Review Article
Revisiting dandruff

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Synopsis
Dandruff is a common scalp disorder affecting almost half of the postpubertal population of any ethnicity and both genders. It may, however, represent a stubborn esthetical disturbance often source of pruritus. Skin biocenosis, in particular the Malassezia spp. flora, plays a key aetiologic role, in combination with the unusual capacity of some corneocytes to be coated by these yeasts. Substantial evidence indicates that keratinocytes play an active role in the generation and expression of immunopathological reactions. This is probably the case in dandruff. Upon stimulation of a critical colonization of corneocytes by Malassezia yeasts, the release of pro-inflammatory mediators is increased. This could lead to the subclinical microinflammation present in dandruff. In seborrheic dermatitis, local deposits of immunoglobulins and the release of lymphokines are responsible for the recruitment and local activation of leukocytes leading to the eventual amplification of the inflammatory reaction. Some ancillary non-microbial causes of dandruff may operate through physical or chemical irritants. Many methods have been described for rating dandruff. Our favourite tools are clinical examination and squamometry. Dandruff can precipitate telogen effluvium and exacerbate androgenic alopecia. Antidandruff formulations exhibiting some direct or indirect anti-inflammatory activity can improve both dandruff and its subsequent hair cycle disturbance.

Résumé
L'état pelliculaire est une affection commune du cuir chevelu atteignant près de la moitié de la population des individus post-pubères, quels que soient leur ethnie et leur sexe. Cette affection peut s'avérer rebelle chez certains. La biocénose cutanée, en particulier la flore des Malassezia spp., joue un rôle étiologique clé, de même que la capacité particulière exprimée par certains cornéocytes de pouvoir se couvrir de ces levures. De nombreux arguments convergent pour affirmer que les kératinocytes jouent un rôle actif dans la génération et l'expression de réactions immunopathologiques. C'est vraisemblablement le cas dans l'état pelliculaire. Lors de la stimulation par une colonization critique de cornéocytes par les levures Malassezia, la libération de médiateurs pro-inflammatoires est accrue. Cela conduirait à la micro-inflammation infraclinique des pellicules. Dans la dermite sèborrhéique, les dépots locaux d’immunoglobulines et la libération de lymphokinones seraient responsables du recrutement et de l’activation locale de leucocytes aboutissant à une amplification éventuelle de la réaction inflammatoire. Certaines causes accessoires non-microbiennes des pellicules peuvent intervenir par le biais d’irritants physiques ou chimiques. De nombreuses méthodes d’évaluation des pellicules ont été décrites. Dans notre laboratoire, l’examen clinique et la squamométrie sont nos outils favoris. Les pellicules peuvent précipiter un effluvium télogène et exacerber une alopécie androgénétique. Des formulations antipelliculaires possédant une
activité anti-inflammatoire directe ou indirecte peuvent améliorer les pellicules et le trouble induit au niveau du cycle pilaire.

**Introduction**

The popular word dandruff (dandriff, dandriffe) is of Anglo-Saxon origin, a combination of tan meaning tetter and drof meaning dirty. Thus, dandruff is ‘itch-dirt’. Other names for this condition are pityriasis simplex, furfuracea or capitis. Dandruff is strictly confined to the scalp, and it is experienced by about half of the postpubertal population, irrespective of ethnicity and gender [1]. This scalp condition may appear trivial from a medical standpoint. It may, however, represent a stubborn aesthetical disturbance often source of pruritus. In any given dandruff-prone subject, the condition may fluctuate with the seasons as it often worsens in winter.

**The dandruff–seborrhoeic dermatitis connection**

Dandruff is anything but monomorphous. However, the spectrum of the dandruff presentations may be difficult to define because it blurs with seborrhoeic dermatitis and some other scaly conditions of the scalp [2]. Indeed, scalp scaling is not a specific criterion distinguishing dandruff from seborrhoeic dermatitis. Inflammation and extension of the lesions outside the scalp exclude the diagnosis of dandruff.

For the vast majority of authors, there is an axiom linking dandruff and seborrhoeic dermatitis [2–5]. The former is the mildest form of a spectrum of clinical presentations. Inflammation is minimal and remains subclinical. The discrete histological inflammation is recognized by the scattered presence of lymphoid cells and ‘squirting capillaries’ in the papillary dermis, hints of spongiosis and focal parakeratosis. Conceptually, dandruff is dander, and dander represents nothing more than physiological scale. Thus, it is considered in the scope of a physiological process calling for cosmetic management. The response to treatment is commonly swift but transient.

By contrast, seborrhoeic dermatitis is obviously a more inflammatory disease often extending outside the limits of the scalp. It represents a pathological process characterized by a spongiotic dermatitis in which mounds of parakeratosis and scale crusts form at lips of infundibular ostia. Medical treatment is often needed to clear the disease although some cosmetics/cosmeceuticals may show efficacy.

**Dandruff composition**

Dandruff scale is a cluster of corneocytes, which have retained a large degree of cohesion with one another and which become detached as such from the surface of the stratum corneum. It may be centred by a pilosebaceous follicle (Fig. 1). Both the size and the abundance of the scales are heterogeneous from one site of the scalp to another and over time [5].

Parakeratotic cells often make up part of dandruff [5, 6]. Their number is related to the severity of the clinical manifestations, which may also be influenced by seborrhoea. In this way, pityriasis simplex or ‘sicca’ indicates the presence of fine squames, usually of a small size, conferring an asteatotic and farinaceous appearance of the process. Steatoid pityriasis or ‘oleosa’ differs by the seborrhoeic, thick and adhesive nature of the dandruff, and the scale of which is often larger in size.

**Microbial aetiopathogeny of dandruff**

There are likely several aetiopathogenic pathways with complex mechanisms, which cause dandruff. The microbial aetiology of the common type of dandruff is, however, straightforward. The scalp normally harbours many micro-organisms. Their density reaches $10^3$ to $10^5$ organisms per mm$^2$, and they include in particular staphylococci, *Propionibacterium* spp. and *Malassezia* spp. [5, 7]. Within this threesome, the relative proportion of
**Malassezia** spp. (Fig. 2) is multiplied by a factor of 1.5–2 or more in dandruff, when they represent almost 75% of the flora [8].

The evidence implicating *Malassezia* spp. in dandruff conditions and seborrhoeic dermatitis has accumulated over time and contrasts with results obtained from quantitative methods used to count yeasts [5]. The majority of technical procedures supported a relationship between the severity and recurrence of dandruff on the one hand, and the global fungal load on the other [6, 8–12]. However, the method of collecting micro-organisms on agar contact plates did not reveal this aspect [4, 13]. This was probably because of a methodological bias as these plates collected only part of the tiny minority of commensal yeasts located at the skin surface without strongly adhering to it. Therefore, this method did not in any way explore the yeasts tightly bound to the skin surface or encased within the stratum corneum (Fig. 3), where they might exert a pathogenic role [12, 14].

To add to the difficulty of interpretation, the quantitative microbiological assessments of all kinds do not indicate the role of the yeast, the abundance of which might have been proportional to the volume of scales which it colonizes or be responsible for the altered desquamation [5]. One other aspect that has not yet received enough attention is the relationship between dandruff and peculiar species of *Malassezia*. There is an ample evidence that *Malassezia* spp. are found in different proportions and amounts according to the body site [15, 16] and to the nature of the *Malassezia*-driven disorder [17, 18].

Eradicating or controlling the abundance of yeasts of the genus *Malassezia* appears to be the cleverest strategy for treating dandruff [5, 7, 11, 12, 19–35]. Using various methods, different clinical and experimental protocols and distinct active ingredients, all indicate that applying antifungal-based antidandruff shampoos lead to a stereotyped sequence of events [1]. Firstly, itching becomes less intense, or disappears, after the second or third application. Yeasts from the genus *Malassezia* decrease in number without, however, being completely eradicated [10]. The bacterial population remains otherwise little affected by most antifungal products [1]. Scale production and parakeratosis decrease in parallel [12, 16]. Two to three weeks after stopping treatment, the initial clinical situation recurs as *Malassezia* spp. increase to their initial levels.

### Corneocyte implication in dandruff

When looking closely at dandruff and seborrhoeic dermatitis, the *Malassezia* distribution is not uniform at the skin surface and inside the stratum corneum [14, 36]. The yeasts appear in clumps restricted over some corneocytes where as other corneocytes in the vicinity harbour few of these micro-organisms. Perhaps, the *Malassezia*-binding sites differ in number on corneocytes. Another possibility calls for the intervention of the natural antimicrobial peptides of the innate immunity. The yeasts should normally boost the expression of β-defensin-2 by human keratinocytes [37]. In dandruff, their expression could be impaired at the site where the *Malassezia* yeasts are abundant.

Further considerations should be given to the fact that *Malassezia* spp. have antigenic and pro-inflammatory properties stimulating both the innate and acquired immune responses, and neuroimmune sensorial responses as well [38].

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**Figure 2** *Malassezia* yeasts at the surface of the stratum corneum.

**Figure 3** Scale of the scalp studded by many *Malassezia* spp. (in black). The yeast density is less prominent at the outer surface of the dandruff (Gomori stain).
Basically, in dandruff and seborrhoeic dermatitis, the immune response is not particularly altered [14, 39]. The ultimate stages of inflammation might share some similarity with other desquamative disorders (eczema, psoriasis, sunburn, etc.) even though the actual mechanisms and clinical presentations differ [40, 41]. It is indeed evident that anti-inflammatory drugs, such as dermocorticoids, have proven efficacy, particularly in severe dandruff and seborrhoeic dermatitis. Eradicating the primary cause of the problem, providing a safe antifungal action, should, however, remain the treatment choice.

The *Malassezia*-corneocyte hypothesis still leaves some doubt. It does not fully explain why low-grade scaling scalps (i.e. 2–5 mg per scalp per 2 days) with a low parakeratotic index may persist when dandruff has resolved and *Malassezia* yeasts have largely been removed from the skin surface. It is possible that the antifungal agents do not eradicate the deep-seated yeasts allowing a minimal inflammatory reaction to be maintained. It is also possible that some anti-inflammatory activity claimed by antidandruff agents [42, 43] is not effective enough *in vivo*. Still another possibility is an adverse reaction such as irritant dermatitis or contact allergic dermatitis is provoked by the shampoo [44].

Another puzzling problem is raised by the actual mode of action of the anti-dandruff shampoos claiming an antifungal activity. Indeed, most active compounds are barely soluble in water and their casual residence time on the scalp is very short [34]. These conditions are at variance with those respected in the treatment of all other pityrosporoses and dermatomycoses. Hence, one cannot exclude other ancillary modes of action of these active antidandruff products, including some direct biological effects on epidermal cells. Actually, this hypothetical modality could recall the mode of action of tar shampoos [45].

**Ancillary non-microbial aetiopathogeny of dandruff**

A dandruff condition without a primary or original fungal involvement is conceivable. The most obvious example is desquamation of the scalp following excessive exposure to sunlight [46]. The intercorneocyte cohesion is then affected [46, 47]. The same phenomenon may occur in minimal chronic irritation of the scalp. Daily routine cumulative minimal insults including hard brushing, over-shampooing, hair frictions [1, 48, 49] and certain cosmetic hair products may be responsible for this event, as well as airborne substances from the environment. Other non-fungal agents may lead to minimal chronic irritation such as sebum-derived products, sunlight activation of follicular-photosensitizing agents such as porphyrins synthesized by *Propionibacterium* spp. [49]. Some neuroimmune influence may be also operative. It is believed that psychological stress may amplify it. There are, however, no experimental and factual observations supporting this assumption.

**Dandruff and lipids**

The human scalp is an androgen-sensitive and sebum-rich region [50, 51], where daily amounts of sebum delivered to the scalp and hair surfaces are in the gram range [1]. Sebum is a nutrient for the scalp biocenosis, and puberty is a prerequisite for the onset of dandruff. Sampling sebum from a scalp surface gives a poor yield because it generates bias and may lead to conflicting results [51, 52]. However, when dealing with any dandruff study, it is recommended to record data on sebaceous physiology, either clinically or experimentally. We found no difference in the sebum excretion rate (SER) on the scalp in non-dandruff vs. dandruff-affected volunteers. SER appeared significantly higher in androgenic alopecia only [51]. In sum, sebum is a prerequisite for dandruff, but it is not a sufficient factor *per se*. Many people who complain about oily scalp have no dandruff. Of note, the seasonal rhythm in sebum excretion gives the minimum values when dandruff is more prevalent [53].

As far as the degreasing process of hair is concerned, it is a common observation that achieving a successful treatment of dandruff often leads to an increased coating of the hair shafts by sebum [1]. Such greasy hair situation has been related to a sponge effect of both squames and stratum corneum. Both elements being decreased, the fraction of sebum they were previously trapping then becomes available to hair surface [1]. However, the sebum flow appeared to us to be more influenced by the shampoo formulation than by the residual amount of dandruff [54, 55].

With regard to epidermal lipids, clear changes are present in dandruff, in both their amount and...
relative composition [56]. Both the inflammatory mediators [38] and the altered ultrastructure of the dandruff cells [57] are improved by an effective antidandruff treatment.

**Dandruff rating**

Dandruff can be assessed through visual scoring performed under controlled procedures. Irrespective of the scale range, the evaluation process should follow precise guidelines. Observers must be trained adequately for the scoring procedure. It is wise to secure a wash-out period by using a bland shampoo for at least 2 weeks prior to the start of any clinical trial. Because of the loss of dandruff scales by shampooing, the visual assessment should be performed at a constant interval after shampooing. A 2-day period is a compromise between sufficient scaling recurrence and a loss of scales from external factors (combing, brushing, contact with pillows, etc.) during this period [1].

The whole scalp or instead a defined specific part, usually the most severely affected, is to be examined. In most subjects, the vertex is the most scaly area, whereas the nape is less involved and possibly scale-free. A split-head procedure is valid for intra-individual comparative trials as dandruff globally shows lateral symmetry. However, it may cause bias by cross-diffusion of the test products [1]. Self-assessments and related parameters (itching, tolerance, stress, medications, environmental conditions, etc...) may be informative for the interpretation of data.

The clinical evaluation should ideally be supported by some quantitative bioinstrumental methods [1, 5]. Among the many ways of collecting dandruff, we have designed the squamometry method [58–60]. Because of its ease and reproducibility, the collection of dandruff is performed using a transparent self-adhesive disc (D-Squame®; Cuderm, Dallas, TX, U.S.A.; Corneodisc; L’Oréal, Paris, France; Corneofix®; C+K Electronic, Cologne, Germany) left in place for a few seconds. Sampling should ideally be performed with controlled pressure on the scalp. The overall density of dandruff is estimated by squamometry, which is a colorimetric method, after staining the sample with a solution of toluidine blue and basic fuchsin for 1 min (Fig. 4). Examination by computerized image analysis under a microscope is another means of quantifying dandruff severity. At the same time, this enables yeasts of the *Malassezia* spp. to be counted. Live fungal cells may be specifically identified by vital staining with neutral red [12]. Another possibility is offered by flow cytometry after simple or double vital staining.

**Dandruff and hair**

Dandruff severity ranges from discrete to severe among subjects. For instance, some Africans seem to have particularly abundant dandruff. It is possible that scales are trapped in meshes of crowded terminal hairs thus preventing them from being lost. This hair–dandruff relationship may in part explain the absence of dandruff on bald pates, and applies equally to hairless or shaved sites and to regions that sport only vellus hairs.

It is a common observation that dandruff adhere to hair. It is possible to quantify this feature [61]. In our experience, the amounts of dandruff on the scalp and on hair are not always correlated.

The presence of dandruff may precede or accompany telogen effluvium [5]. It may also exacerbate alopecia [62–64]. On a 2-day collection, non-dandruff scalps lead to a 50–100 hair loss whereas those affected by dandruff may range from 100 to 300, although a positive correlation with clinical grades of dandruff cannot be drawn [1]. This hair shedding process associated with some cases of dandruff may result from alterations in the teloptosis process (exogen phase) and in the hair eclipse phenomenon [65–67]. This event is perhaps related to the subclinical inflammation demonstrated under the microscope [42]. It has been shown that specific products used to combat dandruff may limit the progression of androgenic alopecia [63, 68]. In addition, ketoconazole has been reported to stimulate hair growth in mice [69].
Conclusion

Dandruff is a reactive response of the epidermis of the scalp to various stimuli. Of these, set of converging features altogether supports the role of Malassezia spp. as the main causative agent. Some environmental factors such as ultraviolet light and airborne irritant agents or those applied deliberately to the scalp are also potential protagonists, which must not be overlooked. Irrespective of the causative factor, the physiopathological events in dandruff could be summarized into a few successive steps involving the intervention of the triggering agent, particularly the increased Malassezia load over some corneocytes, discrete subclinical inflammation, parakeratosis and scale formation. The process can also ensue in hair cycle disturbance.

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