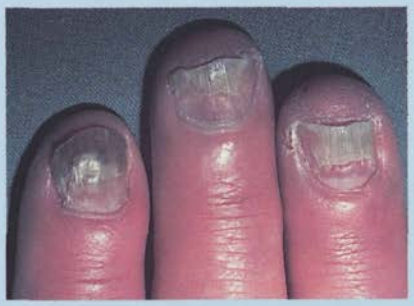
Fungal Infection of the Nail

Second Edition



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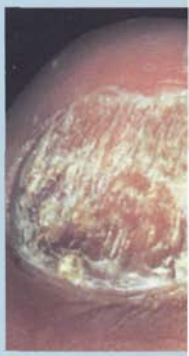

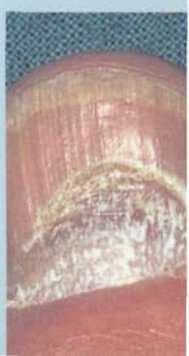

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Contents

Chapter One

Introduction

The distorted, discoloured or otherwise damaged nail is of mechanical and cosmetic importance to the patient as well as being of diagnostic significance. The integrity of the nail plate can be disturbed by a number of factors which may reflect the patient's age, occupation and general health as well as by specific disease of the nail itself.

The main aim of this small book is to discuss the diagnosis and therapy of fungal infection of the nail (onychomycosis). It is important that fungal infections, which can be treated effectively, are correctly diagnosed and differentiated from other nail disorders, the majority of which are irremediable in terms of direct treatment.

Fungal infections are common but there is a tendency for those not experienced in the examination of nails to diagnose almost every abnormality as 'fungal' and to subject the patient to weeks, months or even years of pointless treatment. In order to evaluate properly the patient with possible onychomycosis, it is necessary to relate the nail changes to the structure of normal nail and to those changes seen in other disorders. Dermatophyte infection (dermatophytosis) is the commonest fungal nail disorder and will therefore be given most attention in this book, particularly in view of

recent significant developments in therapy. However, other fungi can and do attack nails and are not always amenable to the same treatment, thus they must be differentiated from dermatophytes.

Chapter Two

Nail Structure

Some knowledge of the structure and property of normal nail is necessary in order to appreciate the patterns of change seen in nail disease.

The nail plate consists of keratin formed by flattening of the keratinocytes of the matrix followed by fragmentation of their nuclei and condensation of the cell cytoplasm to form a flat, compact, horny layer. The matrix extends forward from beneath the proximal nail fold

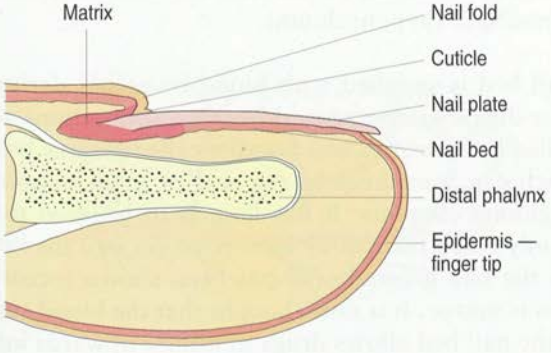

Fig. 1. Structure of the nail

and is delineated by the lunula or 'half moon' which marks its distal end. About one quarter of the nail is beneath the nail fold and the exposed part is attached to the nail bed which has a profuse blood supply thus providing the nail with its pink colour. The tip of the nail which is not attached to the nail bed is an opaque white colour and this can extend down the nail if it becomes detached from the bed, a condition known as onycholysis. The area immediately adjacent to the junction of the nail plate and the nail bed is known as the hyponychium.

The nail fold is attached to the nail plate via the cuticle, which is watertight. When the cuticle becomes detached from the nail plate its waterproof properties are lost allowing various organisms and irritants to wash under it and potentially setting up infection or irritation in the area of the matrix. The nail fold swells in such circumstances, detaching the cuticle even further and a vicious circle of infection and inflammation is set up. This is known as chronic paronychia and it will ultimately distort the nail plate proximally. This will in turn delay the reattachment of the cuticle.

Some fungi, notably *Candida*, enter the nail by this route but the portal of entry of dermatophyte fungi, the main pathogens of nails, is through the distal and lateral undersurface (hyponychium).

The nail bed is supplied with blood by arches derived from the digital arteries. Arterio-venous connections are controlled by neurovascular bundles called glomus bodies which can sometimes be the seat of small tumours called glomus tumours. It has long been believed that drugs only reach the nail by incorporation into the keratin as the nail grows but it has been shown recently that this is untrue. It is now thought that the blood supply to the nail bed allows drugs to diffuse upwards into all parts of the nail and not, as previously believed, only

into the proximal area of the matrix. Therefore antifungal drugs arrive at the nailtip in adequate concentration within a few weeks of the start of treatment; a consideration which is likely to be important in terms of length of therapy with the newer antifungal drugs.

In addition to keratin the rigid structure of nail contains numerous trace minerals. Calcium is found in moderate concentration but there is little evidence to support the widely held belief that it contributes directly to nail hardness.

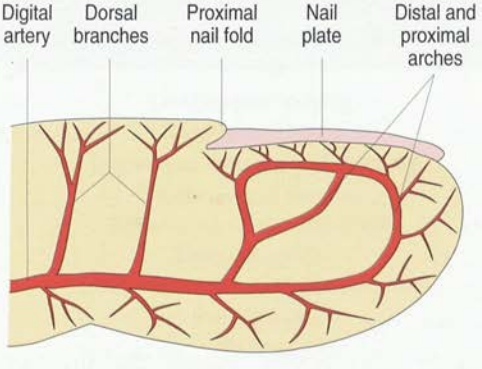

Fig. 2. Blood supply of the nail

NAIL STRUCTURE

POINTS TO NOTE

1. Nail itself is translucent. The pink colour is provided by the nail bed and will change to white whenever the nail becomes detached from the bed.

2. The cuticle must remain attached to the nail plate to keep it waterproof.

3. Antifungal drugs can probably diffuse into the whole length of the nail simultaneously.

Fig. 3. Nail structure: points to note

Chapter Three

Types of Abnormality

Nail disease can affect just the nail plate or the perionychial tissues or both. The disorders which involve the nail plate may alter nail configuration, modify the nail surface or lead to colour change. Some common physical signs which are often confused with fungal infection are discussed below. Other well recognised abnormalities are less frequently mistaken for fungal nail disease and therefore are not discussed in detail.

PHYSICAL SIGNS OFTEN CONFUSED WITH FUNGAL INFECTION OF THE NAIL

Longitudinal ridging
Transverse ridging
Transverse layering and splitting
Thickening of the nail
Separation of the nail plate
Discolouration
Inflammation around the nail fold
Painful nails
Pitting

Fig. 4. Physical signs often confused with fungal infection of the nail

Longitudinal Ridging

LONGITUDINAL RIDGING	
Physical signs	**Underlying causes**
Shallow parallel furrows	Age Twenty nail dystrophy Lichen planus Rheumatoid arthritis Peripheral circulatory disorders Several genetic diseases
Deeper parallel furrows	Lichen planus Alopecia areata Darier's disease Trauma
Deep wide longitudinal groove	Tumours eg. myxoid cysts and warts
Single longitudinal defect usually in thumb nail	Median nail dystrophy

Fig. 5. Causes of longitudinal ridging

Shallow parallel furrows separated by low ridges are physiological and become more prominent with age. They can also occur to a pathological degree in twenty nail dystrophy, lichen planus, rheumatoid arthritis, peripheral circulatory disorders and several genetic diseases.

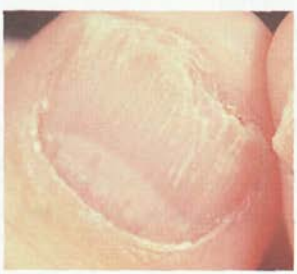

Fig. 6. Shallow parallel furrows in twenty nail dystrophy

Deeper parallel furrows can become discoloured by ingrained dirt and may be severe enough to result in splitting of the free edge of the nail. They may be seen in lichen planus, alopecia areata, Darier's disease and trauma.

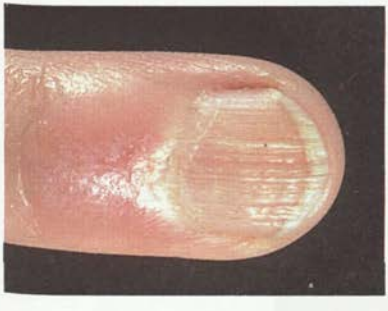

Fig. 7. Longitudinal ridging due to lichen planus

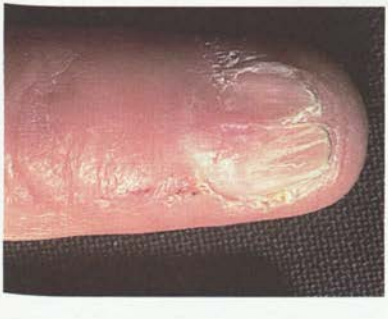

Fig. 8. Lichen planus showing pterygium

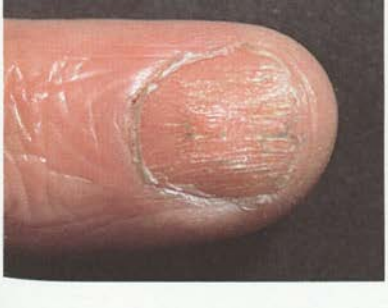

Fig. 9. Alopecia areata affecting the nail

Tumours such as **myxoid cysts** and **warts** located in the proximal nail fold sometimes exert pressure on the matrix and produce a deep, wide longitudinal groove which is usually single. If the cause can be removed without further damage to the nail matrix the abnormality will resolve.

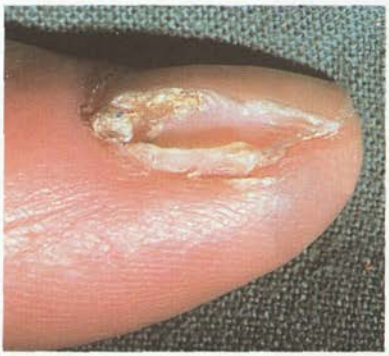

Fig. 10. Deep wide longitudinal groove due to fibroma

Median nail dystrophy is an uncommon condition of unknown aetiology, consisting of a single longitudinal defect, which nearly always affects both thumb nails. It starts at the cuticle and grows out to involve the free edge. The nail will often eventually return to normal but the condition can recur.

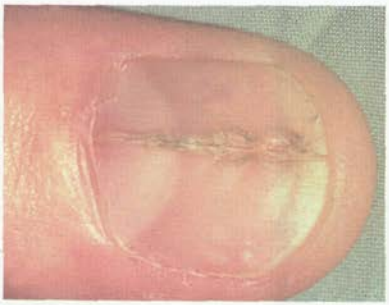

Fig. 11. Median nail dystrophy

Transverse Ridging

TRANSVERSE RIDGING	
Physical signs	**Underlying causes**
Transverse depressions	Previous illness (Beau's lines) Chronic eczema Trauma Raynaud's disease Carpal tunnel syndrome
Fine transverse grooves	Chronic paronychia

Fig. 12. Causes of transverse ridging

Transverse depressions which are sometimes slightly elevated proximally are called eponymously 'Beau's lines'. They were considered by him to be retrospective indicators of a number of disease states. They appear some weeks after an illness or fever and grow out with the nail. The condition is sometimes seen in neonates and marks the transition from intrauterine to extrauterine life.

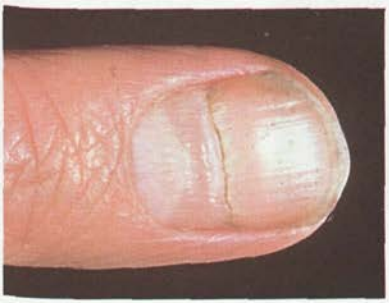

Fig. 13. A Beau's line

Transverse depressions in the nail may also be secondary to chronic eczema around the nail fold or they may occur as a result of injury, Raynaud's disease or carpal tunnel syndrome. **Fine transverse grooves** starting proximally occur in chronic paronychia, which is usually the result of a yeast infection.

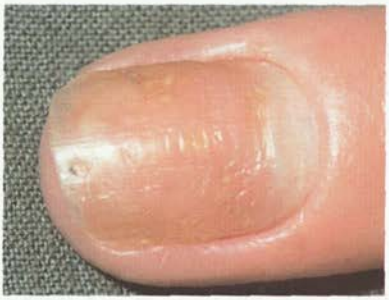

Fig. 14. Chronic paronychia showing loss of the cuticle and fine transverse depressions

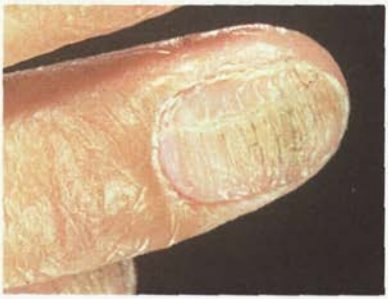

Fig. 15. Eczema showing transverse depressions

Trauma to the nail, either occupational (eg. tile fixers) or deliberate (*onychomania*), can cause quite marked **transverse grooves** parallel to the proximal fold. They may also be seen in patients who obsessionally push back the cuticle of the nail, usually the thumb nail, either with the opposite thumb or with an instrument, for example those sometimes found in manicure sets. This problem is sometimes seen as a habit analogous to nail biting and the patient is often unaware that he or she is doing it.

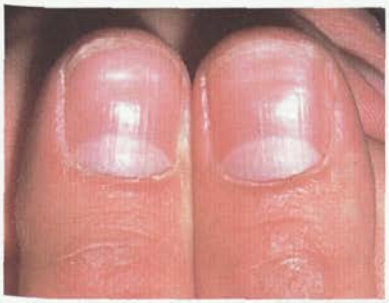

Fig. 16. Occupational trauma (tile fixer) showing marked transverse grooves

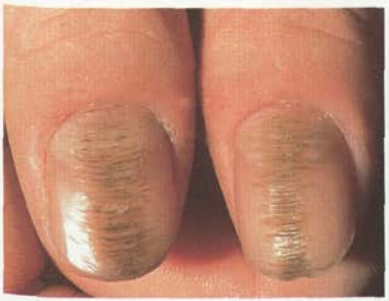

Fig. 17. Self-inflicted transverse ridges with ingrained dirt

Transverse Layering or Lamellar Nail Splitting

This frequent abnormality describes splitting of the distal portion of the nail into layers. It is commonly seen in housewives and others who frequently immerse their hands in water.

TRANSVERSE LAYERING / LAMELLAR NAIL SPLITTING
Underlying causes
Trauma Wet occupation

Fig. 18. Causes of transverse layering/lamellar nail splitting

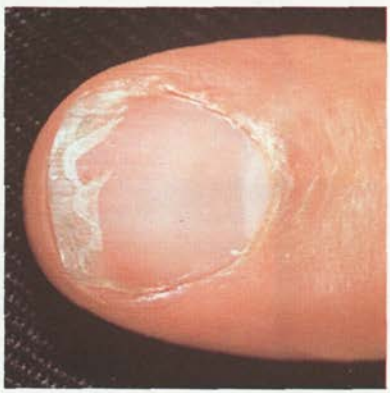

Fig. 19. Lamellar nail splitting

Thickening of the Nail

Thickening or hypertrophy of the nail plate can be acquired as a result of dermatological or systemic disease, or may be congenital.

THICKENING OF THE NAIL
Underlying causes
Onychogryphosis
Psoriasis
Lichen planus
Dermatophyte infection
Congenital pachyonychia

Fig. 20 Causes of thickening of the nail

Onychogryphosis is usually an acquired abnormality of the toenails seen most frequently in the elderly. It often results from the long term use of ill-fitting footwear and neglect. The big toe is most often involved. The nail is very difficult to cut and eventually grows into a large horny protuberance. Secondary mould infection can occur in this condition.

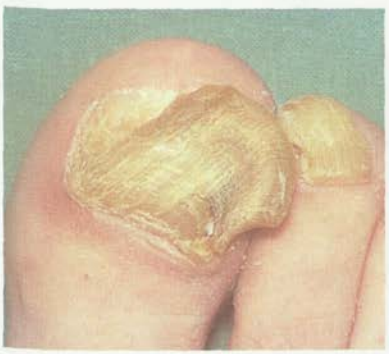

Fig. 21.
Onychogryphosis

Psoriasis, lichen planus and other skin conditions, when they affect the nail, ultimately lead to thickening of the nail plate. Other signs of these disorders should be sought on the skin surface. Psoriasis causes a number of different nail abnormalities which are discussed in this chapter under the headings of relevant physical signs. Lichen planus is much less common although it produces a variety of nail changes.

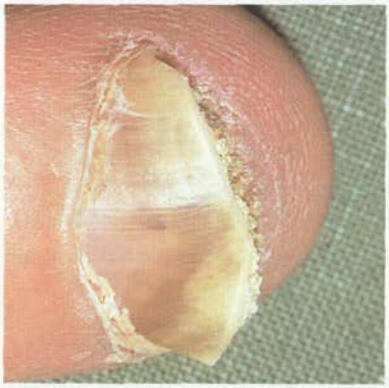

Fig. 22. Thickening of the nail due to psoriasis

Dermatophyte infection, which begins distally, results in thickening of the nail plate which starts on the underside of the nail and has a soft friable texture; eventually the whole of the nail plate becomes affected and crumbles away.

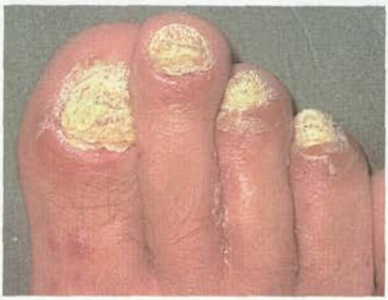

Fig. 23. Psoriatic nail showing destruction of the nail plate.

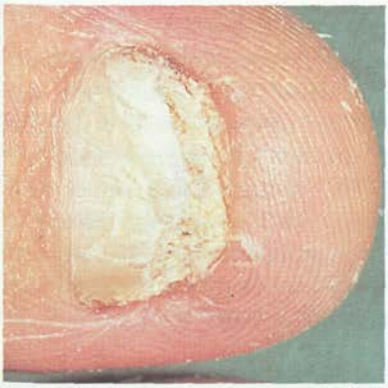

Fig. 24. Thickening and disintegration of the nail due to dermatophyte infection

Congenital pachyonychia is an autosomal dominant condition which causes thickening of the nail plate. The fingernails and to a lesser extent toenails become yellowish and extremely hard. Similar congenital changes sometimes affect only the great toenails. The diagnosis should be considered in patients presenting with thickening of the nails in early childhood. In addition to the nail changes a variety of other abnormalities have been described including palmar and plantar hyperkeratosis, warty lesions on the limbs and bullae of the feet.

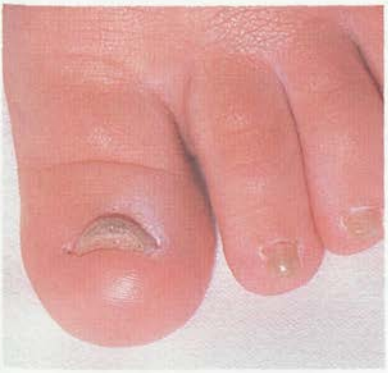

Fig. 25. Thickening of the nail due to congenital pachyonychia

Separation of the Nail Plate

Normal nail is translucent and its pink colour is provided by the nail bed. The distal free edge of the nail appears white because of air beneath it and if the nail becomes separate from the bed the white colour will extend down the nail. This change is known as onycholysis and is a common, early presenting feature of nail disease. Sometimes the space between the plate and nail bed fills up with dirt and infecting organisms which leads to further black or green discoloration.

SEPARATION OF THE NAIL PLATE	
Common causes	Minor trauma Psoriasis Dermatophyte infection (distal) Candidosis (proximal)
Less common causes	Photosensitivity Circulatory disorders Endocrine disease Pregnancy Syphilis Iron deficiency anaemia Carcinoma of the lung

Fig. 26 Causes of separation of the nail plate

Onycholysis commonly results from repeated **minor trauma** to the underside of the nail. It is seen in females who have long fingernails. As a result of leverage, upward pressure is exerted on the underside of the nail which slowly and progressively becomes separated from the bed. The patient will sometimes not present until the condition is well advanced, preferring instead to cover the discoloration with nail varnish. Onycholysis can also occur in men, secondary to occupational trauma but this is less frequent if the nails are kept short.

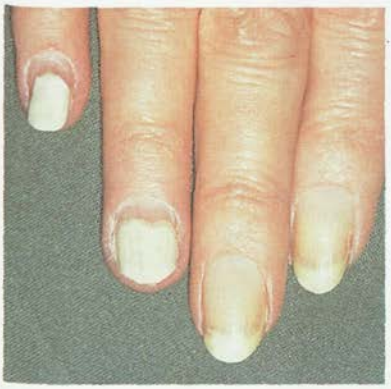

Fig. 27. Onycholysis due to minor trauma (note length of nails)

Psoriasis is another condition which leads to onycholysis. It can usually be recognised because the nails also contain small pits.

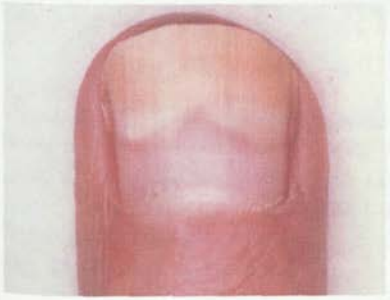

Fig. 28. Onycholysis due to psoriasis

Dermatophyte infection of the nails causes a distal onycholysis whilst **candidosis** of the nails secondary to a paronychia can lead to a proximal onycholysis.

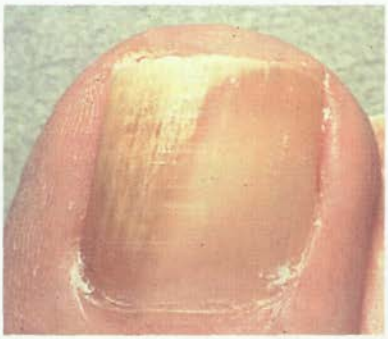

Fig. 29. Onycholysis due to dermatophyte infection

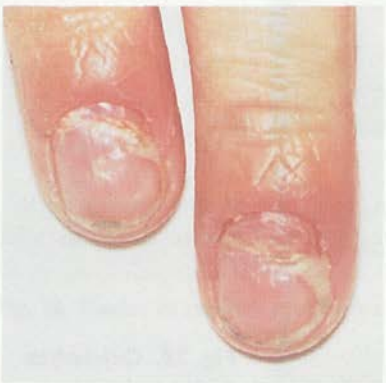

Fig. 30. Proximal onycholysis due to *Candida*

Other less common causes of onycholysis include photosensitivity, circulatory disorders, endocrine disease, pregnancy, syphilis, iron deficiency anaemia and carcinoma of the lung.

Discoloration

A number of drugs, chemicals and other physical agents can modify the normal colour of the nail and may be applied therapeutically, deliberately or accidentally. Naturally acquired nail discoloration is usually white, black, green or yellow.

DISCOLORATION	
Colour	**Underlying causes**
White	Trauma Severe stress Cardiac disease Gastrointestinal disease Renal disease Surgery Infectious diseases Autoimmune disease Neoplasia Metabolic disorders Psoriasis Dermatophyte infections
Black or dark brown	Naevi Trauma Melanoma Fungal infection
Green	*Pseudomonas* infection *Candida* infection *Aspergillus* infection
Yellow	*Candida* infection Slow growth Yellow nail syndrome Drug effects

Fig. 31. Causes of discoloration

Whitening of the nails or **leukonychia** can be divided into two main types: true leukonychia where the nail plate is discoloured or apparent leukonychia resulting from onycholysis or involvement of the tissue beneath the nail.

True leukonychia may be congenital or acquired as a result of exogenous or endogenous factors. It may be total, striate or punctate. In the striate form the striae may be transverse or longitudinal. Over enthusiastic manicuring can produce both punctate and transverse striate leukonychia. Endogenous leukonychia can result from severe stress and cardiac, gastrointestinal or renal disease. It is also associated with surgery and various infectious diseases. Autoimmune conditions, neoplasia and metabolic disorders may also result in white nails.

In general there is very little disturbance to the integrity of the nail plate in leukonychia. Psoriasis and some dermatophyte infections, especially those due to *Trichophyton mentagrophytes* (var. *interdigitale*) also cause whitening.

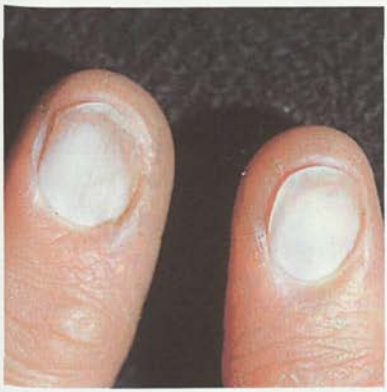

Fig. 32. Diffuse leukonychia

Fig. 33. Transverse leukonychia

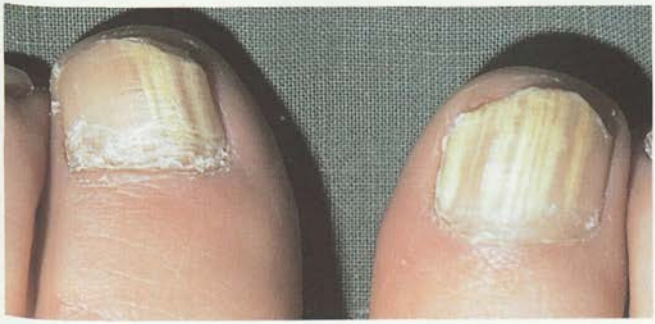

Fig. 34. Longitudinal white streaks due to dermatophyte infection

Black or **dark brown discoloration** of the nails may result from melanin deposition within the nail or from blood collecting beneath it. Naevi originating in the area of the matrix can cause a dark longitudinal streak to appear on the nail. When such naevi occur in adults a biopsy should always be undertaken to exclude a melanoma although they are usually benign. Similarly black discoloration beneath the nail plate should not automatically be diagnosed as resulting from bleeding due to trauma because it is a serious mistake to miss a melanoma in such a situation. Any patient with blackening of the nail without a history of trauma and without evidence of the black area growing out should be referred for specialist opinion.

Some fungi, notably *Scytalidium* (*Hendersonula*) and *Scopulariopsis*, can cause black, grey or brown discoloration of nails and such discoloration is also occasionally seen in *Trichophyton rubrum* infection.

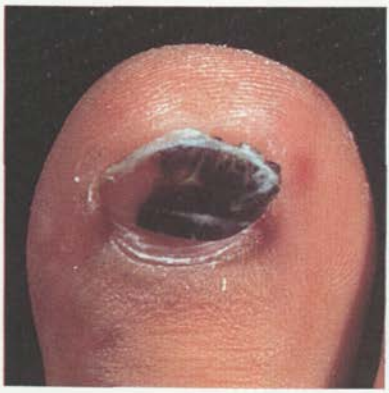

Fig. 35. Subungual haematoma

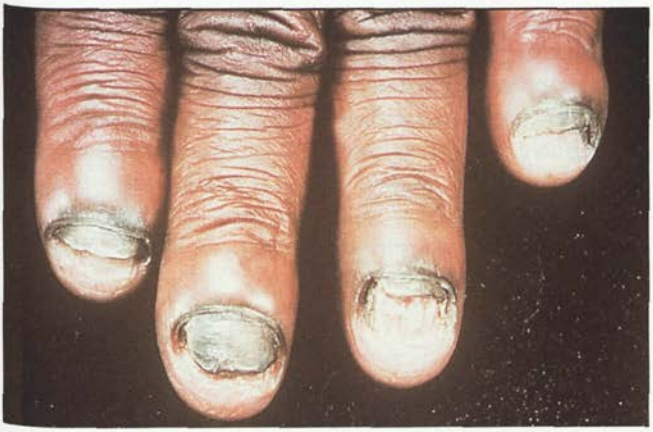

Fig. 36. Black discoloration of nails due to *Scytalidium* (*Hendersonula*) *dimidiatum*

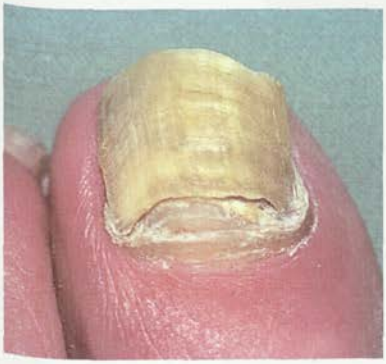

Fig. 37. Greyish-black discoloration due to *Scopulariopsis brevicaulis*

Green nails are characteristic of infection or secondary infection with *Pseudomonas*, which produces pigments such as pyocyanin and fluorescein. The former is soluble in water and chloroform and the latter in water only. A definitive diagnosis can thus be made if the affected portion of nail is soaked in water or chloroform. If the solvent turns green it is indicative of a current or past infection with *Pseudomonas* which can be confirmed by culture.

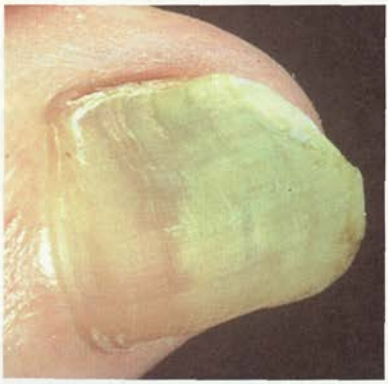

Fig. 38. Green discoloration due to *Pseudomonas* beneath a lytic nail

Yellow nails can occur in candidal infection and also as a result of slow growth, particularly in the yellow nail syndrome which sometimes is associated with lymphatic abnormalities. Drugs such as tetracyclines can also cause yellow discoloration of nails.

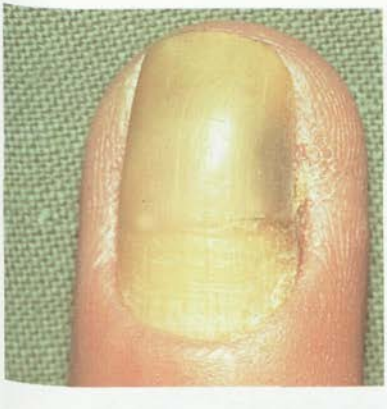

Fig. 39. Yellow nail syndrome

Inflammation of the Nail Fold

Inflammatory change affecting the proximal and lateral nail folds is regularly seen in dermatological disorders which affect the fingers. The inflammation may be primary or secondary to separation of the nail fold from the nail plate caused by swelling. This separation leads to infection in the periungual tissues which in turn makes the inflammation worse. Any chronic inflammatory change in the nail folds will tend ultimately to disrupt the nail plate and changes described previously such as transverse ridging or separation of the nail plate can occur.

INFLAMMATION OF THE NAIL FOLD

Underlying causes

Acute paronychia
Chronic paronychia
Eczema
Plaque psoriasis
Pustular psoriasis
Sarcoidosis
Collagen disorders

Fig. 40. Causes of inflammation of the nail fold

Acute paronychia is a well recognised bacterial infection, usually due to *Staphylococcus aureus*, which is extremely painful and eventually points and discharges pus. When pointing occurs a small incision can be made allowing the pus to discharge. This generally leads to rapid resolution of the infection. Acute paronychia itself does not cause disruption of the nail plate although an incorrectly sited drainage incision can.

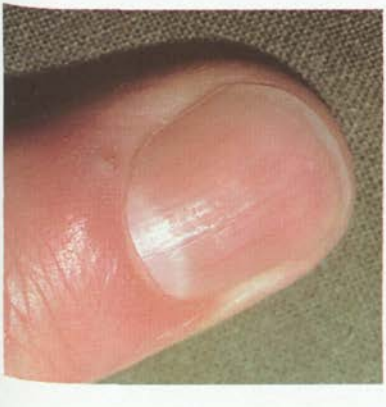

Fig. 41. Acute paronychia

Chronic paronychia results from separation of the cuticle which thus loses its waterproof properties and allows infection to wash beneath it. This causes swelling of the nail fold and further separation of the cuticle, which eventually causes disruption to the nail plate. Various bacteria and yeasts of the *Candida* genus are usually involved.

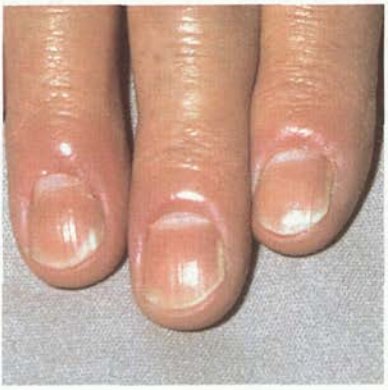

Fig. 42. Inflammation due to early chronic paronychia

Eczema of the distal area of the fingers produces similar changes. There is swelling of the tissues of the nail fold which results in a secondary paronychia. Such changes can occur in all forms of eczema and also in infants who suck their thumbs.

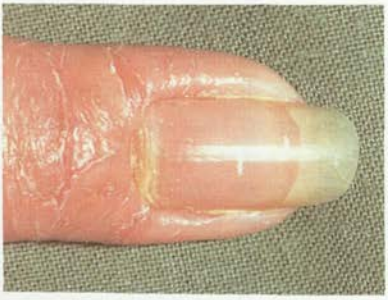

Fig. 43. Inflammation due to eczema

Plaque psoriasis, if it affects the distal area of the fingers or toes, can appear inflammatory and also give rise to a **secondary paronychia.**

Pustular psoriasis (acropustulosis) occurs mainly on the palms or soles but can affect the fingertips. It results in sterile pustules developing around and sometimes beneath the nail plate. These pustules initially appear a creamy-white colour which is distinct from the yellow colour of bacterial pus and as they resolve they tend to leave hard brown macules which are of diagnostic appearance. When severe it can lead to complete separation of the nail plate.

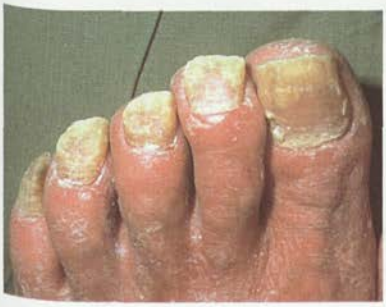

Fig. 44. Inflammation due to psoriasis

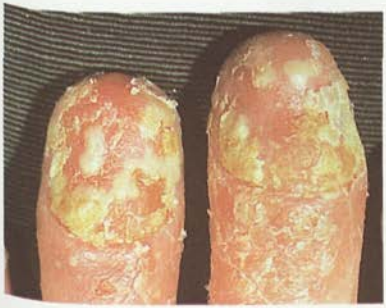

Fig. 45. Pustular psoriasis

Sarcoidosis can affect both the nail plate and the nail folds resulting in disruption and fragility of the nail plate together with erythema, scaling and fissuring of the surrounding skin. Splinter haemorrhages can also occur.

Collagen disorders classically cause inflammation of the proximal nail fold. To the naked eye, this manifests itself as erythema of the nail fold, but examination with a good hand lens will reveal tiny telangiectatic vessels which are almost diagnostic of collagen disease, particularly when taken in conjunction with other skin and systemic changes. The nail plate is rarely disturbed in these conditions.

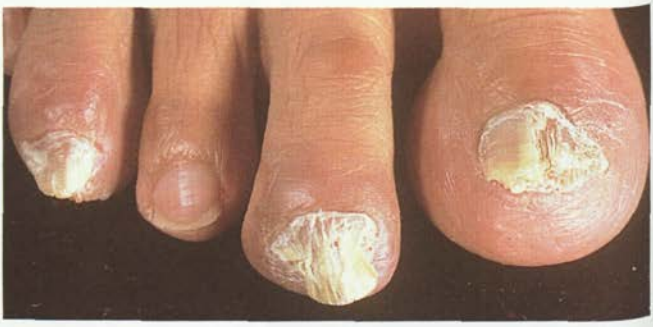

Fig. 46. Inflammation due to sarcoidosis

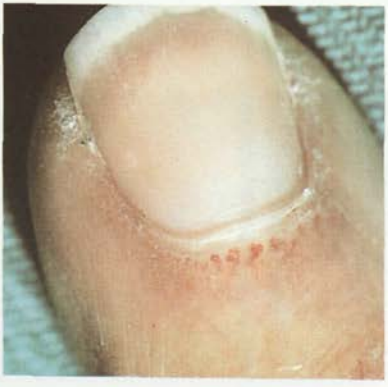

Fig. 47. Nail fold telangiectasia

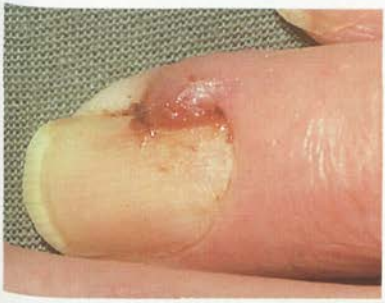

Fig. 48. Periungual granulation tissue in systemic sclerosis.

Painful Nails

Pain or discomfort is a subjective sensation and given the rich sensory innervation of the fingertips it can be a presenting symptom of almost any nail disorder. In general however, trauma, inflammation and tumours are the commonest causes of pain affecting the nail apparatus, in addition that is to acute paronychia.

PAINFUL NAILS	
Causes	**Examples**
Trauma	Subungual haematoma Ingrowing toenail
Acute or chronic inflammation	Paronychia Acropustulosis Herpetic whitlow
Tumours	Melanoma Subungual fibromata Glomus tumours

Fig. 49. Causes of painful nails

Trauma to the nail is often very painful especially when it results in a subungual haematoma. Direct trauma from the nail itself as in an ingrowing toenail also causes extreme discomfort.

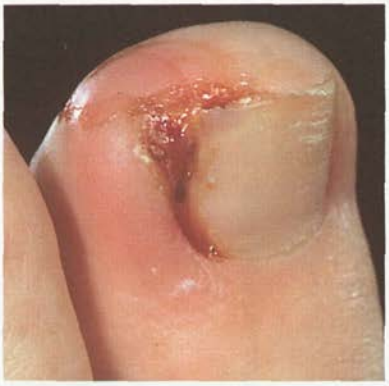

Fig. 50. Ingrowing toenail

Acute or chronic inflammation of the nail folds or the nail bed can cause pain especially on pressure and this symptom is seen in paronychia, acropustulosis and herpetic whitlow.

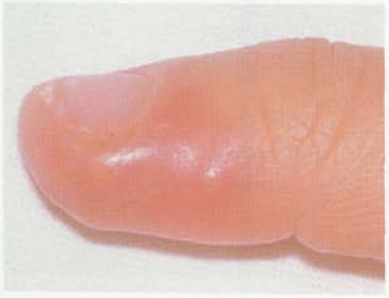

Fig. 51. Herpetic whitlow

Tumours such as melanoma, or subungual fibromata are painful when they become large enough or pain can be elicited by pressure. Glomus tumours are almost invariably painful and the discomfort can be severe on occasions.

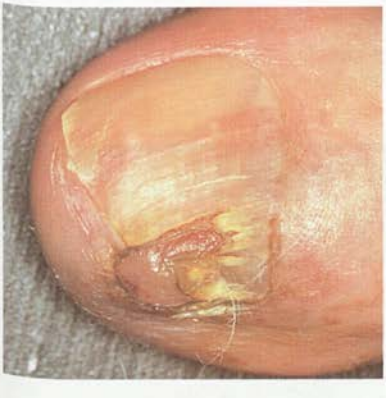

Fig. 52. Amelanotic melanoma

Pitting

Pitting occurs as a result of a defect in nail formation. The surface of the nail becomes covered in small punctate depressions which vary in number, size, depth and shape. Deep pits are associated with psoriasis whereas shallow pits are seen in alopecia areata, eczema, the curious idiopathic condition known as 'twenty nail dystrophy' and sometimes trauma.

PITTING	
Physical signs	**Underlying causes**
Deep pits	Psoriasis
Shallow pits	Alopecia areata Eczema Twenty nail dystrophy Trauma

Fig. 53. *Causes of pitting*

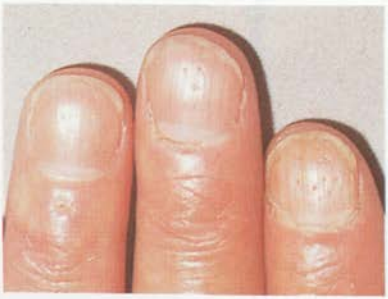

Fig. 54. Pitting

Other Abnormalities

There are numerous other visible changes of diagnostic importance which might be seen in the nails. **Splinter haemorrhages** are most commonly due to trauma in which case they are found in the distal portion of the nail. Conditions such as psoriasis which cause onycholysis will predispose to their occurrence. In subacute bacterial endocarditis they can occur in the proximal half of the nail as well.

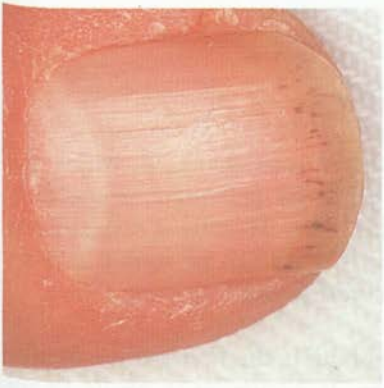

Fig. 55. Splinter haemorrhages

Spooning of the nails or **koilonychia**, classically seen in iron deficiency anaemia, also occurs as a physiological variant in young infants. It may also result from thinning of the nail plate from, for example, candidal infection, excessive exposure to detergents, alopecia areata or twenty nail dystrophy.

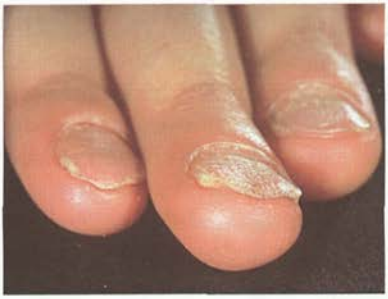

Fig. 56. Koilonychia in twenty nail dystrophy

Pterygium is the name given to a change in which the cuticle becomes fused with the nail plate, completely obliterating the nail fold. Most typically it results from severe lichen planus but it is also to be found in graft versus host disease, sarcoidosis and following injury.

The classical sign of **clubbing** is the best known abnormality of nail curvature. It occurs as a result of an increase in the soft tissue beneath the nail fold which causes loss of the normal angle between the nail fold and the nail plate. In addition to cardiac and pulmonary disease it may be an isolated idiopathic finding, sometimes inherited as a Mendelian dominant. Clubbing of just one or two digits may result from a localised arterio-venous anastamosis.

Lateral over-curvature is so frequently seen in the little toenails that it can be regarded as normal. In other toenails it can be idiopathic or the result of trauma or pressure from ill-fitting shoes.

Longitudinal over-curvature or 'beaking' of the nails can result from the loss of soft tissue and is a characteristic feature of systemic sclerosis. Another occasional cause of beaking of a solitary nail is trauma.

Nails may be **shed** for a number of reasons and here again trauma must rate as the most frequent cause, particularly in the great toenails. Severe Beau's lines may cause a complete transverse fracture in the nail plate and the nail may be lost in severe inflammatory conditions such as pustular psoriasis. In the rare nail patella syndrome the nails are absent or vestigial.

TYPES OF ABNORMALITY

POINTS TO NOTE

1. Nails can be affected by many local and systemic conditions.
2. Most nail disorders are not amenable to treatment.
3. Always refer a black or partly black nail for specialist opinion if there is no certain evidence of trauma.
4. Fungal infection is by far the commonest disorder which can respond to treatment and therefore it is very important not to miss it.

Fig. 57. Types of abnormality: points to note

Chapter Four

Fungal Nail Disease

Fungal nail disease or onychomycosis is a relatively common chronic infection and a frequent cause of nail deformity. Fungal infection does not normally involve the nails uniformly or symmetrically and can frequently be seen affecting only one or two nails. It can be caused by a number of different fungi, both moulds and yeasts. The majority of infections are caused by moulds called dermatophytes and the infection is variously named either tinea unguium, ringworm or dermatophytosis. Yeasts of the genus *Candida*, notably *Candida albicans*, are the second most common cause of nail infection.

More rarely moulds such as *Scopulariopsis*, *Fusarium*, *Aspergillus* and *Scytalidium* (*Hendersonula*) affect nails; these infections are referred to under the general title of onychomycosis. Most of these mould fungi are now generally considered to be secondary invaders of nail which has been previously damaged by trauma or by a dermatophyte infection. Although these mould infections are relatively rare, it is important that their aetiology is correctly identified since in most cases they respond poorly, if at all, to the available antifungal therapies. *Scytalidium*, however, is a primary pathogen of nail and it is also able to infect skin. In some parts of the world,

for example the Far East, it is a common cause of foot and nail infection. Like the other non-dermatophyte moulds it responds poorly to the currently available antifungals.

Clinical Features

Fungal infection of the nail is classified into five different types.

Distal and lateral subungual onychomycosis (DLSO) is invariably the result of a dermatophyte infection and is the commonest type of fungal nail dystrophy. *Scytalidium* infection produces a similar clinical picture with characteristic black discoloration of the nail.

Superficial white onychomycosis (SWO) is a specific superficial type of dermatophyte nail infection caused by *Trichophyton mentagrophytes* and is relatively uncommon; it may also be caused by *Acremonium* species. Dermatophyte infection in AIDS patients involving the whole thickness of the nail produces a powdery white deposit on the nail surface which is similar to but more exaggerated than the appearance in SWO.

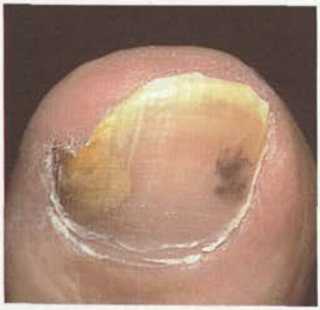

Fig. 58. Distal and lateral subungual onychomycosis (DLSO)

Fig. 59. Superficial white onychomycosis (SWO)

Proximal subungual onychomycosis (PSO) arises from the proximal part of the nail and is seen very rarely in dermatophyte infection. It is invariably secondary to intercurrent disease which may be immunological (AIDS) or vascular.

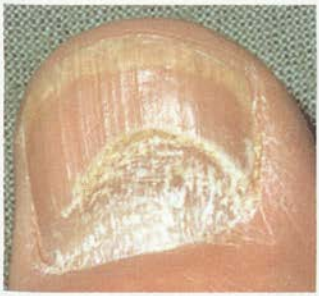

Fig. 60. Proximal subungual onychomycosis (PSO)

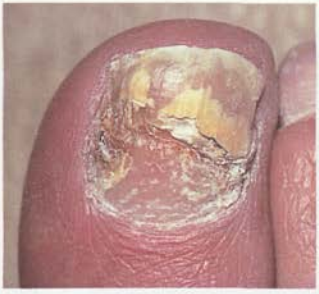

Fig. 61. PSO in a patient with peripheral vascular disease

***Candida* onychomycosis** is subdivided into three types:
(i) chronic paronychia
(ii) distal onychomycosis related to Raynaud's disease
(iii) chronic mucocutaneous candidosis (CMC).

Fig. 62. Distal candidal onychomycosis in a patient with Raynaud's disease

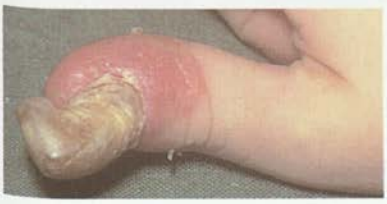

Fig. 63. Chronic mucocutaneous candidosis

Total dystrophic onychomycosis (TDO). This final type of nail dystrophy where the whole of the nail plate is destroyed can be a consequence of any of the first four types.

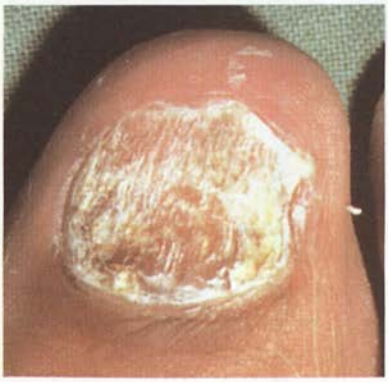

Fig. 64. Total dystrophic onychomycosis (TDO)

The clinical appearances of these patterns of infection vary, as do the nails involved.

In **DLSO** the fungus usually invades the hyponychium through the distal and lateral undersurface of the nail, though direct invasion of the nail plate is also possible. The fungus produces proteolytic enzymes which enable it to invade the nail and to slowly digest the nail keratin. Initially the nail becomes detached from the bed (onycholysis) thus changing to a creamy-white opaque colour. Thereafter reactive hyperkeratosis develops on the underside of the nail. This leads to thickening which will eventually affect the full thickness of the nail plate, the top surface consequently becoming ridged and eventually crumbling away. DLSO affects the toenails four times as often as the fingernails.

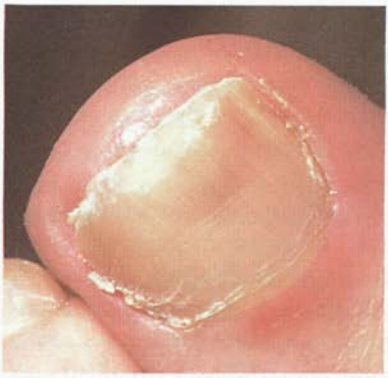

Fig. 65. Early DLSO

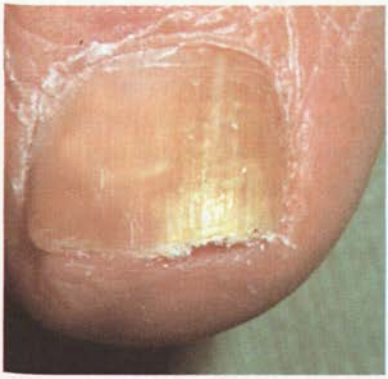

Fig. 66. DLSO

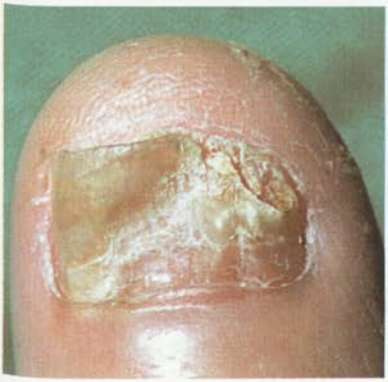

Fig. 67. DLSO due to *Aspergillus*

In **SWO**, which is associated with a *T. mentagrophytes* (var. *interdigitale*) infection or *Acremonium* infection, the nail plate assumes an obvious white colour. This condition also predominantly affects the toenails but here the site of entry of the fungus is less clear.

Chronic paronychia is virtually confined to the fingernails of patients with 'wet' occupations such as cooks, hairdressers, and mothers of young children. The risk is increased if there is, in addition, a poor peripheral circulation. Constant immersion leads to separation of the cuticle from the nail plate which allows organisms to enter the subcuticular space causing secondary inflammation and consequent swelling of the posterior nail fold. This in turn leads to a vicious circle of more cuticular separation and further infection. Ultimately the inflammation and infection affects the nail matrix leading to a proximal nail dystropy. *Candida* yeasts are invariable pathogens in this cirumstance although bacteria are also likely to have a role. Some authorities believe that the inflammatory change affecting the posterior nail fold is related to a contact reaction but the resulting pathological process is essentially similar.

Distal nail dystrophy in patients with Raynaud's disease often yields *Candida* yeasts on culture. This nail dystrophy is similar to that seen in a dermatophyte infection but again predominantly affects the fingernails and there tends to be less destruction of the nail plate. Whether or not the onycholytic process precedes yeast invasion or is caused by such invasion is unknown but there is no doubt that the clinical appearances sometimes improve following anti-yeast treatment.

Chronic mucocutaneous candidosis is an uncommon condition resulting from a defect of cell mediated immunity whereby both nails and mucous membranes are chronically infected with *Candida*. This is not a specific

disease entity but results from a variety of syndromes of differing severity. When the immune defect is profound the nails become heavily superinfected with *Candida* leading to gross hyperkeratosis, sometimes amounting to granuloma formation in the nails and surrounding skin. Such patients undoubtedly benefit from long-term therapy with drugs active against yeasts.

Candida yeasts are sometimes cultured from many other types of dystrophic nail but only in the three circumstances described above are yeasts likely to play a causal role.

It is thus possible to categorise various types of infection on clinical grounds, but a clinical diagnosis should be supported by laboratory confirmation of infection. Certainly therapy should not be started before confirmation of infection because treatment needs to be continued until resolution which may take months. Success or failure cannot be gauged accurately without definitive evidence of infection before the start of treatment. Laboratory confirmation of infection is considered in detail in Chapter 6.

FUNGAL NAIL DISEASE

POINTS TO NOTE

1. Clinical patterns of change in fungal nail disease give a clue to the type of infection present.
2. Dermatophyte (ringworm) infection is commonest, and toenails are affected twice as often as fingernails.
3. Proximal fungal infection is nearly always caused by *Candida* and is secondary to paronychia.

Fig. 68. Fungal nail disease: points to note

Chapter Five

Mycology and Epidemiology

It is important to consider briefly the prevalence of onychomycosis and also the origin and types of fungi involved in the different forms of nail infection. However, the pathogenesis of these infections and the host's response to them is a complex, poorly understood area and detailed consideration of these aspects is beyond the scope of this brief text.

The Fungi

There are two main groups of fungi:

(i) **moulds**, where the fungal cells are joined together to form filaments called hyphae which branch to form an interwoven mass, the mycelium, on which the fungus produces its spores; the type and number of spores produced varies from species to species and is the characteristic used most often to identify mould fungi.

(ii) **yeasts**, in contrast to moulds, are predominantly unicellular, usually with round or oval cells. These cells reproduce by a process called budding where a small protuberance develops usually at the poles of the cell; this bud balloons out to form a daughter cell which eventually separates from the parent. In some yeasts the budding cells become elongated and adhere in chains

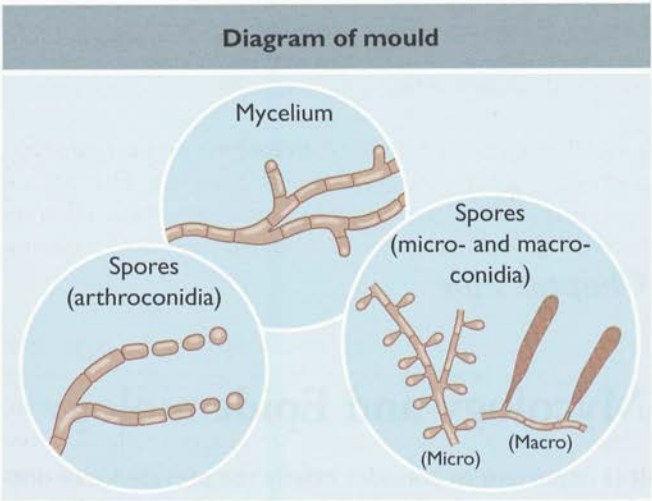

Fig. 69. Diagram of mould

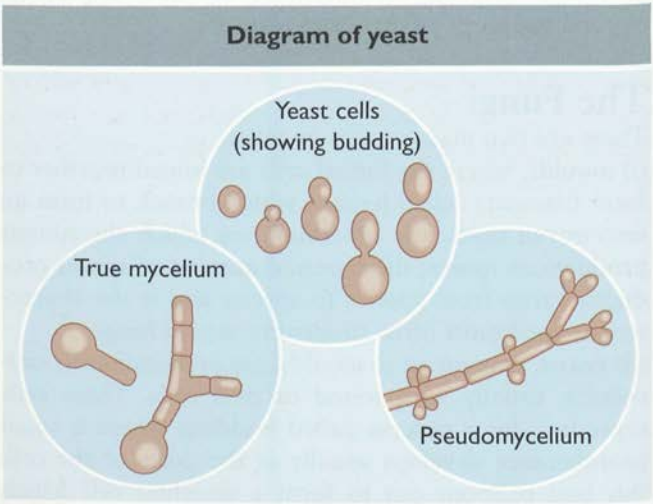

Fig. 70. Diagram of yeast

forming what is known as a pseudomycelium. Some yeasts produce true mycelium indistinguishable from that produced by moulds.

A small number of fungi are **dimorphic** and are capable of growth in either the yeast or mould form. The type of growth they produce is dictated by environmental conditions. A number of the fungal pathogens of humans are dimorphic.

Very few of the large number of species of fungi are pathogenic to humans and animals. Some of these fungi can cause infection in either man or animals, whereas others are species specific and for many of these latter fungi man is the sole host. Infections caused by pathogenic fungi (mycoses) are grouped into three types, namely, **superficial, subcutaneous** and **systemic.**

Superficial infections, although generally less serious than the others are the most common and account for a great deal of morbidity in the general population. The principal superficial mycoses which may affect the skin, hair, nail and mucous membranes, are: ringworm, or tinea caused by dermatophytes; candidosis, caused by *Candida* species; and pityriasis versicolor caused by the yeast *Malassezia furfur.*

Pathogens of Nails

In general those fungi which affect nails, particularly in temperate zones, are specific to man. For the sake of simplicity it is as well to divide nail pathogens into moulds and yeasts.

Dermatophytes

Dermatophytes are a group of mould fungi that have an ability to digest keratin; a property that is fundamental to their ability to infect skin, hair and nail. These moulds are the commonest nail pathogens. Although there are some twenty species of dermatophyte, only three species regularly cause infection of the nail. Channels and quite large lacunae may be seen in the nail plate. These channels are often considerably larger than the hyphae contained within them suggesting that there is extracellular proteolytic enzyme activity, but it has proved difficult to isolate specific keratinolytic enzymes in dermatophyte extracts. It is likely therefore that both mechanical and enzymatic destruction of keratin takes place. Although it is possible to demonstrate both humoral and cell mediated immune responses to dermatophytes and indeed some dermatophyte infections of the skin surface do resolve spontaneously, it is highly unlikely that a nail infection will ever do so.

Dermatophyte infection of nails is associated with athlete's foot (tinea pedis). There is a classical pattern of spread of ringworm infection from the skin of the feet, usually the toewebs, to the toenails, groin, hands and fingernails. Therefore, dermatophytosis of the nails is nearly always associated with current or past dermatophyte infection of the feet. Consequently, its occurrence and spread is associated with the use of communal bathing places and its prevalence, like that of tinea pedis, is highest in adult males.

Tinea pedis and its associated infections are caused by one of three species of dermatophyte fungi, namely, *Trichophyton rubrum*, *Trichophyton mentagrophytes* (var. *interdigitale)* and *Epidermophyton floccosum*. Most dermatophyte infections of nails, some 85%, are caused by *T. rubrum*, with *T. mentagrophytes* (var. *interdigitale)* found in around 12% of cases and *E. floccosum* in 2–3%. Occasionally there are mixed infections and also on rare occasions infections caused by other dermatophyte species. The preponderance of *T. rubrum* nail infection probably reflects the persistent nature of skin infections due to this species, its relative resistance to therapy and also the fact that *T. rubrum* is better able to invade nail keratin than other species.

All of these organisms are endemic on the floors of communal bathing places and the incidence of foot infection is high in regular users of these facilities; these include regular swimmers, sportsmen, coalminers, members of the armed forces and any other regular user of communal showers and baths. It is likely that nail infections take a long time to develop and a history of regular use of communal bathing facilities may be some time in the past. For this reason nail infection is not very common in children and occurs progressively more often into adult life. However, the increasing use of leisure facilities, involving communal bathing by families is leading to an increase in nail infection at a relatively younger age.

Other moulds

Dermatophytes are by far the commonest cause of DLSO (distal and lateral subungual onychomycosis) SWO (superficial white onychomycosis) and TDO (total dystrophic onychomycosis). A number of surveys confirm that they account for around 90% of all cases of fungal nail infection. Non-dermatophyte moulds are frequently cultured from samples of dystrophic nail but in the vast majority of cases they are there as saprophytes; already damaged nail is a suitable substrate for growth. More often than not the primary cause of such nail dystrophy is a dermatophyte infection which may be masked in culture by mould overgrowth. In these cases eradication of the dermatophyte will allow the nail to grow out normally and saprophytic moulds will simply disappear. In diseases such as onychogryphosis, attempts to treat saprophytic moulds grown in culture will fail to improve the clinical appearance and are thus fruitless. *Scytalidium dimidiatum*, formerly known as *Hendersonula toruloidea*, is a soil fungus and also a pathogen of fruit trees confined to tropical zones. It is the only non dermatophyte mould which is an undoubted primary pathogen of nails. It also infects skin and produces toecleft infection and nail dystrophy indistinguishable from dermatophyte infections; in some parts of South East Asia it is the commonest cause of fungal foot infection. The pattern of nail infection is the same as with dermatophytes although *Scytalidium* produces characteristic black discoloration of the nail because of its intrinsic colour. Whilst not very common in the Western world it is increasingly seen in immigrants and travellers from endemic regions and its prevalence may well increase. This would be unfortunate as it is known not to respond well to any antifungal agent.

In the UK, *Scopulariopsis brevicaulis* is isolated from dystrophic nails in 2–5% of all cases and is the commonest non-dermatophyte mould found on culture. The organism is unlikely to be a primary pathogen and most often it co-exists with a dermatophyte. However, it will invade nails previously damaged by trauma and produces a characteristic grey-black discoloration. The pattern of infection is again distal and lateral and medical treatment is usually not indicated. The mould is slow to respond to antifungal drugs and in any case is unlikely to be the primary cause of the dystrophy. In such cases removal of the nail is almost always indicated if it is symptomatic or cosmetically troublesome. *Scopulariopsis* has characteristic spores and an experienced mycologist is usually able to recognise these on microscopy.

A large number of other moulds have been reported as occasional causes of onychomycosis including *Aspergillus*, *Fusarium* and *Alternaria* species. In such cases these moulds are unlikely to be responsible for the primary nail dystrophy except when the patient is immunosuppressed and again are unlikely to respond to antifungal therapy. It is recognised that these moulds will spread in some immunosuppressed patients; *Fusarium* in particular has been known to prove fatal following dissemination from an infected nail.

Yeasts

Nail infections caused by yeasts are predominantly due to *Candida* species in particular *Candida albicans*. These organisms are common commensals of the mouth, gastrointestinal tract, vagina and to a lesser extent the skin. Estimates vary but it is thought that approximately 20% of the population carry yeasts as a commensal and most infections with *Candida* are believed to be endogenous in origin.

A number of *Candida* species can produce nail changes and although *C. albicans* is overwhelmingly the commonest pathogen, *Candida tropicalis* and *Candida parapsilosis* often produce disease in the distal nail. There is no definite evidence that yeasts are keratinolytic but given the clinical patterns of disease it is likely that they must at least have some proteolytic activity which destroys the integrity of the keratin.

C. albicans is the predominant organism in chronic paronychia in which it produces chronic inflammation beneath the nail fold and secondarily disrupts the nail plate. Whether or not the organism originates from the patient's own gut or some other body site, or arises from another source, is a matter of continuing debate. However the evidence is that *Candida* species do cause nail disease in both of the patterns described above and would respond to an effective form of anti-candidal treatment.

Chronic mucocutaneous candidosis is a rare form of candidosis in which a specific T-cell defect leads to a diminished immune response to *Candida*. Sometimes this T-cell defect is inborn or can be a result of various endocrine disorders. It is very rare but does cause total dystrophy (TDO) in some nails, usually fingernails, as well as candidosis of the mucous membranes of the eyes, mouth and genitalia.

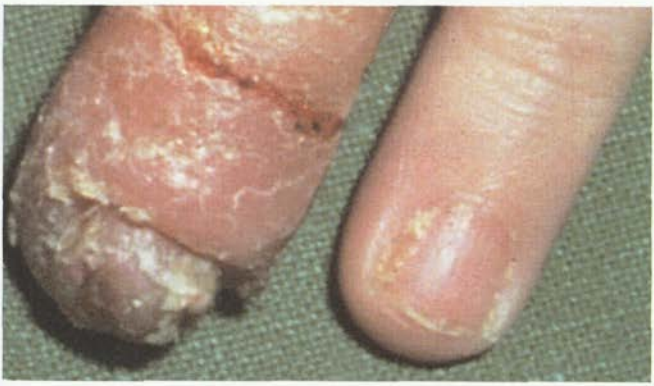

Fig. 71. Chronic mucocutaneous candidosis

Prevalence of Fungal Nail Disease

Most UK patients with dermatophytosis who are referred to dermatology clinics show evidence of nail involvement. However, until very recently, there have been no good large scale studies carried out on the prevalence of fungal nail disease in the general population and the only possible approach has been to look at the figures available for the prevalence of foot ringworm and to extrapolate from these. However, most of the studies carried out on the incidence of foot ringworm have been done on at-risk groups of individuals who regularly use communal bathing facilities, such as swimmers, miners, servicemen, industrial workers, etc. It is clear from these studies that the greater the frequency of use of communal bathing places the greater the likelihood of developing foot ringworm. Coalminers who use communal bathing facilities every day have the highest prevalence.

PREVALENCE OF FOOT RINGWORM	
Group	**Prevalence of infection %**
Swimmers	8.5
Day schoolboys	8.9
Boarding schoolboys	22.0
Longstay hospital males	39.0
Coalminers	≤80.0

Fig. 72. The relationship between exposure to communal bathing facilities and prevalence of foot ringworm (based on published studies)

There have been few studies of the prevalence of foot ringworm in the general population. It has been shown that amongst users of a swimming pool 8.5% had fungal infection of their feet and that among the male swimmers over the age of 16 there was a prevalence of 21.5%. A further study of office and shop workers in the UK revealed a 14.8% prevalence of foot infection. It would appear therefore that 10–15% of the population could have a fungal infection of feet. The proportion of individuals with tinea pedis with concurrent dermatophyte infection of the toe or fingernails or both has been found in different surveys to be as high as 30%. It can be assumed therefore that up to one third of those with foot ringworm are likely to develop a nail infection.

In the UK a large survey of the prevalence of fungal nail disease in the general population has been carried out using a pictorial questionnaire. This survey was epidemiologically valid in terms of geographic distribution, age, and social class and a population of 10,000 was surveyed. This revealed a prevalence of dermatophyte nail infection of 2.71%. A similar survey carried out in Spain revealed an almost exactly similar prevalence. Such

surveys are not mycologically controlled and may be an underestimate of the true prevalence. More recently three surveys carried out in Finland, the USA and Canada, which were mycologically controlled, although they studied a much smaller population, revealed a prevalence between 8 and 10%. All surveys show an increasing prevalence with age. It would seem likely therefore that dermatophyte onychomycosis is one of the most common dermatologic diseases and extrapolation from these figures would mean that up to 5.5 million people in the UK and up to 25 million people in the USA could be affected by fungal nail disease.

MYCOLOGY AND EPIDEMIOLOGY

POINTS TO NOTE

1. Dermatophytes slowly destroy nail keratin causing the nail to crumble.
2. *T. rubrum* is the commonest nail pathogen.
3. Various *Candida* species can cause nail infection.
4. Some fungi which cause nail disease do not respond to antifungal drugs.
5. Dermatophyte infection is generally contracted in communal bathing places.
6. Dermatophyte infection of the nail is almost always preceded by athlete's foot.

Fig. 73. Mycology and epidemiology: points to note

Chapter Six

Diagnosis of Fungal Nail Infection

Clinical Diagnosis

The pattern of clinical infection of nails tends to fall into one of the four broad groups described on pages 42–44, but it is not possible to make a definitive diagnosis of fungal infection on clinical grounds alone. Laboratory confirmation is essential for an accurate diagnosis and also for monitoring antifungal therapy.

Laboratory Diagnosis

General principles

The laboratory diagnosis of fungal infections is based on the examination of clinical material by microscopy in potassium hydroxide (KOH) and by culture. The reliability of these procedures is determined by the expertise of the laboratory staff and by the quality of the sample sent for examination. Nail clippings should be sent to a mycology laboratory experienced in the diagnosis of fungal infections. Such specialist laboratories are relatively few in number but should certainly be utilised in preference to local bacteriology laboratories unless the latter are experienced in fungal diagnostic techniques. It

is a fortunate fact that fungi will remain viable in nail keratin for several months, so sending such material to a laboratory by post presents no problems. In the main, a good sample of nail material (subungual debris and clippings) is all that is required to diagnose the majority of fungal nail infections and this is easy and quick to take and can be sent very conveniently to a suitable laboratory.

Collection of Samples

Subungual debris and clippings should be obtained from the affected portion of the nail. These samples should be taken as proximally as possible to improve the chances of obtaining viable fungus. Subungual material is the most valuable for laboratory investigation as dermatophytosis of nail is primarily an infection of the nail bed. This material can be removed from the underside of the nail, where the nail is most thickened, with a curette. Nail clippings should also be collected with a pincer-type nail clippers of adequate size as scissors are usually useless for sampling purposes. As much material as possible should be obtained and either folded in small squares of paper (preferably black) kept closed with a paper clip, or placed within one of the sample transport kits which are available commercially.

Where the nail dystrophy is wholly proximal it is not possible to obtain a specimen of subungual debris or clippings. In such cases a scraping can be taken from the surface of the affected portion of the nail with a scalpel blade or material can be obtained by the use of a small biopsy punch. Care must be taken not to cause pain by penetrating the nail. Although fungi can be visualised and isolated from biopsy specimens, the procedure requires a local anaesthetic and special expertise in the technique and therefore is not a practical routine diagnostic method.

Candida can be specifically isolated from beneath the proximal nail fold by running a bacteriology swab dipped in saline along the length of the fold. This allows the saline to wash under the detached cuticle collecting the organism. The swab can then be replaced in its holder and sent to the laboratory. The swab should be processed as soon as possible because if it is allowed to dry out, it will adversely affect the viability of the yeast. The use of a swab sent in plain transport medium prevents this problem. Alternatively, a wire or plastic loop can be passed underneath the nail fold where the cuticle is detached and rubbed directly onto a culture plate but this requires special facilities which are not likely to be generally available.

Laboratory procedures

Once the nail specimen has arrived in the laboratory it is cut into portions of 2–3 mm in size. Part of the sample is mounted in 10–20% KOH on a glass microscope slide, a coverslip added and the preparation allowed to stand for 10–20 minutes for the material to 'clear' (digestion of the keratin), the coverslip squashed lightly and examined at up to ×400 magnification. The bulk of the sample though is cultured on an appropriate agar medium, usually Sabouraud's agar, and incubated for up to 3 weeks at 27–30°C; when yeasts are the suspected causal agents, incubation may be at 37°C for a shorter period (up to 1 week).

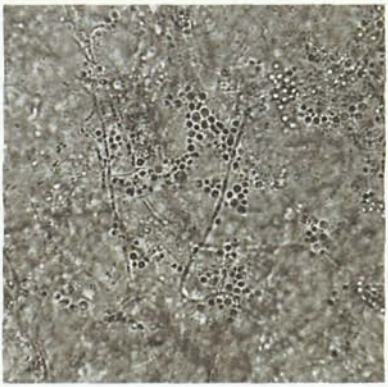

Fig. 74. *Candida albicans* in skin showing yeast cells and mycelium (20% KOH mount)

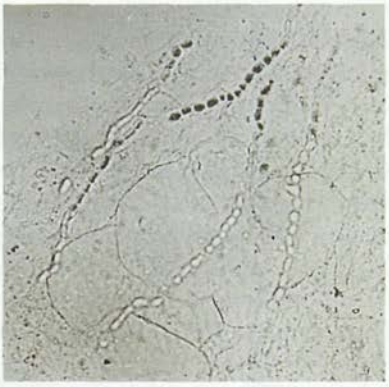

Fig. 75. Dermatophyte mycelium and spores (arthroconidia) in skin scales (20% KOH mount)

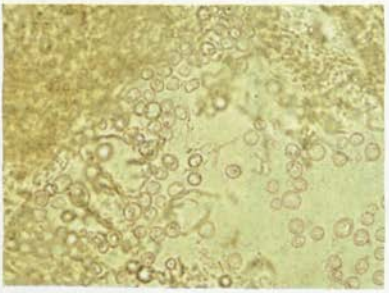

Fig. 76. Nail mounted in 30% KOH showing thick-walled, lemon-shaped spores and scanty hyphae of *Scopulariopsis brevicaulis*

Interpretation of results

Recognition of fungal elements in nail is a technique which requires considerable experience and expertise and this is an important reason for utilising a specialist laboratory. Fungal elements within the specimen may be scanty and be missed by the inexperienced, resulting in false negatives. Conversely, cell walls, fibres and other artefacts may be mistaken for fungi and result in false positives. For these reasons, without specific training, it is unhelpful to examine nail material in a clinic side room, as the results are not reliable.

Visualising fungal elements by direct microscopy does not identify the species of fungus involved, except that dermatophytes can be differentiated from yeasts and non-dermatophyte moulds such as *Scopulariopsis* or *Scytalidium* can be identified by the characteristic spores produced in nail or their atypical mycelial morphology. The extent of the differentiation possible depends primarily on the experience of the observer.

A reliable identification of the causal agent can only be made by culture. Yeasts grow within 2–3 days and are subsequently identified by biochemical tests. Since most dermatophytes tend to grow very slowly in culture, it is unlikely that the causal fungus can be identified in less than 7–10 days and cultures must be continued for 3 weeks before they are pronounced negative.

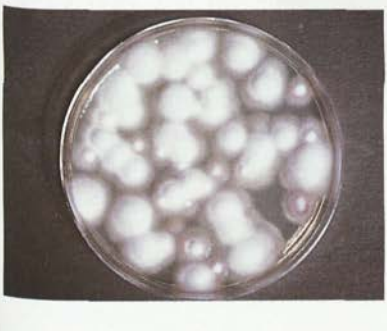

Fig. 77. Culture of *Trichophyton rubrum* on Sabouraud's agar showing red pigment at the periphery of colonies at 14 days

Fig. 78. Culture of *Trichophyton mentagrophytes* on Sabouraud's agar at 14 days

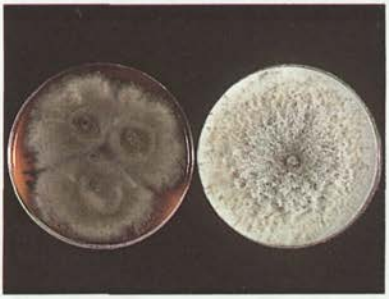

Fig. 79. Cultures of *Scytalidium dimidiatum* at 14 days on Sabouraud's agar showing two colony types

Fig. 80. Culture of *Epidermophyton floccosum* on Sabouraud's agar at 10 days

Any dermatophytes or moulds that develop on culture are identified by the macroscopic appearance of the fungal colonies and by the type of microscopic structures (especially spores) they produce. A definitive diagnosis of the fungal species involved is sometimes of importance in selecting an appropriate therapy. Unfortunately, however, even in the best laboratories, the fungus will fail to grow in culture in up to 50% of nail samples which were positive for fungus by microscopy. This may reflect poor sampling but in most cases it is due to the fact that the fungus in the accessible, distal parts of the nail may be up to 12 months old and consequently is non-viable. If it is essential that the fungus be cultured then a repeat specimen will need to be sent to the laboratory.

Dermatophytosis of nails needs to be distinguished from other mould and yeast infections that may not respond to anti-dermatophyte therapy. Therefore, it is important to identify correctly the species of fungus involved by culture. It is also important for the results of culture to be interpreted correctly. If, for example, a few colonies of yeasts or a non-dermatophyte mould develop in a culture which is positive for a dermatophyte, then it is likely that only the dermatophyte is significant. Moulds often contaminate nail samples and it is also common to isolate a few colonies of yeasts from such material. In true yeast infections, for example, there is usually heavy growth of the yeast and also the direct microscopy shows numerous yeast cells and mycelium. When a non-dermatophyte mould is the cause of nail dystrophy, then again the direct microscopy should show atypical hyphae which do not resemble dermatophyte mycelium. Laboratories should only report significant fungal isolates so as to avoid confusing clinicians as to the true cause of the nail disease.

Culture results are available two-three weeks later than direct microscopy results. Nevertheless, it is by-and-large sufficient to visualise the fungus in nail microscopically in order to confirm infection and to institute treatment. Culture results obtained subsequently will serve to confirm the correct choice of therapy or indicate any changes that may be required.

DIAGNOSIS OF FUNGAL NAIL INFECTION

POINTS TO NOTE

1. Infection should be confirmed by laboratory investigation, preferably in a specialist mycology laboratory, before treatment is started.

2. Specimens must be taken from the most affected part of the nail. A curette should be used to remove the subungual debris and a pincer-type clippers should be used to take nail clippings.

3. Nail material can be sent by post.

4. Looking at nail material microscopically in the clinic side room is liable to error, unless the observer has had special training.

Fig. 81. Diagnosis of fungal nail infection: points to note

Chapter Seven

Treatment of Fungal Nail Infections

Nails can be treated topically or systemically but in either case the assessment of success or failure should be based upon mycological cure. Dermatophytes are not commensal organisms in the immunocompetent and in the vast majority of cases eradication of the fungus will lead to significant clinical improvement. Because of the nature of the nail plate as a barrier to the penetration of topical agents, systemic treatment with an effective antifungal agent is always likely to prove more satisfactory. The prime function of any antifungal preparation is to eradicate the pathogen as quickly as possible and a drug which has a primarily fungicidal mode of action is therefore likely to be preferable. Until recently the results of treatment of fungal nail infection were disappointing even after prolonged therapy but clinical trial results with new, more effective antifungal agents have demonstrated dramatic improvement in cure rates. If infection with same organism is evident within a short time of stopping therapy, it is likely to be a relapse but if it occurs more than approximately 2 years later it is more likely to be reinfection; fungicidal agents are associated with lower relapse rates than fungistatic drugs.

Topical treatment

Fungal skin infections, unless they are extensive, are usually adequately treated with topical preparations containing either an azole, morpholene or allylamine antifungal agent. There are a number of preparations available for topical use in cream, lotion or spray form and, because of the high levels of drug achieved locally, they are all effective in the treatment of skin infection. The only topical agents designed specifically for nails contain either azole or morpholene drugs.

Tioconazole (Trosyl®) lotion contains tioconazole as a 28% solution in a penetrating vehicle. It is specifically designed for nail infection and when used alone is successful in around 22% of cases. It is better used in combination with a systemic agent and studies of it with griseofulvin revealed cure rates of 60–70%, less than those obtained with the newer systemic agents. Furthermore treatment must continue for the whole of the outgrowth period of the nail which is six months in fingernails and 12 months or more in toenails.

Amorolfine (Loceryl®) lacquer contains the morpholene amorolfine (0.25%), again in a penetrating vehicle. Morpholenes inhibit the production of ergosterol in the fungal cell wall. Used alone it appears to produce cure rates of 50% in both fingernails and toenails. Patients who responded had distal infection only.

Another approach, often suggested by chiropodists and podiatrists is to remove the diseased nail either chemically or surgically and to treat the new nail with a topical agent as it grows. Whilst appealing in theory the data available show disappointing cure rates which are not comparable with modern systemic agents. There is also a danger that the removal process will damage the nail matrix resulting in permanent deformity of the nail.

Other older topical preparations contain old fashioned antifungal agents such as salicylic acid, tannic acid, boric acid and undecenoic acid but there is little proper information available on their effectiveness. Their use can no longer be recommended.

In summary, it is probable that infections involving the whole of the nail plate are unlikely to respond to topical agents used alone. These are only likely to be successful in distal infection and mostly in fingernails which grow out much faster than toenails. In the majority of cases therefore topical agents cannot be recommended as first line treatment. The two possible exceptions are in patients where systemic treatment is contraindicated and in some cases of superficial white onychomycosis where the infection starts and spreads on the surface of the nail plate. Such cases are likely to respond to topical preparations although there is no published work comparing topical and systemic treatment.

Systemic Treatment

Griseofulvin

Griseofulvin, a weakly fungistatic agent which is toxic to fungal cell nuclei has, until recently, been the mainstay of systemic treatment of dermatophyte nail infection since its introduction 40 years ago. It must be administered during the whole outgrowth phase of the nail: 6–12 months in fingernails and 12–18 months in toenails. Cure rates of up to 70% can be obtained in fingernail infection but are rarely better than 30% in toenail disease and furthermore relapse rates are high. These poor cure rates together with a 20% incidence of minor but often troublesome side effects such as headache and nausea have now rendered griseofulvin obsolete in the treatment of nail infection in those countries where newer and much more effective agents have been introduced.

Azoles

The discovery of azomycin (2-nitro-imidazole) in 1955 resulted in the development of the imidazole antifungals followed more recently by the triazole group compounds. Many imidazoles are available as topical antifungal agents and ketoconazole can be used systemically. Ketoconazole is active against dermatophytes as well as yeasts but its use in the treatment of dermatophyte nail infections is limited due to hepatotoxicity and it is less effective than the newer triazole drugs.

Azoles inhibit a cytochrome P450 dependent fungal enzyme system which is involved in the final stages of ergosterol biosynthesis and leads to depletion of ergosterol in the fungal cell membrane. Their mode of action is primarily fungistatic in that the minimum fungicidal concentration (MFC) of azole drugs is significantly greater than the minimal inhibitory concentration (MIC). Azoles may also competitively inhibit human cytochrome P450 enzyme systems in the liver thus delaying the breakdown of many other drugs which are metabolised by the same route. Hepatotoxicity is very significantly less with triazoles and they have supplanted ketoconazole in the treatment of nail infections. Itraconazole has been more extensively studied than fluconazole and a dose of 200 mg daily for three months has been shown to be effective in the treatment of toe and fingernail infections. In an effort to reduce the total dose of drug, and thus the cost, pulse or intermittent therapy with itraconazole has recently received much attention. The drug is given in an increased dose of 400 mg daily for one week per month repeated at least three times. This regimen works because the drug remains in the nail for a long time after cessation of treatment. Three pulses remain in the nail long enough to cover the outgrowth period of fingernails but more may be necessary to cover the outgrowth period of a toenail. Cure rates of over 70% can be achieved using pulsed regimens.

Fluconazole has been tried in a single weekly dose of 150 or 300 mg for periods of three months or longer; the optimum dose and duration of treatment is as yet unclear.

Allylamines

Allylamine antifungal agents also inhibit the sterol biosynthetic pathway in the fungal cell membrane but they act at a different point in the pathway and inhibit

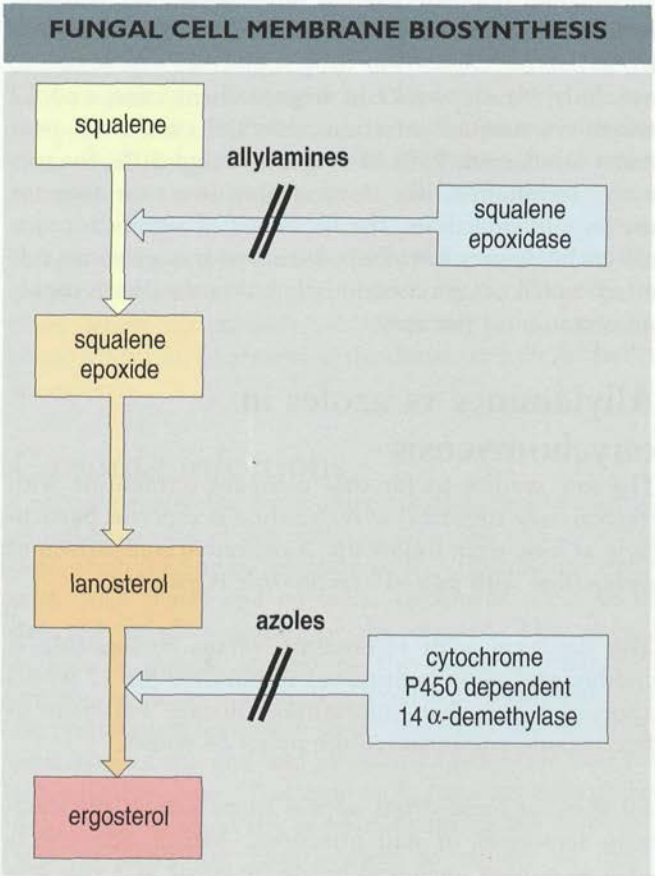

Fig. 82. Fungal cell membrane biosynthesis

the enzyme squalene epoxidase. This gives rise to the dual effect of ergosterol depletion and squalene accumulation, which is in itself toxic to the fungus, and it is this latter effect which results in the primarily fungicidal activity of the allylamines. As squalene epoxidase is not a cytochrome P450 enzyme this mode of action also gives rise to far less competitive interference with the metabolism of other drugs compared with azole antifungals.

Terbinafine (Lamisil®) is the only allylamine available for topical and oral use and it has been extensively studied in nail infections. The drug is given in a dose of 250 mg daily for six weeks in fingernail infection and 12 weeks for toenail infection. Average cure rates over many studies are 95% in fingernails and 80% for toenails. Terbinafine, like the triazoles, is a safe drug for use in nail infections, the incidence of significant side effects being very low. Taste disturbance is a curious side effect which occurs occasionally but is always reversible on cessation of therapy.

Allylamines vs azoles in onychomycosis

The few studies so far that compare terbinafine with itraconazole suggest that terbinafine is superior particularly at long-term follow up. A definitive comparison of terbinafine with pulsed itraconazole is awaited.

The situation with terbinafine versus fluconazole is similar, and again continuous terbinafine for 12 weeks appears better than intermittent dosage regimens of fluconazole administered for up to 24 weeks.

All three of these drugs appear to be safe in the long-term treatment of nail infections. Minor side effects such as nausea, rash and headache occur at a rate less

than half of that of griseofulvin and more serious effects such as idiosyncratic hepatitis, cholestasis and serious skin effects are very unusual and occur at a rate similar to many other drugs used long-term. Routine monitoring of liver function and blood count is not indicated with the allylamines but is advisable when itraconazole is given continuously for periods of longer than four weeks.

It would appear, on the basis of the evidence available thus far, that terbinafine is recommended for firstline treatment of dermatophyte nail infections with itraconazole as the alternative. Although terbinafine is active against many fungi it has a poor activity against the yeast phase of *C. albicans*. In nails affected with this yeast azole drugs are likely to be the better choice when systemic treatment is indicated.

Infections caused by non-dermatophyte moulds do not respond well to any available antifungals. However, in cases where the moulds are secondary to a dermatophyte infection, treatment of the dermatophyte is always necessary.

Candida infections

Chronic paronychia is a multifactorial disease consisting of inflammation of the posterior nail fold and cuticular separation leading to infection of the subcuticular space with both yeasts and bacteria. Treatment needs to be directed at all elements of the disease. This should include a topical steroid to the posterior nail fold together with both an antibacterial and antifungal topical preparation used once daily, dropped onto the proximal area of the nail and allowed to penetrate into the subcuticular space. This approach, together with gloves to keep the hands as dry as possible during wet work will lead to significant improvement in almost all cases. Sometimes the initial inflammation results from a contact

reaction, often to food stuffs and patch testing should be considered in recalcitrant cases. Systemic anticandidal drugs are almost never indicated in chronic paronychia. However, there is no doubt of their value in chronic mucocutaneous candidosis and the introduction of the oral azole ketoconazole materially improved the prognosis in these fortunately rare cases. Ketoconazole (Nizoral®) has now been supplanted by itraconazole (Sporonox®) and fluconazole (Diflucan®) which are much safer drugs. Depending upon the severity of the underlying immune defect they must be given long-term, either continuously or intermittently. The minimum dose of itraconazole necessary is 200 mg daily and this is currently the drug of choice in CMC as the optimum dose of fluconazole in such cases is unclear.

Distal candidal infection in association with vascular insufficiency and Raynaud's phenomenon is the most difficult type of candidal nail disease to treat because it is impossible to be certain whether or not the nail dystrophy results from vascular insufficiency with secondary yeast invasion or the converse where the yeast causes the nail dystrophy. Certainly if the nail signs do not improve following protection of the hands from cold then systemic therapy should be strongly considered. In the case of fingernails 6–12 weeks of itraconazole 200 mg daily should be given.

Why treat?

Fungal nail infection is erroneously regarded by some as a trivial condition. However, it is a disease of relentless progression which does not resolve spontaneously. Ultimately it will involve the whole of the nail bed and potentially destroy the nail plate. The disease thus increases in severity as the patient ages. The ageing process may well be accompanied by peripheral vascular disease, which, coupled with thickening and distortion of the toenails, may cause significant morbidity.

Although toenails have little in the way of mechanical function it is recognised that discoloured and distorted nails adversely affect quality of life and may impair normal social function by, for example, severely restricting the choice of footwear.

The case for treatment is more obvious in fingernail infection where the handling of small objects may be seriously compromised when fingernails are damaged or destroyed. In addition there is clearly significant embarrassment to the patient.

Finally, if nails are left untreated, contamination of communal bathing places will increase thereby leading to increased disease prevalence. It is also recognised that the recurrence rate of foot infections is much higher in patients with untreated nails.

There is therefore a strong case to be made for treating affected individuals as they present.

Why Does Treatment Fail?

Modern antifungal agents, particularly terbinafine, have a low MIC against all dermatophytes and achieve concentrations well above this level in the distal nail

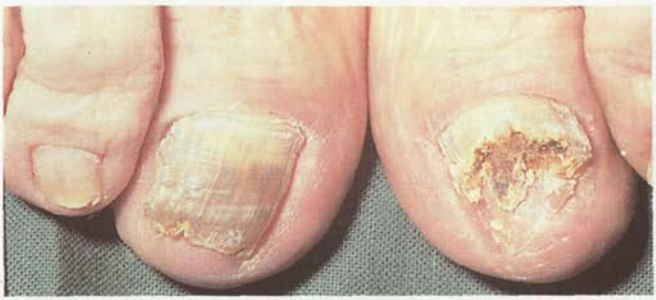

Fig. 83. Destruction of the nail in a patient with dermatophyte infection

relatively quickly after the start of therapy. Despite this mycological cure rates in toenail infection are all around 80% at best and it is relevant to ask why this should be in view of the activity of these drugs and their kinetics.

There are a number of possible reasons for treatment failure:

- lack of compliance
- poor drug absorption
- dermatophyte resistance
- immunosuppression
- impaired nail growth
- rapid reinfection
- kinetic problems within the nail.

Much has been made of the relative compliance between a continuous and pulsed regimen. There are no studies which show better cure rates with pulse regimens so differences in compliance between the regimens are unlikely to be an explanation. The persistence of the drug within the nail after cessation of therapy again suggests that missing the occasional dose is unlikely to be crucial when continuous regimens are employed. Lack of compliance therefore cannot explain a 20% treatment failure rate. Likewise poor absorption, dermatophyte resistance and immunosuppression are likely to account only for the occasional failure.

Damaged or diseased nail cannot regenerate and the nail must grow out to achieve clinical cure. In some patients, particularly the elderly, nail growth is virtually non existent or occurs only very slowly. Such patients will not achieve clinical improvement. They can sometimes be identified before the start of therapy in that they will admit to hardly ever cutting their toenails and so all patients should be asked this question. It is likely that nail infection proceeds very slowly and treatment failure or rapid relapse are unlikely to be explicable on the

grounds of reinfection. A number of studies with terbinafine have shown virtually no relapse at two years follow up which is indicative of the fungicidal nature of this drug. Follow up for longer than two years is unlikely to be able to differentiate between relapse and reinfection unless DNA typing techniques are employed.

The commonest reason for treatment failure is likely to be the result of the pattern of distribution of the fungus within the affected nail. Some nails are not kinetically homogenous and drug penetration may not be uniform. Nails which clinically show dense white areas which may be either linear or circular are likely to fall into this category. These areas represent a dense concentration of fungus amounting to a subungal 'dermatophytoma'. When the nail is cut back, and this can be done quite simply without anaesthetic, the subungual hyperkeratotic area which contains the fungus is not particularly adherent either to the nail plate or the nail bed and there is some anecdotal evidence that if the nail is cut back as far as possible in such cases, together with curettage of the debris, then cure rates will rise much closer to a 100%.

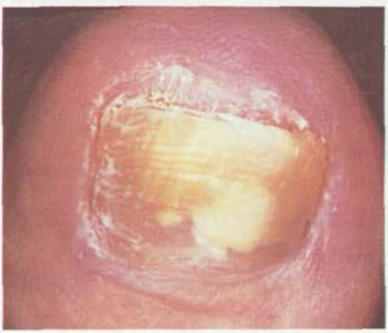

Fig. 84. White area indicative of subungual dermatophytoma

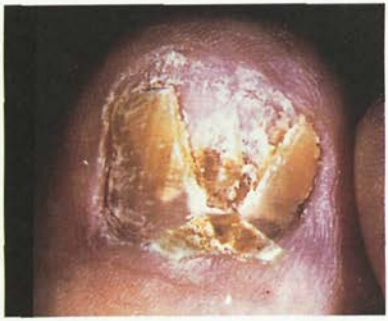

Fig. 85. Nail reflected showing dermatophytoma

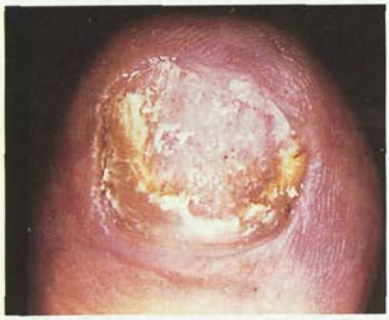

Fig. 86. Nail cut back and dermatophytoma removed

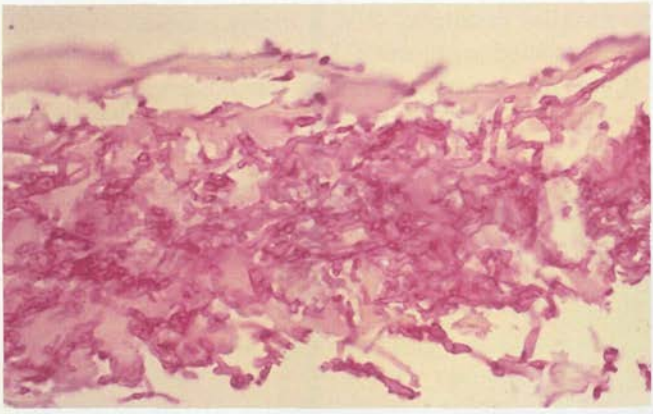

Fig. 87. Dermatophytoma stained with PAS showing densely packed fungal hyphae

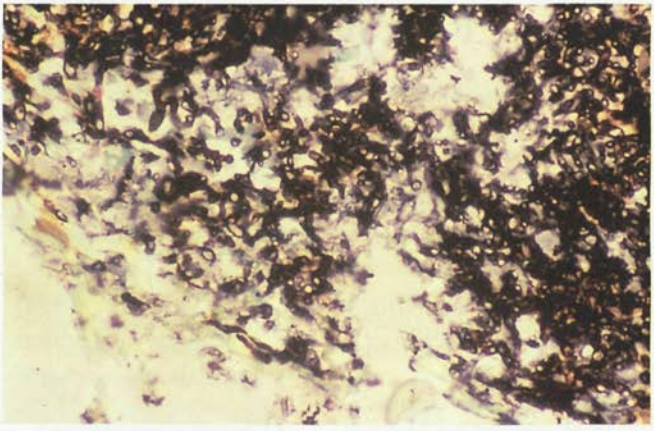

Fig. 88. Dermatophytoma stained with methenamine silver showing densely packed fungal hyphae

If all of the above factors are considered before starting therapy it is likely that cure rates can be improved well above the 80% average.

TREATMENT OF FUNGAL NAIL INFECTIONS

POINTS TO NOTE

1. Local treatment is less effective than systemic treatment.
2. Griseofulvin is only effective in 30% of toenail infections and 70% of fingernail infections.
3. Terbinafine is effective in 80% of toenail infections and 95% of fingernail infections.

Fig. 89. Treatment of fungal nail infections: points to note

Further Reading

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Midgley, H., Clayton, Y.M., & Hay, R.J. (1997) *Diagnosis in Color: Medical Mycology*. London: Mosby International.

Kibbler, C.C., Mackenzie, D.W.R. and Odds, F.C. (1996) *Principles and Practice of Clinical Mycology*. Chichester: Wiley.

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