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CONTINUING PROFESSIONAL DEVELOPMENT PROGRAM

Grover's disease: 34 years on

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SUMMARY

Grover's disease is an entity reported worldwide and recognized as a common disease since Grover first described it in 1970. Its cause remains obscure, but hospitalized, febrile and sun-damaged patients are particularly prone. It is frequently associated with some other skin diseases, including eczemas, psoriasis and solar keratoses. Acantholysis is the universal histological finding in all the varying clinical presentations. Treatment in the past has been *ad hoc*, but topical therapy, acitretin and phototherapy can suppress symptoms.

Key words: acantholytic dermatosis, histopathology, phototherapy, retinoids, therapy.

INTRODUCTION

It is now 34 years since Ralph Grover, a dermatologist from Greenport, New York, USA, described the disease which now bears his name.[1] He reported six patients who presented with a papular truncal rash accompanied by intermittent severe itch occurring during changes of season, but which regressed after a few weeks. Skin biopsies taken from these patients revealed small foci of acantholysis, an histological change usually seen in conditions clinically very unlike this hitherto undescribed eruption, which he dubbed 'transient acantholytic dermatosis'.

In 1977, 54 more cases were reported from the USA[2] and in 1980, 24 cases from Australia.[3] Many of the cases reported after the initial six[2–6] described a persisting eruption, prompting the suggestion that because the disease was frequently not transient it should therefore be named Grover's disease.

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AETIOLOGY AND PATHOGENESIS

Grover's disease has been reported from many different countries and climates. It is not an uncommon disease. It is seen mostly in white men from middle to old age. The cause is unknown, but many authors have linked the disorder to heat and sweating.[4,6] Solar damage is a common association in Australia,[3] whereas in colder climates xerosis and asteatotic eczema are frequent triggers.[7]

Bed rest in hospital seems to be a common trigger for its appearance, and regular associations include any febrile illness, immunodeficiency or malignancy, including leukaemia and lymphoma.[8–14]

It has been proposed that pathological changes involving the acrosyringia, as in miliaria, may be important in its causation, but this has not been demonstrated convincingly.[8]

CLINICAL FEATURES

The disorder manifests as papules, papulovesicles and small nodules, many of which are excoriated, on the trunk and proximal limbs (Figs 1,2). In our clinical experience there are three recognisable variants:

(i) Transient eruptive. There may be sudden sensation of itch sometimes out of proportion to the small number of lesions or there may be numerous lesions. The itch may be severe, preventing sleep and generally being aggravated by heat. The disorder settles in a few weeks but does so more promptly with treatment.

(ii) Persistent pruritic. These cases may have less severe pruritus than the former type, but may persist for months or years showing only a moderate response to therapy. Various series have reported mean durations of 47 weeks,[3] 94 weeks[9] and 360 weeks.[8]

(iii) Chronic asymptomatic. The clinical presentation of persistent truncal papules, typically submammary, in men simulating folliculitis can be as a result of Grover's disease. Acantholysis can be demonstrated in these cases histologically, but without follicular involvement. A series of asymptomatic cases was reported in oncology patients.[14]

Grover's disease is frequently associated with other skin disease, principally eczemas of various types, particularly

seborrhoeic and asteatotic, psoriasis[7] and actinic skin conditions such as solar keratosis.[3]

PATHOLOGY

Acantholysis with vesicle formation is the characteristic epidermal change occurring in all four main histological patterns: (i) acantholysis with spongiosis; (ii) acantholysis of Darier's disease-like pattern (Fig. 3); (iii) acantholysis of pemphigus-like pattern; and (iv) acantholysis of Hailey–Hailey disease-like pattern.

These patterns may occur alone, but are more often seen with one of the other forms, the Darier type being the most common.

The acantholysis usually occurs in a suprabasal location in lesions of the Darier and pemphigus vulgaris types and throughout most layers of the epidermis in those resembling Hailey–Hailey disease, resulting in the formation of small intraepidermal clefts or, infrequently, bullae (Fig. 4). The acantholysis in some cases affects only the uppermost layers of the epidermis, resembling pemphigus foliaceus.

The epidermis in lesions of the Darier type shows marked dyskeratosis, with grains and corps ronds, whereas dyskeratotic changes in lesions of the other types are usually mild and often absent. Additional epidermal changes include hyperkeratosis, acanthosis, and parakeratosis.

These changes tend to be most severe in lesions of the Darier type, which sometimes have vertical columns of parakeratosis overlying dyskeratotic, acantholytic foci, whereas other changes are less severe or absent in lesions of the pemphigus type.[3]

The dermis in most cases contains a superficial perivascular infiltrate of lymphocytes and histiocytes, sometimes

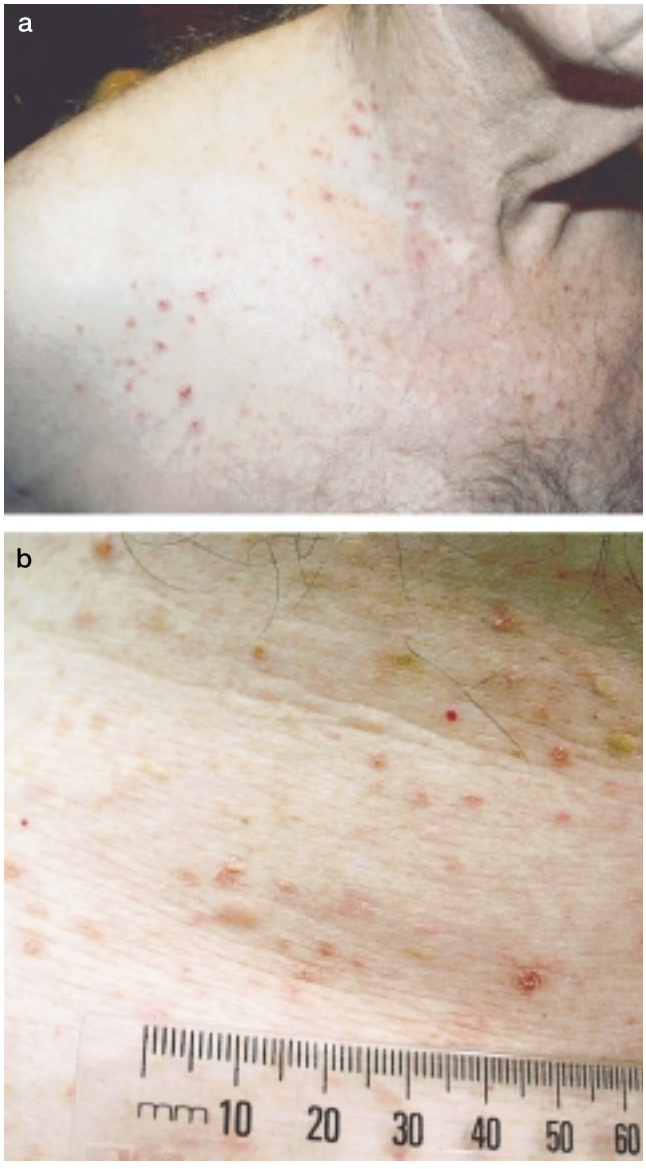

Figure 1 (a) Papules on the right side of the chest in a 76-year-old man. (b) Close-up view of papules, some excoriated.

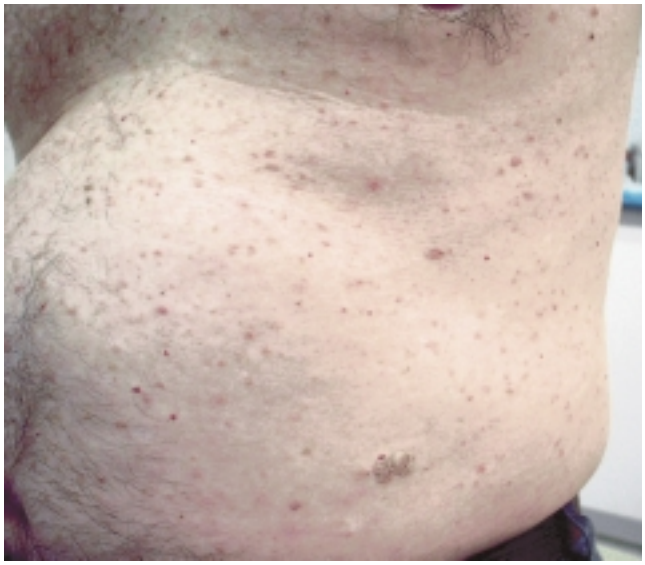

Figure 2 Left flank of a 52-year-old man with Grover's disease. The submammary and lateral abdominal distribution is characteristic. Among the papules are seborrhoeic keratoses and Campbell de Morgan angiomas.

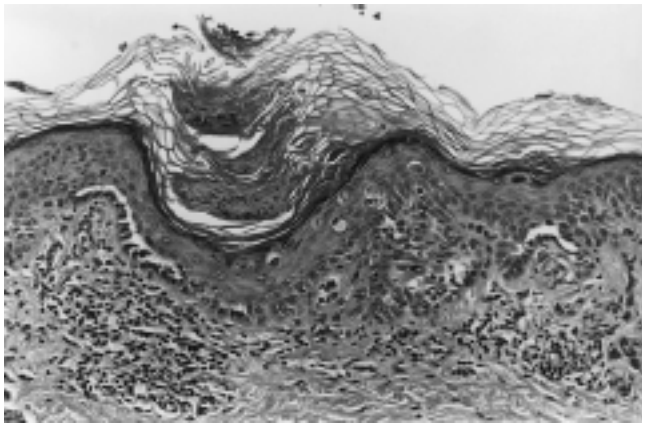

Figure 3 Parakeratosis overlies acantholysis, dyskeratosis and suprabasal clefting producing a Darier-like pattern (H&E).

with scattered eosinophils; plasma cells are most often present in excoriated lesions. It has been asserted that the number of eosinophils in the infiltrate is proportional to the patient's pruritus,[15] but this has not always been our experience.

Lesions are sometimes seen in association with an acrosyringium (Fig. 5), but attempts to show this finding consistently in order to elucidate an aetiology tied to sweating have not been successful. An association was found in only two of 11 cases examined in one study.[16]

Three cases where histological features of pemphigus foliaceus were found, but with negative immunofluorescent findings, presented clinically with blisters.[17]

The histological changes typically occupy tiny, circumscribed foci, so that several biopsies and multiple sections are often necessary to demonstrate the characteristic features (Fig. 4). It is common for small foci to be missed and the histology to be misinterpreted as apparently unrepresentative of Grover's disease.

Focal acantholytic dyskeratosis, as a secondary phenomenon, can be seen in biopsies from many diseases: herpes virus, impetigo, solar keratoses, squamous cell carcinoma and others, but in Grover's disease the acantholysis appears to be the primary change and should not be confused with secondary acantholysis.[15]

Immunofluorescence[3,4,13,18,19] and immunohistochemical[13,20] studies have not demonstrated consistent patterns of positivity in the disease and have not helped to elucidate its aetiology.

The few electron microscopic studies of Grover's disease have shown ultrastructural changes resembling those of true Darier's disease (intradesmosomal separation, diminution in the number of desmosomes and perinuclear aggregation of tonofilaments)[7,21,22] and pemphigus, whereas some differences in detail from Hailey–Hailey disease have been reported.[15]

TREATMENT

It is difficult to assess effectiveness of therapy as some cases spontaneously remit and others show a fluctuating course. Where there is an associated dermatosis, such as an eczematous process, treatment for this is essential as Grover's disease may have been triggered by it.[7] Avoidance of heat and sweat-inducing activities is helpful[10] and rapid temperature changes often aggravate the condition. Emollients to alleviate xerosis are beneficial.[7]

Moderately potent topical corticosteroid creams and ointments and antipruritics are helpful in controlling the pruritus in mild cases. Systemic therapy with prednisolone (25 mg daily initial dose reducing over 2 weeks) is generally effective in the more severe cases, but relapse is frequent on withdrawal of the drug.

Anecdotal reports of success using antibiotics (e.g. tetracycline and erythromycin) and antimycotics (e.g. itraconazole) to treat Grover's disease are to be found in Internet discussion groups, newsletters and other sources, but their apparent success suggests the possibility of an incorrect diagnosis in the first instance rather than a successful therapy for true Grover's disease.

Because of its use in Darier's disease,[23] vitamin A was used in Grover's disease in a relatively high dose (150 000 IU/day) in the early 1980s[24] and this led subsequently to the synthetic retinoids: etretinate, acitretin and isotretinoin.[25,26] The literature contains many examples of retinoid use that testifies to its presumed effectiveness. Double-blind trials have not been performed with either these drugs or with vitamin A.

Photochemotherapy with systemic PUVA therapy has met with some success,[27] but further reports of its use are lacking. However, the phototherapy used now for Grover's disease in Australia tends to be narrowband (nb) UVB (311 mm). Its efficacy in Grover's disease is likely to be a result of its effect on inflammation.

In addition to general measures the authors' favoured regimen for therapy of Grover's disease is: (i) morning emollient, for example 10% glycerine in sorbolene or emulsifying ointment BP; (ii) nightly mometasone furoate 0.1% ointment; with (iii) acitretin 0.3 mg/kg for 2 weeks, then reducing over 4 weeks as the process settles; and (iv) failure to respond promptly to acitretin prompts the addition of nb UVB therapy at 70–100 mJ/cm^2: the starting dose depending on skin type, rather than on minimal erythema dose.

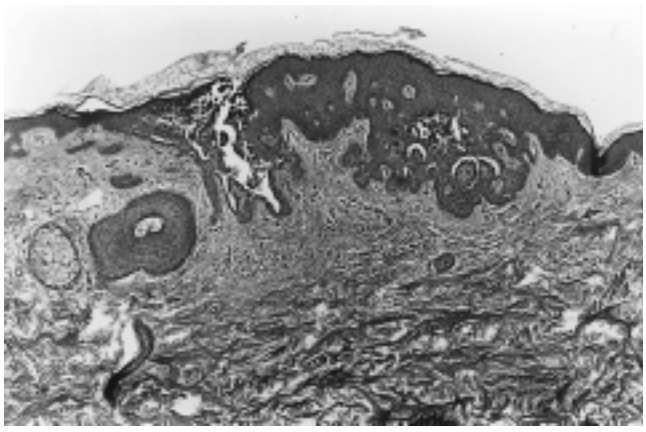

Figure 4 Full-thickness acantholysis (left) in a focus of Hailey-Hailey type, and suprabasal clefting (right) of Darier type (H&E).

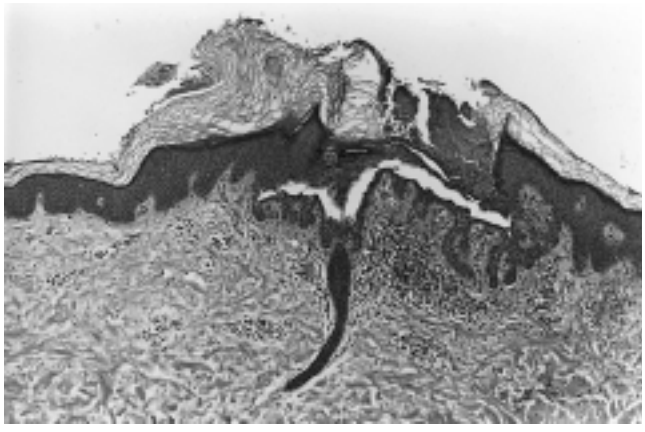

Figure 5 Acantholytic dyskeratosis involving an acrosyringium and adjacent epidermis (H&E).

Although UVB has been reported to trigger acantholysis in other primary acantholytic disorders, such as Darier's disease and Hailey–Hailey disease,[28,29] its anti-inflammatory effect is probably responsible for its efficacy in Grover's disease, as it is in other itching dermatoses. The nb UVB is continued twice or thrice weekly until there is a satisfactory response. The retinoid and phototherapy are reduced gradually as long as there is no recrudescence.

CONCLUSION

Progress in identifying the aetiology of Grover's disease has been slow, but no doubt the next 34 years will produce better answers to this question. Meanwhile, current therapy offers patients symptomatic relief.

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Select the most correct answers — multiple answers possible for questions 1–11

1. Grover's disease:
   a. May be associated with xerosis.
   b. Is not seen in association with malignant disease.
   c. May be seen with bed rest in hospital.
   d. May occur in patients with solar keratoses.
   e. May be associated with seasonal changes.
2. Regarding Grover's disease:
   a. Does not occur in cold climates.
   b. Mainly affects white men in middle to old age.
   c. Has been seen in patients with lymphoma.
   d. Sweating may act as a trigger.
   e. Is known to be caused by pathological changes at the acrosyringium.
3. Regarding pruritus associated with Grover's disease:
   a. May be intermittent.
   b. May be aggravated by heat.
   c. Is always proportional to the number of lesions.
   d. May be absent.
   e. Is short-lived.
4. Lesions of Grover's disease include:
   a. Papules.
   b. Papulovesicles.
   c. Excoriated nodules.
   d. Urticarial weals.
   e. Blisters.
5. Other skin diseases associated with Grover's disease include:
   a. Asteatotic eczema.
   b. Hailey–Hailey disease.
   c. Pemphigus.
   d. Seborrhoeic eczema.
   e. Psoriasis.
6. Patterns of Grover's disease include:
   a. Profuse intensely itchy papules of a few weeks' duration.
   b. Folliculitis-like lesions in submammary area.
   c. Asymptomatic papules.
   d. Pruritic papules of more than 5 years' duration.
   e. A nodular eruption.
7. Aggravating factors in Grover's disease include:
   a. Sweating.
   b. Dry skin.
   c. Coexisting solar dermopathy.
   d. Febrile illness.
   e. Leukaemia.
8. Regarding the course of Grover's disease:
   a. Spontaneous remission does not occur.
   b. May show a fluctuating course.
   c. May be symptomatic and chronic.
   d. Is never transient.
   e. Maximum mean duration is 3 months.
9. Regarding the histopathology of Grover's disease:
   a. Immunofluorescence studies show a consistent pattern of positivity.
   b. Characteristic changes are seen throughout lesions.
   c. Acantholysis occurs only suprabasally.
   d. Bullae are never seen.
   e. Corps ronds may occur.
10. Histopathologically, Grover's disease may resemble:
    a. Pemphigus vulgaris.
    b. Psoriasis.
    c. Pemphigus foliaceus.
    d. Keratosis follicularis.
    e. Hailey–Hailey disease.
11. Regarding treatment of Grover's disease:
    a. Oral corticosteroid therapy leads to permanent clearing in most cases.
    b. PUVA has been a successful therapy.
    c. Treatment with emollients is beneficial.
    d. Double-blind trials confirm effectiveness of etretinate therapy.
    e. Topical corticosteroids may improve pruritus.

Directions for questions 12–23. For each numbered item, choose the appropriate lettered item. There is only one correct answer to be chosen, but the same letter can be chosen more than once in any question.

With respect to questions 12–15:
   a. Number of eosinophils in dermis.
   b. Focal acantholytic dyskeratosis.
   c. Intradesmosomal separation.
   d. Horizontal columns of parakeratosis underlying acantholytic dyskeratosis.

12. Seen in electron microscopic studies of Grover's disease.
13. Present under light microscopy of impetigo biopsies.
14. May correlate with the degree of pruritus in Grover's disease.
15. Seen under light microscopy of Darier-type Grover's disease.

With respect to questions 16–19:
   a. Acitretin.
   b. UVB phototherapy.
   c. Rapid temperature changes.
   d. Erythromycin

16. Can aggravate Grover's disease.
17. Efficacy in Grover's disease is likely to be a result of its anti-inflammatory effect.
18. Reported in the medical literature to help Grover's disease if taken orally.
19. May trigger acantholysis in Hailey–Hailey disease.

With respect to questions 20–23:
   a. Plasma cells.
   b. Grains.
   c. Secondary acantholysis.
   d. Immunodeficiency.

20. Present in the epidermis of Darier-type Grover's disease.
21. Associated with Grover's disease.
22. Present in dermis in excoriated lesions of Grover's disease.
23. Seen in squamous cell carcinoma.

The correct answers for the questions published in Vol. 45, No. 1, are as follows:

1. d, e	9. b, e	17. a
2. c, e	10. b, c, d	18. b
3. a, d, e	11. b, c, d	19. c
4. a, c, e	12. b	20. d
5. b, c	13. b	21. a
6. b, c	14. a	22. b
7. a, c, d, e	15. c	23. c
8. a, b, c, d, e	16. d	

The Australasian College of Dermatologists

Continuing Professional Development Program
Category I

Australasian Journal of Dermatology
Volume 45, No. 2, 2004

Name: ..... **CPDP No.:** .....

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Questions 1–11
Circle the most appropriate answers — multiple answers possible. Each question must have all correct answers circled in order to receive points.

1.	A	B	C	D	E
2.	A	B	C	D	E
3.	A	B	C	D	E
4.	A	B	C	D	E
5.	A	B	C	D	E
6.	A	B	C	D	E
7.	A	B	C	D	E
8.	A	B	C	D	E
9.	A	B	C	D	E
10.	A	B	C	D	E
11.	A	B	C	D	E

Questions 12–23
Circle the correct answer.

12.	A	B	C	D
13.	A	B	C	D
14.	A	B	C	D
15.	A	B	C	D
16.	A	B	C	D
17.	A	B	C	D
18.	A	B	C	D
19.	A	B	C	D
20.	A	B	C	D
21.	A	B	C	D
22.	A	B	C	D
23.	A	B	C	D

Pass Mark: 75% (if you obtain this mark or higher you will be granted 1.5 hours Category 1 CPDP credit).

If you feel the need to indicate ambiguity in a question, please do not write comments on the answer sheet.

Please return your answer sheet to College by 1 July 2004. Answer sheets received after this date will not be accepted.