

## CONTINUING PROFESSIONAL DEVELOPMENT PROGRAM

# Prurigo nodularis: A review

Michael R Lee and Stephen Shumack

Department of Dermatology, Royal North Shore Hospital, Pacific Highway, St Leonards, New South Wales, Australia

### SUMMARY

Prurigo nodularis is a chronic condition characterized by a papulonodular pruriginous eruption of unknown aetiology. This condition is a difficult disease to treat and causes frustration to both the patient and the treating doctor. A variety of systemic conditions have been reported to be associated with prurigo nodularis. The mechanism by which these disorders may trigger prurigo nodularis is unknown. Nerve growth factor has been implicated in the pathogenesis of prurigo nodularis. Calcitonin gene-related peptide and substance P immunoreactive nerves are markedly increased in prurigo nodularis when compared with normal skin. These neuropeptides may mediate the cutaneous neurogenic inflammation and pruritus in prurigo nodularis. Topical or intralesional glucocorticoids are the treatment of choice. Other topical treatments such as topical vitamin D<sub>3</sub>, and topical capsaicin have also been reported to be effective. Oral treatments such as cyclosporin and thalidomide have been shown to improve both appearance of the skin and pruritus. We review the clinical features, associations, pathology, pathogenesis and treatment of prurigo nodularis.

**Key words:** calcitonin gene-related peptide, circumscribed neurodermatitis, lichen simplex chronicus, nerve growth factor, picker nodules, substance P.

### INTRODUCTION

Hyde first described pruritic nodules on the extensor surfaces of the lower extremities in middle-aged women and labelled the condition PN.<sup>1</sup> Since that time cases affecting

children and men have also been reported.<sup>2</sup> Individuals with PN can be divided into those who are atopic and non-atopic.<sup>3</sup> In the setting of atopy, PN has an earlier age of onset and may be accompanied by cutaneous hypersensitivity to various environmental allergens.

### CLINICAL FEATURES

The classic lesion in PN is a firm pruritic nodule that is hyperkeratotic, numbers from few to hundreds, and ranges from several millimetres to 2 cm in diameter. There is a tendency for symmetrical distribution, with a predilection for extensor surfaces of the limbs; however, the trunk may be involved. The face and palms are seldom affected although no part of the body is exempt.<sup>4</sup> A linear arrangement of the PN lesions is common and prominent features include crusting and excoriations with post-inflammatory hyperpigmented and hypopigmented macules. The skin between the lesions is usually normal but can be xerotic or lichenified.<sup>5</sup>

### AETIOLOGY

The aetiology of PN remains unknown. There is uncertainty as to whether PN is a primary cutaneous disease or whether it is a pathological reaction secondary to pruritus and scratching provoked by a separate cause.

A variety of systemic conditions have been reported to be associated with PN (Table 1). The mechanism in the majority of associated diseases that have been reported is unclear and the link between PN and these associated disorders is based on case reports. Psychosocial disorders such as depression and anxiety may be postulated to be a primary association or secondary to the itch in PN.<sup>4</sup> Secondary

#### Abbreviations:

$\alpha$ -MSH	$\alpha$ -melanocyte stimulating hormone
Ig	immunoglobulin
NGF	nerve growth factor
NGFr	nerve growth factor receptor
PDL	pulsed dye laser
PN	prurigo nodularis
TNF	tumour necrosis factor
trk	tyrosine kinase

Correspondence: Dr Michael R Lee, Department of Dermatology, Royal North Shore Hospital, Pacific Highway, St Leonards, NSW 2065, Australia. Email: mick155@bigpond.net.au  
Michael R Lee, MB BS. Stephen Shumack, FACD.  
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hyperparathyroidism<sup>10</sup> and higher dermal levels of calcium, magnesium and phosphorous may result in microprecipitation of calcium or magnesium phosphate salts in the skin and may be the cause of uraemic pruritus.<sup>11</sup> Aluminium toxicity has been considered as a cause of severe uraemic pruritus and PN in a case series of dialysis patients.<sup>12</sup> Three maintenance haemodialysis patients with PN and aluminium overload were treated with an aluminium chelating agent and their skin lesions disappeared after treatment. A case of a moderately differentiated tubular adenocarcinoma of the stomach has been reported to be associated with PN.<sup>15</sup> Transforming growth factor- $\beta$  is known to be produced by gastric malignancies and it is postulated that this results in eosinophilia. Additionally, epidermal growth factor, which stimulates keratinocytes, has been reported to be elevated in gastrointestinal carcinomas that might contribute to PN lesions.<sup>15</sup>

**Table 1** Disorders reported in association with prurigo nodularis

Associated disorder	Reference no.
Focal causes of pruritus	
Insect bite reactions	4
Venous stasis	4
Folliculitis and discoid eczema	4
Psychosocial disorders	4
Hyperthyroidism	6
Haematological	
Iron-deficiency anaemia	4
Polycythaemia rubra vera	6
Lymphoma	7
Leukaemia	8
Chronic renal failure	9–12
Gastrointestinal	
Gluten-sensitive enteropathy (coeliac disease)	15,14
Gastric malignancy	15
Obstructive biliary disease	16
$\alpha$ -1 antitrypsin deficiency	17
Infectious diseases	
Mycobacteriae ( <i>M. avium-intracellulare</i> and <i>M. malmoense</i> )	18
HIV	19
Hepatitis B virus	20
Hepatitis C virus	21

It is postulated that the extrahepatic manifestations of hepatitis C may be attributed to the appearance of circulating immune complexes that may be deposited in the skin.<sup>21</sup> Several mechanisms for HIV involvement in PN have been postulated. Direct viral infection of peripheral nerves by HIV could possibly stimulate pruritus<sup>22</sup> and it has been demonstrated that viral infection of nerves can cause the direct release of substance P.<sup>25</sup> Prurigo nodularis in HIV infection may result from an immunological abnormality within the skin. Infection with HIV is associated with a reversal of the normal CD4 : CD8 ratio and this may result in faulty recognition of one or more endogenous proteins. Additionally, it has been demonstrated that there is a reduction in the number of Langerhans cells that function abnormally, resulting in faulty antigen processing and presentation.<sup>23</sup> Patients with HIV infection also have increased titres of IgE directed to HIV-1, levels that rise as CD4 counts diminish. Finally, because HIV infection leads to polyclonal activation of B-cells, the possibility of immune-complex deposition has been proposed as a possible aetiology of PN.<sup>24</sup>

## PATHOLOGY AND PATHOGENESIS

Histologically, PN is characterized by marked hyperkeratosis, often focal parakeratosis, and marked irregular acanthosis that is often of pseudoepitheliomatous proportions. The characteristic neurological changes observed include hypertrophy and proliferation of dermal nerves.<sup>25</sup> Calcitonin gene-related peptide<sup>26–28</sup> and substance P<sup>26,27</sup> immunoreactive nerves are markedly increased in PN. These neuropeptides may mediate the cutaneous neurogenic inflammation and pruritus in PN. Table 2 outlines the neuropeptides involved in PN and their actions.

There are increased numbers of Merkel cells in the epidermis of PN nodules that have been postulated to be a component of the neurocutaneous abnormality.<sup>59</sup> The inflammatory infiltrate in the dermis includes lymphocytes, mast cells, histiocytes and occasionally eosinophils.<sup>25</sup>

Mast cells in PN lesions are increased in number and show characteristic morphological changes such as an enlarged cell body size and a dendritic shape compared with the round or elongated shape seen in normal

**Table 2** Neuropeptides in prurigo nodularis

Neuropeptide	Changes in prurigo nodularis	Actions	Reference
Substance P	Increased	Stimulates expression of intercellular adhesion molecule 1 and vascular cell adhesion molecule 1	29
		Activates mast cells to secrete tumour necrosis factor- $\alpha$ , histamine, prostoglandin D2 and leucotriene B	30–35
		Activate keratinocytes to secrete interleukin 1	34,35
		Vasodilation and protein extravasation	36
		Enhances chemotaxis and proliferation of fibroblasts	37
		Enhances growth of keratinocytes	37,38
Calcitonin gene-related peptide	Increased	Vasodilation and protein extravasation	36
		Induces interleukin 8 production in dermal microvascular endothelial cells	31

skin.<sup>40-42</sup> The PN mast cells also have an abundant cytoplasm with a decreased number of granules inside, suggesting that many of the granules have been released into the surrounding tissue.<sup>40</sup> Mast cells, which are known to release NGF, are seen in close proximity to nerves expressing increased levels of NGFr.<sup>40,45,44</sup> Nerve growth factor has, therefore, been implicated in the pathogenesis of PN and its known actions are listed in Table 3.<sup>45</sup> A study has demonstrated that NGF is overexpressed in PN, which could lead to neurohyperplasia.<sup>45</sup> The NGFr is made up of two components: a trk high-affinity receptor and p75, a low-affinity receptor. The expression of both subunits is increased in the perineurium cells and Schwann cells of the hyperplastic nerves found in lesional PN skin. This may result in increased NGF binding and hence neural hyperplasia.<sup>57,58</sup> Subsequently, neural hyperplasia could be related to the strong itch caused by increased axon firing.<sup>57-59</sup> The increased NGF-NGFr interaction may not only cause itch through neurohyperplasia but may also contribute to the release of neuropeptides that initiate and mediate neurogenic inflammation.<sup>58</sup> Other mast cell products that may contribute to pruritus in PN are listed in Table 4.

Eosinophils containing eosinophil cationic protein,<sup>70</sup> eosinophil-derived neurotoxin/eosinophil protein X<sup>70</sup> and major basic protein<sup>41</sup> are increased in lesional PN skin and are in close proximity to afferent sensory nerves. The eosinophilic granular proteins exacerbate inflammation and are responsible for damaging nervous tissue<sup>71</sup> and organisms such as parasites.<sup>72</sup> This close relationship between nerves and eosinophils suggests

that eosinophil cationic protein and eosinophil-derived neurotoxin/eosinophil protein X can be released to local tissue and cause injury that may be manifested as itch. Additionally, it has been reported that eosinophils can release NGF and may contribute to the neurohyperplasia in PN.<sup>45</sup>

Endothelial cells in the upper dermis of PN lesional skin express  $\alpha$ -MSH.<sup>75</sup> It has been postulated that one of the roles of  $\alpha$ -MSH is to act as an immune suppressor in inflammation.<sup>74</sup> The role of  $\alpha$ -MSH in PN is presently unknown, although its function may be to counter the cutaneous inflammation.

Dermal Langerhans cells, unlike epidermal Langerhans cells, are increased in PN.<sup>75</sup> This suggests that dermal Langerhans cells and other dermal dendritic cells may be implicated in the development or persistence of PN.

## TREATMENT

Prurigo nodularis is a challenging condition to treat and causes significant frustration to both the patient and the treating doctor. It is important that the patient is informed of the natural history of the disease and its resistance to therapy. The difficulty in treating this disease is reflected in the number of treatments. Once the itch-scratch cycle 'takes over', it is extremely difficult to stop.

## Investigations

An important first step in therapy is to identify any underlying associations and treat accordingly. Table 5 lists the suggested investigations for these underlying associations. Biopsies requesting histopathology and direct and indirect immunofluorescence studies may be indicated, as pemphigoid nodularis that precedes bullous pemphigoid may present as PN.<sup>76</sup> Serum IgE levels may be elevated in atopic PN patients.<sup>5</sup> Patch testing should be performed to exclude contact sensitivity to metals, fragrances or other chemical compounds.<sup>77</sup>

## General measures

Simple measures such as clipping the fingernails and recommending the use of gloves or mittens can be helpful. Table 6 outlines the topical and systemic treatments currently used for PN. It is important to stress to the patient the requirement to apply emollients as xerosis usually worsens the pruritus.

**Table 5** Actions of nerve growth factor

Actions of nerve growth factor	Reference
Normal development and survival of peripheral nervous system	46, 47
Chemotactic for neurones	48
Upregulates expression of substance P and calcitonin gene-related peptide in neurones	49,50
Increases number of mast cells	51
Promotes myeloid progenitor cell growth	52
Induces proliferation and differentiation of B lymphocytes	53
Enhances histamine release by basophils	54
Accelerates cutaneous wound healing	55
Chemotactic for melanocytes	56

**Table 4** Mast cell products that are mediators of itch

Mediator	Mechanism underlying pruritic potency	Reference
Histamine	Induction of itch via H1-H5 receptor stimulation present on sensory nerve fibres	60
Tryptase	Induction of itch via proteinase-activated receptor 2 stimulation	61, 62
Prostaglandins	Potentiates histamine-induced itch	63, 64
Leucotrienes	Unknown	
Interleukins 2,4,6	Interleukin 2 activates subpopulation of cutaneous C-fibres. Interleukin 6 acts on its receptor expressed in nerve and Schwann cells	65-69

**Table 5** Suggested investigations for associated disorders in prurigo nodularis

Full blood count
Liver function tests
Urea, creatinine and electrolytes
Parathyroid hormone level
Thyroid function tests
Hepatitis serology
HIV serology (if indicated)
Total serum IgE levels
Tuberculin skin testing (Mantoux test)
Skin biopsies for
– histopathology
– direct immunofluorescence
– microscopy (Ziehl–Nielsen stain) and culture
Indirect immunofluorescence
Patch testing

### First-line agents

Topical antipruritics such as 1% menthol or phenol in a creamy base may be used to reduce the itch. Oral antihistamines such as promethazine hydrochloride 25–75 mg at night, or oral antidepressants such as doxepin 10–75 mg at night may be administered to reduce the pruritus.

Potent topical glucocorticoid creams or ointments, such as betamethasone dipropionate 0.5 mg/g, glucocorticoid creams under occlusion, and intralesional glucocorticoids, such as triamcinolone acetonide 10 mg/mL increasing to 40 mg/mL suspension, are often employed. Occlusive bandages are useful as they interrupt the itch–scratch cycle.

### Second-line agents

UV light exposure has been shown to lessen the pruritus and can be beneficial in the treatment of PN.<sup>78,79</sup> The main effect of UV light treatment in PN is to break the cycle of itching and scratching. In a Scandinavian study, bath PUVA was shown to be efficacious in 13 of 15 patients.<sup>78</sup> In one study, patients preferred 8-methoxypsoralen topical PUVA over more painful therapies such as intralesional glucocorticoids.<sup>79</sup> Broadband (presumed, although not stated in the article) UVB has been reported to be more effective than 8-methoxypsoralen topical PUVA in cases with generalized PN.<sup>79</sup>

Cryotherapy is a useful therapeutic agent for the treatment of PN.<sup>80,81</sup> The total time of liquid nitrogen applied to the nodules varies from 10–30 s with two to four freeze–thaw cycles depending on the size of the nodule. Blistered nodules may take 2–4 weeks to heal and be replaced by hypopigmented macules. Cryotherapy is thought to cause destruction of sensory nerves and impairment of nerve regeneration.<sup>98,99</sup> Treated patients may not complain of pruritus for up to 3 months.<sup>81</sup> A combination of cryosurgery, intralesional triamcinolone acetonide 40 mg/mL diluted 1:3 with lignocaine 1% may be an effective method for treatment of PN.<sup>82</sup> The immediate post-cryosurgical erythema that develops as the thaw wears off represents an oedematous state that facilitates the injection of triamcinolone acetonide.

**Table 6** Current treatments available for prurigo nodularis

Treatment	Reference
Topical antipruritics: menthol and phenol	
Oral antihistamines: promethazine hydrochloride	
Oral tricyclic antidepressants: doxepin	
Topical and intralesional glucocorticoids	
Narrow-band UVB, and PUVA	78,79
Cryotherapy	80–82
Topical vitamin D	83,84
Capsaicin	85–87
Cyclosporin	88
Thalidomide	89–95
Laser	96
Naltrexone	97

Recently, topical vitamin D3 has been reported to be effective in the treatment of PN.<sup>83,84</sup> Vitamin D3 downregulates cellular adhesion molecule expression by inhibiting TNF- $\alpha$  mRNA expression.<sup>100</sup> Vitamin D3 also reduces the number of epidermal FcR1+ dendritic cells in PN lesions. A double-blind, right/left comparison of calcipotriol ointment (50  $\mu$ g/g) and betamethasone valerate ointment (0.1%) in the treatment of PN has shown calcipotriol to be more efficacious in reducing the size and number of pruriginous nodules.<sup>84</sup>

Capsaicin has been shown to reduce pruritus and induce complete disappearance of lesions.<sup>85–87</sup> When applied topically it induces itch and a burning sensation as well as erythema.<sup>101,102</sup> Capsaicin exerts its effects via binding to the vanilloid receptor, which is located on free nerve endings. Repeated topical application of capsaicin releases and prevents specifically the accumulation of neuropeptides in unmyelinated polymodal C-type and small myelinated A $\delta$ -type cutaneous nerves. Nociceptive sensations are mediated by these nerve fibres and depleting neuropeptides from these nerves impede the perception of pain and itch sensations, whereas tactile sensations remain.<sup>105–105</sup> A study of 33 patients with PN treated with topical capsaicin (dose range from 0.025% to 0.3%) four to six times daily for 2 weeks up to 10 months demonstrated complete remission of itching in all within 12 days.<sup>86</sup> On average, concentrations of 0.05%, 0.075% and 0.1% appeared to be the most effective. After discontinuation of capsaicin, pruritus returned in 16 of 33 patients within 2 months. Capsaicin is no longer commercially available in Australia. It also should be applied four to six times daily to prevent reaccumulation of neuropeptides and recurrence of itch. Capsaicin is an effective and safe approach to the treatment of PN; however, the practicality of capsaicin therapy is limited by the high application frequency and high recurrence after discontinuation of therapy.

### Third-line agents

Cyclosporin has demonstrated unequivocal improvement of PN as well as a reduction in the severity of pruritus.<sup>88</sup> Cyclosporin inhibits lymphokine transcription and lymphocyte activation and proliferation.<sup>88</sup> Oral doses of

3.5–4 mg/kg/day for periods of 24–36 weeks have demonstrated a reduction in the severity of pruritus after 2 weeks. However, the use of cyclosporin is limited by its side-effects of hypertension and renal damage and relapse of disease after cessation of treatment. Regular monitoring of the patient is required while on cyclosporin.

The first reported use of thalidomide in the treatment of PN was in 1975.<sup>89</sup> Thalidomide inhibits polymorphonuclear leucocyte chemotaxis and selectively inhibits TNF- $\alpha$  production by enhancing degradation of TNF- $\alpha$  mRNA.<sup>106</sup> It has been postulated that thalidomide causes central nervous system depression without causing incoordination, respiratory depression or narcosis.<sup>90</sup> Through its central sedative effect, it causes a decreased perception of peripheral stimuli. Thalidomide may have a direct peripheral action on the proliferated neural tissue in the lesions causing PN.<sup>90</sup> There have been reported cases where oral thalidomide at doses of 200 mg daily demonstrated improvement of pruritus and flattening of lesions with no serious adverse events.<sup>90,91</sup> It was not until a study of eight patients that the neurotoxic side-effects were reported.<sup>92</sup> Seven of the eight patients developed a predominantly sensory neuropathy mainly involving the lower limbs after 6–14 months of thalidomide. An oral daily dose of 150–400 mg thalidomide was initially given, after which it was gradually reduced to a daily dose of 25–100 mg. Their PN improved dramatically, but treatment had to be discontinued due to sensory neuropathy. In three of the patients followed up, the neuropathy was irreversible. An Australian case series demonstrated improvement in pruritus and a decrease in nodules in three of five patients with PN treated with oral thalidomide.<sup>95</sup> Remissions were not achieved in any PN patient. This was thought to be due to the low thalidomide doses (100–200 mg). Three adverse events were reported, two of which were peripheral neuropathy. Other adverse events reported included dizziness, angina and poor control of blood glucose levels associated with underlying diabetes mellitus.

Zinc and iron concentrations in lesional skin have been reported to be increased in PN.<sup>94</sup> Four patients received oral thalidomide at a dose of 300–400 mg/day. In one patient, a remission time of 17 months was achieved and this was associated with a decrease in the lesional zinc and iron concentrations towards that of uninvolved skin. In a second patient, a lesion on the elbow demonstrated clinical improvement for 7 months and this again correlated with a reduction in the lesional zinc and iron concentrations. Treatment with thalidomide decreased the lesional zinc and iron levels towards the reference range.<sup>94</sup> Other reports have confirmed the efficacy of thalidomide with its immediate pronounced effect on pruritus and significant decrease in the size and number of skin lesions.<sup>20,107</sup>

Sequential combined therapy with thalidomide and narrow-band UVB has demonstrated improvement in PN with minimal side-effects. The side-effects of the two therapies are distinct and not synergistic.<sup>95</sup> In a prospective open label trial, four patients received oral thalidomide 100 mg daily for 8–16 weeks (average 12 weeks) then narrow-band UVB treatment was initiated. After a mean of eight narrow-band UVB treatments (6–12 treatments), the pruritus had

decreased dramatically and most lesions had disappeared. Thalidomide therapy was ceased while narrow-band UVB therapy was maintained until complete remission was achieved. This occurred after an average of 52 narrow-band UVB treatments. After a median follow up (after the end of treatment) of 6 months (4–18 months), only one needed topical glucocorticoids to control minor symptoms.

Thalidomide is currently an unregistered drug in Australia and prescribing is through the Special Access Scheme on an individual basis. Its use is restricted to severe disabling conditions that cause an unacceptable interference with normal life, and only after other treatments have been trialled and failed.

Little data have been reported on the use of laser in the treatment of PN. One patient with PN was successfully treated with a 585 nm PDL using a 5-mm beam at an energy fluence of 6.5 J/cm<sup>2</sup>.<sup>96</sup> Treatment was performed six times at weekly intervals 1 hour after the application of topical anaesthesia. After six treatment sessions the lesions resolved. The PDL emits the wavelength that is close to one of the absorption peaks of oxyhaemoglobin. The rationale for the use of PDL is that one of the histological features in PN is vascular hyperplasia and this vascular hyperplasia may provide the PDL with a high density of oxyhaemoglobin to act as its target chromophore. The treatment is well tolerated with a low risk of scarring.

Naltrexone has been reported to have a high antipruritic effect in patients with PN.<sup>97</sup> Opiates have been shown to evoke or potentiate itch, independently from their histamine-releasing effect.<sup>108,109</sup> The actions of the opiates results from binding to peripheral and central opiate receptors.<sup>110</sup> As pruritus is modified by opioids, antagonizing opioids suppress localized and systemic pruritus. In 17 patients with PN, nine had an improvement of 50% or more in pruritus. Naltrexone 50 mg daily orally was shown to reduce scratching, which led to the subsequent re-epithelialization of lesions, flattening and softening of nodules, and final healing with some scarring and hyperpigmentation. Relief of pruritic symptoms can be observed within 2–8 days.<sup>97</sup> The half-life of naltrexone is approximately 9 hours,<sup>111</sup> therefore after discontinuation of naltrexone, abrupt exacerbation of pruritus may occur. Contraindications for the use of naltrexone include severe liver insufficiency, acute hepatitis, pregnancy, breast-feeding and opiate abuse.

A case report of an experimental oral retinoid, arotinoid acid Ro-137410, has demonstrated a reduction in the degree of pruritus and nodule formation.<sup>112</sup> Arotinoid acid is the active metabolite of arotinoid ethyl ester. It has antitumour, antimetaplastic, differentiation-inducing, anti-inflammatory and immunomodulatory properties.<sup>115</sup> Etretinate 50–75 mg/day has also been reported experimentally to reduce the severity of pruritus and the size of itching nodules.<sup>114</sup>

## CONCLUSION

Prurigo nodularis presents as a treatment dilemma for doctors and is frustrating to patients. There remain many

unanswered questions regarding the aetiology of PN. While PN may be associated with a systemic disorder, it is the repetitive rubbing, scratching and picking of the skin that perpetuates the disease.

Recent understanding of molecular changes in PN offers an exciting approach for dermatologists to the novel treatment of PN involving the neuro-endocrine axis. Pharmacological agents for research and the development of new therapies will include those that antagonize or deplete neuropeptides such as calcitonin gene-related peptide and substance P, neuropeptide receptor antagonists, proteases that degrade neuropeptides, and agents that antagonize the effects of neurotrophins at either the ligand or the receptor level. These novel approaches will hopefully bring about skin homeostasis in diseased states and may be beneficial for the treatment of not only PN but also other inflammatory disorders. Further studies are warranted to assess the role of these therapies in the therapeutic armamentarium for PN.

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## Continuing Professional Development Program

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

1. Regarding the clinical features of prurigo nodularis (PN):
    - a. There is a tendency for asymmetrical distribution.
    - b. There is a predilection for extensor surfaces of limbs.
    - c. Post-inflammatory hypopigmentation may occur.
    - d. Lesions are often in a linear arrangement.
    - e. The face is never affected.
  2. With respect to the aetiology of PN:
    - a. Iron-deficiency anaemia has been associated.
    - b. Insect bites are not associated.
    - c. Aluminium toxicity has been postulated as a causal factor in some cases.
    - d. HIV may be involved in some cases.
    - e. Hepatitis C virus has not been linked.
  3. Histopathological features of PN include:
    - a. Hyperkeratosis.
    - b. Focal parakeratosis.
    - c. Regular acanthosis.
    - d. Decreased numbers of Merkel cells in the epidermis.
    - e. Hypertrophy of dermal nerve fibres.
  4. Substance P in PN:
    - a. Suppresses expression of intercellular adhesion molecule 1.
    - b. Stimulates expression of vascular adhesion molecule 1.
    - c. Activates mast cells to secrete tumour necrosis factor- $\alpha$ .
    - d. Induces vasoconstriction.
    - e. Enhances proliferation of fibroblasts.
  5. Nerve growth factor in PN:
    - a. Upregulates expression of substance P in neurones.
    - b. Downregulates expression of calcitonin gene-related peptide in neurones.
    - c. Increases mast cell numbers.
    - d. Enhances histamine release by basophils.
    - e. Decreases wound healing.
  6. Mast cells in PN:
    - a. Are increased in number in lesions.
    - b. Show similar morphological characteristics to those in normal skin.
    - c. Are known to release nerve growth factor.
    - d. Produce interleukin 6.
    - e. Produce tryptase.
  7. Thalidomide:
    - a. Enhances degradation of tumour necrosis factor- $\alpha$ .
    - b. Does not cause respiratory depression.
    - c. Induced sensory neuropathy is always reversible.
    - d. Induced improvement in PN is associated with a decrease in lesional zinc and iron levels.
    - e. May adversely affect blood sugar control in diabetic patients.
  8. With regard to the treatment of PN:
    - a. Topical 1% menthol or phenol cream may be used to reduce pruritus.
    - b. The oral tricyclic antidepressant doxepin 10–75 mg nocte can be used to reduce pruritus.
    - c. Emollients do not help to relieve pruritus.
    - d. Topical cryotherapy to individual nodules has not been reported to alleviate the pruritus of PN.
    - e. Calcipotriol ointment has been shown more efficacious than betamethasone valerate 0.1% ointment in reducing the size and number of pruriginous nodules.
  9. With regard to capsaicin:
    - a. Topical application causes itch, erythema and a burning sensation.
    - b. Binds to the vanilloid receptor on free nerve endings.
    - c. 1% cream is the most effective concentration for PN.
    - d. Prevents accumulation of neuropeptides in unmyelinated polymodal C-type cutaneous nerves.
    - e. Discontinuation results in increased pruritus rates for PN.
  10. In the treatment of PN:
    - a. Cyclosporin increases lymphokine transcription.
    - b. Pulsed dye laser has not been shown to be effective.
    - c. Naltrexone reduces scratching.
    - d. Naltrexone may be used in pregnancy and lactation.
    - e. PUVA therapy has been reported to be effective.
  11. Regarding PN:
    - a. Pulsed dye laser has a high risk of scarring.
    - b. Etretinate 50–75 mg/day has been reported to reduce the size of nodules.
    - c. Pruritic nodules may be up to 2 cm in diameter.
    - d. May cause secondary depression.
    - e. Only affects middle-aged women.
- Directions for questions 12–25. For each numbered item, choose the appropriate lettered item. There is only one correct answer to be chosen and the same letter cannot be chosen more than once in any question.
- With respect to questions 12–15:
- a. Transforming growth factor- $\beta$ .
  - b. Aluminium chelating agents.
  - c. Elevated levels of epidermal growth factor.
  - d. Secondary hyperparathyroidism.
12. Seen in PN associated with gastric carcinoma.
  13. Used to treat PN in some cases.
  14. Causes eosinophilia.
  15. Associated with uraemic pruritus.
- With respect to questions 16–19:
- a. Eosinophilic granular base proteins.
  - b. Calcitonin gene-related peptide.
  - c. Microprecipitation of magnesium phosphate salts in the skin.
  - d. Tyrosine kinase high-affinity receptor.
16. May cause uraemic pruritus.
  17. Increased in Schwann cells of hyperplastic nerves in PN lesions.
  18. Induces interleukin 8 production in dermal microvascular endothelium.
  19. Involved in damage to parasitic organisms.
- With respect to questions 20–25:
- a. Dermal Langerhans cells.
  - b. Prostaglandins.
  - c. Increased axon firing.
  - d.  $\alpha$ -Melanocyte stimulating hormone.
20. Expressed by endothelial cells in upper dermis in PN lesions.
  21. Basis of severe itch in PN.
  22. Implicated in persistence of PN lesions.
  23. Potentiate histamine-induced itch.
- The correct answers for the questions published in Vol. 46, No. 3, are as follows:
- |          |           |       |
|----------|-----------|-------|
| 1. a,b,d | 10. c,d,e | 19. b |
| 2. c,d,e | 11. a,b   | 20. c |
| 3. a,c   | 12. b     | 21. b |
| 4. b,e   | 13. c     | 22. d |
| 5. a,c,e | 14. a     | 23. a |
| 6. a,c,d | 15. d     |       |
| 7. d,e   | 16. c     |       |
| 8. a,d   | 17. a     |       |
| 9. b,c,e | 18. d     |       |

# The Australasian College of Dermatologists

## Continuing Professional Development Program Category I

*Australasian Journal of Dermatology*  
Volume 46, No. 4, 2005

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

State:.....

### 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 12–25

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 January 2006. Answer sheets received after  
this date will not be accepted.**