

# Mesotherapy, definition, rationale and clinical role: a consensus report from the Italian Society of Mesotherapy

M. MAMMUCARI<sup>1</sup>, A. GATTI<sup>1</sup>, S. MAGGIORI<sup>2</sup>, C.A. BARTOLETTI<sup>2</sup>, A.F. SABATO<sup>1</sup>

<sup>1</sup>Emergency Care, Critical Care Medicine, Pain Medicine and Anesthesiology Department, Tor Vergata Polyclinic, University of Tor Vergata, Rome (Italy)

<sup>2</sup>SAMEST, International Foundation Fatebenefratelli, Rome (Italy)

**Abstract. – Objective:** Since its introduction in the 1950s, the use of mesotherapy has generated much interest among clinicians and patients. The Italian Society of Mesotherapy (SIM) brought together a panel of experts to review available evidence and to draw up a series of recommendations on the use of intradermal therapy (LIT) in clinical practice.

**Consensus Report:** There was overwhelming agreement among Consensus Group members that, when used correctly, LIT is a valuable therapeutic option in the treatment of painful, loco-regional conditions. They also emphasised that the clinical efficacy of LIT has been demonstrated in the management of chronic venous lymphatic insufficiency, oedematous fibrosclerotic panniculopathy and facial skin aging. The experts were unanimous on the use of LIT in vaccination. Mesotherapy is not a substitute for other therapeutic options and should only be used when the patient has been fully informed of its advantages and limitations. Likewise the procedure should only be carried out by an experienced qualified physician.

**Conclusions:** Although there was widespread agreement among the Consensus Group on the place of LIT in several indications, the Authors reiterated the need for more large-scale clinical trials to determine the specific benefits and limitations in some areas of the application of intradermal therapy.

*Key Words:*

Mesotherapy, Intradermal therapy, Consensus Report.

## Introduction

Pharmacological products have been given intradermally for over a century<sup>1-6</sup>, but it was not until much later that this method became more

widely accepted. A French physician, Michel Pistor<sup>7</sup>, reported encouraging results with small doses of drugs administered intradermally to patients with a variety of clinical conditions. The term “mesotherapy” comes from the Greek word “mesos” – referring to the mesoderm (or middle germ cell layer) in the early embryo which differentiates into tissues and structures, including bone, cartilage, muscle and connective tissue.

Initially, mesotherapy consisted of the use of a mixture of active ingredients combined with procaine in the same syringe<sup>8-10</sup>. These “cocktails” of agents showed many beneficial effects, although systematic well-conducted preclinical/clinical studies were lacking. Furthermore, no trials were conducted to determine the safety/toxicity or pharmacological (pharmacokinetic/pharmacodynamic) interactions of these mixtures in humans.

The Italian Society of Mesotherapy (SIM) was conceived in 1975 with the primary objective of evaluating and validating mesotherapy in Italy using scientific methods. In some of the first trials the pharmacokinetics and tolerability of a single pharmaceutical agent administered intradermally were investigated and since then the first treatment protocols were applied. At the outset the SIM took an important decision – to use a single active ingredient instead of a mixture of products in the same syringe – in this way the efficacy and tolerability of individual agents could be closely monitored. Recently, we brought together a Panel of Experts from a range of specialities to review and validate the scientific rationale, advantages, indications and contraindications on the use of mesotherapy, with the aim of formulating a series of recommendations on the appropriate use of local intradermal therapy (LIT).

This review describes current views on the use of LIT from the perspective of the SIM. Guideline statements and recommendations were selected and voted on using formalised consensus procedures.

### **Definition of Mesotherapy by SIM**

Mesotherapy is a minimally invasive technique that consists of LIT with pharmaceuticals or other bioactive substances given in small quantities through dermal multi-punctures, where the injection site corresponds to the area of the pathological condition<sup>11</sup>. LIT is used when no other therapy options exists; when other therapies have failed (or for whatever reason cannot be used); when there is a possible synergistic benefit with other pharmacological/non-pharmacological therapies, and importantly when LIT can have a systemic drug-sparing role.

Pharmacological and clinical experience is required for the correct application of mesotherapy and disregard for the correct medical procedures constitutes medical malpractice. Used correctly, mesotherapy is effective in the treatment of painful musculoskeletal conditions, chronic venous lymphatic insufficiency (CVLI), oedematous fibrosclerotic panniculopathy (OFP, more commonly known as *cellulite*), intradermal vaccination, and in the management of facial skin aging. It should be emphasised that mesotherapy should only be used when the patient has been fully informed of its advantages, limitations and possible risks.

### **Rationale, Pharmacology and Basic Research**

Mesotherapy is based on the principle that LIT produces a “micro deposit” of the drug in the dermis which is then slowly released into the sur-

rounding tissues. In other words, LIT allows effective concentrations of products to reach the target area and (in theory) allows lower doses to be administered compared with p.o./i.m. routes. The concept of the slow release of substance following LIT has already been confirmed in pre-clinical trials<sup>12-15</sup>. With LIT the “first pass effect” is avoided and, therefore, using a prodrug is not appropriate. While it is well known that cytochrome P450-dependent enzymes in the liver play an important role in metabolism of many substrates, the role of the cutaneous cytochrome enzyme system is less well understood<sup>16-18</sup>. It is thought to play an important, but as yet not completely understood, role when a substance is administered transcutaneously or intradermally. One of the main advantages of LIT is the rapid rate of onset, due to the short time necessary to reach the site of action, as well as a prolonged local action. This method does not alter the mechanism of action of a given drug, which remains unchanged irrespective of the administration site. However, it is clear that, for example, intradermal administration of a loop diuretic to the skin of the lower body with the aim of reducing oedema does not make pharmacological or clinical sense.

In order to accept the concept of mesotherapy it is necessary to demonstrate that a drug administered intradermally remains in the surrounding tissue for longer than the same drug administered i.m. In the first series of pre-clinical studies the pharmacokinetics of drugs administered intradermally and i.m. were compared. A group of researchers<sup>19</sup> demonstrated that higher concentrations of procaine chloride reach the underlining tissues (muscles and joints) following intradermal compared with i.m. administration (Table I). Furthermore, intra-articular levels of the drug

**Table I.** Tissue levels of procaine (µg) following LIT or i.m. administration. Modified with permission from (19).

Time after i.m. (hours)	Skin		Muscle		Articular tissue	
	LIT	i.m.	LIT	i.m.	LIT	i.m.
0.5	27.40	ND	2.60	ND	0.30	ND
1.0	9.60	ND	1.80	ND	1.15	ND
2.0	2.80	ND	0.80	ND	0.65	ND
4.0	0.80	ND	0.70	ND	0.10	ND
7.0	0.50	ND	0.20	ND	0.05	ND
10.0	0.20	ND	0.02	ND	0.01	ND

ND – not detectable.

were detectable after LIT only and not with i.m. administration (Tables II-III). Likewise, tissue levels of sodium-ketoprofen were detectable for a longer time post-LIT compared with post-i.m. administration (Figure 1)<sup>20</sup>.

Based on these results it has been suggested that LIT allows the total drug dosage necessary to treat a given loco-regional condition to be reduced. In pre clinical it has also been demonstrated that the anti-tetanus vaccine injected intradermally produces a greater immune response (both primary and secondary) compared with the same antigen administered i.m.<sup>21</sup>, reinforcing the drug sparing effects of LIT. It has been referred that mesotherapy has a dual mechanism of action – in addition to the local effect of the drug – the process of introducing needles into the skin stimulates a reflex action thereby increasing endorphin levels<sup>22</sup>.

The observations that intradermal administration results in micro drug deposits that allow a slow and progressive diffusion of the drug into the surrounding tissues and that LIT has additional benefits on peripheral sensitivity, led many workers to study the use of LIT in a range of conditions including the musculoskeletal disorders. Initial clinical trials investigated the effects of a number of active ingredients to determine the optimal dosage and frequency of administration (plasma half-life of drugs administered intradermally does not necessarily correspond with the duration of the loco-regional effects).

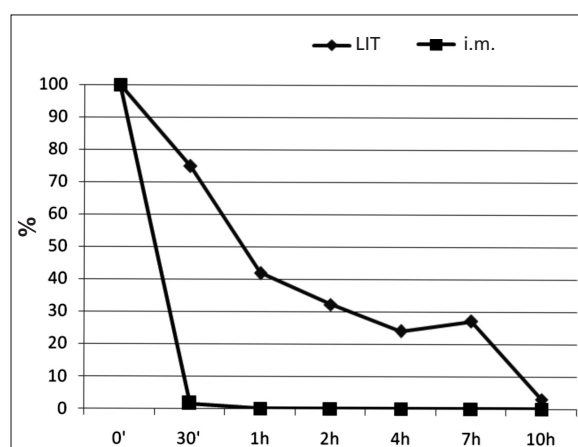
### Materials and Methods for Performing LIT

Mesotherapy is characterized by its unique method of injection – active ingredient is injected superficially using special short needles, directly over the site of the underlying structures affected. Practitioners usually use 4 mm (27 gauge) or 13 mm (30 or 32 gauge) needles where the needle is positioned at a steep angle. The SIM recommends the use of a single needle instead of multi-

**Table II.** Tissue levels of procaine (%) after LIT and i.m. administration. Modified with permission from (19).

Time (hours)	LIT	i.m.
0	100	100
0.5	74.8	1.6
1.0	41.9	ND
2.0	32.2	ND

ND – not detectable.



**Figure 1.** Skin, dermal, muscle and articular tissues levels (%) following i.m. and intradermal administration of ketoprofen sodium. Modified from (20).

ple injections. In general 0.10-0.20 mL of product is used and injection points are usually 2 or 3 cm apart. Where large areas of skin need to be treated, the drug may be diluted but this reduces the dosage and, therefore, additional or more frequent injections are necessary. However, the increased number of injections may not be advantageous for the patient. As a result, the SIM recommends using a standard protocol with slight modifications to reduce injection site effects (pain and bruising). It is important that the needle is inserted quickly, but gently, and that the syringe is emptied slowly. Clearly, the treatment protocol (choice of drug, duration of treatment, patient management and follow-up) varies depending on the nature, severity and site of the condition being treated as well as pharmacological and clinical parameters<sup>11</sup>. In some cases the pH of LIT can cause severe pain but regulating the pH with sodium bicarbonate can reduce this effect<sup>23</sup>.

We do not recommend the use of a mixture of drugs in the same syringe because this procedure is not without risks. There are no *in vitro*/*in vivo* data on possible drug interactions, although changes in pH, colour and precipitation/flocculation have been observed when mixtures of drugs are used. Moreover, when using drug mixtures it is not possible to identify the exact effects of individual drugs both in terms of efficacy and tolerability. The risk of allergic reactions preclude the intradermal administration of a muscle relaxant plus a non-steroidal anti-inflammatory agent (NSAID) in the same syringe – as

it is not possible to determine which drug has caused the allergy. However, in a recent study it was shown that NSAIDs can be used safely in combination with other active agents<sup>24</sup>.

A number of devices (mechanical and electronic) are now readily available for LIT. The manufacturers of these devices claim that some devices allow rapid and painless injection while others deliver drugs to the skin without the need for needles. None of the currently available devices is recommended by the SIM. At present, only the "physician's hand" guarantees "true" intradermal administration.

### **Role of LIT in Acute and Chronic Pain**

Pain, an unpleasant sensory and emotional experience, acts as a natural alarm associated with actual or potential tissue damage; if pain persists it can become a syndrome/condition in its own right<sup>25,26</sup>. Nociceptive pain is caused by stimulation of peripheral nerve fibers that respond to stimuli approaching or exceeding harmful intensity (nociceptors). When pain persists the sensitive feedback system is altered and the microglia cells are activated<sup>25,27</sup>. The glia release neurotransmitters which in turn activate the nociceptive defence system<sup>25</sup>. It is, therefore, important that pain therapy is started quickly and in a systematic manner to prevent it becoming chronic. The dual mechanism of action of LIT – pharmacological and local stimulation – has a rationale scientific basis as part of a therapeutic strategy for localised pain control. In 1975 the SIM instigated a series of multicentre studies with the aim of testing the effect of LIT in patients with osteoarticular pain (arthritis of the hip/knee/hand, neck pain, lower back pain, tendinopathy)<sup>28-33</sup>. The results of these studies confirm the efficacy and tolerability of anti-inflammatory/analgesic administered as LIT (Table III).

Several Authors have reported encouraging results with LIT in combination with physical therapy<sup>34,35</sup>, in sports injuries<sup>36</sup>, in the management of neuropathic pain<sup>37</sup>, as adjuvant therapy in the treatment of osteoporosis pain<sup>38</sup> and calcified tendinitis of the shoulder<sup>39-41</sup>. Others have used the technique for the treatment of musculoskeletal pain<sup>42-49</sup>. The use of anti-inflammatory/analgesic drugs intradermally in osteomuscular conditions appears to be one of the best and important indications for mesotherapy. The drug-sparing effect of this procedure, when combined with other systemic therapies, should be quantified to measure also advantages in cost effectiveness.

### **The role of LIT in Veno-Lymphatic Edema**

Certain drugs when administrated intradermally exhibit a local trophic action. This effect was first noted clinically when the healing of decubitus ulcers was improved following mesotherapy in spinal patients<sup>50</sup>. Likewise LIT improved subjective and objective symptoms (venous pressure and calf circumference) in patients with veno-lymphatic insufficiency<sup>51,52</sup>.

LIT has also be reported to improve OFP<sup>53</sup>. The exact cause of OFP is the subject of much debate but it is thought changes in the microcirculation and chronic oedema (as a result of structural changes in the adipose cells and the formation of micronodules) are important predisposing factors<sup>54,55</sup>. Active substances that affect the microcirculation administered intradermally may, therefore, produce clinical improvements (both subjective and objective) in patients with CVLI and those with OFP<sup>56</sup>. Subcutaneous echography has made it possible to investigate microcirculatory changes following LIT and to establish better inclusion/exclusion criteria to improve the risk/benefit ratio<sup>57,58</sup>.

**Table III.** Initial studies with clinical benefits in pain diseases.

Pain disease (reference)	Number of patients	Outcome (%)
Osteoarticular pain (28)	492	79.9
Osteoarticular pain, acute myositis, tendino-muscular pain syndrome (29)	484	83.6
Osteoarticular pain, tendinitis, epicondylitis (30)	193	91.0
Osteoarticular pain (31)	46	78.0
Osteoarticular pain (32)	256	52.7
		(54.7 improvement in articular function)
Pain from gonarthrosis (33)	20	90.0



### ***LIT in Skin Aging***

Skin aging is in part genetically-determined and in part the result of lifestyle and environment. There are essentially two types – intrinsic or chronological aging and extrinsic or photoaging. In chronological aging the protective function of the skin barrier is impaired; the production of sebum and perspiration are reduced; immune function is decreased and pigmentation, keratinisation and temperature regulation are altered. These factors taken in concert reduce the structural function of the epidermis and dermis.

Photoaging describes damage to the skin caused by intense and chronic exposure to sunlight. The visible effects of photoaging are fine wrinkles, mottling and pigmentation and skin roughness. Cutaneous biostimulation is the process of injecting into the skin medical devices (approved in Italy with directive 93\42\CEE June, 14th 1993) or drugs to improve skin elasticity/appearance and to reduce the signs of chronological and photoaging. The use LIT in skin rejuvenation (in particular for facial skin) is now widely used and improvements can be monitored using echographic techniques<sup>58</sup>.

During skin aging there is a loss of subcutaneous fat, structural remodelling of cartilage and bone, and the formation of fine/expression lines from repetitive muscle activity. Hypertrophy of the subcutaneous tissue and the pull of gravity mean that excess skin forms into folds, lines and wrinkles – which can be treated by the administration of completely absorbable fillers<sup>59,60</sup>.

### ***LIT – Local Lipolytic Effects***

Likewise in the management of local adiposity, LIT has demonstrated encouraging clinical results<sup>61-66</sup> but there are still doubts regarding the true efficacy and safety of the products administered. In many papers Authors do not distinguish between LIT, subcutaneous and deep intralesional administration and there is a tendency to group these three types of administrations under one single entity: mesotherapy<sup>67</sup>. This is one of the reasons why LIT in cosmetic medicine is not without its critics<sup>67-69</sup>. Controlled large scale clinical trials, conducted in accordance with Good Clinical Practice (GCP) are, therefore, urgently required to determine the safety and lipolytic effects of pharmaceutical active products administered as LIT.

This is the reason why a long time ago the Italian Society of Mesotherapy decided to exclude this indication from clinical protocols. Recently also the Minister of Health in France decided to prohibit cocktails administered by mesotherapy in this

clinical condition (decree n 382-2011). RCT in this area are needed to clarify this issue.

### ***Role of LIT in Dermatological Conditions***

Many skin lesions can potentially benefit from local injections, and early reports have described good results with a corticosteroid, in patients with cystic acne, alopecia and keloids<sup>70</sup>. However, this class of drugs should be used with special care because of multiple effects on the skin. The LIT plays an important role when in reducing the systemic dose of drugs and consequently adverse events<sup>71</sup>. However, many treatments describe an intralesional injection (as in cystic acne or keloids) not intradermally (as in the case of alopecia).

### ***Role of LIT in Vaccination***

Among the first reported uses in the literature of LIT were in vaccination<sup>1,2</sup>. The dermis has a microcirculation which can interact with the immune system and intradermal inoculation of vaccines provides a number of advantages over i.m. administration – including a reduction in the antigen dose required, reduced need for adjuvant, a greater immune-response and a simpler mode of administration<sup>21,72,73</sup>. The efficacy of LIT provides the stimulus to research new devices/methods so that (for example) mass vaccinations can be carried out in a simpler manner.

### ***Role of LIT in Pediatric Patients***

The use of LIT in children has also been investigated in studies conducted in Italy. Following initial preclinical trials with ACTH and prednisolone administered intradermally, efforts were made to reduce the stress caused with p.o. administration by employing the intradermal route<sup>74,75</sup>. Preliminary data with intradermal prednisolone in babies with asthma have shown encouraging results with a dose of prednisolone 3-10 times lower than that required with p.o. therapy and with the added benefit that it is not necessary to gradually reduce the dosage<sup>76</sup>. More controlled large trials in this patient group are required.

### ***Role of LIT in Otolaryngology (ENT)***

LIT has also been used in some otolaryngology or ENT (ear, nose, and throat) conditions to reduce the systemic dosage of drugs and related side effects. In fact, interesting results have been reported in patients with tinnitus, both versus placebo<sup>77</sup> and active oral therapy<sup>78</sup>. Reduction of phlogosis and pain and no side effects were reported in auricular perichondritis of the external

auditory canal when low dosages of drugs were administered intradermally<sup>79</sup>. As with other clinical conditions, clinical and pharmacological expertise is required to select patients for LIT or systemic treatment.

### Informed Consent

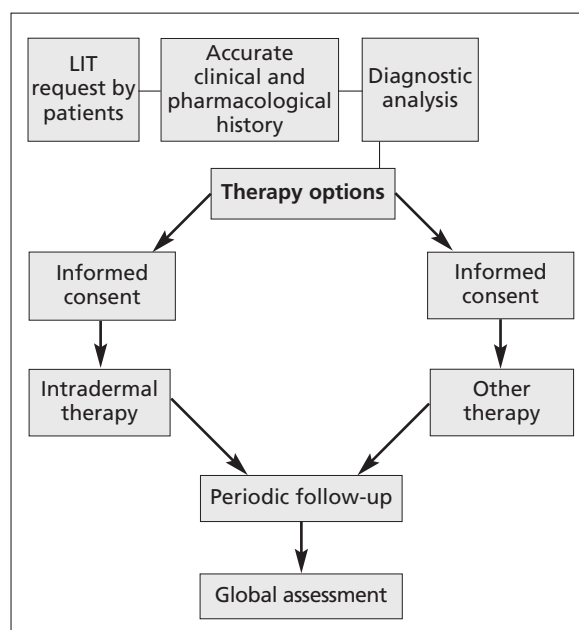
In Italy the law states (judgment of the Court of Turin 19/10/1985) that intradermal administration should be performed by a qualified medical doctor only (and not by paramedics) and as with other medical procedures, should be carried out with prudence, diligence and due skill. Obtaining informed consent from the patient is obligatory. Patients should receive clear and complete information on the treatment proposed, based on the diagnosis made, as well as information on the availability of therapeutic alternatives. Before giving consent, the patient should be fully aware of what the procedure involves. Importantly, if the doctor recommends the off-label use of a drug or of a treatment the patients should fully understand the risks and benefits (written consent).

In order to improve the risk/benefit ratio the SIM has undergone a process to revise and simplify treatment protocols by reducing the number of drugs in use and to discourage the use of a cocktail of drugs in the same syringe. It should be remembered that Italian law (Decree-Law No 23, 1998) states that drugs can be administered by a method different from their approved indication – if there is no suitable approved alternative or if there are international published papers supporting off-label use (as also the code of medical ethics states in article 13).

Information on LIT should be given to the patient in a clear and concise manner and the patient should be told if the drug is approved for intradermal administration or not. Informed consent ensures that patients do not receive treatment with products whose efficacy and safety has not been fully established, as sometimes it has been reported<sup>80</sup>. Physicians should include obtaining informed consent in their diagnostic/therapeutic work-up (Figure 2).

### Pros and Cons of LIT

LIT is the administration of low doses of a drug directly at the site of the condition thereby reducing the need for systemic treatment of loco-regional conditions. Rare transitory and reversible local and systemic adverse reactions (allergies, ecchymosis, urtica, granulomata) following mesotherapy have been reported<sup>11</sup>. However,



**Figure 2.** Diagnostic/therapeutic work-up for intradermal therapy (LIT) for patients who require it and when it represents a therapeutic option.

in many published reports, details of treatment are not given<sup>81-87</sup>. For example, the drug or mixture injected, the number of treatments, co-administration of systemic therapy, if therapy was administered by a qualified physician or not, and site and depth of administration (if drug was administered into the dermal layer or deeper). Importantly, it is often not stated if standard hygiene procedures were adhered to or if treatment was carried out in a hospital setting by personnel trained in the management of drugs<sup>88</sup>.

Patients often ask their physicians for LIT for aesthetic reasons but they frequently underestimate the possible adverse events. This means that physicians need to carefully select patients and not to treat those who withhold important information in order to get LIT. It is vital that the physician outlines the benefits and risks of therapy with reference to published clinical experience so that patient expectations are not unduly raised.

Physicians have a duty to report to the pharmacovigilance authorities any adverse events probably/possibly related to a given drug or procedure, including details of the treatment protocol and concomitant medications.

### Clinical Report Form

As in other areas of medicine, the importance of accurately compiling a clinical report form

should not be underestimated for patients ongoing LIT. Patient files should record routine clinical characteristics as well as follow-up. The SIM recommends the use of a specific clinical file to record the protocol but also adverse events (see part of the record as an example in Figure 3). The SIM strongly recommends the need to report accurately the efficacy and tolerability of LIT for each patient. Moreover, in Italy the medical record, must also report the characteristics of pain experienced, its evolution, as well as the dosage, mode of administration and type of analgesic drugs used as well as the pain control achieved (Decree-Law No. 38, 2010).

### Treatment Algorithm

LIT protocols allow for one or more cycles of treatment depending on the symptoms and severity of the underlying condition and the individual patient's response to therapy. For example when treating a chronic painful condition there are normally three distinct phases – *attack* – when four

weekly treatments are administered, a subsequent *control* phase – four fortnightly treatments are given to confirm results and prevent short-term recurrences and finally the *maintenance* phase – monthly or seasonal treatment. When treating resistant pain twice weekly therapy is recommended in the “attack phase” depending on the analgesic effect obtained<sup>11</sup>. Likewise in patients with CVLI treatment can be more regular depending on the clinical response and beneficial effects observed<sup>11</sup>. The task force of experts is now defining specific protocols/algorithms to implement LIT in several conditions.

### Consensus and Recommendations

To validate the recommendations for the correct use of LIT in Italy we used the Delphi Method – a group decision making technique which seeks to achieve a Consensus among group members through a series of questionnaires<sup>89,90</sup>. Web-based questionnaires were drawn up by the scientific committee and questions are answered anony-

8. INTRADERMAL THERAPY								
	YES/ NO	DATE	DRUG	ACTIVE COMPOUND	Dose for session	Number of sessions for week	Number of weeks of treatment	Totale number of sessions (COMPLIANCE)
1° DRUG	<input type="checkbox"/>							
2° DRUG	<input type="checkbox"/>							
3° DRUG	<input type="checkbox"/>							
4° DRUG	<input type="checkbox"/>							
DILUTION	<input type="checkbox"/>							
OTHER	<input type="checkbox"/>							

Diseases treated	SPECIFY	Concomitant Therapy	SPECIFY
Pain Disease		<input type="checkbox"/> Oral Therapy	
VLI		<input type="checkbox"/> Parenteral Therapy	
OFP		<input type="checkbox"/> Physical Therapy	
Other		<input type="checkbox"/> Other	

Side Effect	<input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> N.a.	If YES Specify	If YES specify the level of effect	<input type="checkbox"/> Light <input type="checkbox"/> Moderate <input type="checkbox"/> Severe <input checked="" type="checkbox"/> N.a.	Outcome <input type="checkbox"/> Resolved <input type="checkbox"/> Solved with consequences <input type="checkbox"/> Unresolved <input checked="" type="checkbox"/> Not Available
Adverse event	<input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> N.a.	If YES Specify	If YES specify the level of effect	<input type="checkbox"/> Light <input type="checkbox"/> Moderate <input type="checkbox"/> Severe <input checked="" type="checkbox"/> N.a.	Outcome <input type="checkbox"/> Resolved <input type="checkbox"/> Solved with consequences <input type="checkbox"/> Unresolved <input checked="" type="checkbox"/> Not Available
Local reaction occurred after LIT	<input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> N.a.	If YES Specify	If YES specify the level of effect	<input type="checkbox"/> Light <input type="checkbox"/> Moderate <input type="checkbox"/> Severe <input checked="" type="checkbox"/> N.a.	Outcome <input type="checkbox"/> Resolved <input type="checkbox"/> Solved with consequences <input type="checkbox"/> Unresolved <input checked="" type="checkbox"/> Not Available

Figure 3. Part of a medical record used to collect data during intradermal treatment.

mously and individually by members of the Expert Panel/Steering Committee (see Appendix). Answers were summarized and sent back to the group members together with the next questionnaire. The process was repeated until a group Consensus was reached. Recommendations with a Consensus >90% were classified as strong (S), those with a Consensus of 75-90% as good (G), those with a Consensus of 50-74% as weak (W) and those with a consensus <50% as rejected (R). The final approved recommendations are summarised in Table IV and Table V.

There was overwhelming Consensus among group members that LIT is a valuable therapeutic option in the treatment of painful, loco-regional conditions. The experts also concluded that the clinical efficacy of LIT has been demonstrated in the treatment of CVLI, OFP and skin aging. How-

ever, additional large-scale trials are required to confirm the efficacy and tolerability of single agents. The Panel were unanimous on the use of LIT in vaccination. They emphasised that used correctly by skilled practitioners, this technique represents an important addition to the clinical armamentarium. LIT has not been tested and it is, therefore, not recommended in the following patient groups – patients with a history of allergic reactions, patients with disorders of coagulation (haemophiliacs, undergoing therapy with anticoagulants or anti-platelet agents), pregnant or lactating women or cancer patients receiving chemotherapy.

### Future Steps

Mesotherapy is used with consent in many countries around the world, although in some its use is under discussion because of the lack of

**Table IV.** Recommendations – general and methodological – from Consensus Panel.

General recommendations	Consensus
Mesotherapy is the intradermal administration of pharmacologically active ingredients directly over the site of the underlying condition, structures, organs, or area affected; it is also known as local intradermal therapy (LIT)	S
LIT should only be administered by a doctor with clinical and pharmacological experience	S
Administration of LIT requires clinical and pharmacological experience so that contraindications to this method of administration can be identified	S
LIT should only be used when there is a sound clinical rationale and after other therapeutic options have been considered	S
It is suggested that only established clinical protocols are used when the risk/benefits are known	S
The use of previously untested compounds should be avoided (the exception being in clinical trials that conform to GCP)	S
The physician should supply the patient with all the necessary information on LIT in a clear and understandable manner so that he/she can make an informed decision	S
The patient's clinical file should contain information on the LIT protocol (drug, dosage, frequency of administration, condition to be treated) as well as details of the concomitant therapy (pharmacological and non-pharmacological)	S
All adverse events should be reported to the Pharmacovigilance Health Authorities	S
Physicians administering LIT should undergo regular CME courses to keep up to date with clinical and pharmacological developments	S
Methodological recommendations	Consensus
The use of more than one drug in the same syringe increases the risk of pharmacological interactions – and therefore single-drug LIT is recommended at least until pharmacological and clinical large studies demonstrate the efficacy and tolerability when one or more active ingredients are combined in the same syringe	S
In some circumstances one or more active ingredients can be used (for example an anti-inflammatory and a muscle relaxant) but not in the same syringe and not at the same site of administration	S
LIT should only be administered in a medical environment using sterile single-use syringes and needles according to accepted standard hygiene regulations	S
The practice of using hospital-type containers from which the required amount of drug is taken is to be avoided because of the risk of introducing microorganism into the container	S
Following use sharps and syringes should be disposed safely in the approved containers and care should be taken not to contaminate sterile material	S



**Table V.** Specific recommendations – indications and contraindications for the use of LIT from the Consensus Panel.

Specific recommendations for the use of LIT in localised pain	Consensus
LIT is indicated for the control of some type of pain but should always be used as an integral part of a clinical management programme	S
Before using LIT pain should be classified based on the type and intensity of the pain preferably using a Numeric Scale (NRS 0-10 pain rating scale) or other validated scale	S
LIT represents a valid pharmacological option in the treatment of pain in particular osteo-muscular and articular pain	S
LIT can be used in combination with other therapies	S
Use of LIT is appropriate when there are no contraindications to the pharmacologically active agents	S
Patients should be clearly informed of the advantages and limitations of LIT	S
Specific recommendations for the use of LIT in aesthetic medicine	Consensus
LIT is a valid method to pharmacologically treat CVLI and its consequence OFP as well as in treating facial skin conditions (scars, aging)	S
A clinical/psychological profile of the patients is recommended before beginning LIT	S
Before starting LIT treatment the patients should be informed on the possible adverse events (caused by needle injury and the process of injecting drugs locally)	S
For the use of LIT in esthetical facial skin aging, patients should be clearly informed of the realistic benefits that the treatment can reach	S
LIT should only be used for esthetical reasons by physicians	S
Clinical indications	Consensus
Musculo-skeletal pain	S
Muscle contraction caused by osteoarticular, tendino-muscular pain syndrome	S
CVLI	S
CVLI with OFP	S
Biostimulation and esthetic effects on facial skin	S
Intradermal vaccination (with vaccines approved for this method of administration)	S
Patients under 18 years of age	R
Pregnancy	R
Lactation	R
Immunocompromised patients	R

CVLI - chronic venous lymphatic insufficiency, OFP oedematous fibrosclerotic panniculopathy.

standards, or because it is used for cosmetic purposes by non-medical personnel<sup>67</sup>. However, there are still many unanswered questions. Scientific Societies have an important role to play in developing and supporting well-conducted clinical trials to address outstanding questions – including the dose-sparing effects of LIT in patients receiving systemic treatment for chronic local pain, and the effects of LIT using different pharmaceutical agents in patients with a range of other conditions. In Italy retrospective studies to identify more selective inclusion criteria for the treatment with drugs<sup>57</sup> and perspective trials are ongoing to investigate the tolerability and the efficacy of pharmacologically active compounds (*data on file*).

In general, well-conducted, large-scale trials are required to define the specific benefits and limits of a given therapy – only in this way patients will be guaranteed to receive the most appropriate mesotherapy. Finally, misleading advertising on injectable products should also be monitored and discouraged<sup>91</sup> and continuing medical education (CME) for physicians by non-partisan organizations should be mandatory to keep up-to-date and to avoid malpractice.

## Conclusions

As with other therapies, mesotherapy (LIT) has advantages and disadvantages. The advan-

tages are greater if LIT is carried out by medical experts. The disadvantages can be reduced if the physician uses only agents that have undergone clinical trials and are approved by the scientific community. The lack of randomised controlled studies, published in the international scientific literature, does not invalidate the work of Michel Pistor† (Honorary President of the Italian Society of Mesotherapy), whom we thank for his contribution to the development and spread of mesotherapy. It is now up to clinical researchers to validate the advantages, limitations and further development of mesotherapy. It is important that National Health Authorities adequately consider the importance of mesotherapy and its potential benefits in terms of effectiveness and drug sparing.

## Appendix

Steering Committee of Italian Society of Mesotherapy (SIM): Maggiori Enrica (1), Bartolletti Emanuele (1), Giardini Manuela (1), Jacovitti Silvia (1), Dario Dorato (1), Trocchi Gloria (1), Salciccia PierLuigi (1) Laurenza Massimo (2), Massironi Alberto (3) Mediati Rocco Domenico (4), Migliore Alberto (5), Rocchi Piergiovanni (6), Vellucci Renato (4), Ferrante Maurizio (7).

Expert Panel: Acinapura Rosa Antonietta (1), Antonaci Luciano (8), Bozzone Myriam (1), Caputo Maria Grazia (1), Carota Alessia (1), Centofanti Domenico (1), Cuguttu Anna (1), De Iulio Cinzia (3), Denni Alessia (1), Di Marzo Raffaele (9), Di Maggio Roberta (1), Domenico Romano (10), Feleppa Domenico (1), Fontevicchia Michele (1), Fraone Nadia (1), Giardini Manuela (1), Giorgio Chiara (11), Guglielmo Costanza (1), Loffredo Fiamma (1), Longo Giuseppe (12), Marchionne Antonella (1), Mariotti Mario (3), Nazzaro Letizia (1), Orlandi Clemente (3), Pompilio Alberto (1), Prosenikliev Vlatko (13), Redaelli Alessio (14), Santini Stefania (1), Savastano Marina (13), Tamburlin Nadia (3), Tomaselli Fulvio (1), Torquati Luca (15), Triulzi Marina (3), Troili Fiammetta (1), Tunesi Lucio (3), Veraldi Maria (1), Zannella Carlo (1).

- 1) Service of Aesthetic Medicine "S. Giovanni Calibita" FBF Isola Tiberina Hospital, Rome, Italy
- 2) Dermatologist, Rome, Italy

- 3) Agorà, Società di Medicina ad Indirizzo Estetico, Milan, Italy
- 4) Palliative Care and Pain Therapy, Careggi University Hospital, Florence, Italy
- 5) OU of Rheumatology "San Peter Hospital" Rome, Italy
- 6) Specialist in Forensic Medicine, Ethics Committee of the Medical College, Bologna, Italy
- 7) Medical Director, S. Giovanni Calibita" FBF Isola Tiberina Hospital, Rome, Italy
- 8) GP, ASL RME, Rome, Italy
- 9) Sanofi Pasteur MSD, Scientific Department, Rome, Italy
- 10) Laboraf, San Raffaele Hospital IRCSS – Milan, Italy
- 11) Rehabilitation Hospital Services, Altamura (Bari), Italy
- 12) Emergency Care, Critical Care Medicine, Pain Medicine and Anaesthesiology Department, Tor Vergata Polyclinic, University of Tor Vergata, Rome, Italy School of aesthetic Medicine, Agorà, Milan, Italy
- 13) Medical-Surgical Specialties Department, ENT Section, University of Padua, Italy
- 14) Vascular Surgery, Padua, Italy
- 15) Dermatologist, Viterbo, Italy

## Acknowledgements

The Authors would like to thank all experts for their participation and support. The Authors thank Content Ed Net who provided editorial assistance and Anna Ammendolia for the web-based consensus and technical support ([www.societadimesoterapia.it](http://www.societadimesoterapia.it)).

## References

- 1) MANTOUX C. L'intradermoréaction a la tuberculine et son interpretation clinique. *Presse Med* 1910; 18: 10-13.
- 2) TUFT L. Active immunization against typhoid fever, with particular reference to an intradermal method. *J Lab Clin Med* 1931; 16: 552-556.
- 3) BRIGGS DJ, BANZHOF A, NICOLAY U, SIRIKWIN S, DUMAVIBHAT B, TONGSWAS S, WASI C. Antibody response of patients after postexposure rabies vaccination with small intradermal doses of purified chick embryo cell vaccine or purified Vero cell rabies vaccine. *Bull WHO* 2000; 78: 693-698.

- 4) BRICKS LF. Percutaneous or intradermal BCG vaccine? *J Pediatr (Rio J)* 2004; 80: 93-98.
- 5) PLOTKIN SA. Vaccines: the fourth century. *Clin Vaccine Immunol* 2009; 16: 1709-1719.
- 6) LE COZ J. History of mesotherapy. *Am J Mesother* 2009; 3: 16-18.
- 7) PISTOR M. What is mesotherapy? *Chir Dent Fr* 1976; 46: 9-60.
- 8) DALLOZ-BOURGUIGNON A. A new therapy against pain: mesotherapy. *J Belg Med Rehabil* 1979; 2: 230-234.
- 9) ROHRICH RJ. Mesotherapy what is it? Does it work? *Plast Reconstr Surg* 2005; 115: 1425.
- 10) EINHOLTZ B, MAUDEET D, BICHERON M. Use of NHA1 via mesotherapy in oral surgery. *Actual Odontostomatol* 1990; 44: 285-298.
- 11) MAGGIORI S. Manuale di intradermoterapia distrettuale. La mesoterapia in Italia. Roma: EMSI Editore; 2004.
- 12) GOODNER K. Further experiments with the intradermal pneumococcus in rabbits. *J Exp Med*. 1928; 48: 413-429.
- 13) McEWEN C, SWIFT HF. Cutaneous reactivity of immune and hypersensitive rabbits to intradermal injections of homologous indifferent streptococcus and its fractions. *J Exp Med* 1935; 62: 573-587.
- 14) ANGEVINE DM. A comparison of cutaneous sensitization and antibody formation in rabbits immunized by intravenous or intradermal injections of indifferent or haemolytic streptococci and pneumococcal. *J Exp Med* 1941; 73: 57-66.
- 15) ANONIMUS. Intradermal injections. *Med J* 1953; 1: 38-387.
- 16) DU L, HOFFMAN SM, KEENEY DS. Epidermal CYP2 family cytochromes P450. *Toxicol Appl Pharmacol* 2004; 195: 278-287.
- 17) SWANSON HI. Cytochrome P450 expression in human keratinocytes: an aryl hydrocarbon receptor perspective. *Chem Biol Interact* 2004; 149: 69-79.
- 18) NEIS MM, WENDEL A, WIEDERHOLT T, MARQUARDT Y, JOUSSEN S, BARON JM, MERK HF. Expression and induction of cytochrome P450 isoenzymes in human skin equivalents. *Skin Pharmacol Physiol* 2010; 23: 29-39.
- 19) BINAGLIA L, MARCONI P, PITZURRA M. The diffusion of intradermally administered procaine. *J Mesother* 1981; 1: 15-28.
- 20) BINAGLIA L, MARCONI P, PITZURRA M. Absorption of Na ketoprofen administered intradermally. *J Mesother* 1981; 1: 85-91.
- 21) PITZURRA M, MARCONI P. Immunogenesis and mesotherapy: the immunoresponse to antigens inoculated intradermally. *J Mesother* 1981; 1: 9-14.
- 22) CRENNNA P, MANCIA P. Reflex actions in mesotherapy. *J Mesother* 1981; 1: 29-40.
- 23) CECCARELLI M, BASSANO P, SERRA VISCONTI A, BARTOLETTI CA. Concerning pain caused by the action of mesotherapy: proposal of a pharmacological buffer. *J Mesother* 1987; 7: 19-24.
- 24) COSTANTINO C, MARANGIO E, CORUZZI G. Mesotherapy versus systemic therapy in the treatment of acute low back pain: a randomized trial. *Evid Based Complement Alternat Med* 2011. pii: 317183. Epub 2010 Sep 1.
- 25) SABATO AF. Idiopathic break through pain: A new hypothesis. *Clin Drug Invest* 2010; 30 (Supp 2): 27-29.
- 26) MANNION RJ, WOOLF CJ. Pain mechanisms and management: a central perspective. *Clin J Pain* 2000; 16 (Suppl 3): 144-156.
- 27) WANG W, WANG W, MEI X, HUANG J, WEI Y, WANG Y, WU S, LI Y. Crosstalk between spinal astrocytes and neurons in nerve injury-induced neuropathic pain. *PLoS One* 2009; 4: 6973.
- 28) RUGGERI F, BARTOLETTI CA, MAGGIORI S. Clinical results of the multicentric experimentation. *J Mesother* 1981; 1: 47-49.
- 29) COLOMBO I, CIGOLINI M, COMBI F. Clinical results of the multicentric experimentation. *J Mesother* 1981; 1: 50-52.
- 30) SARACENI V, PALIERI G, DE PEDIS M. Clinical results of the multicentric experimentation. *J Mesother* 1981; 1: 53-59.
- 31) PIAONTONI D, COTICHELLI E, DI GIANVITO P. Clinical results of the multicentric experimentation. *J Mesother* 1981; 1: 60-63.
- 32) PEZONE A, VILLA L, MARTINI D. Clinical results of the multicentric experimentation. *J Mesother* 1981; 1: 64-66.
- 33) CURRÒ F, BEARZATO A. Use of the S-adenosil l-methionine (Same) in the treatment of degenerative arthropathies of arthrosis. *Nature* 1981; 1: 99-107.
- 34) COLOMBO I, CIGOLINI M. An interesting therapeutically synergism: mesotherapy and laser. *J Mesother* 1981; 1: 113-117.
- 35) MONTICONE M, BARBARINO A, TESTI C, ARZANO S, MOSCHI A, NEGRINI S. Symptomatic efficacy of stabilizing treatment versus laser therapy for subacute low back pain with positive tests for sacroiliac dysfunction: a randomised clinical controlled trial with 1 year follow-up. *Eura Medicophys* 2004; 40: 263-268.
- 36) CERESER C, GANZIT GP, GRIBAUDO C. Injuries affecting the locomotory system during the game of rugby. Reports of 133 cases treated with mesotherapy. *J Mesother* 1985; 5: 9-19.
- 37) CURRÒ F, BEARZATO A. Mesotherapy in the treatment of post-zoster neuritis. *J Mesother* 1985; 5: 37-43.
- 38) PIAONTONI D, COTICHELLI E, SANTILLI W. Use of calcitonin in regional osteoporosis. *J Mesother* 1985; 5: 21-23.

- 39) CACCHIO A, DE BLASIS E, DESIATI P, SPACCA G, SANTILLI W, DE PAULIS F. Effectiveness of treatment of calcific tendinitis of the shoulder by disodium EDTA. *Arthritis Rheum* 2009; 61: 84-91.
- 40) SONCINI G, COSTANTINO C. The treatment of pathologic calcification of the shoulder tendons with EDTA bisodium salt by mesotherapy. *Acta Biomed Ateneo Parmense* 1998; 69: 133-138.
- 41) GAZZI A, PONZETTI F, RICCI L, CORTESE G, BUOSI C. La mesoterapia con EDTA nella periartrite scapolo-omerale calcifica (morbo di Duplay), risultati incoraggianti. *Riabilitazione* 1984; 17: 141-145.
- 42) DI CESAREA A, GIOMBINI A, DI CESARE M, RIPANI M, VULPHANI MC, SARACENI VM. Comparison between the effects of trigger point mesotherapy versus acupuncture points mesotherapy in the treatment of chronic low back pain: A short term randomized controlled trial. *Complement Ther Med* 2011; 19: 19-26.
- 43) PALERMO S, RIELLO R, CAMMARDELLA MP, CAROSSINO D, ORLANDINI G, CASIGLIANI R, LAUNO C. TENS + mesotherapy association in the therapy of cervico-brachialgia: preliminary data. *Minerva Anestesiol* 1991; 57: 1084-1085.
- 44) GUAZZETTI R, IOTTI E, MARINONI E. Mesotherapy with naproxin sodium in musculoskeletal diseases. *Riv Eur Sci Med Farmacol* 1988; 10: 539-542.
- 45) SOLINAS G, SOLINAS AL, PERRA P, SOLINAS FL. Treatment of mechanical tendinopathies by mesotherapy with ergotein in combination with laser therapy. *Riabilitazione* 1987; 20: 281-288.
- 46) RIVELLA L, GALLIERA F, GANIO D. Treatment of post traumatic reflex algodystrophy: mesotherapy with calcitonin. *Riabilitazione* 1986; 19: 5-11.
- 47) REGA V, CIGOLINI M, COLOMBO I. Biofeedback technique in evaluation of efficacy of mesotherapy in acute low back pain. *Riabilitazione* 1984; 17: 113-117.
- 48) SANTILLI V, DI GIROLAMO G, FINUCCI S, CAPACI S, PARIS E. Back pain: low back pain model, treatment with physical and injective therapy. *Riv Neurobiologia* 1999; 45: 279-286.
- 49) PARRINI M, BERGAMASCHI R, AZZONI R. Controlled study of acetylsalicylic acid efficacy by mesotherapy in lombo-sciatic pain. *Minerva Ortoped Traumatol* 2002; 53: 181-184.
- 50) PEZONE A, MARTINI D, IACONO M. Mesotherapy in the treatment of deb-sores in spinal patients. *J Mesother* 1981; 1: 67-69.
- 51) GALLO R. Mesotherapy in phlebology. *Phlebologie* 1980; 33: 153-156.
- 52) TOMASELLI F, SCONDOTTO G, SFORZA G. First data on the use of mesotherapy controlled in the treatment of phlebolymphedemas. *J Mesother* 1981; 1: 71-76.
- 53) BARTOLETTI CA, GUALTIEROTTI R, TOMASELLI F. Mesotherapy and gel frigotherapy in the treatment of "cellulitis" and phlebolymphoedemas in the lower limbs. *J Mesother* 1981; 1: 127-138.
- 54) MERLEN JF, CURRI SB, SARTEEL AM. Cellulitis, a conjunctive microvascular disease. *Phlebologie* 1979; 32: 279-282.
- 55) MERLEN JF. Physiopathology of sclerosis cellulites. *Phlebologie* 1981; 34: 537-541.
- 56) PEROTTI F. Treatment of edematous fibrosclerotic panniculopathy (PEFS) with pure diosmin associated with topical treatment with isophoresis. *Dermatol Clin* 2007; 27: 91-95.
- 57) MAGGIORI E, BARTOLETTI CA, MAGGIORI S, TOMASELLI F, DORATO D. Local intradermotherapy (ITD) with mesoglycan in PEFS and CVLI, retrospective study. *Trends Med* 2010; 10: 73-78.
- 58) LACARRUBA F, TEDESCHI A, NARDONE B, MICALI G. Mesotherapy for skin rejuvenation: assessment of the subepidermal low-echogenic band by ultrasound evaluation with cross-sectional B-mode scanning. *Derm Ther* 2008; 21 (Suppl 3): 1-5.
- 59) CARRUTHERS JD, GLOGAU RG, BLITZER A. Facial Aesthetics Consensus Group Faculty Advances in facial rejuvenation: botulinum toxin type a, hyaluronic acid dermal fillers, and combination therapies—consensus recommendations. *Plast Reconstr Surg* 2008; 121 (Suppl 5): 5-30.
- 60) SCUDERI N, BARTOLETTI CA, MICALI G, SILVESTRI P, CIRILLO PF, BARTOLETTI E, BENCI M, BERTANA C. Consensus Conference Italiana sui dermal filler 2007. [http://www.dermatologialegale.it/news.php?id\\_news=29092008](http://www.dermatologialegale.it/news.php?id_news=29092008), last accessed 29 April 2011.
- 61) ROTUNDA AM, KOLODNEY MS. Mesotherapy and phosphatidylcholine injections: historical clarification and review. *Dermatol Surg* 2006; 32: 465-480.
- 62) DUNCAN D, RUBIN JP, GOLITZ L, BADYLAK S, KESEL L, FREUND J, DUNCAN D. Refinement of technique in injection lipolysis based on scientific studies and clinical evaluation. *Clin Plast Surg* 2009; 36: 195-209.
- 63) CARUSO MK, ROBERTS AT, BISSON L, SELK KS, GUILLOT TS, GREENWAY FL. An evaluation of mesotherapy solutions for including lipolysis and treating cellulite. *J Plast Reconstr Aesthet Surg* 2008; 61: 1231-1324.
- 64) CO AC, ABAD-CASINTAHAN MF, ESPINOZA-THAEBTHARM A. Subdermal fat reduction by mesotherapy using phosphatidylcholine alone vs phosphatidylcholine and organic silicium: a pilot study. *J Cosmet Dermatol* 2007; 6: 250-257.
- 65) ROTUNDA M. Injectable treatments for adipose tissue: terminology, mechanism, and tissue interaction. *Lasers Surg Med* 2009; 41: 714-720.
- 66) VEDAMURTHY M. Mesotherapy. *Indian J Dermatol Venereol Leprol* 2007; 73: 60-62.
- 67) MATARASSO A, PFEIFER TM. Mesotherapy and injection lipolysis. *Clin Plastic Surg* 2009; 36: 181-192.
- 68) KALIL A. Aesthetic mesotherapy: the US approach and contribution. *Cosmet Dermatol* 2006; 19: 753-758.



- 69) ATIYEH BS, IBRAHIM AE, DIBO SA. Cosmetic mesotherapy: between scientific evidence, science fiction, and lucrative business. *Aesthetic Plast Surg* 2008; 32: 842-849.
- 70) LAURENZA M, RIBUFFO M. Trattamento dell'acne cistica e delle cisti infette con mesoterapia, *Proceedings of the 3rd International Mesotherapy Congress, Rome, 1982: May 12-13.*
- 71) KASHANI MN, SADR B, NILFOROUSHZADEH MA NILFOROUSHZADEH MA, ARASTEH M, BABAKOOHI S, FIROOZ A. Treatment of acute cutaneous leishmaniasis with intralesional injection of meglumine antimoniate: comparison of conventional technique with mesotherapy gun. *Int J Dermatol* 2010; 49: 1034-1037.
- 72) COUDEVILLE L, ANDRE P, BAILLEUX F, WEBER F, PLOTKIN S. A new approach to estimate vaccine efficacy based on immunogenicity data applied to influenza vaccines administered by the intradermal or intramuscular routes. *Hum Vaccin* 2010; 6: 841-848.
- 73) STICCHI L, ALBERTI M, ALICINO C, ALICINO C, CROVARI P. The intradermal vaccination: past experiences and current perspectives. *J Prev Med Hyg* 2010; 51: 17-14.
- 74) BOTTONE E, GIORDANI G. Experimental observations on the role of the hypothalamus in the hypophyseal and adrenal response to intracutaneous ACTH. *Minerva Pediatr* 1956; 19: 728-731.
- 75) BOTTONE E, GIORDANI G. Experimental observations on the effects of intracutaneous prednisolone succinate. *Minerva Pediatr* 1957; 29: 998-1001.
- 76) FERRETTI O, VENEZIA A. Therapeutic effects of prednisolone hemisuccinate in intracutaneous administration in asthmatic syndromes. *Riv Clin Pediatr* 1959; 64: 16-24.
- 77) SAVASTANO M. Lidocaine intradermal injection—a new approach in tinnitus therapy: preliminary report. *Adv Ther* 2004; 21: 13-20.
- 78) SAVASTANO M, TOMASELLI F, MAGGIORI S. Intradermal injection vs. oral treatment of tinnitus. *Therapie* 2001; 56: 403-407.
- 79) SAVASTANO M, FERRARO SM, MARIONI G. Perichondritis with or without external otitis and intradermal injection: a new therapeutic approach. *J Otolaryngol Head Neck Surg* 2009; 38: 568-572.
- 80) CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC). Outbreak of mesotherapy-associated skin reactions—District of Columbia area, January-February 2005. *MMWR Morb Mortal Wkly Rep* 2005; 54: 1127-1130.
- 81) YAAR R, GARG A, AL-DAWSARI N, GOLDBERG L. Delayed idiosyncratic inflammatory reaction to cosmetic injection of vitamin E. *J Cutan Pathol* 2009; 36: 137.
- 82) TAN J, RAO B. Mesotherapy-induced panniculitis treated with dapsone: case report and review of reported adverse effects of mesotherapy. *J Cutan Med Surg* 2006; 10: 92-95.
- 83) KIM JB, MOON W, PARK SJ, KIM KJ, LEE JN, KANG AJ, JANG LL, CHANG HK. Ischemic colitis after mesotherapy combined with anti-obesity medications. *World J Gastroenterol* 2010; 16: 1537-1540.
- 84) CARBONNE A, BROSSIER F, ARNAUD I, BOUGMIZA I, CAUMES E, MENINGAUD JP, DUBROU E, JARLIER V, CAMBAU E, ASTAGNEAUL P. Outbreak of non-tuberculous mycobacterial subcutaneous infections related to multiple mesotherapy injections. *J Clin Microbiol* 2009; 47: 1961-1964.
- 85) CORREA NE, CATANO JC, MEJIA GI, REALPE T. Outbreak of mesotherapy-associated cutaneous infections caused by mycobacterium chelonae in Colombia. *J Infect Dis* 2010; 63: 143-145.
- 86) NAGORE E, RAMOS P, BOTELLA-ESTRADA R. Cutaneous infection with Mycobacterium fortuitum after localized microinjections (mesotherapy) treated successfully with a triple drug regimen. *Acta Derm Venereol* 2001; 81: 291-293.
- 87) ROSINA P, CHIEREGATO C, MICCOLIS D, D'ONGHIA FS. Psoriasis and side-effects of mesotherapy. *Int J Dermatol* 2001; 40: 581-583.
- 88) SHALADI AM, CRESTANI F, BOCCHI A, SALTARI MR, PIVA B, TARTARI S. Cervical lymphadenopathy due to pseudomonas aeruginosa following mesotherapy. *Infez Med* 2009; 3: 169-172.
- 89) THE DELPHI METHOD TECHNIQUES AND APPLICATIONS. New York: Murray Turoff and H.A. Linstone Editors; 2002.
- 90) ROWE AND WRIGHT. The Delphi technique as a forecasting tool: issues and analysis. *Int J Forecast* 1999; 154: 353-375.
- 91) WARNING LETTER FROM FDA. <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm207658.htm>. Last accessed 29 Apr 2011.