Review Article

# Compensatory Phenomena in Dermatology

**Abstract**

Compensatory mechanisms in the human body are generally set in action when there is an absence or deficiency of an attribute to make up for the same. Such mechanisms may be intended to compensate for either the quantitative deficiency or functional impairment of an attribute performing a particular function. Frequently, in an attempt to normalize the homeostatic milieu, the compensatory mechanisms may work more than necessary producing undesired effects as well. In this review, we describe some of such compensatory phenomena in relation to clinical, immunological, pathological, and few other aspects of dermatology, as well as such phenomena characterizing some of the dermatotherapeutics.

**Keywords:** *Compensatory hyperhidrosis, desmoglein compensation, extramedullary hematopoiesis*

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## Introduction

Compensatory phenomena can be described as the mechanisms in the body which compensate for the diminished or complete lack of a particular attribute that normally performs a function with the intent to maintain the normal homeostatic milieu. Such phenomena can be mediated by the mechanisms that over-function to compensate for the loss or diminished function of a part of the same (e.g., compensatory hyperhidrosis) or can be mediated by other but related mechanisms (e.g., chronic granulomatous disease). However, such overactivity may produce undesired manifestations and/or be responsible for the typical clinicopathological findings associated with a certain disorder. Table 1 summarizes some of the compensatory phenomena in different aspects dermatology discussed in this review.

## Immunological Compensatory Phenomena

### Desmoglein compensation in pemphigus

Desmogleins (Dsgs) are the principal components of the desmosomes – the intercellular adhesion molecules which are the predominant antigenic determinants in the pemphigus group of immunobullous disorders. The Dsg 1 and Dsg 3 are the major Dsg isoforms whose expression patterns in the epidermis of the skin and the mucosa differ. The Dsg 1 is expressed throughout the epidermis of the skin; more so in the subcorneal region, whereas Dsg 3 is expressed weakly and only in the basal and suprabasal regions. Although both the Dsg 1 and Dsg 3 are expressed throughout the mucosal epidermis, the expression of Dsg 1 is quantitatively much less. These variable expression patterns of Dsgs in skin and mucosal epidermis account for the different clinical patterns of blistering in different forms of pemphigus.

In the mucosal-dominant pemphigus vulgaris, antibodies are produced essentially against Dsg 3 and the increased expression of the Dsg 1 compensates for the loss of Dsg 3 in the skin preventing blister formation. Mucocutaneous pemphigus vulgaris is characterized by both skin and mucosal lesion as antibodies are produced against both the Dsg 1 and Dsg 3. However, despite the presence of anti-Dsg 1 antibodies, the epidermal split in the skin is only suprabasal. This is possibly due to weaker intercellular adhesion in this region due to lesser desmosomes and better access to the antibodies to this region traversing through the dermal vessels. Pemphigus foliaceous is characterized by only anti-Dsg 1 antibody production and the compensation for the loss of Dsg 1 in the mucosa by the intensely expressed Dsg 3 prevents intraoral lesions. In the skin too, the blisters are only subcorneal as the Dsg



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**Table 1: Compensatory phenomena in dermatology**

| Category | Associations |
|---|---|
| Immunological | Desmoglein compensation in pemphigus |
| | Chronic granulomatous disease |
| Endocrinological | Addison's disease |
| | Hyperandrogenism-insulin resistance-acanthosis nigricans syndrome |
| | Vitamin D dependent rickets |
| Metabolic | Hypermetabolism in erythroderma |
| | Congenital lipodystrophies |
| Compensatory hyperhidrosis | Ross syndrome |
| | Leprosy |
| | Diabetes |
| | Miliaria |
| | Congenital erosive and vesicular dermatosis |
| | Postsympathectomy |
| | Local axillary surgery for hyperhidrosis |
| | Botulinum toxin therapy for hyperhidrosis |
| Cutaneous extramedullary hematopoiesis | Congenital infections |
| | Hemoglobinopathies and other blood dyscrasias |
| | Myeloproliferative disorders |
| | Malignancies |
| Dermatopathological | Verrucous stage of incontinentia pigmenti |
| | Thickening of the skin in ichthyosis |
| | Elongation of dermal papillae in psoriasis |
| | Basal layer proliferations in Darier's disease |
| | Hair follicle cycle and wound healing |
| Iatrogenic | Extrarenal excretion of doxycycline |
| | "Catch-up" growth on discontinuation of corticosteroids |

3 in lower epidermis (though minimal) compensates for the loss of Dsg 1.[1]

### Chronic granulomatous disease

Chronic granulomatous disease is a rare primary immunodeficiency disorder characterized by deficient mechanisms to kill the phagocytosed microbes. This defect occurs due to the mutations in one of the genes encoding the subunits of the superoxide-generating phagocyte nicotinamide adenine dinucleotide phosphate oxidase enzyme complex responsible for the microbicidal respiratory burst. Among the four forms (one X-linked recessive and three autosomal recessive), the X-linked recessive form of the disease is the most common and the most severe form characterized by complete absence of the enzyme activity due to mutation in the cytochrome B-245 beta chain gene.

In the absence of superoxide production within the phagocytic vacuole, the activation of the proteases by them leading to killing of the organisms does not take place. As a result of this immunological deficiency, several compensatory mechanisms act in an attempt to keep the infection confined. These include granuloma formation, overactivity of humoral immunity, and an exaggerated cellular inflammatory reaction which account for the clinical manifestations such as suppurative lymphadenitis, pneumonitis, inflammatory bowel disease, and the characteristic granulomata of the gastrointestinal tract, lymph nodes, liver, spleen, and lungs. Mucocutaneous involvement occurs in 60%–70% of the cases and the common manifestations include gingivostomatitis, periorificial seborrheic dermatitis-like rash, recurrent cutaneous staphylococcal abscess, and lupus erythematosus-like rash.[2-4]

## Endocrinological Compensatory Phenomena

### Addison's disease (primary adrenal insufficiency)

The pathognomonic diffuse noninflammatory cutaneous hyperpigmentation of primary adrenal insufficiency is attributed to compensatory overproduction of adrenocorticotropic hormone (ACTH) by the pituitary to normalize the reduced adrenal cortisol and mineralocorticoid secretion. The excess circulating ACTH exerts a stimulatory effect on the melanocytes by binding to the melanocortin 1 receptors expressed on them. Although generally diffuse, the hyperpigmentation of Addison's disease preferentially involves the sun-exposed and pressure-bearing areas, nails (longitudinal melanonychia), palmar creases, and any existing scars. Darkening of the normally pigmented structures (e.g., nipples and areola, flexures, perineum, and perianal regions) and of the pigmented lesions (e.g., melanocytic nevi and café-au-lait macules) is noted as well.[5,6]

### Hyperandrogenism-insulin resistance-acanthosis Nigricans syndrome

The hyperandrogenism-insulin resistance-acanthosis nigricans (HAIR-AN) syndrome is one of the inherited insulin resistance syndromes characterized by insulin receptor and/or postreceptor pathway defects. The insulin resistance in HAIR-AN syndrome is quite severe that results in a compensatory hyperinsulinemia which, in early stages of the disease, is able to maintain a normal fasting blood glucose. The hyperinsulinemia also increases the steroidogenic action of luteinizing hormone resulting in hyperandrogenism. The acanthosis nigricans and virilization due to such intense hyperinsulinemia and hyperandrogenism, respectively, are hence quite severe, with the latter often raising the suspicion of an androgen-secreting tumor until proven otherwise by radiological and endocrinological assays. The patients are also at a greater risk of

developing type 2 diabetes mellitus, hypertension, and cardiovascular disorders.[7,8]

### Hyperparathyroidism in Vitamin D-dependent rickets

Vitamin D-dependent rickets (VDDR) type I and II are rare autosomal recessive disorders associated with impaired calcium and phosphate absorption resulting in hypocalcemia and early onset rickets. Type I VDDR is characterized by deficiency of 1α-hydroxylase enzyme and is associated with low serum levels of calcitriol, whereas in type II VDDR, there is defect in the Vitamin D receptor signaling pathways which is associated with normal or even markedly elevated serum calcitriol.

To compensate for the hypocalcemia in either, there is secondary hyperparathyroidism with markedly elevated serum parathormone leading to increased bone resorption evidenced by increased serum alkaline phosphatase and serum cross-linked type I collagen carboxy-terminal telopeptide levels and increased urinary excretion of cross-linked type I collagen *N*-telopeptides. This mechanism, however, becomes progressively inadequate in untreated and the patients develop the characteristic rachitic manifestations. The type II VDDR is dermatologically important as generalized early-onset (within first few months of life) noncicatricial alopecia seen in this disorder resembles atrichia congenita. Although the latter is a distinct entity, infants with such presentation must be evaluated radiologically and biochemically for VDDR.[9-11]

## Compensatory Metabolic Phenomena

### Hypermetabolism in erythroderma

Erythroderma (any inflammatory skin disorder involving >90% of the body surface area) is associated with many internal derangements, most notably the deranged thermoregulation. It occurs due to excessive heat loss through the skin attributed to increased cutaneous circulation and to impaired cutaneous thermoregulatory barrier. Patients with chronic erythroderma can develop cachexia due to hypermetabolism occurring as a compensatory mechanism to counter the chronic and excessive heat loss and to maintain the core body temperature. This hypermetabolism is unassociated with increased thyroid activity.[12,13]

### Congenital lipodystrophies

Congenital lipodystrophies are a heterogeneous group of inherited syndromes characterized by variable absence of adipose tissue in the body. Conventionally, these disorders are classified based on the degree of adipose tissue deficiency as generalized, generalized but partial, and localized lipodystrophies. The congenital generalized lipodystrophy (Berardinelli-Seip syndrome) is characterized by universal loss of adipose tissue often at birth. In the inherited partial lipodystrophies, the lipoatrophy commences at about puberty or early adulthood and is characterized by significant loss of subcutaneous fat in the limbs and gluteal region associated with a compensatory excessive accumulation of fat involving the face, neck, back, and trunk, often in a Cushingoid manner, resulting in an overall increased body adipose tissue in some cases.

In either of these inherited lipodystrophies, there is a compensatory upregulation of the visceral fat increasing the risk of metabolic syndrome. The metabolically active visceral fat produces more tumor necrosis factor alpha and interleukin 6 and less adiponectin which lead to insulin resistance. The degree of insulin resistance is variable depending on the extent of fat loss which leads to compensatory hyperinsulinemia and its consequences such as type II diabetes mellitus, hyperlipidemia, acanthosis nigricans, and virilization in females (as described under HAIR-AN syndrome).[14,15]

## Compensatory Hyperhidrosis

Compensatory hyperhidrosis is an example for the functionally normal anatomical structures that overwork to make up for the loss/inactivity of a part of the same. The loss may be a quantitative reduction of sweat glands or their functional inactivity.[16] Compensatory hyperhidrosis can occur at a site distant from the affected area and is graded as mild, moderate, and intense based on the volume of sweat production, discomfort caused to the patient, and the resultant social embarrassment.[17] The causes of quantitative and functional deficiency of the sweat glands associated with compensatory hyperhidrosis are outlined in Table 2.

The most common cause of compensatory hyperhidrosis encountered in clinical practice is following sympathectomy for palmoplantar or axillary hyperhidrosis. The trunk is the most common site of increased sweating following sympathectomy. The pathomechanism proposed in this condition is the lack of negative feedback to the hypothalamus due to sectioning of the afferent neuronal pathways.[17] In the Ross syndrome, the hypo- or anhidrosis (accompanied by tonic dilated pupil and areflexia) is segmental, progressive, and associated with compensatory contralateral segmental hyperhidrosis. The exact pathophysiology of this disorder is unknown. The hypo- or anhidrosis is due to damage to the postganglionic sympathetic innervations of the sweat glands. The compensatory hyperhidrosis is believed to be due to the overactivity of the sweat glands whose innervations are still intact but reduces overtime, and complete anhidrosis eventually ensues.[19,20] Harlequin syndrome, characterized by unilateral anhidrosis and reduced flushing due to damaged efferent sympathetic nerves, also demonstrates compensatory hyperhidrosis usually associated with excessive flushing contralateral to the affected segment. Spinal injuries also can produce segmental hypohidrosis with contralateral compensatory hyperhidrosis.[21]

The most common acquired disorders associated with autonomic dysfunction are diabetes and leprosy. Diabetics may develop hypohidrosis of the extremities due to microangiopathic and neuropathic complications of the disease, which is associated with two types of compensatory hyperhidrosis – a thermally induced hyperhidrosis of the upper half of the body and a compensatory gustatory hyperhidrosis.[18,21] In untreated long-standing lepromatous leprosy, the peripheral anesthesia is associated with hypo- or anhidrosis due to involvement of autonomic nervous system. This hypo- or anhidrosis is often accompanied by compensatory hyperhidrosis of the trunk and axillae.[22] A similar pattern of compensatory hyperhidrosis due to decreased postganglionic stimulation of sweat glands of palms is seen Parkinson's disease.[23] Other primary chronic forms of dysautonomias-like Bradbury-Eggleston syndrome (pure autonomic failure), multiple system atrophy, and Parkinson's disease with orthostatic hypotension are also associated with diminished sweating and compensatory asymmetrical hyperhidrosis.[24]

Examples for quantitative deficiency of sweat glands associated with compensatory hyperhidrosis include miliaria,[16] congenital erosive and vesicular dermatosis,[25] and following local surgery for axillary hyperhidrosis.[18,26] Although botulinum toxin therapy has been a successful modality for gustatory, axillary, palmoplantar, and for compensatory hyperhidrosis following sympathectomy,[27] it has, however, also been reported to produce compensatory nonaxillary hyperhidrosis when employed in the treatment of axillary hyperhidrosis.[28]

## Cutaneous Extramedullary Hematopoiesis

Extramedullary hematopoiesis is a compensatory phenomenon that coexists with disorders associated with compromised normal bone marrow hematopoietic function. The most common associations include myeloproliferative disorders and the hemoglobinopathies. The most common sites of extramedullary hematopoiesis are liver, spleen, and paraspinal regions.[29] Extramedullary hematopoiesis in the skin is rare and has been described with myelofibrosis. The cutaneous lesions have varied morphology and clinically manifest as erythematous firm papules, infiltrated plaques, nodules, ulcers, or angiomatous nodules. Histology demonstrates precursor hematopoietic cells.[30] Cutaneous extramedullary hematopoiesis represents the ability of the skin to resume dermal hematopoiesis when the need arises which otherwise is an *in utero* feature that normally ceases before birth.[31]

Continuation or persistence of dermal erythropoiesis in the neonatal period was first described with congenital rubella. However, several other infections, hematologic disorders and malignancies, and certain other disorders also are associated with this phenomenon [Table 3]. Clinically, persistent dermal erythropoiesis in these settings manifests as congenital multiple, diffuse, rubbery papules and nodules exhibiting a characteristic bluish or magenta color – "the blue-berry muffin baby" [Figure 1]. These lesions normally regress into faint brownish macules in a few weeks after birth.[32] Although a compensatory demand, deficient replacement, or dysfunction of cellular elements of blood have been speculated, the exact cause resulting in persistent dermal erythropoiesis is unclear.[33]

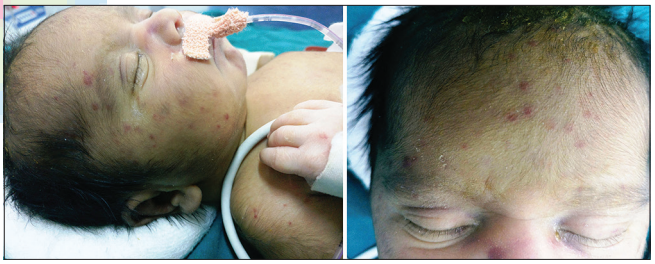

**Figure 1: "Blueberry muffin" rash in a newborn with congenital rubella**

**Table 2: Causes of compensatory hyperhidrosis**

| Causes | Area of hypo- or anhidrosis | Area of compensatory hyperhidrosis |
|---|---|---|
| Disorders | | |
| Ross syndrome | Progressive segmental | Regressive segmental (contralateral to the hypo-or anhidrotic segment) |
| Harlequin syndrome | Unilateral segmental | Contralateral |
| Leprosy | Peripheral | Trunk and axillae |
| Parkinson's disease | Acral | Face, trunk, and axillae (axial hyperhidrosis) |
| Diabetes | Extremities | Upper half of the body (thermally induced), and gustatory |
| Miliaria | Affected areas | Normal area |
| Congenital erosive and vesicular dermatosis | Affected areas | Normal area |
| Iatrogenic | | |
| Postsympathectomy | Intended area of treatment (palmoplantar, axillary or facial) | Predominantly trunk |
| Axillary curettage | Treated area | Residual untreated area |
| Botulinum toxin therapy for axillary hyperhidrosis[18] | Axilla | Nonaxillary |

**Table 3: Disorders associated with cutaneous extramedullary hematopoiesis**

| |
|---|
| Congenital (blueberry muffin lesions) |
| Infections |
| Rubella |
| Toxoplasmosis |
| Cytomegalovirus |
| Herpes simplex |
| Coxsackie virus |
| Parvovirus |
| Epstein–Barr virus |
| Syphilis |
| Blood dyscrasias |
| ABO and Rh incompatibility |
| Hereditary spherocytosis |
| Twin-twin transfusion syndrome |
| Hematological and other malignancies |
| Congenital leukemia |
| Langerhans cell histiocytosis |
| Neuroblastoma |
| Congenital rhabdomyosarcoma |
| Others |
| Neonatal lupus erythematosus |
| Adult onset |
| Myelofibrosis |

## Compensatory Phenomena in Dermatopathology

### Incontinentia pigmenti (Bloch-Sulzberger syndrome)

Incontinentia pigmenti is an X-linked dominant disorder due to mutation in the nuclear factor-κβ essential modulator (*NEMO)* gene that normally prevents tumor necrosis factor-alpha-induced keratinocyte apoptosis. Hence, the first stage of the disease is characterized by inflammatory and vesicular lesions due to apoptosis of the *NEMO*-deficient cells along the Blaschko's lines. The verrucous (second) stage is the result of replacement of the *NEMO*-deficient cells with keratinocytes expressing the normal allele and their compensatory hyperproliferation. The keratinocyte damage is associated with melanin incontinence into the upper dermis that produces the conspicuous linear streaky hyperpigmentation of the skin in the third stage. The pigmentation gradually fades away and may be replaced by hypopigmentation (the fourth stage).[5]

### Congenital ichthyosis

The congenital ichthyosis is a group of disorders inherited due to mutations in the genes encoding the proteins necessary to essentially maintain a homeostasis between the epidermal turnover and desquamation rates, thereby maintaining the integrity and barrier properties of the epidermis. The various clinical manifestations of different types of congenital ichthyosis are basically results of compensatory mechanisms in an attempt to normalize the epidermal structural and functional properties. Increased epidermal lipid synthesis and epidermal hyperproliferation are the notable among such mechanisms. The latter is typically exemplified in harlequin ichthyosis, lamellar ichthyosis (especially in patients with adenosine triphosphate binding cassette, subfamily A, member 12 gene mutation), and keratinopathic ichthyoses. The compensatory epidermal hyperproliferation is not only intended to normalize its barrier properties but also as a protective effect against blistering due to external noxious stimuli.[34-37]

### Psoriasis

In psoriasis, the normal homeostasis between the epidermal turnover, maturation, and desquamation is disturbed and there is an increase in the ratio of the proliferating epidermal keratinocytes to the resting ones. As a result, a substantial increase in the quantum of the germinative basal layer occurs and to accommodate the same, there is enlargement and elongation of the rete pegs. This is associated with compensatory elongation of the dermal papillae as well, thereby increasing the dermoepidermal interface and physiochemical interactions.[38,39]

### Darier's disease

In Darier's disease, the focal suprabasal clefting due to acantholysis and overlying dyskeratosis of the keratinocytes are the pathognomonic histopathological features. As a compensatory mechanism to this abnormality, the basal keratinocytes proliferate and project into the suprabasal cleft as "villi" which are also an important diagnostic feature.[38,40]

### Hair follicle cycle and wound healing

Animal studies have demonstrated that wounds heal faster in hair bearing areas compared to the ones on non-hairy areas. Further, wounds heal faster when the hairs in the wounded area are in anagen phase as opposed to telogen phase. This phenomenon is attributed to the contribution of hair follicle stem cells in accelerating the onset of wound reepithelialization, which under normal circumstances are not involved in maintenance of epithelial homeostasis. After wounding, the stem cells in the hair follicles migrate to the epidermis and assist reepithelialization. In the anagen phase, both the interfollicular as well as outer root sheath epithelia proliferate rapidly at the onset of wound reepithelialization which effect faster healing of the wound. This proliferative process begins later in telogen phase probably to compensate for the initial slower rate of healing and effects a "catch-up" complete reepithelialization. The role of anagen hair follicles in hastening the wound healing is not just limited to their harboring of stem cells but the alterations in the local microenvironment during this phase of hair cycle (increased expression of late terminal differentiation markers of epithelium, decreased inflammation, increased angiogenesis, and accelerated matrix deposition) also promote faster wound healing.[41-43] These observations, however, still need to be proven in humans.

## Compensatory Phenomena in Relation to Common Dermatotherapeutics

### Doxycycline

Doxycycline shares several metabolic properties with the other tetracyclines. However, a feature unique to this drug is the non-accumulation in body tissues in the presence of renal failure even though the renal excretion accounts for up to 50% of the administered drug. This phenomenon is due to the fact that, apart from the kidneys, the drug is also excreted through hepatic and gastrointestinal routes. In the presence of renal failure, there is a compensatory increase in the gastrointestinal secretion of the drug and hence, although the urinary concentration and total urinary excretion of doxycycline are significantly diminished, the renal tissue concentration is normal. Therefore, doxycycline is considered to be a safe antibiotic even in advanced renal failure.[44-46] However, administration of the drug in renal failure with concomitant impairment in the extrarenal excretory pathways can deteriorate the renal condition.[47]

### "Catch-up" growth on discontinuation of steroids

Linear growth retardation in children receiving long-term corticosteroids is a well-known entity which one should be mindful of while treating. However, the dose of corticosteroids necessary for such growth suppression in much greater than the physiological dose and also there is a compensatory spurt in the linear growth on discontinuation of steroids. This "catch-up" growth is attributed to factors intrinsic to the epiphyseal growth plate. The antiproliferative effects of corticosteroids slow down the senescence of the growth plate chondrocytes. Once the steroids are discontinued, the epiphyseal plate resumes its proliferative function and compensatory linear growth spurt occurs. This compensatory growth may occur at a much accelerated rate and may even extend beyond expected for that age as the epiphyseal growth plate would not have "aged" as far as it normally should have.[48-50] However, administration of glucocorticoids before the age of 2 years, and just before puberty may not be associated with this compensatory "catch-up" linear growth phenomenon.[51]

## Conclusion

A preliminary knowledge of such phenomena in relation to different aspects of dermatology is helpful for the clinicians as well as learners to correlate the clinical findings, ascertain the diagnosis, and to preempt certain events following a treatment which would be helpful in their prevention and management.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

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