Guidelines for the management of leprosy reactions; Sri Lanka College of Dermatologists

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Introduction

Leprosy rseactions are immunological phenomena that occur before, during or after completion of multi drug therapy (MDT) for leprosy. Two major types of reactions have been defined, namely type 1 (T1R) or reversal reaction and type 2 or erythema nodosum leprosum (ENL) reaction. Silent neuropathy is also an entity that leads to disability in leprosy[1]. As the management of silent neuropathy is similar to the management of neuritis due to type 1 reaction, silent neuropathy too has been included under type 1 reaction.

The occurrence of T1R and ENL in the same patient either simultaneously or at different stages of the disease process is a well described phenomenon. Even though this has been named "mixed reaction", this terminology has not been accepted yet in the world literature.

In this publication we have reviewed the existing literature on the management of leprosy reactions and formulated a guideline to suit the conditions and resources in Sri Lanka.

1. Type 1 reaction and silent neuropathy

1.1 Definition

Type 1 reaction

Occurrence of either or both of the following signs and symptoms in a patient with leprosy (mostly borderline forms)

- Increased inflammation of skin lesions
- Inflammation of nerves (manifesting as new motor/sensory impairment, nerve pain or tenderness)

T1R could occur before, during or after treatment with multi drug therapy (MDT). The majority (about 50%) of reactions occur during treatment with MDT but approximately 25% of patients present with a type 1 reaction at the time of diagnosis. Approximately 30% of patients with borderline leprosy go on to develop T1R at some point during their illness[2].

Silent neuropathy

Sensory or motor impairment without skin signs of either TIR or ENL, without evident nerve tenderness or without spontaneous nerve pain, paraesthesia or numbness[1].

1.2 Risk factors

Extensive disease (involvement of either the skin or nerves in more than two body areas) and having a positive skin smear are risk factors for T1R[3]. Persons who present with WHO disability grades 1 and 2 are at more risk for further reactions[4]. T1R are frequently seen after starting MDT and during the puerperium[5].

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1.3 History and examination

Early detection of a T1R is the most important factor to prevent permanent disability. A careful history and examination are essential to make a prompt diagnosis.

Look for the following clinical features

- Inflammation (swelling, redness and pain) of the existing skin lesions
- Painful, tender and swollen peripheral nerves
- Signs of nerve damage – loss of sensation and muscle weakness
- Signs of eye involvement: weak eye closure, red eyes due to exposure keratitis
- Swelling of hands and feet

Sometimes there may be new skin lesions. The appearance of a few new lesions in a patient already on MDT or recently completed MDT should be considered as a sign of reaction rather than relapse. Some questions that you can ask to make a diagnosis of T1R are;

- Is there any pain, swelling or ulceration of your skin lesions?
- Do you have any difficulty in closing the eyes?
- Have you developed any new weakness in the limbs?
- Do you feel any weakness when you attempt to do any activities of daily living using your hands and feet?
- Are there any areas of numbness which were not there before?

Pain in the affected limb without any other signs of a reaction may be due to neuropathic pain rather than a reaction.

1.3.1 How to look for nerve function impairment

Voluntary motor testing (VMT)

Test for facial, ulnar, radial, median and lateral popliteal nerves on each side, using the modified MRC grading for muscle power.

Facial nerve – Normal and forced eye closure (orbicularis oculi)

Median nerve – Thumb abduction (abductor pollicis brevis) index finger abduction (first dorsal interosseous)

Ulnar nerve – Little finger abduction (abductor digiti minimi)

Radial nerve – Wrist extension (extensor muscles)

Common peroneal nerve – Foot dorsiflexion (tibialis anterior, peroneus longus and brevis)

Table 1. Modified MRC grading for muscle power

Hands and feet	*MRC grade*
Full range of movement (ROM) full resistance	5
Full ROM, reduced resistance	4
Full ROM, no resistance	3
Reduced ROM, some joint movement	2
Flicker only	1
Full paralysis	0

Sensory testing (ST)

Sensory testing is ideally done with graded monofilaments, 2g for the palms and 4g for the soles. As monofilaments are not widely available in Sri Lanka we propose that a ballpoint pen or a tooth pick be used for sensory testing. An alternative would be to use a folded piece of paper.

Test for sensory impairment

- Place hand flat, palm upwards on a table
- Explain to patient what you are going to do
- Ask patient to close the eyes
- Using a ballpoint pen or a tooth pick touch the four places shown in the palm. Press gently just enough to make a depression on the skin. Do not press too hard
- If you are using Semmes Weinstein monofilaments, exert enough pressure to bend the filament
- Ask the patient to point to the place that you touched using the index finger of the other hand ("touch where I touch/where am I touching?")
- Test both hands
- Repeat the same process for the soles of the feet, touching the places indicated in the diagram
- Record whether the patient can feel the ballpoint pen in each instance (annexure 1: Neurological Assessment Form)

If the patient cannot feel the monofilament/ballpoint pen/tooth pick you may conclude that the patient has sensory impairment.

1.4 Investigations

The diagnosis of T1R is based on clinical criteria rather than investigation findings. But the following investigations can be used as adjuncts to the diagnosis in special situations.

Skin biopsy may show changes in only about 50% of clinically diagnosed reactions. Loose granuloma formation due to intra and inter – granuloma oedema, plasma cells and granuloma fraction are more sensitive indicators of a T1R[6].

Sometimes it may be difficult to differentiate between a relapse and a reaction. A positive slit skin smear or an increase in BI from the baseline or lesions occurring more than 3 years after completing a course of MDT will be more suggestive of a relapse. A recent study from Pakistan proposed a scoring system to differentiate relapse from a late T1R. This score takes into account, the time since RFT, risk factors and clinical presentation at relapse[7].

Table 2. Relapse or reaction?

Criteria	*Relapse*
Time since release from treatment	>3 years
Progression of signs and symptoms	Slow
Site of skin lesions	Also in new places
Pain, tenderness or swelling	Not seen
Damage	Occurs slowly
General condition	Not affected

1.5 Non-pharmacological management

Supportive measures are as important as steroid therapy in the management of T1R and neuritis.

- Pain relief with simple analgesics or non steroidal anti inflammatory drugs (NSAIDs) may be necessary in some patients.
- Resting of the affected limb in case of neuritis is essential to prevent further deterioration. Splinting in the functional position with gentle joint movements to prevent contractures is best[8].
- Once the acute inflammation has subsided physiotherapy to regain the function of the affected muscles should be started.
- In case of established nerve palsy; e.g. ulnar claw or foot drop, appropriate splints and appliances should be provided and the patient should be taught simple exercises to be done at home to improve the function of the affected muscles. The help of the occupational therapist and physiotherapist is necessary for this purpose.

1.6 Pharmacological management

It has been shown that corticosteroids can reverse the nerve function impairment in about 33-73% of nerves of patients with T1R[9,10]. There are only a few studies on the use of corticosteroids for the management of T1R. A recent *Cochrane Database Review* concluded that there is inadequate evidence on the optimal dose or duration of corticosteroids to prevent nerve damage[11]. However there is evidence that a 5 months' course of prednisolone is significantly superior to a 3 months' course of prednisolone to reduce the need for further steroids in the management of T1R[12].

Even though a type 1 reaction is an acute phenomenon it is well accepted practice to treat nerve function impairment of less than 6 months' duration with a course of prednisolone with the objective of reversing the existing nerve damage.

It may be necessary to tailor the regime according to individual patients but a longer course of steroids than the current 12 week course suggested by the WHO can be more beneficial. A study done in Nepal which compared the use of pulsed methylprednisolone versus the 16 week course of prednisolone found that 50% of the patients on the 16 week regime required additional steroids during the period of follow up[13].

We suggest the use of the following regime of prednisolone in severe type 1 reactions

Daily dose of prednisolone	duration
40 mg	2 weeks
35 mg	2 weeks
30 mg	2 weeks
25 mg	2 weeks
20 mg	2 weeks
15 mg	2 weeks
10 mg	2 weeks
5 mg	2 weeks

The alternative regime used by Rao *et al* is as follows

Daily dose of prednisolone	duration
30 mg	2 weeks
25mg	2 weeks
20 mg	8 weeks
10 mg	4 weeks
5 mg	4 weeks

The course of prednisolone can be tailored according to each individual patient's need for and the response to therapy. This will have to be based on the improvement of the nerve function with treatment. We suggest that all patients with active neuritis be seen at the clinic every 2 weeks and their nerve function assessed and recorded at each visit (Annexure 1: Nerve Function Assasessment Form).

The steroid dose can then be adjusted according to the response to steroid therapy. The suggested approach would be:

- If nerve functions deteriorate: go one step up the ladder
- If nerve functions remain the same: maintain the same dose of steroids
- If there is improvement in nerve function: reduce dose according to the fixed duration regime.

1.6.1 Monitoring and supportive care for individuals on long term steroids[5]

- Exclude contra-indications to therapy like tuberculosis
- Monitor weight and blood pressure at each visit
- Urinalysis or blood glucose measurements regularly
- Gastric protection with H2 blockers or proton pump inhibitors
- Osteoporosis prevention

1.6.2 Second line therapy

It may be necessary to use second-line drugs for patients who cannot tolerate or become dependent on steroids. Azathioprine (in a dose of 3mg/kg/day) used in combination with an 8 weeks' reducing course of prednisolone has been shown to be as effective as a 12 weeks' reducing course of prednisolone[14]. Azathioprine can be recommended to be used as a steroid sparing agent but its use in sufficiently large doses is hampered by the lack of monitoring for bone marrow toxicity.

Ciclosporin (5mg/kg/day) too has been used with some success[15]. The use of ciclosporin is precluded by the cost and adverse effects like hyperkalemia and hypertension.

These are the only agents that have been proven in clinical trials to be of benefit for T1R.

1.7 Role of decompressive surgery

Decompressive surgery for the relief of mechanical compression in cases of severe neuritis or in patients with neuritis not responding to medical therapy has been advocated. A *Cochrane Database Review* failed to show any benefit of surgery over medical management with prednisolone[16].

In the absence of good data on the efficacy of decompressive surgery the following recommendations have been laid down by the ILEP[17].

- In a certain percentage of patients after medical management surgery may be necessary to prevent/recover further nerve damage.
- Surgery should not be attempted without medical management
- The following surgical techniques are not recommended
  - Complete fascicular neurolysis
  - Nerve decapsulation

Surgery should not be undertaken without pre and post procedure nerve function testing (VMT/ST) to assess the efficacy of the procedure.

2. Erythema nodosum leprosum (ENL) reaction

ENL or type II reaction is an immunological phenomenon with the involvement of both the humoral and cell mediated immune responses. It is a chronic illness with systemic features. ENL usually occurs in lepromatous and borderline lepromatous leprosy. Recurrence is the rule rather than the exception[18].

There is a paucity of well designed studies on the management of ENL. Systemic corticosteroids are the first line of treatment but no studies have been done on the optimal dose or the duration of treatment.

2.1 Definition

ENL is defined as the occurrence of crops of painful erythematous nodules in a patient with lepromatous or borderline lepromatous leprosy. The following signs and symptoms can also occur:

Fever
Malaise
Peripheral oedema
Arthralgia/arthritis
Bone pain
Eye involvement
Lymphadenitis
Orchitis
Nerve impairment
Protein/haematuria

2.1.1 Mild ENL

In mild ENL skin nodules occur with or without low grade fever and malaise.

2.1.2 Severe ENL

Severe ENL may include one or more of the following:

- Neuritis with painful or markedly tender nerves with or without loss of nerve function.
- Prolonged moderate or high fever along with severe general malaise.
- Pustular skin lesions which may progress to extensive ulceration.
- Tender and enlarged lymph nodes.
- Iridocyclitis, orchitis, periostitis or joint swelling.
- Albumin and red blood cells in the urine.

2.2 Risk factors

Lepromatous leprosy and a bacillary index of more than 4 are the proven risk factors for ENL[18,19].

Pregnancy, lactation, intercurrent infection, vaccination and psychological stress have been implicated as risk factors but these have not been proven[20]. It may be useful to look for these likely precipitating factors in patients who develop recurrent ENL.

2.3 History and examination

Clinical features of ENL have been already dealt with in the definition. But the following features need special mention.

- ENL can occur before, during or after completion of MDT. ENL could sometimes occur without overt signs of leprosy except for subtle features like peripheral neuropathy.
- Skin lesions of ENL should be differentiated from erythema nodosum especially when they occur without overt signs of leprosy. Nodules of ENL are transient, more numerous and occur in areas other than the shins, the usual site of erythema nodosum[20]. Furthermore erythema nodosum does not ulcerate.
- Skin lesions could occur alone or in association with systemic symptoms. ENL can be considered as mild when only skin lesions are present.
- Bone pain and tibial tenderness can occur with ENL.
- Iridocyclitis, a potentially sight threatening complication can manifest as painful red eye, photophobia and small, irregular pupil.
- Nerve impairment can occur in ENL.

2.4 Differential diagnoses

- Erythema nodosum
- panniculitis
- Sepsis
- Sweet's syndrome

2.5 Investigations

ENL is a clinical diagnosis but a skin biopsy can be performed if there is any doubt. The following features can be seen in ENL[21]:

- Inflammatory infiltrate composed mainly of neutrophils in a biopsy taken early in the course. In an older lesion the infiltrate may resemble that of chronic inflammation.
- Oedema of the dermis and subcutis
- Vasculitis
- Panniculitis

2.6 Management

2.6.1 Mild ENL

Mild ENL can be managed with rest, and analgesia with simple analgesics or NSAID.

Look for possible precipitating factors like infection.

2.6.2 Severe ENL

Patients with severe ENL should be initially managed as in-patients whenever possible.

2.6.3 First line therapy

2.6.3.1 Corticosteroids

Even though the dose and duration of corticosteroids have to be decided on an individual patient basis the following regime of prednisolone has been suggested by the ILEP for the control of ENL[17]:

- Starting dose 30-60 mg daily
- Reduce by 10 mg every week until a daily dose of 20 mg has been reached
- Reduce by 5 mg weekly until 10 mg daily is reached
- Maintain at 5-10 mg daily for several weeks in patients with chronic ENL

There is no fixed regime for the use of prednisolone in ENL. In patients with recurrent ENL the dose may have to be increased or a new course may have to be started.

There is a significant risk of prednisolone dependence in patients with ENL. Such patients may require a daily prednisolone dose of 15-20 mg to keep them free of ENL.

Care should be taken to monitor patients for possible adverse events due to prolonged use of prednisolone. (1.6.1).

2.6.3.2 Clofazimine

Clofazimine has a slow onset of action (4-6 weeks) and should only be started as an adjunct to corticosteroids[22]. It can be used as a steroid sparing agent in patients with steroid dependence or those with adverse effects due to prednisolone.

Clofazimine can be started at 300 mg daily in 3 divided doses (to reduce GI discomfort). This dose can be maintained for 3-4 months and then gradually reduced to a daily dose of 100 mg. this dose can be maintained for 3-4 months. The total duration of clofazimine therapy can be 8-12 months or more.

Once the ENL is under control with clofazimine and prednisolone (6-8 weeks) prednisolone can be tailed off. If the ENL recurs while the patient is on clofazimine, the dose of clofazimine can be increased first (before increasing prednisolone).

Adverse effects due to clofazimine
Skin pigmentation
Dry skin
Cramping abdominal pain
Diarrhoea
Clofazimine crystal enteropathy (rare, but potentially life threatening)[23]

2.6.4 Second line therapy

2.6.4.1 Thalidomide

Thalidomide is a very effective drug for ENL but its use is limited by the potential teratogenicity. Prospective clinical trials have shown that it has a quicker onset of action and reduces symptoms more rapidly than pentoxifylline and non steroidal anti inflammatory drugs[24].

Indications for thalidomide in ENL[25]

- Severe ENL not responding to prednisolone and clofazimine
- Moderate to severe ENL in patients with serious adverse effects due to prednisolone
- Moderate to severe ENL in patients who are dependent on prednisolone

Dosage of thalidomide in ENL[25]

- In severe ENL 300 mg of thalidomide can be given at night or in 3 divided doses. Reduce the dose to 100 mg nocte slowly, looking for worsening of ENL.
- Patients should be stabilized on the lowest possible dose of thalidomide to control symptoms (50-100 mg daily) and be maintained on this dose for 2-3 months.

The following guidelines should be strictly followed when starting a patient on thalidomide

We suggest that a register be maintained at every dermatology clinic recording the details of patients on thalidomide and the dates, dosages and the duration for which thalidomide is issued.

Who can be given thalidomide?

- Men who fulfill the above indications
- Post menopausal women
- WHO or the ILEP do not recommend the use of thalidomide in women with child bearing potential. But it can be given to women with very severe ENL but under strict supervision of the treating dermatologist.

Procedure for prescribing thalidomide to women of childbearing potential

- The responsibility of preventing a pregnancy while the patient is on thalidomide lies with the treating dermatologist. Whenever possible women of childbearing potential should be treated as in patients.
- Two dermatologists should agree that thalidomide is absolutely necessary to control the symptoms. The treating dermatologist can discuss the case with a colleague before making the decision to start thalidomide and the names of both the dermatologists should be recorded in the thalidomide request form.
- The patient and her partner should be counseled by the treating dermatologist as to the potential risk of teratogenicity.
- The patient should be started on a semi permanent method of contraception (DMPA injections or intra uterine devise) before starting on thalidomide. The couple should be advised to use a second method of contraception (barrier) while the female is on thalidomide.
- In case of unmarried women they should be counseled on the risk of teratogenicity and started on the oral contraceptive pill before starting thalidomide.
- A pregnancy test should be done and the negative report should be sent with the thalidomide request form.
- The consent form (in the patient's mother tongue) should be given to the patient and the partner to read. Once they have gone through it the contents of the form should be discussed with the patient by the dermatologist and any clarifications should be given.
- The patient should sign the consent form. This should be done in triplicate, one copy for the patient, one for the patient's records to be kept in the treating centre and the other should be sent to the Medical Supplies Division (MSD) when the request for thalidomide is made.
- The thalidomide request form should be filled and signed by the treating dermatologist. The contact details of the dermatologist should be given clearly.
- The thalidomide request form and the consent form together with the negative pregnancy test should be sent to the MSD.
- Only one month's supply should be issued at any given time to ensure that pregnancy is excluded before the next dose.
- The pregnancy test should be repeated every month before the next supply of thalidomide is issued.
- The issue of teratogenicity and the importance of not sharing the medication with anyone should be reiterated at every visit.
- Thalidomide should be given for the minimum possible duration.
- When stopping thalidomide the patient should be advised to continue the contraception for at least one more menstrual cycle.

The S.T.E.P.S. programme in the USA has been highly successful in prevention of pregnancies in patients treated with thalidomide. We suggest that such a programme where central monitoring of all patients and prescribers who use thalidomide be established in Sri Lanka too.

Thalidomide and neuropathy

Thalidomide can cause neuropathy, which can manifest as painful paraesthesia and/or numbness in a glove and stocking distribution, where the feet are affected before the hands. In case of patients with leprosy this may be difficult to assess as they may already be having neuropathy due to leprosy. The following steps can be taken to reduce the risk of further nerve damage due to thalidomide.

- All patients should undergo a clinical assessment for peripheral neuropathy before starting on thalidomide. Voluntary muscle testing and sensory testing should be done and the results should be clearly recorded in the patient's notes.
- Whenever possible a baseline nerve conduction study (NCS) should be performed. As this is not practical due to non availability of resources steps should be taken to do NCS at the earliest possible instance.
- Clinical assessment of nerve function should be repeated at least every 2 months, and recorded in the patient's notes. The results of the examination should be compared with the previous results regularly to detect early deterioration of nerve function.
- If a patient complains of numbness or weakness this should be taken seriously and the patient should be examined immediately.
- The NCS should be repeated every year if the patient is on long term thalidomide.

Other adverse effects due to thalidomide

- Thrombo-embolism; especially when used in combination with dexamethasone (in the treatment of myeloma)[26]
- Cutaneous side effects including erythema multiforme and Steven Johnson syndrome
- Drowsiness
- Constipation

2.6.4.2 Other second line drugs

There are reports on the use of many agents for the management of severe and chronic ENL. This in itself is an indication of the difficult to treat nature of this condition. But a recent *Cochrane Database Review* on interventions for ENL concluded that there is no strong evidence for the use of any of these agents[27].

Pentoxifylline (at a dose of 1.2 - 2.4 g daily) is the most used drug among the other second line agents. Several studies have shown that pentoxifylline is inferior to thalidomide for relief from symptoms[24,28].

Other drugs that have been used for the management of ENL either alone or in combination with steroids are azathioprine[29,30], colchicine, chloroquine, methotrexate[31], oral zinc[32] and infliximab[33]. But none of these drugs have been proven to be effective.

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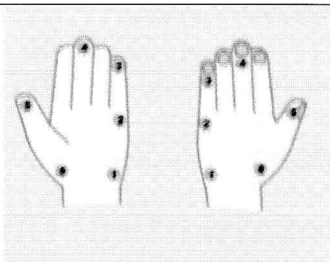
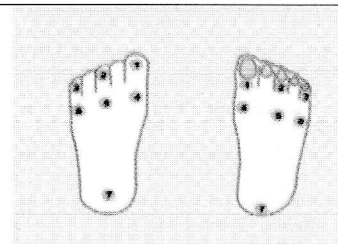
Annexure 1

SRI LANKA COLLEGE OF DERMATOLOGISTS

NEUROLOGICAL ASSESSMENT FORM

Name:

BHT number:

<table>
<tr><td colspan="9">Date</td></tr>
<tr><td>R L</td><td></td><td>ADM</td><td>1DI</td><td>APB</td><td>DF</td><td>EHL</td><td>EYE</td><td>R L</td></tr>
<tr><td rowspan="2">  </td><td>R</td><td></td><td></td><td></td><td></td><td></td><td></td><td rowspan="2">  </td></tr>
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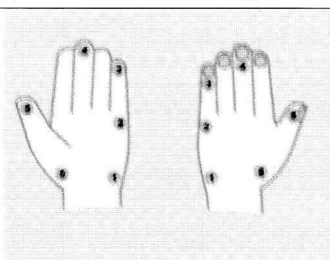
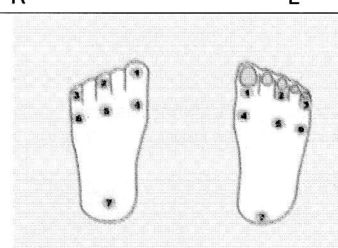
<tr><td rowspan="2">  </td><td>R</td><td></td><td></td><td></td><td></td><td></td><td></td><td rowspan="2">  </td></tr>
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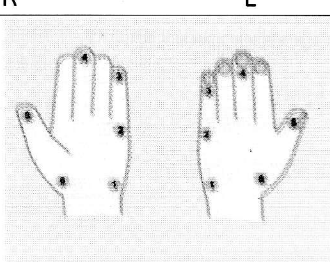
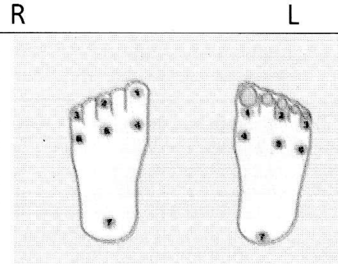
<tr><td rowspan="2">  </td><td>R</td><td></td><td></td><td></td><td></td><td></td><td></td><td rowspan="2">  </td></tr>
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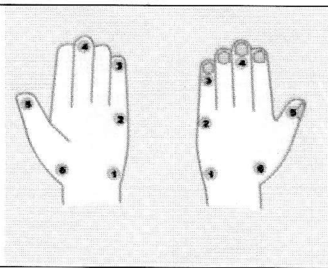
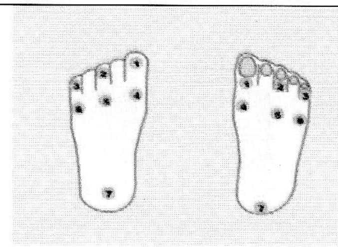
	R							
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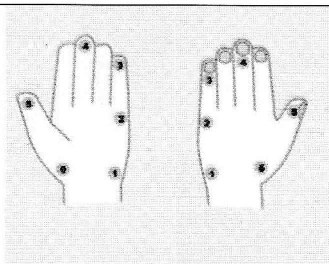
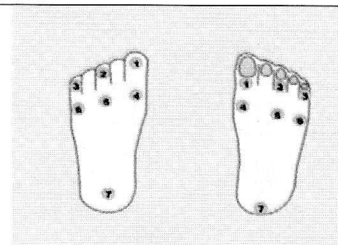
	R							
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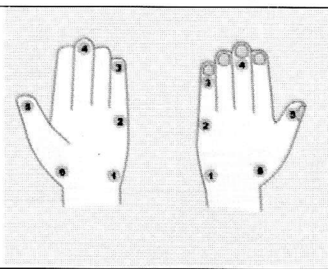
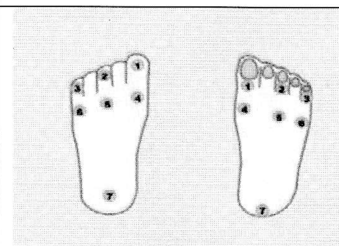
	R							
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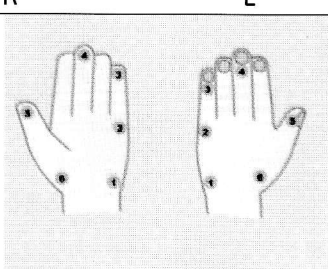
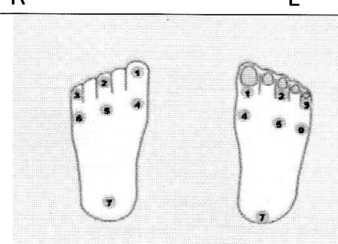
	R							
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