

# ed.derm.101: core concepts

almost everything you need to know to survive dermatology\*

*"Learning results from what the student does and thinks and only from what the student does and thinks. The teacher can advance learning only by influencing what the student does to learn." Herbert Simon, Nobel Laureate.*

\*the first of many **outright lies** exaggerations. You need to know [skincancer909](#) and much else, too. Or get lucky...

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[reestheskin.me](#): about me

[skincancer909](#): an online textbook of skin cancer for medical students

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## Preface

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The purpose of **edderm101: core concepts** is to cover the foundational concepts that underpin clinical practice in dermatology. As much as is possible I use disease as a vehicle to explain the fundamentals. This is skin biology for the medic — not the cell biologist.

It is tempting to say we are 'just reminding you of stuff you learned in year 1 and 2', but unfortunately this is a big lie isn't entirely accurate. It isn't so much that you have forgotten what you were taught, but rather that most of you were never taught cutaneous physiology or cell biology or, for that matter, much about the most ubiquitous carcinogen that humans are exposed to: ultraviolet radiation (UVR). But I do think you can use the material to teach yourself if you are so inclined.

There are a series of videos (numbered 01 to 09) that accompany **edderm101: core concepts**. Most are heavily clinically illustrated and only one is over 15 minutes in length. I suggest you may want to watch the videos *before* reading the text. The videos do not match the chapter order of edderm101:core concepts.

Copies of the Core Concept videos are on my teaching page. There are also links to the figures used in the videos, as well as separate Q&A videos underneath each Core Concept video. If you just want to browse the core concept videos you can do so on [Vimeo](#) but the supporting material is only on my web page.

My main teaching page is [here](#). URL: <https://reestheskin.me/resource-1/>

For completion, below you will find direct links to each video on Vimeo, but it is easier to go via my teaching page, as the supporting material and other links are there too. If you are a year 1 student, the lectures are based around the first three videos only. The others can be ignored till later in the course.

- 1 Video 1. [An introduction to skin biology.](#)
- 2 Video 2. [Sunburn, DNA and skin cancer.](#)
- 3 Video 3. [The biology of human pigmentation.](#)
- 4 Video 4. [Urticaria, from nettle stings to autoimmunity.](#)
- 5 Video 5. [Itch, and the utility of scratch.](#)
- 6 Video 6. [The biology of the skin barrier: the eczema connection.](#)
- 7 Video 7. [Physics matters: UVR and the skin.](#)
- 8 Video 8. [Blisters, molecular glues and pemphigus.](#)
- 9 Video 9. [Skin immunology: KISS.](#)

Text in blue like [this](#) is a hypertext link to a web page.

A link to a video is shown as .

A link to an image is shown as .

At the end of each chapter there is a link to the contents page ([Link to contents page](#)) — there is no reverse link.

# Contents

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## **Chapter 1: Basic cell biology of the epidermis and dermis**

I cover the basic cellular anatomy of skin, including the epidermis and dermis, and the main cell types including keratinocytes, melanocytes and Langerhans cells. I explain keratinocyte differentiation, the formation of the cornified envelope, and the bricks and mortar model of the skin barrier. I explain the various types of melanin, and the importance of melanin in protecting against UVR. Some of the key molecules or structures I mention include: melanin, keratins filaggrin, tyrosinase, desmosomes, collagen, mast cells. All of these components are associated with particular skin diseases.

## **Chapter 2: Skin appendages**

Eccrine glands, sebaceous glands, hair follicles and nails are all skin appendages. They are largely composed of keratinocytes, and represent a variation of the normal architecture of interfollicular (between follicle) skin. Some of these appendages are essential for life, others are subject to personal taste and culture. You will learn that whilst your eyelashes do grow at the same rate as your scalp hair, there is a reason they do not grow to a metre in length.

## **Chapter 3: Itching for an explanation**

Itch is the main symptom of skin disease. I explain what we know about its physiology and pharmacology. We explore the relation between pain and itch, and explain the main evolutionary drive that led to the utility of itch, and sadly its highjacking by disease processes. Finally, I explain that whilst itch is invisible, the response to itch is not; and that scratch — and not just its cause — may be viewed as infectious.

## **Chapter 4: A primer of immunology**

Most skin disease in European populations is either a result of damage from ultraviolet radiation, infection, or an 'unnecessary' immunological reaction. The latter two causes are intimately connected. A simple schema of the main types of hypersensitivity reaction goes a long way in the clinic. This chapter is, as you expect from a dermatologist, rather superficial — but it should cure the itch, if not satisfy the immunological aficionados.

## **Chapter 5: Ultraviolet radiation and the skin**

Ultraviolet radiation (UVR) is probably the most ubiquitous carcinogen humans are exposed to. It is also the cause of the most common human cancer in European populations, as well as being a therapeutic modality for some of the most common skin diseases. Ironically, we even treat some UVR induced skin diseases with more UVR. This aspect of dermatology encompasses physics, biology and human behaviour.

## **Chapter 6: Epidemiology of skin disease**

This is a very brief overview of the epidemiology of skin disease. Skin diseases are the commonest reason to visit a doctor in the UK but most skin diseases have a low case-fatality. This picture is not the same in all parts of the world. But it is not just skin disease that varies by population: the organisation of dermatology and skin disease management also varies too, with the UK being an outlier in many ways.

## **Chapter 7: Revision questions**

As well as questions following each of the videos, here are some questions covering all of **ed.derm.101: core concepts**.

# Chapter 1: Basic cell biology

This is skin biology for the medic — not the cell biologist.

Core concepts video 01 [here](#)

## Anatomy and physiology: a quick glance

There are two anatomical compartments in skin:

1. **Epidermis**, which is between 50 and 100 micrometres thick, and
2. **Dermis**, which on average is around 1-1.25mm thick (or 1000-1250 micrometres).

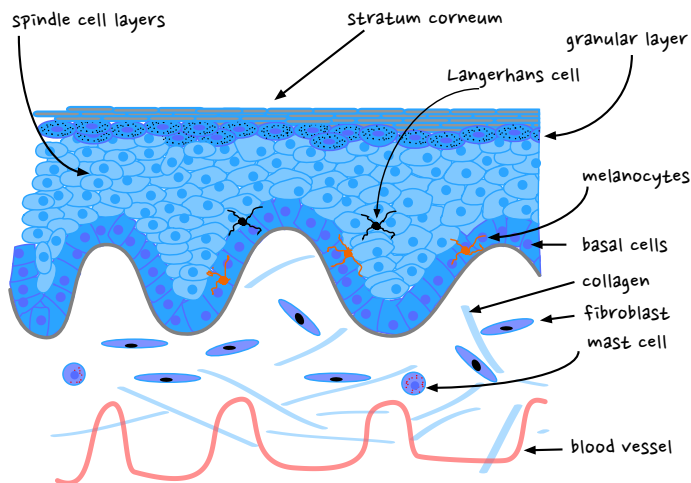


Figure 1: A schema of skin. Note, it is not to scale — in real life the dermis (white) is much thicker ( $\sim 1250\mu$ ) than the epidermis (blue) ( $50-100\mu$ ) — but it is shown this way for simplicity.

If you pinch the skin on your forearm, the fold, which will comprise a double layer of skin, will measure around 2.0-2.5mm ( $2000-2500\mu$ ). Most of this thickness is dermis. The relative thickness of the epidermis and dermis will vary by body site (feel your eyelids then pinch your own posterior).

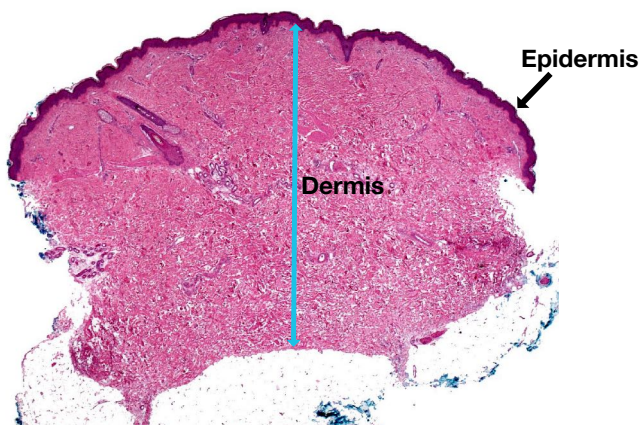


Figure 2. Note how the dermis accounts for most of the bulk of skin.

*Men have thicker skin than women, something women have known for a long time. Those differences are largely due to men having a thicker dermis.*

The epidermis is extremely cellular, whereas the bulk of the dermis is made up of acellular material, including collagen and elastin, and glycosaminoglycans. The major resident cell type of the epidermis is the **keratinocyte** and the major cell type of the dermis, the **fibroblast**.

Other cell types within the epidermis include:

- **Langerhans cells**, bone marrow derived macrophages
- **Melanocytes**, neural crest derived pigment producing cells. (■ Core Concepts video 3)
- **Merkel cells**, neuroendocrine cells that are associated with particular nerve endings in the epidermis.

In the dermis the range of cell types is larger:

**Fibroblasts:** mesenchymal derived cells, the chief function of which is the production and remodelling of the extracellular protein collagen.

**Mast cells:** a type of tissue basophil, which contain and may discharge (degranulate) a range of vasoactive chemicals including histamine. (■ see core concepts video 4)

**Inflammatory cells:** including lymphocytes, polymorphs, and a range of dermal macrophages and antigen presenting cells.

**Nerves:** either in free or highly structured endings in the dermis, or passing via the dermis into the epidermis.

**Vessels:** including capillaries, arterioles and venules. There are no vascular elements within the epidermis.

### **Appendageal structures**

The term **appendageal**, refers to hair follicles, sebaceous glands, eccrine glands and apocrine glands. All these glands are epidermal derived structures that arise during embryonic development towards the end of the first trimester.

*Appendageal structures cannot be formed after the early second trimester— so if they are destroyed, they are gone forever.*

The term **pilosebaceous unit** is used as a simple descriptive term to cover both the hair follicle and the sebaceous gland. In man, most sebaceous glands exit directly into a hair follicle.

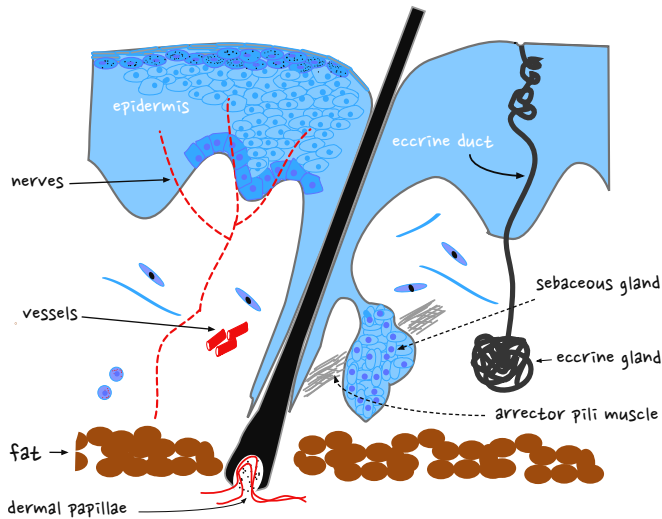


Figure 3: The main appendage structures are shown as well as some of the other components that make up skin

### Structure of the epidermis

The epidermis is a stratified squamous epithelium. It comprises the following layers (moving from deep to superficial):

- Basal layer (aka stratum basale)
- Spindle cell layer (aka prickly cell layer or stratum spinosum)
- Granular cell layer (aka stratum granulosum)
- Stratum corneum (horny cell layer)

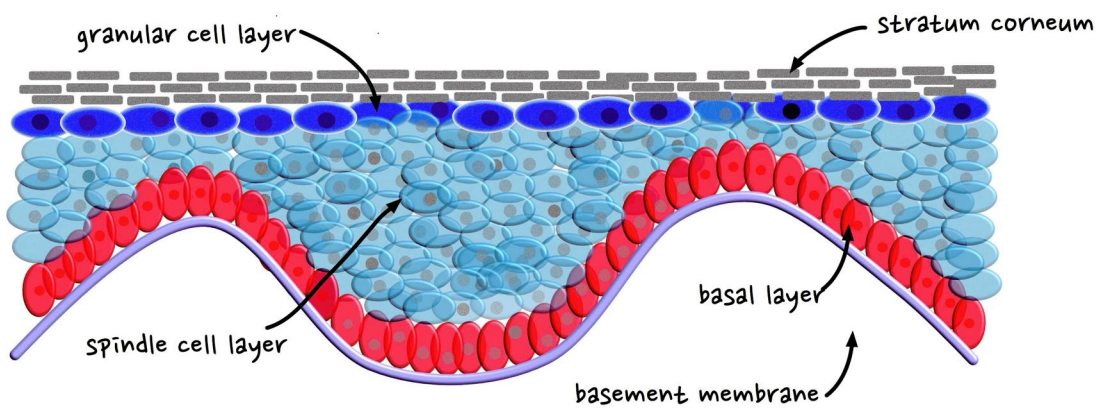


Figure 4: In the above figure the basal cells are marked in red for clarity (they are not red in reality — although mine do support the Welsh rugby team).

For a real histopathological image of the epidermis showing the various layers, including the stratum corneum, see [here](#) (but please **ignore** the term 'stratum lucidum')

**Basal cells** are cuboidal keratinocytes that sit on the **basement membrane** that separates the epidermis from the dermis. The basal cell layer is only one cell layer thick. **Stem cells** located in the basal layer undergo asymmetrical cell division, with one daughter cell being another stem cell, and the other a transient amplifying cell. Transient amplifying cells can undergo several rounds of division before they lose their ability to divide and differentiate into terminally differentiated keratinocytes.

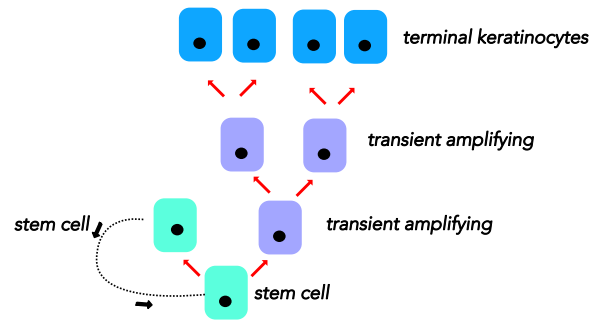


Figure 5: The asymmetrical division of stem cells in the basal layer

There are two pools of keratinocyte **stem cells** in skin (Figure 5). The first is discussed above (interfollicular stem cell pool), with the second situated in the hair follicle close to where the sebaceous glands join the follicle. These two pools are independent, but if the pool situated in the interfollicular skin (the one discussed above) is removed, stem cells from the hair follicle can repopulate the interfollicular stem cell pool. Can you imagine a reason why this makes sense?

The spindle cell layer is so named because of the spindle shape of the cells. It is also known as the **prickle cell layer**, because the tight desmosomal attachments between cells after fixation tend to resemble spines, or prickles, under the microscope (histopathological fixation often shrinks tissues, so the cells pull away from each other, except where the desmosomes 'glue' the cells together). This spindle cell layer forms the bulk of the thickness of the epidermis, and has multiple layers (>4).

The cell layer above the spindle cell layer is called the **granular layer**. The granules are made of **keratohyalin** (comprised of the proteins filaggrin and keratin). Also present in the granular layer, are **lipid lamellae**, intracellular membrane bodies which discharge epidermal lipids into the intercellular space in the high epidermis (lipid extrusion).

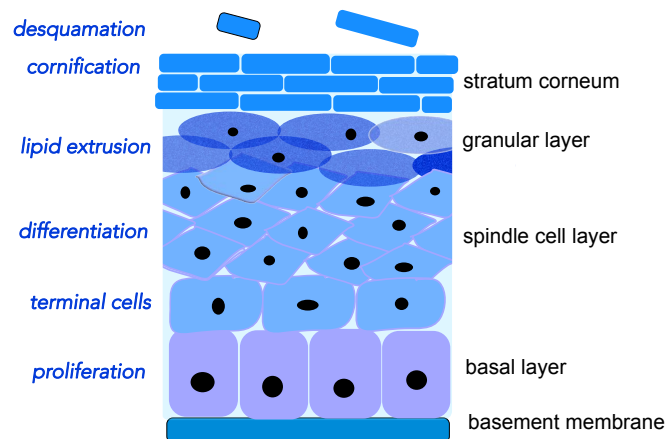


Figure 6. The layers of the epidermis with a summary of activity or processes on the left.

The **stratum corneum** (or horny layer) is made up of multiple layers of flattened keratinocytes called '**cornified envelopes**' (corneocytes, or squames). Cornified envelopes begin to form in the granular layer, with the plasma membrane being replaced by covalently cross-linked proteins including keratins and filaggrin (and other proteins). The enzyme **transglutaminase** is essential to this process. These cells are dead and have no nuclei (i.e. they are *anucleate*).

Individual squames (dead cells) of the stratum corneum eventually break off and fall into your surroundings. This **desquamation** relies on a **protease** mediated breaking down of the desmosomes. Such is the fate of our poor keratinocyte! If this final process is deranged, such that instead of individual cells falling off, large chunks of cells stick together, then this will be visible as '**scale**', as you will see in so many skin diseases such as eczema or psoriasis.

*Much household dust is made up of your dead squames (dead keratinocytes), and those who you choose to live with — including pets.*

### **Epidermal differentiation**

As keratinocytes move from the basal layer to their terminally differentiated dead state in the stratum corneum (horny) layer, they produce:

- a range of different proteins (including different **keratins** and **filaggrin**)
- a variety of lipids.

We have mentioned the names of these two key proteins already, keratin(s) and filaggrin, but there are many others, mutations of which may cause a variety of (rare) skin diseases.

*Of the myriad of molecules involved in keratinocyte differentiation we only expect you to know a little about keratins and filaggrin. But do not learn keratin numbers (K1, K10 etc).*

### **Keratins and filaggrin**

Keratins comprise a family of alpha-helical proteins, which are bound together in pairs, one acidic with one basic. There are over 60 different types of keratins, each coded for by a different gene. Do not bother getting into the details.

Keratins are aggregated together by filaggrin (so named, because it is the **filament aggregating protein**). The combination of keratins and filaggrin is visible under the light microscope as keratohyalin granules.

*Mutations of some keratins cause some skin diseases, including some types of [epidermolysis bullosa](#), a blistering disorder. Mutations of filaggrin are associated with two conditions; atopic eczema, and [ichthyosis vulgaris](#) (both discussed later in ed.derm.101).*

### **Physical integrity of the epidermis and frictional stress**

■ Core concept video 8 : Blisters, Molecular glues and pemphigus (~4 minutes)

Keratins are viewed (in part) as structural proteins that provide physical support for the cell. The framework they provide within the cell is however neither static nor fixed. For instance, when a cell divides, the keratin structures have to be dissolved and then reformed. They are therefore dynamic structures.

In the epidermis, keratins attach to the **desmosomes**, points of cell adhesion between keratinocytes. Protection against, and an appropriate response to frictional forces applied to the skin, is a key design constraint on skin. If you stretch your skin or, for example, rub your palms together, you exert considerable frictional force on your epidermis. We shall learn later that pathological processes that affect the desmosomes — or the keratins — may cause blistering in response to such frictional stress. We can therefore view blisters as one end result of a breakdown of the physical integrity of the skin in response to frictional force.

*Most blisters arise as a result of the breakdown of the normal processes by which cells are attached to each other, or to the basement membrane, or to other anchoring structures in the superficial dermis.*

Repeated **frictional forces** on the skin provoke thickening of the epidermis: there is an increase in proliferation in the basal layer (more mitoses are visible), and an increase in daughter cells moving up into the spindle cell layer. This process results in a thickening of the spindle layer (aka **acanthosis**), and thickening of the stratum corneum (aka **hyperkeratosis**). This is why your skin thickens if your shoes do not fit, or your hands develop callosities in response to manual work (a hazard for orthopaedic surgeons).

*The various molecules concerned with mediating attachment within the epidermis may be the target of various disease processes. Molecules may be functionally inactive due to mutation. For instance, some cases of [epidermolysis bullosa](#) are due to mutations in keratins, whereas others are due to mutations in desmosomal proteins. On the other hand, in some acquired blistering disorders such as 🧴 [pemphigus 03](#), auto-antibodies inactivate desmosomal proteins.*

### **Bricks and mortar model of the epidermal barrier**

■ Core concepts video 6 : Biology of the skin barrier (~10 minutes)

One key attribute of the skin is to act as a relatively impermeable barrier. One way to understand how this is achieved is through the '**bricks and mortar**' metaphor.

In this model, the bricks are made up of the individual dead keratinocytes in the stratum corneum. The cornified envelope of these anucleate cells is comprised of various components including cross-linked and aggregated keratins. The result is a hydrophobic protein rich box. In between these bricks is the mortar: the lipid.

This structure results in a very hydrophobic barrier that is relatively impermeable to water. A practical therapeutic point follows: delivery of drugs via the skin is extremely difficult unless the drugs are lipid soluble, and the molecules small.

*If your skin was not such a hydrophobic barrier, you would tend to dissolve in the bath and undergo an osmotic shock!*

### **Disturbance of the skin barrier**

An effective skin barrier is essential for cutaneous health. Disturbances of it may either lead to skin disease, or be a result of skin disease. For instance, in atopic eczema, or in 🧴 [contact irritant eczema](#), the barrier function is impaired. The result is that foreign material — chemicals such as detergents or soaps, or microorganisms or antigens — may penetrate

into the epidermis, causing damage, and provoking an inflammatory or immunologically mediated response.

In general, damage or assault to the skin, whether from friction, or toxic assaults from say sunburn or direct contact with alkali or acids leads to an increase in proliferation of the basal keratinocytes and thickening of the spindle layer (acanthosis) and the stratum corneum (hyperkeratosis).

### Other non-keratinocyte cellular components of the epidermis

Keratinocytes are the major cell type within the epidermis but there are other cell types present too. These include:

- Melanocytes
- Langerhans cells
- Merkel cells and other neural components
- Various other immunocompetent cells such as occasional lymphocytes that pass through the epidermis.

### Melanocytes and melanin

■ Core concepts video 3: Biology of pigmentation (~15 minutes)

Melanocytes are neural crest derived cells that migrate into skin at around 10-12 weeks of gestation. Melanocytes are highly dendritic and produce a complex polymer called **melanin**. There are 2 main classes of [melanin](#)

- **eumelanin**, which is brown or black
- **pheomelanin**, which is red or yellow (as in red hair).

The ratio between these two types, and the total amount of each, is the chief determinant of skin and hair colour. If you have predominantly pheomelanin in your hair, your hair is red. If you have mainly eumelanin, it is black. If you have only small amounts of either melanin, your hair is blonde.

Individuals with different skin colour across the world have the **same number of melanocytes** in their skin: the colour differences are due to differences in the **amount** and **type** of melanin produced by the same number of melanocytes.

Because melanin biosynthesis is fairly toxic to the cell, melanin is produced in lysosome like organelles called **melanosomes**. Melanosomes are passed down the dendrites of the melanocytes into the surrounding keratinocytes. The colour of skin largely reflects the amount and characteristics of these melanosomes that are passed into the surrounding keratinocytes. Because keratinocytes greatly outnumber melanocytes, skin colour reflects the melanin within the keratinocytes rather than the melanin within the melanocytes.

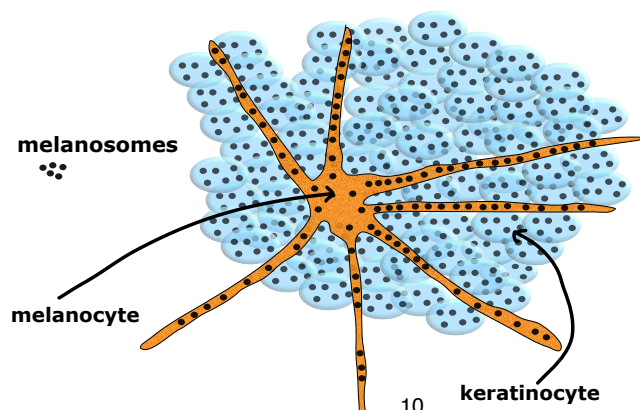


Figure 7: Melanin is synthesised in melanosomes in melanocytes — then these melanosomes are passed into the surrounding keratinocytes

The principle practical function of melanin is to protect interfollicular skin against ultraviolet radiation. Per unit weight, melanin is much more effective than any man made sunscreen.

*Albinism* refers to a collection of genetic disorders in which the amount of melanin produced by melanocytes is reduced. Note: the number of melanocytes is normal. One of the commonest types of albinism is due to recessive mutations in the gene for **tyrosinase**, a key enzyme in the biosynthesis of melanin (note: the albinism web link is in this case not due to a mutation in tyrosinase). The lack of melanin in albinism results in an abnormal sensitivity to ultraviolet radiation and therefore an increase in the rate of skin cancer. Students often confuse tyrosinase with **tyrosine kinase** — both have links to cancer, but refer to very different pathways.

#### Other pigments contributing to skin colour

Melanin is the main determinant of skin colour, along with haemoglobin. Other contributors to skin colour (apart from makeup and lipstick) are much less important, but include bilirubin (in jaundice), extraneous pigments from drugs or heavy metals, and ingested pigments from food (e.g. carotenoids).

#### Langerhans cells

[Langerhans cells](#) are professional antigen presenting cells. It is thought that antigens or haptens are gathered and metabolised by Langerhans cells before being presented to T-cells in the regional lymph node. On further exposure to the antigen in skin, sensitised T-cells mediate an immunological response.

Recent evidence suggests that cells other than Langerhans cells may also be important. For instance, there are other antigen presenting cells found in the dermis, and Langerhans cells may even play a role in down regulating certain aspects of the cutaneous immune system. From a clinician's perspective, this is of little clinical importance.

#### Merkel cells

These are neuroendocrine cells, derived from keratinocytes, that are found in the basal layer. They are highly innervated and are involved in mechanoreception.

*There is a rare type of severe skin cancer called [Merkel Cell Carcinoma](#), but this is **not** developmentally related to Merkel cells.*

#### Basement membrane

■ Core concepts video 8: Blisters, Molecular Glues, and Pemphigus (~4 minutes)

Just as for the epidermis, nature has had to give some thought as to how to resist frictional forces and attach the various elements of skin together: the epidermis has to be attached to the basement membrane which, in turn, has to be attached to the dermis.

The basement membrane is a complex acellular protein structure made of many modified proteins situated between the epidermis and the dermis. A large number of separate gene products contribute to its production. Just as one suprabasal keratinocyte is attached to another keratinocyte by **desmosomes**, basal keratinocytes are attached to the basement membrane by **hemidesmosomes**. In turn, the basement membrane is attached to the deeper collagen fibres in the dermis using smaller "adapter" collagen molecules.

Functional defects in the basement membrane may be due to mutations of key proteins, or due to autoimmune inactivation of proteins. An example of autoimmune inactivation, would be bullous [pemphigoid](#), the commonest autoimmune blistering disease of man, in which the hemidesmosomal attachments between basal keratinocytes and the basement membrane are targeted. (**Bullous** is just another word for blister).

You **do not need to know** the names of the various basement membrane components.

## The Dermis

The bulk of skin is made up of dermis, and the largest components of the dermis are extracellular collagens and glycosaminoglycans. The dominant cell type is the fibroblast.

Dermal thickness varies greatly with age, sex and site. Males, for instance, have thicker skin than females. Pinch the skin on your eyelid and on the lower back. Which has the thicker dermis? Why do you think there is such variation?

The dermis is ordered into two layers

1. The superficial **papillary** dermis and
2. The deeper **reticular** dermis.

These differences are apparent on microscopy, with the former having a finer fibre structure, whereas the latter is much coarser. You cannot observe or feel these differences clinically.

## Collagen

Collagen is synthesised by, secreted by, and remodelled by fibroblasts, a process which is poorly understood. Collagen is a triple alpha helix rich in glycine and proline, which is initially secreted as **procollagen** by fibroblasts. Modifications at the extracellular level involve cleavage of amino and carboxyl extensions and crosslinking of individual fibres. Individual molecules are then built up into complex microfibrils, which are then twisted into collagen fibres.

Vitamin C is essential for normal collagen production acting as an enzyme cofactor. Interference in this process contributes to the dermatological features of scurvy ( including 🦠 [corkscrew hairs](#), 🦠 [perifollicular haemorrhages](#) and gingivitis).

There are a large number of different collagens present in skin, details of which **you do not need to know**, nor do you need to know the details of collagen biosynthesis and assembly, except for the following:

- Mutations in collagens that attach the basement membrane to the dermis will result in blistering disorders (example: mutations of collagen VII cause dystrophic epidermolysis).
- Mutations in a range of collagens will produce diseases such as 🦠 [Ehlers-Danlos syndrome](#) (a group of syndromes that can involve the skin, joints, heart and other structures, in which the skin and joints are often hypermobile).
- Changes in collagen biosynthesis and remodelling are clinically important. Corticosteroids act so as to reduce the amount of collagen present in skin, and chronic ultraviolet exposure results in increased cross-linking of collagen and an apparent loss of collagen content that is clinically evident as a reduction in skin (dermal) thickness and a tendency to easy bruising (known as solar purpura).

Imagine the following. Gently pinch the back of the hand of a frail, elderly, patient and compare it with your own (I am assuming you are not frail and elderly, yet). Your own skin will be much thicker, and most of this difference will be accounted for by chronic ultraviolet

radiation exposure diminishing the apparent volume of the dermal component and, to a lesser degree, ultraviolet independent changes in collagen with age.

*Dermal collagen in the dermis provides padding ('like cotton wool') around the dermal vessels. Loss of this collagen therefore underpins the tendency to bruise you may see in old people with thin skin; and in Cushing's syndrome.*

### Elastic fibres

Elastic fibres account for a few per cent of the dry weight of skin. They appear to impart a resilience and stretchability to the skin. Microfibril proteins are found in association with elastin fibres. The most well known of these microfibril proteins is fibrillin, mutations of which underlie 🧬 [Marfan's syndrome](#). Ultraviolet radiation also changes elastic fibres with age, contributing to the differences in appearance of skin with age.

### Extracellular material in the dermis

Surrounding the fibroblasts and the various structural proteins are proteoglycans incorporating core proteins and glycosaminoglycans (mucopolysaccharides).

The main glycosaminoglycans in skin are hyaluronic acid, heparin sulphate, chondroitin sulphate and keratin sulphate. Many of these molecules seem to fascinate cell biologists, but not clinicians, so you do not need to know much about them. At one time they were viewed as fairly inert, but that view is now known to be mistaken, with many of them seemingly having important effects on the cellular components of the dermis. You can survive academically and clinically without knowing anything about them (I have.....).

### Other cellular elements that contribute to the dermis

A number of other structures and cell types are found within the dermis.

### Mast cells

🎬 Core concepts video 4: Urticaria: from nettle stings to autoimmunity (~10 minutes)

These are tissue basophil-like cells that migrate into skin. They contain a range of inflammatory mediators, most notably histamine, but also prostaglandins, leukotrienes and various other cytokines. Many of these inflammatory mediators are grouped together within granules within the mast cell.

Particular triggers lead to mast cell degranulation with release of the mediators including histamine into the surrounding extracellular area. One mechanism (there are many) of degranulation involves crosslinking of IgE molecules that are found on the surface of mast cells. This process is the basis of many type I hypersensitivity reactions (allergy) such as allergy to peanuts, and may lead to anaphylaxis.

The archetypal clinical lesion due to mast cell degranulation is the 🧴 [weal](#) (aka hive), which is the lesion you see on your skin after a nettle sting (or 🧴 [similar](#)), or after the injection of histamine superficially into skin or a range of other stimuli (such as firm stroking in patients with 🧴 [dermographism](#)).

If you inject **histamine** superficially into skin you see:

- an initial **erythema** close to the site of the injection
- a larger **flare** of erythema
- a collection of dermal oedema (the **weal**)

This is known as the **triple response**.

- The erythema close to the site of the injection is due to a direct effect of histamine on the vessel walls.
- The flare is a type of axon reflex in which stimulation by histamine of peripheral nerves is transmitted along sensory nerves and then travels 'backwards' along other sensory nerves causing release of mediators at the distal nerve endings resulting in vasodilation (antidromic stimulation). This 'reflex' is within skin and does not involve the spinal cord.
- the weal is due to a transient increase in permeability in small vessels causing local oedema until the fluid is reabsorbed

The relevance of this reaction induced by histamine is that it mimics to varying degrees what we see when mast cells degranulate in a disease called **urticaria**.

*Histamine is a key mediator of the changes we call the triple response. However, although we can block histamine pharmacologically, we cannot block all the effects of mast cell degranulation: this is because there are other non-histamine mediators that have similar clinical effects.*

#### **Other inflammatory cells in the dermis**

Under normal circumstances, only occasional circulating inflammatory cells are present in the dermis and, to a far lesser degree, the epidermis. This circulation of inflammatory cells, particularly T-cells through skin, is a key component of the cutaneous immune system.

#### **Vascular system**

Skin has a rich vascular network comprising superficial and deeper plexuses. You do not need to know the details, but should appreciate that the blood supply to the skin is greater than the blood supply to the brain. Even a neurologist's brain, or that of a cardiologist's ego.

[Link to contents page](#)

## Chapter 2: Skin appendages

Students often appear bewildered by various skin structures, such as hairs or nails and diseases affecting these structures. The basic components of skin have been described in earlier chapters, and it is variation in the arrangement and qualities of these individual components that diversity is produced: compare the skin of your eyelid, palm, nail, buttock, and wherever else you feel at home. Appendages are key to understanding this diversity and some are essential to human life: if they weren't present, you wouldn't be either.

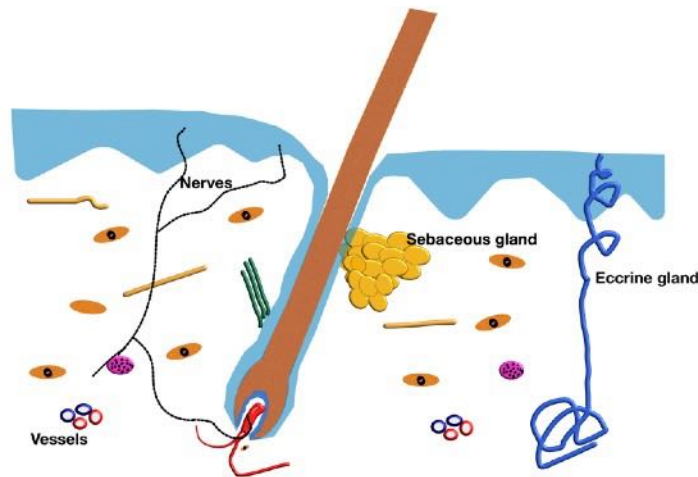


Figure 8: Schematic of some key skin appendages

### Skin appendages

Sebaceous, apocrine and eccrine glands, as well as hair follicles, are all keratinocyte derived structures that geographically are mainly located mainly in the dermis. They are made up of specialised types of keratinocytes, with the exception that specialised fibroblasts are found within the **dermal papilla** of the hair follicle (on the figure above, the 'red' vessel loops are shown in the position of the dermal papilla). These dermal papilla fibroblasts play a key role in hair growth and hair pigmentation, interacting with the hair follicle keratinocytes.

All these anatomical structures develop by the end of the first trimester. If destroyed later in life, they cannot be regenerated. One further thing they all have in common is that they are all androgen end-organs.

*Skin appendages are like nephrons: once they are destroyed, they are gone for good, as they cannot regenerate.*

### Eccrine sweat glands (usually abbreviated to sweat glands)

Over 3 million sweat glands cover most of the body surface. Per unit area they are most common on the palms and soles. There are no sweat glands on the lips or in the external ear canal. They are innervated by cholinergic post-ganglionic fibres of the sympathetic nervous system.

Eccrine sweating is essential for human viability, as humans are 'designed' to be able to run hot from exercise, with the proviso that they are able to lose heat more effectively by sweating than any other mammal. The 'need' for such efficient sweating probably drove the loss of the dense fur coat that many mammals possess (the fur impairs the efficiency of evaporation that is key to sweating).

Sweating serves 2 functions in man:

- **Evaporative cooling.** This is an essential thermoregulatory mechanism in man. Sweat evaporates 'pulling' the latent heat of evaporation energy from the skin.
- **Frictional grip.** On the palms, slight to moderate sweating may lead to increased frictional grip in the fight-or-flight response (usually maladaptive in medical students in clinical exams).

*Children born without functional sweat glands may die soon after birth from hyperthermia.*

Anatomically, sweat glands comprise a coiled secretory portion, a long duct that rises almost vertically through the dermis and then a tightly **coiled duct within the epidermis** (see Figure 8 above). The coiled structure in the epidermis is designed such that the duct doesn't become occluded (i.e. blocked) due to pressure. When sweat is secreted into the coil (in the lower secretory portion), it is an isotonic fluid and gradually changes to a hypotonic fluid by the selective reabsorption of salts as the duct moves through the skin ('salt saving').

In a resting state, evaporative loss via sweating is less than 1 litre a day. With increased temperature and physiological activity, sweat rates can peak at around 4 litres an hour. Obviously this rate cannot be sustained for long, however fast you drink beer in the midday sun.

Living in a hot climate, or prolonged physical activity, leads to changes in skin physiology such that eccrine sweating is increased, but the electrolyte loss from sweating is diminished ('**sweat gland training**').

Like the other appendages, eccrine sweat glands are an androgen end-organ, and eccrine sweating is greater in adult males than in adult females. ('horses sweat; gals perspire').

### **Apocrine (sweat) glands**

These glands are usually just referred to as apocrine glands. They are usually associated with hair follicles and are most common in the axillae, nipples and groin. Although freshly secreted oily apocrine gland material is odourless, bacterial decomposition produces the characteristic axillary (body) odour. The milk glands of the breast are closely related to apocrine glands. Apocrine glands are androgen sensitive, but details of their neural control are unclear. You do not need to know any more.

*Do not get hung up on understanding the mechanisms or typology of apocrine vs eccrine vs holocrine excretion—life is too short, and it is clinically irrelevant.*

### **Sebaceous glands**

Like apocrine and eccrine glands, the basic cell type of the sebaceous gland is the keratinocyte.

Sebaceous cells (sebocytes) are specialised however for the production of various lipids that make up sebum. Sebum is a mixture of triglycerides, fatty acids, squalene and cholesterol (you do not need to delve any deeper into lipid biochemistry).

Occasional sebocytes resting on the basement membrane divide, the daughter cells move up, differentiate and synthesise lipid. Eventually, they die and burst, releasing their contents into the hair follicle lumen.

The highest density of sebaceous glands is found on the scalp, face and the upper chest and back (the sites where acne is worst because.....)

*Contrary to what is often said, sebum appears to play no useful physiological role in humans postnatally. Indeed, children have negligible sebum production (except when they are in utero and maternal sex hormones drive sebaceous activity to contribute to the vernix caseosa). By contrast, in some other mammals sebum plays a key role in waterproofing fur.*

Sebaceous glands are androgen end-organs with androgens acting so as to increase sebum production: sebum rates are therefore higher in males than females. Progestogens increase sebum excretion too, and whereas oestrogens decrease sebum excretion. The quantitative effects of oestrogens or progestogens are smaller than that of androgens. These hormonal actions are clinically relevant (especially re: contraception), because without sebum, there is no acne, and there is a positive (causal) correlation between sebum excretion and acne.

*You should not be surprised by the fact that sebocytes produce lipid and that their 'goal' is to die and end up as a collection of lipid that passes into the hair follicle duct. Normal interfollicular epidermis produces abundant lipid (the mortar in the bricks and mortar model) and of course the fate of all differentiated keratinocytes is death!*

Once sebaceous glands have been exposed to high levels of androgens, even severe androgen blockade may only have a modest effect on sebum excretion rates. If, however, there is a congenital insensitivity to the effects of androgen, or the individual is eunuchoid, then sebum excretion rates will remain negligible. Prepubertal eunuchs tend to have perfect skin, at a cost however, that many would not willingly choose. Females with severe PCOS may have worse acne because of skin virilism. Body builders (of either sex) may also have worse acne if they take exogenous androgens.

■ Explanatory core disease video: [Acne in five minutes](#) (~6 minutes)

*"No woman, no cry: No sebum, no acne", to paraphrase the great Bob Marley (who, incidentally, died from a melanoma of his foot).*

## Hair follicles

A typical adult has about 5 million hairs, of which perhaps 100,000 are on the scalp. As for the other appendages, hairs are formed in utero, and once a follicle is destroyed, **it cannot be regenerated.**

Hairs are epidermal structures, comprised largely of a downgrowth of epidermal keratinocytes, although within the hair bulb there is a specialised dermal structure called the **dermal papilla** made up of specialised fibroblasts (mentioned previously).

The archetypical hair comprises a central medulla, a cortex, and an outer cuticle, with the cortex being the main component. The exact process of how hairs are formed from this 'invaginated epidermis' is a triumph of biology — but you can survive clinical dermatology without knowing about it.

*Do not bother to learn about the outer or inner root sheaths, Henle layer etc.*

## Types of hair

There are three main types of hair:

- **Lanugo hairs** are fine hairs seen only on premature infants. They don't have a medulla, are soft, and have no pigment.
- **Vellus** hair are normally short, (less than a few centimetres) and very thin. They have no medulla and lack significant pigment (i.e. they appear white). They are found all over the body postnatally, and comprise the majority of hairs (e.g. most facial hair in women).
- **Terminal hairs** are long, thick, pigmented hairs with a central medulla (e.g. scalp, eyelashes).

**Sexual hairs** can be considered a subset of specialised terminal hairs, which appear during puberty as a response to androgens acting on vellus hairs in areas such as the genitalia and the beard area. The pattern of sexual hair growth varies between the sexes (e.g. the extent of genital hairs towards the umbilicus; chest hair)

## The hair cycle

Hairs go through 3 growth phases that comprise the **hair cycle**.

**Anagen:** a growth phase which typically might last 3 years

**Catagen:** a 3 week transitory period in which each hair bulb undergoes apoptosis and regression and in which the lower part of the hair moves up close to the skin surface.

**Telogen:** A period lasting approximately 3 months in which the hair is relatively quiescent. Then the new hair pushes out the old one which is shed. (Some refer to this shedding as exogen.)

Almost 80% of hairs at any particular time, are in anagen with most of the remaining in telogen.

## Hair growth

Differences in hair length on different body sites reflect variation in the components of the hair cycle rather than just variation in the absolute rates of growth. For instance, many scalp hairs grow at the rate of around 1.25cm per month. On the scalp, hairs will be in anagen (and hence grow) for 3 years or more and therefore if uncut, grow long. Whereas on areas such as the chest, anagen only continues for 3 to 4 months, resulting in shorter hairs.

*Think yourself lucky your eyelashes have a (relatively) short duration of anagen.*

At birth, hair growth is **synchronous**, that is, all the follicles are at the same stage of development (as is common in many adult animals). However, postnatally hair cycling becomes asynchronous between hairs. This is why babies born with a head of hair may lose most of it after birth— before regaining it. (I live in hope — perhaps I am just developmentally slow).

Certain states, such as childbirth or severe illness, may force most hairs, at whatever stage of the hair cycle, through catagen into telogen. This leads to a clinical condition called **telogen effluvium** where most of your hair falls out at the same time (synchronous loss, rather than the usual asynchronous loss). The hair will usually reappear with time; asynchrony ('disorder' will reassert itself).

## Nails

Nails are skin! It is just that the familiar components are arranged slightly differently. The components of the nail include:

- **Nail plate:** This is the hard material that forms the bulk of the nail that is made up of dead keratinocytes (just like the stratum corneum). This is the bit you paint (or not).
- **Nail bed:** This is found under the nail plate and contributes slightly to the growth of the underside of the nail (known as ventral nail)
- **Nail matrix:** This is the main growth zone of the nail and extends beneath the proximal nail fold and as far as the end of the lunula (the crescentic pale part) of your nail. The matrix contributes most of the growth of the nail plate, but some of the ventral nail arises from the nail bed.

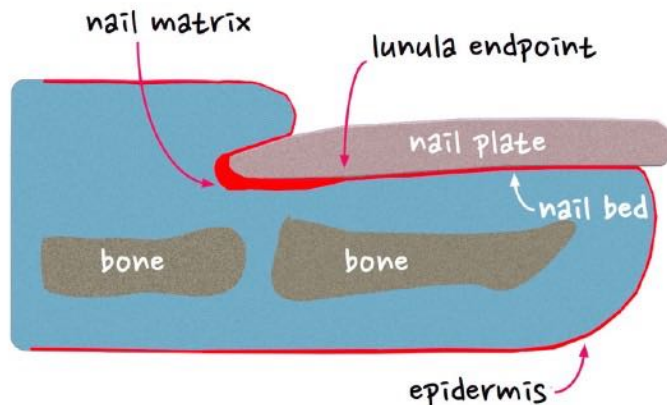


Figure 9. Schematic of the human nail. Note how the epidermis (shown in red) wraps round like a 'Z' to form the nail matrix — the main contributor to the nail plate. The lunula edge marks the visible end of the nail matrix (where it becomes the nail bed).

An average rate of growth for finger nails is around a tenth of a millimetre per day (3mm/month), but it varies between fingers, being fastest for the middle finger and less for the ring fingers (why do you think this is?). Fingernails grow faster than toenails. A fingernail may grow completely out over 3-6 months, whereas for toenails it might be 24 months (~1mm/month).

The bulk of the nail is produced by the dorsal nail matrix, which grows longitudinally out (i.e. along the longitudinal axis of the digit). This means that focal abnormalities within the nail matrix result in lines, because the abnormality is propagated in the direction of growth. If, for instance, there is a freckle, or a melanocytic nevus ('mole'), within the dorsal nail matrix, then this will result not in a round area of pigment in the nail, but a longitudinal bar of pigment as the dead differentiated pigmented keratinocytes cells move out along the nail. (An analogy would be the way a 'spot' on a balloon becomes a line when it is blown up).

## Chapter 3: Itching for an explanation

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### Cutaneous innervation and the pathophysiology of itch (pruritus)

■ Core concepts video 5: Itch and the utility of scratch (~8 minutes)

The basic biology of skin is shaped by the role of skin as a barrier: it keeps the outside out and the inside in. However this barrier is not absolute. We want to be able to sense the outside world in many ways: we want to know about things that might damage us (e.g. pressure, heat, sharp objects) or other living organisms (bacteria, arthropods) that might seek to invade us.

We may also want to use the expanse and proximity of skin to the outside world to allow us to move products from the body outwards; or vice versa. A clear example here would be the need to lose heat from the body via the skin's rich blood flow or, eccrine sweating; or alternatively to absorb the sun's heat (an all too rare event in Edinburgh).

Central to some of these roles is innervation of skin. Skin has a very rich sensory supply and a variety of different fibres and specific receptors for sensation are found in skin. Fortunately (for you), from a dermatology perspective you do not need to know anything about the details of the cutaneous nerve supply except for that described below.

#### Sensation

- Sensory nerves can be **myelinated** or **unmyelinated**. Conduction speeds of the former are faster.
- Some unmyelinated nerves are found extending into the epidermis. Fibres mediating itch fibres are found in the epidermis as well as the dermis).
- Loss of sensation may lead to the development of 🏠 [trophic ulceration](#) from repeated trauma. Examples would include foot ulcers in advanced diabetes, or pressure sores in anaesthetic areas.
- It is possible that cutaneous sensory nerves have some sort of trophic role — that is, if they are damaged, surrounding tissue does not grow properly or repair itself properly. Robust evidence for this role in man (as compared with other animals) is unclear.

The most important sensory modality in terms of clinical dermatology is that of itch (discussed later in this chapter).

#### Effector nerve supply

The only effector nerves in skin are sympathetic nerves —**there is no parasympathetic supply to skin** — of both cholinergic and adrenergic post-ganglionic varieties. Two important effector roles are: control of vascular tone, and eccrine sweating. Both of these are key elements of thermoregulatory control.

**Thermoregulation:** More blood flows through skin than the brain, and the ability to vary heat loss by changing blood flow patterns is critical. This is achieved by opening and closing of a variety of shunts in skin that determine how superficially blood flows. This function may be deranged in cases of widespread skin disease (so called 🏠 [erythroderma](#) ; because the inflammatory processes drive increased blood flow. The result is that patients 'overcool' themselves, resulting in central hypothermia, but because they are 'red all over', they look 'hot' (i.e. they are vasodilated).

The term **concealed hypothermia** is not much used, but it is worth understanding the concept. Normally, if someone is vasodilated and red (such as after heavy exercise), it reflects the body trying to lose heat, to avoid **central hyperthermia**. However, in the presence of extensive skin disease, the ability to vasoconstrict is lost, and the heat loss, if extensive, leads to central hypothermia (they look hot, but are in reality centrally cold). Hence the term 'concealed hypothermia' — they cannot stop losing heat.

Eccrine sweat glands are largely under the function of post ganglionic cholinergic fibres (but) of the sympathetic nervous system. Neurological damage to sweat glands in one body site leads to compensatory increases in sweating at other sites.

#### **Arrector pili smooth muscles**

These are under sympathetic control, and they cause your hairs to 'stand on end' (goosebumps). In mammals with a dense coat of fur, this is a useful means of trapping air under the fur. This trapping increases the insulation afforded by fur, and therefore helps conserve heat. This process plays no useful role in humans, however. It may be occasionally seen in clinical exams — on the candidate, not the patient.

Hyperhidrosis refers to pathologically increased sweating (e.g. on the palms or axillae). This can be more disabling than you might imagine. The (central) neural basis for hyperhidrosis is unclear.

## **The physiology and pathophysiology of itch**

■ Core concepts video 5: Itch and the utility of scratch (~8 minutes)

*I saw two propped together, as a pan  
Is placed against another one to warm,  
And both were thick from head to foot with scabs*

*As furiously as these two raked their nails  
Across themselves in madness at the itch  
Which has no other remedy but this.*

*Their fingernails were scratching off the scabs  
Just as a knife will strip the scales of bream  
And other kinds of fish with larger scales*

(from: [Dante's Inferno](#), Sean O'Brien, Picador)

Itch and pruritus mean the same thing. The most useful definition of itch is: **a sensation which provokes the desire to scratch**. The sensation of itch is confined to the skin and some mucosal membranes, i.e. the eye, the nasal mucosa.

In evolutionary terms itch provokes scratch, and scratch is a very effective way to remove parasites that stick to your skin's surface. We can therefore view any itch that is not associated with such a cause as maladaptive (yet another human 'design fault').

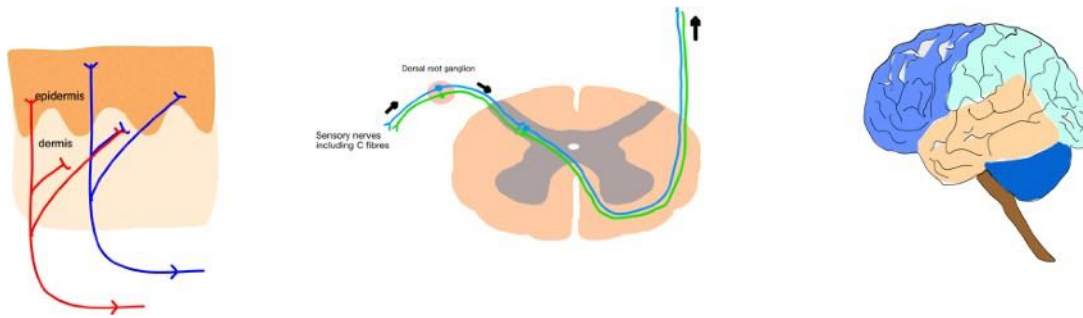


Figure 10: the itch conduction pathway. The different colour for receptors is explained below.

The likely correlation between scratching and infestation with parasites in evolutionary terms may explain the lack of empathy that is apparent for people who keep “scratching madly” (note the adverb): rather than sympathy, they are shunned or ridiculed — and perhaps excluded from the social group — so that the spread of the infection is limited.

### Itch pathways

Itch receptors are found in both the dermis and very superficially in the epidermis. Itch is principally conducted along unmyelinated C fibres that conduct at rates of  $\sim 5\text{cm/sec}$  (i.e. slowly). These fibres have large receptive fields (i.e. they may cover a large area of skin).

The fibres cross over in the spinothalamic tract in the spinal cord and synapse with ascending fibres and intermediate neurones that mediate the itch-scratch reflex. Many cortical areas ‘light up’ in neuroimaging studies when itch is elicited — some of the signal in these cortical areas changes when the area is then scratched. There is no single ‘itch centre’ in the brain.

Itch receptors respond to a variety of different signals (shown in blue and red in the figure above). The most well known is histamine. Histamine applied superficially to skin that has been abraded elicits a sensation of pure itch. This signalling can be blocked or diminished by pharmacological H1 blockade. By contrast, if histamine is injected deeper in skin, pain rather than itch is elicited: clearly location is important.

There are however **non-histamine mediated pathways** — most likely, due to a variety of mediators. In the itch video (see Core Contents video 5), I outline how proteases can activate Proteinase Activated Receptors (PAR) on nerves (shown in red in the figure above).

Some of the fibres conducting itch respond in addition to different non-itch stimuli (e.g. mechanical) and, as we shall see next, the sensation of itch may arise from other types of ‘non-itch’ fibres.

### Alloknesis

If you induce an area of skin to itch, using histamine, the itch within this focus is conducted along C fibres. However, the term alloknesis describes how skin around the central focus also may appear itchy when it is lightly touched. This latter sensation reflects a reinterpretation of light touch as itch, at the level of the spinal cord: it is conducted along subtypes of A fibres, not C fibres. (An analogous phenomenon (allodynia) occurs in the context of pain sensation).

### Itch versus pain

It used to be thought that itch was a subliminal type of pain, and that pain and itch shared the same neural wiring. In this theory, low level stimulation would lead to itch, whereas if the severity of the symptom was greater, pain would result. **As explained above, this view is now known to be wrong.**

However, there are still some interactions between the two sensations. For instance:

- When people scratch vigorously, itch often appears to be replaced by pain — and most patients prefer pain to itch even without having read the [Marquis de Sade's](#) treatise (I haven't...)
- Opioids diminish pain but may provoke itch. This action is not just due to opioids causing mast cell degranulation, but seems to reflect reciprocal inhibitory pathways at the level of the spinal cord.
- Both itch and pain travel as crossed modalities in the spinothalamic tract up to the thalamus and onward to a cortical representation.

### Chronic response to scratch

Prolonged scratching leads to at least two different responses.

- An exaggeration of the normal skin markings, and hyperplasia of the skin, across large areas, a change known as 🧴 [lichenification 01](#).
- By contrast you may see focal changes and scratching centred around individual nodules, so called 🧴 [nodular prurigo](#).

Both these changes may be seen in patients with atopic dermatitis, but why one occurs and not the other is unknown. Both are due to scratching in response to itch.

### How and why does scratch resolve itch?

Itch provokes the desire to scratch, and scratch removes any offending parasite. The 'reward' that 'drives' the reflex, is therefore freedom from itch. For instance, scabies infestation (👁️ [live scabies video](#)) can, and still does occasionally, lead to a secondary streptococcal systemic infection and death. Itch, provokes scratch that removes this parasite, and the reward is freedom from itch (and a reduction in the chance of secondary infection).

The exact basis for the inhibition of itch by scratch is unclear. Two non-exclusive mechanisms have been suggested.

- Itch fibres are remarkably superficial in the skin (some within 50µ of the surface) and they may be damaged by scratch such that they no longer function. In keeping with this hypothesis, as the damage heals, the itch becomes apparent again presumably as these fibres start working.
- Pain from scratch may inhibit itch via inhibitory mechanisms at the level of the spinal cord ("gate theory"), analogous to the way rubbing may help pain.

### Inhibition of itch

We have no specific blockers of itch (only) propagation along the neural pathway (with the possible exception of some classes of opioid receptor subtype blockers). This means that the therapeutic approach is usually limited to blocking the causes of the itch. An example of 'blocking the cause' would be in the treatment of atopic dermatitis, a condition for which we are ignorant of the exact itch mediator(s).

One confusing aspect of the use of antihistamines in dermatology is that most skin diseases are not mediated by histamine, but sedative antihistamines are employed therapeutically. This naturally causes students confusion. The explanation is as follows.

Some antihistamines are **sedatives** due to central CNS effects. Sedation, from whatever cause, results in less scratching. The therapeutic effect is not due to peripheral histamine blockade, but sedation ('you are not conscious enough to scratch'). Similar therapeutic effects are seen with other sedatives such as benzodiazepines or some neuroleptics. In practice, sedative antihistamines are easy to obtain and fairly safe, so they are often the treatment of choice even when the itch is not mediated by histamine.

*I would have retired rich to Monaco long along with my collection of Porsche 911s if I received £1 for every student who said that antihistamines worked in atopic dermatitis because the itch of atopic dermatitis is mediated by histamine. I am still working to earn a crust riding a scooter round town.....*

### **Itch is contagious!**

The sensation of itch is influenced by a whole host of factors many of which are not understood. For example many normal people itch after a hot bath; wool causes atopic individuals to start itching, as does sweating in some people.

The mind also plays tricks: just watch students start scratching when diseases such as lice or scabies are discussed. Are you scratching now?

*Confusion about how antihistamines work in pruritus is widespread. Remember: histamine plays a role in only a minority of the causes of itch (mainly urticaria), and for most patients with itch, sedative antihistamines are being used as sedatives not as antihistamines. We use sedative antihistamines in eczema not because the itch is mediated by histamine, but because sedative antihistamines are convenient and safe sedatives. Non-sedative antihistamines do not work for most skin diseases (the biggest exception to this generalisation is the example of urticaria).*

[Link to contents page](#)

## Chapter 4: A primer of skin immunology

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■ Core concepts video 9: Skin immunology KISS! (~4 minutes)

### Some (very) basic immunology

With the exception of some genodermatoses (inherited skin conditions) it is difficult to think about any skin disease without taking at least some account of the immune system (I say this as somebody who doesn't always warm to immunology).

Even if we take skin cancer as an example, we cannot ignore the immune system. Think about the raised incidence of [Kaposi's sarcoma](#) in AIDS, and the greatly increased rates of skin cancer we see in organ transplant recipients who are immunosuppressed. Fortunately, some of the principles are fairly straight forward, and a few basics goes a long way. We do not expect you to know details of T-cell subsets for any disease, nor in depth knowledge of interleukins 1,2,3,4.....∞

The following classification (Gel and Coombs) is dated, and some immunologists are critical of it, but as a dermatologist it is a useful scaffold on which to hang your knowledge of skin disease.

### Type I hypersensitivity reactions (immediate type hypersensitivity)

This reaction is mediated by crosslinking of IgE molecules on mast cells by allergen (■ Core Contents video 04) This results in the degranulation of mast cells, and the clinical lesion is urticaria.

For reasons that are not entirely clear, some people degranulate their mast cells in response to pressure (dermographism). This is what it [looks like](#), although whether IgE is involved is not clear.

Note a key point:

*Degranulation of mast cells may be caused by IgE mechanisms, but it may also occur by non-IgE mechanisms, or in some cases by **non-immunological mechanisms**.*

Here are two examples where **IgE is known to be critical**:

- **Peanut allergy**, where the peanut antigen cross-links IgE bound to mast cells in the skin and mucosae. In skin, the clinical response is urticaria. The peanut antigen might provoke the response via systemic absorption, or via the mucosae or, in somebody who is extremely sensitive, directly from skin exposure. In some instances, anaphylaxis may occur.
- **Latex allergy**, where the protein antigen is in the rubber found in some surgical gloves. Direct contact with the latex allergen in the gloves causes IgE dependent mast cell degranulation. Clinically, there is intense itching and swelling of the hands. If it is the patient who is sensitive, then they will react wherever they are touched: think the mouth if the gloved operator is a dentist; or the abdomen, pelvis or genital tract if there is a surgical or gynaecological procedure being undertaken. Again, anaphylaxis may develop leading to a potentially fatal reaction (loss of airway, circulation etc).

*Note this is an **immediate reaction** (0-20 minutes — not hours).*

Imagine a patient who is known to be sensitive to penicillin, but is given the drug intravenously because the medical history was unreliable (as I once did). The antigen, penicillin in this case, binds to specific IgE on mast cells. The mast cells degranulate, and release a variety of vasoactive compounds, as well as various cytokines. The patient will

then develop urticaria, and possible angioedema, bronchospasm, and circulatory collapse. This reaction is so immediate that it may literally be as you are giving the penicillin injection. One moral: always take a good drug history, paying particular respect to the type of drug reaction. Not all side-effects are equal.

### Diagnosis


Assessment of type I hypersensitivity involves:

A detailed **clinical history** by an experienced clinician with expertise in this area. Interpretation of the subsequent investigations (below) depends on this.

1. Measuring serum specific IgE to particular antigens (what were once called RAST tests),
2. Application of the stimulus with a needle to the skin ([prick testing 01](#); [prick testing 02](#) ).  
A positive response, elicits what I have already described as the triple response: erythema, wealing and an axon reflex.


Serum antigen specific IgE is easier and safer, and is usually preferred initially. Prick testing may however be necessary. These two types of investigation may not always 'agree'.

Prick testing is potentially dangerous in somebody who is very sensitive. Why do you think? Would you undertake this test in the Lauriston Building?

*Remember that not all cases of urticaria are type 1 allergic reactions or even immunologically mediated. Mast cells degranulate for reasons other than IgE crosslinking, and in some cases of chronic immune urticaria, the crosslinking of the IgE antigen is by an autoreactive IgG molecule (autoimmune urticaria) — dealt with in  Core Contents video 4*


Although allergic mechanisms are one cause of urticaria, non-immunological causes are common too.

### Type II hypersensitivity

This refers to IgG antibody mediated cytotoxicity. Examples include the autoimmune blistering disorders such as pemphigoid and  [pemphigus](#) we have already mentioned, and some of the systemic vasculitides involving ANCA (antineutrophilic cytoplasmic antigen).

### Type III hypersensitivity

This is where immune complexes form and deposition of these complexes in the vessel may lead to a series of changes including complement activation, and activation of polymorphs and macrophages, and subsequent tissue damage to vessels and surrounding tissue.

The most common clinical example would be leucocytoclastic  [vasculitis](#) which can be a response to drugs, infections or a cutaneous manifestation of a systemic inflammatory disorder such as rheumatoid arthritis or SLE.

### Type IV hypersensitivity (delayed type hypersensitivity)

This is a T-cell mediated reaction, and clinically presents as [eczema](#) (dermatitis). A common example would be nickel allergy, or allergic contact dermatitis in response to a plaster

Up to 20% of the population are type IV sensitive to nickel. This means that prior exposure to the nickel antigen to skin has resulted in presentation of the antigen to T cells, and the development of immunological memory. Any future exposure — will provoke an eczema response where the skin comes into direct contact with the nickel.

This reaction peaks between 24 and 96 hours — hence it is also called a **delayed type hypersensitivity** reaction to contrast it with the (type I) immediate response I described above.

Clinically type 4 hypersensitivity is investigated by using [patch testing](#), in which skin is exposed under controlled conditions to a range of likely antigens. See a positive patch test response to 🧑🏻 [nickel here](#), and you may see reactions that are not so brisk at sites of exposure (🧑🏻 [studs of jeans](#), under rings or under watch straps).

(Strictly speaking nickel is a hapten, that is, it has to bind to proteins to be antigenic, rather than a true antigen, but clinically we can ignore this distinction).

*Make certain you are clear about the differences between type 1 and type 4 reactions in skin. The time course is different; and the morphology of the skin changes they induce is different. Students get them wrong frequently. Type 2 and type 3 reactions seldom confuse.*

*Do not confuse **prick testing** and patch testing. Prick testing (not a test for pricks...) is a test to determine whether there is a type I allergic reaction to an antigen (think **peanut allergy**). It is carried out less and less because of the perceived risks attached to it (the patient might theoretically have an anaphylactic reaction if they were very sensitive, although many believe this risk is without empirical support).*

*By contrast **patch testing** is a widely used investigation for determining whether a delayed type response is the cause of a patient's eczema. (Think **contact allergic eczema** caused by **nickel**).*

[Link to contents page](#)

## Chapter 5: UVR and the skin

I could rename this chapter 'Physics matters!' but I fear readership would drop like the function that describes radioactive decay. The video linked to below below covers much but not all of the content that is described below. I suggest you look at the video first, and then come back and pick up on some of the more isolated — but useful — facts.

■ Core concepts video 07: Physics matters (~20 minutes)

### Types of electromagnetic radiation

From a dermatological perspective we are principally concerned with:

- ultraviolet radiation
- visible light
- infrared radiation

Obviously, other types of electromagnetic radiation can be relevant (e.g. radiotherapy in the treatment of some skin cancers).

**Infrared** is only of note in the condition 🧴 [erythema ab igne](#), in which infrared damage to skin causes a characteristic pigmented rash in the pattern of the dermal vasculature. This rash is most commonly seen on the shins of older people who cannot afford to heat their homes adequately, and huddle close to a fire. In Scotland the epithet, is 'granny's tartan' (reflecting the lack of central heating in the homes of many older people).

It may also be seen secondary to heat from laptops — more common in hackers than grannies: and from hot water bottles applied to skin to relieve pain.

**Visible:** Visible light (and not just ultraviolet radiation) may provoke some photodermatoses. An example is shown in the video that accompanies this chapter (📺 Core Concepts video 07).

### Ultraviolet radiation (UVR)

Understanding the figure shown below is key. Look at the figure first, then read on. Note that the Y axis is logarithmic.

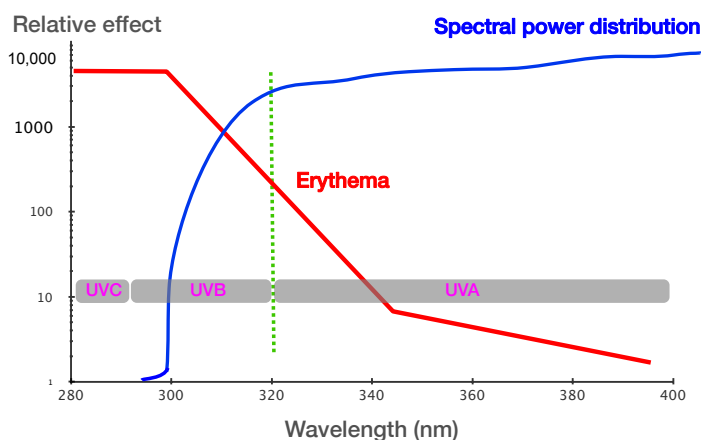


Figure 11. Graph of the erythema action spectrum and solar UVR output at ground level.

In the context of dermatology and clinical photobiology, UVR is divided into wavelength groupings

- UVA: 320-400nm
- UVB: 290-320nm
- UVC: below 290nm

UVC does not penetrate the atmosphere, and will not be discussed further. Anything over 400nm (to 700nm) is **visible light**.

The red line in Figure 11, shows the **erythema action spectrum**. This is a measure of the ability of radiation at any wavelength to induce erythema. Note the scale is logarithmic. Radiation at ~300nm is over three orders of magnitude more potent at inducing erythema than radiation at 390nm. Understanding the critical dependency of any biological effect on wavelength is central to clinical photobiology.

Although I have shown the **erythema action spectrum**, as it is the most important one from a clinical perspective, any endpoint will have its own action spectrum (e.g tanning).

The **green dotted line** merely highlights the boundary between UVB and UVA. Note that it is an arbitrary point on the erythema action spectrum. The classification into UVB and UVA is useful, but does not 'cleave nature at the joints'. Radiation at say 319 nm is virtually identical to radiation of 321nm. There is however a lot of difference in activity between UVA of 321nm and 399nm.

The blue line shows the **spectral output** of the sun at ground level. Note that most (~95%) radiation is in the UVA part of the spectrum. UVB only comprises 5% of the spectral output.

If we combine the action spectrum and the spectral output we can see that **most of the erythemal activity of sunshine (~80%) comes from the UVB component**. So, although most radiation is UVA, UVB is so much more effective at inducing erythema, that most burning is due to the UVB component.

When you burn from a day at the beach, you are burning as a result of mainly UVB exposure (> 80%).

### Human behaviour in the sun

It is not just the 'physics' that matters, but human behaviour too. And in particular there are some interactions between the two that are very important.

The first thing to say is that we are unable to sense UVR exposure in real time, in the way that we sense visible light. Because any effect on skin (such as sunburn) only appears after a delay, then it is easy to be fooled as to how much UVR we are exposed to. For instance visible light and heat, are not the same as UVR, and neither light nor temperature are precise guides to ambient UVR.

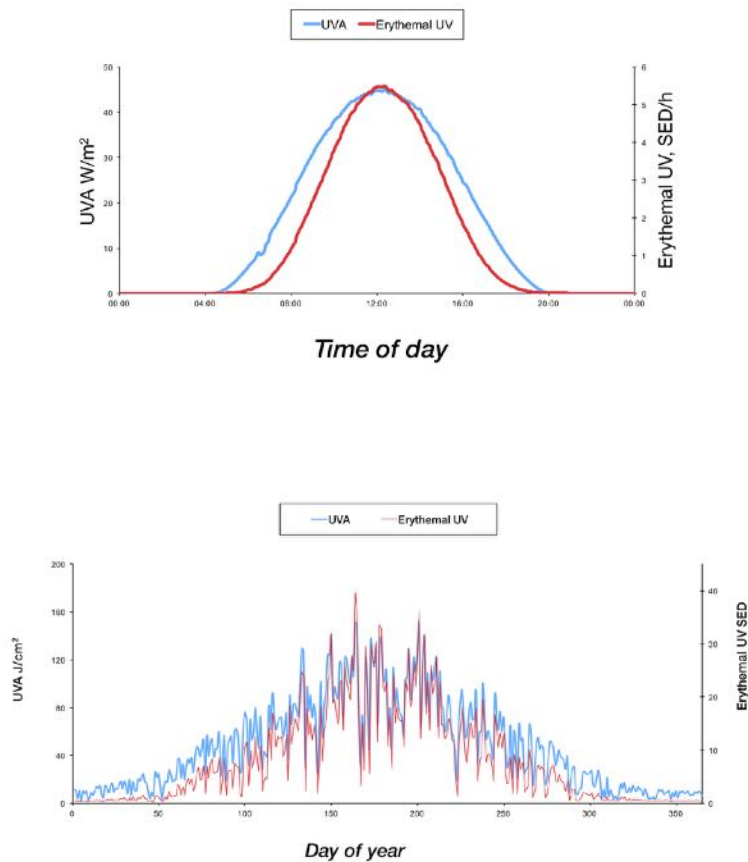


Figure 12. UVR at ground level

UVR peaks at midday, for both UVA and UVB. The pattern throughout the year is also as you might expect in the Northern hemisphere).

**The length of the day matters.** Close to the equator, UVR is compressed into a shorter day. Avoidance of the sun in the middle of the day proportionately reduces UVR exposure more than at higher latitudes.

**As the sun lowers in the sky,** radiation from a fixed solar angle is distributed over a larger area. However, the longer length of atmosphere UVR traverses also attenuates UV of all wavelengths but especially those <320 — the main erythrogenic (sunburn) wavelengths.

**Clouds attenuate UV due to scattering,** and also attenuate infrared radiation. However clouds attenuate infrared more than UV, therefore temperature is misleading as a proxy for UVR, in that you may underestimate the amount of UVR present. As a rough guide, and over a whole year and depending on latitude, clouds reduce UVR exposure by about 30% over what would be received if the skies were clear. Increases in temperature tend to make most of us wear fewer clothes, and spend more time *al fresco*

**UVR passes through water,** so snorkelers will burn on their backs, unless they take precautions. Water only reflects ~5% of incident UVR, more if the sea is choppy.

**Snow reflects up to 90% of UVR.** It is easy to burn skiing in the Alps in April or May. Reflection from most other surfaces is low.

**Annual exposure.**

Summer holidays contribute disproportionately, as shown below. If people take long holidays or retire to Spain, and behave as many do, annual UVR doses rise considerably.

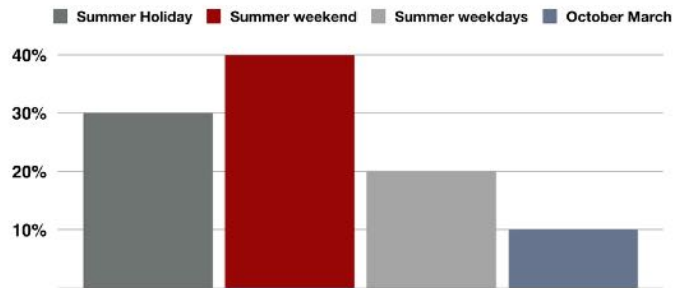


Figure 13. Exposure to UVR as a percentage of annual total exposure. I have not normalised for the length of each activity (the summer holiday accounts for 30% annual exposure, but might only occupy 4% of the year).

**Differences within a geographical area as well as between geographical areas matter.**

A caricature: the Australian teenager who spends all his time gaming on a PC, gets less exposure than the rugby mad kid from Llanelli (Wales!).

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## Chapter 6: Clinical Epidemiology

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*What follows is a very brief primer of skin disease epidemiology. There are lots of names that will be new to you, so do not sit down and try and learn it all straight off. But this view from '10,000 metres' might be useful to you once we delve a little deeper into the individual diseases themselves. I suggest you revisit this section again when you have learned a little more. I have put image links in to some of the diseases discussed, but all of these will reappear in later chapters.*

### **An overview of skin disease in the UK**

**Skin disease is the commonest reason to consult a GP in the UK.** Skin disease is common – very common. Each year in the UK there are about 15 million visits to a primary care physician with a dermatological problem.

### **One million patients are referred from primary to secondary care each year with skin problems.**

About half of these patients are referred because of skin cancer, or lesions that may be confused with skin cancer, and where there is clinical uncertainty of the correct diagnosis. Dermatology units in some hospitals see almost as many outpatients as all the subspecialties of internal medicine combined.

### **Skin cancer is the commonest cancer in the UK**

Up to 20% of the population are affected at some point in their life. Many of these will have multiple primary skin cancers (pre-malignant lesions are, as you can expect, even more common)

### **Inflammatory diseases of the skin are the commonest inflammatory diseases of all.**

Eczema affects ~ 15% of the population, psoriasis 2%, and moderate or severe acne ~20% of teenagers. Add in rosacea, seborrhoeic dermatitis and the like, and it almost seems that there are very few people left — may be they are the photoshopped models we see in glossy magazines.

### **Skin disease mortality is low.**

Despite the high morbidity from skin disease, death from skin disease is rare (i.e. the case-fatality is low). Each year in the UK about 3500 people die from skin disease. The main causes of death from skin disease are:

- skin cancers (particularly [melanoma](#) or [squamous cell carcinoma](#))
- blistering eruptions (e.g. pemphigoid, pemphigus)
- cutaneous adverse effects of drugs (e.g. [toxic epidermal necrolysis 01](#) ; 🧴 [toxic epidermal necrolysis 02](#)).

### **Are skin diseases usually infectious?**

The majority of patients with skin disease seen in secondary care (hospital) will not have an infectious disease. In primary care, infectious skin disease is more common, with examples including:

- viral warts
- impetigo (usually due to a staphylococcal infection) 🧴 [impetigo](#)
- 🧴 [herpes simplex](#); 🧴 [shingles](#) (herpes zoster)
- Candida ('thrush') (🧴 [candida 02](#)) or ringworm (🧴 [ringworm 01](#); [ringworm 02](#); 🧴 [ringworm 03](#)) (types of fungal infection, of skin, scalp or nails)

Non-infectious skin disease however still accounts for the majority of patients with skin disease in primary care in the UK.

Whereas most dermatological diseases in the UK are not infectious, in some populations within Africa (as an example), most cases of skin disease have either an infectious aetiology

or are due to infestations. Examples would be staphylococcal or streptococcal bacterial infections, and scabies (🦠 [scabies mite](#); 🎥 [video of scabies mite](#)). In some sub-Saharan populations the point prevalence of infectious skin disease or infestations is as high as 30% in children.

### **Are most skin diseases the result of systemic disease?**

It is a common misconception (beloved by physicians who have never practiced dermatology) that most skin diseases result from disorders, or abnormalities, in other organ systems. In reality, the vast majority of skin diseases are confined to the skin itself. It is for this reason that in most dermatological practice, examination or enquiry into the rest of the patient's health plays less of a role than in, say, the assessment of a frail older patient, or somebody who has suddenly collapsed.

There are of course some skin diseases that are caused by systemic abnormalities. [Vasculitis](#) 🦠 can affect internal organs and the skin; liver and renal disease both cause itch; and, if you are a real maestro, you might be able to diagnose a patient as being thyrotoxic merely because of 🦠 [onycholysis](#) (a term that describes lifting away of the distal nail plate, seen in a range of skin conditions *and* thyroid disease). Suffice to say, that the time honoured 'cutaneous features of internal disease' are more in evidence in exams than in the clinic — but beware this is, of course, a very good reason not to ignore them, as physicians tend to dominate most undergraduate exam boards. For the real world however, remember: haematuria in your patient with a purpuric 🦠 [vasculitic](#) rash likely reflects glomerulonephritis — they need a renal assessment, not just a skin exam.

One area that you must not neglect is a relevant drug history. Of course, it is much better to know before you undertake surgery that the patient is on clopidogrel and aspirin (they cause increased bleeding), but drugs are also a common cause of many rashes (🦠 [fixed drug eruption](#)), including some of the most serious ones such as 🦠 [toxic epidermal necrolysis 03](#).

### **Are most skin diseases the result of psychiatric disorders?**

This is a variant of the above. Many patients, and some doctors too, are fixated on the idea that skin disease is commonly secondary to some nervous disorder or 'stress'. With the exception of atopic eczema and pruritus (where anxiety or stress causes more scratching), there is remarkable little hard experimental evidence to support this claim. This doesn't mean that patients are necessarily wrong, rather it may be that the relationship is real, but hard to demonstrate experimentally. In the clinic it is best not to argue with patients who have firm views on this topic.

I personally think it more likely that in the majority of instances any disturbance of mind is secondary to the skin problem. Disturbance of sleep due to itch is a major problem in atopic eczema; and you do not need to be a budding supermodel to realise that a widespread scabby or pustular disease affects your self-esteem and your interactions with friends and partners. In severe acne, for example, we know that patients avoid eye contact, and tend to 'stare at the floor'. We also know that some older studies show increased suicide rates in those with severe acne.

*Most skin diseases are not secondary to systemic disease, nor to psychiatric disease.*

### **Infection and stigma**

As I mentioned above, most skin diseases in the developed world are not infectious. However, it is a commonplace observation that people stigmatise those with skin disease. If a person is clearly in pain from rheumatoid arthritis, sympathy from those around them is usually forthcoming. A person covered in scabs, who constantly fidgets as they scratch their skin is usually not so lucky. Often they are ridiculed or excluded — just think of the connotations of the word 'scab'. If the only one empty seat on a bus is next to the person who is scratching 'madly', people tend to stay standing. Why do we say 'madly' in this context?

*We do not understand why many skin diseases often appear to elicit a sense of disgust, rather than sympathy; or a tendency to shun the individual, rather than care for them. One obvious possibility is that because in our recent evolutionary past, many diseases were infectious or due to infestations, isolation of the diseased individual may have been a 'sensible' biological strategy.*

*Of course, even in my lifetime, there are counter examples: prior to effective vaccination against rubella, parents would seek to **deliberately expose** their young daughters to other children with rubella (to avoid the complications of primary rubella during a later pregnancy).*

### **Location, location, location**

It is not just infectious skin disease that is more or less common depending on geography. The worldwide incidence of skin cancer varies dramatically too, being most common in pale-skinned populations that live in areas with high ultraviolet radiation (UVR) exposure. Parts of Northern Australia have rates of non-melanoma skin cancers or precursor lesions 30-100 times higher than those seen in UK populations.

There are also extensive health care variations in how skin disease is managed. For instance, the distribution of dermatologists is highly variable:

- Germany, 1: 16,000
- USA, 1: 30,000
- UK, 1: 150,000
- Africa, 1: >1,000,000

These differences reflect at least 2 factors. First, overall health expenditure. Second, different patterns of health delivery. In much of Europe and the rest of the world, 'primary care' or office practice for patients with skin disease is provided by dermatologists, who have a specialist qualification in dermatology (such as is required to become a consultant in the UK).

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## Chapter 7: Revision questions

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1. Skin has two main components. One is thick, one thin; one cellular the other less so. Tell me more.
2. In addition to keratinocytes, name three other cell types found in the epidermis.
3. What is the main role of fibroblasts in the dermis?
4. Name three appendageal structures.
5. Name the four layers of the epidermis
6. What are the granules in the granular layer made up of?
7. If you inactivate desmosomes, what physical sign or type of lesion might you see?
8. Name two ways in which desmosomes may be inactivated.
9. Explain the components of the 'bricks and mortar' model. How do they work?
10. What are lipid lamellae? What function do they serve?
11. A range of different agents that damage skin (friction, irritants) produce two changes in the epidermis: what are they, and what names do we use for them?
12. Name an enzyme important in melanin biosynthesis. Mutations of it cause what disease?
13. Name and describe the two classes of melanin. What phenotypes are associated with them?
14. Is there more melanin in melanocytes or keratinocytes?
15. Do women have thicker skin than men?
16. Name two diseases associated with collagen mutations.
17. Why do those treated with steroids or those who are old, bruise easily?
18. Name a mediator released from mast cells. Describe 3 effects of release of this agent.
19. Why may the absence of or significant malfunction of sweat glands be fatal?
20. Describe the action of three hormones on sebum excretion.
21. Name three types of hair, and name three phases of the hair cycle
22. Why is your hair longer on the scalp than on your chest?
23. Which grow quicker, finger or toenails? Why do you think there is this difference?
24. Is there a parasympathetic nerve supply to skin?
25. Name three arguments for why pain and itch appear to have some relation.
26. How do sedative antihistamines work in atopic dermatitis? Are you sure?
27. Compare and contrast Type 1 and Type 4 hypersensitivity reactions (list 3 differences). Name some example diseases that we can ascribe to these reactions.

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