers in Germany, included 165 patients with psoriatic arthritis (PsA), 34 of whom took methotrexate alone, 52 who used biologics (including adalimumab, infliximab, etanercept, certolizumab, golimumab, secukinumab, and ustekinumab) and 79 who did not take a disease-modifying drug. Those using biologics took the drugs for an average of four years.

Specialised imaging was used to determine bone density and bone microstructure.

Overall, results show that treatment with biologics – but not methotrexate – was associated with significantly better bone structure and function in patients with PsA. The authors conclude that blocking the action of bone-destroying inflammatory cytokines with biologic agents is a key factor in preserving bone health in patients with psoriatic arthritis.

6. Turmeric

Although most natural psoriasis remedies have no scientific research to support their use, a key exception is that of the bright yellow spice turmeric. Its main ingredient, curcumin, can block the protein TNF-alpha, which triggers psoriasis inflammation. Turmeric can be mixed into food or taken as a supplement. But it has also been used in the form of a topically applied gel, with encouraging results.

One trial involving 647 patients with mild to severe psoriasis used curcumin gel, topical steroids, avoidance of contact allergens and avoidance of dairy products for those who were lactose intolerant, as the therapeutic regimen.[4] At 16 weeks follow-up, 72.2% of patients were completely clear of psoriatic activity (PASI = 0). The problem with this trial is obviously that there were several treatments being applied simultaneously, so the specific contribution made by the turmeric gel could not be established.

A better-quality study, using a specially formulated curcumin microemulgel, also showed positive results.[5] This was a placebo-controlled, double-blind, clinical trial of 34 people with plaque psoriasis, who were treated with the microemulgel. The study showed that the microemulgel was well tolerated and that, when compared to those subjects receiving the placebo, participants showed greater improvement in symptoms such as skin redness, itching, thickness and scaling. They also reported an improved quality of life.

Taken together, these studies suggest that various topical formulations of curcumin – while not becoming standalone treatments for psoriasis - may be a useful, low-risk, adjunct therapy.

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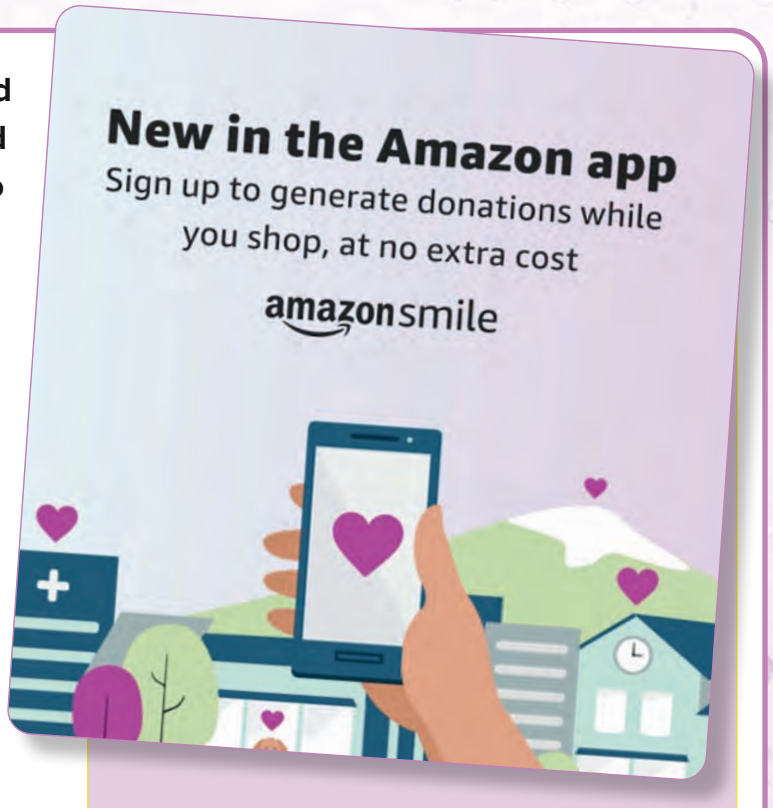

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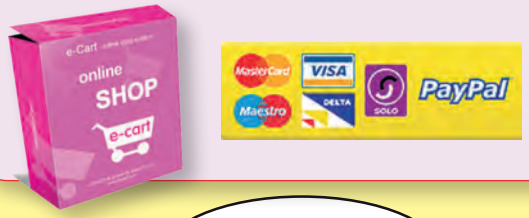

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