The skin on the move but cold adapted: Fundamental misconceptions in the laboratory and clinic

Terence J. Ryan

Department of Dermatology, University of Oxford, Oxford-Brookes University, Oxford, UK

ABSTRACT

The skin is constantly on the move and at a temperature below 37°C. The epidermis is a factory, and its blood supply and lymphatic drainage, as well as adipose tissue, are much dependent on movement and influenced by cooling. Neither histopathology (still pictures) nor *in vitro* studies at 37°C reflect the true picture. Recent publications neglect older literature exploring these issues.

Key words: Basics, misconceptions, physiology, skin

Access this article online

Website: www.idoj.in

DOI: 10.4103/2229-5178.73248

Quick Response Code:

Address for correspondence:
Prof. Terence J. Ryan, Professor Emeritus, Department of Dermatology, University of Oxford and Oxford Brookes University, Brook House, Brook Street, Great Bedwin Wilts SN8 3OZ, UK
E-mail: UserRy282@aol.com

INTRODUCTION

Describing the skin's behavior as a series of static pictures and dehydrated fixed sections ignores the motility of its cells and the almost non-stop movement to which it is subjected by pulse and muscular movements. There are benefits from drawing attention to the functions of an animated skin rather than to the static appearance of a piece of leather and the importance of maintaining the balanced physiology of a highly dynamic organ. Physiology is the study of living things which are not static but observers who see the skin as a still picture, an instant spot diagnosis or as a histopathologic section may misinterpret much of what they see. Ninety percent of Dermatology Texts may be a library of half truths.

The skin is not living at 37°C; so why do most *in vitro* studies choose that temperature? Many enzymes work best at their chosen optimal temperature and there are many cold adapted enzymes.

AN OUTER SLEEVE

Our outer sleeve has both epithelium and dermis, and subcutaneous tissue acting as an interface between the chemical and physical influences of the environment and as a container of all that is inside. The subtleties and kinetics of its barrier function cannot be observed in a single photograph or section. The multiple ways in which it is affected by other systems, for example, the neurologic or the endocrine system, or in which it acts as a sensory, endocrine or immunosurveillance organ, cannot be measured by a single observation but requires estimates of change. To give an example, for the endocrine system, this includes the atrophy of steroid overuse, the surface dryness and swelling of myxedema, the pigmentation of Addison's disease or the changes that diabetes inflicts over time.

The epidermis is constantly on the move. Such movement is macro and micro, physiological and pathological, passive and active. Macro movement occurs when we smile or grimace or when there is flexion and extension of joints, when we stand, lie or otherwise compress the skin. Very little of the skin does not get stretched at sometime during an hour. Even at a microscopic level, the arrector pili muscle is to be taken into account as a mechanical force on the bulge of the hair follicle. For most of the skin, shearing forces as well as compressive forces are frequent. To this may be added stroking and scratching, often as a repetitive and substantial distorting force compelling a response from stressed cells. Continuous pressure or shearing forces are resisted by thickening of the skin of the palm and sole or buttock and less. The skin just distal to or over the elbow and knee may

experience this rather more than the mid shin. But there are risks over bony points that may eventuate in pressure ulcers in the sick who fail to move. A scratched plaque of lichen simplex chronicus or psoriasis may have the greatest experience of external manipulation and will tend to move as a disk with the greatest distortion occurring at the edge, rather as an adhesive hydrocolloid dressing acting as a splint but directing forces to its edge. The difference between a scratched skin and a skin at rest is one of cellularity and fiber. The skin at rest shows few mitotic figures. At one time, mitotic figures were counted with greater enthusiasm than today, especially as the folic acid antagonists and their effect in psoriasis became a focus of the investigator. In repair mode, the basal cell reduplication has become of lesser interest than secretion of cytokines by the epidermis, which invites cells to flood the tissues from the blood stream. In repair mode, fibroblasts are stimulated to produce more collagen and elastin is broken up. Skin experiences little stress such as in the astronauts of the early days of space travel before they learned to exercise, or in a paraplegic who develops increased transparency of the skin similar to that of an osteoporotic. Truly dead and unmoved skin eventually as Shakespeare wrote “Thaws into a dew”.

Micro movement of the epidermis includes that of mitosis and migration. The cell doing neither is fixed by grip and stick to other cells or connective tissue. The migrating cell in the epidermis may be self-propelled or jostled out of position. I have argued with world authorities in the past that no cell habitually migrates away from all it needs and so the direction of growth of epidermis is logically inward and wrongly stated to be outward, and thus away from all the essentials which the dermis provides.[1-3] One implication is that for one cell to move outward by self-propulsion means that it alone has to release its grip and stick; but for a cell to be jostled out of position as other cells force their way to the basement lamina, requires several cells to collaborate in releasing their grip. This has implications for stem cell biology. There may be a difference between an environment of cells actively communicating and an environment in which a cell loses all contact as it loses grip and is jostled out of position.

THE EPIDERMIS AS A FACTORY

Over the last four decades, the epidermis has become recognized as not just a manufacturer of a keratin barrier, but a factory of, amongst many agents, eicosanoids, proteases and their activators or inhibitors, cytokines and growth factors. Even *in vitro*, the skin subjected to injury switches on the repair mode and releases cytokines. At rest, it produces almost none of these. But the epidermis is hardly ever at rest, so all these are often switched on. We, dermatologists, spend most of our time trying to switch them off, and in the olden days, immobilization was enforced by tying the itchy patient to the bed side so that the epidermis was rested. Today, the resting of the epidermis depends on surface applications and moisturization which plays an important role in quietening the skin and allowing it to be manipulated with reduced surface cracking and lesser inflammatory response to stretch.

One certainty is that the epidermis collaborates with other cells in immunosurveillance. The role of movement of the whole skin in assisting cells to migrate from the epidermis to lymph nodes is little considered by observers of the langerhans cell. The migration to and fro through the dermis is in huge numbers and to travel along the preferential pathways of least resistance requires for some cells long distance travel to find a lymphatic. It has been argued that these low resistance preferential pathways are elastin fibers (surrounded by water and lined by the spreading factor vitronectin and the other factors controlling the grip and stick of proteases), along which dendritic cells travel passively only as a result of movements of the tissues.[4] It is a phenomenon not seen by observing only static systems. Observers of lymphatic content note that red cells also are to be found in no small numbers therein and indeed the occasional red cell can be found in an inflamed epidermis. Such an anucleate cell can only migrate because of passive flow. It is clearly an efficient mechanism, so why not consider it as a mechanism to shift other cells whose active migration is too slow to account for the numbers flowing to the lymph nodes; a phenomenon which is not lost but is significantly less swift and directed when collagen replaces the low resistance and preferential elastin pathway. Lymphatic function is wholly dependent on adjacent tissue movement.

THE BLOOD SUPPLY OF THE SKIN

The capillary bed supplying the epidermis ranges in shape from atrophy to hypertrophy, from a flat, horizontally disposed system to the commonest pattern of the hairpin shape and to the cotton wool ball of the kind of vessel seen in chronic hyperplasia of psoriasis or wound beds. The way in which these differing patterns of end capillaries correlate with different shapes of the dermal papillae or epidermal rete pegs has a profound effect on how they and the tissue fluid leaking from them respond to movement of the skin from stretching or compression. The technique of measuring the relative water content of the upper dermis with ultrasound clearly reveals how a leaky vessel in a papilla when the skin is externally compressed, as Pinkus, a 20th century histopathologist well aware of skin dynamism, once noted, will “squirt” excess of its contents. A horizontally disposed vessel will not. Such squirting will raise tissue tension in the papilla and forcibly elongate the capillary. There are many questions posed by such a mechanical effect including how much transduction of biochemical signals is induced.[5] At the time of earlier studies of mechanical forces, we were not aware of cytokines such as vascular epithelial growth factor

(VEGF). When we became so, we noted that the tensions in the papillae induced by the presence of a vascular growth factor that also increased vascular permeability several thousand-fold adds to the need to take mechanical factors into account. The microcirculation field more often addresses this question than does the dermatologist. No serious investigator of the endothelial cell would ignore flow as a factor determining behavior and they would mostly assume that the endothelial cell is exquisitely sensitive to mechanical forces but not unique. The epidermal cell at the peak of the papilla will similarly be aware of stretch. As such forces have profound effects on proteases, the release of some cells from grip and stick and the increase of grip by other cells is likely to be one effect. For a long time, emphasis on pressure relief was the main feature of pressure ulcer management. More recently, the emphasis has switched to shearing forces. At the cellular level, the fluidity of the bipolar system of the cell membrane and the switching of some cell membrane attached enzymes from cytosol to the external surface can be determined by either mechanical or chemical distortions of the membrane. Forces to which all tissues respond are blood pressure and pulsation, both tending to stimulate the fibroblast to manufacture collagen and elastin. Like fibrin, these fibers are in balance, being constantly formed as well as lyzed and remodeled. Fibrin is a more temporary fiber and its formation by clotting mechanisms illustrates the dynamism of fiber control. A fibrin wall film lines the internal surface of the blood vessel, but is almost invisible as it is formed and lyzed so rapidly. Outside the vessel, fibrin is patchily disposed in the peri-capillary matrix and basement lamina of the epidermis. It is seen especially in response to venous hypertension and leakage. It is patchy in its distribution when observed in histologic sections, but it could be that fibrin and its lysis is in flux and continuously forming and being removed, a pattern unlikely to be recorded in a single histologic section.

Some pressure and shearing strain is of benefit to stimulate cells to grip and stick to avoid being dislodged. The major response of the fibroblast to stretch is the production of adhesive factors and fiber, largely controlled by a balance between activators and inhibitors of proteases such as plasminogen or metalloproteinases. After the discovery that the epidermis manufactured plasminogen activator inhibitor, our group wrote several articles about its role in tissue injury,[6,7] from which it was clear that any stimulus of the epidermis inhibited fibrinolysis in the upper dermis, and a later review[5] sought to show how it played a role in the transduction of biochemical signals generated by skin movement. It is a topic recently renewed without reference to past literature.[8,9] However, we still do not know what forces stimulate collagen versus elastin, or determine which type of collagen is manufactured with differing length and thickness of fiber. Recent publications take a static view.

The lymphatics in the upper dermis responds best to gentle circulatory movement but pressure tangentally encourages deeper fluid to shift outward, like a deep bruise, to the surface to be drained by the more effective lymphatic system found there.

THE LYMPHATIC SYSTEM

Lying less than 0.3 mm below the epidermis are the drains that almost completely rely on tissue movement to take away most of the excess fluid and the macromolecules of degraded tissues, cytokines and growth factors. These drains are highly sensitive to tissue movement and are designed to be so. As already mentioned, these drains also carry away to lymph nodes, much material of up to cell size that cannot be self-propelled, including red cells, melanin and foreign bodies. I have argued that impediments to such flow, such as immobilization or blockage of the drains, prevent information getting from the skin to the lymph nodes,[10] a feature of lymphedema named as a local AIDS by Peter Mortimer (personal communication). On the other hand, excess movement, as from the scratching of the atopic or flooding as in the patient with venous hypertension of the lower leg, results in heightened information traveling centrally, creating an altered environment in the lymph node and often increases their size. More “allergy” may be a consequence simply because the center is more aware of what is happening in the periphery. One may note that as soon as lymphatic overload from a failing venous system progresses to failure, contact dermatitis, which in early ulceration is very common from medicaments, becomes a rarity and is difficult to induce. The low T cell counts of AIDS can be raised by massage which releases sequestered cells from the periphery.

Surprisingly neglected by dermatology are the grotesque changes in the skin which may result from lymphedema. It is a mixture of overgrowth of the epidermis, the dermis or the subcutaneous tissue.[11] It is seen in millions of persons who have blocked lymphatics. Such persons are characteristically immobile due to the discomfort of heavy limbs. It is remedied by vitalizing the skin by movement. The effect of movement on skin by reducing quite rapidly such a gross morbidity is extraordinary and it is surprising that such a common stimulus to overgrowth of skin components is ignored by the dermatopathologist. As demonstrated by the Institute of Applied Dermatology, Kerala, gross seborrheic keratosis like changes and huge adipose tissue deposits are reversed by the movements of Yoga [Figure 1]. Quietening the skin’s frantic attempts to repair itself is done by adding to movement, washing and emollients, to reduce the epidermal inflammatory induction of dermal inflammation and reduce the stimulus of having cracks and entry points for activators of inflammation.[12] The lymphedema literature also delves into great detail about dermal elastin and its precursors with insights unread in dermatology literature.[13-17]

Figure 1: (a) Gross epithelial (seborrheic keratosis like pathology); (b) gross dermal pathology of which only about 5% is fluid. The figures show a response to a movement regimen (Institute of Applied Dermatology, Kasaragod, Kerala)

ADIPOSE TISSUE

While fat is recognized as insulating, body contour moulding, energy storing and having an endocrine function, it has not attracted attention as an essential component of a living skin, also sensitive to movement. Recent discussions in the dermatology literature have at last given it the credit it deserves.[18] But first it should be noted that it is a disperser of mechanical forces, and when immobilized, a rather pain sensitive one. We stand on, sit on and, on our palmer surface, grasp fat cells. It is a nuisance when trying to apply compressive forces using a compression bandage. Its piezo qualities make it tender whenever its pliability is impeded. Obesity, immobility and discomfort are common partners. Adipose tissue has a rich slow flowing capillary blood supply, but it is deprived of an effective lymphatic drainage system.[19] It undergoes hyperplasia wherever the lymphatic system fails to function effectively. Since one such function is to support the immune system, it has been recently emphasized that the fat cell is part of an effective immune system supplying locally essential fatty acids. Recent research has not only enhanced our knowledge of the hormones it produces but also has emphasized the wealth of cytokines to meet local and systemic needs. For many years it has been known that epithelium brought into proximity to adipose tissue develops characteristics such as the anagen hair, whisker or antler. Long observed for bruising as a result of movement of the skin, the essential products of the subcutaneous tissue can be propelled through the tissue planes and through the lymphatic system to the epidermis by massage.

COLD ADAPTATION

It is an astonishing fact that although the skin is mostly cooler than the body, this fact is ignored. It matters because of the viscosity increase of the tissues when the temperature is reduced. This modifies responses to movement. It is especially a factor in skin microcirculation of blood and of the effect on the neutrophil stiffness, as it circulates through superficial capillaries, in particular.[20] More important is the fact that many enzymes are cold adapted. One only has to "Google" *cold adapted enzymes* to see how important they are. While most of the reports are about the very cold, temperate is also studied.

The role of avoiding cooling during dressing changes in wound healing has been emphasized[21] because recovery of temperature of a cool skin is very slow and enzymes not cold adapted, like some of the metalloproteinases so important to wound healing, need a little warmth. To my knowledge, there is no laboratory that examines skin *in vitro* at a temperature below 37°C, a temperature it hardly ever achieves. Each degree of temperature increase raises the metabolism by 15%.

THE MACRO MOBILITY OF A COMMUNICATING ORGAN

Most textbooks introducing the functions of the skin discuss only its barrier, sensory and thermoregulatory roles. These are not as instantly apparent as its communicating function which includes the subtleties of rapidly changing facial expression and body posture. When this fails and there is no smile, it creates the worst disability which is unwelcome and this severely affects the social function of participation. In the control of display and privacy, the skin is subjected to constantly fluctuating opinion and the marketing of a cosmetic and fashion conscious social system. The sexual and erotic exchange of signals can be interrupted by isolation or the yashmac. For that matter, they are rarely revealed when stationary as in a passport photograph.

REFERENCES

1. Ryan TJ. The direction of growth of epithelium. Br J Dermatol 1966;78:403-15.
2. Ryan TJ. Direction of epithelial growth. Br J Dermatol 1970;83:701-2.
3. Ryan TJ. The direction of epithelial growth is inwards. Proc R Soc Med 1975;68:159-61.
4. Ryan TJ. Grip and stick and the lymphatics. Lymphology 1990;23:1-4.
5. Ryan TJ. Biochemical consequences of mechanical forces generated by distension and distortion. J Am Acad Dermatol 1989;21:115-30.
6. Turner RH, Kurban AK, Ryan TJ. Fibrinolytic activity in human skin following epidermal injury. J Invest Dermatol 1969;53:458-62.
7. Nishioka K, Ryan TJ. Inhibitors and proactivators of fibrinolysis in human epidermis. Br J Dermatol 1971;85:561-5.
8. Bhadal N, Wall IB, Porter SR, Broad S, Lindahl GE, Whawell S, *et al*. The effect of mechanical strain on protease production by keratinocytes. Br J Dermatol 2008;158:396-8.
9. Ogura Y, Matsunaga Y, Mishiyama T, Amano S. Plasmin induces degradation and dysfunction of laminin 332(laminin 5) and impaired assembly of basement membrane at the dermal-epidermal junction. Br J Dermatol 2008;159:49-60.
10. Ryan TJ, Mallon EC. Lymphatics and the processing of antigen. Clin Dermatol 1995;13:485-92.

11. Ryan TJ. Elephantiasis and chronic wound healing, 19th century and contemporary viewpoints that are relevant to hypotheses concerning lymphoedema, leprosy, erysipelas and psoriasis. Lymphology 2009;42:19-25.
12. Narahari SR, Ryan TJ, Mahadevan E, Bose KS, Prasanna KS. Integrated management of filarial lymphoedema for rural communities. Lymphology 2007;40:3-13.
13. Mortimer PS, Cherry GW, Jones RL, Barnhill RL, Ryan TJ. The importance of elastic fibres in skin lymphatics. Br J Dermatol 1983;108:561-6.
14. Ryan TJ. Structure and function of lymphatics. J Invest Dermatol 1989;93:18S-24S.
15. Ryan TJ, Jones RL, Mortimer PS, Singh G. Lymphatics in leprosy: Relationship to elastic fibres and observations following intra-lesional injections of colloidal carbon. Lepr Rev 2002;73:52-63.
16. Gerli R, Alessandrini C. Initial lymph vessels of the skin and elastic fibres form an integral morphofunctional structure. Ital J Anat Embryol 1995;100:579-87.
17. Solito R, Alessandrini C, Fruschelli M, Pucci AM, Gerli R. An immunological correlation between the anchoring filaments of initial lymph vessels and the neighboring elastic fibers: A unified morphofunctional concept. Lymphology 1997;30:194-202.
18. Klein J, Permana PA, Owecki M, Chaldakov GN, Böhm M, Hausman G, *et al*. Controversies in experimental dermatology, section editor Ralf Paus, What are subcutaneous adipocytes really for....? Exp Dermatol 2007;16:45-70.
19. Ryan TJ, Curri S. The cutaneous adipose tissue. Clinics in Dermatology. Philadelphia: J B Lippincott; 1989. p. 1-163.
20. Ryan TJ. Blood vessels of the skin. In: Jarrett A, editor. Physiology and Pathophysiology of the Skin. Vol. 2, Chapter 16-21. London: Academic Press; 1973. p. 638.
21. Ryan TJ. Warming the skin: A review. In: Ryan TJ, Cherry GW, Harding KG, editors. Royal Society of Medicine Press. International Congress and Symposium Series 237 Warming and wound healing: Warm-Up® active wound therapy. Proceedings of a symposium on Thermal Regulation in Wound Care February 1999, 2000. p. 3-13.

Source of Support: Nil, **Conflict of Interest:** None declared

Author Help: Online submission of the manuscripts

Articles can be submitted online from http://www.journalonweb.com. For online submission, the articles should be prepared in two files (first page file and article file). Images should be submitted separately.

1) **First Page File:**
Prepare the title page, covering letter, acknowledgement etc. using a word processor program. All information related to your identity should be included here. Use text/rtf/doc/pdf files. Do not zip the files.
2) **Article File:**
The main text of the article, beginning with the Abstract to References (including tables) should be in this file. Do not include any information (such as acknowledgement, your names in page headers etc.) in this file. Use text/rtf/doc/pdf files. Do not zip the files. Limit the file size to 1024 kb. Do not incorporate images in the file. If file size is large, graphs can be submitted separately as images, without their being incorporated in the article file. This will reduce the size of the file.
3) **Images:**
Submit good quality color images. Each image should be less than **4096 kb (4 MB)** in size. The size of the image can be reduced by decreasing the actual height and width of the images (keep up to about 6 inches and about 1800 x 1200 pixels). JPEG is the most suitable file format. The image quality should be good enough to judge the scientific value of the image. For the purpose of printing, always retain a good quality, high resolution image. This high resolution image should be sent to the editorial office at the time of sending a revised article.
4) **Legends:**
Legends for the figures/images should be included at the end of the article file.