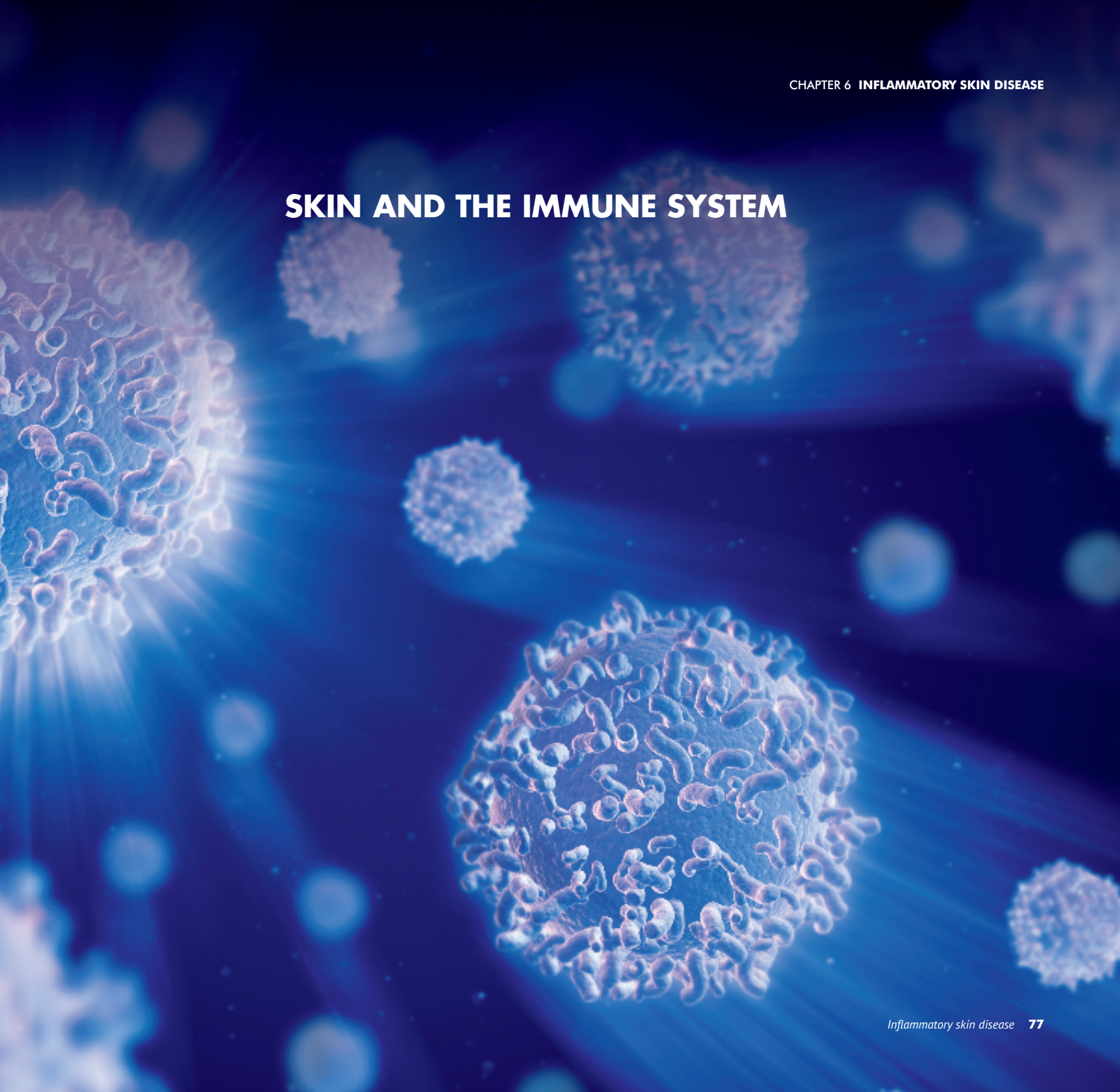


SKIN AND THE IMMUNE SYSTEM





Inflammatory skin disease forms a major component of dermatology – which includes the red and scaly condition psoriasis, the itchy weals of urticaria and the blistering skin disorders of immuno-bullous disease.

Psoriasis is the most common – affecting one in 50 of the population worldwide, more than one million in the UK. The best known sufferer is still fictional hero Philip Marlow, the louche, cynical mystery writer and star of Dennis Potter's BBC TV series "The Singing Detective", broadcast in 1986.

Hospitalised by severe *psoriasis* and *psoriatic arthritis*, creamed, bandaged and feverish, Marlow falls into a fantasy world in which the hospital, the noir thriller and wartime England merge. The series was voted the 20th best all time TV programme by the British Film Institute in 2000. Potter was himself a lifelong sufferer from *psoriasis* and *psoriatic arthritis* - and was treated at St Johns. Like Marlow, he was an awkward patient.

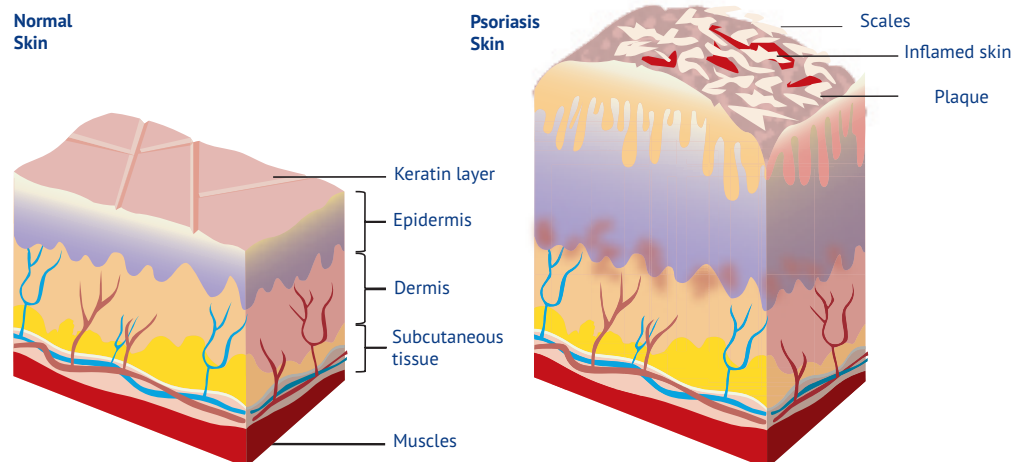
Psoriasis

St John's runs one of the major tertiary services for severe psoriasis in the country (the other is in Manchester). Although the condition is common, a minority have severe disease accounting for 10-20 per cent of the total. It is caused by the skin cells being replaced too quickly, the product of an over-active immune system. Normally skin cells take three to four weeks to replace themselves but in psoriasis they take less than a week.

The mainstay of treatment for most sufferers is creams and ointments to soothe and moisturise the red, scaly and cracked skin that may become sore and painful. Until a decade ago *Dithranol*, and also crude coal tar, applied directly to the psoriatic plaques as a paste was a mainstay treatment but because it could burn normal skin it had to be applied in hospital by trained nurses and required a stay of two to three weeks.

Psoriasis – from the Greek word psora meaning itch – was known as the "antidote to the dermatologist's ego". Severe cases would spend weeks in hospital or were treated with immunosuppressants such as *ciclosporin* and *methotrexate*, to damp down over-active immune systems. These drugs are still used but are only effective in some patients and occasionally have serious side effects. *Methotrexate* is linked with problems of the bone marrow and liver and patients require regular monitoring.

At the turn of the millennium there was a dramatic change. The introduction of the new biologic drugs, custom designed to target specific parts of the immune system, has transformed the outlook for patients severely affected with *psoriasis*. At St John's the first patient was infused with the drug *infliximab*, a monoclonal antibody, in 2001.



More than one million people are affected by psoriasis in the UK of whom 10-20 per cent have severe disease



The psoriasis team at St John's: there has been an 80 per cent reduction in in-patient episodes

Three more biologics have since become available – *ustekinumab*, the most recent, can be self-injected by the patient just three to four times a year.

Professor **Catherine Smith**, consultant dermatologist, said: “People with *psoriasis* used to come in and out of hospital. Now we have had an 80 per cent reduction in in-patient episodes. These

drugs are life-transforming. Almost 70 per cent of patients on treatment are clear or near clear.”

She added: “Some patients comment that they almost forget they have psoriasis.”

Before the advent of the biologic drugs, doctors struggled with the most severely affected patients in an attempt to make their lives bearable. Searching



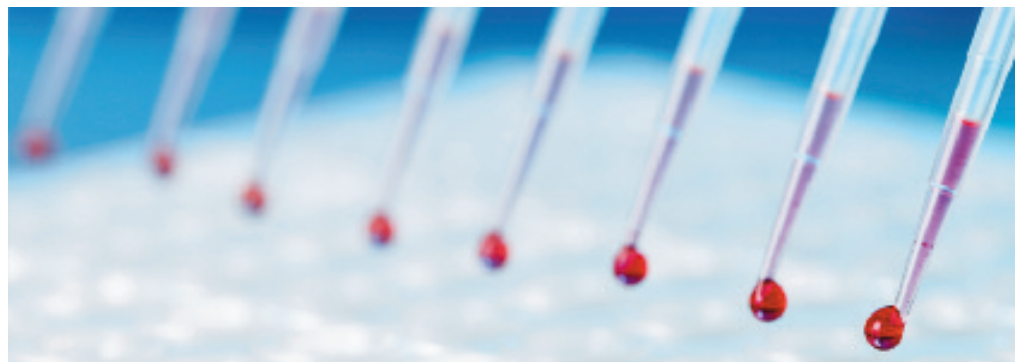
Several biologic drugs are now available

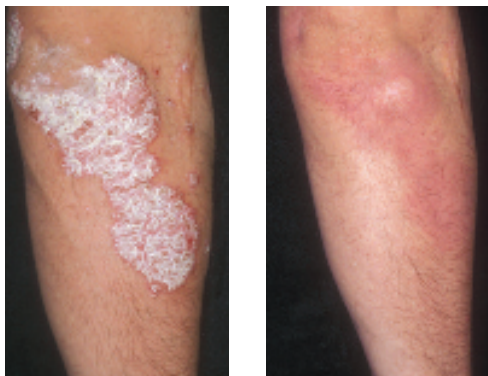
for a treatment that worked, they used multiple immunosuppressants in combination to increase the drugs' impact – but at the risk of over-suppressing the patient's immune system leaving them vulnerable to a serious infection.

Psoriasis is not fatal but in its worst manifestation it is so severe that sufferers cannot function.



Powerful immunosuppressants were used in severe cases of psoriasis, and sometimes still are. But the new biologic drugs have transformed the outlook for patients





Psoriasis plaque before and after treatment

Professor **Jonathan Barker**, consultant dermatologist, said: “It is socially disfiguring. Having a partner, wearing dark suits, going swimming are all problematic. Physically the skin is sore and weeping and if the hands and feet are affected they can’t work or walk. There is a high incidence of depression, and also in some patients alcohol misuse in order to cope.”

Those days are now past for many patients with severe disease. If Dennis Potter was alive today he and his fictional alter ego would have a very different outlook.

But there is a downside. While the drugs leave most patients clear or near clear (70 per cent) – that leaves many still not helped. And much depends on which areas of the skin are clear. If sensitive areas such as the face remain affected then the impact of the drug is greatly diminished. Complete clearance of the condition is achieved in only half of patients.

Professor Smith said: “Expectations have been



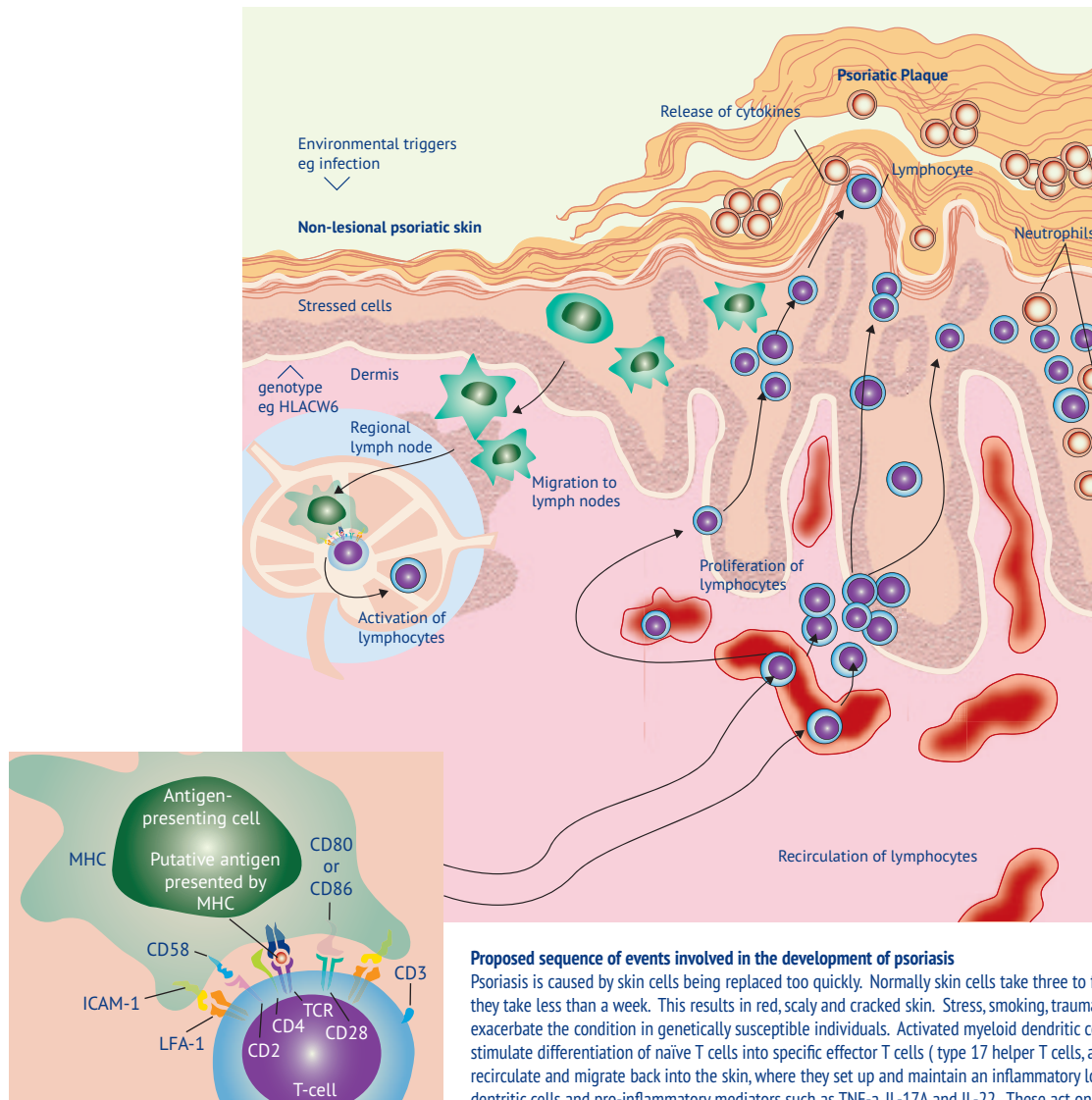
Although the new biologic drugs are very effective, they do not help all patients, and they are costly

raised. But at least 30 per cent of patients are not helped and 50 per cent are not fully clear. That is a problem.”

Even in those who have a good response, some will fail later. Some suffer side effects – these are powerful drugs. Around 15 per cent stop responding after a year, and this is ongoing, year by year. The drugs are also most effective in *plaque-type psoriasis*, much less so – if at all – in other types such as *pustular psoriasis*.

Finally, there is the question of cost. The drugs are expensive, at around £10,000 per patient per year and St John’s has around 400 currently taking them. They consume 60 per cent of NHS spending on *psoriasis* therapies though they help only a minority of patients.

This underlines the need for further research. A consortium of institutions, including St John’s, has won a £7 million grant from the Medical Research Council to investigate the best way of prescribing



Proposed sequence of events involved in the development of psoriasis

Psoriasis is caused by skin cells being replaced too quickly. Normally skin cells take three to four weeks to replace themselves but in psoriasis they take less than a week. This results in red, scaly and cracked skin. Stress, smoking, trauma and infection are among the triggers that can exacerbate the condition in genetically susceptible individuals. Activated myeloid dendritic cells migrate to draining lymph nodes and stimulate differentiation of naïve T cells into specific effector T cells (type 17 helper T cells, and type 1 helper T cells). These T cells then recirculate and migrate back into the skin, where they set up and maintain an inflammatory loop, driven by release of IL-23 from dermal dendritic cells and pro-inflammatory mediators such as TNF- α , IL-17A and IL-22. These act on keratinocytes which also drive inflammation and further cell recruitment (eg: neutrophils).

the new drugs. The Psoriasis Stratification to Optimise Relevant Therapy (PSORT) project is designed to identify the markers that will enable doctors to target treatments more effectively. These may be genetic, immunological, pharmacological (for example, the best dosing regime) or clinical.

"The aim is to get the right dose into the right patient at the right time," said Professor Barker.

Much is known about the genetic and immunological mechanisms underlying the pathogenesis of *psoriasis* and the key role of tumour necrosis factor, an immune system mediator. In 2009, researchers at St John's, together with their collaborators, uncovered genetic evidence to explain the mechanism of action of the biologic drugs, which had up till then been used on a trial and error basis. Their paper, published in *Nature Genetics*, revealed the specific parts of the immune system that are involved in causing psoriasis including the IL-17 pathway. The discovery represented a key piece of the jigsaw in the search for new treatments.

Professor Barker said: "Our genetic research delineated exactly how and why the biologics work. Drug development can now proceed in a targeted way. It is science-led as opposed to being driven by serendipity."

The breakthrough underlined the importance of having researchers working with patients on the wards, something St John's prides itself on.

Professor Barker said: "The unique thing about St John's is that researchers and clinicians collaborate together. Having clinical academics with joint appointments at the Trust [Guy's and St Thomas'] and the university [King's College London] means they can do patient-based

research. True collaboration of this kind is very unusual. As a result, St John's can provide state of the art treatment for patients with severe disease, high quality teaching for clinicians as well as conducting cutting edge research."

Professor Smith added: "You need to see what is happening to the patients as a researcher so you can go back to the lab and make adjustments. Involvement of clinicians and patients with clinical research ensures the right research questions are being asked."

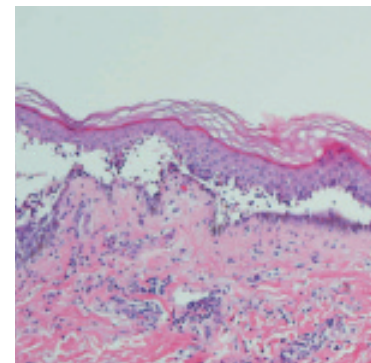
Professor Smith chaired a scientific panel of the National Institute for Health and Care Excellence (NICE) that produced the first guideline for health care professionals on the management of psoriasis in 2012 – another illustration of the influence of St John's.

Immuno-bullous disorder

There are many types of blistering skin disease, some of which are caused by the body's immune system attacking the proteins that bind the skin cells in the epidermis (the outer layer) and that also attach the epidermis to the dermis (inner layer). These proteins are in effect the glue that holds the skin together - when damaged the layers separate and a blister forms.

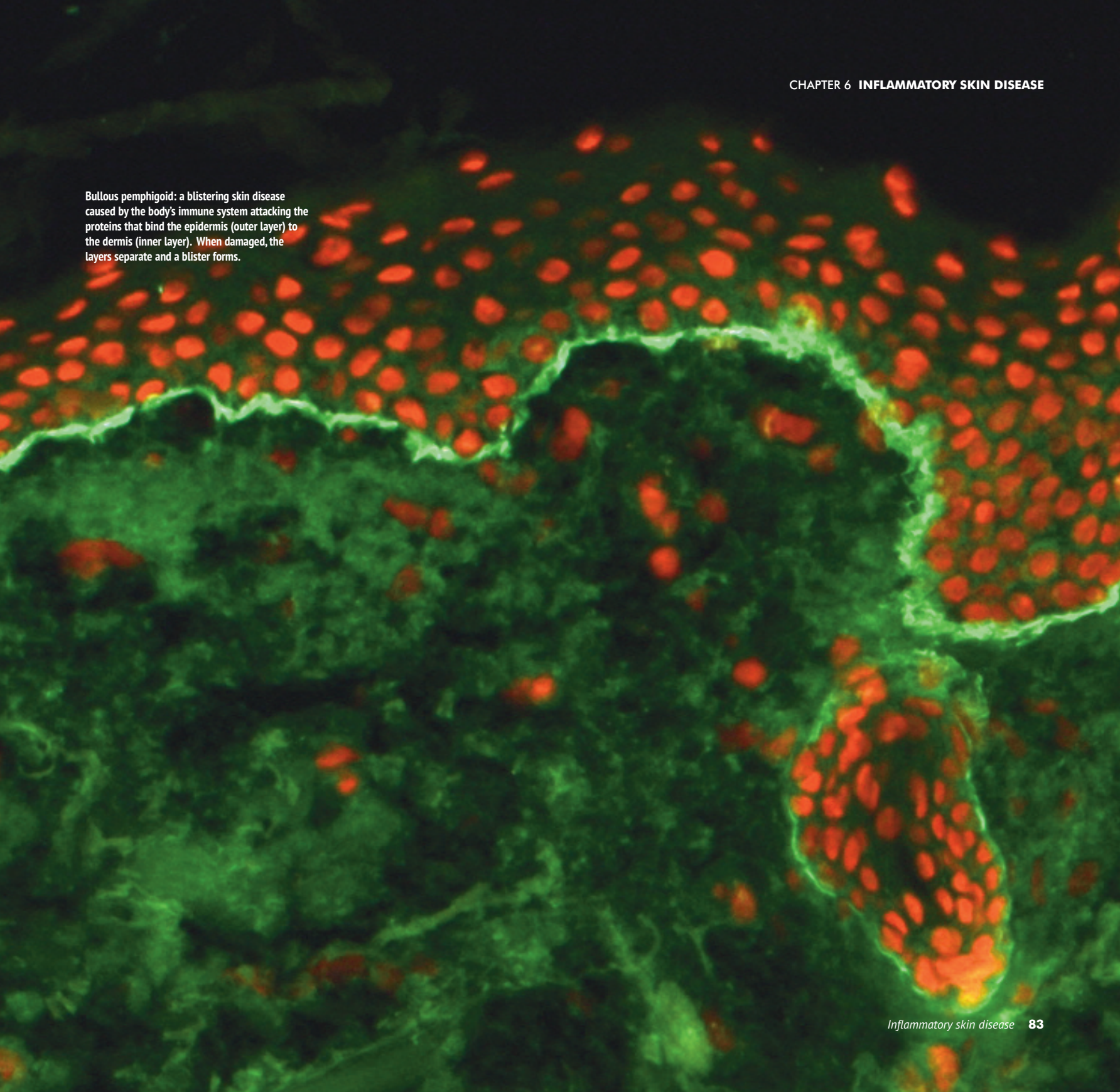


Bullous pemphigoid



Pemphigus vulgaris

Bullous pemphigoid: a blistering skin disease caused by the body's immune system attacking the proteins that bind the epidermis (outer layer) to the dermis (inner layer). When damaged, the layers separate and a blister forms.



Immunobullous diseases are uncommon but potentially serious disorders that result in blisters affecting all parts of the skin, the eyes, mouth and genitalia. In the past, before steroid treatment became available, patients would often die from overwhelming infection and fluid loss through the skin.



Martin Black

The commonest types of immunobullous disease are *pemphigus*, which causes raw sores in the mouth and blisters on the skin, and *pemphigoid* which is associated with deep blisters appearing at the junction between the epidermis and underlying dermis.

The conditions can be difficult to diagnose because many other diseases also cause blistering, and must be excluded.

St John's runs the UK's largest clinical service for the disorder, which is highly regarded in part because diagnosis, treatment and research are brought together in one department.

"The laboratory is an integral part of the service. We do not have to send biopsies away to be examined. Pathology is not separate so we can relate the clinical signs to the appearance of the specimen on the slide. That is significant for outcomes and for research," said consultant

Dr **Richard Groves**.

The department has led research into prognostic biomarkers for the disease, thanks to the creation of a biobank of blood samples from patients built up over an unparalleled 20 years thanks to the foresight of Professor **Martin Black** who set up the IMF lab.

Chronic Urticaria

Chronic urticaria is a condition where an itchy nettlerash comes and goes daily or almost daily for at least six weeks. It is often accompanied by deeper swellings called angio-oedema. Patients feel unwell when it is severe and find it difficult to sleep because of the irritation.

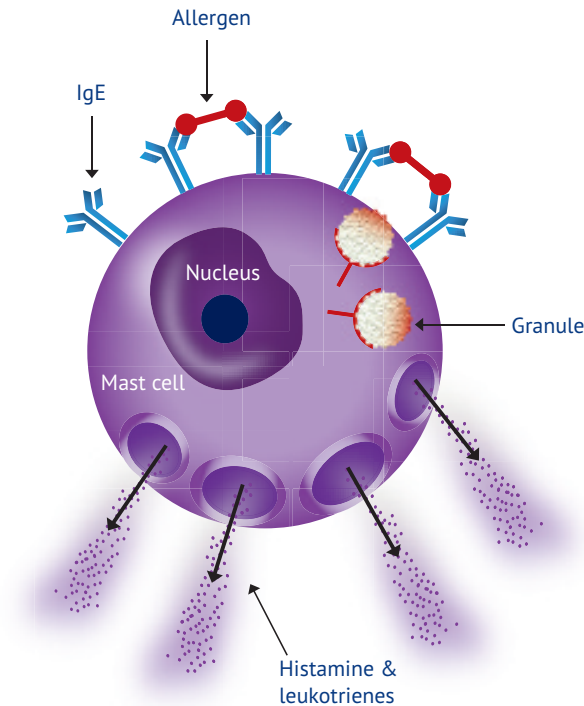
It is distinguished from *acute urticaria* which typically develops suddenly and unexpectedly. It may follow a viral infection but the cause of many cases remains unknown. It is often believed that allergy is responsible but it is unusual to find a specific food, drug or sting trigger. The illness may last up to 6 weeks but usually resolves over a few days.

Acute urticaria is common – about one in six people will have at least one bout during their life and it can strike at any age. *Chronic urticaria* is less common affecting one in 1000 people and in some cases can last for years. It may be very disabling for some patients and result in problems with employment, education and self-esteem.

Urticaria is caused by the release of histamine and other inflammatory substances from mast cells in the skin in response to a trigger. Often the trigger is unidentified - until 25 years ago it was known as *chronic idiopathic urticaria* – of "unknown cause". Today the term *chronic spontaneous urticaria* is preferred because the cause can be found in some patients.



Chronic urticaria affects one in 1,000 people causing an itchy nettlerash often accompanied by deeper swellings



The release of histamine causes fluid to leak from the tiny blood vessels under the skin forming itchy red weals.



Malcolm Greaves



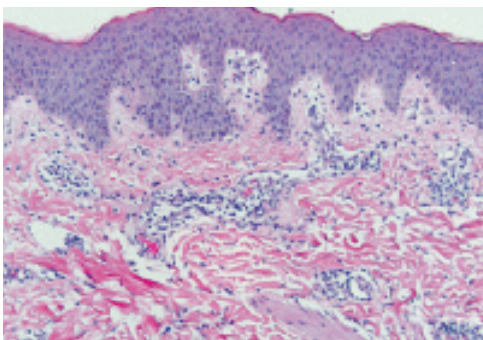
Clive Grattan

The release of histamine causes fluid to leak from the tiny blood vessels under the skin which collects to form itchy red weals. In half of cases, anti-histamines provide at least partial relief.

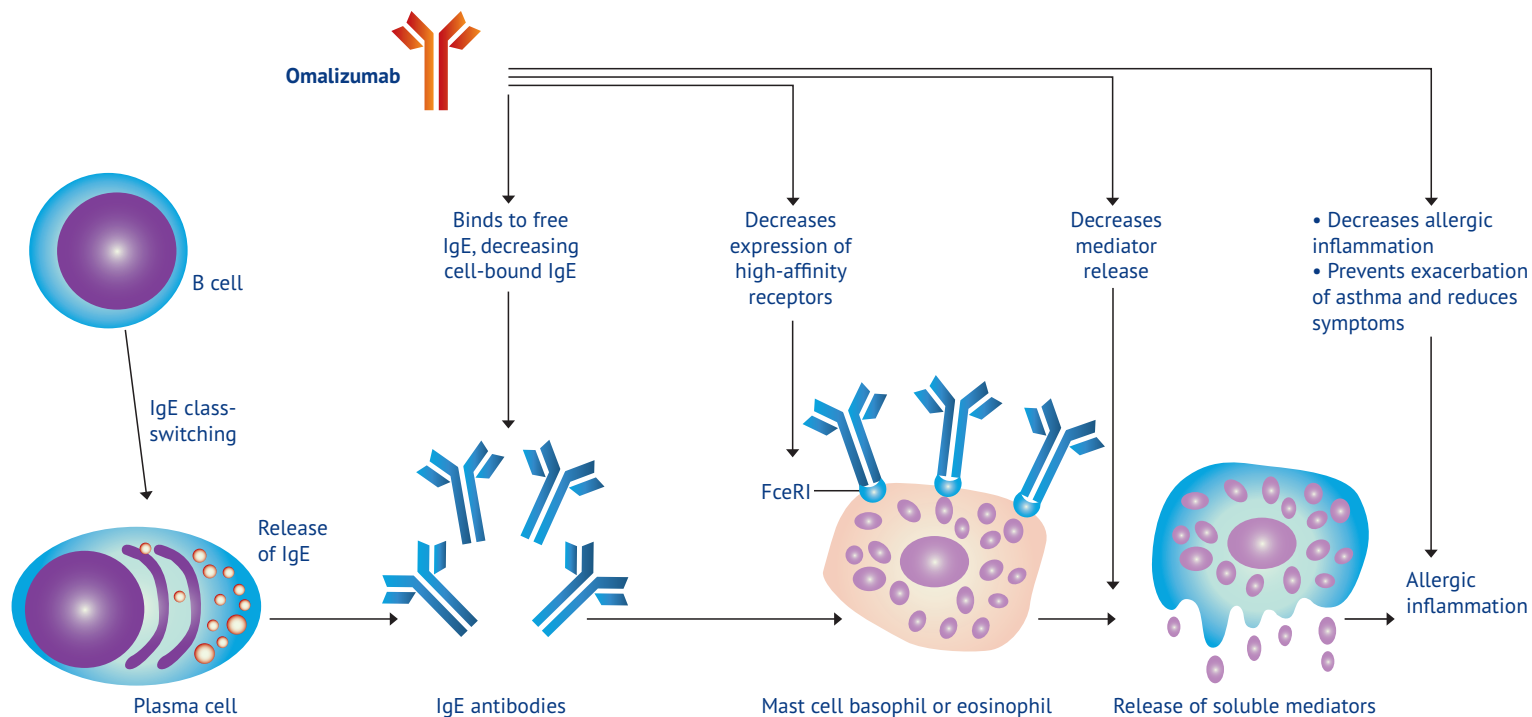
The worst affected patients may develop *angio-oedema* – swelling of the tissues. If the swelling affects the throat and breathing becomes difficult, emergency treatment is required with an injection of adrenaline.

In the 1990s, Professor **Malcolm Greaves** and **Clive Grattan** of St John's uncovered the mechanism that underlies around 30 per cent of patients with *chronic spontaneous urticaria*. They isolated and described the antibodies circulating in the blood that triggered IgE and its receptors on the mast cells leading to the release of histamine.

The discovery marked a paradigm shift in understanding the disease and led to the realisation that up to 30 per cent of patients with *chronic spontaneous urticaria* in fact have *autoimmune chronic urticaria*. The diagnosis was important because it carried implications for the appropriate treatment.



In the 1990s the mechanism that underlies 30 per cent of cases of chronic spontaneous urticaria was uncovered at St John's



Omalizumab: the first biologic drug to be licensed in the UK for chronic urticaria can be life changing for patients with severe disease

For people with *chronic urticaria* who do not respond to anti-histamines, the treatment options have been few. More severe cases are treated with immunosuppressants such as *ciclosporin* or *methotrexate*. Some patients have needed steroids to control their condition.

Now a monoclonal antibody, *omalizumab*, which has been used for a decade to treat severe asthma, is the first biologic drug to be licensed in the UK and Europe for the treatment of *chronic urticaria* (March 2014). It probably works, at least in part, by

preventing the autoantibodies, identified by Prof Greaves and Grattan, from binding to mast cells

Professor **Clive Grattan** said: "This can be a life changing drug for patients with severe, intractable disease."

Some patients at St John's are already having it. But like the other biologics, *omalizumab* is expensive.

Women's Dermatology Service

Some skin diseases, such as *lichen sclerosus*, specifically target the genital region. Others can affect the genitalia as well as other parts of the body, but because the vulva is a sensitive body site, with thinner and more vulnerable skin, it requires different treatment. As these women have specific needs, both physical and psychological, a separate service was developed at St Johns for them in the early 1990s. [An equivalent service for men is offered at the Chelsea and Westminster Hospital, London.]



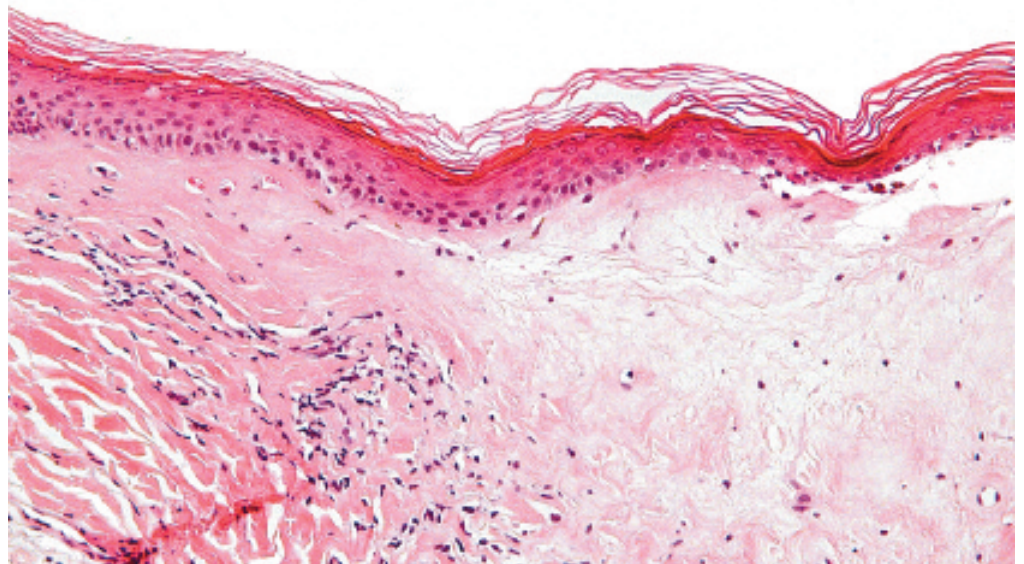
A separate service for women was established in the 1990s

It was the brainchild of **Marjorie Ridley**, consultant dermatologist, who established the first clinic for the diagnosis and treatment of genital dermatoses at the Elizabeth Garrett Anderson hospital in the 1970s and published a textbook 'The Vulva.' (1975). After retiring in 1991, she became an honorary consultant at St John's and helped establish the vulval clinic.



Marjorie Ridley

Dr **Fiona Lewis** said: "In the past, some women underwent extensive and unnecessary surgery for genital dermatoses. Marjorie's contribution was to emphasise the importance of early dermatological diagnosis and promote a more rational approach to treatment. She was also important in helping educate dermatologists, gynaecologists and other specialists about vulval disorders."



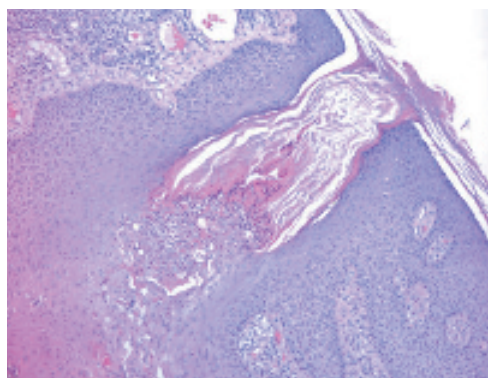
Lichen sclerosus targets the genital region and led in the past to unnecessary surgery

Hidradenitis suppurativa

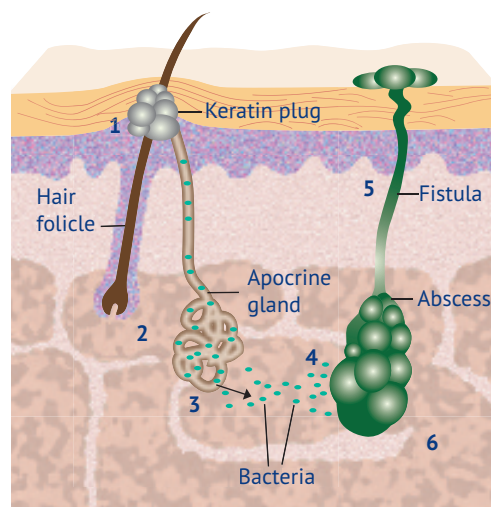
Hidradenitis suppurativa (HS) is a painful long term condition that causes abscesses and scarring on the skin. It is a disease of the skin carrying the apocrine (sweat) glands that principally affects the armpits and groin area but can extend to the buttocks, lower abdomen, chest and neck. It can be associated with severe acne, arthritis and inflammatory bowel disease.

An estimated 1 per cent of the population is affected though people are often too embarrassed to seek help.

The disease ranges from mild to severe. Dr Nemesha Desai, clinical lead of the HS service said: "Patients with severe disease have very difficult lives with recurrent painful boils and malodorous wounds that chronically discharge pus. They may be subjected to disfiguring surgery to remove the abnormal skin and replace it with grafts from other areas and require treatment with long term antibiotics and immunosuppressive therapy. There is a huge unmet need."



Hidradenitis suppurativa: causes abscesses



- (1) Keratin plug blocks hair follicle
- (2) Bacteria multiply in apocrine gland
- (3) Apocrine gland bursts releasing bacteria
- (4) Secondary bacterial infection leads to abscess formation
- (5) Abscess drains creating fistulous tract
- (6) Healing leads to scarring and fibrosis of skin

St John's has taken the pioneering step of establishing the first tertiary referral service for *hidradenitis suppurativa* in the UK. It is a multidisciplinary service set up in 2010 by Nemesha Desai, consultant dermatologist. The team includes specialists from other services such as plastic surgery, gastroenterology and colorectal surgeons, who are involved in the management of HS and related conditions such as inflammatory bowel disease. The HS Service has an active research interest, working closely with the Skin Therapy Research Unit at Kings College London investigating the genetic basis of the condition.



Hidradenitis suppurativa is a disease of the skin carrying the sweat glands and principally affects the armpits (above and below) and the groin



CASE STUDY - JOHN WEST

As a teenager growing up with psoriasis in the 1960s, John West suffered twice – once from the condition and secondly from the reaction people had to it. Aged 16, following an operation, the disease flared and became very acute.



John West: "To have a drug that cleared my psoriasis has been absolutely wonderful."

"It was all over my body. It affected me very badly. I couldn't go swimming or play football – it was changing with other people, that was the embarrassing part."

Treatments at that time consisted of creams and lotions. Coal tar lotion was an important stand-by but it was messy, stained clothes (and hospital floors) and made patients "smell like a motorway".

Nothing was effective. There was no choice but to learn to live with it. "In winter you knew your skin would become red, sore, cracked and bleeding. You knew it was coming – it was unpleasant to contemplate."

That was how things stood for most of John's adult life. He got married, had children and pursued

a career in business.

In the 1990s he was given a trial of *ciclosporin*, the immunosuppressant prescribed for transplant patients to prevent rejection of a new organ.

"*Ciclosporin* was 70 per cent effective, which for someone in my condition was fantastic. But it affected my kidneys and liver and my consultant had to take me off it – much to my annoyance."

Then in 2006, he was asked if he wanted to participate in a trial of a new drug, a monoclonal antibody called *ustekinumab*, which helps regulate over-active immune systems.

"Within a few weeks my *psoriasis* started getting better. You could almost watch it improve by the hour. And that is the way it has remained

for the past seven years. All that is left are a few patches on my elbows and knees."

Today, aged 66, he runs an exhibition company, lives in Maidstone, Kent and comes up to St John's every three months for an injection of the drug.

"I have not looked back since. My grandchildren – the eldest is 9 – have never known their grandad with funny skin. I have had absolutely no side effects. That is what is remarkable. It has allowed me to go swimming and I have joined a gym."

"To have a drug that cleared my *psoriasis* has been absolutely wonderful. It has completely changed my life."

