THERAPEUTICS

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TREATMENT OF WRINKLES AND SKIN SLACKENING USING THE INTRADERMAL INJECTION OF A COMPLEX HOMEOPATHIC REMEDY *(MADE OMEO WRINKLE)*

RESULTS OF A COHORT CLINICAL STUDY ON 681 PATIENTS

SUMMARY:

Wrinkles and skin slackening are the most obvious sign of the passing of time, i.e., ageing from a mere biological viewpoint. However, they also reflect the psycho-neuro-endocrino-immunological (PNEI) vision of the human being: in other words, the skin is the main target of one's psychological experiences during the somato-psychic process, whereas it is the starting point of organic wounds that will eventually become the "soul scar" during the psychosomatic process.

The beauty of the face has been always connected with a smooth, glowing and young skin. Therefore, in order to exorcise ageing, our society makes us turn to Plastic Surgery or Aesthetic Medicine, which are not often completely successful or do not satisfy the patients' requirements fully.

For more than five years, the homeopathic remedy MADE, has been an effective alternative to conventional pharmacological treatment and can certainly be regarded as a refe-rence drug in Aesthetic Medicine. The cohort study hereunder, carried out between 1998 and 2003 on 681 patients, has proved the efficacy and good tolera-bility of MADE both in preventive and therapeutic terms, in the homeo-mesotherapic treatment of skin slackening as well as all types of wrinkles, especially linear periocular and peri-labial wrinkles, showing the best results in patients aged between 30-40 years and 40-50 years.

KEY WORDS:

SKIN AGEING, WRINKLES, MADE, HOMOTOXICOLOGY

INTRODUCTION

The most significant and obvious sign of the transition from youth to old age is the appearance of facial wrinkles.

"Beauty" has always been associated with having young, smooth and glowing skin. However, apart from external beauty, the skin also reflects a person's troubles, anxiety and pain - it is a mirror of the soul and every wrinkle *tells the story* of that person's experiences in life.

The skin is the pattern on which the **psycho-neuro-endocrino-immunological (PNEI)** vision of Medicine is based and where the psychosomatic signs of psychological troubles become clearly visible over the years. The skin is also the starting point for the organic wound that will eventually become the *"soul scar"* (non-acceptance of the self) during the somato-psychic process. It is not a case if in Reckeweg's table of Homotoxicosis skin and neuroderm have the same blastodermic ectodermic origin.

On this basis, we can understand why nowadays, regardless of one's level of education, social class or religion, it has become so important to "exorcise" the aging process, starting with trying to eliminate the problem of wrinkles.

According to the *American Society of Plastic Surgeons (www.plasticsurgery.org)*, blepharoplasty and face lifts account for just a third of the total number of plastic surgery operations requested by Americans. Even in the non-surgical sector of Aesthetic Medicine, figures are still impressive: Collagen implants, hyaluronic acid fillers, goretex implants, botulinic toxin, mechanical dermal abrasion and CO2 laser skin resurfacing are still the most common therapeutic stronghold for specialists.

However, results do not always meet the patients' high expectations.
For more than five years, the homeopathic remedy MADE (GUNA, Milan), has been an effective alternative to conventional pharmacological treatment.
In this article, the biological interpretation of the etiopathogenesis of skin aging and wrinkles will be on the basis of the correct therapeutic rationale for these problems: by studying the composition of MADE, we will be able to identify this rationale in its homeopharmacological structure.

The results of an observation study, carried out between 1998 and 2003 on **681 male and female patients**, on the efficacy of MADE in the treatment of wrinkles and slackening of the face and neck tissues, will be examined and described later on.

SKIN AGING

Chronological aging of the skin is the result of a mixture of biological, biochemical and molecular events established by the genetic code of each individual *(chronoaging)*. This is why not all people grow old in the same way and the skin is not the same in all individuals. Other environmental chemical and physical factors contribute to aging, and these are of varying importance in determining its type and severity *(photoaging)*.
In order to fully understand the pathogenic mechanisms leading to aging of the skin, we need to analyse and consider the same mechanisms that lead to general organic aging and examine the metabolic and structural characteristics of human skin.
We also need to consider that *chronoaging* and *photoaging* could have a significant impact on the alteration of some physiological cutaneous mechanisms, not only as independent events but also as synergic factors.
The results of skin aging are clearly visible in *loss of elasticity* and *turgidity*, and the *appearance of wrinkles*. It can be traced back to a slowdown in cell turnover (SYCOTIZATION process according to classic Homeopathy), with a subsequent reduction in elastic tissue and loss of the support structure (but not just the support structure as maintained by Pischinger and Heine) represented by the subcutaneous, loose fibrillar connective tissue (dermis).

SKIN PHYSIOPATHOLOGY AND THE ROLE OF SUBCUTANEOUS CONNECTIVE TISSUE

The normal physiological process of **chronoaging** affects all the structures of the tegumental system: at epidermis level, one can see a reduction in mitoses, a tendency towards premature keratinisation, the dispersion of melanocytes, and a reduction in Langerhans cells.
The basal membrane shows a progressive smoothing with the disappearance of the epithelial crests and dermal papillae.
The dermis shows a loss of thickness and thinning out of the vascular support; the collagen fibres are fragmented; the elastic fibres are disorganised; the interstitial substance tends to become uniform, and there are lower numbers of fibroblasts, mastocytes and Langerhans cells.

But what causes these phenomena?
There are two main theories:
1) according to the first theory (**"programmatic"**), the programming of cell death lies within the genetic code;
2) according to the second theory (**"degenerative"**), aging is a process that is dependent on exogenous factors (especially *photoaging* for the skin) and endogenous factors (hormonal and immunological factors, for example) that synergically cause a series of **metabolic failures** (Deposition Phase according to the Table of Homotoxicosis) and alterations in molecular syntheses. You need only to think about what happens in particular areas of the face, such as the eyelids and some periocular areas – here a reduction in collagen type I synthesis is clearly linked to age, but ultraviolet radiation, and the subsequent production of free radicals, causes a drastic reduction in elastin and collagen storage and this probably affects post-transcription mechanisms.

WRINKLES

Wrinkles are the most visible evidence of cutaneous atrophy and are caused by damage to the collagen and elastic fibres. We must remember that, as the skin does not have its own muscular structures, it is the contraction of the muscles below it that determines its shape. As time goes by, due to changes in tone and elasticity, the skin can no longer relax and the first marks remain etched on the skin and gradually get worse.
Wrinkles can be divided into the following categories:

- *Linear wrinkles:* these are linked to facial expressions; at first they are reversible and are more common in women. They mainly appear around the eyes *(crow's feet)*, between the eyes (from frowning), around the mouth (vertically on the upper lip or around the mouth), horizontally on the forehead (related to emotions, in particular to anxiety);
- *Glyphic wrinkles:* these are related to a greater accentuation of the ordinary cutaneous structure. They appear on cheeks in particular;
- *Creases:* these are caused by prolonged facial expressions (for instance while sleeping);
- Wrinkles between the nose and mouth: these are deep incisures appearing between the external edge of the mouth and the nose wings, delimited by muscles (mouth orbicular and buccinator muscles).

HOMOTOXICOLOGICAL INTERPRETATION OF THE ETIOPATHOGENESIS OF WRINKLES AND SKIN SLACKENING

According to homotoxicological physiopathology, wrinkles can be categorised under **Deposition Phase – Impregnation of the Tegumental System**

(FIGURE 1). From a homotoxicological point-of-view, it is clear how wrinkles and the slackening of face and neck tissues are caused by **changes in the MATRIX** (in fact, both the Deposition Phase and the Impregnation Phase are part of the "Matrix Fundamental Substance Phases").
The connective tissue has mistakenly been regarded as just a support tissue; the dermis, has always been regarded as just the tissue on which the skin lays.
However, Homotoxicology regards the matrix as a truly specialised organic structure, the "*Basic Regulation System*": all changes in the internal and external environment affect cell mechanisms via the interstitial substance.
It is via the matrix that the cells are able to communicate with the external environment - the amount of information stored in the matrix and passed on to cells as instructions on their physiological functioning is enormous. The matrix is the place where the neurovegetative endings unravel and the psycho-neuro-endocrino-immune information is conveyed through the neural and endocrine substances and cytokines.
We know that correct cell functioning is based upon the anatomical and functional integrity of the matrix, and ultimately on its "*cleanliness*" and its detoxification levels. An accumulation of stress factors at this level can lead to a potential triggering of a pathological process. If these changes in the loose fibrillar connective tissue are in the dermis, then a subsequent pathological alteration will obviously appear.
In fact, it is essential to keep the dermis well-drained and metabolically efficient in order to keep the skin looking young.

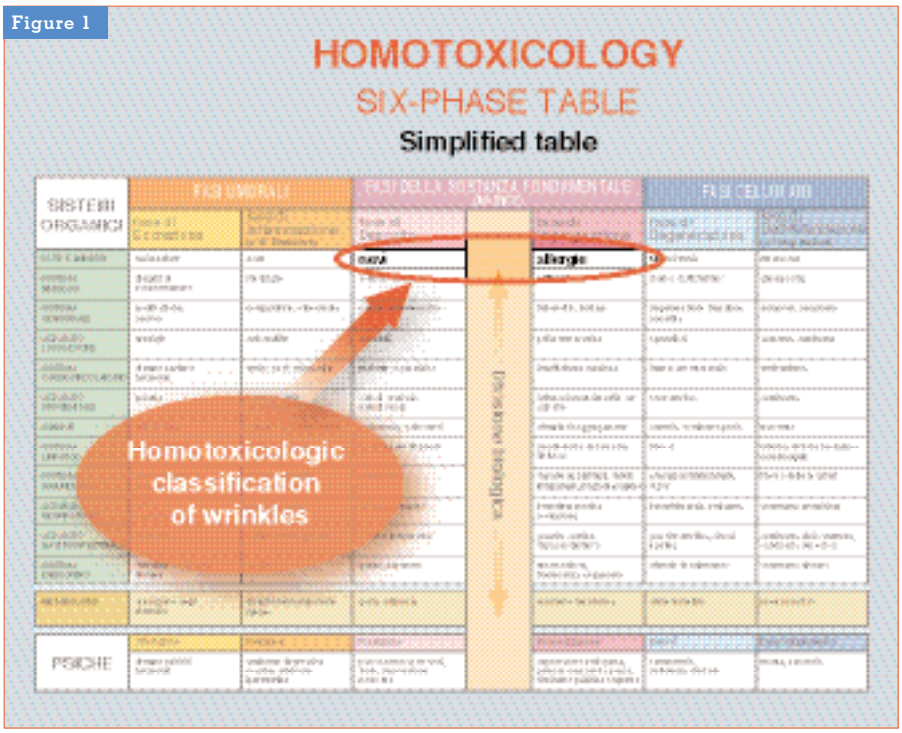
The dermis is composed of:

- *Fibroblasts* and *fibrocytes* and their *extracellular metabolites*
- *Collagen fibres* and *elastic fibres*
- *Glycosaminoglycans (GAGs)* and *proteoglycans (PGs)*
- *Blood vessels* and *nerves*
- *Immunocompetent cells*

There are two different areas in the dermis:

1. the **papillary dermis**, which is superficial and thin and located near the dermatoepidermal junction, and is rich in matrix but poor in collagen and elastin;
2. the **reticular dermis**, a thicker area located between the papillary dermis and the subcutaneous adipose tissue: it is rich in collagen and elastic fibres, contains lower quantities of matrix, and is well vascularised (blood and lymph capillaries afferent from the underlying subcutaneous adipose tissue).

Figure 1

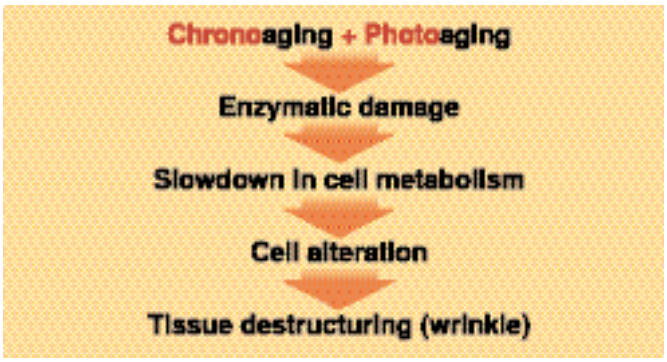


The action of the **homeopathic drug MADE** is targeted on these two structures.

The etiopathogenetic process that leads to the destructuring of the dermis and, therefore, to wrinkles is characterized by a series of connected events (TABLE 1):

- ***Phase 1***: a reduced supply of O_2 and nutrients to the dermis cells caused by the pollution of the matrix due to catabolites produced in cell turnovers (chronoaging) and by undrained toxins (free radical photoaging), causes a **slowdown of intracellular metabolisms** and subsequent enzymatic damage;
- ***Phase 2***: the metabolic distress of the fibroblast affects its activity leading to a drastic reduction in the incretion of the matrix components (in particular hyaluronic acid) and the collagen and elastic fibres;
- ***Phase 3***: the connective tissue weave loses compactness. The lack of glycosaminoglycans has a dramatic effect on skin hydration (hyaluronic acid is a highly hydrophilic molecule) and its turgidity; the reduced vascularisation of the epidermis causes the skin to lose its

Table 1



brightness and normal lymphatic drainage is slowed down, resulting in a vicious cycle that is difficult to break.
If any wrinkle treatment is to be reliable then it must take all these pathogenic processes into consideration and not just act on one aspect of them.
A therapy that is simply a means of compensating for a deficiency in hyaluronic acid from chronoaging or in other components of the dermal matrix, would not take into account the fact that **wrinkles are primarily a METABOLIC ALTERATION** (a result of suffering aged cells).

Instead, a wrinkle treatment should be an integrated therapy where fibroblasts can begin their synthesizing activity (after specific organ preparation stimulation) as their proper metabolic function has returned as a result of the action of the coenzyme substrates of the Krebs cycle and they, therefore, have sufficient "energy" levels to maintain their neosynthesis activity.
At the same time, the integrity of the functional structure of the dermis should be maintained by means of continuous detoxification and drainage.
The homeopathic drug MADE acts on this "cascade" via the synergic action of its four nuclei of components (FIGURES 4-5).

1. **INTERMEDIATE CATALYSTS**
   Vitamin C D6, Vitamin B1 D6, Vitamin B6 D6, Nicotinamid D6, Ac. Cis aconitum D6, Ac. Fumaricum D6, Ac. Alpha-ketoglutaricum D6, Baryum oxalsuccinicum D6, Natrium oxalaceticum D6, Natrium pyruvicum D8, Magnesium gluconicum D6, Manganum phosphoricum D10;

2. **"SUIS" ORGANOTHERAPIES**
   Collagen suis D8-D30, Funiculus umbilicalis suis D10-D30, Cutis suis D8-D30, Placenta suis D10, Musculus suis D20, Hepar suis D10, Glandula suprarenalis suis D10;

3. **CLASSIC HOMEOPATHIC REMEDIES**
   Sulphur D12, Mercurius solubilis Hahnemanni D20, Calcium fluoratum D30, Galium aparine D6, Thuja D6;
4. **HOMEOPATHIZED ENZYMES**
   Hyaluronidase D8-D30.

Through its own components, each of the drug's four nuclei develops a **structural and functional tropism that is specific** *to each of the steps in the process of the etiopathogenic cascade of wrinkles (FIGURES 2-3-5):*

1 - THE NUCLEUS OF INTERMEDIATE CATALYSTS

Its elective target is the mitochondrion and, in particular, the Krebs cycle. It has a release action on the mechanisms assigned to energetic metabolism, via the enzymatic stimulation induced by homeopathic dilutions.
The intermediate catalysts in MADE are therefore vital, as without the release of the oxidative phosphorylation processes and the cells' renewed production of energy, the fibroblasts could not react to the proliferative trophic stimulation simultaneously induced by the "Suis" organotherapies.
The core of the nucleus of catalysts is α-ketoglutaric acid, a Krebs cycle substrate that acts on the enzyme, α-ketoglutaric-dehydrogenase, which is often blocked in the initial phases (still reversible) of fibroblast degeneration.
Homeopathized vitamins are, of course, included for their antioxidant activity (action against photoaging and protection of the matrix glycosaminoglycans).
Vitamin C was included as it is an important cofactor in the transformation of *proline* into *hydroxyproline*.
The two oligo elements (**Magnesium gluconicum D6, Manganum phosphoricum D10**) are particularly important for their catalytic action on collagen metabolism.

2 - THE NUCLEUS OF "SUIS" ORGAN PREPARATIONS

In accordance with the observations of Dr. H. H. Reckeweg, "Organotherapy" with homeopathized organ preparations is based on the use of pigs as donors.
From a homeopathic point of view, we can confirm that a pig organ or homeopathized pig tissue represent the **"simile"** of the human homologous organ and as a result of this "**similarity**" (greater than that of other animal species), the therapeutic efficacy of a homeopathized preparation is even greater.

This likeness is particularly apparent at **immunological** level.
The result is the **marked organotropism** of the "*Suis*" protein for the human homologous protein.

Due to pigs' almost completely ineffective detoxification systems, their tissues are particularly toxic (steatosis degeneration).
Therefore they have a structure that has the potential characteristics of a nosode, plus the specific properties of organotropism.
A "Suis" organotherapeutic homeopathic preparation is an **organ-specific nosode**, that, via a subliminal immunological mechanism, triggers the immune response of not only the entire RES system (hystiocytic macrophagic), but also of the target organ or tissue. We can confirm that the use of organotherapies in treatment causes a localized "*microinflammation*", which although not clinical (because of the dilution), is sufficient to "*waken*" the functionality of the connective matrix.

Their action is also partly "*trophic*": these *Suis* proteins, or some substances contained in them, are substrates for the enzyme reactions of protein synthesis ("*codifying matrices*"). The fact that they are diluted in accordance with the Laws of enzyme kinetics, makes them perform as inductors, speeding up protein synthesis.

The following are of particular interest:

- **Collagen suis**

Although Collagen suis triggers, with the immunological mechanism, the function of the loose fibrillar connective tissue of the dermis via a subclinical inflammatory type process, it also carries out a trophic action by stimulating the fibrob-

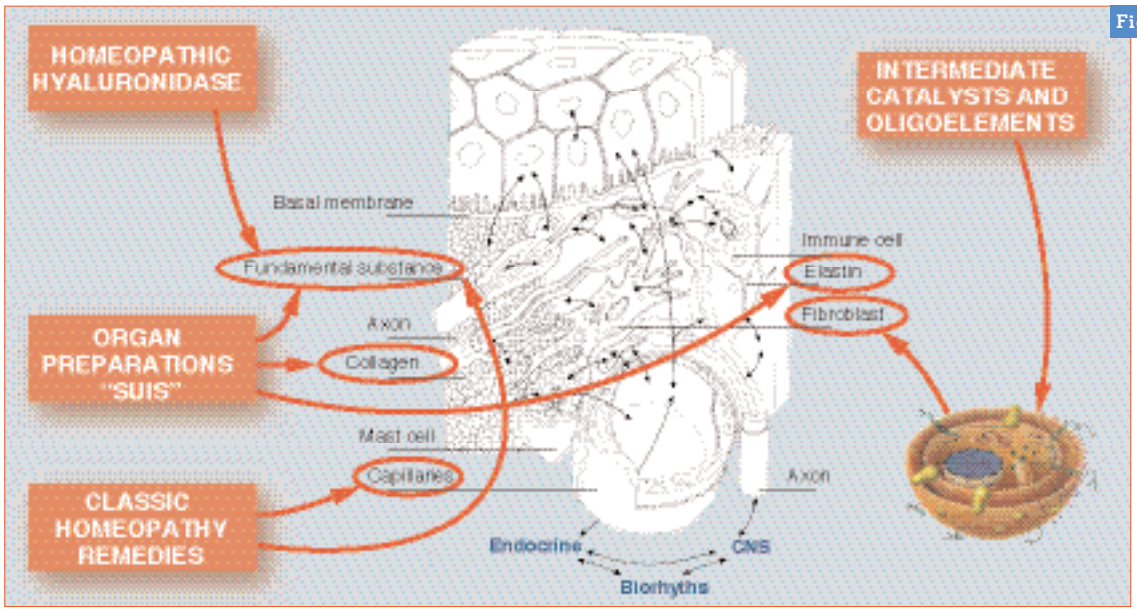


Figure 2

Target sites of MADE components

last to increte autologous collagen.
Therefore, we cannot refer to Collagen suis simply as having a supplementation, and, therefore plastic action, but real biostimulation.

• **Funiculus umbilicalis suis**
It is well-known that this organ preparation is extremely rich in glycosaminoglycans (especially hyaluronic acid). When these substances are homeopathically diluted, according to enzyme kinetics Laws, they act as inductors, *starters*, and codifying matrices for the synthesis of autologous glycosaminoglycans.

• **Musculus suis and Cutis suis**
It is easy to guess at the rationale behind the action of these remedies - they stimulate the function of their respective targets, performing an anti-degenerative action and stimulating their trophism.

• **Placenta suis**
Some of the Growth Factors contained in the placenta are of particular interest – especially **FGF** (*Fibroblast Growth Factor*) that can stimulate the fibroblast receptors to activate their metabolism; and **EGF** (*Epidermal Growth Factor*), a polypeptide that acts on the epidermal metabolism.
Placenta suis is also well-known for its action on microcirculation.

• **Hepar suis**

Figure 3

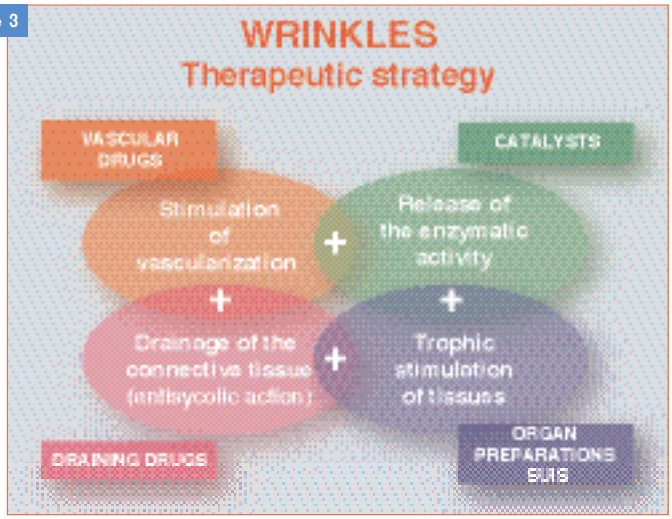
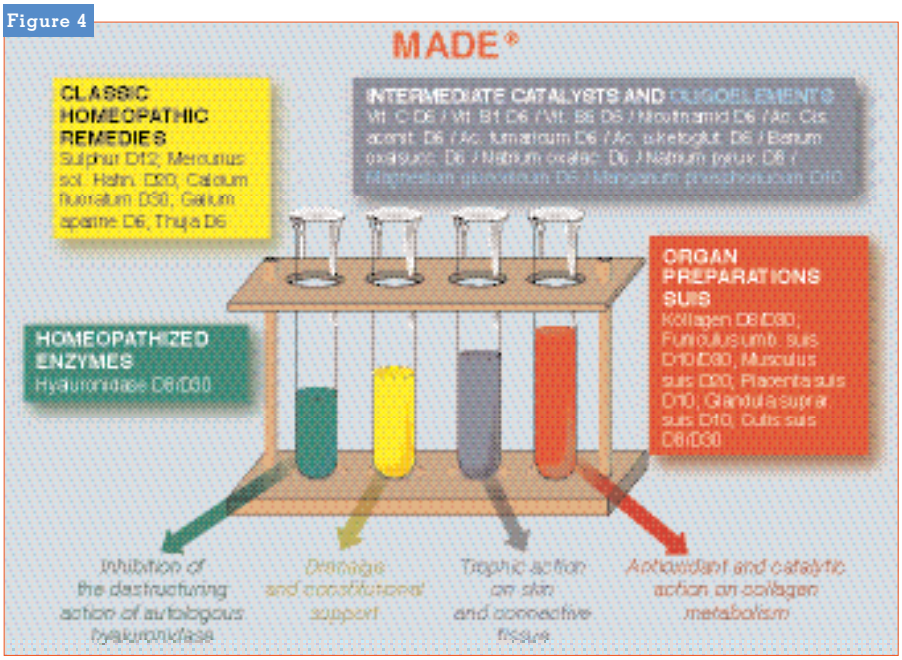


Figure 4



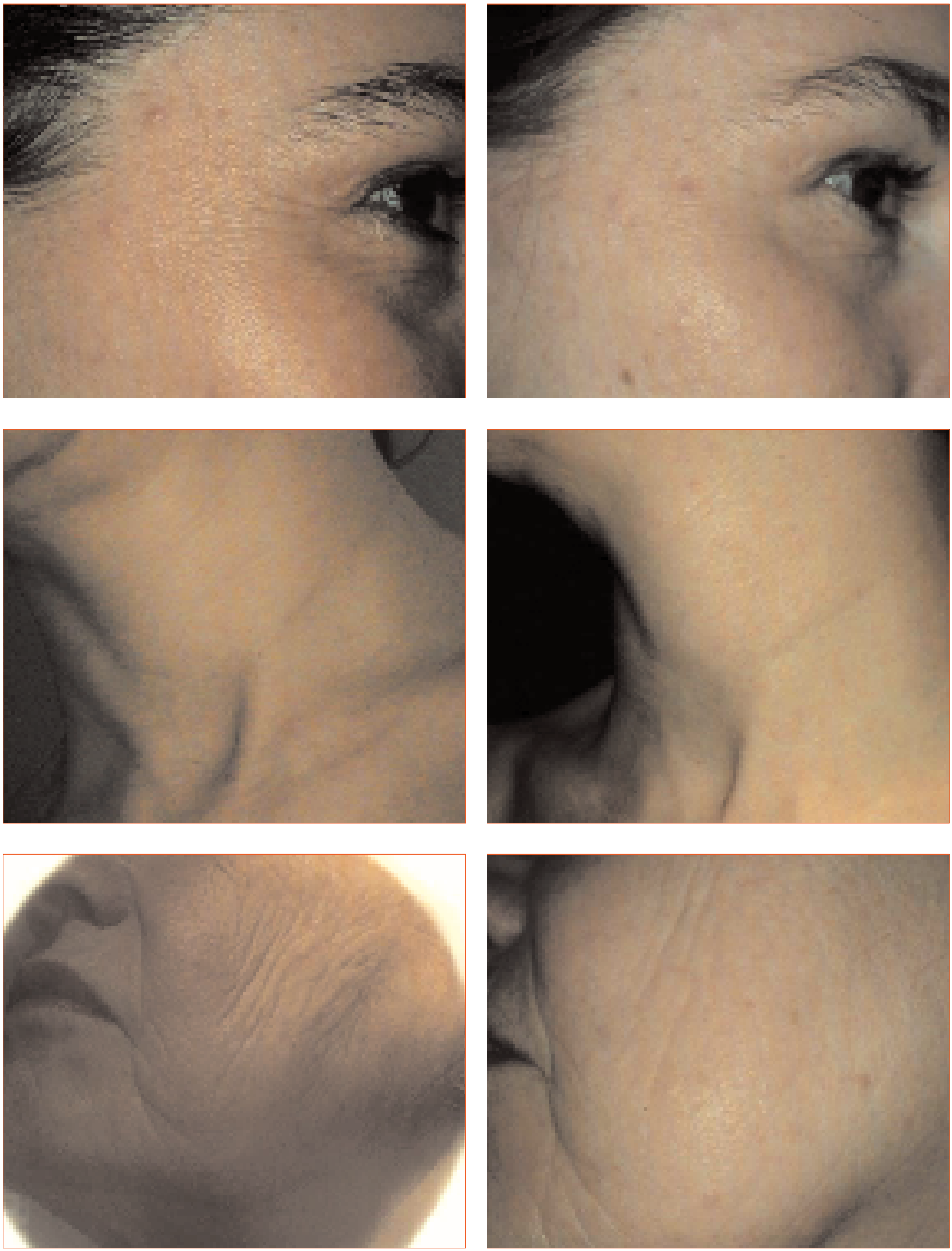


Table 2

Some examples of tratment with MADE. Left side: before **treatment; right side:** after **treatment.**

The inclusion of this organotherapy was necessary for activating the emunctory drainage of this organ, which is closely linked to the skin, both from an energetic (Traditional Chinese Medicine) and an ontogenetic point of view.

• **Glandula suprarenalis suis**
According to Homotoxicology, the stimulation of the suprarenal gland is the basis for the treatment of pathologies that are degenerative or somehow connected with ageing.

3 - THE NUCLEUS OF CLASSIC HOMEOPATHIC REMEDIES

The main homeopathic polycrests with recognised anti-degenerative properties were selected, such as **Galium aparine** (essential detoxifying and cleavage action on toxins acting on connective tissue metabolism) and **Thuja** (main remedy against dysmetabolic mesenchymal pathologies which are the source of the pathogenesis of wrinkles).
Sulfur is the most suitable remedy for the skin – the skin contains large amounts of cysteine, a sulfur amino acid (-SH). The sulfur enzymes are extremely important for the proper functioning of the tegumental system. Sulfur also has an important toxin centrifugation action and, therefore, a drainage action as well.
Calcium fluoratum and **Mercurius solubilis Hahnemanni** act on areas prone to wrinkles – typical of the *"Fluoric"* Homeopathic constitution - where we can see the "*wearing out*" of the connective tissue leading to varicose veins, ptoses and wrinkles. In its pathogenesis, Mercurius solubilis Hahnemanni is characterized by signs of *destruction*.

4 - THE HOMEOPATHIC ENZYME NUCLEUS

The inclusion of **Homeopathic Hyaluronidase** is MADE's real innovation. The D8 and D30 homeopathic dilutions of this enzyme regulate and limit the physiological destructuring activity of the autologous hyaluronidase. As a result, the interstitial substance is *compacted* and the wrinkle is reduced. It is essential to act on the integrity of the hyaluronic acid and "protect" it as, to all intents and purposes, it can be regarded as the true "conductor" of the connective matrix structure and function - it packs the main macromolecular components of the dermis around itself, such as collagen, proteoglycans, fibronectin and fibropectins.

*This remedy is, therefore, a true **therapeutic unit** whose structure provides the correct homotoxicological strategy for treating degenerative skin diseases.*
In order to apply an effective wrinkle treatment, we should assume that wrinkles are a **metabolic alteration**. We can then understand the *therapeutic importance of the nucleus of intermediate catalysts, the importance of including "suis" organotherapies and homeopathized Hyaluronidase* and the action of classic homeopathic remedies:

▶ The physiological metabolic activity of the fibroblast is re-established as a result of the enzymatic release promoted by these substances and this is a fundamental condition for the dermis cells to be able to respond to the stimulus induced by the suis organotherapies via the neosynthesis of the components of the Interstitial Substance. The modulation of the degenerative process, controlled by the classic homeopathic remedies, slows down the alteration of the connective stroma. The homeopathic remedies are assisted by the homeopathized hyaluronidase which, by reducing the activity of the corresponding enzyme, fosters the slowing down of the degenerative process and, encourages the compacting of the dermis.

BIOSTIMULATION OF THE SKIN. MATERIALS AND METHODS

Both the mesotherapy needle (4 mm. 30G) and the collagen needle (13 mm – 30G, FIGURE 6A) can be used for this procedure. The mesotherapy needle is used for making classic intradermal wheals in accordance with the mesotherapy method, injecting 0.2-0.3 ml for each wheal (FIGURE 6B).

- The collagen needle is used for cannulating the wrinkle by moving the needle gently from left to right while injecting the contents of the syringe (FIGURE 7).

We recommend treating the whole affected area and possibly, some acupuncture points:

- **LI 18** (**Large Intestine 18**): on the anterior margin of the sternocleidomastoideus, on a level of the upper margin of the thyroid cartilage.
- **ST 4** (**Stomach 4**): about 1 cm laterally to the corner of the mouth.
- **ST 5** (**Stomach 5**): on the vertical line of the pupil, below the inferior margin of the orbit.
- **TH 23** (**Triple Heater 23**): superiorally and posteriorally to the extremity of the eyebrow.
- **GB 1** (**Gall Bladder 1**): 1 cm laterally to the external margin of the orbit.
- **SI 19** (**Small Intestine 19**): anterior to the auricular tragus.

The treatment generally consists of **7-10 treatments carried out once a week**, followed by one or more maintenance sessions which can be monthly, bi- or tri-monthly.

With homeo-mesotherapic biostimulation, one can see an overall ***revitalization***, a considerable **improvement** in **tissue tone** and a **clear easing** of the **wrinkles**.
The improvement is gradual and, above all, lasting. The end result of the therapy is a relaxed and rested face with toned, glowing skin.
MADE can be used both as a treatment for **reducing** the signs of aging and as a **preventive** treatment for maintaining a

Figure 5

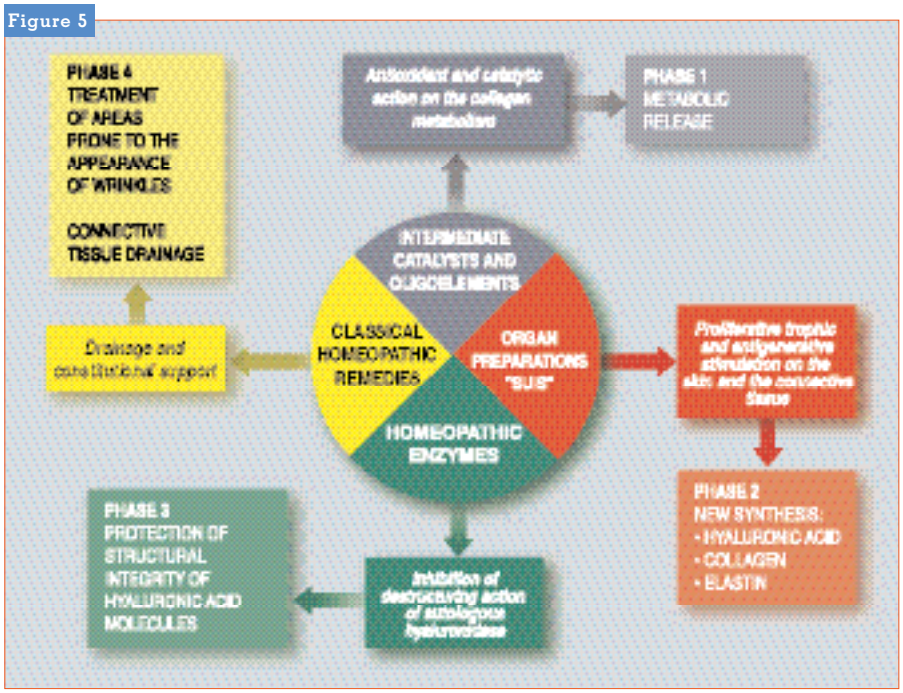
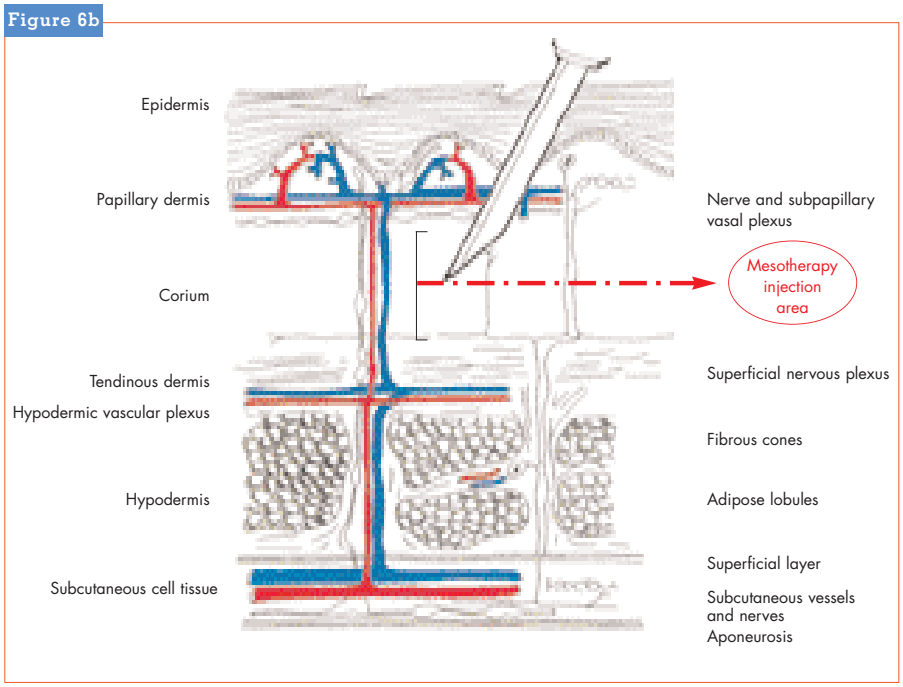


Figure 6a

Figure 6b



youthful face.

As a result of its specific homeopathic preparation, the medicine has no collateral effects or contraindications. No biocompatibility test is therefore needed.

PATIENTS AND METHODS

In this study, we evaluated the effectiveness of the ***homeopathic complex remedy MADE*** in the treatment of wrinkles and skin slackening via a series of subjective and objective clinical indicators.

It was an observation multicentric study, carried out according to the *Good Clinical Practice* Rules.

For this study we included **681 patients** of both sexes **(578 female – 103 male)** aged between 35 and 75 (female) and between 40 and 70 (male), divided into different age ranges.

All patients attending the practices of the doctors taking part in this study have been included, without exclusion criteria.

The period of the study lasted 5 years from 1998 to 2003.

The treatment consisted of **8 sessions** on a weekly basis. For some patients the treatment was continued on the basis of one session a month after the end of the treatment and another every 2-3 months.

3.8% of the patients dropped out of the treatment after the first few sessions, for reasons that were not dependent on the programme.

The method applied involved making linear infiltrations, 1 cm apart, which were parallel to the skin surface in the medium and medium-deep dermis, according to the mesotherapic technique, or making infiltrations inside the wrinkles, according to the *tunnelling* technique. (FIGURE 7)

The results were evaluated before and

WRINKLES Compromised face skin (visual and tactile characteristics)	Cheek (Glyphic wrinkles) N° patients (%)		Perilabial area N° patients (%)		Periocular area N° patients (%)		Forehead area N° patients (%)		Eyebrow area N° patients (%)	
	B	A	B	A	B	A	B	A	B	A
Absent	70 (93)	73 (97)	69 (92)	73 (97)	34 (45)	53 (70)	67 (89)	72 (96)	45 (60)	50 (67)
Slight	5 (7)	2 (3)	6 (8)	2 (3)	36 (49)	21 (29)	5 (7)	2 (3)	22 (29)	18 (24)
Obvious	0 (0)	0 (0)	0 (0)	0 (0)	5 (6)	1 (1)	3 (4)	1 (1)	8 (11)	7 (9)

Table 3
Group A (female patients – 30-40 years old), before (B) and after (A) therapy; n = 75

Figure 8

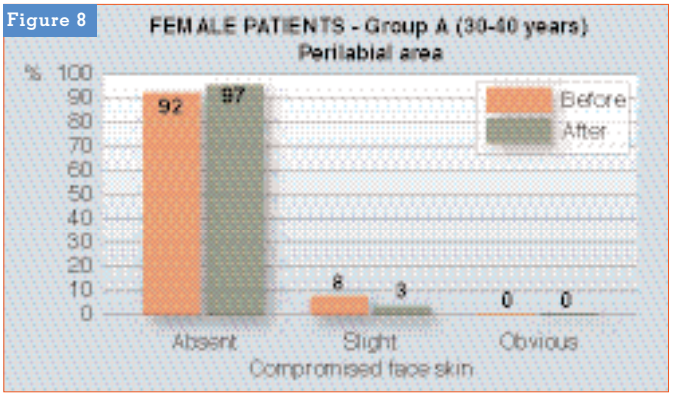
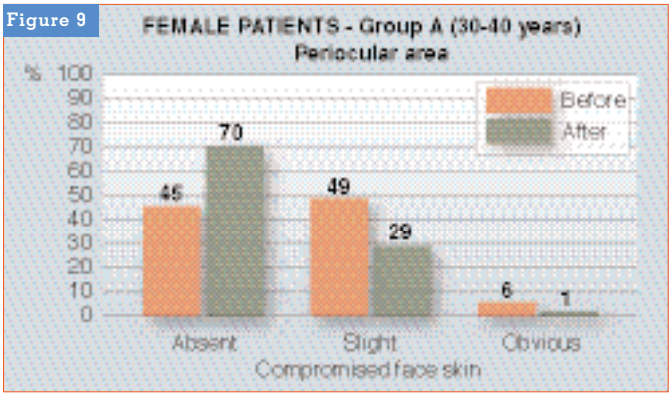


Figure 9



WRINKLES Compromised face skin (visual and tactile characteristics)	Cheek (Glyphic wrinkles) N° patients (%)		Perilabial area N° patients (%)		Periocular area N° patients (%)		Forehead area N° patients (%)		Eyebrow area N° patients (%)	
	B	A	B	A	B	A	B	A	B	A
Absent	85 (89)	90 (94)	65 (68)	73 (76)	28 (29)	58 (60)	61 (64)	64 (67)	49 (51)	50 (52)
Slight	6 (6)	3 (3)	19 (20)	15 (16)	45 (47)	23 (24)	28 (29)	26 (27)	34 (35)	35 (36)
Obvious	5 (5)	3 (3)	12 (12)	8 (8)	23 (24)	15 (16)	7 (7)	6 (6)	13 (14)	11 (12)

Table 4
Group B (female patients – 40-50 years old), before (B) and after (A) therapy; n = 96

Figure 10

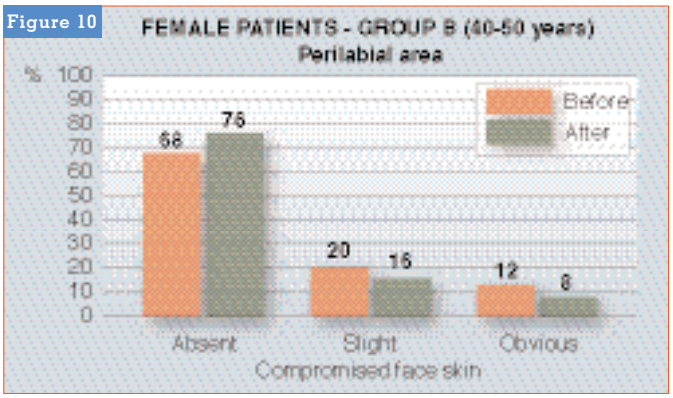


Figure 11

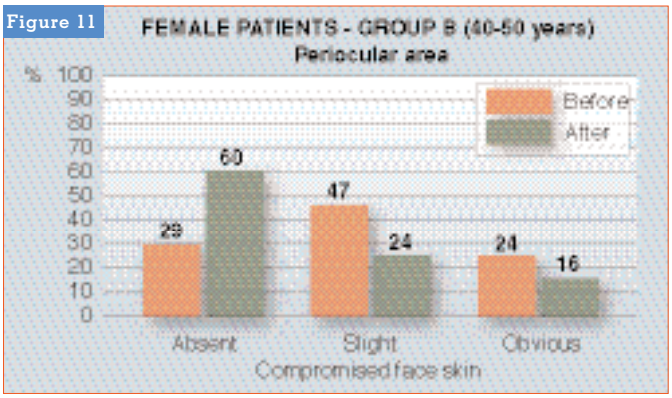


Table 5
Group C (female patients – 50-60 years old), before (B) and after (DA) therapy; n = 188

WRINKLES Compromised face skin (visual and tactile characteristics)	Cheek (Glyphic wrinkles) N° patients (%)		Perilabial area N° patients (%)		Periocular area N° patients (%)		Forehead area N° patients (%)		Eyebrow area N° patients (%)	
	B	A	B	A	B	A	B	A	B	A
Absent	133 (71)	146 (78)	48 (26)	75 (40)	7 (4)	10 (5)	2 (1)	1 (1)	0 (0)	1 (1)
Slight	35 (18)	27 (14)	110 (58)	95 (51)	125 (67)	133 (71)	99 (53)	103 (54)	99 (53)	102 (54)
Obvious	20 (11)	15 (8)	30 (16)	18 (9)	55 (29)	45 (23)	87 (46)	84 (45)	89 (47)	85 (45)

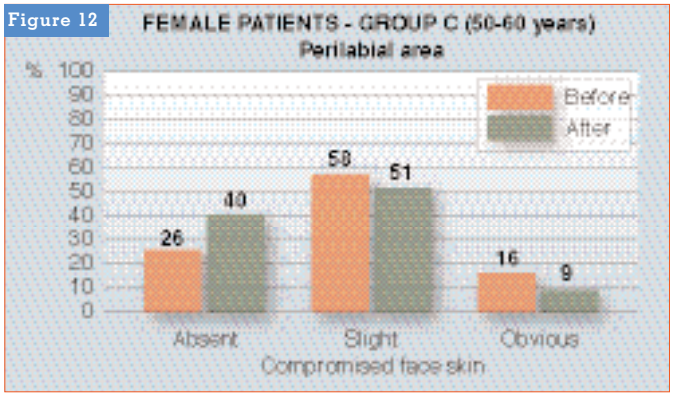
Figure 12


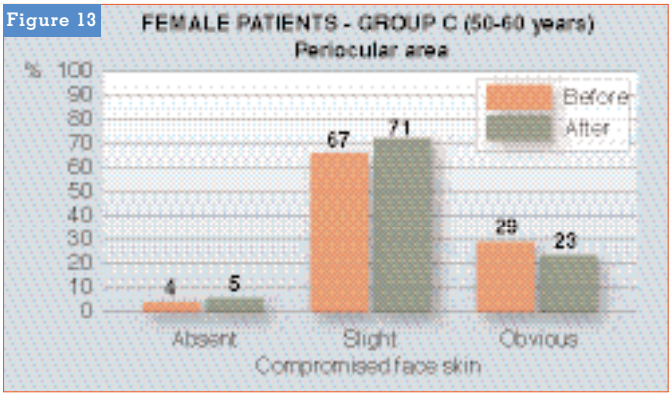
Figure 13


Table 6
Group D (female patients – 60-70 years old), before (B) and after (A) therapy; n = 116

WRINKLES Compromised face skin (visual and tactile characteristics)	Cheek (Glyphic wrinkles) N° patients (%)		Perilabial area N° patients (%)		Periocular area N° patients (%)		Forehead area N° patients (%)		Eyebrow area N° patients (%)	
	B	A	B	A	B	A	B	A	B	A
Absent	19 (16)	27 (23)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)
Slight	52 (45)	45 (39)	55 (48)	66 (57)	52 (45)	66 (57)	57 (49)	59 (51)	57 (49)	62 (53)
Obvious	45 (39)	44 (38)	61 (52)	50 (43)	64 (55)	50 (43)	58 (50)	56 (48)	59 (51)	54 (47)

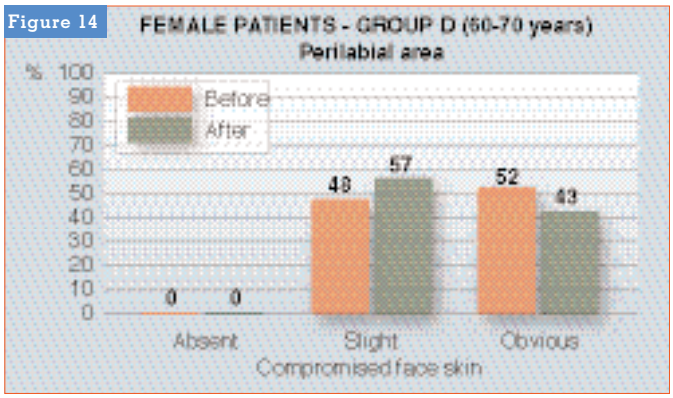
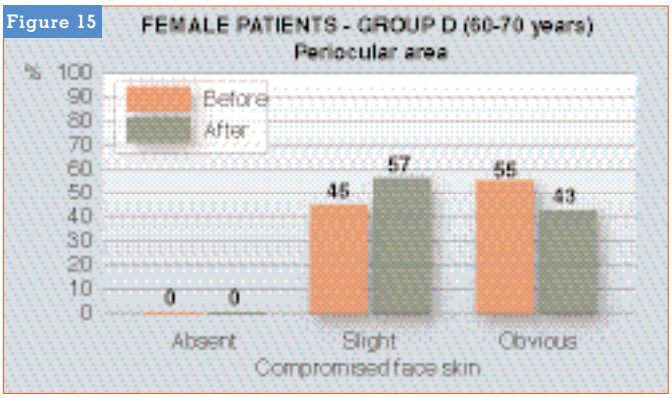
Figure 14


Figure 15


WRINKLES Compromised face skin (visual and tactile characteristics)	Cheek (Glyphic wrinkles) N° patients (%)		Perilabial area N° patients (%)		Periocular area N° patients (%)		Forehead area N° patients (%)		Eyebrow area N° patients (%)	
	B	A	B	A	B	A	B	A	B	A
Absent	3 (3)	3 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Slight	49 (48)	56 (54)	47 (46)	53 (51)	47 (46)	51 (49)	47 (46)	48 (47)	44 (43)	44 (43)
Obvious	51 (49)	44 (43)	56 (54)	50 (49)	56 (54)	52 (51)	56 (54)	55 (53)	59 (57)	59 (57)

Table 7
Group E (female patients – > 70 years old), before (B) and after (A) therapy; n = 103

Figure 16

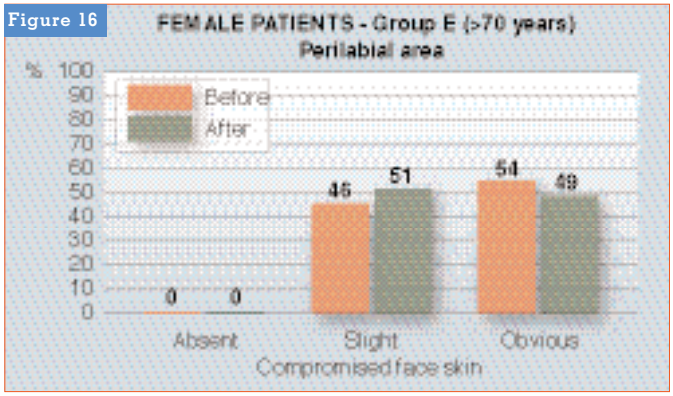
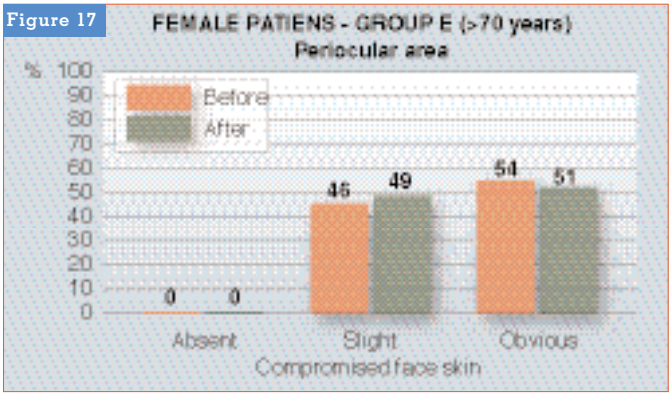


Figure 17



WRINKLES Compromised face skin (visual and tactile characteristics)	Cheek (Glyphic wrinkles) N° patients (%)		Perilabial area N° patients (%)		Periocular area N° patients (%)		Forehead area N° patients (%)		Eyebrow area N° patients (%)	
	B	A	B	A	B	A	B	A	B	A
Absent	40 (80)	43 (86)	38 (76)	41 (82)	18 (36)	21 (42)	38 (76)	40 (80)	36 (72)	39 (78)
Slight	7 (14)	5 (10)	7 (14)	5 (10)	22 (44)	20 (40)	10 (20)	10 (20)	12 (24)	10 (20)
Obvious	3 (6)	2 (4)	5 (10)	4 (8)	10 (20)	9 (18)	2 (4)	0 (0)	2 (4)	1 (2)

Table 8
Group B (male patients – 40-50 years old), before (B) and after (A) therapy; n = 50

Table 9
Group C (male patients – 50-60 years old), before (B) and after (A) therapy; n = 43

WRINKLES Compromised face skin (visual and tactile characteristics)	Cheek (Glyphic wrinkles) N° patients (%)		Perilabial area N° patients (%)		Periocular area N° patients (%)		Forehead area N° patients (%)		Eyebrow area N° patients (%)	
	B	A	B	A	B	A	B	A	B	A
Absent	25 (59)	25 (59)	22 (51)	25 (58)	15 (35)	15 (35)	24 (56)	26 (60)	24 (56)	24 (56)
Slight	15 (34)	16 (37)	14 (33)	12 (28)	20 (46)	21 (49)	16 (37)	14 (33)	16 (37)	17 (39)
Obvious	3 (7)	2 (4)	7 (16)	6 (14)	8 (19)	7 (16)	3 (7)	3 (7)	3 (7)	2 (5)

Table 10
Group D (male patients – 60-70 years old), before (B) and after (A) therapy; n = 10

WRINKLES Compromised face skin (visual and tactile characteristics)	Cheek (Glyphic wrinkles) N° patients (%)		Perilabial area N° patients (%)		Periocular area N° patients (%)		Forehead area N° patients (%)		Eyebrow area N° patients (%)	
	B	A	B	A	B	A	B	A	B	A
Absent	2 (20)	2 (20)	2 (20)	3 (30)	1 (10)	1 (10)	1 (10)	1 (10)	3 (30)	3 (30)
Slight	5 (50)	6 (60)	5 (50)	5 (50)	6 (60)	7 (70)	5 (50)	6 (60)	5 (50)	6 (60)
Obvious	3 (30)	2 (20)	3 (30)	3 (30)	3 (30)	2 (20)	4 (40)	3 (30)	2 (20)	1 (10)

Evaluation	Very poor N° (%)	Poor N° (%)	Acceptable N° (%)	Good N° (%)	Excellent N° (%)
Doctor's evaluation	0 (0)	0 (0)	0 (0)	**211** (31)	**470** (69)
Patient's evaluation	0 (0)	0 (0)	0 (0)	**191** (28)	**490** (72)

Table 11 - **Global evaluation on the treatment: results**

Evaluation	Very poor N° (%)	Poor N° (%)	Acceptable N° (%)	Good N° (%)	Excellent N° (%)
Doctor's evaluation	0 (0)	0 (0)	0 (0)	**7** (1)	**674** (99)
Patient's evaluation	0 (0)	0 (0)	0 (0)	**20** (3)	**661** (97)

Table 12 - **Global evaluation on tolerability**

after the specific treatment via the subjective classification of the visual and tactile characteristics of the wrinkles and the slackening of the face and neck tissues (TABLE 2).

Mild reactions to the treatment were observed in 20 cases (3%) with slight erythema in the injection site, which disappeared spontaneously after a few minutes.

DISCUSSION - CONCLUSIONS

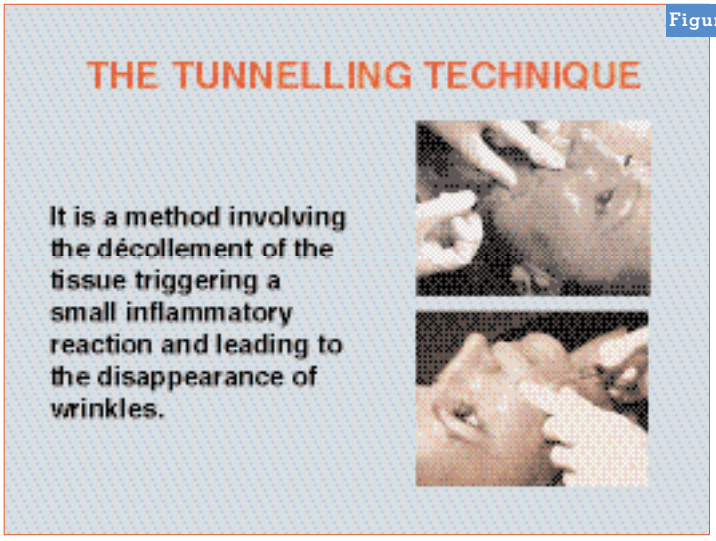
This observation multicentric study has shown that MADE is highly effective and has high levels of tolerability in the homeo-mesotherapic treatment of all types of wrinkles and skin relaxation, especially linear periocular and perilabial wrinkles and the revitalisation of the face and the neck - in Groups A and B, in particular, there was a considerable reduction in the compromisation of these 2 areas of facial skin, with the disappearance of wrinkles; in Groups C, D and E there was a steady improvement, with the compromisation of the areas progressing from being obvious to slight {groups A (TABLE 3; FIGURES. 8, 9) and B [TABLE 4 (FIGURES. 10, 11) TABLE 8 }; Groups C [TABLE 5 (FIGURES. 12, 13) TABLE 9], D [TABLE 6 (FIGURES. 14, 15) TABLE 10] and E [TABLE 7 (FIGURES 16, 17)]

The best results were observed in **female patients between 30-40 and 40-50 years old (groups A and B)**: this is particularly significant as it corresponds to the results one would expect from a biostimulating therapy, which regards a young and adult responder as an individual who still has an optimum reaction capacity both from a metabolic and a histologic point of view, and with a state of connective tissue that has not yet been compromised.

The compliance was extremely good both for the patients **(low cost, visible and lasting results, satisfied the request for biological therapies)** and for the doctors **(absence of any risk, appreciable results).**

▶This study has proved the practicability, tolerability and the efficacy of MADE both in preventive and therapeutic terms, and it can therefore be regarded as a **reference drug in Aesthetic Medicine**. ■

Figure 7



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Pyscho-Neuro-Endocrino-Immunology (PNEI), studies the interaction between stress attacks and the responses of the nervous, neuro-endocrine and immune systems

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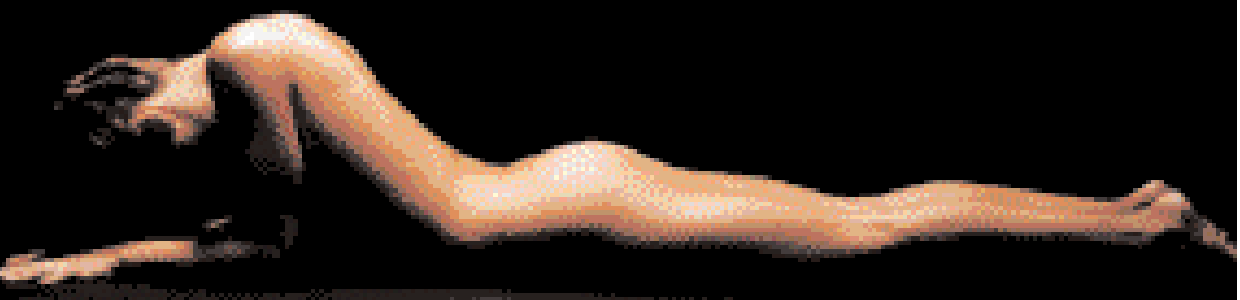
In fact, it has been proved that persistent stress factors (such as affective problems, worries, anxiety and phobias) can have considerable effects on the entire body.



The correlation between PNEI and the well being of women is the key idea supporting the conception of the Natur cosmetics line of Guna

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