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What is the biological basis of pattern formation of skin lesions?

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Abstract: Pattern recognition is at the heart of clinical dermatology and dermatopathology. Yet, while every practitioner of the art of dermatological diagnosis recognizes the supreme value of diagnostic cues provided by defined patterns of 'efflorescences', few contemplate on the biological basis of pattern formation in and of skin lesions. Vice versa, developmental and theoretical biologists, who would be best prepared to study skin lesion patterns, are lamentably slow to discover this field as a uniquely instructive testing ground for probing theoretical concepts on pattern generation in the human system. As a result, we have at best scraped the surface of understanding the biological basis of pattern formation of skin lesions, and widely open questions dominate over definitive answer. As a symmetry-breaking force, pattern formation represents one of the most fundamental principles that nature enlists for system organization. Thus, the peculiar and often characteristic arrangements that skin lesions display provide a unique opportunity to reflect upon – and to experimentally dissect – the powerful organizing principles at the crossroads of developmental, skin and theoretical biology, genetics, and clinical dermatology that underlie these – increasingly less enigmatic – phenomena. The current 'Controversies' feature offers a range of different perspectives on how pattern formation of skin lesions can be approached. With this, we hope to encourage more systematic interdisciplinary research efforts geared at unraveling the many unsolved, yet utterly fascinating mysteries of dermatological pattern formation. In short: never a dull pattern!

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Prelude 1: Tracing skin patterns

Pattern recognition is the quintessential skill of a dermatologist. His ability to recognize the target lesions of erythema multiforme, the Wickham's striae of lichen planus and the geometric picture of factitial dermatitis affords him an advantageous position in therapy. Furthermore, the pattern of fingerprints provides a means of identifying every single one of the 6 000 000 000 people on our planet. It even distinguishes between identical twins. In addition, the distinctive palmar lines have spawned the thousands of spurious predictions of palmistry.

Some patterns are indicative of ageing, such as wrinkles and the similar ridging of the fingernail plate. Onychogryphosis and pincer nail also reflect ageing keratin synthesis. The shoreline nail pattern and Beau's lines hark back to prior illness. Leukonychia is the sign of prior local injury to the nascent nail plate. The cutaneous horn stands as a dramatic sculpture of sun damage.

We first learn to recognize the distinctive branching Christmas tree pattern of pityriasis rosea, with its heraldic mother patch. Similar symmetrical branching patterns are seen at times with seborrheic keratoses. The peripheral nerve routes are revealed by the patterns of pain and blisters in herpes zoster.

More patterns arise from the disease. These range from the rare, tinea imbricata to the common alopecia areata and the fish scaling of ichthyosis. Moreover, genetic determinants account for a singular lot of common as well as rare patterns. Think of the common horizontal versus the V-shaped anterior hairline. Think of curled versus straight hair and then consider the rare genetic uncombable hair. No one can fail to recognize the patterned hair loss of age.

Among the rare congenital and gene responsible cutaneous patterns, we see linear markings at embryonic closure lines such as linea pigmentosa. We see the grooves of nasal lines, branchial fissures and preauricular sinuses.

The most remarkable and often inapparent patterns are those resulting from the fact that we may inherit two distinct embryonic skins. This mosaicism accounts for the lines of Blaschko. These are V- or S-shaped lines of the embryonic juncture of the twin skins. They account for

Figure 1. Peacock feather.

the localization of epidermal naevi as well as the distribution of a variety of skin diseases.

It is these genetically distinct skins that swirl, but do not mix, on the coating of the embryos. The most vivid result is seen in incontinentia pigmenti. Such mosaicism was first recognized by Mary Lyons, hence the descriptor, lyonization.

Many of the skin patterns require special techniques for their sighting. Thus, to see the pattern of sweat pores, one requires surface staining with *o*-phthalaldehyde. Magnification brings out the tiny patterns of the scabietic burrows. Others are without recognition because of our failure to understand their hieroglyphic nature. We must await a Champollion to reveal them. Confocal microscopy, scanning electron microscopy, skin resistance measurements and sweat prints are a few of the tools available for enlarging our atlas of skin patterns. Magnification of our patient's skin as well as of our imagination will reveal new exciting patterns.

And recall that patterning of the skin extends three dimensionally to the cross-sections of the histopathologist. I was taught that a diagnosis could be made by simply viewing a slide under low power to recognize diagnostic patterns.

Human skin has evolved into a bland, uniform, largely hairless covering. It has little of the dramatic coloring of animals, butterfly wings or peacock feathers. This has led to skin envy on the part of many humans, and in turn to the exquisite colorful skin patterns drawn by tattoo artists.

The essential reference for understanding patterns is *The Self Made Tapestry: Pattern Formation in Nature*, by Phillip Ball, Oxford University Press, 1999. In that work, you will learn how an activator–inhibitor system accounts for the pelt pattern of the giraffe, and with your computer you can explore the recent finding that the eye pattern of a peacock feather comes from the diffraction of light by precision arrays of microscopic photonic crystals (Fig. 1).

Enjoy the poetry of your patients' many patterns, for they are all unique!

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Prelude 2: Pattern formation in skin diseases – thoughts and predictions

It is axiomatic to state that normal skin is highly patterned and its disorders reflect that patterning (1). No two regions of skin are identical excepting the conservation of bilateral symmetry. The heterogeneity of skin ecology, its patterning, is based on unique gross and cellular make-up, which in turn reflects the heterogeneity in molecular constitution, molecular expression and molecular interaction.

The sharp and easily recognizable patterns of skin disease reflect the underlying differences in regional skin. Morphologically, this is seen, for example, in acne vulgaris of the sebaceous follicle in the seborrheic areas and androgenetic alopecia of the hormone-sensitive hair follicles on the scalp. Disease pattern, however, is based on the pathology or aberrations of constituent regional molecules, induced by multiple aetiologies: genetic, immunological, physical, chemical, infectious, etc. Studies of molecular mechanisms of skin disease have revealed many examples of molecular aberrations, which are responsible for the disease.

A good example of heterotopic distribution of members of a gene family is amongst the keratins (2). Genetic mutations in specific keratins generate disorders unique to specific histological regions, for example, mutation of K6a expressed in palmar/plantar skin (pachynychia congenital), of K4 and K13 in mucosal skin (white sponge naevus), of K5 and K14 in truncal skin (epidermolysis bullosa simplex), of K1 and K10 in interfollicular skin (epidermolytic hyperkeratosis) and of hHb6 keratin in the hair shaft (monilethrix). Mutations in members of collagen and associated gene families give rise to distinct cutaneous clinical presentations (e.g. 3). Amongst autoimmune disorders, aberrant antibodies to specific epidermal desmogleins give rise to either superficial or deep pemphigus depending on the specific desmoglein attacked (4). The specific location of the immunosuppressive molecule CD200 to the follicular bulge could explain the preservation of that structure in alopecia areata (5). Even in infectious diseases, the distribution of infection appears to depend on some specific regional molecular characteristic. Recently, it was found that the papilloma virus preferentially infects hair follicle stem cells (6,7); indeed, this association could explain the discrete lesion generated by this infection.

In our view, we would predict that when the disease pattern is not typical, the molecular basis for that disorder is also not typical. In the latter case, the agent may differ molecularly, such as a mutant variety of an infectious agent, or the resident skin may differ such as a genetic polymorphism of a structural or regulatory molecule. The prediction would extend to the idea that the therapeutic approach may have to be modified to meet the situation – pharmacogenomics.

In summary, it is our opinion that dermatological diseases are highly patterned because the molecular make-up of skin is also highly patterned: pattern reflects function, function reflects morphology, morphology reflects molecular structure and disease reflects molecular perturbation – caused by manifold and sundry aetiologies. By understanding molecular structure, molecular networks, molecular properties and the control of molecular expression, we will understand the disease and its therapies. What generates cutaneous patterning and controls it? Ah, but that is the question…! (e.g. 8–13).

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Viewpoint 1

The skin is like a living canvas. As this canvas covers the surface of an individual, changes that lead to non-random patterns are likely to catch people's attention, triggering fascination or revulsion, astounding the experts and providing invaluable diagnostic clues to the dermatologist. Patterns on the skin can be due to physiological, pathological or artifactual causes. Distinct regions, skin appendages, skin ridges, cutaneous nerves, blood vessels, etc. contribute to skin pattern in a manner that is either visible to the naked eye or only apparent under the microscope. When skin lesions develop, they either follow obvious anatomical differences or follow 'hidden' patterns based on genetic/developmental mechanisms that were laid down earlier and that were not obvious in the adult. Then, time adds another dimension to skin patterns through temporal cyclic regeneration of some skin appendages. It is upon this dynamic landscape of the skin that skin lesions often develop, distribute, arrange themselves and change in striking patterns that have been meticulously recorded and commented on since the earliest days of modern clinical dermatology.

And yet, the key question – 'why do all these visible patterns of (and even within) skin lesions form?' – remains one of the least investigated and most neglected among the central problems of dermatology. [Note that this question should not be confused with *histopathological* pattern formation, which is observed when these skin lesions are examined under the microscope (e.g. 1); histopathological pattern formation is *not* covered here.]

Perhaps, the most promising way to reduce the enduring controversies over what really causes skin lesion patterning is to explore the biological basis of these patterns. This exercise may greatly improve our understanding of the pathogenesis of a given skin disorder and allow unique insights into the general basis of pattern formation in biology as well. To this end, we propose several defined categories of biological mechanisms that produce skin patterns and that also serve as the basis for patterned skin lesions (Table 1). In the following, we attempt to define and briefly survey these categories, as an aid to future, systematic research into the biological basis of skin lesion patterns.

Categories of skin patterns

1. Lineage-based genetic mosaicism

The basis for this pattern is that some cells are changed genetically or epigenetically during development. The abnormal functions of these cells then manifest themselves in the skin. The reason they are not distributed randomly is because these inactivation events occur very early during development and are transmitted to the progeny of these early precursor cells. In their migratory paths into the skin, the defects become outwardly visible. The changes can be transmitted through cell division because they involve somatic mutations in DNA or are mediated by epigenetic mechanisms such as X chromosome inactivation, DNA methylation, etc. (see Viewpoint 2). There are several striking examples in which lesions are limited to the left or right side of the body, regional segments, checker board patterns or linear distributions, which have been analysed so ingeniously by Rudolf Happle (2–4 and Viewpoint 2).

The patterns become macroscopically discernible if these progenies are distributed in a particular fashion. The most striking example in the epidermal lineage is the Blaschko lines (5). A recent case of linearly distributed acne turns out to be due to a somatic mutation in the fibroblast growth factor (FGF) receptor in one epidermal cell lineage (6). The mechanism leading to the Blaschko lines is fundamental and not limited to humans. When early chicken embryo epidermal cells (embryonic day 2) were labelled along the dorsal midline with replication defective virus expressing beta-galactosidase, their progenies showed multiple parallel blue lines radiating from the midline across

Table 1. Categories of patterned skin lesions

Category	Manifestation	Mechanism
1. Genetic mosaicism, lineage based	Blaschko lines, segments, checkerboard patterns	Somatic mutations, epigenetic changes
2. Region-specific patterns	Regional specificity: types of skin and appendages, arrangement of appendage elements in a region	Based on developmental processes, stochastic events (reaction–diffusion)
3. Interactions with melanocytes	Melanocyte distribution pattern, vitiligo	Pigmentation
4. Anatomically or physiologically based	Acne vulgaris fungi in nails, flea in hairs, atopic eczema, hypertrophic scar, keloid, pressure sore	Particular structures, local moisture, local chemistry, physical tension, pressure
5. Hair cycle based	Alopecia, cyclic alopecia, transversing hair waves	Regulation of hair cycle phases
6. Modulation by hormones	Sexual dimorphism, androgenic alopecia	Different responses to sex hormones
7. Interactions with environment	UV dermatitis, liverdo reticularis, summer/winter coats of some animals	Sun exposure, cold exposure, seasonal changes
8. Artificial	Tattoo, breast implantation, liposuction, alteration of body contour	Culture based, message display, cosmetic surgery, iatrogenic

the dorsal skin of late chicken embryos resembling Christmas tree branches (7).

2. Region-specific patterns

Regional specificity implies that different skin regions such as the scalp, beards, eyebrows, facial region, lips, palms, nails, mammary glands, sweat glands, etc. have different characteristics. Epidermal precursors are initially multipotent and competent to form all these different structures. During development, special domains of dermis begin sending specific messages to the epidermis. Through a series of epithelial–mesenchymal interactions, these different skin domains with special structures and functions gradually emerge. The integument diversifies to endow different functions to different parts of the human skin. When a molecule fundamental to these processes is mutated, multiple epithelial organs may be affected as seen in ectodermal dysplasia (8). When lesions are specific to certain regions, they form specific patterns. For example, inherited structural defects of hair and nails evidently are limited to where these types of skin appendages are present.

How these dermal specificities and epidermal competence are set up in development is still under investigation. A model based on a skin Hox code was proposed, suggesting that different combinations of Hox gene expression may be the basis of skin regional specificity, and may set up the subsequent differences in diffusible morphogens and adhesion molecules (9). Indeed, there are spatiotemporally defined, specific HOX expression patterns in human skin (10) and the Hox expression patterns of dermal cells derived from different topological skin regions are different (11). Most interestingly, the characteristics of these different skin regions have been shown to 'intraconvert', i.e. respecification to an ectopic fate from the original characteristics through pathological process or experimental manipulation.

For example, the engrailed pathway was shown to be involved in defining the mesenchymal characteristics of the ventral versus the dorsal paw (12). Tbx4 and Tbx5 are shown to be involved in defining the identity of the chicken leg versus wing and hence scale or feather forming dermis (13). Epidermal cells can trans-differentiate and convert hairs into glands or scales to feathers under the influence of retinoic acid or by ectopic expression of specific molecules such as beta-catenin (14–16). A recently engineered K14–noggin transgenic mouse shows that sweat glands are transformed to hairs (17), while noggin overexpression under the neuron-specific enolase promoter can convert outer root sheath keratinocytes into sebocytes (18). An adult cornea can also be diverted to form pilosebaceous units when they are confronted with embryonic hair forming dermis (19). These observations imply that the establishment of specific regions is based on a balance of molecular signalling networks. Understanding the regulation of skin regional specificity has the potential to enable the manipulation of epidermal stem cell fate for medical applications.

Another interesting aspect is the arrangement of individual appendage elements within the region. During skin development, hair primordia are laid out in sequential order and their arrangement and orientation reflect a propagating global wave of skin appendage formation. Loss of frizzled 6 in transgenic mice leads to the formation of multiple whirls (20), suggesting the involvement of the wnt pathway in this process. In humans, the whirls of scalp hairs are most apparent [reviewed in Ref. (21)], yet the formation of hair whirls is not entirely under genetic control. A pair of homozygotic twins was shown to have one and two whirls, respectively (22). Likewise, fingerprints of homozygotic twins are similar but non-identical (23). Therefore, stochastic events involving physico-chemical interactions such as reaction–diffusion are likely to be involved [reviewed in Ref. (24) and references therein]. Knowing how these morphogenetic processes work is not only important for understanding the biological basis of skin lesion patterns, but also for individual identification and engineering of the skin.

3. Pattern formation by interactions with melanocytes

The patterns observed in categories 1 and 2 involve only epidermal and dermal cells. As development proceeds, the presumptive skin continues to build its complexity by interacting with other tissues, such as nerves and blood vessels. One most apparent interaction is the immigration of melanocytes. Melanoblasts from the neural crest migrate into the presumptive skin and may form dramatic visible patterns as seen in zebra stripes and leopard spots. In humans, individuals also have skin regions with different levels of pigmentation (8). For example, the palm is of lighter colour than the dorsal part of the hand. This is

because there are fewer melanocytes in the palm, while the reverse is true for skin in the anogenital region and the nipple. Recent work suggests that the high DKK (a wnt pathway antagonist) level secreted by palm fibroblasts may contribute to the establishment of this pattern (25). In piebaldism, the white tufts of frontal and eyebrow hairs result from a mutation in the stem cell factor receptor, KIT, with the subsequent absence of melanocytes in a defined skin region (8). While the biochemical basis of this lesion is now clear, how such a sharply demarcated region is defined or how melanocytes enter or avoid a particular region in human skin is still totally unknown.

4. Anatomically or physiologically based patterns

Because sensory skin nerves innervate a defined dermatome, some lesions may be manifested along this domain when this nerve is preferentially affected. For example, herpes varicella-zoster virus spreads along sensory nerve fibres, and patient's skin lesions follow a strikingly segmental, zonal distribution (26). Likewise, Lesions can be distributed along the blood supply delivered by the peripheral skin blood vessels. Venous and arterial ulcers as well as vascular malformations are patterned by the underlying blood vessel pathology. In diabetes, the skin ulcers occur more in the distal end of the lower extremities because of poor blood supply to reach these skin regions. And infectious agents that selectively target specific skin appendages (e.g. *Demodex folliculorum* mites, lice: hair follicle) will evidently cause skin lesion patterns explained by the distribution of these skin appendages in a given skin territory.

Along the same lines, different regions of human skin show different, developmentally determined characteristics, which translate into different skin lesion patterns, based on the different physiological and anatomical properties of each region. For example, in seborrheic dermatitis, the follicular distribution pattern of hyperkeratotic or inflammatory skin lesions is determined by the distribution of pilosebaceous units and the microflora that colonize them. Atopic eczema tends to favour particularly moist flexural skin. Candida and dermatophyte infections preferentially target intertriginous skin. Regions with high physical pressure tend to develop wounding or ulcers or display pressure urticaria, especially in conditions of stasis and a relative lack of oxygenation. During wound healing, hypertrophic scars tend to develop more frequently in anatomical areas, exhibiting higher skin tension (27). Prevention or treatment of patterned skin lesions may be achieved by changing or respecting these local characteristics (e.g. by adapting surgical procedures so as to reduce tension and thereby the amount of scar tissue formation in a given skin region).

5. Hair cycle-based patterns

A special subcategory of 'Anatomically or physiologically based patterns', which for practical purposes we treat here as a separate pattern-forming mechanism, relates to the cycling transformation of hair follicles between phases of growth (anagen), regression (catagen), hair shaft shedding (exogen) and relative rest (telogen) (28,29). The differentiation products of these skin appendages (hair shafts) can disappear and reappear temporally. If club hairs are retained in the follicular canal, the macroscopic appearance will remain largely unchanged. If hair filaments are dislodged while new hairs have not grown back, instead, bald regions form. The classical clinical example for this is alopecia areata, an autoimmune disorder whose pattern is hair cycle based in a dual sense: the inflammatory cell infiltrate in alopecia areata exclusively attacks hair follicles that are in their active growth stage (anagen), and then alters their normal cycling behaviour by prematurely catapulting them into catagen, along with – sometimes dramatic – wave-patterned hair shaft shedding (8,30).

If hairs fall out at a rather specific time point of the hair cycle, followed by later regrowth, this can produce a moving wave of bald and hairy regions. This is not only seen in alopecia areata, but, e.g. also in the premature and precise shedding of hair shafts in *Foxn1* and *Msx2* null mice (31,32). In humans, hair follicles cycle independently ('mosaic' hair follicle cycling) so that the dramatic wave patterns typically seen in mice (33) are quite unusual. In any case, the pattern-forming mechanism here is that certain skin structures have been developmentally programmed to undergo cyclic transformations (29), which can produce patterned skin lesions in later life.

6. Hormonally based patterns

Upon puberty, skin appendages in specific regions are transformed when sex hormone pathways, estrogens and androgens are activated. Sex steroids not only prominently affect hair follicles, but also the hypertrophy/atrophy status of sebaceous glands or the melanogenic activity of epidermal melanocytes, giving rise to hormonally based patterns of skin lesions, as seen, e.g. in acne, androgenetic alopecia and hirsutism. Different sexual dimorphism characteristics are endowed in mammals including humans (34). A dramatic example of this is also seen in birds, namely in the different feathering between roosters and hens (35). In human beard, axilla and genital regions, hair follicles are transformed from the vellus to the terminal hair. With increasing age, the reverse tends to occur, leading to androgenic alopecia, while vellus hairs can be transformed into unwanted terminal hairs (e.g. on the upper lip and lower legs) when properly stimulated by androgens, leading to hirsutism. Here, terminal hairs in the frontal and parietal scalp are affected but not those in the occipital region. As a result, the hairline recedes gradually on a patient's foreheads.

The long unclear molecular question as to why scalp and occipital hairs have different responses to sex hormones is becoming increasingly understood because hair follicles of a defined skin region seem to be developmentally programmed to respond with strikingly distinct changes in gene and protein expression, namely of key hair growth-modulatory agents, to stimulation with androgens or estrogens (29,36,37). Thus, hormonally based skin lesion patterns are also results of region-specific developmental programming.

7. Environmentally based patterns

Skin patterns can also result from interactions with the environment, particularly in terms of light and temperature. For example, chronic sun exposure of human skin leads to the characteristic signs of actinic skin damage, with the UV light-induced patterns corresponding to unclothed skin regions. Cold exposure triggers the reticular patterns of livedo reticularis and livedo racemosa and causes blood and/or blood vessel-based pathology to become clinically apparent in defined vascular territories (e.g. in

Raynaud syndrome and cryoglobulinemia) (8,26,38). In nature, changes in the length of the light period that are translated into changes in the plasma melatonin and prolactin level can trigger animals to change to a longer/shorter or whiter/darker coat so as to improve their chances for survival during a given season (39). Now that we know that human and rodent skin and hair follicles are even extrapituitary sites of melatonin synthesis (40–42), one wonders to which extent environmental cues (such as the length of the light period) can also affect seasonal changes in the quality, quantity and distribution of patterned skin lesions.

8. Artificial

In this category, we can liberally group culture-based patterns of skin 'lesions', such as tattoos, breast implants, hair transplants, abdominal liposuction, etc. These artificial patterns are meant to alter the body contour and display body messages to a defined social environment. Of course, some diseases can arise secondarily from these procedures and then also present as skin patterns (e.g. allergic eczema against henna allergens arising in a tattoo).

A true understanding of abnormal conditions is bred by a genuine understanding of what is normal. Here we have surveyed possible biological and other mechanisms that underlie patterns of skin lesions. Through this exercise, we also hope to get closer to explaining the many – still mysterious – patterns of reoccurring skin lesions (often even *in loco*!) that characterize many chronic inflammatory skin diseases such as psoriasis, lichen planus, dermatomyositis, lupus erythematosus and Reiter's disease (8,30). None of these patterns can as yet be convincingly classified into one of the above categories for which reasonable biological explanations are available. Also, once we have been able to explain the remaining mysteries of pattern formation in and of skin lesions, chances are that we will also have come much closer to clarifying the pathogenesis of these dermatoses. This will confirm the classical insight that pattern formation is at the very basis of life and its many states of dysfunction (43,44). Viewed from this perspective, the skin and its lesional patterns become far more than a living canvas, and turn into a window to an as yet undiscovered world of biology and pathology.

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Viewpoint 2

During my entire professional life, I was interested in pattern formation of cutaneous mosaicism. Some of my concepts and hypotheses have been confirmed in the meantime, some turned out to be wrong, whereas others are still waiting to be challenged at the molecular level.

Here I would like to discuss some concepts and doctrines that are still controversial, and to describe perspectives regarding further research in this field.

The lines of Blaschko, a well-established pattern

The concept that Blaschko's lines (Fig. 1) visualize the dorsoventral outgrowth of a mutant cell clone (Fig. 2) was advanced, in German language with English summaries, during the years 1977/1978 (1,2). Today this view is generally accepted. I still take pride in the fact, however, that my first paper written in English on this subject, entitled 'Genetic mechanisms which may explain the pattern of Blaschko's lines', was rejected in 1977 by the British Journal of Dermatology. One of the reviewers thought that my ideas were too hypothetical and far-fetched. At that time, I was so demoralized that I did not submit my paper to another journal. But 8 years later essential parts of the manuscript were published, with only minimal updating, in *Human Genetics* (3), and the article still turned out to be taken as novel.

Presently, mosaicism has been proven at the cellular level in many disorders following Blaschko's lines (4). From animal experiments, we can conclude that the concept of dorsoventral proliferation of two different cell clones holds true (5,6), although a direct proof in human skin does not exist and is unlikely to be feasible.

Genomic versus epigenetic mosaicism

Two major categories of mosaicism can be distinguished (4). The pattern of Blaschko's lines may reflect genomic mosaicism that is usually caused by a postzygotic mutation, but occasionally may also originate from a prezygotic event in the form of gametic half-chromatid mutation (7). Or, it may reflect epigenetic mosaicism that would be either X-linked or autosomal.

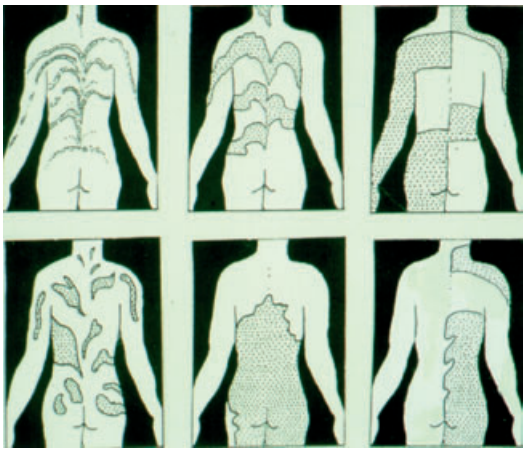

Figure 1. Archetypical patterns of mosaicism in human skin. Type 1a: lines of Blaschko, narrow bands; type 1b: lines of Blaschko, broad bands; type 2: checkerboard pattern; type 3: phylloid pattern; type 4: patchy pattern without midline separation; type 5: lateralization.

Figure 2. Proposed explanation of the fountain-like pattern of Blaschko's lines on the back. The transversal proliferation of precursor cells starts from the primitive streak and interferes with the longitudinal growth and increasing flexion of the embryo.

Lyonization: X-linked retrotransposons and the lines of Blaschko

Functional X-chromosome mosaicism (lyonization) explains the systematized linear patterns as observed in incontinentia pigmenti, Goltz syndrome, Conradi–Hünermann–Happle syndrome, Partington syndrome and various other X-linked genodermatoses (4,7). These linear skin disorders most likely reflect the action of retrotransposons (4).

As far as we know today, experimental evidence indicates that both X-linked and autosomal epigenetic mosaicism is caused by the action of retrotransposons (8). On the X chromosome, a significant accumulation of LINE-1 retrotransposons was found in the region of the X-inactivation centre at Xq13 (8), and this finding most likely reflects a functional significance (9).

Heritable autosomal mosaicism: the role of retrotransposons

Retrotransposons are particles of retroviral origin. They are interspersed in large numbers in the genome of plants and animals (10). Some retrotransposons are able to silence or activate the expression of a neighbouring gene by methylation or demethylation. At an early developmental stage, the action of such 'metastable epialleles' may result in heritable – but non-Mendelian – traits characterized by a variegated coat pattern reminiscent of the lines of Blaschko. Examples are the mouse mutant viable yellow agouti (11,12) and the brindled trait in dogs (13).

In human medicine, cases of autosomal pigmentary mosaicism visualizing the lines of Blaschko may show, by way of exception, a familial aggregation (14,15). In the past, this was difficult to explain. It seems conceivable that the

action of a retrotransposon may account for such familial cases (13).

In the near future, research on retrotransposons will almost certainly play a major role in the elucidation of the genetic basis of mosaic phenotypes visualizing the lines of Blaschko, but also of other disorders including skin cancer.

Heritable autosomal mosaicism: paradominance and the lines of Blaschko

An alternative explanation of the familial occurrence of autosomal mosaic traits is the concept of paradominant transmission (16). Heterozygous individuals are usually healthy. Only if allelic loss would occur at an early developmental stage and gave rise to a homozygous cell clone, the disorder would become manifest as a mosaic.

This concept has been proposed to explain familial cases of sebaceous naevus (17) as well as of other mosaic phenotypes such as Klippel–Trenaunay syndrome (18). Molecular proof is so far lacking.

Are Blaschko's lines of ectodermal origin?

Some authors are convinced that the pattern of Blaschko's lines is exclusively of ectodermal origin (19). Celia Moss has advanced the hypothesis that epidermal cells follow Blaschko's lines, but fibroblasts may not (20).

I hesitate to believe this. For example, the lesions of focal dermal hypoplasia clearly follow Blaschko's lines, and they are definitely of mesodermal origin. Other examples suggesting the possibility of a mesodermal origin of Blaschko's lines are linear atrophoderma of Moulin (21) and linear progressive fibromatosis (22).

To reconcile her ectodermal theory with such mesodermal disorders, Moss (20) has offered the auxiliary hypothesis that the dermal deficiency may be secondary to epidermal pathology. I think that this is a less likely explanation of mesodermal defects along Blaschko's lines. Future research may show which view is correct.

Facial lines of Blaschko are intersecting

Another problem arose when we studied the arrangement of Blaschko's lines on the head and neck (23). We documented a definite crossing of lines, sometimes even at an angle of 90° (Fig. 3). Does this mean that the direction of embryonic movements is highly variable on the head? Or do particular disorders give rise to particular patterns? I feel that the second explanation is less likely, but the question has so far not been settled.

Lateralization: a unique pattern of lyonization

Congenital hemidysplasia with ichthyosiform naevus and limb defects (CHILD) syndrome F is caused by mutations in NSDHL localized at Xq28 (24,25). NSDHL controls the production of 3β-hydroxysteroid dehydrogenase, an enzyme involved in cholesterol metabolism. In typical cases, the CHILD naevus shows a unilateral, diffuse involvement with a clear-cut midline demarcation (Fig. 4) (26). This lateralization has to be categorized as a pattern of lyonization which is, however, strikingly gross. I have hypothesized that the origin of a clone of organizer cells coincides and interferes with the event of X-inactivation

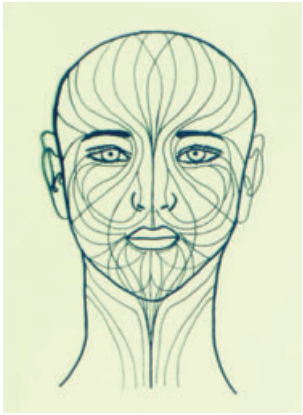

Figure 3. Facial lines of Blaschko showing definite crossing (23).

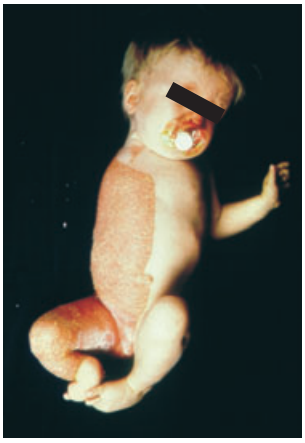

Figure 4. Lateralization pattern of CHILD syndrome.

(7,27). Another explanation would be a defective function of the sonic hedgehog pathway in which NSDHL is involved, resulting in a disturbed left–right asymmetry (28).

However this may be, the lateralization pattern of CHILD syndrome apparently heralds a gene that plays a pivotal role in pattern formation at an early developmental stage.

The checkerboard pattern

The human pigmentary system appears to be particularly divergent with regard to mosaic patterns (Fig. 1). A flag-like arrangement with a strict midline separation has been observed in cases of chimaerism (29). Clinical examples visualizing a mosaic checkerboard pattern are speckled lentiginous naevus and Becker's naevus (4,30).

The phylloid pattern: a new subject of dermatological research

The phylloid pattern is characterized by multiple leaf-like or oblong macules reminiscent of the floral ornaments of art nouveau style (Fig. 5) (30). The recognition of this new pattern of cutaneous mosaicism resulted, within a

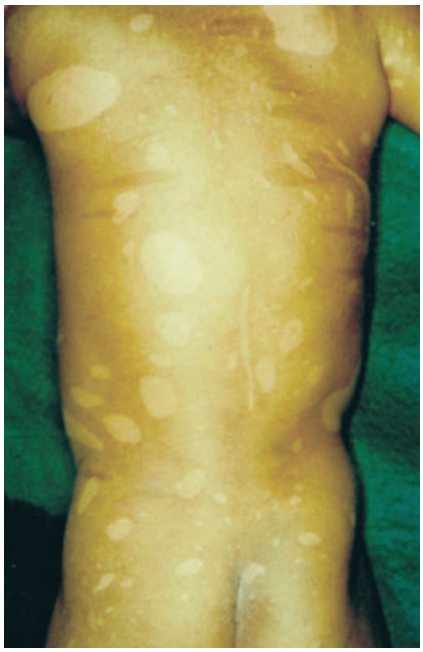

Figure 5. Phylloid hypomelanosis.

short period of time, in the delineation of a novel neurocutaneous syndrome in the form of phylloid hypomelanosis (31). This disorder is caused by mosaic trisomy 13 (32).

It is so far unknown which mechanism may cause this peculiar pattern, and why phylloid hypomelanosis is so closely related to numerical anomalies of chromosome 13.

Patchy pattern without midline separation

Large congenital melanocytic naevi usually occur sporadically. Because we never observe a corresponding disorder that involves the entire integument, I have proposed the concept of a lethal mutation surviving by mosaicism (33). Molecular evidence supporting this concept is so far not available, but can be expected for the near future.

In 2004, Mehraein (34) reported, in a case of ring chromosome 7, somatic mosaicism showing significant gain of chromosome 7 within a highly proliferating melanocytic congenital naevus. Admittedly, however, this skin lesion was not a giant melanocytic naevus.

What is a naevus?

In 1995 I proposed a new definition of the word naevus (35): 'Nevi are visible, circumscribed, long-lasting lesions of the skin or the neighboring mucosa, reflecting mosaicism. With the exception of melanocytic nevi, they do not show neoplastic growth. They never show malignant neoplasia.' My essential point was to postulate genetic mosaicism.

This paper aroused many excited discussions, especially in the French literature (36), because French dermatologists had decided, some years ago, to create an exclusively French definition of the term naevus (37). For example, I had difficulties to decide whether I should be amused or not by a commentary of Drs Delescluse and Broeckx from Brussels (38) who wrote in 1995: 'The Francophones had proposed that the European currency should be named ECU, the Germans didn't accept it, and our ECU shall now bear the name EURO. With regard to dermatology, we should not bow to the new German suggestion, and keep our French terminology.' Fortunately, this bizarre story has come to a good end. Some years later, at a cocktail reception of an AAD meeting, Dr Delescluse took my arm and said: 'Your definition of naevus was right! Let's have a photograph together.' And so we did. In the meantime, the concept of mosaicism has been confirmed in many different types of naevi (4).

I must admit, however, that in the last sentence of my definition, I have expressed myself unclear. My statement that naevi 'never show malignant neoplasia' was misunderstood by some critics (39). Of course, naevi can undergo malignant degeneration, but the resulting malignant tumors are no longer naevi. For instance, a malignant melanoma originating from a melanocytic naevus cannot be categorized as a naevus.

If we accept the concept that all naevi by definition represent mosaics, we have to acknowledge that the salmon patch, a vascular macule that is found in about half of neonates and only in particular midline areas such as the nuchal or glabellar region, is certainly not a true naevus, but should rather be categorized as a nevoid lesion. I think that this is acceptable. Otherwise, we had to create, as suggested by some critics (40), a neologism to denote the naevi fulfilling the definition as described above (35), and this would be preposterous.

Zosteriform naevi do not exist

The arrangement of naevi according to Blaschko's lines or to the checkerboard pattern is sometimes described as 'zosteriform' (41,42). It should be borne in mind, however, that this designation is incorrect (43). So far, I could not find in the literature any naevus being truly zosteriform, i.e. showing a dermatomal arrangement similar to that of herpes zoster.

'Naevus unius lateris' is an irrelevant term

Even in our times, the outdated name 'naevus unius lateris' is still used by some authors (44,45). From a genetic point of view, it does not matter whether a naevus is unilateral or bilateral in a given case. Even the CHILD naevus, the hallmark of CHILD syndrome, rather often shows, in addition to lateralization, a mild contralateral involvement (26). In other words, a 'naevus unius lateris' does not exist. This term reveals the absence of genetic thinking and is entirely useless.

Naevus flammeus is an indispensable term

According to a presently prevailing doctrine, facial naevi flammei do no longer exist because they are now called 'capillary malformations' (46–48). Dermatologists who are using this fashionable term should realize that there is no specific nosological entity to be called 'capillary malformation'.

In other words, naevus flammeus is a specific disorder reflecting mosaicism, whereas 'capillary malformation' has a rather broad meaning that includes naevus flammeus, naevus anemicus, the non-mosaic vascular lesions of Rendu–Osler disease and various other skin lesions.

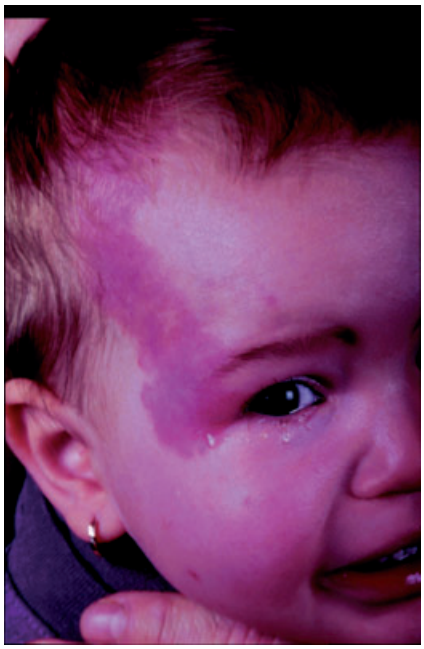

Figure 6. The arrangement of facial telangiectatic nevi is often at variance with the dogma of trigeminal branches.

Hypothesis: naevus flammeus is not dermatomal

With regard to the so-called trigeminal distribution of facial naevi flammei, we are still living in medieval times. When examining photographs of such vascular lesions (Fig. 6), I wonder why the strange belief of a causal relationship to the ophthalmic, maxillary and mandibular branches of the trigeminal nerve has been taken as a dogma since more than 100 years. Most of the presently available textbooks say that the vascular naevi of Sturge–Weber syndrome are visualizing the branches of the trigeminal nerve (46,48).

I seriously doubt that this is correct. Fortunately, I am not entirely alone with my scepticism. Many years ago Alexander (49) has voiced similar doubts. Perhaps, the arrangement of naevi flammei corresponds to a checkerboard pattern (4). This problem should be investigated by the application of modern techniques of examination to determine which view is correct.

Conclusion

Cutaneous mosaicism continues to be a fascinating field of research. Besides the problems of pattern formation as treated in this debate, there are other mosaic phenomena waiting for further elucidation such as revertant mosaicism in autosomal recessive skin diseases (50), type 2 segmental manifestation of autosomal dominant skin disorders (51,52) or didymosis (twin spotting) (53).

With regard to pattern formation in mosaic skin disorders, the role of retrotransposons will hopefully be explored soon by a new generation of investigators devoted to experimental dermatology.

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Viewpoint 3

Pattern formation in nature is best thought of as a process of *symmetry breaking*. That is, an initially homogeneous system becomes spatially, and sometimes temporally, inhomogeneous. Examples include the wind-dependent generation of sand dunes, the abrupt appearance of hexagonal convection cells in a thin layer of oil heated from below and a remarkable phenomenon known as the *Belusov–Zhabotinsky reaction* where a chemical reaction in a shallow dish can spontaneously form a chemical concentration pattern (1). These latter patterns can be *stationary*, manifest as unchanging spots or stripes, or *wave like*, in which a chemical concentration profile can propagate, producing macroscopically visible expanding concentric circles or spirals.

In biology, although symmetry breaking is ubiquitous, understanding the mechanisms involved has met with limited success. Embryogenesis is a paradigm of pattern formation in nature and is still poorly understood. What makes the heart localize to the left and the liver to the right? In development the heart does not remain a midline structure; nature makes a choice between left and right and the axial symmetry is broken. The correct outcome is not always guaranteed – witness dextrocardia – but there are extremely robust mechanisms in place to ensure such anomalies are rare. In some cases, symmetry breaking may not occur where it should; an example is the uniformly pigmented zebra, or it may occur where it should not; an example from human dermatology is the unilateral icthyosiform eruption found in the CHILD naevus (2).

What can be learnt from the study of pattern formation in relatively simple physical systems, such as the Belusov–Zhabotinsky reaction, and how can such knowledge increase understanding of the more complex processes occurring in biology? First, inanimate systems can undergo a process of *self-organization* provided they exchange energy and/or matter with their environment (3). Second, biological systems may exploit physical constraints, such as surface tension, to generate structure without the need for an explicit genetic message (4). Finally, the analogies between inanimate pattern formation and biological pattern formation offer the tantalizing prospect that the latter may be approached and understood in a quantitative manner. Indeed, Alan Turing, the British mathematician, wrote down a series of *reaction–diffusion* equations in 1952 under the title 'The chemical basis of morphogenesis' that show how chemicals that react and diffuse can form spontaneous patterns in solution (5). This is perhaps the simplest mathematical model that can exhibit self-organization. As such, it should not be interpreted in a literal sense, rather it should be considered a paradigm model. Other models for self-organization have been proposed based on different biological hypotheses, but, intriguingly, many of these models make similar predictions, suggesting possible developmental constraints which are independent of the exact details of the biological processes involved (6). It is reaction–diffusion theory that will be used here to explain symmetry breaking in dermatology.

Consider naevoid patterns. How do the patterns arise? The answer remains unresolved despite many attempts at an explanation. Most authors have suggested that the patterns are due to the clonal outgrowth of abnormal cell lines during embryogenesis. For example, the morphology of quadrant naevi has been considered the result of a postzygotic mutation such that the destination of abnormal clones reflects the patterning (7). Similar arguments have been applied to bathing trunk naevi. Likewise, the lines of Blaschko have usually been attributed to clonal outgrowths of clones of cells either from the primitive streak (8) or from the neural crest (9). Yet there is evidence that suggests these explanations are inadequate. Lineage studies on embryonic mice show that early postzygotic mutated cell clones become widely dispersed throughout the body; they do not remain localized (10). In humans, evidence supporting these results is provided by studying the McCune–Albright syndrome, a genodermatosis thought to be due to a postzygotic mutation, and human chimaerism. Although both conditions exhibit large patches of uniformly brown skin over a background of normal skin, it has been shown that fine-grained mosaicism is present *throughout* the skin in the former (11), and present *throughout all* tissues studied in the latter (12). Patterns following the lines of Blaschko are occasionally observed in the McCune–Albright syndrome, but are more commonly seen in X-linked conditions where there is a random inactivation, termed *lyonization*, of one of the X chromosomes in each cell early in embryogenesis. In contrast to the previous example, it has been demonstrated that *clonality* may exist in tissue specimens of lesions following the lines of Blaschko (9,13) despite the expectation that fine-grained mosaicism secondary to lyonization should be present. The issue is confounded by a lack of data. It is

not known whether lesional tissue from *all* naevi following the lines of Blaschko is clonal. It is also unclear in some naevi as to which cell types are involved, so the relevant cell type may have been overlooked. Some authors have suggested the lines of Blaschko may represent the paths of migrating melanocytes (14,15), but this is unlikely. Mintz's allophenic mice (mosaic for black or white coat colour where the relevant genes are expressed by melanocytes) do not exhibit patterns that look like the lines of Blaschko in humans (16). In addition, it is difficult (although not impossible) to see how a gene expressed by a melanocyte could cause, for example, the blistering and hyperkeratosis seen in incontinentia pigmenti.

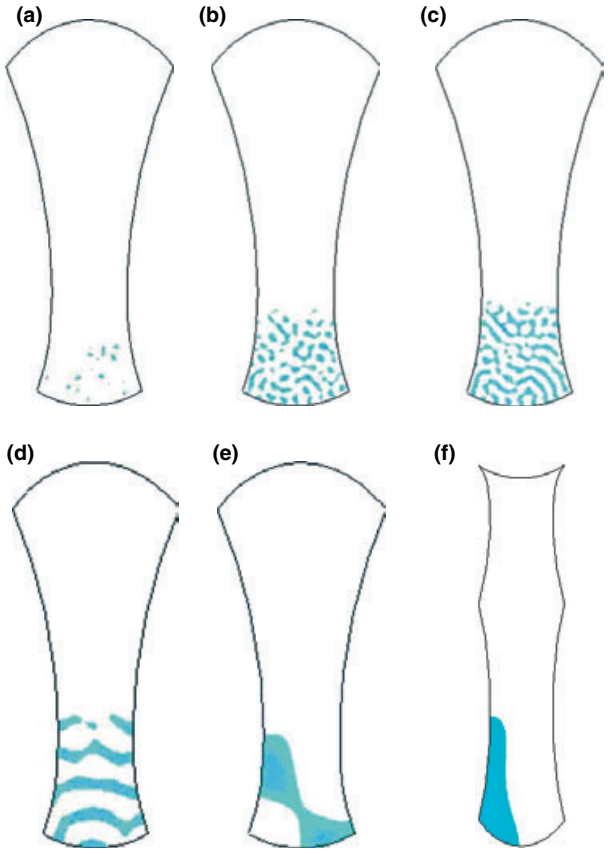

Figure 1. The spontaneous generation of chemical concentration patterns over the dorsum of the early human embryo. Here the evolution of the 'Brusselator' (22), a simple chemical scheme involving six distinct compounds, is modelled using two coupled non-linear partial differential equations and solved using a finite element scheme over the domain as shown. This domain is a representation of the shape of the ectodermal surface of the day 25 tri-laminar embryo (a)–(e) and the day 24 embryo (f). The bottom quarter of the surface of the day 25 embryo is the region associated with the developing thoracic somites. In (a)–(c), the temporal evolution of pattern is shown culminating in a pattern resembling the narrow-banded lines of Blaschko. Images (d), (e) and (f) represent, in the order of decreasing complexity, the broad banded lines of Blaschko, quadrant naevi and the unilateral CHILD naevus, respectively.

Here it is suggested that the patterning found in *all* naevi, ranging from the simple to the complex, can be accounted for by assuming that they are secondary to *chemical prepatterns* laid down early in embryogenesis (Fig. 1) (17). A chemical prepattern is a spatially varying chemical concentration gradient that remains fixed. Its generation from uniformity is a striking example of symmetry breaking and in the example shown it is produced by a *reaction–diffusion* process. Given the presence of the prepattern, there are three possible ways in which macroscopic pattern can subsequently develop. First, when the concentration reaches a threshold, spatially dependent gene activation may occur. It is then possible to see how the abnormal clone becomes activated in regions that follow the prepattern. The distribution of the naevus over the skin will be independent of the presence of the abnormal clone, but not of the presence of the activated gene of the abnormal clone. Second, the prepattern may act as a chemoattractant gradient for the abnormal clone (18). In naevi following the lines of Blaschko abnormal clones may aggregate as they migrate laterally within the surface ectoderm [one ectodermal cell, as it proliferates and migrates laterally cannot be expected to produce a macroscopic band with the exclusion of the normal cell type (19)]. Finally, the chemical prepattern may be the trigger for a spatially dependent selective proliferation of one cell type over another. An interesting consequence of the chemical prepattern hypothesis is that the pattern-forming process itself may be pathological, so that in people unaffected by naevoid skin disease the lines of Blaschko *do not exist*.

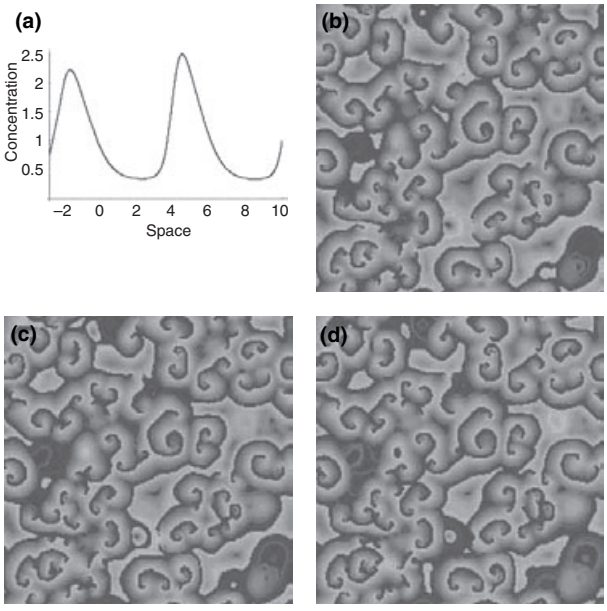

Figure 2. Modelling erythema gyratum repens. In (a) the one-dimensional solution to a reaction–diffusion scheme is shown (21). This chemical concentration waveform is repeated end-to-end and propagates to the left with a speed of the order 1 cm per day and with a wavelength approximately 1 cm. In (b)–(d), the model shown in (a) is approximated by a cellular automaton simulation known as the *Hodgepodge machine* (21,23). Note the morphology and evolution of the rash is accurately represented; the features include growing arcs, spirals and collision fronts.

Next consider erythema gyratum repens. Here a pattern-forming process must account for the appearance of the rash, including expanding rings and spirals, and collision fronts, as well as its dynamic evolution. Hitherto, the rapid spread of the bands of inflammatory skin across the skin surface (up to 1 cm per day) has defied explanation. Some authors have suggested it is due to diffusion, but a simple calculation shows that the rate of diffusion for even small macromolecules is orders of magnitude too small (17). Once again, consider the chemical prepattern hypothesis as a possible solution to the problem. In contrast to the stationary patterns described above, in this case, the chemical gradient is a *wave* that propagates across the skin surface. Many features of the rash, including its morphology and rapid evolution, emerge naturally as a consequence of this reaction–diffusion mechanism (Fig. 2) (20,21).

Here the concept of symmetry breaking found in dynamical systems theory is applied to pattern formation in some examples of human skin disease. Although as yet unproven, the mathematics show that the mechanisms are physically well founded. Quantitative approaches to the problem of pattern formation in skin disease result in falsifiable predictions and offer the prospect of new and counterintuitive insights into pathogenesis.

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Viewpoint 4

Patterns can be defined by passing from a homogeneous to a heterogeneous state, together with motif repetition and order of appearance. Every organ in the body harbours pattern, the most obvious being observed in skin. Embryonic and postnatal development results in three distinct steps in skin patterning.

Skin patterns belong to three main types, determined at three steps of embryonic and postnatal development

First, humans are vertebrates that harbour a bilateral, dorsoventral and right/left symmetry; they are characterized by a dorsal location of neural tube, and a metamerism resulting from the segmentation of the paraxial mesoderm; all together determined at a very early stage of development. The mesodermal segmentation forms the somites, which give rise not only to the vertebrae, but also to segmented dorsal dermis progenitors, as well as striated muscle progenitors, the latter migrating all over the entire body. Thus, at this first stage, the formation of different cell lineages or clones takes place. Moreover, the neural roots emerging at the intervertebral level also show such a metamerism and their distinct innervating territories are well known from the physicians.

During mid-embryonic stages, the establishment of cutaneous underlying muscles, nerves and blood vessels pattern, as well as the arrival by migration of melanocyte progenitors, occurs. Almost concomitantly, the primarily homogeneous skin becomes heterogeneous, leading to the formation of cutaneous appendage displaying characteristic patterns, like hair follicles, sebaceous, sweat or mammary glands.

Finally, during postnatal life, endogenous hormonal events like sexual hormones or lack of insulin, which

are genetically dependent on conception or can also depend in the second case on alimentary behaviour, as well as environmental events because of radiations, microbiological or wounding injuries might create or let out pre-existing skin patterns.

Such patterns have for a long time attracted the attention of dermatologists not only as they might help them in disease diagnosis, but also by the intriguing fact that they appear to follow some rules and did not simply form by accident. Adult, normal or pathological patterns might reflect or be the consequence of pre-existing patterns established during embryogenesis. During development, molecular signals occur between the mesoderm, or the migrating neural crest and their environment, like the neural tube, as well as between the forming dermis and epidermis. Some patterning events, which appear autonomous, are the results of physical diffusion of molecular signals. Moreover, new adult patterning might be the consequence of adult interactions with underlying muscles or even bones, patterning of which have been established during embryogenesis.

Biological patterning is a highly interesting mathematical topic which implies the understanding of shape creation, periodicity and symmetry breaking. We are convinced that physical and mathematical approaches might help skin pattern understanding. While skin patterns have been studied in some cases, they still deserve new interest as new results have been obtained in developmental biology.

(1) Skin macropattern is determined during early embryogenesis and is related to the establishment of body axes and body regions

Skin macropattern in mammals can be mainly distinguished as head, dorsal/ventral trunk, mammary, plantar and palm regions, all of them being linked to the establishment of anterior–posterior and dorsal–ventral axes, showing a bilateral symmetry. Experiments have been mostly performed in chick and mice embryos. Skin clonal lineages have been analysed in β-galactosidase transgenic mice displaying an abnormal duplication in the LacZ gene, leading to the formation of a non-functional enzyme (1). The rare occurrence of homologous recombination leads to the formation of clones of β-galactosidase expressing cells that in skin forms lines on each side of the mid-dorsal line (Fig. 1a). A late occurrence of such an event can allow us to identify cell lineages occurring from the base of the hair matrix in hair follicle (Fig. 1b).

Likewise, local transgenesis in early chick embryo by means of replication defective virus that expresses β-galactosidase showed blue lines radiating from the midline across the dorsal skin (2). Thus, Blaschko's lines (3,4) may correspond to a clinical expression of a genetically altered clone that forms during early embryogenesis. They may also correspond to the segmented pathways of sensory skin nerves as some lesions such as herpes zoster may be manifested along a nerve domain.

At early embryogenesis stage, the Hox code along the anterior–posterior axis of the trunk, as well as along the proximal–distal axis of the limb, is expressed not only in the mesoderm, but also in the skin progenitors and is responsible for the future skin regional identities (5).

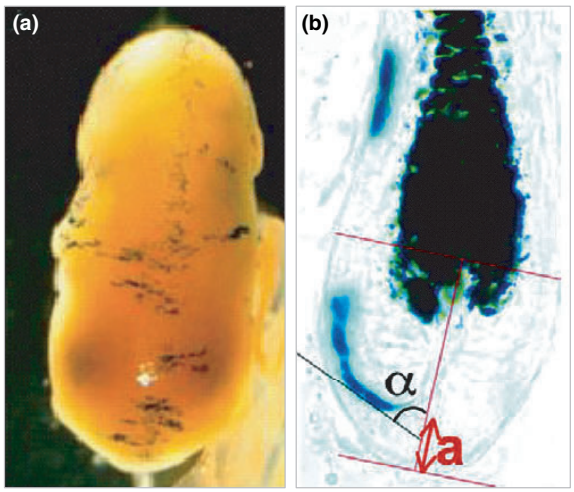

Figure 1. Skin clonal lineages in mouse embryo dorsal skin (a) and hair follicle (b). By courtesy from J. F. Nicolas.

Likewise, homeobox genes exhibit spatial changes in expression during human skin development (6).

The specification of dermal progenitors and their migration in the sub-ectodermal space (7,8) depend on intercellular interactions with their environment, which are mediated mainly by Wnts, Shh and Noggin. Skin field formation, i.e. skin macropattern, also depends on epidermal competence. The complex formation of a feathered skin, which can be triggered even in chick extra-embryonic area (8), results from a basic genetic ectodermal programme. The simplest formation of a scaled skin requires the feather program inhibition, which occurs before 8.5 days of development in the chick hind limb (9). Likewise, the choice between foot dorsal pelage and plantar skin in mice (10) or between foot dorsal scutate and ventral reticulate skin in chick (11) depends on En1 expression in the ectoderm at the limb bud stage. Another related question relies on the pattern of pigmentation of the hand and foot of black people, a pattern that exactly corresponds to the dorsal and ventral regions of the autopode, which are specified at an early stage of limb bud morphogenesis. Why does the migration of neural crest cells giving rise to melanocytes not cross the dorsal/ventral border? In fact, an increased expression of Dickkopf1 by palmar and plantar fibroblasts inhibits melanocyte growth and differentiation (12).

Many dermatological questions that appear to be related to those early embryogenesis events remain unresolved. The giant child naevus may exhibit a clear-cut pattern corresponding with the mid-ventral line (13). The pattern of human male alopecia frequently spares the occipital region. Intriguingly, its dermis originates from the paraxial non-segmented mesoderm, while both the frontal and parietal dermis are issued from the neural crest (14). How might those different origins be related to a dramatic difference in their respective sensibility to testosterone? It should be noted that hair follicles of a region, of which identity is known for a long time to be defined by the dermis (15), are developmentally programmed to respond to hormonal stimulation, as they kept those properties when transplanted (16). Another still unresolved question concerns the pattern of the mammary line. The presence of

abnormal supernumerary nipples in humans always follows the primary line, which has been established at an early stage of development. What exactly is the origin of the mammary dermis? What are the signals responsible for its specification? Moreover, for each skin field the following question arises: what triggers the appearance of the first cutaneous appendage primordium? Most of the time, the first primordia in chick skin are arranged in one first row parallel to the anterior/posterior axis of the trunk or the proximal/distal axis of the limb. Moreover, in the latter case, the first scutate scales appear over the foot bone joints (17). This general rule presents exceptions, characterized by a circular or a whirl appearance of the primordia, from a centre point. This is often observed on the top of the human scalp. Experimentally, the loss of Frizzled 6 (a receptor of a Wnt family signal) leads to the formation of multiple whirls in transgenic mice (18). This is also the case when a supernumerary feather field is induced in the prospective area of the chick mid-ventral apterium (i.e. nude skin) by the graft of a clump of Noggin or Shh producing cells (8).

Finally, all the questions related to the early establishment of skin macropattern may deserve to be studied on a mathematical point of view, which has not yet been the case, in contrast with the skin micropattern.

(2) Skin micropattern: Biomathematical explanations of the formation of cutaneous appendage and pigment motifs during mid-embryogenesis

Cutaneous appendage primordial, composed of a placode and a dermal condensation form during mid-embryogenesis, is a step of development characterized by the transformation of a homogeneous skin into a heterogeneous skin. In chick embryo, the feather micropattern is hexagonal, corresponding to the best filling of space. Once triggered by a Wnt dermal signalling [among others: (19–21)], the placode formation, which requires Eda/Edar signalling (19) and precedes that of the dermal condensation, becomes autonomous (F. Michon, unpublished results). It should be noted that mutations of Eda or Edar genes affect not only the formation of hair follicles, but also of sweat glands and teeth as shown in several ectodermal dysplasia (22). Numerous dermal–epidermal interactive signals comprising diffusible (among others: BMPs, Wnts, Shh) or trans-membrane signals (Notch system) are then involved in primordia maintenance and differentiation [for a review, see Ref. (23)]. Another unresolved question is the patterning of cutaneous nerves and blood vessels: prior to or consequence of the skin micropattern?

Skin micropattern provides a very suitable application of the most known theory of the biomathematics: reaction–diffusion. Some precursors are Kolmogorov and Rashevsky (24,25), but this theory was clearly developed by Alan Turing (26). In this framework, two substances, at least, u and v are considered. These substances evolve spatiotemporally according to diffusion and reaction. Substances are represented by their concentration $u(x,t)$ and $v(x,t)$ which depend on space (variable x) and time (variable t). The temporal variation $\partial u/\partial t$ and $\partial v/\partial t$ at each point x, of these concentrations are ruled by a partial differential equation (Eqn 1):

$$\begin{cases} \frac{\partial u}{\partial t} = D_u \Delta u + f(u, v) \\ \frac{\partial v}{\partial t} = D_v \Delta v + g(u, v) \end{cases} \quad (1)$$

In Eqn 1, $D_u\Delta u$ (resp. $D_v\Delta v$) is the diffusion term for u (resp. v) and $f(u,v)$ (resp. v) is the reaction term of u (resp. v), accounting for their kinetics of production, degradation, etc. D_u and D_v are the diffusion constants for u and v, respectively. Turing has demonstrated the capacity of this system to generate symmetry breaking from an initial homogeneous concentration only perturbed by small random perturbations (typical of a living organism). This system is able, under some conditions notably on diffusion constants and on capacity to amplify small perturbations, to generate stable non-uniform concentration patterns in space. Substances u and v are called 'morphogens' by Turing because of their supposed ability to generate order and form. This theory is inspired by some concepts of Waddington who insisted on the importance of global factors (epigenetic), called 'evocators', in the establishment of form and order in biology (27). Turing formalism was intensely applied to various biological examples. Reference works presenting a wide class of applications of reaction–diffusion in biology are those of Meinhardt and Murray (28–31). Terms were added in some cases in the equations to generalize the original model and for taking chemotactic effects into account. When considering the interaction between a chemical and a cell population, cell movements are preferentially oriented to the high concentration value of the chemical (32). In the case of pure diffusion no privileged direction is determined. If chemotaxis steps in, the cellular flux includes a chemotactic term that depends on the gradient of the guiding substance. The most studied application of reaction–diffusion is far from skin patterning.

With respect to cutaneous appendages patterning, the reaction–diffusion theory relies on the biological existence of various activators and inhibitors of cutaneous appendage formation. This theory has been developed with respect to feather hexagonal pattern by C. M. Chuong laboratory (33,34), and considers BMP2 and follistatin as being, respectively, the leading inhibitor and activator proteins.

However, is this theory, declined with some variations of functions and parameters, able to explain all the different skin micropatterns? How, for example, could the triad pattern of pelage hair follicle be explained? Moreover, how could the wide and intriguing variety of pigmented patterns be explained? The introduction of morphogen kinetics (activators and/or inhibitors) also permits us to obtain spots and stripes and to control the pattern regularity by playing with interactions between morphogens, in particular with their non-linearity of allosteric type (in which we can tune the cooperative and allosteric coefficients) or competitive type (Michaelian or Meinhardt kinetics). It was spectacularly adapted for the generation of stripe (tiger, zebra, etc.) and spot patterns (hexagonal spots of a cheetah, less structured spot pattern of a giraffe). Modelling of spots and stripes uses either a diffusion–reaction system (35) or a non-Turing system like the Potts model (36). In these last models, condensation results from random cell diffusion biased by preferential attachment of cells to extracellular matrix (ECM) and enhanced local cell–cell adhesion. In the reaction–diffusion approach, bifurcation schemes to spatial patterns in two-

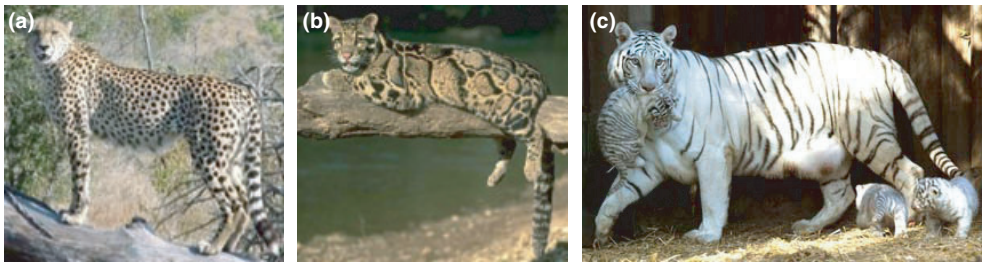

Figure 2. Skin spotting and stripping in the big cats: cheetah (a), nebulous panther (b) and white tiger (c).

dimensional reaction–diffusion medium are considered (35), showing, for example, that the selection of stripes versus spots depends on the non-linear terms and cannot be discerned from the linearized model. The absence of quadratic terms in the reaction leads to stripes, but in most common models quadratic terms will lead to spot patterns (35). Studies have also shown that the size and the shape of the geometry have a great influence on the solution of the equation. A general trend is that the same equation, with the same parameters can produce different patterns that can then be studied in terms of size: mice and elephants do not have any pattern, angelfish are stripy and cheetahs are spotty. One hypothesis for the difference of pattern between cheetah and tiger, both similar in size, would be the size of the embryo at the stage of formation of the pigmented pattern. This provides an explication of the difference of pattern in one species between its spotty body and its stripy tail. The cheetah has spots on its body and a spotty (at the start) and stripy tail depending on its diameter – but it is not possible for a stripy animal to have a spotted tail (Fig. 2). In cheetahs, a progressive change appears on the tail from spot to stripe as the diameter of the tail decreases (Fig. 2a). When the spots are large, as in the case of the nebulous panther (Fig. 2b), stripes appear rapidly on the tail. Reversely, according to the trends of equation comportment with size, it is not possible for a stripy animal to have a spotty tail (Fig. 2c). The adequacy of the reaction–diffusion system was also studied in growing organisms (37). For instance, angelfish exhibit observed changes in the number, size and orientation of their stripes while growing. It should be noted that some pigmented patterns do not seem to rely on the reaction–diffusion family, such as some black and white patterns, which just present a global axial symmetry and no micropattern (many examples may be found in birds or cats). In those cases, pattern may only be due to early embryonic movements of groups of melanocyte progenitors from the neural crest and should be related to the first step of patterning during development. Finally, the wide variety in skin micropattern is a challenge to mathematicians and to the reaction–diffusion formalism.

(3) Skin patterns related to adult life

Many adult skin patterns that are linked with various diseases let out pre-existing patterning that has been established during early embryogenesis, in relation with the underlying tissues or organs. However, new patterns may occur during postnatal life, for example ulcers, eschar or wound healing. Those patterns again are related to the skin underlying muscles or bones. Prevention of skin lesions may be achieved by respecting local characteristics. During the past century, guidelines developed by surgeons have searched for elective opening incisions. Many surgeons prefer Langer's lines (Fig. 3a) developed by Karl Langer from cadavers in rigor mortis (38,39). These lines correspond roughly to empirical minimal stretch and contraction lines by looking both at the local dermal tension (essentially because of elastic fibres) and at the loco-regional tendon–muscular action. Other surgeons (40) preferred lines oriented perpendicular to the action of the underlying muscles. More recently, Borges (41) described relaxed skin tension lines, which follow furrows formed when the skin is relaxed and are produced by pinching the skin. In Fig. 3b, arrows are oriented along the relaxed skin tension lines. Linear scars following the arrows are minimally noticeable. Their location may vary slightly among individuals. Borges's and Kraissl's lines are considered by some surgeons as the better guides for elective incisions of the face and body, respectively. Elastic fibres underlying Langer's lines are parallel or perpendicular to the epidermis, while they are perpendicular to Kraissl's and Borges's lines. Langer's lines also partly follow Blaschko's lines (3,4), corresponding to zones of eruption of herpes zoster correlated with dermatomes.

Numerous authors (42,43) have suggested that traumatic or surgical wound healing follows reaction–diffusion models. Applications of the simulation results in such modelling are important in surgery and traumatology. This gives a rational basis to the use of the empirical surgical lines networks mentioned above, helping in particular the surgeon to avoid cheloids, which are observed after either traumatic wounds or surgical openings. For

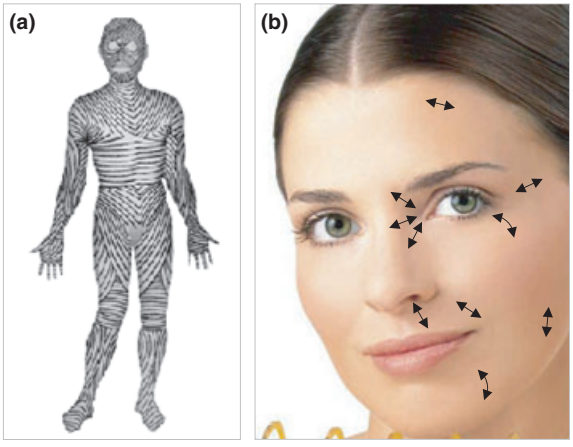

Figure 3. Two cases of empirical surgical lines networks: Langer's lines (a) and the best surgical opening incisions in the case of face (b).

instance, both aesthetic and functional results of the healing process are highly dependent on the original orientation of the primitive cuts.

The master equations corresponding to the modelling of wound healing are given in the framework of differential systems and can be summarized as follows, where $n(x,t)$ [resp. $r(x,t)$] is the cell (resp. ECM) density in a spatial point x at time t and $u(x,t)$ [resp. $\partial u(x,t)/\partial t$] is the displacement (resp. the velocity) of the ECM with respect to the fixed x referential:

1. Cell conservation equation:

$$\underset{\text{cell density variation}}{\partial n/\partial t} \quad \underset{\text{convection}}{+\partial(n\,\partial u/\partial t)/\partial x} =$$

$$\underset{\text{diffusion}}{D\,\partial^2 n/\partial x^2} + \underset{\text{proliferation}}{Rn(N-n)r} - \underset{\text{migration (haptotaxis)}}{h\,\partial(n\,\partial r/\partial x)/\partial x}$$

2. ECM conservation equation:

$$\underset{\text{ECM density variation}}{\partial r/\partial t} \quad \underset{\text{convection}}{+\partial(r\,\partial u/\partial t)/\partial x} =$$

$$\underset{\text{biosynthesis}}{knr} \quad \underset{\text{degradation}}{-k'n(N-n)r}$$

3. Displacement balance equation:

$$\underset{\text{viscosity}}{\mu\,\partial^3 u/\partial x^2\,\partial t} + \underset{\text{elasticity}}{E\,\partial^2 u/\partial x^2} -$$

$$\underset{\text{stabilizing effect}}{\beta\,\partial^4 u/\partial x^4} \quad \underset{\text{active cell traction stress}}{+d\,\partial[n(N-n)r]/\partial x} = \quad \underset{\text{restoring forces}}{\sigma f(u,r)}$$

The signification of the above equations is underlain by simple physical–chemical considerations: the cell and ECM balance equations indicate that the cell or ECM matter created or destroyed in a spatial point x at time t has only biological (proliferation, migration, biosynthesis and degradation) or physical (convection and diffusion) origin. The displacement equation synthesizes the balance of the forces exerted on the ECM that are responsible for its displacement. We summarized these different components responsible for the cell and ECM dynamics in Fig. 4. The parameters of the above equations are the cell diffusion coefficient D, the proliferation rate r, the haptotaxis coefficient h, the maximal cell density N, the secretion rate k, the catabolism rate k', the Young coefficient E, the Poisson coefficient β, the viscosity coefficient μ, the cell traction amplitude d and the restoring force coefficient σ.

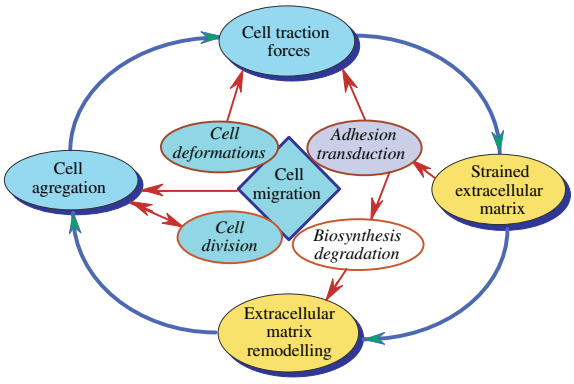

Figure 4. Components of the skin, cell migration and proliferation processes that must be taken into account in wound healing.

Such a general model has to be simplified to simulate lines networks like those described by Langer or Blaschko, keeping only, in the above equations, the diffusion and proliferation terms in the first equation, the biosynthesis and degradation terms in the second equation, and the viscosity, elasticity and cell traction stress terms in the third equation. The main difficulties lie in estimating initial conditions for the variable r: they have to take into account all viscid–elastic forces related both to dermal and muscular tensions and the present anatomic atlases are only giving data about the general direction of muscle contraction. An interesting challenge, especially for reconstructive surgery, would be now to obtain a precise functional atlas giving the local mean values of the parameters appearing in the simplified model.

In conclusion, the history of the major morphogenetic equations in mathematics has been often pushed by the necessity of explaining complex life's forms, especially those occurring in the skin wound healing, skin annex development and skin pigmentation patterning.

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