

## Fortnightly Review

### Fungal nail disease: a guide to good practice (report of a Working Group of the British Society for Medical Mycology)

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The term onychomycosis refers to fungal infection of the nails whether this is a primary event or a secondary infection of a previously diseased or traumatised nail. Infection may be due to dermatophyte (ringworm, tinea unguium), yeast, or other non-dermatophyte (mould) species, and the clinical appearance may indicate the nature of the infecting organism. In paronychia chronic infection of the nail fold is most often caused by *Candida* species, but bacterial infection with Gram negative species such as *Pseudomonas* may coexist. Acute paronychia (whitlow) due to staphylococcal infection may also occur, and the presence of these bacterial infections will influence management. Invasion of the nail plate by *Candida* species may occur in the presence of paronychia, immune deficiency states (including chronic mucocutaneous candidiasis), Raynaud's disease, or endocrine disorders.

This paper reviews the clinical features of onychomycosis and the differential diagnosis of nail dystrophy, gives the reasons for appropriate mycological investigation, and discusses guidelines for appropriate treatment on the basis of laboratory findings and particular clinical situations.

#### Epidemiology

Treating onychomycoses is difficult but is important because they do not resolve spontaneously. About 30% of all superficial fungal infections affect the nail.<sup>1,2</sup> A

Summary points
● Onychomycosis is usually caused by dermatophytes (85-90%), but several fungi that are difficult to treat affect toenails
● Paronychia is caused by many <i>Candida</i> species, some resistant to azole drugs
● Samples for mycology should be taken as proximally as possible in the nail
● Demonstration of hyphae in a nail specimen by microscopy is sufficient to start treatment
● Choice of treatment depends on many factors including patient's age and preference, infecting fungus, number of nails affected, degree of nail involvement, whether toenails or fingernails are infected, and other drugs being taken

recent population survey of dermatophyte onychomycosis has suggested a prevalence of 2.8% for men and 2.6% for women in the United Kingdom.<sup>3</sup> Earlier surveys of swimming pools,<sup>4</sup> schools,<sup>5</sup> hospital patients,<sup>6</sup> and office workers<sup>7</sup> have shown a prevalence of tinea pedis of 8-40%. Of those people with tinea pedis, 20-30% also have affected nails.<sup>8</sup> This suggests that the prevalence of onychomycosis in adults could therefore be about 3-8%. This is difficult to assess, however, since some reports do not distinguish between dermatophytosis and other forms of onychomycosis or between infection of fingernails and toenails.

Toenails are more commonly infected than fingernails.<sup>3</sup> This applies particularly to dermatophyte and mould infections, whereas *Candida* infections are more likely to affect the fingernails and fingernail folds.<sup>9-11</sup> Mixed infection can account for up to 5% of onychomycotic infections.<sup>1,12</sup> There is wide geographical and ethnic variation in the causative species, but in Britain about 5% of cases are due to non-dermatophyte moulds such as *Scopulariopsis* (see box 1) and these almost exclusively affect nails. There are many cases of patients who have been inappropriately treated for years because the correct diagnosis has not been established. Nail infection due to *Scopulariopsis* will not respond to the standard treatments for dermatophyte or yeast onychomycosis.

The increase in foreign travel has led to the introduction of some exotic species. In addition fungi previously considered to be non-pathogenic may now be found as pathogens in patients with immune

#### Box 1: Causes of fungal nail infection

Common	Uncommon
<b>Dermatophytes</b> <i>Trichophyton rubrum</i> <i>Trichophyton interdigitale</i>	<i>Trichophyton erinacei</i> <i>Trichophyton soudanense</i> <i>Trichophyton tonsurans</i> <i>Trichophyton violaceum</i> <i>Epidermophyton floccosum</i> <i>Microsporum canis</i>
<b>Yeasts</b> <i>Candida albicans</i> <i>Candida parapsilosis</i>	<i>Candida glabrata</i> * <i>Candida guilliermondii</i> * <i>Candida krusei</i> * <i>Candida tropicalis</i> *
<b>Non-dermatophytes (moulds)</b> <i>Fusarium</i> spp <i>Scopulariopsis brevicaulis</i>	<i>Aspergillus</i> spp <i>Acromonium</i> spp <i>Scytalidium dimidiatum</i> <i>(Hendersonula)</i> <i>Scytalidium hyalinum</i>

\*Primarily causes of paronychia.

## Box 2: Typical clinical appearance of fungal nail dystrophy

### Dermatophyte

Distal and lateral nail involvement spreading proximally *or*  
Proximal subungual dystrophy *or*  
Superficial white dystrophy  
White or yellow thickened nails, crumbling of nail plate  
Adjacent web or skin involvement may be present

### Candida

Chronic paronychia  
Shiny red bolstered nail fold  
Almost exclusively affects fingernail folds  
Loss of cuticle  
Pus exuding from under nail fold  
Usually proximal nail involvement  
Distal nail dystrophy—associated with circulatory disorders  
Total dystrophic onychomycosis—chronic mucocutaneous candidosis  
Nails white, green, or occasionally black

### Non-dermatophyte

Superficial white onychomycosis  
Often solitary nail involvement—more often toenail  
Colour of nail may be influenced by nature of infecting mould. For example:  
*Acremonium* spp—superficial white onychomycosis  
*Scopulariopsis* spp—white, yellow, brown, or green  
*Scytalidium* spp—white or black  
*Fusarium* spp—white  
*Alternaria* spp—brown  
*Aspergillus* spp—green or black

deficiency and are often associated with a high mortality. For example, *Fusarium* species may cause onychomycosis, usually with a solitary toenail infection and sometimes with paronychia. This may provide a portal of entry leading to disseminated infection in immunocompromised patients, particularly those with haematological conditions and AIDS.

## Clinical appearance

The clinical picture of a fungal nail infection varies according to the nature of the infecting organism (see box 2). Involvement of adjacent skin should be noted, since if this is due to fungal infection the treatment may be different. If fungal infection is included in the differential diagnosis then mycological examination is essential, even if another disease exists. Non-dermatophyte moulds may be present as a secondary invader if a nail has previously been diseased or traumatised. This may account for the fact that such infections often affect only one nail.

Distal or lateral involvement of the nail plate occurring at the free end of the nail and spreading proximally is particularly associated with *Trichophyton rubrum* infection or some non-dermatophyte infections. Eventually the whole nail may be affected, and there may be proximal subungual nail dystrophy with separation of the nail from the bed. In superficial white onychomycosis, crumbly white areas are evident on the nail surface particularly in patients with AIDS. *T interdigitale* causes this type of appearance. Paronychia is seldom present in a dermatophyte infection, but *Candida* infection often begins in the proximal nail plate and paronychia is common. In chronic mucocutaneous candidosis, a rare T cell disorder with disabling mucosal candidiasis, total nail dystrophy is usual.

## Differential diagnosis

Several conditions may be associated with nail dystrophy, including bacterial and fungal infection (see box 3). Sometimes bacterial infection may coexist with fungal infection and may require treatment in its own right. Many other conditions can cause a change in the appearance of the nail, but the nail surface does not usually become soft and friable as in a fungal infection. If there is any doubt a specimen should be taken for mycological examination.

In some cases of psoriasis and eczema there may be fungal superinfection of the nails. Yeasts and bacteria are often found in subungual debris from psoriatic

## Box 3: Non-fungal conditions particularly associated with nail dystrophy

### Bacterial nail infection

*Pseudomonas aeruginosa*—green or black discoloration  
*Staphylococcus aureus* may present as acute paronychia (whitlow)

### Onychogryphosis

Grossly thickened and distorted horn-like appearance of nail  
Overcurvature of nail  
Great toenails most commonly affected  
May follow trauma

### Psoriasis

Yellow friable nails with pitting and onycholysis (lifting of nail from bed)  
Distal subungual hyperkeratosis  
Usually several nails affected  
Usually evidence of psoriasis elsewhere, not necessarily on adjacent skin

### Eczema

Irregularly pitted nail dystrophy  
Irregular transverse ridging and thickening  
Cuticles usually maintained (unless associated with chronic paronychia)  
History of eczema on adjacent skin

### Beau's lines

Transverse lines across nails corresponding to episodes of illness

### Lichen planus

Pterygium formation from cuticle  
Longitudinal ridging of nails  
Total nail loss, usually permanent  
May be lichen planus elsewhere

### Alopecia areata and alopecia totalis

Solitary or multiple nail dystrophy  
Variable severity of nail dystrophy  
Diffuse fine pitting, often in transverse lines  
Frequent onychorhexis (fragmented nails) and ridging  
Onset of nail dystrophy may not coincide with hair loss

### Yellow nail syndrome

Slow growing nails  
Smooth overcurved thickened yellow nails  
All nails affected  
No skin involvement  
Leg oedema and pleural effusions may be present

### Twenty nail dystrophy

Roughened nail surface, brittle free nail edge  
May not involve all 20 nails  
May resolve spontaneously  
Variable association with autoimmune disorders (lichen planus, alopecia areata)

### Leuconychia

Congenital or acquired  
Partial, total, or striate forms  
May be associated with general disease  
Usually occurs spontaneously or with minor trauma

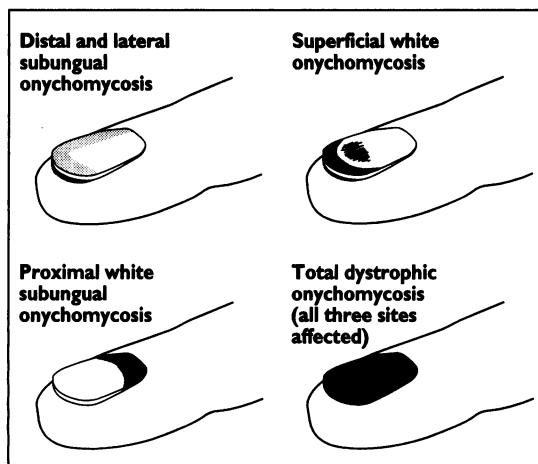


FIG 1—Patterns of fungal nail involvement

nails,<sup>13</sup> but dermatophyte infection is seldom found and is more likely to affect the toenails. Chronic paronychia due to *Candida* infection is commonly associated with psoriasis and eczema of the fingers.<sup>14</sup> It is important to detect coexisting infection since treatment will ensure a more rapid improvement in the appearance of the nails in these conditions.

#### Mycological diagnosis

When fungal infection is suspected, specimens for confirmation of the diagnosis should be obtained before treatment is started. As mentioned above, several dermatological conditions can produce nail changes that mimic fungal infection, and these can account for apparent failure of treatment with antifungal drugs.

#### TAKING SPECIMENS

An adequate specimen is required for microscopy and culture. Having a specimen taken should be painless apart from occasional slight discomfort when subungual specimens are taken. Figure 2 shows the appropriate sites from which nail specimens should be obtained. Scrapings taken with a blunt scalpel or clippings should be transported in a folded square of paper, preferably fastened with a paper clip, but commercial mycological packs are also available (such as Dermapak, Dermaco, Toddington, Bedfordshire, and MycoTrans, MycoTrans, Biggar, Lanarkshire).

#### MICROSCOPY AND CULTURE

In the laboratory 20–30% potassium hydroxide solution is added to part of the specimen to macerate the nail keratin so that the specimen can be examined for fungal elements by direct microscopy. The rest of the specimen is inoculated on to several different media to test for the presence of non-dermatophytes as well as dermatophytes and yeasts. This is important because infection with most non-dermatophyte species—such as *Scopulariopsis*, *Scytalidium*, *Fusarium*, and *Acremonium*—will not usually respond to oral treatment.

The results of culture can be positive even if microscopy is negative, but it is more common for microscopy to be positive while culture is negative (30–50%). Specimens from nails (subungual debris and clippings) should be taken as proximally as possible since this increases the probability of obtaining a positive culture result as well as positive microscopy. Although fungal elements may be seen in material from the distal end of the toenail, the culture may be negative. This probably reflects the slow rate of toenail growth, so that the fungal elements seen are no longer viable. Subungual material may yield helpful positive culture results since dermatophyte infection is

primarily a disease of the nail bed. It is desirable to show the presence of fungal hyphae or spores within nail keratin by microscopy to confirm that the nail is actually affected. In chronic paronychia culture of pus from the nail fold is extremely helpful.

When the clinical diagnosis of a dermatophyte infection is suspected, it may sometimes be necessary to repeat scrapings to confirm the presence of infection. It may also be helpful to repeat cultures after treatment has started to ensure that the infection is responding to treatment. However, susceptibility testing is rarely appropriate unless a treatment fails unexpectedly in a proved infection. Sometimes a fungus may be resistant to a treatment *in vivo* but not *in vitro*. In a particular patient drug interactions or failure of absorption may also account for apparent unresponsiveness to treatment.

Full laboratory mycological diagnosis is justifiable for the following reasons:

- Confirmation of fungal infection before starting prolonged oral treatment with antifungal drugs since a non-fungal dermatological condition may be present
- To optimise treatment as certain fungi are less responsive to treatment, especially toenail infections caused by *Trichophyton rubrum* and non-dermatophytes
- On epidemiological grounds to identify contacts (for example, tinea pedis in families or institutions, identification of unusual fungi, animal contacts in cases of animal ringworm)
- To test for mixed infection (important for treatment).

The results of direct microscopy should be reported as soon as possible, with an indication of the nature of the fungal elements found. A positive microscopy result is an indication for starting treatment. Results of culture should be available in two to three weeks but are sometimes available earlier. While treatment for chronic toenail infection can await the result of culture, it may be desirable to start treatment immediately for more inflammatory conditions such as *Candida* paronychia. *Candida* should be speciated if isolated—rather than reported as “*Candida* species” or “yeasts isolated”—because some species do not cause onychomycosis. In the past only *Candida albicans* has been assumed to have a pathogenic role, but it is now evident that other *Candida* species, especially *Candida parapsilosis*, may be playing an active rather than passive role. A *Candida* species isolated in culture is much more likely to be clinically important if direct microscopy shows the presence of yeast cells or pseudohyphae within the nail keratin. In paronychia other *Candida* species are pathogenic, and some isolates are resistant to imidazole and triazole drugs.

#### Treatment

##### TOPICAL TREATMENTS

Localised dermatophyte onychomycosis may be treated with nail paints such as 28% tioconazole with undecylenic acid (Trosyl) twice daily<sup>15</sup> or amorolfine

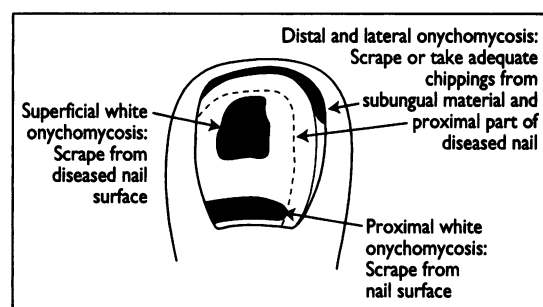


FIG 2—Where to take samples from nails

(Loceryl) once weekly<sup>10</sup> provided that there is only localised involvement of the distal ends of nails (see box 4). These preparations have superseded 8-ciclopirox paint in clinical practice. A 40% cure rate with Trosyl may be possible, especially with dermatophyte and *Candida* species,<sup>15</sup> but treatment needs to be continued for at least six months for fingernails and 12 months or longer for toenails. A similar cure rate for toenails can be obtained with amorolfine, but a rather better cure rate of 50% after six months is likely with affected fingernails.<sup>10</sup>

Proximal nail disease or severe nail bed involvement is extremely unlikely to respond to topical treatment, even if this is preceded by chemical dissolution of the diseased nail with 40% urea paste.<sup>16</sup> Urea paste should normally be applied by a chiropodist. Nail avulsion may occasionally be necessary for non-dermatophyte (mould) disease but is undesirable since it may result in damage to the nail matrix and subsequent permanent damage to the nail. Some non-dermatophyte infections may respond to systemic treatment. When the skin is affected as well as the nails this will require treatment in its own right and, if extensive, may be an indication for systemic treatment.

Topical treatment with an imidazole cream or paint twice daily for up to six months will often cure chronic paronychia, especially when this is localised to finger-nail folds, which is the common clinical situation. From a practical viewpoint, paint formulations may be easier to use than creams. Measures to reduce maceration of the nail folds should be incorporated into the management of such cases. The associated proximal nail dystrophy will often improve with treatment of the nail fold. Localised distal infection of the nail by *Candida* species requires use of Trosyl nail paint twice daily or weekly use of amorolfine nail paint. Severe *Candida* onychomycosis or paronychia is likely to require systemic treatment, especially since such cases are usually associated with an immune deficiency state.

#### SYSTEMIC TREATMENTS

##### *Terbinafine*

The allylamine terbinafine (Lamisil) is now the treatment of choice for dermatophyte onychomycosis. Terbinafine has fungicidal activity against all dermatophytes and various *Candida* species, including *Candida parapsilosis*. However, it shows only fungistatic activity against *Candida albicans*.<sup>17</sup> It is therefore inappropriate for a mixed dermatophyte and *Candida albicans* infection unless the *C albicans* infection is localised and can be treated topically. With more extensive mixed infection, itraconazole would be more appropriate.

Infection of fingernails requires terbinafine 250 mg daily for between six weeks and three months, whereas toenail infection requires treatment for three months or possibly up to six months. A repeat culture at three months may be useful in patients undergoing treatment with terbinafine, since a positive culture at this stage would indicate whether a longer course was required. From a clinical viewpoint, it may be difficult to assess whether a fingernail or toenail is completely free of infection at three months since the distal dystrophic part of the nail may not have grown out. Treatment with oral terbinafine will also clear any associated skin infection without the need for additional topical treatment. Although it is not yet licensed in Britain for use in young children, it may be used in children aged 12 and over when other options are unsuitable or have failed.

Cure rates of 80-95% in dermatophyte nail infection<sup>18</sup> and of about 95% in dermatophyte skin infection can be expected with terbinafine. This drug has the additional advantages that it interacts with relatively few other drugs and is generally well tolerated.

#### Box 4: Recommended treatments for onychomycosis

##### Dermatophyte infection

Localised distal nail disease  
28% Tioconazole with undecylenic acid (Trosyl) paint twice daily  
Amorolfine (Loceryl) paint weekly  
Dissolution with 40% urea paste

##### Proximal or extensive nail disease

Terbinafine (Lamisil) 250 mg daily for 3-6 months  
Itraconazole (Sporanox) 200 mg daily for 3-6 months  
Griseofulvin 10mg/kg/daily (500 mg twice daily); for 6-9 months for fingernails, for 15-18 months for toenails  
Possibly also a nail paint (see above) especially for toenails

##### Candida infection

*Chronic paronychia (localised)*  
Imidazole creams or paints  
Nystatin ointment  
Terbinafine cream (Lamisil)

##### Distal candidal nail infection

28% Tioconazole with undecylenic acid paint (Trosyl) twice daily  
Amorolfine (Loceryl) nail paint weekly

##### Severe candidal nail infection or severe chronic paronychia

Itraconazole 200-400mg daily for 3 months

##### Non-dermatophyte (mould) onychomycosis

###### Localised nail disease

28% Tioconazole with undecylenic acid paint (Trosyl) twice daily  
Amorolfine (Loceryl) paint weekly  
Possibly also dissolution with 40% urea paste or avulsion

###### Persistent nail disease

Itraconazole 200 mg daily for 3-18 months

Although it shows some in vitro activity against *Scytalidium dimidiatum*, its activity in vivo is limited. Its place in the treatment of non-dermatophyte (mould) onychomycosis is not as well defined as that of itraconazole,<sup>17</sup> and itraconazole may be preferable for some of these infections.

##### Itraconazole and other azole drugs

Itraconazole is active against most *Candida* species, including *Candida albicans*, and is also effective in dermatophyte infection. Up to 5% of cases of onychomycoses have mixed cultures,<sup>11</sup> and itraconazole will usually successfully treat those requiring oral treatment. Pulsed treatment with itraconazole (in which a week of treatment is alternated with three weeks without treatment for several cycles) has been advocated, but this drug is also available for continuous treatment and can be taken for at least three months. Itraconazole 200 mg daily for at least three months is the most appropriate treatment for severe nail disease or for immunocompromised patients, especially when non-dermatophyte moulds such as *Aspergillus* species are implicated. Itraconazole has superseded ketoconazole in treating nail infection because of its better safety profile. Itraconazole persists in nail keratin for at least six months after the end of treatment. Cure rates for dermatophyte and candidal nail infection are about 80% and are similar to those with terbinafine. However, itraconazole may interact with several other drugs, and this limits its usefulness in certain situations. Fluconazole is not yet licensed for nail disease, but it may be required for severe candidal nail infection or chronic paronychia in doses up to 400 mg daily in immunocompromised patients.

Neither itraconazole or fluconazole is currently licensed for use in children. In older children

(weighing over 20 kg), however, a 100 mg capsule of itraconazole or 50 mg capsule of fluconazole may be prescribed. In younger children fluconazole suspension of 3 mg/kg may be appropriate.

### Griseofulvin

Griseofulvin is effective only for dermatophyte infection and is therefore inappropriate in cases of mixed infection unless it is combined with a nail paint that has a wider antifungal spectrum. Griseofulvin may cure up to 90% of fingernail infections in four to eight months, but its low cure rate of 40% in some toenail infections<sup>19</sup> means that it is now less appropriate (treatment with terbinafine or itraconazole gives more than double the cure rate). However, griseofulvin is currently the only oral drug licensed in the United Kingdom for treating dermatophyte infection in children. Other considerations that should be borne in mind include the relative risk of side effects, the cross reaction of penicillin hypersensitivity with griseofulvin, and interactions with other drugs already prescribed.

### COST BENEFITS

When the relative benefits of a particular drug are considered, the advantages—such as shorter length of treatment, greater efficacy, and lack of side effects or drug interactions—need to be balanced against the cost. When topical and systemic treatments are combined to obtain a higher rate of cure, the total cost of such a combination may be greater than that of a single more expensive but more effective drug used for a shorter time. For this reason, terbinafine has become the first line treatment of choice for most cases of dermatophyte infection whereas itraconazole may be preferred for mixed infection.

Costs can be justified if the most appropriate drugs are chosen according to the nature of the organism isolated. When the diagnosis is not immediately obvious it is worth waiting for the final culture result to

avoid unnecessary treatment, especially if the condition is not life threatening. An exception to this rule may be made if there is extensive disease or if the patient is immunocompromised even if the disease process is localised.

Evaluation of recent drugs such as amorolfine, itraconazole, fluconazole, and terbinafine is still continuing.

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## A MEMORABLE PATIENT

### Hearing voices

I spent the winter of 1994-5 in Osho Commune International, the largest spiritual health centre in India, where I carried out a research project. A slim, intelligent yet distressed European woman in her early 40s asked me for a talk. For about five years she had been hearing voices of several men and women talking to her and each other in different European languages. She resisted their instructions but thought that they influenced her body and changed her feelings. Friends' advice to "withdraw her antennas" had been helpful. Recently she had been hearing plants commenting on her thoughts and actions. These experiences had become so uncomfortable that she wanted to get rid of them. She had never mentioned them to doctors, afraid of being regarded as mad and given medicines.

She did not seem a risk to herself or others and had no features of major depression. I explained the benefits of antipsychotic medication but she declined, afraid of side effects and reduction in sensitivity. What to suggest? She decided to try meditation, painting, and gardening.

A week later the voices were worse and she found it hard to concentrate. I urged her to consider antipsychotic drugs. She felt devastated. She was determined to get rid of her experiences without medicine. She attended painting classes, meditated, and did gardening. She booked craniosacral balancing (soft bodywork) and Tibetan pulsing healing (meditative bodywork) sessions.

In the following weeks she flourished. She described increasing self worth and dignity, became more lively and

energetic, and the voices did not disturb her any more. She stopped gardening but maintained her progress and returned to Europe a few months later.

I felt I had not done anything for her and yet she was grateful. I regard antipsychotic drugs as a mainstay in treating psychosis. But her symptoms reduced with methods doctors tend to discount. When she left India she was not symptom free, but confident and cheerful.

Psychosis can fluctuate in severity independent of antipsychotic treatment. But why had I not seen such improvement in patients with chronic psychosis in Germany or in Britain? Do such patients avoid psychiatrists? Are they not referred or seen only once in a clinic, never to return again? Do we treat too hastily? Are we hindering improvement by reducing self respect, sensitivity, and motivation through stigma, neuroleptic medication, or side effects?

I do not expect to find an answer. Osho Commune International discourages people with mental health problems, as a visit can be destabilising and psychiatric facilities for visitors are minimal. So it is unlikely that I will have a similar experience there. I feel enriched and grateful. I became aware of treatment options which I never considered before and probably would not consider in a Western health service. I learnt to pay attention to the possibility of improvement without drugs, unusual treatments which patients may suggest, and of the value of their motivation.—KAMALA-MARIA MUELLER is a locum senior registrar in psychiatry in Colchester