Cellulite
Pathophysiology and Treatment

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Cellulite
BASIC AND CLINICAL DERMATOLOGY

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Cellulite
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Series Introduction

During the past 25 years, there has been a vast explosion in new information relating to the art and science of dermatology as well as fundamental cutaneous biology. Furthermore, this information is no longer of interest only to the small but growing specialty of dermatology. Clinicians and scientists from a wide variety of disciplines have come to recognize both the importance of skin in fundamental biological processes and the broad implications of understanding the pathogenesis of skin disease. As a result, there is now a multidisciplinary and worldwide interest in the progress of dermatology.

With these factors in mind, we have undertaken this series of books specifically oriented to dermatology. The scope of the series is purposely broad, with books ranging from pure basic science to practical, applied clinical dermatology. Thus, while there is something for everyone, all volumes in the series will ultimately prove to be valuable additions to the dermatologist’s library.

The latest addition to the series, volume 37, edited by Drs. Goldman, Bacci, Leibaschoff, Hexsel, and Angelini is both timely and pertinent. The editors are well known authorities in the field of dermatological surgery and cosmetic dermatology. We trust that this volume will be of broad interest to scientists and clinicians alike.

Alan R. Shalita, M.D.

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What exactly is cellulite? Is it a disease or a normal finding in postpubertal women? Should it be treated or ignored? Is it nothing more than a convenient marketing opportunity for cosmetic manufacturers or something worthy of medical attention? These are but a few of the controversies surrounding the condition commonly known as “cellulite.” Perhaps the only point of agreement is that cellulite is unattractive and undesirable. It appears shortly after the initiation of menstruation in young girls on the upper outer thighs and buttocks and continues to worsen with the passage of time. Cellulite seems to affect tall and short, fat and thin, asthenic and curvy females. For many women, cellulite marks the end of the idyllic youthful body and the onset of the aging, declining female shape. Certainly, there must be something that technologic medical science can offer. Even in the 1960s, cellulite treatments abounded with the vibrating belt machines designed to firm the buttock and thighs while minimizing cellulite. At the time of this writing, there are many creams, devices, and procedures that attempt to deal with the ubiquitous problem of cellulite, but an organized scientific treatise is lacking.

This text is the first serious evaluation of the etiology and treatment of cellulite. The editors have assembled an international panel of cellulite researchers and clinicians to share their combined knowledge on the subject. The book is nicely organized with an introduction into the social impact of cellulite, followed by a characterization of the problem through visual and noninvasive techniques, with a major focus on the various treatment modalities. Cellulite improvement through the use of topical agents, Endermologie, surgery, lymphatic drainage, electroporation, and mesotherapy are investigated by practitioners of each of the arts. The editors thus provide a full critical evaluation of how each of these treatments impacts the appearance of cellulite.

Most dermatologists would agree that not a day goes by in clinical practice without a patient asking about cellulite treatments. To date, it has been difficult to find any reputable reference source on the subject. This text is a large step forward in characterizing the etiology of cellulite and evaluating worthwhile treatment approaches. The editors and their
authors should be congratulated for tackling a complex subject and organizing a text to highlight and discuss the controversies. This book is an illuminating treatise on the cloudy topic of cellulite.

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Beauty has been extolled and made a cult object in all cultures and civilizations, whatever their geographic distribution, ethnic origin, or religion. In ancient Egypt, beauty was associated with a sacred nature and personified by Queen Nefertiti, a woman who had high brows, wide and well-delineated eyes, rich lips, a dignified countenance, and an upright bearing, the very image of subtle energy; the ancient Egyptians regarded beauty closely akin to “holiness.”

The Greek aesthetic ideal was characterized by “perfect proportions” in the sense of the geometric relationships defining body harmony. Aphrodite, the goddess of beauty, was also worshipped as the goddess of love. Among the Etruscans, the Venus of Melos represented beauty and harmony; this has remained intact and unpolluted throughout subsequent civilizations.
Etruscan Venus of Melos.

The Three Graces (1640).
Peter Paul Rubens.
During the Renaissance, the tall figures of Aphrodite and Venus, slim but muscular at the same time although somewhat androgynous, became impressive and important, as is evident in the works of Rembrandt and Rubens. The beauty of women was embodied in figures with abundant localized adiposity, though not obese: the faces were round and blissful and expressed a superb femininity and kindness that conveyed the idea of motherhood and protection.

After the French Revolution, the standard representation of the woman took a new turn. The feminine body started to express activity, labor, functionality, precision, and harmony, losing some traits of Renaissance femininity. In the new society established after the Revolution, women slowly acquired new roles, carried out new activities, and achieved an unprecedented independence. As time went by, women even started to smoke cigarettes and practice sports. There were no objections to this new role as long as the exaggeration and myths of a sculptured body—such as those characteristic of the 1960s—are avoided.

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WHY CELLULITE IS A CONCERN FOR US

The disorders characteristic of cellulite involve endocrino-metabolic alterations that affect the microcirculatory system. They also draw our attention to the functionality and the cleansing process of the whole organism. Besides, it involves hardly controllable changes in the locomotor, digestive, and endocrine system. Last, but not least, it is a cause of discomfort and an ill-tolerated lack of aesthetics that drives the patient to accept any type of so-called therapeutic treatments in order to solve the problem. Too frequently such “treatments” have no scientific basis.

Unfortunately, the “industrial exploitation of peau d’orange” results in permanently new offerings of therapeutic methods outside the medical sphere. Remedies for this situation are not simple, but the medical world is accountable for leaving plenty of room for other actors, perhaps in collusion or motivated by self-interest, but often because no serious scientific research on the physiopathology and therapeutics of cellulite syndromes is available.
Our efforts should be focused on the recovery of trophism and tissue tone, as well as on the control of endocrino-metabolic alterations that may entail irrecoverable tissue damage, not only from an aesthetic point of view. Let us recall, for example, damages resulting from hard massages on tissues affected by lipolymphedema, those derived from liposuction and vacuum applied on soft tissues, or from local, uncontrolled application of heat, as well as those arising from desperate attempts to reduce hip circumference in a few centimeters, a reduction which is often the evidence of tissue damage rather than of its improvement.

Physicians should be reminded that in their diagnostic activity as well as in therapeu
tic practice the Hippocratic Oath is still in force: “Primum, non nocere.” This also applies to paramedical professionals, such as physical therapists, nurses, and podiatrists. Even those who are not physicians should be highly professional and serious. Their practice should be guided by sound common sense and be aimed at prevention and health care.

Aesthetic considerations are not unbecoming for the physician and should not be deemed as such. If it comes to it, we may say they are a kind of sublimated medical attitude and therefore require still greater professionalism. We should always bear in mind that ineffective or hardly effective aesthetic treatments have three inescapable consequences: clinical damage, aesthetic injury and, more frequently, serious psychological damage.

In summary, only within the last three decades has today’s society defined the ideal female and male body as youthful and almost pre-pubertal. Well-defined muscles with very little body fat being the ideal. This recent definition of beauty has led to the development of a new medical “disease,” cellulite.

Cellulite can best be described as a normal physiologic state in post-adolescent women whose purpose is to maximize adipose retention to ensure adequate caloric availability for pregnancy and lactation. Almost all women who are not cachectic have cellulite.

The treatment of cellulite is extremely popular in Europe and Latin America. Sales of various topical therapies in those countries is a multimillion dollar business with an entire division of ROC (Johnson & Johnson) devoted to its sales and development. Unique to those countries is the purchasing and development of equipment to treat cellulite. It is estimated that the sales of cellulite equipment is over 10 million dollars each year. This supports the popularity of awareness of cellulite outside of the United States.

The time is right for a textbook on the treatment of cellulite. This subject is not taught in medical schools or in residency programs and there is no textbook in the English language on this subject. As patients go to their physicians (mostly Cosmetic, Dermatologic and Plastic surgeons) to seek advice on the pathophysiology and treatment of cellulite, physicians will need to educate themselves on this subject.

To this end, this textbook represents the work of the world leaders in cellulite research. We present new ideas to challenge current medical thought on the pathophysiology of cellulite as well as a review of many different techniques for its treatment. We hope this book stimulates an interest in this underserved condition. As in many other fields of medicine and surgery, the advances in one field may be utilized in other fields. We believe that this textbook will serve this function.

Mitchel P. Goldman
Pier Antonio Bacci
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REFERENCES

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INTRODUCTION

Almost all women have or believe they have cellulite. As it is more common to expose the body in certain cultures and in sunny countries such as Brazil, cellulite is of great concern to many women and also represents a problem of great social impact.

In today’s globalized culture, physical well-being, including the care taken with appearance, is highly valued. From this perspective, it is very important to evaluate the impact on quality of life (QOL) of such cosmetic problems as cellulite, wrinkles, and aging. The fact that these have an impact on the QOL is indirectly shown by the growing interest in the investigation and treatment of these problems, which until recently were considered to be of minor significance. New studies involving QOL will benefit all those who suffer to a greater or lesser degree from these problems, and will be of great value in assessing the need for new scientific research into the treatment of these problems.

Sarwer et al. published a review of the literature that focused on psychological and social–cultural aspects, their relation to physical appearance, and their influence on the decision to undergo cosmetic treatments (1). Their study revealed that in the 37 different cultures studied, men and women gave greater priority to sexual attraction in the choice of partners than to aspects of personality such as independence, emotional stability, and maturity (1). Dermatological diseases and cosmetic problems significantly affect self-esteem. As the symptoms are visible, the discomfort and psychoemotional effects are frequently more serious than the physical alterations caused by the disease. Thus, it becomes very important to assess and quantify the emotional and social parameters in these patients in order to understand the disruption that the problem causes in various daily activities. This will facilitate the follow-up and treatment evaluation, and consequently allow for improvements in the QOL of the patients.

The great importance given to QOL evaluation in clinical investigation and patient care has led to the development of questionnaires designed for the collection of information from
patients on the impact of the disease on their everyday lives. This knowledge allows the medical professional to better observe how the disease affects the patients physically, psychologically, and socially, and facilitates the evaluation of the effects on the lives of the patients.

In the case of cellulite, the reasons that lead the patient to seek treatment are generally social and, sometimes, also emotional. These may include the embarrassment caused by cellulite in social, affective, and sexual relations as well as the avoidance of normal everyday activities such as visiting a swimming pool or beach, practicing sports, or exposing the body during intimacy.

A number of studies have been published that deal with QOL and recognize the value of specific questionnaires for dermatological diseases such as psoriasis, acne, melasma, atopic dermatitis, hyperhidrosis, and alopecia among others (2–9). These studies have revealed the existence of similar facets related to QOL in patients from various countries (10) and point to the discomfort and the psychoemotional effect on the patients. However, in general, little research has been done on the psychological, environmental, and social aspects of dermatological diseases. Moreover, to date, no study on the QOL of those afflicted by cellulite has been published.

Patients suffering from skin diseases should not be treated merely for the physical harm caused by the disease (10). The skin is the most external and apparent organ, and skin contact contributes to the formation and structure of the personality.

ASPECTS OF CELLULITE RELATED TO QOL

Cellulite is a clinical and aesthetic condition affecting most women. It may appear in preadolescence, adolescence, or adulthood. With cellulite, the connective tissue and adipose tissue undergo alterations, resulting in blood and lymphatic alterations (11). Clinically, cellulite is characterized by alterations to the cutaneous surface, especially on the buttocks and thighs, giving the skin an orange peel or mattress appearance (12,13). Clinically, cellulite is classified into degrees that range from 0 to III according to the clinical characteristics (14). As well as classifying the cellulite, it is suggested that associated factors such as obesity [measured by the body mass index (BMI)] and degree of flaccidity (classified as light, moderate, or severe) be characterized.

Our clinical experience has shown that cellulite is a problem that has an impact on the QOL of both younger and more mature women, though the impact is greater in younger women. It also seems that cellulite is more frequent nowadays than many years ago.

We report here on a clinical study carried out in 62 female patients, aged between 18 and 45 years (average age 32) with BMIs between 18 and 25 (average 21.8), having various degrees of cellulite on the buttocks and thighs. Over a period of two months, these patients received mechanical treatment in both legs and topical treatment in only one randomly chosen leg. The degree of cellulite in each patient was evaluated before and at the end of the treatment and attributed a classification between 0 and III, according to the clinical appearance of the cellulite. No patients included in this study had a cellulite classification of 0.

The patients also answered a nonvalidated questionnaire created by the authors at the beginning and end of the treatment. This questionnaire evaluated the patient’s self-esteem and highlighted changes in the behavior of the patient with cellulite such as avoiding wearing tight or small clothing; feeling embarrassed when frequenting swimming
The impact of cellulite in relation to age group was also evaluated, together with factors that patients believe may influence the cellulite, such as inheritance, diet, and physical activity, as well as the treatment performed and the self-perception of the severity of their cellulite. A survey of the answers given to the questions permitted an assessment of:

1. patient’s impression of the problem of cellulite;
2. the everyday situations that result in restrictions or embarrassment for patients with cellulite; and
3. the impact of treatment on a patient’s QOL.

Some factors, in the opinion of the patient, may influence cellulite. When questioned regarding diet, 65% of patients believed that there is a relationship between cellulite and diet. For 60% of the patients interviewed, a specific diet can help with cellulite. Along the same lines, 90% of patients believed that practicing physical exercise is an efficient treatment for cellulite and may, in isolation, moderately reduce cellulite.

Cellulite was perceived before 20 years of age by 65% of patients. With regard to family inheritance, 80% of patients reported having first- or second-degree relatives with cellulite. Because it is a clinically diagnosed and easily recognizable problem, this information is highly indicative of the presence of positive family cases, bearing in mind that the great majority of patients reported a family member of the first degree, mother or daughter, as having the same problem.

Regarding the restrictions caused by cellulite, when patients were questioned in a generalized way about the degree to which cellulite hampered their lives with the options of “not at all (1),” “a little (2),” “moderately (3),” or “greatly (4),” it was found that 70% of the interviewed patients considered that cellulite hampered their lives greatly. Regarding specific daily situations, it was noted that those suffering from cellulite experience some day-to-day restrictions. Each situation was evaluated by the patient and attributed a value from 1 to 5, in which “1” was given to situations in which having cellulite had no effect, “2” to little effect, “3” to a moderate effect, “4” to a significant effect, and “5” to a very significant effect.

The situations included wearing a bikini and or tight clothing, sexual activity, practicing sports, and crossing the legs and sitting, which indicate the great social impact caused by cellulite. Keep in mind that, in all the situations presented and even after treatment, having cellulite influences to a moderate or significant degree the daily lives of the patients. We notice that the treatment, even though it might not be 100% effective for the problem, may modify the behavior of cellulite patients. The results obtained from the studied sample reveal that the presence of cellulite after treatment interferes less in certain activities when the responses from before and after treatment are compared. This reduction is most evident in the item “sexual life” when the total sample is examined: 21.9% of the patients mentioned that cellulite had great or very significant influence on their sexual life before treatment and, although the treatment may not have led to a marked improvement in the cellulite, only 8.3% of the patients gave the same response following treatment. The sitting position, a position that supposedly makes the cellulite more apparent, reveals that before treatment, 48.9% of the patients interviewed considered the influence very significant, while after treatment this percentage fell to 15.1%. With regard to the embarrassment caused by the presence of cellulite in the practice of sports, the answers both before and after treatment were very similar. The results suggest that, for women,
exposing the body during sports is not as embarrassing as other situations, as for example during sexual relations.

According to Jorge (10), the psychological impact and the impact in interpersonal relations, respectively, is more prejudicial for women than for men. Studies that evaluated patients with dermatosis, carried out in Sweden and Norway, suggest that those at risk of the greatest harm are females who are young and in whom the disease exists over an extended period of time (10). As cellulite appears basically in women, this condition should be investigated in terms of its impact on QOL.

A study by Harlow et al. that evaluated the impact of dermatological diseases on QOL during primary attention noted the differences between men and women in relation to the various forms of constraints caused by the diseases from which they suffered (15). Ten attributes were evaluated: physical symptoms, feelings, daily routine, clothing, social and leisure, sport and exercise, work and study, personal relations, sexual relations, and treatment. Of these, only the degree to which the condition affected the practice of sports and exercise was the score given by males higher than that given by women (15). This shows that the practice of sports may have greater significance in the male group than in the female.

We also checked the impact of treatment on the QOL of patients with cellulite. Each patient attributed a value from 0 to 9, with 0 representing very low self-esteem in relation to the fact of having cellulite, and 9 representing very high self-esteem. The clinical evaluation considered the improvement on the left and right sides, which were treated differently. Even without any improvement in the degree of cellulite noted by the examiner, there was an increase in self-esteem (evaluated from 0 to 9) after treatment. This improvement can be seen in the difference in the percentage of scores found before and after treatment. This shows that the treatment did have a positive effect on the self-esteem of the patients, indicating that the simple fact of treating the cellulite and caring for themselves, even in the absence of any clinical improvement, influenced the well-being of the patients, who described themselves as better and more confident following the treatment. It may suggest that treatments should be tried, even if there is no cure for this condition.

CONCLUSIONS

Thorough QOL evaluations will be necessary to evaluate not only the importance given to the problem of “cellulite,” but also the need to develop new treatments for cellulite (16).

It is interesting to note that, even without techniques that can guarantee significant improvement of cellulite in its different degrees, cosmetic patients want alternatives and their emotional improvement is not directly related to clinical improvement. Care and attention to cosmetic problems can lead to improvement in the emotional state of the patients.

Cellulite has a real impact on the QOL of patients, as it restricts those that suffer from the condition in everyday situations and activities. This causes damage in the psychological area in interpersonal relationships, as also occurs with other conditions that afflict the skin.

It is important that the doctor not only offers a diagnosis of and treatment for the patient’s condition, but also attempts to understand the impact that the condition has on the life of patients, their beliefs regarding the problem, and their expectations regarding the cure or treatment.
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DEFINITION

“Cellulite” is a very common topographical alteration (1,2) in which the skin acquires an orange peel or mattress appearance (Fig. 1) (3,4). In this condition, alterations occur to the adipose tissue and microcirculation that result from blood and lymphatic disturbances causing fibrosclerosis of the connective tissue (2). It is considered a noninflammatory, degenerative phenomenon that provokes alterations to the hypodermis (5) producing irregular undulations on the skin overlying affected areas.

Cellulite results from many complex events that involve the epidermis, dermis, and subcutaneous tissue (1). Cellulite can be divided into four stages:

1. alterations to the precapillary arteriolar sphincter, leading to changes in vascular permeability and capillaceous ectasia resulting in pericapillary and interadiposity transudation, leading to edema;
2. edema, provoking metabolic changes that result in hyperplasia and hypertrophy of the reticular network, leading to the formation of pericapillary and periadipose deposits with an increase in interstitial viscosity;
3. organization of collagen fibers around groups of adipocytes, forming micronodules; and
4. union of the micronodules to form the macronodules that cause sclerosis (6).

Anatomically, the cutaneous alterations found in cellulite are largely due to fibrosis of the connective tissues present in the dermis and/or in the subcutaneous tissue (7). The
**Figure 1**
Clinical aspect of cellulite.
connective tissue of the reticular dermis is connected to the deep fascia by means of interlobular trabeculas (fibrous septum) from adipose tissue. Subcutaneous fat lobules are separated from one another by these thin, usually rigid strands of connective tissue that cross the fatty layer and connect the dermis to the underlying fascia. These strands stabilize the subcutis and divide the fat (8). The shortening of these septa due to fibrosis provokes retraction at the insertion points of the trabeculas (9), causing the depressions that are characteristic of cellulite.

Nurnberger and Müller studied the anatomy and histology of fat and the connective tissue structure of the subcutaneous tissue. They demonstrated, on anatomical bases, the characteristic mattress aspect of cellulite and pointed out the differences in the organization of the subcutaneous tissue between the two sexes (10,11). They also showed that in women the fibrous septa are usually orientated perpendicularly in relation to the cutaneous surface, while in men they have a crisscross pattern (11). Several studies have shown that fat is divided into lobules, and that in women, these are larger and more rectangular when compared with those in men (4,11–15). These anatomical and histological findings explain the greater frequency of cellulite in women.

**NOMENCLATURE**

In France in 1920, Alquier and Paviot described cellulite as an unaesthetic condition (6,16). In the same decade, Laguëse described cellulite as a disease of the hypodermis, characterized by interstitial edema and an increase in fat (17).

Initially, Curri defined cellulite as nodular liposclerosis (6,18) and later adopted the term “cellulitic dermohypodermosis” (19). In 1958, Merlen defined cellulite as a histangiopathy (20), and in 1978, Binazzi and Curri, after a histopathological study, suggested the term “sclerotic-fibrous-edematous panniculopathy” (21,22). Nurnberger and Müller used the name “panniculosis of the dermis” (16,23) to describe cellulite from the histopathological viewpoint. Bacci and Leibaschoff suggest the use of the nomenclature “cellulitic hypodermosis” (16).

In recent years, the term “gynoid lipodystrophy” has been used in some studies (2,9,24). The terms “hydrolipodystrophy” and “herniation” of the fat with hypodermic tension bands are still in use for describing cellulite (25,26).

The presence of the suffix “ite” in a medical term indicates inflammation; therefore, the term “cellulite” is more appropriately used to designate inflammation and/or infection of the subcutaneous tissue (27). However, the term “cellulite” has become very popular, and its use has been consecrated (20,28) by its being accepted throughout the world. Other synonyms often used for cellulite are listed in Table 1.

**CLINICAL ASPECTS**

Although it is found in all age groups and in both sexes (10,29,30), cellulite occurs mainly in women (6,31) especially after puberty (32) and in obese people, being considered a normal manifestation of obesity by Burton and Cunliffe (12,29).

There is evidence to suggest that estrogen is the element most probably involved in the initial dysfunction, aggravation, and persistence of cellulite (1,20,33). The greater
incidence of cellulite in the female sex, its appearance postpuberty, the worsening of the condition in relation to pregnancy, the menstrual cycle, and the use of contraceptives and hormonal replacement are cited as supporting this hypothesis (1).

Cellulite normally manifests itself in areas of greatest fat accumulation, such as the buttocks, thighs (Fig. 2) (29), flanks, abdomen (6,29), and upper legs (26,29,32).
The lesions are essentially asymptomatic. However, in an advanced degree of cellulite, symptoms such as a sensation of weight and pain may occur in the affected areas (10,20,29). These probably occur as a result of compression of the nervous terminals or the presence of inflammatory reactions (16,19).

The main manifestations of clinical cellulite are:

1. Flaccid “mattress-like” skin, with multiple depressions and some elevations, caused by irregular retraction of the skin, forming a surface where protuberances and depressed areas alternate (Fig. 1) (6,16,34);
2. “Orange peel” skin due to the tumefaction of the epidermis and dilation of follicular pores (6,16,34).

The cutaneous surface alterations that characterize cellulite are predominantly depressed, when compared to cutaneous surface of the affected area (29). These depressions have the same color and consistency as normal skin, and the number of lesions may vary from one to many (29). The shape of these lesions is varied (29): rounded, oval, or linear (Fig. 3). Most lesions are oval, as the longest axis of the lesions lies parallel to the relaxed skin tension lines (Figs. 4A–E). It is interesting to note that those lesions that do not have the same disposition in relation to the relaxed skin tension lines in general originate from secondary fibrosis of the subcutaneous tissue, such as injections, trauma, etc. They are usually found in the lower portion of the buttocks and the upper thigh (Fig. 4). In both the buttocks and the upper thigh, just below the gluteal fold, the longest axis is in the horizontal direction, with the lateral extremities slightly elevated. In these locations, cellulite may be more evident due to flaccidity of the epidermis, which tends to become aggravated with age. This can be demonstrated by the diminishing or even the disappearance of the lesions when the buttocks are lifted to their original position.

CLASSIFICATION

Several authors have classified cellulite into four clinical stages or degrees (Table 2), based on the clinical alterations observed with the patient at rest and after the application of the pinch test or muscular contraction (6,29,34).

Because cellulite is diagnosed by clinical alterations, without histopathological findings or anatomical or pathognomonic characteristics, it can also be classified into primary and secondary cellulite. In primary cellulite, there are no aggravating factors involved. In secondary cellulite, the alterations are provoked by secondary factors such as localized fat, flaccidity, surgical or accident trauma mainly from liposuction, after injections that cause lipoatrophy, or after subcutaneous fibrosis from any inflammatory or infectious process. These circumstances may aggravate or even bring about primary cellulite and should be detected through the medical history and physical examination. Treatment, in this case, implies the correction of the primary factor.

CLINICAL APPROACH

As with other pathologies, the medical history should be detailed in the evaluation of cellulite. The patient should be questioned regarding the age at which cellulite appeared, prior occurrence of trauma, liposuction or injections in the affected area, history of prior
disease or surgery, family history, presence of chronic vascular or associated hormonal
diseases, the occasional or regular use of medications, and previous or current history
of hormonal treatment or the use of any medicine that may contribute to the increase
in the deposit of fat in the affected areas, such as corticosteroids and estrogens. Other
aspects that should be researched are sedentarism, diet, psychosomatic factors, smoking,
prior pregnancy, and the behavior of cellulite during pregnancy.

Although smoking and circulatory problems are frequently cited as causative agents
of cellulite, in the experience of the present authors, in a sample of 1200 patients with
advanced cellulite, the vast majority were neither smokers (more than 80%) nor those hav-
ing varicose veins or other circulatory problems.
Figure 4
(A) Relaxed skin tension lines mapped on a body scheme. The left half shows the frontal view and the right half, the back view. (B–E) Cellulite lesions follow the relaxed skin tension lines.
Physical Examination

The physical examination should be performed with the patient in a standing position, with muscles relaxed (9,10,29). Cellulite can be better observed with the application of the pinch test, in which the skin in the area to be examined is pinched between the thumb and index finger to form a fold by skinfold plicometry or through the contraction of the muscles in the

<table>
<thead>
<tr>
<th>Classification</th>
<th>Evaluation results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree or stage 0</td>
<td>There is no alteration to the skin surface</td>
</tr>
<tr>
<td>Degree or stage I</td>
<td>The skin of the affected area is smooth while a subject is standing or</td>
</tr>
<tr>
<td></td>
<td>lying down, but undulations on the skin surface can be seen on pinching</td>
</tr>
<tr>
<td></td>
<td>the skin or during muscle contraction (Fig. 5)</td>
</tr>
<tr>
<td>Degree or stage II</td>
<td>The “orange peel” or “mattress” appearance is evident when standing,</td>
</tr>
<tr>
<td></td>
<td>without the use of any manipulation (skin pinching or gluteus muscle</td>
</tr>
<tr>
<td></td>
<td>contraction) (Fig. 6)</td>
</tr>
<tr>
<td>Degree or stage III</td>
<td>Presence of alterations described in second degree or stage II, plus</td>
</tr>
<tr>
<td></td>
<td>presence of raised and depressed areas and nodules (Fig. 7)</td>
</tr>
</tbody>
</table>

Figure 5

First degree cellulite, in which there are no alterations to the skin surface in a standing position and with relaxed gluteous muscles. Alterations are found under the pinch test applied to the skin of the affected area.
area (Figs. 8 and 9) (9). Overhead or tangential illumination of the patient facilitates the visualization of cellulite (29). There are significant differences in the appearance of cellulite, depending on the position and the method used for its classification. For this reason, the standing position is recommended for the examination of a patient with cellulite.

Palpation should always be performed to check the elasticity of the skin (6) and subcutaneous tissues. However, at present there are no exact parameters for the classification of skin elasticity. Venous or lymphatic insufficiency may, in theory, aggravate cellulite and should also be checked during the physical examination (35). One should make note of the presence of varicose and telangiectatic leg veins as well as any pitting edema or induration of the skin. A Doppler or duplex ultrasound examination of the superficial venous system will also help to classify the significance of venous insufficiency. Even if venous insufficiency is not found to be an etiologic factor in the pathogenesis of cellulite, its presence or absence will help direct appropriate treatment regarding graduated compression.
AGGRAVATING FACTORS

A number of clinical conditions or circumstances frequently accompany or aggravate cellulite, especially obesity, localized fatty accumulations, and skin flaccidity.

Obesity promotes a generalized increase in body weight (skeletal, muscular, interstitial fluid, organ hypertrophy, etc.). After a return to the original baseline weight is achieved, an increased accumulation of fat is observable (36). The clinical manifestation of localized adiposity is an increase in the ill-defined symmetrical and bilateral diffuse volume, owing to an increase in the adipose tissue (29). The localized increase in adipose tissue in the subcutaneous tissue leads to the aggravation of cellulite lesions by contributing to a worsening of the irregular undulations of the skin. The increase in fat volume leads to an augmentation of tension forces within the fat lobules. This tension is projected to the skin surface and aggravates the depressions, causing an effect similar to that of a stuffed quilt (29). These alterations contribute to the appearance of the mechanical and circulatory alterations that occur in cellulite. Greater thickness of the subcutaneous fat in the affected areas may be seen by histopathological examination and can be measured by special instruments or by the pinch test (Fig. 9) (36).

Rosenbaum et al. described the exacerbation of cellulite with weight gain and its correlation with the body mass index (BMI). This study demonstrates the protrusion of adipose tissue into the dermis when the volume of subcutaneous fat is augmented, which explains the mattress-like appearance (31).

Flaccidity is caused by physiological ptosis of subcutaneous structures, making the skin permanently distended and loose. This condition frequently occurs in the buttocks,
thighs, the region above the knee, and the inner surface of the arms, regions where the skin probably has less retentive capacity and suffers the mechanical action of weight exerted by the adipose tissue and by the other subcutaneous structures (29). The weight of these structures increases the effect of gravity, causing alterations to the skin surface in these areas, which is seen as laxity and looseness (29). The reduced elasticity of the skin and sudden loss of weight (29) or subcutaneous fat due to liposuction (37) are conditions that can bring about or aggravate skin flaccidity.

Although it is of great importance, the presence of flaccidity or other aggravating conditions is usually not mentioned in present day classifications of cellulite. In the absence of flaccidity, a distension test in the antigravity direction tends not to diminish the lesions. In the presence of flaccidity, however, such a test can lead to a reduction or even disappearance of cellulite lesions (Fig. 10). The pinch test causes an increase in

**Figure 8**
Pinch test using a special device, the skinfold plicometry.
Figure 9
Patient with cellulite secondary to flaccidity or loose skin. Alterations to the skin surface became more evident on pinching the skin.

Figure 10
The patient shown in Figure 9 showing improvement to the skin surface when stretching the skin in the direction opposite to forces of gravity.
tension inside the lobes, and the cellulite becomes apparent as the lobes bulge and aggra-
vate the traction of the septa in the pinched area (Fig. 11). Moreover, flaccidity has an
effect similar to that of pinching by compressing the lobes and, thus, augmenting the ten-
sion within them. This situation is responsible for the emergence or worsening of cellulite
lesions, especially after the fourth or fifth decade of life when the elastic properties of the
skin diminish (38). This, together with the weight of the subcutaneous fat, determines the
worsening of distension of the skin.

Other notable conditions that cause secondary cellulite or that aggravate cellulite are
subcutaneous fibrosis caused by previous surgery, mainly liposuction, and the subcuta-
neous fibrosis and lipoatrophy originating from the trauma caused by injections in the
affected areas. Alterations to the cutaneous surface resulting from liposuction usually
appear late, from three months to one year after surgery. They may be slight, moderate,
or severe, and always emerge in previously treated areas, such as the lateral and posterior
thighs, buttocks, abdomen (Fig. 12), flanks, and the region above the knees. Like cellulite,
the cutaneous sequelae from liposuction are predominantly depressed subcutaneous tissue,
but raised and depressed areas may intercalate and vary in number and shape as a reflec-
tion of the number and variety of liposculpture cannula insertions, as well as the size and
type of cannulas. Generally, they form larger depressions with bizarre shapes and do not
necessarily follow the direction of the relaxed skin tension lines. Instead, they follow the
direction of cannula insertion (Fig. 12).

The cutaneous surface alterations caused by previous injections (such as insulin
injections in diabetics) occur in places where the injections are normally applied, that is,
in the upper, outer quarter of the buttocks. They also vary in number and shape, and
do not follow the force lines of the skin.

The presence of atrophic scars in the areas frequently affected by cellulite can also
simulate or aggravate cellulite.

Many factors can cause cellulite, and other factors can make it worse. The classifica-
tion in Table 2 is useful for generic diagnostic purposes, but is not appropriate for an accu-
rate measure of the results of treatments, other than surgical treatment. To evaluate the
results of other treatments, such as topical or systemic treatments, alternative objective
and subjective measures are needed; these are presented in the appendix to this chapter
in the form of a protocol used in our clinics.

COMPLEMENTARY EXAMINATIONS

The BMI is widely used and cited by some authors as a simple, low-cost examination
considered fundamental for the evaluation of the clinical cellulite (6,39). This is a quan-
titative method that uses measures of weight and height to assess the degree of obesity
(39). By using this index, it is not possible to distinguish the percentage of body fat in
the muscular mass. BMI is an uncertain diagnostic index of obesity (40). Studies reveal
that the estimated standard error of the percentage of body fat of BMI is approximately
5% to 6% (39).

A clinical evaluation of a sample of 32 patients ranging from 18 to 45 years of age,
performed by the present authors by means of physical examination, BMI calculation, and
assessment of body fat percentage by skinfold plicometry (39), revealed that cellulite man-
ifested even in patients with a low percentage of body fat and a normal BMI.
Two-dimensional ultrasound is a noninvasive method of evaluating variations (41,42) and alterations of the subcutaneous fatty tissue, and with the assistance of Doppler, it evaluates the local circulation (6). This examination has been used in some studies for the evaluation of cellulite, and has demonstrated a diffuse pattern of extrusion of underlying adipose tissue into the reticular dermis in affected individuals, but not in unaffected individuals (2,31).

Computed tomography (43) and magnetic resonance imaging (44,45) are examinations used for measuring the thickness of adipose tissue, which do not allow evaluation of the dermis or microcirculation (6). In one study, the magnetic resonance imaging quantified deeper indentations of adipose tissue into the dermis and evidenced for the first time a great increase in the thickness of the inner fat layer in women with cellulite (46).

Although invasive, histological examination may be useful as a method for evaluating cellulite (3,6,13). The stains used in this examination include hematoxylin–eosin for routine histological examination; Alcian blue for polysaccharides; periodic acid–Schiff for basement membranes; Weigert–Van Gieson (fuchsin–resorcin and acid fuchsin) for highlighting elastic, collagen, and flat muscle fibers; and Masson trichromic, which demonstrates contrast between collagen and muscle fibers (6). With this examination, it
is also possible to observe the diffuse extrusion pattern of underlying adipose tissue distending the reticular dermis in people with cellulite (31). The macroscopic aspect of subcutaneous fat from corpses is shown in Figure 13.

**Differential Diagnosis**

Of particular importance in the differential diagnosis of cellulite are the localized deposits of fat (13), flaccidity, surgical sequelae (from liposuction) (Fig. 12) or other trauma (47),

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**Figure 12**

“Cellulite-like” liposuction sequelae on the abdomen, one year after the surgery.

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**Figure 13**

Macroscopic aspect of subcutaneous fat from a corpse.
Figure 14
Lipomatosi from cellulite.

Figure 15
Lipomatosi from cellulite.
the presence of lipomas or lipomatosis (Figs. 14 and 15), and depressions that occur in multiple atrophic scars, after furunculosis or other pathologies in the affected areas. It is also necessary to differentiate from cellulite, those cutaneous depressions that occur as a result of injections of medicines that cause fibrosis or atrophy of the subcutaneous tissue; for example, corticosteroid injections (48). When unilateral, localized scleroderma or morphea should be part of the differential diagnosis (29). In these cases, the treatment of the primary condition is fundamental and mandatory.
REFERENCES

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**APPENDIX**

**CELLULITE ASSESSMENT PROTOCOL**

- **Name:** ______________________________________________________________________
- **Age:** __________________________________________________________________________
- **Skin color:** ____________________________________________________________________
- **Phototype:** ____________________________________________________________________
- **Ethnic descent:** ________________________________________________________________
- **Height:** ______________________________________________________________________
- **Weight:** _______________________________________________________________________
- **BMI:** _________________________________________________________________________
- **Cellulite family history:** □ Yes  □ No
- **Age of onset:** __________________________________________________________________
- **Compromised areas:** ____________________________________________________________
- **Previous treatments:** __________________________________________________________
- **Concomitant diseases:** _________________________________________________________
- **Drug utilization:** _______________________________________________________________

**Assessed region:** _______________________________________________________________

**Date:** _________________________________________________________________________

1. Predominant lesions and shapes (over 75%):
   - □ depressions  □ round
   - □ elevations  □ linear
   - □ mixed  □ orange peel appearance

2. Number of lesions:
   - □ less than 5
   - □ over 5 and less than 10
   - □ over 10 and less than 20
   - □ over 20

3. Relief in relation to normal skin:
   - a. Depressed:
      - □ superficial (up to 1 mm underneath the cutaneous surface)
      - □ medium (1 to 3 mm underneath the cutaneous surface)
      - □ profound (over 3 mm underneath the cutaneous surface)
   - b. Elevated:
      - □ discrete elevation (up to 1 mm over the cutaneous surface)
      - □ moderate elevation (1 to 3 mm over the cutaneous surface)
      - □ severe elevation (over 3 mm over the cutaneous surface)
4. Associated factors:
   a. Localized fat: ☐ Yes ☐ No
      Localization: ______________________________________________________________
      Thickness by skinfold plicometry: __________________________________________
   b. Flaccidity: ☐ Yes ☐ No
      ☐ unapparent (only evidenced by the distension test)
      ☐ apparent (noticeable without the distension test)
      ☐ slight (does not determine relief alterations)
      ☐ moderate (determines relief alterations classified as cellulite degree II)
      ☐ severe (determines relief alterations classified as cellulite degree III)

5. Other lesions:
   a. Surgical sequelae: ☐ Absent ☐ Present
      Localization: ______________________________________________________________
   b. Scars: ☐ Absent ☐ Present
      Localization: ______________________________________________________________
   c. Other: ___________________________________________________________________
INTRODUCTION

The understanding of the structure and function of the interstitial (or extracellular) matrix constitutes a relatively recent conceptual revolution. Prof. Francesco Albergati of Milan, student of Prof. Sergio Curri, was the first to study and describe the clinical relevance of this microvascular-tissue unit (1). A brief overview is given here.

CELLULITE

The body’s silhouette is characterized by a particular localization of the subcutaneous adipose tissue over the osteomuscular structure. The human body is characterized by the presence of rigid fasciae and especially deep muscular fasciae that start from the base of the cranium and continue to the ankles and metatarsus promoting various physiological functions: vascular, neurophysiologic, and orthopedic. Cellulite is a degenerative and evolutionary affect on subcutaneous tissue. The authors describe cellulite from a histomorphologically point of view, defining it as a PEFS: “panniculopatia edematofibrosclerotica (edematofibrosclerotic dermo-lipodermic pathology)” (2).

Cellulite is considered as a series of events characterized by interstitial edema, secondary connective tissue fibrosis, and consequent sclerotic evolution. Recent clinical observations demonstrated that if PEFS is a true part of cellulite, it does not represent all the various clinical aspects of cellulite. In fact there are often particular forms of connective and interstitial damage or diffuse syndromes characterized by a lipedema associated with a lymphedema and/or lipodystrophy. Such pathologies are mainly observed on the gluteal muscle and on the lower limbs of women.

Fundamental here is acceptance that cellulite is not a female whim or something considered unsightly, but a real disorder, or rather, different disorders that represent aesthetic pathologies that must be cared for from a medical and cosmetic point of view.

The cellulite disorder normally is an expression of lipolymphedema, or more precisely a typical expression of mesenchimopathy with microvessel alterations.
It is, above all, an endocrine-metabolic disorder that may or may not be associated with lipolymphedema, localized adiposity, and lipodystrophy with an alteration of the interstitial matrix and connective tissue. It, therefore, presents various aspects that call for different therapies.

First and foremost, it displays alterations of the purifying organs that must be controlled and brought back into balance. There are also alterations of the basic regulation of temperature, pH, and the oxidation–reduction systems.

Such alterations can be discovered with tests to assay free radicals and heavy metals, and by video capillaroscopy. These dismetabolic situations can be corrected through diet (especially protein therapy in two-week cycles), physical activity, and polyvitaminic, alkalinizing, and orthomolecular therapy (3–10).

Cellulite is often also associated with venous lymphatic insufficiency; however, cellulite formation occurs before, not after, the venous disease. It is the cause, not the effect.

Lipolymphedema and cellulite are the greatest expressions of an alteration of the functionality of the cleansing organs. We also know that unnecessary nongraduated elastic stockings are one of the causes of superficial cellulite due to compression and the slowing of microcirculation (11).

We know that three forms of edema can be associated with cellulite disorder: venous edema, lymphatic edema, and lipedema.

1. What is venous edema?
   Venous edema is basically characterized by a release of kinins, toxic substances, and iron that carries calcium with it. It is an edema associated with phlogosis of the tissues and deposition of hemosiderin.

2. What is lymphedema?
   Lymphedema is a pathological condition characterized by a state of tumescence of the soft tissues, usually superficial, due to accumulation by stasis of high protein-content lymph caused by primary and/or secondary alterations of the lymphatic vessels. Lymphatic edema is linked to alterations of the lymphatic vessels, and is characterized by free water in the interstices that has bonded with proteins and solutes, forming an edema of lymph with interstitial hyperpressure (12).

3. What is lipedema?
   Lipedema is a particular syndrome characterized by subcutaneous deposition of fatty tissue and water, especially in the buttocks and lower limbs, which may or may not be associated with lymphedema and/or lipodystrophy (13,14). It is an edema characterized by an increase of free water in the interstices; it is not lymph—it is free water and fatty tissue.

LYMPHEDEMA

Lymphedema is a chronic and progressive affliction that is very difficult to cure. The aim of treatment is to keep the disease stable in order for the patient to live normally. In this type of pathology, the first component is edema and the second is fibrosis. The increase of protein levels in the tissues contributes to the development of edema and probably causes chronic inflammation and subsequently the fibrosis.
The basic clinical sign of lymphatic problems, either mechanical or dynamic, is a cold and pale swelling, which is initially viscous and later hardens but is not painful in most cases. With the increase in severity of edema, there is an increase in limb volume. At this point, it is not sufficient to hold the limb in an elevated position in order to reduce edema; fibrosis is already present.

LIPEDEMA AND LIPOLYMPHEDEMA

Lymphedema is described as a pathology characterized by a tumescent state of soft tissues, usually superficial (15), and is related to an accumulation of lymph with high protein content due to stasis in the interstitial space. It is determined by primary and/or secondary damage of the transport vessels. In contrast, lipedema is a particular syndrome with a poorly understood etiology characterized by fat and water deposits in the subcutaneous tissue (particularly in lower limbs and gluteal muscle), and associated with lymphedema and/or lipodystrophy.

Lipedema was described for the first time as an accumulation of subcutaneous fat with hard leg edema excepting the feet. In various descriptions (16), the following observation has always been underlined: foot hypothermia with a localized gradient of temperature. Such pathology, often superficially defined as a lymphedema or venous insufficiency or cellulite, is observed in more than 65% of women between the ages of 14 and 35 years, becoming lipodystrophic lipolymphedema after the age of 40. The common characteristics of a lipolymphedema are the absence of venous insufficiency (eventually secondary) and the close relation with the fat tissue metabolism.

Lipolymphedema is a syndrome of unknown etiology, characterized with fat deposition in the subcutaneous tissue and associated with orthostatic and recurrent edema in the legs and gluteal muscle that induces the impression of an increased volume in the limbs. Lipedema always begins in the legs, excluding the ankle and foot, which makes it different from lipolymphedema. It can be related to weight increase but is often independent of it. It is often related to familial factors. The characteristic of this extremely frequent disease is that edema always succeeds fat deposition. The latter is subsequent to endocrinometabolic disorder of the interstitial matrix and is not accompanied with obesity.

The edema here is not caused by structural changes of veno-lymphatic vessels, but by the modified ratio of the distance from the adiposity and connective structure with a loss of support. It is an edema that worsens with walking and standing, in contrast to phlebolymphedema. Another difference from lymphedema is its softness and the possibility of its making a skin fold that is not obstructed by the viscosity. Thus it is different from lipolymphedema, phlebolymphedema, Barraquer-Simmond disease (characterized by upper body thinness), and Dercum syndrome; the latter, which is clinically similar, has an etiology related to toxicities of the autonomous nervous system linked to an intestinal dysbiosis.

DERCUM SYNDROME

The word “lipodystrophy” means a pathology characterized by structural and functional damage of adipose tissue. Lipodystrophy can be associated with some form of lipolymphedema, the more typical being Dercum lipodystrophy or painful lipodystrophy. Women are affected early with recurrent lipedema. Typically painful fat nodules are often preceded by the appearance of lipedema and are often associated with asthenia, neuropsychic and
adynamical troubles (depression or anxiety), and intestinal dysbiosis. Limb pain is different from the pain of lipolymphedema or from superficial hypoxia, where pain is induced by pinching the subcutaneous tissue and is associated with tissue viscosity due to interstitial hyperpressure of toxic lymph.

Pathogenesis of the Dercum syndrome is not endocrine or metabolic (as in recurrent lipedema), but from nerve damage of the neurovegetative—either the hypothalamic or the peripheral—system. Interstitial inflammation phenomena have been demonstrated to be related to the nervous network linked to the adipose tissue in the environment of the extracellular matrix. In this context, bacteria from intestinal origin have also been found. This disease is certainly attributable to a suffering of interstitial mesenchyma with exaltation of the lipogenesis (slowdown of the microcirculatory flux and damage of the α-2-fibers) due to the damage to the peripheral neurovegetative regulatory system.

“BIG LEG”

For Robert Stemmer (16), famous French phlebologist and memorable president of International Union of Phlebology, “big leg” means a lower limb in which volume increase is measurable and palpable. A total or partial big leg can be observed, but there are also different kinds of big leg such as venous, post-phlebitis syndrome, posttraumatic, angiodisplasic, lymphatic, adipose, or cellulitic big leg. The main characteristic of big leg is edema—systemic, lymphatic, venous, or interstitial edema. Considering that lymphatics run in the interstitial subcutaneous tissue, it is easy to assume that the increase of lymphatic edema or of adipose tissue could induce a lymph slowdown. We know that there is a neoangiogenesis, stimulated by collagen production, obtained after adipocyte rupture. Such collagen production also stimulates fibrinogenesis and vascular formation. The difference between localized adiposity and lipodystrophy or angiolipodystrophy is this: Localized adiposity means physiological or pathological accumulation of fat tissue in determined body areas, without a dystrophic process. Lipodystrophy means a pathologic affection of both supporting tissue and subcutaneous adipose tissue, characterized by various circulatory and metabolic damages. For this type of pathology, we now essentially use liposculpture.

INTERSTITIAL MATRIX

These cells represent the functional units of all living organisms by virtue of their specific structural organization. They possess complicated biochemical and molecular systems, complexly organized and highly sophisticated. Such systems not only guarantee the survival of the cell, but they also (above all) allow numerous fundamental activities to take place for the biological life of the cell. This affirmation could appear banal at first; In reality the cell and its functional organization represent an extraordinary example of “natural functionality,” as the natures of both are able not only to organize the constitutive elements of the tissues but also to predispose them, in the functional sense, to their precise and mutable adaptation in answer to the different biological changes that happen every second in the living organism.

An example of the importance of such sophisticated mechanisms is that some cellular passages are open only to sodium but not to potassium ions, while others are open only to
glucose but not to amino acids. The protein in the transport membrane functions as a real "organ" to a degree that allows, through specific sites of recognition, the selective entry of substances into cells, determined by some precise passages. The ionic transport has extreme importance in biology. Perfect operation of the ionic pumps is vital for cellular life. The ionic movement through the membrane is also at the base of the production of adenosine triphosphate (ATP) in all cells, and particularly for the nervous system.

The ionic concentrations in the intra- and extracellular environments are shown in Figure 1 (18).

<table>
<thead>
<tr>
<th>Component</th>
<th>Intracellular (nM)</th>
<th>Extracellular (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>5–15</td>
<td>145</td>
</tr>
<tr>
<td>K⁺</td>
<td>140</td>
<td>5</td>
</tr>
<tr>
<td>Mg²⁺ (citosol)</td>
<td>0.5</td>
<td>1–2</td>
</tr>
<tr>
<td>Ca²⁺ (citosol)</td>
<td>1/100000</td>
<td>1–2</td>
</tr>
<tr>
<td>H⁺</td>
<td>7 x 1/100000</td>
<td>4 x 1/100000</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>5–15</td>
<td>110</td>
</tr>
<tr>
<td>Fixed anions</td>
<td>Tall</td>
<td>0</td>
</tr>
</tbody>
</table>

*Figure 1*

The ionic concentrations in the intra- and extracellular environments.

As is known, the large concentration of Na⁺ outside of the cell is compensated by the concentration of Cl⁻, while the strong concentration of K⁺ is counterbalanced by a series of negative intracellular ions. For example, this narrow joining ensures the activity of the pump only when there are proper ions to transport, so that there is no wastage of ATP (Fig. 2).

Every cell, as a separate living cellular mechanism, has the vital necessity “to feel” its environment and “to interact” with it, to be able to survive dispatching its vital functions.

We could say that every cell necessarily has to have a “social life,” and it therefore must develop “senses” that allow it to communicate with other cells and with the whole extracellular environment, or rather with the “extracellular matrix.”

In a multicellular organism, cells have to coordinate their behavior in many different ways, exactly as happens in a community of human beings; here, in fact, communication is constant and fervent: Nearby individuals are spoken to and discussions are held with them; public announcements are transferred to whole populations; urgent messages are delivered from near or far to precise individuals; and precise alarms are sounded when dangers or threats draw near. What would seem difficult to humans is in reality...
even more difficult (but not impossible) for the individual constituents of our body, firmly created to be gathered in “organs” and “apparatuses” developing precise and defined functions.

To transmit a message “person to person,” we can write it on paper, then repeat it by voice, sending it in the form of “sensorial” impulses, for example by telephone. This sensorial impulse will come to another individual that will turn it into nervous impulses.

In the various phases of this simple communicative run, the same message is represented with different forms of signals: The real critical points of the transmission meet when information is converted from one form into another. This process of conversion is known as “translation of the signal.”
Cells come into contact with the complicated extracellular world through their surface, constituted by lipid and protein molecules composing the plasma membrane. Additionally, they come into contact with the specific areas of these molecules that are found, because of their steric and biochemical encumbrance and their conformation, in the extracellular environment, forming intimate and complex biochemical–functional relationships with the extracellular matrix. Thanks to the continuous activity of this real interface of cellular contact, the cells are able to recognize other cells, near or distant, as real functional entities of a similar subject, or as structures extraneous to them; to send and to continually receive chemical and physical signals; and to stick to other cells or other substances present in the interstitial spaces of the extracellular matrix. For example, cellular receptors have great importance, especially the receptors that tie the molecular protein conducting the signal to the extracellular matrix, where the union happens with the membrane (Fig. 3).

The cellular membranes are responsible for the internal organization of cells as well as for interaction with external stimuli and for “structural integrity.” The plasma membrane prevents a mixing of cellular contents with extracellular molecules and acts as the first element of “contact” between the cells and the extracellular environment.

*Figure 3*
Schematic representation of a G protein coupled receptor. The receptors that tie the protein molecules (signal protein) ask for a site at the extracellular matrix level, formed by the polypeptidical substance identified on the figure. Smaller molecules (signal protein), such as adrenaline, ask for a small extracellular site.
The composition and the maintenance of this structure is essential for the generation and regulation of different functional signals and biochemicals, both in the normal and in the pathologic cells (19,20).

The extracellular matrix is represented by a complex structural entity that surrounds, nourishes, and furnishes support to all the cells. The extracellular matrix is generally described as being composed of three biomolecular classes of substances:

1. structural proteins (collagens and elastin)
2. specialized proteins (fibrillates, fibronectin, laminin, etc.)
3. proteoglycans (composed of a “core” of protein with long chains of two saccharides of glycosaminoglycan forming, in such a way, complexes of high molecular weight that represent a cardinal part of the extracellular matrix)

The connective system has great importance in the interstitial matrix. Many trials could be represented by the scheme in Figure 4, reported to be the interpretative scheme of the formation of elastin by tropoelastin.

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**Figure 4**  
Interpretative scheme of the formation of the elastin from the tropoelastin.
Therefore, it appears fundamental to begin to consider cellular homeostasis, both in a molecular and in an anatomic-functional biological sense, as a complex interaction of mechanisms and reactions that can begin and also evolve from the outside of the cell in the extracellular matrix (21). The cellular matrix, the fundamental substance for life, is found as a rule as a solution. Some alterations can make it vary into a gel. These variations play a role in physical, chemical, and metabolic changes, among which are the alterations typical of cellulite (22). In the dermal site and in the superficial subcutaneous site, we can have an activation of “metalloproteases-2” directly connected with the evolution of lymphedema, lipolymphedema, and mesenchymopathies.
REFERENCES


WHAT IS CELLULITE?

Cellulite is certainly not a serious condition from the medical point of view, but it does represent the most widespread and least tolerated aesthetic complaint among women. The condition is very well known through intense publicity campaigns in the mass media and the cosmetics industry targeted at increasing the market for cosmetic creams, electro-medical equipment, pills, and therapeutic fantasies that often lack a scientific basis though they sometimes improve the aesthetic aspect of the problem. Most aesthetic treatments might be compared to a “coat of white paint” painted over a damp patch on the wall. By adding subsequent layers of paint, the wall may improve its appearance, but our medical duty is to eliminate the dampness itself so that the wall may “recover” its good state rather than merely “seem” sound.

However, the importance of the purely aesthetic problem should not be underrated. “Appearance,” the most popular theme of cosmetics, may seem superficial and frivolous but it ends up being an essential element during consultation. Both in medicine and surgery, especially in cosmetic surgery, nothing should be considered frivolous.

Cellulite is an actual pathology, something uncomfortable and unaesthetic, which results in a disease for the patient. Our duty as physicians is to suggest the best scientific methods that are appropriate (or available) to repair tissue damage and pathological disorders, and are effective in improving aesthetics.

DEFINITION

Nobody denies that the term “cellulitis” has been misused, because in medicine the suffix “itis” refers to inflammation, phlogosis, or infection. Therefore, “cellulitis” might refer to an inflammation of the cells involved. Cells, the basic vital units, integrate (with additional
interstitial structures) the microvascular–tissular unit of all living tissues. In so-called cellulite, there is no phlogosis of the cells, but perhaps an alteration of interstitial tissues. Why has such an empirical misuse been applied for so long in medicine and everyday life? There was a time when cellulite was conceived as a mere increase of fat in subcutaneous tissues associated with an altered lymphatic and venous flow and lymphatic stasis. Furthermore, there was a deeply rooted notion that cellulite was closely related with the specific stasis subsequent to hypotonia or venous and lymphatic disease and, therefore, it was assumed that a previous varicose disease should exist for cellulite to appear. In fact, this is true in some infrequent cases. Most often the interstitial alterations of cellulite disease appear first and the varicose or lymphatic pathology manifests itself only later. In any case, the characteristic peau d’orange appearance of cellulite is either caused by an increase in the fat or interstitial liquid content, or to the alteration and retraction of connective tissue layers occurring at different times and in different manners.

Venous–lymphatic stasis is the outward expression of malfunctioning in the endocrine–metabolic regulation of the interstitium. From our point of view, however, this definition does not include all the stages of the disease as far as their evolution in time is concerned and, worse, it does not consider all its etiological and physiopathological variants.

There are clearly three stages of development: edema, fibrosis, and sclerosis, but the initial edema is not always the first pathological manifestation since an alteration of the interstitial matrix, the connective structure, or the adipose tissue often precedes its appearance.

In some particular cases, such as lipedema and lipolymphedema, the edema—characterized by the presence of free water instead of lymph—results from an alteration of the interstitial or adipocytic metabolic mechanisms.
In Dercum’s syndrome, for example, an alteration of interstitial structures due to phlogosis of the nervous axon was suggested, associated with bacteria from the intestine. German authors [especially Letzel (1)] have found such bacteria in “cellulite” tissues or, at least, the presence of lesions caused by these bacteria. The question is, then, where do these bacteria come from?

It is well known that all nutrients needed for life are distributed from the intestine to the whole organism through blood and lymph. They are accompanied, however, by toxic substances, heavy metals, bacteria, etc. Thus, defense reactions are activated in the form of lymphocytes, macrophages, or immune reactions to protect tissue health. Therefore, the etiology of different cellulite disease cases may be associated to the after effects or sequelae of toxic, metabolic, and—why not—bacterial attacks.

**HOW TO DEFINE THE UNAESTHETIC SIDE OF CELLULITE**

First, two observations should be made:

1. In medical pathology, the term “cellulite” refers to an inflammation of infective origin in the interstitial and perivisceral connective tissues. A redefinition of such pathologies is therefore needed, assigning to each one of them the appropriate expression “*xx* bacterial cellulite,” where *xx* stands for the affected region (e.g., “retrorenal bacterial cellulite”).

2. In cosmetic medicine, as in everyday language, the term “cellulite” has a long history and refers to a frequent unaesthetic condition in women. If the word “cellulite” is not applied to a mere feminine whim but refers to different pathologies of the subcutaneous tissue, we believe it is necessary to use it for understanding conditions such as “cellulite hypodermosis *xx*” where *xx* stands for the associated disease, for example, “cellulite hypodermosis with lymphedema” or “cellulite hypodermosis with hyperplastic lipo-dystrophy,” and also “cellulite hypodermosis with localized adiposity.”

The conclusion is that, in the future, the various cellulite syndromes should be defined more accurately.

**CLASSIFICATION**

Today the term “cellulite” includes unaesthetic conditions that, despite involving a volumetric alteration in the limbs and irregularities in the outer cutaneous appearance, correspond to different etiologies and require, therefore, specific corrective or therapeutic treatment. Consequently, an adequate clinical–instrumental categorization is essential before starting either physical therapy or medical, surgical, or cosmetic treatments.

Histopathological alterations may be attributed to several different disorders and have been studied using different approaches through time.

The term “cellulite” was first used by Alquin and Pavot in France in 1920. Their insightful observations led them to associate this unaesthetic condition with a possible pathology accurately described a little later by Lagueze as a subcutaneous pathology characterized by “interstitial edema associated with an increase in fat content.”

In 1940, Allen described cellulite mainly as a typical lipedema not accompanied by edema of the foot. He further highlighted the prevalence of the metabolic alteration over the venous–lymphatic impairment.
In 1972, Braun and Falco made references to the predominantly vascular disease describing it as a lymphedema with various manifestations.

Finally in 1976, Reinharez, who had a deep knowledge of the lymphatic system, described this disease as an endocrine-metabolic pathology having secondary vascular and lymphatic manifestations (2).

In 1978, Binazzi, and later Curri—perhaps the greatest specialist on microcirculation together with Merlen—histologically proved the existence of microvascular alterations, dividing them into three groups: edema, fibrosis, and sclerosis (hence the acronym EFP corresponding to edematous fibrosclerotic panniculopathy).

In his excellent book, published in Italy in 1978 and entitled *Le microangiopatie*, Curri says: “From a long time ago, nobody has questioned the fundamental axiom that capillaries play the most important role in the circulatory system, including the heart. This axiom is currently under review and latest findings are perplexing.” As early as that date,
Prof. Curri suspected there was something else beyond the capillary itself though he was unable to prove his assumption (3–7).

Recent discoveries have led to different evaluations and, in 1997, we described in *Le celluliti* and in *Flebologia Oggi* our own conception of the cellulite disease as a “predominantly interstitial endocrine-metabolic pathology” (8–14).

Disorders of cellulite may be attributed to three different conditions:

1. *Alterations in the figure*: Such alterations do not always involve a pathological condition, but they do determine a lack of harmony in the figure. They may also be associated with hereditary diseases or with a peculiar bone structure of the pelvis and rachis. Nearly always, however, they are associated with postural or foot alterations that should be studied dynamically for the diagnosis.

   Although they often elicit changes in the figure and cause the true cellulite disease, definite assistance for such alterations is not always possible because they sometimes require physical therapy and a change in lifestyle.

2. *Systemic and localized adiposity*: The general contour of the human body derives its characteristics from the particular arrangement of the adipose panniculum upon the structure of bones and muscles. The human body is characterized by the presence of rigid fasciae, particularly, the deep muscular fascia that, starting from the skull base, extends continuously to the ankle and the metatarsus supporting many vascular, neuro-physiological, and orthopedic functions. In certain areas, the fascia is divided
into two layers of hormone-dependent adipose tissue (steatomery), especially associated with procreation and containing insulin, estrogen, and calcium receptors. Such steatometric adiposities, in their turn, provide roundness to the figure.

It is also well known that such localized adiposities may only be eliminated through surgical therapy or liposculpture.

Alterations in the figure are mainly determined by disorders in adipose areas, either steatometric in nature (hereditary and sensitive to endocrine-metabolic signals) or subcutaneous (sensitive to unbalanced diets, toxic substances, bacteria, and heavy metals).

Excessive localized adiposity may involve numerous normal-sized cells (hyperplasia), a normal amount of big-sized cells (hypertrophy), or a combination of both. Localized areas of adiposity are frequently found in the lower part of a woman’s body, in the glutei, the abdomen, the flanks, the upper external side of the hip, and the knee.

The volume of some adipose tissues is conditioned, to a certain extent, by hormonal activity and should therefore be considered as normal. However, when such adipose characteristics do not agree with current aesthetic canons in fashion or when they elicit symptoms, surgical intervention may be considered legitimate. Localized adiposity should be distinguished, nevertheless, from cellulite itself, even if an association of these two pathologies is frequent.

3. **EFP**: It is the traditional evolutionary degenerative disease of subcutaneous tissues that develops on a constitutional substrate closely linked with a series of predisposing and triggering factors.

Localized areas of cellulite are frequently found in the lower part of a woman’s body, in the glutei, the abdomen, the flanks, the upper external side of the hip, and the knee.
According to the authors who described its histomorphology, it involves a sequence of events characterized by interstitial edema, connective fibrous reaction, and the resulting sclerotic evolution. Each of these histopathological stages is associated with a different vascular stage (15,16).

Thus T0 indicates normal vascularization, T1 the initial appearance of hypoxic areas, T2 the presence of hypoxic and hypometabolic areas, and T3 and T4 indicate the cold nodular evolution characterized by a thermographic plate resembling the skin of a leopard (70).

Clinical studies and recent observations have demonstrated that EFP effectively represents some types of the cellulite disease though it does not cover all clinical manifestations.

**EVOLUTION**

**WHEN DOES CELLULITE BECOME EVIDENT?**

Nearly always the process starts in puberty, affecting particularly the lower limbs. Other triggering periods are pregnancy, periods of sexual dissatisfaction, lack of human or family understanding in combination with an altered lifestyle, wrong diet, and intestinal dysfunctions. Very few women above 18 years of age are totally free from some form of cellulite.

**WHAT IS THE RELATIONSHIP BETWEEN CELLULITE AND OBESITY?**

A clear distinction between cellulite and obesity should be made, even though confusion is frequent. Though they may coexist, the two processes are definitely different.

- Adiposity is the simple accumulation of adipose tissue in the available space. When fatty tissues exceed the normal value of 30%, there is obesity.
- Cellulite, instead, involves a transformation and alteration of subcutaneous interstitial tissues and is certainly not a mere accumulation of fat.
- The widespread confusion between these two conditions leads women to attempt, at the first manifestation of cellulite, to lose weight using all the methods available. A diet that
is poor in nutrients and aimed at reducing localized volume has an initial harmful consequence: tissues lose their structure and different areas slim down. After such therapeutic attempts, muscular tone and tissue structure are often irrecoverable. In this regard, the damage caused by needless chondroitin sulfatase infiltrations should be recalled: glycosaminoglycans release free water, and tissues give way causing or resulting in “permanent unevenness.” The same is true for ozone infiltrations and therapies that apply heat and ozone simultaneously.

**PREDISPOISING FACTORS**

Among predisposing factors the following should be highlighted:

- **Ethnic origin.** White women show the highest predisposition.
- **Family background,** especially hereditary endocrine–metabolic syndromes, and also common nutritional deficiencies.
- **Body structure,** especially postural and spinal column alterations.
- **Hormone imbalances** in patients suffering from hormone functional alterations and patients consuming progestagen or hormone-supplemented food.
- **Dietary disorders,** particularly an excess of sugar, fat, and hormones.
- **Digestive disorders,** especially those associated with intestinal flora alterations.
- **Disorders of the intestinal flora,** which is the initial pathology in all degenerative tissue alterations such as arthrosis, myalgia, angiopathies, and cellulite pathologies.
- **Postural problems** associated with foot orthopedic pathologies or with an ill-functioning (e.g., inadequate) footwear.
- **Psychosomatic disorders,** especially depressive anxiety or languid, apathetic, and faltering character frequently associated with cultural deficiencies.
- **Sexuality.** Sexual activity is one of the basic activities of life, as essential as feeding oneself, sleeping, and breathing. Every human being requires sexual satisfaction and may achieve it in different ways, but such satisfaction should always exist so that the remaining normal metabolic functions work properly. Sexuality has a “physiological” manifestation characterized by the urge to elicit “organic functions and reactions,” and a “spiritual” manifestation characterized by the need to arouse “emotions.” Both should be fulfilled, because they are the chemical catalyst of many other functions.
- **Lifestyle.** A proper balance is needed among diet, evacuation, work, sleep, and exercise.
- **External compression.** Tight dresses, jeans, and unnecessary elastic hoses do not help the intestinal lymph adipose system in its functions or the cutaneous microcirculatory system, thus favoring cellulite pathologies of the metabolic hypoxic type.
- **Infections** may cause tissue damage, which, in turn, results in alterations in tissue structure and fibrosclerosis.
- **Smoking.** It certainly slows down microcirculation in the cutaneous arterioles and is thus lipogenetic, generating the cutaneous hypoxia traditionally known as peau d’orange. On the other hand, hormone and thyroid stimulation induced by smoke itself activates noradrenaline and speeds up tissue catabolic processes, thus favoring lipolysis at the subcutaneous level. Finally, in order to balance cutaneous peau d’orange, subcutaneous lipolysis occurs. However, permanent and deceitful damages in the interstitium, due to an excess of free radicals when defense mechanisms such as superoxide-dismutase fail, should also be assessed.
The intake of estro-progestagens such as those included in birth-control pills and food preservatives favors interstitial liquid retention generating endothelial edema and activating Fenton reactions (Fe–Ca). The process inevitably generates some form or other of lipedema and lipolymphedema, which in their turn result in lipodystrophy. Besides, women who are administered hormones show a high level of free radicals as may be easily seen in reactive oxygen metabolites (ROMs) test (17,18).

**TRIGGERING FACTORS**

Several factors should be highlighted:

- **Obesity and overweight**: All forms of overweight are characterized by an increase of fat in subcutaneous tissues. In normal interstitial and microcirculatory exchanges, adipose cells interfere with water, oxygen, and protein ions, unleashing processes that alter the interstitium due to hyperinsulinemia.

- **Hormone intake**: Estro-progestagens in particular, but all hormones present in food, generate typical alterations, either at the endocrine–hypophyseal feedback level, or at the peripheral receptor level, giving rise to various phenomena such as lipogenesis, lipedema, and calcium loss in venous and lymphatic walls, with a concomitant increase in capillary permeability, and alterations in tissue oxy-reduction reactions.

- **Anatomic alterations**: Postural alterations and gait disorders interfere with normal metabolic and microcirculatory processes.

- **Dietary deficiencies**: Diets poor in protein, vitamins, and fibers—often associated with intestinal flora alterations—result in stagnation of feces and dilatation of the ampulla recti, as well as in compression of iliac veins and subsequent hampering of the venous and lymphatic flow in the lower limbs.

- **Metabolic alterations**: Metabolic alterations at the interstitial matrix level are still more important.
LIPEDEMA AND LIPOLYMPHEDEMA: PATHOPHYSIOLOGIC HYPOTHESES

By “lipolymphedema,” we understand a particular and widespread syndrome characterized by edema associated with a certain form of lymphedema and/or lipodystrophy. It is a frequent pathology of glutei and lower limbs in women.

According to Campisi (19), lymphedema is characterized by a state of tumescence of superficial soft tissues originating from a stasis that increases the amount of high-protein-content
lymph in the interstitial space, a phenomenon characterized by primary and/or secondary alterations in transport routes.

Lipedema instead, is a specific syndrome of almost unknown etiology at present, which is characterized by fatty tissue and subcutaneous liquid deposits (particularly in the lower limbs and glutei) that may or may not be associated with lymphedema and/or lipodystrophy.

In 1940, Hallen and Hynes first described lipedema as an accumulation of subcutaneous fat accompanied by hard edema of the leg except the feet. Subsequent definitions always remarked Merlen’s observation that it involved “foot hypothermia with a significant difference in local temperature.” Bilancini and Lucchi have recently described this syndrome (20–22).

This pathology, often cursorily defined as lymphedema, venous insufficiency, or cellulite, is widespread among 65% of women between 14 and 35 years of age, and the percentage increases among individuals over 40 years under the form of lipodystrophy and/or lipolymphedema. In this instance, venous insufficiency is absent or is present only as a secondary trait, but a positive correlation with the peripheral metabolism of fatty tissues may be observed.

Although incomplete, the following physiopathological considerations derive in part from recent studies in microangiology, personal clinical observations, and response to a treatment protocol applied to over 500 patients between October 1, 1995, and December 30, 1999.

This protocol foresees the combination of several traditional and natural methodologies aimed not only at local therapy but also, and mainly, at cleansing and restoring general organic balance.
It was published in 1997 as “BIMED Protocol for the Treatment of Lipolymphoedema and Cellulite Pathologies.” The acronym BIMED stands for “biorheological integrated methodology with endermology and dynamic systems” and is also a mnemonic for the names of the authors (Bacci–Izzo–Mariani) (23–26). All these authors participated in the scientific works of the Phlebolymphology Center of the University of Siena where, under the direction of Prof. Sergio Mancini, many interesting studies about aesthetic pathologies of legs was organized.

Our starting hypothesis was that the metabolism of the interstitial matrix and the adipocytic activity are fundamental in the manifestations of lipolymphedema and various forms of cellulite disease.

We further noticed that there is a preferential adipocyte-lymph route, so that the hypothesized functional lymph–adipose system might provide local metabolic control and originate degenerative pathologies.

These hypotheses have been confirmed by the recent studies on the function and role of the extracellular matrix in the economy of the metabolism of all the tissues today.

LYMPH

Lymph is a fluid generated in the argentophilic cells of every tissue. It is formed in the interstitial matrix and later flows through the lymph vessel system. Additionally, lymph composition is different from the composition of the interstitial liquid. The interstitium contains many “sol” droplets that, under certain conditions, form a “gel” or coagulated mass of intertwining hyaluronic acid filaments into which protein molecules cannot penetrate.

The enzymatic rupture of hyaluronic acid molecules entails an immediate increase in osmotic pressure due to incoming protein molecules. Besides, the interstitial fluid does not contain free water; water is bound to other components that flow along the fibroblast fibers and fibrils.

According to Starling’s and Pappenheimer’s hypotheses, water and solutes are filtered away from arterial blood because capillary pressure is higher than oncotic pressure. In the venous system, however, pressure relationships are exactly the opposite, and thus water and solutes are reabsorbed. In normal conditions, blood contains approximately 3 L of water, whereas interstitial tissue contains approximately 11 L. During the course of 24 hours, 18 to 22 L of water and solutes are filtered away. Approximately 16 to 17 L are reabsorbed by the venous system, and the remaining 2 to 5 L constitute lymph.

Beside this filtering process, there is a diffusion process favoring the passage of solutes and water through the capillary membrane (27–33).

The capillary membrane is absolutely permeable to water and solutes, but only partially permeable to proteins. Thus, lymph proteins (originated in blood plasma and filtered through the capillary wall) cannot reenter into the bloodstream and are forced into the lymphatic system. Therefore, the lymphatic system is an optional route for solutes and water from the interstitium and a compulsory route for protein transport.

Hence, the primary function of the lymphatic system is to carry proteins into blood, but it also has a secondary homeostatic function in maintaining both transcapillary and oncotic pressure gradients.

Moreover, lymph contains all clotting proteins and other thromboplastic substances needed to induce thrombin and fibrin formation. Even though no platelets are present, these substances have coagulating potential and increase “lymph density.”
This phenomenon slows down and blocks intralymphatic circulation, which is sensitive, however, to prothrombotic drugs acting on active thromboplastine (TPA). (This justifies the clinical activity of the profibrinolytic substance “defibrotide” in the therapy of lymphatic pathologies and also requires further scientific research.)

There is also evidence that fats absorbed in the intestine do not enter directly into the liver but instead follow the lymphatic routes upward and flow into the thoracic canal and blood. Lipids in the intestinal interstitial cells are not free fatty acids (FFA): they are organized in micelles (chylomicron) and huge lipoprotein compounds that can enter only into lymph vessels. Glycerol, steroids, and smaller fatty acids, instead circulate through blood vessels. Hence, lipoproteins underlie an extravascular circulation following the route “blood–interstitium–lymph–blood.”

The whole process occurs in the mesenteric interstitium and the subcutaneous interstitium of lower limbs and some other tissues, particularly in areas characterized by the presence of hormone-dependent white adipose tissue.

THE LYMPHATIC SYSTEM

The lymphatic system is composed of lymphoid tissue, lymph nodes, lymph vessels, and interstitial lymphatic spaces.

Lymph vessels start at lymphatic capillaries and have flimsy endothelial walls devoid of basal laminae. They join later, forming precollection capillaries, which constitute the genuine lymph vessels containing the already formed lymph that flows through channels.

Further on, pre- and postlymphatic node collecting vessels as well as the main vessels interrupted by such nodes may be found.

But lymph life begins before the precollection vessels because droplets are formed and evolve within interstitial spaces and slide through the complex of sheaths and small channels (similar to the fibrovascular vein structure of vegetal leaves), which constitute a genuine paralymphatic system. Some structural observations and descriptions suggest direct connections at this level among lymph, the water involved, and adipocyte metabolism, as if, according to requirements and local conditions, the adipocyte activity itself determined water release and protein transport under the form of lymph.

LYMPHATIC CIRCULATION

In fish and reptiles, lymph circulation is supported by genuine peripheral lymphatic hearts. In mammals, such structures have almost disappeared, except in intestinal vessels, where a spontaneous activity has been noticed.

The walls of all other lymphatic vessels show a smooth muscle structure similar to that of the veins, regulated by sympathetic fibers and adrenaline.

Initial lymphatic collectors are integrated by three leaflets folded upon themselves and separated along their borders by a variable space forming an open cylinder. Such leaflets are connected to nervous fibers and fibroblast fibrils on which the droplets of water or lymph slide along.

Lymphatic flows increase in speed with the different respiration stages. It is also well known that leaflet passive distension may activate lymph flow within collectors.

Besides, there are indications that an externally induced (through manual lymphatic drainage and Endermologie® techniques) or internally induced (through pressure increases) passive distension of lymphatic vessels increases the speed of the lymphatic flow.
Lymphokinetic action may also be attributed to alpha adrenergic or electric stimulation of tissues. Such activity releases and drains a great amount of water from tissues and, mainly, a substantial amount of proteins.

Intense body exercise increases the amount of tissue water and proteins transported from the lymphatic system, as long as they are free and functional, particularly at the inguinal and paraaortic nodes.

Clinical observations and recent research have shown that—in the case of pathologies characterized by lymphedema—there is something else besides lymphatic vessel damage. An hypothesis is developing in which the autonomic nervous system and fibroblast contractility play a relevant role in the formation of lymphedema in addition to adipocyte activity.

**VARIATIONS IN LYMPH**

The amount of lymph may increase and stagnate as a consequence of an increase in mean capillary pressure, due either to variations in permeability or osmotic gradients or to peripheral venous pathologies. Cases were reported where tissue hypoxia initially increased the lymphatic flow and was later followed by stagnation and a concomitant increase in interstitial pressure.

In fact, it is well known that individuals with intestinal absorption disorders, especially those involving flora alterations of the putrefying–fermentative type, show liquid retention and a decrease in peripheral lymphatic flow.

Although this may be partially attributed to a cleansing deficit in kidney and liver efferent vessels, it is more likely due to compositional alterations of the interstitial liquid involving lipoprotein excess on the thematic side derived from a toxic-induced peripheral metabolic blocking of the “interstitial tissue–lymphatic tissue–adipocyte” cycle. Tissue acidification and, in some cases, even a bacterial component belonging to the *Streptococci* family have been detected.

It seems, then, that there are important relationships between the time during which lymph is formed and the metabolic life of adipocytes: when water from the interstitial matrix is available, it may be either included in the lymph or used for metabolic processes.

The existence of a “lymph adipose system” might be hypothesized to explain the main peripheral metabolic processes in tissues. Such a system would be represented mainly by the subcutaneous tissue, the mesenterium, and perivascular tissues.

**THE FIBROBLAST AND THE INTERSTITIAL MATRIX**

The connective tissue includes the dermis and the subcutaneous tissue, which are made up of three main elements: fibroblast cells; collagen and elastin macromolecules; and the extracellular matrix.

1. The fibroblast is the genuine connective tissue synthesizing proteoglycans, tropocollagen, and tropoelastin. It plays a fundamental role in tissue repair. Fibroblasts issue filaments connected with different cells—adipose cells among others—that make the cell sensitive to traction (hence the therapeutic response to Endermologie techniques). Droplets of water or lymph slide along the surface of these filaments.

2. Collagen and elastin are the major products of fibroblasts and play the essential plastic role within the matrix.
3. The extracellular matrix is mainly composed of proteoglycans (besides glycoproteins), which collaborate in the regulation of osmotic pressure and fluid movement. If there is an excess of hyaluronidase, the tissue is in a sol phase and liquids are able to flow, whereas in the gel phase, liquids are bound. Proteoglycan macromolecules are rich in anions that capture other positively charged ions such as sodium and calcium, thus regulating cell and matrix polarity (34–36).

THE ADIPOCYTE

Adipose tissue is characterized by the presence of a high number of adipose cells forming a tissue with scarce ground reticular substance.

Adipocytes are closely associated with local and systemic metabolism and are a two-fold source of energy with respect to glycides and proteins. According to the area, activity, and embryological origin, primary fat (brown colored and preferentially located in cavities) may be distinguished from the secondary type (whitish fat located at subcutaneous level, within the muscle interstitium and in the omentum, mesenterium, and peritoneum).

While cells of the primary fat tissue are steatoblastic from the embryological point of view, white fat tissue cells instead derive from normal mesenchimal (mesenchymal) cells.

In fact, every fibroblastic cell may be transformed into an adipose cell under specific conditions or body requirements. Under electron microscopy, secondary adipose cells show a complex of Golgi’s corpuscles, mitochondria, and ribosomal spread within a cytoplasm, which becomes thinner near the central fat drop. The adipose drop has no membrane of its own and proffers filaments that extend to the cell surface.

The plasmatic membrane—which has pinocytotic invaginations—is surrounded by a glycoprotein membrane varying according to metabolism. On the surface of the adipose cell, nude nervous axons may be seen. Intercellular substance characterized by connective fibers in reticular phase is also typical, and fibroblast filaments adhere to the capillary structure.

We know that lipids in adipose tissue are mobilized from cells under the form of FFA and glycerol when signals derived from a negative energetic balance are emitted. However, adipose cells are also sensitive to neuro-hormone stimuli. Moreover, lipolysis is stimulated by sympathetic fibers and adrenaline, whereas lipogenesis is stimulated by insulin, estrogen, and prostaglandin.

A particular feature of peripheral adipose tissue is that, under the stimulus of peripheral hyperinsulinemia, it may generate certain proteins during lipogenesis, a process that may be triggered by hypoxia and mere cold.

Thus, the adipocyte is a cell acting mainly as a hormone receptor and reacting through lipolysis and lipogenesis.

Lipolysis is generated not only by nervous and endocrine stimuli, but also by an increase in blood flow. Hence, flow decrease inhibits lipolysis and the outflow of FFA and glycerol (this might explain surface lipodystrophy in the lower limbs of non-phlebo-lymphopathic patients who wear nonprescribed elastic hoses).

On the other hand, lipogenesis is the synthesis of lipids from sugars, carried out in the liver and fat tissues. Whenever energy or thermoregulation is needed, the body starts circulating fatty acids.

The regulation of the adipose tissue varies according to body areas and depends mainly on sexual hormones (37–41).
HYPODERMIS AND FAT METABOLISM

Subcutaneous tissue (also known as Camper’s fascia) is a loose cellular layer of tissue located between the deep musculoaponeurotic fascia and the superficial one. In this case, adipose units are enclosed within a network of connective tissue also traversed by a reticulum of nervous fibers and vessels.

In some regions of the body, such as women’s hips and abdomen (and also the flanks and abdomen of men), a second structure may appear beyond Scarpa’s fascia, which contains a reserve amount of fat also called “steatomery.”

In these areas, the number of adipocytes is higher, and the adipose cells themselves are more sensitive to sugar and less sensitive to blood flow variations, because they are included in a connective tissue of lamellar structure, which hinders lipolysis. Hence, this adipose tissue is mainly sensitive to peripheral insulinemia and estrogenic stimuli.

Both lipolytic and lipogenic hormones are involved in fat metabolism. Among the lipolytic hormones, thyroid-stimulating hormone (TSH), adrenaline, glucagon, somatotrophin, adrenocorticotropic hormone (ACTH), and thyroid hormones are the most important. Mainly insulin and estrogens represent the lipogenetic group.

This observation evidences the relationship between subcutaneous lipodermosclerosis in the lower limbs of women and their dietary habits.

Nowadays, the usual diet is not so much characterized by an excess in fats as by an excess in sugar. Above all, the intake of lipids and proteins is essential because sugars can be synthesized by the body. Carbohydrates are essential, but our current diet includes an excess of refined sugar and starch. Almost all (prepared) food and daily beverages include refined sugar.

Besides, dietary habits lead us to consume bread and pasta containing refined flour from which only starch is useful for the body. Too frequently, the Mediterranean diet is confused with a diet consisting of only pasta and bread, when in fact fibers, legumes, and proteins are also part of it.

At the peripheral level, the excess of absorbed sugar triggers an increased absorption of fat and a subsequent storage of lipids in the adipose tissues following peripheral hyperinsulinemia.

Besides, there is an excessive consumption of exogenous estrogens provided through estro-progestagen therapies, popular especially among the young people, or through the hormones used in food industry and soil treatment.

Exogenous estrogens are absorbed and enter the body as exogenous substances that cannot be bound to liver proteins, and are not recognized by the hypophysis feedback mechanism. Thus, free exogenous estrogens are transported through the vascular system and are usually distributed among peripheral adipose tissues resulting in later lipogenesis and water retention in the extracellular matrix, while endogenous estrogen secretion is carried on continuously.

Peripheral hyperinsulinemia and hyperestroneginaemia might then become the main cause of the peripheral lipodermosclerosis observable in areas with a steatometric structure of adipose tissue, such as the hips, abdomen, and flanks in women, and the abdomen, flanks, and the back in men.

Fermentative disorders of the intestinal flora seem to add their own contribution to this phenomenon. They occur mainly in the colon after an excess of glycides and lipids in the diet or after the absorption of exogenous toxic substances.
Intestinal disorders may generate toxins, which, when disseminated through the vascular system, become fixed in the extracellular matrix (the vital basic unit of the organism) and bring about toxic and metabolic alterations due to their acidifying activity and cellular oxidation. Hence, the subsequent slowing down of metabolic exchanges plus retention of bound water in the interstitium.

Presumably, such conditions entail an increase of intracellular ions and an alteration in metabolic exchanges that increase the amount of macromolecules to be drained by the lymphatic system, i.e., an increase of lymphatic work.

Electron microscopy provides evidence about the relationship between adipocytes and fibroblasts on the one hand, and re-collecting lymphatic vessels on the other, the latter being ultimately stimulated by such fibril stretching owing to lymphokinetic activity. When lipolysis occurs, the adipocyte may diminish in volume and the fibroblast may contract: the water derived from metabolism may flow through the network and be incorporated along with protein molecules into the lymph that cleanses cells and tissues.

When lipogenesis occurs accompanied by tissue metabolic alterations, fibrils decontract and lymphokinetics becomes slower. This occurs in the case of lipedema (characterized by high interstitial pressure due to an increase of bound water) and also lymphedema (characterized by high vessel and interstitial pressure of free water and proteins, that is, lymph, accompanied by higher osmotic pressure).

Thus, a definition might be suggested for this lymph adipose system that may provide a key to understanding the etiology of a widespread unaesthetic pathology that potentially entails local and systemic degenerative processes such as lipolymphedema.

A closer view of the various clinical manifestations usually classified under the generic term “cellulite” provides—sometimes ready and often evasive—evidence of the specific clinical and symptomatological differences among lymphedema, lipedema, lympholipedema, lipomatosis, and lipodystrophy.

### Lipodystrophy

Lipodystrophy is a subcutaneous adipose tissue disease of the atrophic or hypertrophic type. Among hypertrophic forms, the most widespread are lipomatous lipodystrophies, Launois–Bensaude’s syndrome, insulin lipodystrophy, and Dercum’s disease (42).

Dercum’s disease shows signs of sequential lipolymphedema with periods of neuropsychological or metabolic disorders and alterations in the lower abdomen and adynamia.

Pathogenesis includes neurovegetative, hypothalamic, and hypophyseal alterations, and might be caused by interstitial phlogosis produced by branches of the nervous system, i.e., by an extracellular matrix pathology accompanied by an increase in lipogenesis.

A similar phenomenon might be assumed for lipolymphedema considering the interstitial phlogosis of nervous and fibrillary branches as the direct or indirect cause of the increase in local lipogenesis. It seems that German authors have identified an intestinal streptococcal microorganism as causing matrix alteration.

In lipolymphedema, there are certainly clear correlations among alterations of the intestinal flora, metabolic acidifying alterations of the extracellular matrix, hyperinsulinenia, and peripheral hyperestrogenism. Therefore, the adipocyte and the extracellular matrix condition would be affected at least at the initial phases (with regard to the lymphatic or venous system).
Over the superficial fascia at the dermal level, an extremely diffuse lipolymphedema may be noticed, which improves with sun exposure and also when the patient stops wearing elastic hose.

This type of “superficial cellulite” might be attributed to superficial vascular alterations due to unnecessary elastic compression, the low energy derived from low arterial flow, lipogenesis, and also cellular oxidation.

Primary vascular alterations would be more evident at the surface than within the subcutaneous tissue, where the extracellular matrix and the lymphoadipose system would be mainly affected.

At the dermal level, microcirculatory turbulences might provide basic conditions for the disease, which might later evolve into liposclerosis.

Therefore, Vage’s observations regarding circulatory factors might be valid, because he says, “blood and lymphatic flows through adipose tissue are inversely proportional to its growth.”

From what has been said, it may be concluded that, in accordance with Curri’s formulation, “slow circulation” involves “lipogenesis,” whereas “quick circulation” involves “lipolysis” (43–45).

**THE LYMPHOADIPOSE SYSTEM**

This hypothetical anatomical structure is essential for understanding the etiopathogenesis of lipolymphedema according to Merlen’s description: that the increase in volume
of adipose cells and the diffusion distance from capillaries to fatty cells are responsible for the emergence of trophic turbulences associated with vasculo–tissular exchange alterations, especially in areas rich in lipolysis-stimulating nerves.

Curri’s histopathological discoveries are in agreement with Merlen’s theory on the relevance of microcirculatory turbulences for diseases that later result in liposclerosis and lipodystrophy.

Curri has proven the existence of local microcirculation disorders by describing several pathological phenomena such as

- Slowdown of microcirculation
- Lymphatic stasis
- Microaneurysms
- Lipedema
- Changes in venous capillary permeability
- Decrease in the amount of glycosoaminoglycan (GAG) in vascular sleeves

Nevertheless, we believe that lipedema and extracellular matrix alterations precede vascular alterations.

In fact, the continuous alteration of evening lipedema in young women generates stasis in capillaries and postcapillary venules and leads to its final installation, a circumstance, which, when added to entry of proteins into the interstitium, favors the evolution of lipedema into lipolymphedema.

Once this stage is achieved, a sclerotic reaction of the interstitium develops on one hand and, on the other, adipose cell dissociation occurs. Therefore, as time goes by, fibrillary reaction from the pericapillar and periadipocyte argentophilic fibers starts, and microgranules and micronodes are formed.

First adipose tissue alterations may involve an accumulation of bound water inside the interstitium, around capillaries, and in the matrix. The subsequent hemodynamic detriment of venous- and lymphatic-return-flow in the vessels of lower limbs might be the result of diffuse microcirculatory damage.
In close relationship with the adipocyte (mainly in affected areas), peripheral hyperinsulinemia and estrogenemia result in adipocyte hypertrophy and changes at the interstitial level, which entail further microcirculatory alterations.

Thus, we find that adipocytes are highly stimulated by estrogens: the action of 17-beta-estradiol leads to adipocyte hypertrophy, a most frequent condition in women’s normal biotype, which is characterized by an increase in the volume of bitrochanteric fat at the hips, glutei, and flanks.

Studies carried out by Bjorntorp in young women show that highest-volume adipocytes are located in the glutei and the bitrochanteric region and that the individual volume of adipocytes increases with age.

In young women, the highest volume of adipocytes are located in the glutei and bitrochanteric region.

Certain authors, among them Jean Vage, mention gynoid obesity, typical of women, when they discuss hyperplastic fatty cells—those present in young individuals. Such cells lead to alterations in the microvascular-tissue relationship and to the increased activity of estrogen-dependent lipoproteinlipase, mainly responsible for triglyceride contributions to the adipose cell.

At the embryological level, fibroblast stimulation transforms the mesodermic adipoblast into an adipocyte, which, from then onward, is stimulated by 17-beta-estradiol and insulin, progressively increasing its fat content.

New stimuli cause the subcutaneous adipose mass to grow and damage the extracellular matrix, affecting microcirculation because the thicker the adipose tissue, the lower
the circulatory flow per unit weight. It follows that alterations in microcirculation due to an ill-distributed capillary flow lead to adipocyte hypertrophy later. The whole process constitutes a feedback circuit, which in turn stimulates adipose tissue growth.

The immediate consequence is a deficient elimination of hormonal catabolic products (catecholestrogens), which remain in the area stimulating lipogenesis and favoring hypertrophy and/or hyperplasia of fatty cells. Besides, adipocyte alteration itself entails modifications in capillary permeability and the subsequent liquid outflow into the interadipocytic space, as well as lipedema and an obvious interstitial disorder. Finally, fatty tissue growth increases lympho-venous capillary stasis.

Estrogen increment may be due to monophasic cycles, hormone-dependent ovary tumors, physiological causes (pregnancy, menarche, and menopause), iatrogenic causes (hormonal contraceptives), or the absorption of exogenous estrogens (food). All of these lead to adipocyte hypertrophy.

Additionally, the volume increase of adipose tissue leads to greater aromatase activity.

In effect, among women, 25% of the androgen production occurs at the suprarenal level, another 25% occurs at the ovary, and the remaining 50% derives from peripheral conversion in muscular and fatty tissues, where androgens of low androgenic activity are transformed into powerful hormones like testosterone.

Within the adipose cells of certain subcutaneous tissues (particularly those involving flanks, hips, and glutei), androgens undergo a different process.

This especially occurs in the case of hypertrophic and hyperplastic cells frequently found in mixed obesity and the adiposogenital syndromes. Because of aromatization, they are in fact transformed into lipogenetic estrogens, thus deteriorating the prevalent conditions of an area already affected by lipolymphedema and altering interstitial microcirculation even further. Such alterations become chronic and thus lead to liposclerosis and lipodystrophy.

### VENOUS–LYMPHATIC STASIS

The expression “hemodynamic stasis” derives from the Greek word stasiz, which means “stagnated,” though in hemodynamics, the concept refers to a slowing down of the normal venous–capillary flow rather than an actual “blood stoppage or stagnation.”

Because of its ubiquity, microcirculation provides oxygen, nutrients, hormones, and enzymes to tissues and, above all, enables catabolic waste and CO₂ elimination.

Thus, to maintain tissular homeostasis, an uninterrupted capillary flow is needed, which is provided either through “vis a tergo” (retrograde effect) or through arteriole vasomotility that contributes to venous or lymphatic flow by means of rhythmic wall compression.

When metabolic or vascular alterations slow down the normal flow and stasis occurs, certain specific structures called arteriovenous anastomosis (AVA) are enabled: they operate as physiological bypasses activated when needed.

AVA represents the venous-return-system response to emergencies. However, if the emergency persists and becomes chronic, short-circuited venous–capillary areas suffering stasis develop endothelial hypoxia. Regulating factor production in the endothelium is stopped or irregularly carried out, and interstitial and structural damage ensues.

The body’s defense system is highly sophisticated and apt to endure brief periods of stasis, which do not entail irreversible damage.
However, when stasis persists for a long time or is cyclical, irreversible alterations of the vascular system, tissues, and the lymphoadipose system occur. Recurrent lipedema, then, illustrates clearly how—under diverse conditions—a mere physiological lipedema may be transformed into a pathological recurrent lipedema entailing lipolymphedema and lipodystrophy.

### HOW CELLULITE DEVELOPS

As a consequence of the physiopathological facts described above, pathologic cellulite undergoes different phases, but the starting point is almost always associated with alterations in the interstitial matrix.

1. Alterations in metabolic reactions at the interstitial matrix level, such as increase in tissue acidity, changes in the oxy-reduction mechanisms, progressive slowing down of arteriole flow, detriment of collagen fibers, and impairment of the fibroblast-adipocyte-nervous axon-lymphocyte system
2. Free water increase and reduce hyaluronic acid, proteoglycan, and glycosoaminoglycan, thus starting to reduce all functionality of the extracellular matrix.
3. Alterations in connective structures and the collagen system
4. Development of pathological lipedema
5. Development of lipolymphedema
6. Disorders in the lipogenesis-lipolysis system
7. Alterations in venous-lymphatic microcirculation
8. Surface hypoxia
9. Lipodystrophy
10. Tissular fibrosis
11. Sclerotic connective evolution

### MANIFESTATIONS OF CELLULITE

Besides the characteristic peau d’orange appearance and alterations in arms, abdomen, knees, and trochanters seen in cellulite, subjective symptoms characterized by alterations in the trophism of subcutaneous tissues may also appear.

The following alterations may be found:

- Altered sensitivity
- Pain
- Cramps
- Heaviness
- Nocturnal restlessness
- Cold feet
- Changes in skin coloration
- Livedo reticularis
- Dry skin
- Ecchymosis
- Edema
- Tiredness
### CLINICAL CLASSIFICATION

Cellulite might be divided into the following types:

1. Adipose cellulite
2. Edematous cellulite
3. Adipoedematous cellulite
4. Edematoadipose cellulite
5. Fibrous cellulite
6. Sclerotic cellulite
7. Mixed cellulite

It may also be characterized by the presence of

1. Soft tissue
2. Soft tissue with skin excess
3. Hard tissue
4. Mixed tissue

To this general classification, an accurate physiopathological and etiological diagnosis should be added.

### WHY CELLULITE IS A CONCERN

The disorders characteristic of cellulite involve endocrine–metabolic alterations that affect the microcirculatory system. They also draw our attention to the functionality and the cleansing process of the whole organism (46–54).

Besides, cellulite hardly involves controllable changes in the locomotor, digestive, and endocrine systems.

Last, but not the least, it is a cause of discomfort and an ill-tolerated lack of aesthetics that drives the patient to accept any type of so-called therapeutic treatments to solve the problem. Too frequently such “treatments” have no scientific basis.

Our efforts should be focused on the recovery of trophism and tissue tone, as well as on the control of endocrine-metabolic alterations that may entail irrevocable tissue damage, not only from an aesthetic point of view.

Although aesthetic considerations are not the primary concern for the physician, they should be considered. We feel concern for the aesthetics are a kind of sublimated medical attitude and therefore require still greater professionalism.

We should always bear in mind that ineffective or hardly effective aesthetic treatments have three inescapable consequences: clinical damage, aesthetic injury, and, more frequently, serious psychological damage.

### LIPOSCLEROSIS AND LOCALIZED ADIPOSEY

The term “cellulite” has been widely discussed and its applicability has been questioned arguing that the suffix “itis” refers to something different, however popular the expression might be in common usage. Throughout history, this pathology received different names and, as early as 1904, Stockman applied the term “panniculosis” to it. Later, other names
appeared in the literature, such as subcutaneous “geloide” (gel-like) fibroedema, which
gave rise to discussions about the edematous process itself and the fibrous evolution of this
disease.

Based on histopathological considerations, Númeroger and Muller mentioned der-
mal panniculosis, but it was Sergio Curri who finally dubbed it liposclerosis, thus defining
the final stage of this panniculopathy, i.e., sclerohyalinotic connectivation of the adipose
tissue (46–49).

Initially, all definitions tended to establish radical differences with localized
obesity—an impossible task from our viewpoint.

Bassas Gran et al. have also mentioned a much alleged polysaccharide modification
characterized by an abnormal increase in their polymerization gradient (hence, the pecu-
liar edematous sensation through palpation). Brown, Falco, and Scherwitz on one hand,
and Snaider on the other, could not confirm this hypothesis. Besides, Curri’s group was
unable to identify elements supporting the assumption of increased polymerization of der-
mal mucopolysaccharides (50–54).

As time went by, microcirculatory alterations that laid the foundations for an accu-
rate description of this ailment were observed.

Mian has remarked that cellulite areas show microangiodystonia and circulation
tonic alterations. The famous French angiologist Merlen was the first to describe this
pathology as a microvasculo–tissular complaint, that is to say, a genuine histoangiopathy.

Binazzi’s words should also be recalled because he said that, from the clinico-
structural point of view, three evolutionary stages should be distinguished. The first is
characterized by hypodermosis derived from localized adiposity. Differences from loca-
ized adiposity may be summarized in adipocyte deformity and damage, incipient lymphat-
ic stasis, small microhemorrhages, or fibrositary proliferations. The second stage involves
skin alterations: fibroblasts become fixed and proliferate, and neogenetic collagen appears.
Slowly but continuously, these alterations lead to a fibrosclerotic condition in certain areas
(abdomen, thighs, and flanks) of complex clinical and ultrastructural aspects that consti-
tute the final stage of EFP.

Let us try to describe the evolution of this disease, in physiopathological terms, to
later attempt a classification leading to therapeutic measures.

According to Curri (6), biopsies of upper external thighs, internal knee, glutei, abdo-
men, and breasts show a capillary increase in adipose tissue and a remarkable continuity
between capillaries and adipocytes.

The capillaries studied were very thin, measuring 4 or 5 μm in diameter. A large num-
ber of unmyelinated nervous fibers were observed inside the interadipocyte interstitium.
Capillaries were surrounded by argentophilic reticular fibrils extending along normal
fibrils around adipose cells and constituting the pericapillary network that continues the
periadipocyte network, also called Renault’s network.

Additional histological samples showed that the number of veins exceeded that of
small arteries, covered by a mucopolysaccharide sheath that provides sphygmic function-
ality. Such anatomic structure is essential to understand the etiopathogenesis of the lipo-
sclerosis diseases.

Based on Curri’s findings, the relationship among capillaries (CAP), fat cell (CA),
and matrix with fibroblast (F) was established.

Merlen’s remarks on the increased volume of adipose cells and the diffusion distance
between capillaries and fatty cells might explain the cause of trophic turbulences closely
associated with vasculo–tissular exchange alterations, especially in nerve areas where stimulation favors lipolysis.

However, it is essential to find correlations with etiopathogenesis sources. This does not mean that cellulite starts as microcirculation pathology but that microcirculation is also affected in regions where the interstitial matrix basal regulation is altered.

Alterations in arteriole flow account for Vage’s findings that “blood and lymphatic flow through adipose tissue are inversely proportional to its growth,” so that “slow circulation” involves “lipogenesis,” whereas “quick circulation” involves “lipolysis.”

All these consequently result in therapeutic difficulties and lead to prolong “localized obesity.” Besides, this explains the lipolytic effects of carboxytherapy.

Curri’s findings prove microcirculatory alterations accompanied by:

- Slowdown of microcirculation
- Venular stasis
- Microaneurysm
- Lipedema
- Alterations in venule capillary permeability
- GAG decrease in vascular sleeves

The continuous alternation of “evening lipedema” through transpiration generated by capillary and postcapillary venule stasis leads to its final chronicity. All this, added to entry of proteins into the interstitium, favors the evolution of lipedema into lipolymphedema.

Once this phase of the process is reached, a sclerotic reaction of the interstitium develops on the one hand and adipose cell dissociation occurs on the other.

Therefore, as time passes, fibrillary reaction from the pericapillar and periadipocyte argentophilic fibers starts, and microgranules and micronodules are formed.

“Liposclerosis” has a deceitful development and is clinically silent for long periods although it entails progressive damage of microvascular and adipose tissue.

Alterations involving hemodynamic disorders are localized at the capillaries, venules, and arterioles, where the following signs may be observed:

- Dilatation
- Microaneurysm
Among the various factors affecting microcirculation associated with hydrodynamic turbulences in adipose lobes, functional disorders in the endoarterial and endoarteriole blocking system should be remarked. Hormone factors are closely linked to the adipocyte (especially in the affected areas) and lead to its hypertrophy, as well as to interstitial changes involving microcirculatory alterations that further deteriorate preexistent conditions.

Thus, we find that adipocytes are highly stimulated by estrogens such as 17-beta-estradiol, which lead to the characteristic hypertrophy of the normal-female biotype and increase bitrochanteric fat volume in muscles, glutei, and flanks.

Studies carried out by Bjorntorp in young women show that highest-volume adipocytes are located in the glutei and the bitrochanteric region and that the individual volume of adipocytes increases with age (55).

Morphometric studies of adipocytes showed that hyperplastic obesity, characterized by an increase in the number of cells occurring in childhood, is exactly the opposite of hypertrophic obesity, characterized by an increase in cell volume occurring in adulthood.

In women suffering from hypertrophic obesity—i.e., showing adipocyte volume increase—the biggest cells are located in the femoral area and glutei, and the smallest in the epigastric area.

The amount of adipose cells is genetically predetermined.

Jean Vage refers to gynoid obesity when discussing hyperplastic fatty cells—those characteristic of youth—that lead to alterations in the microvascular–tissue relationship and to a higher activity of estrogen-dependent lipoproteinase, the enzyme associated with triglyceride supply to the adipose cell.

It should be remembered that adipose cells are provided with two different adrenergic receptors: beta-adrenergic receptors having a lipolytic activity, and alpha-2 adrenergic receptors having antilipolytic activity. The highest number of alpha-2 receptors is located in the glutei and the upper part of the thigh. Among other reasons, this is why these areas do not respond to isolated medical, cosmetic, and/or physiatric treatments and, least of all, to aesthetic treatments.

If we were to explain liposclerosis from the point of view of adipose mass increase, we should first say that there is a direct correlation with microcirculation, because the greater the mass of adipose tissue, the lower the circulatory flow per weight unit. In other words, alterations in microcirculation due to an ill-distributed capillary flow inescapably lead to adipocyte hypertrophy.

This is precisely what happens in the case of peau d’orange, often derived from the patient’s wearing nonprescribed elastic hose that slows down cutaneous microcirculation. In fact, this kind of cellulite responds well to carboxytherapy and Endermologie methods.

Adipose dystrophy may also be hormone dependent. Incremental increases in estrogen may be due to monophasic cycles, hormone-dependent ovary tumors, physiological causes (pregnancy, menarche, and menopause), or iatrogenic causes (hormonal contraceptives). All of them lead to adipocyte hypertrophy.
The volume increase of adipose cells entails alterations in interadipocyte microcirculation. On the one hand, compression disturbs venous and lymphatic return, and prevents hormone catabolic products and catechol–estrogen elimination, which remain in the area stimulating lipogenesis and favoring fatty cell hypertrophy and/or hyperplasia. On the other hand, such adipocyte alteration modifies capillary permeability: liquids flow away into the interadipocytic space, lipedema develops, and subsequent interstitial alterations occur. Thus, the third element favoring this disease is clear: fat tissue growth tends to aggravate venular capillary stasis.

We should always bear in mind that a volume increase of adipose tissue is associated with higher aromatization areas. But what does it all really mean?

Among women, 25% of androgen production occurs at the suprarenal level, another 25% occurs at the ovary, and the remaining 50% derives from peripheral conversion in muscular and fatty tissues, where androgens of low androgenic activity are transformed into powerful hormones like testosterone.

Within adipose cells—especially in the case of hypertrophic and hyperplastic cells (frequent in mixed obesity)—androgens undergo a different process. Because of aromatization, they are in fact transformed into lipogenic estrogens, thus deteriorating the prevailing conditions of an already lipodystrophic area and altering interstitial microcirculation even further.

It should be remembered, therefore, that such adipocyte alterations derived from hormonal disorders of the adipose tissue entail microcirculatory consequences due to compression and constitute the first step toward the transformation of localized adiposity into EFP.

There is obviously a close correlation between fatty tissue, microcirculation, and the endocrine’s constellation, as described earlier in the discussion of microvascular vasomotility. Therefore, microcirculatory conditions and alterations leading to adipocyte hypertrophy should also be taken in account.

The purpose of adipose tissue capillary network is to speed up flow velocity to favor adipose tissue performance. Wherever flow slows down, adipocyte hypertrophy ensues.

Common alterations include slowing down of capillary flow, adipocyte hypertrophy, and capillary permeability disorders leading to edema (lipedema and microedema).

The second term of this equation is associated with the circulatory unit and fat mobilization within the hypertrophic adipocyte that enables catabolite elimination.

Mechanical or hydrodynamical obstacles such as microaneurysm, stasis, and lipedemas prevent catabolite elimination. Alterations in glycosaminoglycans, in (pericapillar or perivenular) mucopolysaccharide sleeves, also have an influence on the diffusion phenomena.

ABOUT GLYCOSAMINOGLYCANS

Glycosaminoglycans are found in fibroblasts and include hyaluronic acid, dermatan, chondroitin-4-sulfate, el chondroitin-5 sulfate, dermatan sulfate, keratan sulfate, heparin, and heparinoids. When they are bound to a protein, glycosaminoglycans yield proteoglycans. Besides, mast cells produce heparin.

Ground substance fibroblasts, mast cells, and connective tissue provide the viscosity needed for molecule movement from and to the adipose cell.

When the amount of glycosaminoglycans increases disproportionately, viscosity increases and prevents molecule movement through the ground substance, thus leading to adipocyte hypertrophy.
The fact that 90% of triglyceride molecules is produced in the liver should also be taken into account: they reach adipose tissue through microcirculation and are included in fatty cells. The physiological journey of triglyceride molecules from the liver to adipose tissue depends on microcirculatory physiological conditions, hormone metabolic balance, a diet adequate for adipocyte physiological needs, and the physicochemical conditions of the ground substance.

Therefore, a proper performance of the peripheral transport and utilization system is essential, as well as performance of the cleansing organs like the liver. Thus, the essential role played by base regulation in the organism becomes evident (56–58).

Nowadays, the notion of a microcirculatory unit named “sausage” hypothesis has been suggested. It involves a close interrelationship among the microvascular-tissue unit in dermis, hypodermis, and muscle.

This is based on the fact that artery-arteriole anastomosis sites were found in small arteries (100–150 μm), in voluntary striated muscle networks that pass through the fascia or the aponeurosis in an upward direction and are later anastomosed with adipose tissue arteries. Additional small branches continue their upward route and anastomose with small arteries in the subpapillary dermal plexus.

This new theory of macro-angio-architecture has paved the way for understanding how modifications in one of the three elements involved (muscle, adipose tissue, or dermis) may benefit the remaining two.

Another important notion is associated with blood volume in the adipose tissue. Microcirculatory disorders of the adipose tissue derive from the total blood volume resulting from its own blood volume plus the additional volume provided by underlying striated muscle tissue and overlying dermal tissue.

Finally, we mentioned adipose tissue and microcirculation, but we did not describe what happens in the interstitium. Obviously, at the microcirculatory level, the increase in capillary pressure, the slowing down of circulation, the increased frailty, microaneurysms, and permeability alterations lead to element, protein, water, electrolyte, and amino acid leakage through the interstitium that entail structural and interstitial milieu complications.

The consequence is acidosis, disruption of the circulatory unit, and subsequent alterations in flexibility and diffusion due to the combined effect of acidotic lesions, microthrombosis, edema, lipedema, and lipolymphedema. This leads to sclerosis and fibrotic lesions that cause interstitial hypoxia.

Secondary complications of lymphatic vessels also lead to functional lymphatic insufficiency.

ETIOPATHOGENIC FACTORS

Clearly, among etiopathogenic factors leading to cellulite, we have included those of microcirculatory origin, those derived from hormone stimulation of adipose tissue, and those affecting the interstitium.

Therefore, this is what we find in adipose cells: nuclei shifted toward the periphery, a big fat droplet occupying nearly 90% of the cell, the nucleus and Golgi apparatus in lateral position, pericapillary and periadipocyte argentophilic fibers, and a capillary of 4 μm in diameter flowing inside the adipose lobe and associated with these blocking devices. All of them are related to the disease evolution, mainly characterized by lipedema, microaneurysms,
stasis, capillary deformation, and edematous transpiration due to hyperpermeable alterations of venule capillarity (lipedema), protein outflow, and progressive lipolymphedema.

Owing to the action of lipedema, adipocytes start dissociating and become distorted—a circumstance known as adipocyte anisopoikilocytosis. All this leads to macrovasculo-tissular alterations. In such adipose cells, nutrition is obviously inadequate, microcirculation is ill distributed, and ensuing adipocyte hypertrophy is inescapable.

An adipocyte hypertrophy effect on Renault’s network—formed by periargentophilic, pericapillary, and periadipocyte fibers—promotes a hyperplastic and hypertrophic reaction that generates procollagen.

The new procollagen fibers derive from argentophilic, pericapillary, and periadipocyte reticular fibers and are later transformed into collagen fibers, which enclose and distort adipocytes forming micro- and macronodules. Macronodules are palpable during the examination. They may be elastic-hard or sclerohyalinous and are essential for treatment selection and therapeutic response, which vary according to the macronodule pathology involved and subsequent skin retraction. A skin sagittal cut might show how these macronodules and retractile fibrosis generate dermis retraction and the typical “pothole” appearance characteristics of peau d’orange.

Hyperplasia and hypertrophy of pericapillary and periadipocyte argentophilic fibers are the characteristic symptoms of this disease.

Binazzi argued that, at the structural clinical level, three evolutionary stages might be noticed. The first one involves panniculosis derived from localized adiposity. Differences from localized adiposity may be summarized in adipocyte deformity and damage, small microhemorrhages, and fibrocystic proliferation. The second stage involves an upholstered “skin of the capitonné” type where fibroblastic reactions consolidate and adipocyte-deforming collagen proliferates. Slowly but continuously, these alterations lead to a fibrosclerotic condition mainly located in certain areas (abdomen, thighs, and internal side of knees). These complex clinical and ultrastructural conditions constitute the final stage of EFP.
In his book, Curri discusses localized adiposity and EFP, two separate processes of different pathogenesis and different clinical evolution, one of them developing flakes.

EFP involves venous alterations, especially at the macrocirculatory level. The determining pathogenic situation is recurrent edema of the adipose tissue with a concomitant venule-capillary permeability increase that unleashes the disease itself. In localized adiposity, the characteristic is adipocyte hypertrophy with preserved morphology, histochemistry, and biochemistry.

The main cause of adipocyte hypertrophy is associated with genetic and hormone evolutionary factors. Hence, EFP may be considered as a pathological process of the adipose tissue, whereas localized adiposity is borderline functional because no regressive adipocytic or stromal alterations may be detected.

THE TERM “CELLULITE”

We agree with Curri when he argues that the generic term “cellulite” should be discarded because it leads to diagnostic and therapeutic errors. Treatments should be different because etiopathogenesis and evolution are different. The term “cellulite” should be qualified somehow to avoid such confusions (59,60).

In other words, localized adiposity and EFP are two different stages of closely related clinical and semiological events. It might be said that EFP occurs on a favorable bed: hypertrophy of some areas of adipose tissue, especially in the lower limbs. Such localized adiposity provides the basis for the development of EFP.

Let us do without the term “cellulite” tout court, and substitute “cellulite” qualified by a specification of the pathology involved.

There are also references in the literature to cellulite being derived from venous-lymphatic insufficiency, but this is not always the case.
Because microcirculatory flow is slowed down, current literature mentions a stasis characteristic of hypotonic phlebopathy, because no sign of venous hypertension has been detected in this pathology. Such venous–capillary stasis with accompanying higher capillary permeability and edema leads to adipocyte damage, as many studies have confirmed, even at breast level. Partsch and coworkers (28) injected lymphography contrast liquid into subcutaneous tissue and found structural alterations of the adipose lobe in liposclerotic patients.

If we aim at establishing sound bases for treatment, all cases involving microcirculatory alterations that entail adipocyte hypertrophy should be taken into account, as well as disorders with manifest connective alterations or showing the typical hormone microclimate favorable to this disease (61–71).

There are many etiological and physiopathological factors. Hence, we are forced to suggest various therapies to achieve satisfactory results. Aesthetic pathology suggests global treatments that include cosmetic or biocosmetic therapies, physical therapies, medical techniques, and surgical techniques that have resulted in actual and effective solutions.
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### PATIENT HISTORY

Taking a patient history is the most important part of the initial patient interview; the recognition of small signs is important in the gathering of data to trace the significant etiological and pathophysiological stages of the pathology. An accurate patient history also enables the detection of possible complementary pathologies (1).

Important information includes:

- medical and family history
- obesity/diet
- diabetes
- hepatitis
- lipid and endocrine alterations
- bowel habits and conditions
- menstrual periods and estro-progestagen therapies
- bone fractures
- systemic diseases
- surgical history
- exercise
- nutrition
- food or drug allergies
- smoking and alcohol use
- previous therapies

### CLINICAL EXAMINATION

Clinical examination should be carried out, guided by patient history and progressing from general concerns to particular questions.

It should include:

- an examination of body structure and posture (Fig. 1)
■ checking for an altered position due to scoliosis and rotation, which may lead to hepatic or renal functional disorders and, in terms of aesthetics, may lead to a different distribution of trochanteric adiposity or cellulite in the back of the thigh
■ a static and dynamic foot study

Once the general examination is complete, local examination of cellulite areas is performed by:

■ inspecting and classifying the cellulite areas
■ checking for edema, lipedema, or lipolymphoedema
■ checking for lipodystrophy or localized adiposity (Fig. 3).

The objective examination should be carried out with the patient standing on a two-step ladder. This position enables the physician to assess posture and structure elasticity.
The patient should be barefoot and, if possible, be wearing only underclothes for a total body assessment. It should be remembered that consultation on cellulite should always include a breast examination for evaluating shape, symmetry, position, hormonal tension, and alterations of the hypodermic panniculi. As the ocular fundus shows arterial circulation, conditions of the lower part of the breast indicate the endocrine–metabolic situation of the patient. In fact, the same videocapillaroscopic alterations found in lower limb cellulite may be found in the breasts (1).

**INSPECTION**

Inspection allows assessment of local volumetric increase, aspect and color of the skin, varicose veins, telangiectasia or edema, and, especially, asymmetries and unaesthetic conditions. Such observations should be associated with the patient history. By the time the inspection is performed, the physician should already have an idea of the possible diagnosis (Fig. 4) (2).

**PALPATION**

Palpation allows us to determine the degree of edema, elasticity, and skin biomechanical capability, and also the presence of lipomatosis and adiposity, lipodystrophic nodules, and lipolymphoedema. It also helps to evaluate cellulite distribution and type (2).

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**Figure 4**

Asymmetrical adipositis (left side)

Asymmetrical adiposity.
POSTURE ASSESSMENT

The posture of the patient is assessed with a podograph. Observations should be associated with plantar support alterations of a limb that shows muscle spastic contracture or with a gross foot structural pathology. This condition leads to an inadequate stimulation of veno-lymphatic circulation and subsequent stasis. On the other hand, dynamic examination allows the physician to determine dynamic alterations. It should be possible, for example, to discover an ill-functioning healthy foot due to inadequate footwear (2).

PHLEBOLYMPHOLOGIC ASSESSMENT

This entails a simple manual and instrumental investigation. In the event of varicose disease, skin conditions should be assessed, detecting indicative signs such as dyschromia, dysthermia, telangiectasia, and edema. If instrumental examination is necessary, the condition of the superficial and deep venous system should be appraised—whenever an associated varicose pathology exists, the patient should undergo Doppler and echodoppler (duplex) studies (Fig. 5) (3,4).

ADIPOSE TISSUE ECHOGRAPHY

This routine procedure is aimed at certain areas:

- trochanteric region
- subtrochanteric region

Figure 5
Echodoppler.
Measurements should include dermal thickness between the epidermal hyperecho-
genic line and the deep dermal line, and adipose tissue thickness between the dermal hyper-
eghostic line and the hyperechogenic muscular fascia (Fig. 6) (5).

As Ceccarelli’s studies have proved, this examination not only shows the differences between localized adiposity and lipodystrophic panniculopathy, but also suggests the disease stage and provides control. Therefore, it is an apt procedure to select the best ther-
egapeutic strategy; above all, it helps the physician make a prognosis when performed with a 7.5 or 8 MHz transducer (Fig. 7) (6).

A 20 MHz scan C may be used for a more detailed study of skin surface.

LABORATORY INVESTIGATIONS

As a rule, it is advisable to investigate the patient’s general condition, even from a hemato-
chemical perspective, studying the following basic parameters:

- glycemia
- serum lipids
hepatic function
renal function
serum electrolytes
hemogram plus differential blood cell count
proteinogram

In the particular case of obesity or recurrent lipedema, further investigations should include:

- examination of thyroid functionality
- measurement of 24-hour urinary hormonal balance in the progestagen period of the menstrual cycle, detecting the 17-ketosteroids (normal values, 6–15 mg/hr), pregnanediol (normal values, 3–10 mg/hr), and follicle-stimulating hormone (122–48 mouse units).

ROM TEST

The so-called ROMs, or reactive oxygen metabolites, are a variety of free radicals characterized by an odd number of electrons in the outer oxygen orbit (2). They are extremely unstable and form highly reactive derived products in plasma and cells with good oxidizing power. When free radicals react with a conveniently buffered chromogen, they yield a colored complex measurable through photometry, with a maximum absorption peak of 505 nm. The amount of colored complex is directly proportional to free radical concentrations in accordance with the Lambert–Beer law.

This research method is based on the capability of metals to catalyze, once released, the chelated form from the carrier and to deposit proteins in plasma and cells—reactions of free radical formation according to Fenton’s reaction. It is known that this reaction,
which activates iron and removes calcium from vessel walls, is triggered when pH decreases and redox systems are altered, forming free radicals that are directly proportional to plasmatic peroxide. Results are expressed in Carr. Units. The value of 1 Carr. U. corresponds to a 0.8 mg% concentration of hydrogen peroxide. Normal values range from 200 to 250 Carr. U.

Unlike the test performed on capillary blood, which is not conclusive, the ROM test, when performed on venous blood, shows the oxidative capacity of plasma. This capacity is expressed by oxygen free radical release, a normal metabolic process in biologic systems and also a fundamental bactericidal as well as chemotactic defense mechanism.

When these free radicals increase, oxidative stress occurs and causes serious structural and functional damage, as complications from ozone infiltrations have clearly proved. The excess of free radicals also has a mutagenic effect on DNA. Measuring the amount of free radicals allows the evaluation of primary metabolic tissue alterations as well as enabling the monitoring of antioxidant therapies increasingly used in medicine.

When screening cellulitic pathologies, free radicals should always be investigated by means of the blood ROM test. Results higher than 250 Carr. U. indicate that nutritional and/or pharmacologic antioxidant therapy is required. Actually, the presence of free radicals becomes evident when damage is identified. At this stage, there is an alteration in pH resulting in acidosis, an alteration in tissue temperature with respect to core temperature, and an alteration in oxi-reduction systems that generate these pernicious free radicals. At this stage, the organism activates all its defense systems based on superoxide dismutase produced by the liver. Together with the vitamin systems of the intestinal lymphoadipose system, this enzyme controls free radicals. When the amount of free radicals is exceedingly high, degenerative alterations that result in lesions occur. At this stage, therapeutic efforts should be aimed at treatment instead of prevention.

**PRIMARY INSTRUMENT EXAMINATIONS**

**VIDEOCAPILLAROSCOPY**

The optical probe videocapillaroscope magnifies samples 10 to 1000 times, but a 200 magnification is normally used. The optic video terminal is a charge-coupled device (CCD) color high-resolution microtelecamera (greater than 500 TV lines). This videocapillaroscope works with an optical probe with epiluminescence and polarized light relayed to an image digitalization system. It is a scientific research method used for angiotectonic mapping, for studying microvessel responses to physical–mechanical and hemodynamic stimuli as well as endocrine responses, and for monitoring drug therapies. For aesthetic pathologies, it represents the basic examination tool for skin, for the diagnosis of localized adiposities and lipodystrophy, and also for monitoring therapeutic responses.

The patient should remain in the supine position in a thermoneutral environment and should not have smoked for the past two hours. Once the optical fiber is in contact with the skin, different morphological aspects of regional microcirculation may be studied, in particular the regional angiotectonic structure. Thus, blood microflow and aggregation or capillary alteration phenomena may be efficiently examined (Fig. 8).

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*a* The name “Carr.” refers to “Carratelli,” a biologist from Grosseto, Italy, who devised the test.
The videocapillaroscopy of optical probe (VCOP) permits a clinical diagnostic classification, which corresponds to histomorphological alterations and anatomo-topography of the adipose tissue.

The VCOP is a noninvasive method that analyzes capillaries in a static and dynamic form and, when joined to the process of digital images, transforms the qualitative characteristics to quantitative characteristics, allowing the physician to compare images taken at different times (Fig. 9).

The number of vertical capillaries increases after therapy, with an increase in the number of horizontal capillaries.

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**Figure 8**
Scope for videocapillaroscopy (scalar VL7 200×).

**Figure 9**
VCOP images before and after CO₂ injection into fat tissue. *Abbreviation:* VCOP, videocapillaroscopy of optical probe.
REFLECTED LIGHT PHOTOPLETHYSMOGRAPHY

This test enables assessment of the deep venous system in ambulatory conditions, as well as microcirculation and the effectiveness of the veno-lymphatic pump. Functional conditions of the venous foot pump may also be assessed. An infrared probe is placed on the medial part of the foot and then on the ankle. Subsequently, flexion and extension movements are required from the patient, while the equipment translates signals to a chart that qualitatively represents the dynamic functions of the lower limb and its pathological alterations. A short refilling time of the superficial capillary plexus, after the superficial blood has been pumped out of the lower leg with calf muscle stimulation, indicates reflux in the superficial and/or deep venous system with resultant venous hypertension. The evolution of veno-lymphatic and interstitial dynamics after eventual surgical or sclerosing procedures on varices may also be predicted through this test (Figs. 10, 11) (8).

ECHOGRAPHY/ULTRASOUND

Echographic examinations are performed with a 7.5 or 10 MHz probe. Venous perforator dimensions, muscular volume and conditions, and subcutaneous and adipose tissue dimensions are evaluated along with an examination of facial lesions. In particular, horizontal-plane alterations of the surface fascia may be appraised (Fig. 12) (5).
Figure 11
Reflected light photoplethysmography.

Figure 12
Alterations of surface fascia shown by echography.
DYNAMIC FOOT STUDY

The dynamic foot study (9) is performed with the patient walking on a platform, according to indications provided by Prof. Saggini from Florence. In addition, the Paromed System may be used via a small sole provided with many piezoelectric devices that is connected to a computer, which the patient holds while walking. The computer records the signals in different charts. The test indicates the etiology of localized cellulite and shows altered systemic functional conditions.

SECONDARY INSTRUMENT EXAMINATIONS

DOPPLER LASER

Doppler laser (10,11) is one of the most important tests for the diagnosis of cellulite pathologies and for therapy monitoring. With the aid of a laser microprobe connected to a Doppler probe for microcirculation, microvessel conditions may be detected and a complete study of flow functions is possible. When this system is connected to an oximeter, tissue-oxygenating conditions may be quantitatively evaluated and used to support systemic or local therapies. Vasomotility, i.e., periodic movements that show that interstitial matrix and connective tissue metabolism functionality, may also be studied through Doppler laser techniques because the connective tissue is not an inert support tissue but the substrate for all vital exchanges.

Due to its expense, this methodology has thus far been limited to particular cases, research, or high-level diagnostic-therapeutic studies. We believe that in the future it should be included in routine examinations for diagnosing cellulite pathologies, along with videocapillaroscopy and dynamic foot studies (Fig. 13).

DOPPLER

Today, the Doppler study (12) should not be considered a special examination tool, but a standard complement in the practice of general medicine. As routinely as the stethoscope...
is used for heart, lung, vascular sound, and intestinal peristalsis auscultation, the Doppler should be used for basic diagnosis of arterial and venous flows. Whenever vascular alterations are detected, a specialized examination through echodoppler or color echodoppler should be requested, even if this is suggested by the diagnosis of cellulite pathology (Fig. 14).

**Figure 14**
Echodoppler device.

**ECHODOPPLER**

Echodoppler/Duplex (12) and color echodoppler represent the most important specialized examination tools in cardiovascular pathologies or phlebology. In phlebology, the cause for varicose veins may be identified and a hemodynamic therapeutic, surgical, or sclerosing strategy may be selected. Normally, cellulite pathologies are not the effect but the cause of veno-lymphatic pathologies, especially when functionality is considered, instead of varicogenesis: Varicose veins should always be associated with foot pathologies or intra-abdominal hypertension. In the case of chronic venous insufficiency in uncompensated varicose veins, subcutaneous damage may also occur. It is characterized by lipodystrophy and phlebolymphedema. This demands addressing reflux and/or venous hypertension in addition to elasto-compressive therapies.
THERMOGRAPHY
Thermography (11) is not very popular among physicians due to variable and poorly reproducible results. Thermal plates are applied to the skin, and temperature is measured secondary to altered microcirculation and hypoxia. This technique is useful to assess advanced stages of connective tissue sclerosis and, therefore, revascularization (Figs. 15 and 16).

PHOTOGRAPHY
It is absolutely necessary to have photographic documentation of the patient at the first visit and after the first therapeutic cycle. If possible, photographs should be taken always under the same conditions, with black or blue background, preferentially against a grid or vertically striped curtain.

A total body photograph and a close-up photograph of areas of concern are essential. It should be recalled that, in compliance with laws that protect privacy, the patient must explicitly authorize the procedure. Thanks to the advances of digitalization, it is possible to scan photographs, and classify and monitor image evolution over time. Another advantage is the possibility of modifying these images to show the patient probable or improbable outcomes (Fig. 17).

DIAGNOSIS
Diagnosis should be as accurate as possible in order to identify the pathology that causes the unaesthetic feature in relation to the observed histopathologic and morphologic
alterations. It is essential to discern if the unaesthetic condition is related to one of the major endocrine-metabolic, dermohypodermic, or lipodystrophic syndromes; or if there is an association of different pathologies; or if it is an initial recurrent lipedema with chances for therapy.

With respect to “unaesthetic cellulite,” we must determine the distribution, consistency, and evolution.

**DISTRIBUTION**

According to distribution, cellulite can be classified as generalized or localized (13).

**Generalized Cellulite**

It may involve any or all regions and is always associated with alterations in fatty tissue distribution or a lipolymphoedema of diencephalic-hypophysial origin, i.e., endocrine origin.
Localized Cellulite

- **Face:** The cellulite may be located in the supraorbital or infraorbital regions. It is frequently painful. If there is no response to anti-inflammatory agents, the possibility of cellulite disease must be considered. Face senescence that starts with skin lipolymphoedematous and dystrophic alterations should always be ascribed, as regards its origin, to a functional alteration of cleansing processes, intestinal flora alterations, and free radicals.

- **Neck:** Here, the cellulite is a painful deformation that causes cervical pain. Frequently, it is related to intestinal flora alterations or Launois–Bensaude syndrome.

- **Trunk:** The cellulite produces pain and arthropathy. In presence of nodules, neoplastic and lipomatosis processes should be ruled out. Any cellulite pathology requires Endermologie® or endermatic treatment. Treatment should begin at the trunk and abdomen to activate neurophysiological reflex mechanisms and muscular relaxation.

- **Abdomen:** The cellulite is always accompanied by abdominal wall adiposity. Intestinal flora alterations, muscular stratum, and dermohypodermic panniculum should be treated. A nutritious diet is always required; today, we prescribe a high-protein diet (Fig. 18).
- **Lumbosacral region**: Here, the cellulite processes are very frequent, simulating low back pain causing rigidity and lumbar arthritis.

- **Lower limbs**: The areas most frequently affected are:
  - trochanteric region
  - medial knee
  - suprapatellar region
  - calf
  - posterior thigh

  In the thigh and the lower leg, cellulite is frequently associated with an edematous lymphatic pathology.

**CONSISTENCY**

Cellulite can be classified as hard, soft, edematous, or flaccid consistency (14).

**Hard Cellulite**

This is typical of young subjects with toned tissues. When skin is pinched, peau d’orange appears as an expression of dermal edema and lipedema. Normally, the area is rigid and
presents adherences between superficial and deep layers; the skin thickness is increased and the skin looks dry because it is poorly nourished and oxygenated due to blood and lymphatic vessel compression. Hard cellulite is typical in women who wear nongraduated elastic stockings or girdles. Endermologie and carboxytherapy are especially indicated for this pathology (Fig. 19).

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**Soft Cellulite**

It is typical of sedentary subjects or older subjects and is observed in patients who have undergone previous intense treatments involving mesotherapy with enzymes, ozonotherapy infiltrations, ozone vaporization, intense mesotherapy, liposuction with large cannulas, and excessive weight reduction. All these treatments, which reduce limb circumference, disrupt hyaluronic acid molecules and proteoglycans and result in a loss of connective tissue support systems with collapse and loss of tissue tone. Flaccidity rarely depends on reduced
muscular tone. It is just a structural or metabolic collapse of tissues that simply give way and is frequently iatrogenic.

Peau d’orange becomes evident even without pinching the skin. Videocapillaroscopy shows hyposphygmic signs and vascularization deficiency; echography shows a morphologic degeneration of the horizontal connective structure. In these subjects, it is possible to find some varicosities due to short refluxes because of lack of support at the muscular fascia level. Capillaries with hemodynamic flow deficiencies are also observed. Superficial carboxytherapy is initially indicated to vascularize tissues, followed by long periods of reconstructive Endermologic treatment (Fig. 20) (15).

**Edematous Cellulite**

Edematous cellulite is primarily found in young patients who take estro-progestagens. It is the so-called “youth cellulite,” of the endocrine-metabolic type, with thick legs that have important physical or psychoemotional sequelae. It is frequently the expression of Dercum’s syndrome or of the traditional lipolymphoedema with lipodystrophy. The peau d’orange sign may be detected early, and a proper diagnosis is needed to discard edematous pathologies. It is a pathology that eventually causes serious arthritic, metabolic, and hormonal sequelae. The aesthetic condition is always affected and most difficult to solve. It requires a base treatment with Endermologie and leg mesotherapy or carboxytherapy on the thighs and abdomen (Fig. 21).

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**Figure 20**
Soft cellulite.
Mixed Cellulite

Normally, the forementioned cellulite pathologies are not found as pure entities but as mixed entities. For example, one may find hard cellulite in the anterior thigh combined with edematous cellulite in the knee and leg. Bitrochanteric lipodystrophy with flaccid cellulite in the internal thigh is characteristic (16,17).

EVOLUTION

Four stages may be noticed:

1. *Metabolism alteration at the interstitial matrix level.* This is frequently accompanied by recurrent lipedema.
2. *Diencephalic and endocrine dysfunction with alteration of local peripheral insulin and lipidic metabolism.* An alteration of hyaluronic acid and mucopolysaccharides is observed with altered ground substance and extracellular fluid. There is an initial lipodystrophy.
3. *Tissue congestion of the lymphatic type with painful tumefaction, lipoymphoedema, and abdominal strain.* Frequently, it is accompanied by the presence of herpes simplex as a result of a reduced immune function due to intestinal flora disorders. There is also a local and systemic neurophysiological disorder due to the alteration of the ionic pump.

*Figure 21*

Edematous cellulite.
4. **Connective tissue alterations.** They hinder veno-lymphatic microcirculation and increase lymph density as well as interstitial ground substance viscosity. Connective tissue fibrosclerotic alterations derived from initial mucoid “geloide” (gel-like) fibroedema and interstitial connective fibrosclerosis may be noticed.

### THERAPEUTIC STRATEGY

Once clinical diagnosis is complete, a therapy aimed at a gradual recovery of the different histopathological, functional, and aesthetic tissue disorders can be devised. Our therapy involves strategic, tactical, methodological, technical, and control measures.

- **Strategical measures** constitute the initial phase focused on an overview of the whole treatment; for example, a six-month treatment involving four methods—cleansing therapy, carboxytherapy, Endermologie®, and mesotherapy—and a high-protein diet.
- **Tactical measures** are intended to put strategy into practice. For example, a cycle of one session twice a week during the first two months may be devised, followed by a session once a week for the remaining months. Initially, treatment may be associated with carboxytherapy before subdermic therapy techniques are applied prior to local treatments, plus a 15-day cleansing therapy and diet.
- **Methodological measures** involve describing the different methods applied; e.g., in the case of carboxytherapy, the CO₂-automated injection system with flows of 50 × 3 minutes per limb should be used. The cleansing therapy will consist of hydroxocolonotherapy associated with the traditional therapy for intestinal flora recovery. For subdermal therapy, Endermologie® should be used in programs for “edematous cellulitis” and “structural recovery.”
- **Technical measures** involve foreseeing the use of different methods according to specific needs. In the case of carboxytherapy, either the micropercutaneous approach or direct infiltrations may be used.
- **Control** refers to histopathologic and evaluative checkups that may eventually confirm the selected therapeutic strategy. Normally, there is a control visit and a therapist meeting after each six- or eight-session cycle in order to adjust diagnosis and therapeutic conditions. These meetings and the physiotherapist’s appraisal are of utmost importance, because ultimately the therapist perceives the patient’s sensations and symptomatology as the cellulite therapy progresses. In fact, it is a chronic therapy for a disease that is frequently evolutive and gets worse, due to perpetuation and worsening of intestinal flora alterations and endocrine-metabolic disorders, not to mention today’s lifestyle, usually sedentary and reckless from a nutritional or environmental point of view.

### MEDICAL HISTORY

Data collected during consultation, diagnosis, and therapy should be recorded in a medical history that must be updated after each session and reviewed after every six or eight sessions. Medical history should include the patient’s structural diagram, details of the cellulite areas, a possible therapeutic strategy, and photographs from different angles taken.
during the first visit, halfway through therapy, and at the end of treatment. Maintenance therapy may vary, being just dietary–hygienic and physical (diet and cycles of monthly sessions of Endermologie®), or medical–physical (monthly sessions of carboxytherapy or mesotherapy plus subdermal therapy) (2).

As for the measurement of bitrochanteric, knee, and calf circumference, we believe they are not important. We know, in fact, that frequently circumference reduction is combined with tissue alterations and loose tissue. Circumference reduction due to a decrease in excessive adipose tissue—subcutaneous or steatometric—is different from circumference reduction in the cellulite pathology. This difference should be thoroughly explained to patients to discredit false popular beliefs.
REFERENCES

### A. TYPICAL MEDICAL HISTORY INTAKE FORM

<table>
<thead>
<tr>
<th>City:</th>
<th>Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr/Mrs:</td>
<td>Address:</td>
</tr>
<tr>
<td>Tel.:</td>
<td>Age:</td>
</tr>
</tbody>
</table>

**Complaint and/or motives:** (Clinical, prevention, control, aesthetic)
(Description of symptoms)

**Past medical history:**

**Family history:**

**Allergies:**
- ☐ Yes
- ☐ No

**Smoker:**
- ☐ Yes
- ☐ No

**Hepatitis:**
- ☐ Yes
- ☐ No

**Diabetes:**
- ☐ Yes
- ☐ No

**Exercise:**
- ☐ Yes
- ☐ No

**MEDICAL HISTORY:**
- **Deliveries:**
- **Surgeries:**
- **Diseases:**
- **Therapies:**

**Current Medical History:**
- **1. Gastrointestinal:**
2. Hemorrhoids:  □ Yes  □ No
3. Menstrual cycle: ____________________________________________
3. Hormones: _________________________________________________

EXAMINATION

ARTERIAL SYSTEM:

VENOUS SYSTEM:
R (Right): _________________________________________________
L (Left): _________________________________________________

LYMPHOADIPOSE SYSTEM:

CUTANEOUS SYSTEM:

LOCOMOTOR SYSTEM AND FEET:

Notes: ROM test: _____________________________________________

Cellulitic pathology
Localization: _________________________________________________
Type: ______________________________________________________
Echography _________________________________________________
Videocapillaroscopy __________________________________________
ROM test __________________________________________________
VEGA expert test ____________________________________________
CLINICAL INSTRUMENT CLASSIFICATION OF CELLULITE PATHOLOGY:

Cellulite pathology code: __________ // __________ // __________ // __________

Clinical instrument examination: __________________________________________________________________________

THERAPEUTIC STRATEGY:

Suggested:
Medical therapy:
Phase 1: Cleansing: __________________________________________________________________________________________
Phase 2: Maintenance: __________________________________________________________________________________________

SPECIFIC THERAPY:
Carboxytherapy: _____________________________________________________________________________________________
Endermologie®: ______________________________________________________________________________________________
Mesotherapy: _________________________________________________________________________________________________
Diet: ______________________________________________________________________________________________________

SURGICAL THERAPY:

LOCAL THERAPY:

LIFESTYLE:
### B. EXAMPLE OF MEDICAL HISTORY

<table>
<thead>
<tr>
<th>City:</th>
<th>Arezzo</th>
<th>Date:</th>
<th>January 2, 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr/Mrs:</td>
<td>PAOLA ROSSI</td>
<td>Address:</td>
<td>Florence</td>
</tr>
<tr>
<td>Tel.:</td>
<td></td>
<td>Age:</td>
<td>27, sedentary</td>
</tr>
</tbody>
</table>

Complaint and/or motives: Aesthetical reasons, cellulite with swollen legs, including foot and calf swelling, which started unexpectedly in summer. Reports evening edema, pain, and heaviness.

Past medical history:

Noncontributory

Family history:

Positive to vasculopathy

| Allergies: | ☐ Yes | ☑ No |
| Smoker: | ☑ Yes | ☐ No |
| Hepatitis: | ☐ Yes | ☑ No |
| Diabetes: | ☐ Yes | ☑ No |
| Exercise: | ☐ Yes | ☑ No |

**MEDICAL HISTORY:**

Deliveries: Two

Surgeries: Appendectomy; tonsillitis episodes

Diseases: Mild overweight

Therapies:  

Current Medical History:

1. Gastrointestinal: **Regular**
2. Hemorrhoids: ☐ Yes ☑ No
3. Menstrual cycle: **Regular**
4. Hormones: **Estro-progestagens since 3 years ago**
EXAMINATION

ARTERIAL SYSTEM:
No lower limb arteriopathy

VENOUS SYSTEM: Normal deep veins, with normal valves
R (Right): NO Varicosis saphena—small saphenous vein normal
L (Left): NO Varicosis saphena—telangiectasia due to knee hyperextension—small saphenous vein normal

LYMPHOADIPOSE SYSTEM:
Mixed adipoedematous hypodermatosis with adiposity in flanks and culotte de cheval.
Lymphedema with positive Semmer test.

CUTANEOUS SYSTEM:
No special features.

LOCOMOTOR SYSTEM AND FEET:
Lower limbs dysmetria + pes valgus varus to the left with thrust deficit and takeoff alteration.

Notes: ROM test: 293 Carr. U.

Typical primary lymphedema observed that started unexpectedly in summer, as usual. Adipoedematous cellulitis with localized adiposity and true bitrochanteric culotte de cheval–knee lymphedema.

Cellulitic pathology
Localization: ________________________________
Type: ________________________________
Echography ________________________________
Videocapillaroscopy ________________________________
ROM test ________________________________
VEGA expert test ________________________________

CLINICAL INSTRUMENT CLASSIFICATION OF CELLULITE PATHOLOGY:
Cellulite pathology code: G1a/S2/V3/A1a-b
Clinical instrument examination: Photoplethysmography-podoscopy-videocapillaroscopy
THERAPEUTIC STRATEGY:

Suggested:

Medical therapy:
Phase 1: Cleansing: Cellulase gold 3 per day
Phase 2: Maintenance: Cellulase gold 2 tablets/day +

SPECIFIC THERAPY:
Carboxytherapy Carboxytherapy six sessions one/week
Endermologie Endermologie® twice a week during one month
Mesotherapy Mesotherapy once a week in calves
Control within 30 days
Diet Hyperprotein 15 days

SURGICAL THERAPY:
Liposculpture in culotte de cheval and knees

LOCAL THERAPY:
Functional plantar + panty hose 15 mm/Hg

LIFESTYLE:
• Walk frequently
• Pay attention to stypsis and control weight
INTRODUCTION

Cellulite is an accepted term for describing an aesthetic problem called the “orange peel effect,” which causes some dimpling of the skin. Cellulite, which affects about 90% of women, is usually associated with lipodystrophy, localized on the thigh, buttock, and hip (1,2).

Histologically, some authors report modifications of the dermal–hypodermal interface, and describe different patterns of the architecture of fibrous septae in adipose tissue in women with cellulite (3,4). Also an increase in the volume of adipocytes in women with cellulite as well as alterations of the lymph vessels and blood circulation has been reported (5).

Few studies have been performed in vivo with noninvasive methods. Most of them use imaging modalities, i.e., ultrasound (US) (6,7), magnetic resonance (MR) imaging (8,9), and dual X-ray absorptiometry (10,11).

In this chapter, we will present a comparison of the skin and adipose tissue properties in women with cellulite compared to normal women without visible signs of cellulite. We used in vivo high-frequency US imaging for skin characterization, and high-spatial-resolution MR imaging and spectroscopy for adipose tissue characterization.

MATERIALS AND METHODS

SUBJECTS

Forty-four healthy women participated in the study, which was approved by the hospital ethics committee. The subjects were recruited by a medical expert according to the following main inclusion criteria—age range: 18 to 45 years; body mass index (BMI): 17 to 27; constant weight during the last year; regular menstrual cycle; and between 0 and 10 days postmenstruation at the date of the experiment. The volunteers were divided into two
groups by experienced medical personnel: women with no visible cellulite even after compression at the study sites \((n = 21, \text{age} = 23.5 \pm 3.4, \text{BMI} = 18.04 \pm 0.65)\) and women with clear visible cellulite with and without compression \((n = 23, \text{age} = 33.6 \pm 8.1, 8.1, \text{and BMI} = 25.78 \pm 1.42)\).

**US IMAGING**

High-frequency US imaging was performed with our home-built scanner equipped with a focused 25 MHz transducer offering an axial resolution of 70 µm and a lateral resolution of 130 µm (12). Series of 64 cross-sectional images \([\text{field-of-view (FOV)} = 4 \text{mm} \times 20 \text{mm} \times 20 \text{mm}]\) were acquired on the upper dorsal thigh (Fig. 1), and on the hip. From these images, the thickness of the skin was measured as well as the topography of the dermal–hypodermal interface.

**Figure 1**

In vivo high-frequency US imaging of skin on the thigh. A resolution of 70 µm in the direction perpendicular to the skin surface allows a clear visualization of hypodermal indentations \(\rightarrow\) within the dermis, and a precise measurement of the skin thickness \(\Rightarrow\).

**MR IMAGING**

High-spatial-resolution MR images were obtained by connecting to a standard 1.5 T whole-body MR scanner, a dedicated skin-imaging device comprised of a surface gradient coil and a high-sensitivity receiving coil (13). With an in-depth resolution of 80 µm,
epidermis, dermis, hypodermis, and fibrous septae within the hypodermis were clearly differentiated. A series of 60 contiguous images at high spatial resolutions were acquired on the upper dorsal thigh (FOV = 18 mm × 50 mm × 30 mm). Firstly, with an in-depth resolution of the skin of 80 μm, the Camper’s fascia was clearly visible and allowed differentiation of the superficial adipose layer from the deep adipose layer (Fig. 2). Secondly, with a slice thickness of 0.5 mm, the 3-D architecture of the fibrous network could be analyzed within a fat volume of 20 mm × 20 mm × 20 mm.

**Figure 2**
In vivo MR imaging of skin and adipose tissue. An in-depth resolution of 80 μm of the skin and a slice thickness of 0.5 mm offer an optimal contrast between fat lobules and fibrous septae.

---

**MR SPECTROSCOPY**
Localized spectra (Fig. 3) were obtained in an area of interest about 2 mm × 5 mm × 6 mm to describe the lipid components and the water fraction within a fat lobule.

**STATISTICS**
Data were analyzed with SPSS software (SPSS, Chicago, Illinois, U.S.A.). All results were expressed as mean ± standard deviation. *p*-Values < 0.05 were considered to be significant.
RESULTS

SKIN THICKNESS

Table 1 shows the values of the skin thickness measured by US imaging on both sites. Women with cellulite characteristically have thicker skin on the upper dorsal thigh compared to normal women ($p = 0.026$).

ADIPOSE THICKNESS

Table 2 shows the thickness values of the adipose layers measured by MR imaging on both sites. Women with cellulite have thickened adipose layers compared to normal women ($p < 0.0001$ on the hip, and $p < 0.0001$ on the upper dorsal thigh). Furthermore, the increase is much greater in the deep adipose layer than in the superficial layer in women with cellulite (Fig. 4).

Table 1
Mean Values (±SD) of Skin Layer Thickness Measured by US Imaging on the Hip and Thigh According to Presence of Cellulite

<table>
<thead>
<tr>
<th>Skin thickness (mm)</th>
<th>Hip</th>
<th>Thigh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women with cellulite</td>
<td>1.70 ± 0.31</td>
<td>1.67 ± 0.25</td>
</tr>
<tr>
<td>Women with no cellulite</td>
<td>1.59 ± 0.20</td>
<td>1.51 ± 0.19</td>
</tr>
<tr>
<td>$p = 0.19$</td>
<td>$p = 0.026$</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.
3-D ARCHITECTURE OF ADIPOSE TISSUE

A 3-D topography of the interface between dermis and hypodermis was assessed after processing of the series of US images (Fig. 5).

Two experts scored the images with an index defined on the heights of adipose indentations and number of indentations on a four-level scale. Results are summarized in Table 3. No statistical difference could be established between experts, whereas the index of irregularity was significantly higher in women with cellulite ($p < 0.0001$ on the hip, and $p < 0.0001$ on the upper dorsal thigh).

The second step is aimed at describing the 3-D architecture of the fibrous septae within the adipose tissue. After image processing of the series of MR images (Fig. 6), only

---

**Table 2**

<table>
<thead>
<tr>
<th>Adipose thickness (mm)</th>
<th>Hip</th>
<th>Thigh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women with cellulite</td>
<td>53.1 ± 10.1</td>
<td>34.0 ± 5.4</td>
</tr>
<tr>
<td>Women with no cellulite</td>
<td>20.0 ± 6.4</td>
<td>8.3 ± 2.4</td>
</tr>
<tr>
<td>$p &lt; 0.0001$</td>
<td>$p &lt; 0.0001$</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviation: SD, standard deviation.*

**Figure 4**

New characteristic marker of cellulite, MR imaging shows that women with cellulite have a much greater increase in the thickness of the deep inner adipose layer compared to women without cellulite.
fibrous septae are visualized. Camper’s fascia is clearly seen as a thin plane structure more or less parallel to the skin surface. Other septae were detected as pillar-like structures. The percentage of fibrous septae was calculated in three directions: perpendicular, parallel to the skin surface, and tilted at about 45° (Fig. 7).

On the upper dorsal thigh, women with cellulite have higher percentages of perpendicular septae \( (p < 0.001) \) and septae at 45° \( (p < 0.001) \), and a smaller percentage of septae parallel to the skin \( (p < 0.001) \) compared to women with no cellulite.

<table>
<thead>
<tr>
<th>Irregularity index</th>
<th>Hip</th>
<th>Thigh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women with cellulite</td>
<td>3.36 ± 0.81</td>
<td>3.50 ± 0.89</td>
</tr>
<tr>
<td>Women with no cellulite</td>
<td>1.20 ± 0.84</td>
<td>1.47 ± 1.02</td>
</tr>
<tr>
<td>( p &lt; 0.0001 )</td>
<td>( p &lt; 0.0001 )</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviation: SD, standard deviation.*
**Figure 6**
Visualization of the 3-D architecture of fibrous septae in subcutaneous adipose tissue after image segmentation of 3-D MR images: (A) woman with cellulite; (B) woman without cellulite.

**Figure 7**
Structured patterns of the fibrous septae network according to presence of cellulite. Quantitative findings give more evidence about the heterogeneity in the directions of the septae, and highly suggest that modeling the 3-D architecture of fibrous septae as a perpendicular pattern in women with cellulite would be an over simplification.
Table 4
Mean Values (±SD) of Lipid Components and Water Fraction Measured by MR Spectroscopy on the Thigh According to Presence of Cellulite

<table>
<thead>
<tr>
<th></th>
<th>Water</th>
<th>Unsaturated lipid components</th>
<th>Saturated lipid components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women with cellulite</td>
<td>6.3 ± 5.8</td>
<td>7.4 ± 2.5</td>
<td>86.4 ± 6.6</td>
</tr>
<tr>
<td>Women with no cellulite</td>
<td>9.1 ± 6.4</td>
<td>8.2 ± 2.6</td>
<td>82.7 ± 6.3</td>
</tr>
<tr>
<td><em>p</em></td>
<td>0.146</td>
<td>0.275</td>
<td>0.074</td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.

LIPID COMPONENTS AND WATER FRACTION IN ADIPOSE TISSUE

Saturated and unsaturated lipid components as well as the water fraction measured in proton spectra are listed in Table 4. There was no difference with regard to cellulite.

**DISCUSSION**

High-spatial-resolution imaging methods are of high interest not only for obtaining in vivo anatomical details of the different skin layers, epidermis, dermis, and hypodermis, but also for their ability to give physiologic information through the measurement of intrinsic parameters such as US attenuation, and MR parameters such as relaxation times and proton density. Moreover, biochemical quantification can be obtained by MR spectroscopy.

High-frequency 3-D US is a very efficient method for skin imaging. Our results confirmed an increase in skin thickness as well as the presence of deep indentations of adipose tissue into the skin in women with cellulite (6,7).

MR imaging assessed an increase of adipose tissue in women with cellulite on both the analyzed sites. At high spatial resolutions, Camper’s fascia, as formerly demonstrated by histology (14), was clearly detected in vivo, so that the superficial and deep adipose layers could be measured independently. A thicker deep adipose layer appears as a notable marker of cellulite. After image processing of 3-D MR images, Camper’s fascia appeared as a thin plane structure “parallel” to the skin surface, and vertical septae as pillar-like structures in contradiction with straight planes proposed in diagrams by Nurnberger, although fine details of the fibrous network, which is typically 30 to 70 µm in thickness (unpublished personal histological pictures), remain undetected; our findings, however, allow quantification of the main directions of this fibrous network. In women with cellulite, we found a higher percentage of septae perpendicular to the skin surface and a smaller percentage parallel to the surface. In some aspects, our results are in agreement with those of Nurnberger, but this present work gives more evidence about the heterogeneity in the directions of the septae. These findings highly suggest that modeling the 3-D architecture of the fibrous septae network as a perpendicular pattern in women, whereas as crisscross in men, would be an over simplification.
Concerning the changes in the physiology of the adipose tissue in the presence of cellulite, it is still a matter of controversy. We evaluated the unsaturated lipid fraction, the saturated lipid fraction, and the water fraction. Values were similar for both groups indicating the absence of any biochemical modification within a fat lobule in women with cellulite. These findings are in good agreement with other studies where no differences in saturated and unsaturated fatty acids in normal adipose tissue were reported (15).

Our MR findings did not confirm the hypothesis of an increase in water content of subcutaneous adipose tissue in case of cellulite as suggested by some authors (5), except if excess water was located in the connective septae, because our measurements were strictly limited within a fat lobule. Unfortunately, this hypothesis will be extremely difficult to confirm by an MR study, as in vivo MR spectroscopy does not have enough sensitivity to acquire a localized spectrum within a single connective septum.

In conclusion, high-spatial-resolution imaging methods allowed us to go a step further in the knowledge of in vivo cellulite anatomy and physiology. Our results revealed some modifications of skin and adipose tissue anatomy in women with cellulite, but no clear physiological modification within fat lobules. This study will help in the future to assess the efficacy of new slimming products.
REFERENCES

INTRODUCTION

Cellulite represents an unaesthetic condition that requires a precise diagnosis and therapeutic treatment. Therefore, an adequate clinical classification is essential before starting physical therapy or medical, surgical, or cosmetic treatments. The attempt to classify cellulite is as old as the history of the first description of cellulite but, because it is difficult to define and register the pathophysiologic evolution of cellulite, it is difficult to define a true classification. In the recent past, there have been various attempts at classification that followed the evolutionary and physiopathological theories. Today, it is agreed that cellulite can be described as a predominantly interstitial endocrine–metabolic pathology (1–7).

BINAZZI’S CLASSIFICATION

The first attempt at classification was by Prof. Binazzi, the famous vascular medicine physician from Bologna University, in 1978. He divided the cellulite into three clinical classes (Fig. 1).

Clinical aspects

1. Soft cellulitis
2. Hard cellulitis
3. Mixed cellulitis

Figure 1
First clinical classification of cellulite by Prof. Binazzi.
Prof. Binazzi classified cellulite as “soft,” which is characterized not by adherent tissue to the deep planes; “hard,” which represents the adipose cellulite with tonic tissues adherent to the deep planes, and “mixed,” an intermediate between the two. Today Binazzi’s is the clinical classification that is most often used in practice; it is easy but does not have the ability to analyze the pathophysiology because it is merely descriptive (8).

CURRI’S CLASSIFICATION

This classification was proposed in 1988 by Prof. Curri, chair of molecular biology in the University of Milan. It is the first true classification that is founded on scientific data. It constitutes the first attempt at classification to aid in pathophysiologic research. It is based on the characteristics of thermography, offering the possibility of having reproducible pictures that can be randomized and computerized (9–11). Curri described five classes characterized by different types of temperature patterns revealed by plotting the microcirculation and oxygenation (Fig. 2).

BARTOLETTI’S CLASSIFICATION

This classification is limited to the external aspect of the tissues; it has clinical value in the diagnosis of superficial aspects of cellulite. Although it does not have scientific value, it is useful in daily evaluation of patients (12,13). It repeats the classification of Binazzi adding a fourth grade class, named as “false cellulite” (Fig. 3).

“False” or “not true” cellulite is characterized by flabby tissues, in excess and not adherent to the deep planes, with scarce muscular tonicity. This situation does not require treatment but only electric stimulations or exercise. We believe that this classification is not exact, because the pathological picture is reported as a structural state. Rather, our
clinical and pathophysiological diagnosis would classify this so-called “not true” cellulite as “true” cellulite that can fall into type 4 of the Curri classification. In fact, from the diagnostic point of view, this form of cellulite is confirmed by an abnormal thermographic test representing microcirculatory alteration, lipodistrophy, and all aspects of the cellulite.

The idea of Prof. Bartoletti to speak about a “Not true cellulite” can be useful to remember that this class of cellulites does not require active treatments, as mesotherapy or carboxytherapy or liposculpture. Used in this cellulite, these treatments can cause more aesthetic pathologies and prolapse of the skin.

### BIMED CLASSIFICATION

This classification suggests a comprehensive therapeutic approach; that is to say, a protocol for cellulite pathologies named BIMED or “biorheological integrated method with Endermologie® and dynamic system.” The methodology named Endermologie® is described in this book in Chapter 11.

The acronym BIMED also points out the initials of those people that conceived and improved upon this classification (Bacci from Arezzo, Izzo from Naples, and Mariani from Siena in 1998 were working about cellulite and phlebolymphedema in the Phlebology Center of the University of Siena with the director Prof. Sergio Mancini) (14–16). This classification involves a more comprehensive and differentiated frame for the various psychopathological and pathological manifestations of cellulite (Fig. 4).

This classification is based on various reference pictures that give a score or number that allows one to build a final code that expresses the entire pathology for research
purposes. The concept derives from the classification of CEAP, which is the classification universally recognized and adopted for classifying venous and lymphatic illnesses—a classification that allows one to standardize clinical studies. The acronym CEAP represents the initial of the classes of classification: C-clinical, E-ethiopathology, A-anatomy, P-physiopathology. It may be useful for planning a more accurate comprehensive therapeutic strategy for collecting epidemiological statistics, and also for therapeutic monitoring. Four main issues may be identified (Fig. 5).

Each group in the classification identifies a characteristic or a particular group of pathologies.

First group (Fig. 6): Indicates the patient’s constitutional type (A as android, G as gynoid, and N as normal) and the presence of objective and subjective symptoms such as heaviness, paresthesia, and pains herein classified as 1 and 2. The small letters a and b indicate what led the patient to consultation: (a) aesthetic motivation and (b) medical motivation. In the case of aesthetic motivation, the physician should ensure aesthetic results besides medical improvement—a twofold target that requires different and specific security measures.

Second group (Fig. 7): Indicates the patient’s constitutional and nutritional characteristics (M for lean patients, S for patients who are overweight, and I for ideal patients). These three groups may be further divided into subgroups indicating the presence or absence of lipodystrophic alterations (1 indicates mild lipodystrophy and 2 indicates advanced lipodystrophy).

M: Lean patients
   a. Showing mild lipodystrophy
   b. Showing advanced lipodystrophy

S: Overweight patients
   a. Showing signs of
      1. Overweight
      2. Slight obesity
      3. Regular obesity
      4. Hyperobesity
   b. Showing mild lipodystrophy
   c. Showing advanced lipodystrophy
**BIMED**

- **Type of structure**
  - A: Android
  - G: Gynoid
  - N: Normo-type

**Sub-groups**

1. Subjective symptoms
2. Without subjective symptoms
   - a) aesthetical motivation
   - b) clinical motivation

---

**Figure 6**

I: Ideal patients
   a. Showing mild lipodystrophy
   b. Showing advanced lipodystrophy

   Third group (Fig. 8): Indicates the three main lesion types characterizing cellulite: lipedema, veno-lymphatic vasculopathy, and cutaneous flaccidity (connective tissue pathology) due to subcutaneous connective damage.

L: Lipedema
   a. Mild lipodystrophic alterations
   b. Advanced lipodystrophic alterations

V: Veno-lymphatic vasculopathies
   1. Showing “varicose disease”
      a. Plus mild lipodystrophy
      b. Plus advanced lipodystrophy
   2. Showing “veno-lymphatic insufficiency”
      a. Plus mild lipodystrophy
      b. Plus advanced lipodystrophy
      c. Plus soft lymphedema
      d. Plus hard lymphedema
      e. Plus lipolymphedema
      f. Plus mild lipodystrophy
      g. Plus advanced lipodystrophy

F. Cutaneous flaccidity (cutaneous hypotrophy of connective origin)
   1. Incipient
      a. Showing mild lipodystrophy
      b. Showing advanced lipodystrophy

Figure 7
A case classified as “S,” an advanced lipodystrophy in overweight patient.
**BIMED**

- **Groups of cellulitic pathologies**
  - L: Lipedema
  - V: Vasculopathy
  - F: Cutaneous flabbiness

- **Surgical indications**
  - A: Localized adiposity
  - G: Lipodystrophy

Figure 8
This figure shows the three different groups of pathologies that require further study: vascular, hormonal, and status of the skin. The indications for surgical treatments must be investigated as well.
2. Advanced

*Fourth group:* Indicates the presence of localized or diffuse adiposity liable to surgical treatment.

A: Localized adiposity

a. Genuine *culotte de cheval* (Fig. 9)

b. False *culotte de cheval*
   1. In abdomen and flanks
   2. In knees and legs
   3. In trunk and arms
   4. Diffuse

*The BIMED code (Fig. 10):* The development of these various pictures allows one to get a final code that offers complete individualization for the type of cellulite and the structure of the patient. Numerical subgroups correspond to the regions affected. For example, the following code is typical: G1a/S1/L2V5/A2ab.

---

**Figure 9**

We can see the typical localized adiposities called culottes de cheval, which represent the typical indication for surgical liposculpture.
From these discussions, the following classification is suggested. It is based on clinico-therapeutic considerations aimed at comprehensive treatment of local and systemic histopathological alterations characteristic of cellulite. For example, within the first group, patients are classified into android, gynoid, or normal type. From the very beginning, this provides indications of local endocrine pathologies and, therefore, of a certain type of constitution. It also provides prognostic indications. Among gynoid patients, Barraquer–Simmons types are more frequent than Launois–Bensaude types. In the presence of lower limb symptoms, presumptive diagnosis may be oriented toward veno-lymphatic insufficiency (lipolymphedema or phlebo-lipolymphedema), which, in turn, suggests eventual therapeutic results.

Wherever phlebo-lymphological symptoms are found, the following treatments should be considered:

- Mesotherapy with phlebotonics
- Sequential pressure therapy
- Manual lymphatic drainage
- Carboxytherapy
- Endermologie treatment
- Use of elastic hose

In the absence of phlebo-lymphological symptoms, nonvascular causes should be investigated. The patient’s motivation is essential because—besides the information it provides—it also indicates actual psychophysical conditions.

Other groups of patients, for example as S3 (patients with medium obesity) must be treated as patients with multifactorial functional diseases and they must be referred to an endocrinologist or a nutritionist.

Prior consent of the patient is required for the following treatments:

- Intake of a cyclic high-protein diet alternated with hyponutritional balanced diet
- Oxygenclasis
- Systemic Endermologie® (action of lymphatic drainage, lipolysis, and depuration)
- Eventual liposculpture associated with postsurgical Endermologie® (drainage/stimulation/invigoration) and carboxytherapy

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**Figure 10**

The result is a final code that contains all criteria to identify our patient and the cellulite. This code can help choose the best method of treatment.

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**BIMED**

A – G - N / Type of structure
M – S-1 / Type of structure and nutrition
L-V-F / Groups of cellulitic pathologies
A - G / Surgical indications

**Gla / S1 / L 2- V5 / A 2ab**
In group S4 (hyperobese patients): The patient should be referred to a specialist. Prior consent of the patient is required for the following treatments:

- Prolonged intake of a high-protein diet alternated with hyponutritional balanced diet
- Mesotherapy
- Systemic Endermologie\textsuperscript{\textregistered} (action of lymphatic drainage, lipolysis, and depuration)
- Local treatment as required
- Consideration of eventual surgery with gastric banding
- Nonindication of liposculpture

In group V1b [varicose disease plus advanced lipodystrophy (LPD)]:

- Hygienic and dietary indications
- Specific exercise
- Manual lymphatic drainage plus sequential pressure therapy
- Endermologie\textsuperscript{\textregistered} cycles
- Mesotherapy
- Eventual superficial carboxytherapy
- Oral administration of phlebotonics plus antiedematous therapy (phytotherapeutic medicines)
- Foot control
- Use of elastic hoses graduated in mmHg
- Surgical treatment/laser/varicose pathology sclerosants

In group V3 (soft lymphedema): The patient should be referred to a specialist for a clinical and instrumental phlebo-lymphological diagnosis:

- Hygienic and dietary indications
- Specific exercise
- Endermologie\textsuperscript{\textregistered} cycles
- Carboxytherapy
- Mesotherapy
- Eventual sequential pressure therapy plus manual lymphatic drainage
- Oral administration of phlebotonics plus antiedematous connective therapy (Cellulase Gold\textsuperscript{\textregistered})
- Foot control
- Use of semirigid bandages alternated in cycles with elastic hoses

In group V5 (lipolymphedema), clinical and instrumental (echodoppler) phlebo-lymphological diagnosis is necessary:

- Hygienic and dietary indications
- Exercise
- Endermologie\textsuperscript{\textregistered} cycles
- Leg mesotherapy
- Abdomen and thigh carboxytherapy
- Antiedematous and connective therapy
- Foot control
- Eventually, use of elastic hoses graduated in mmHg
In group F1a (initial flaccidity plus mild lipodystrophy):
- Endermologie® treatment (action of tonification and vascularization)
- Occasional mesotherapy and carboxytherapy
- Ultrasonic endolifting (internal ultrasound without suction)
- Foot control

In group F2 (advance flaccidity):
- Exercise
- Use of active skin cosmetics
- Endermologie® treatment (action of tonification and vascularization)
- Nonindication for mesotherapy and carboxytherapy.
- Physiotherapeutic electrotherapy
- Surgical considerations (eventually, in selected cases, only tunnellization without aspiration)
- Ultrasonic endolifting (a second dermolipectomy stage should also be considered)

In group A1 (false culotte de cheval): These cases have prolapse of the skin and subcutaneous structure with a muscular lipotropy:
- Endermologie® treatment (action of tonification and remodeling deep endermogym)
- Glutei stimulation
- Physiotherapeutic electrotherapy
- Surgical evaluation of lipofilling, prosthesis, or glutei lifting

In group A1 (true culotte de cheval): These cases mean a typical indication for surgical liposculpture associated with:
- Endermologie® treatment (action of lymphatic drainage, tonification, and remodeling)
- Ultrasonic hydrolipoclasis
- Oral antiedematous and connective therapy
- Postsurgical therapy including high-protein diet for a short period

It has been mentioned previously that this classification is an attempt to group the greatest number of patients into similar classes to prescribe similar therapeutic treatments. Thus, a scientific cost–benefit evaluation is possible, and indications of effectiveness are available. Certainly, this classification may and should be improved. Returning to our initial example of a patient coded as G1a/S1/L2V5/A2ab, we realize at once that she belongs to the gynoid type, complains of subjective—therefore Mediterranean—symptoms, shows an increase of insulin and estrogen receptors in the lower limbs and glutei, and is probably affected by veno-lymphatic insufficiency. The patient complains of pain in both legs but comes to consultation because “she dislikes her appearance.” Hence, outer appearance is more important for her than subjective painful symptoms: anxious or anxious-depressive characteristics are highly probable. Slight overweight is observed, outside of the obesity range. The patient may be controlled through mild diet and later maintenance diet. Lipedema is also detected with advanced lipodystrophic alterations plus lipolymphedema, in full accordance with local endocrine metabolic alterations and veno-lymphatic insufficiency (in the absence of vascular insufficiency, symptoms may be attributed to foot pathology with local hypoxic dysmetabolic paresthesia or to psycho-emotional dysfunction). Additionally, genuine adiposity may be detected in the abdomen and legs. After examining for oxidative stress and prescribing cleansing, localized liposculpture should be attempted followed by rehabilitation focused on
carboxytherapy and Endermologie® techniques applied in combination with drainage plus stimulation and leg mesotherapy.

The code N2a/1a/L1/A2, for example, describes an ideal normal type patient showing mild lipodystrophic alterations plus initial lipedema and genuine culotte de cheval. Localized adiposity may also be detected so that the appropriate prescription is diet and Endermologie® techniques (vascularization plus stimulation) plus localized liposculpture.

Similarly, the code G1a/Mb/L2/Ab refers to a symptomatic gynoid patient who expresses aesthetic motivations and shows lipedema accompanied by lipodystrophy, though no lipolymphedema may be detected in lower limbs (i.e., no foot edema). Localized adiposity of the lipedemic type is also noticeable in the legs. The patient might be included in the traditional classification for Dercum’s syndrome (Fig. 11). A comprehensive treatment should include specific therapies described for each group; in this case:

- Endocrine-hormonal investigations
- Oxidative conditions test
- High-protein diet for a short time
- Oral administration of phytotherapeutic medicines

**Figure 11**

This case can be classified as Dercum’s syndrome, a typical lipolymphedema with lipodystrophy caused by a constitutional endocrine–metabolic syndrome.
Carboxytherapy
Endermologie® (drainage and liporeduction)
Eventual lipolymphosuction with a postsurgical treatment with Endermologie®
Calf mesotherapy

BIMED–TCD CLASSIFICATION

No literature provides an exact blueprint for the visual and quantitative classification of cellulite. Bacci, in 2001, with the purpose of organizing a vast, controlled, and randomized study on the diagnosis and treatment of the cellulite, created a clinical classification that resulted in a numeric value that could be analyzed by computer. Therefore, the following classification is proposed: T, Thermatographic; C, Clinical; D, Symptomatic (TCD).

The final result will be a numerical conclusion relating to the variations gathered according to a basic classification carried out with the TCD code (Albergati/Curri, modified Bacci–self-assessment) supplemented by a subjective clinical evaluation.

The final value will therefore be a parameter consisting of the result of the numerical sum of TCD factors integrated with a probable factor of medical correction (17,18).

T FACTOR: AS A THERMOGRAPHIC OUTLINE OF ALBERGATI/CURRI (11) ON A SCALE OF 0 TO 25

The thermographic methodology is simple, repeatable, and precise. The classical and traditional thermographic staircase proposed by Curri has been separated into 25 classes each characterized by a number (Figs. 12 and 13). This scale is provided with IPS Thermo-Cell-Test-Mac® High-Resolution System (8 colors) with RW-S Professional Kit micro-encapsulated liquid crystal (ELC) plates.

The values 0 to 3 indicate normality from the microvascular and histological point of view (T0), values 4 to 7 indicate initial microcirculatory alteration (T1), values 8 to 13 indicate venulocapillary stasis (T2), and values 14 to 19 indicate cold zones with hypothermic zones or “black holes” (T3). Finally, values 20 to 25 indicate clear liposclerosis (T4).

THE C FACTOR

The C factor is clinical:
C1—orange peel skin invisible to the naked eye
C2—orange peel skin noticeable only when palpated
C3—orange peel skin visible only when the patient is seated
C4—orange peel skin just visible to the naked eye
C5—orange peel skin clearly visible to the naked eye (Fig. 14)
C6—orange peel skin very clearly visible to the naked eye
C7—orange peel skin very clearly visible to the naked eye and compacted
C8—orange peel skin very clearly visible to the naked eye and fibrous
C9—orange peel skin very clearly visible to the naked eye and accompanied by hypotrophic tissue
Figure 12
Thermograph pictures of "normal zone" T0.

Figure 13
"Pathological zone."
The D factor is symptomatic:

- D0—cellulite not painful when pinched
- D1—cellulite slightly painful when pinched
- D2—cellulite painful when pinched
- D3—cellulite slightly painful when compressed
- D4—cellulite painful when compressed
- D5—cellulite very painful when compressed
- D6—cellulite painful without compression
- D7—spontaneously painful cellulite accompanied by a sensation of heaviness in the legs

**TCD CODE**

The final number is the sum of different numerical values; physicians may then add a corrective factor at their own discretion, based on personal judgments and clinical experience. The final number ranges from 5 to 40 and can then be inserted in the database; its variations will point out the reported variations to the effected treatment (Fig. 15).

Figure 16 points out a follow-up of various treatments of the same type of cellulite with placebo, phytherapeutic drugs, Endermologie alone, and phytherapeutic drugs plus Endermologie. As shown, the integrated treatment has allowed a more evident improvement in comparison with the other treatments and with placebo.

This classification, in partnership with the BIMED classification, allows a complete clinical diagnosis, a contemplated therapeutic strategy, and also allows one to appraise the treatment results, also constituting the basis for scientific studies and research.
Today we know that cellulite is not only a “lipodermal” degenerative alteration due to or in partnership with venolymphatic stasis, but is also the result of one of a series of biochemical and metabolic alterations that probably begin at the level of the interstitial matrix and the connective structures, involving the microvascular system.

Today three schools of thought exist:

1. An older school with many adherents in Italy and Argentina, and tied to the ideas of Prof. Curri in 1986 (19), reports cellulite as beginning from a venolymphatic stasis with edema that instigates fibrosis and then sclerosis in an evolutionary way.
2. Another school, more diffused in the United States, and tied to plastic surgery, considers cellulite as a concomitance of localized adiposity or lipodystrophy and, therefore, liposuction is a treatment of election (20). A part of U.S. culture considers cellulite a nonexistent illness (21).
3. Another line of thought popular in Italy considers cellulite not as a cosmetic pathology but as a condition caused by various pathologies including mesenchymal-endocrinopathy to hormones and feeding, where venolymphatic damage is secondary to functional dysfunctions of the interstitial matrix and adipose tissue (22–27).

Cellulite can be defined as “that irregularity of the skin appearing as an orange peel or mattress (dimpled skin), that may be secondary to an alteration of dermoeipidermal tissue, adipose tissue, connective tissue, or venolymphatic system of the interstitial matrix.”

Cellulite can be expressed as five “principal dimensions”:

1. Increase of the subcutaneous adipose tissue and free water (lipedema)
2. Increase of the subcutaneous adipose fabric and the quantity of lymphatic liquid (lipolymphedema)
3. Fibrosclerosis of the connective fibers (fibrous cellulite)
4. Interstitial alteration and adipose dystrophy (lipodystrophy)
5. Increase of the localized adipose tissue (localized adiposity)

In daily practice of the treatment of the cellulite, various methodologies are used for different indications:

- Liposuction (localized adiposity—lipomatosis)
- Controlled diet (overweight)
- Mesotherapy (edema)
- Oxygentherapy (superficial lipolisis)
- Carboxytherapy (vascular lipodystrophy)
- Endermologie® (connective tissue stimulation)
- Administration of pharmacological drugs (basic treatment)

From the preceding classifications, we have extrapolated some protocols for treatment (BIMED–TCD by Bacci in 2003) that constitute the common denominator of the different forms of cellulite. We have adopted a physiopathological classification and have divided cellulite into four groups:

1. Edematous cellulite
2. Adipose cellulite
3. Interstitial cellulite
4. Fibrous cellulite

Figure 17A–C reveals the physiopathological basis and the treatment.

The association of the classification BIMED–TCD with the physiopathological classification described by Bacci has generated some treatment protocols of practical utility (28).

**EDEMATOUS CELLULITE**

The physiopathologic aspect is characterized by a dermo-hypodermal tissue with lymph stasis and the presence of subcutaneous adipose tissue, where orange-peel skin is provoked by the stretching of the connective tissue fibers by increases in interstitial fluid.
Figure 17
Videocapillaroscopy of edematous cellulite.
Principal symptoms:
- Pain
- Edema
- Sense of periodic swelling
- Intestinal disbiosis (hypogastric swelling)
- Constitutional tendency to reservedness and depression

Differential diagnosis:
- Phlebedema
- Lymphedema
- Phlebolymphedema
- Lipolymphedema
- Lipedema
- Dercum’s syndrome
- Vilain’s syndrome
- Lipodystrophy

Diagnostic examinations (first level):
- Echography (stasis plotted connective fibers stretched on the vertical plane)
- Circumference measurements
- Light reflexion rheography
- Echocolordoppler
- Thermography (middle temperatures stadium T1/T2)
- Blood examinations plus oxidative stress test
- Depurative picture (liver and kidney functionality)

Diagnostic examinations (second level):
- Videocapillaroscopy (middle reduction of the capillary ones)
- Lymphoscintigraphy
- Pain test (Braun test)

**THERAPEUTIC PROTOCOL (60 DAYS)**

**Phase 1 (20 Days)**
- Systemic medical therapy: Cellulase Gold\textsuperscript{a}: 2 cps per day + Daflon 500\textsuperscript{b} mg 2 cps per day.

\textsuperscript{a} The phytotherapeutic drug (Cellulase Gold\textsuperscript{c}) (29–31) can be used as basic treatment of the different forms of cellulltic syndromes because it provides an increase in metabolic activity of the connective structure, local interstitial matrix, and microvascular system. This product is sold under the trademark Cellulase Gold\textsuperscript{c} by Medestea Internazionale, Turin, Italy, and is composed of bioflavonoids expressed as polyphenols (Vitis vinifera), Recaptacell\textsuperscript{d}, *Ginkgo biloba*, Ruscus, Melilotus, Centella, and Fucus.

\textsuperscript{b} This product represents the phlebotonic drug that has been in use for about fifteen years almost all over the world. It has a direct action on the venous walls with an interesting anti-inflammatory and antiedematose activity. This product is sold under the trademark Daflon 500\textsuperscript{c} by the French company, Servier (32).
Local medical therapy: None.
Physical therapy: Endermologie—two sessions per week (lymph draining and phleboactive action) plus pressotherapy two sessions per week (20 minutes to 40 mmHg).
Surgical therapy: None.
Other possible therapy: Two fleboclisis × week: physiological 100 cc + three vials of Fleboside. After 20 days: Check up by the physician.

Phase 2 (40 Days): Basic Scheme of Treatment that May Vary Based on the Individual Patient
Systemic medical therapy: Cellulase Gold: 2 cps per day + Daflon 500 mg 2 cps per day.
Local medical therapy: Mesotherapy (aminophyllin—physiological sol and phlebotonics drugs or sodium bicarbonate).
Physical therapy: Endermologie: One or two sessions per week (lymph draining and phleboactive action).
Surgical therapy: Possible liposculpture (adipoedematous form).
Other therapy: Pressotherapy: Two sessions per week (20 minutes to 60 mmHg). Walking, sun, and sea are recommended for this type of cellulite. Other local therapy can be thermal baths with carbonat-jodium water to 30°C.
After 60 days: Check up and maintenance therapy.

**ADIPOSE CELLULITE**

The physiopathologic aspect is characterized by a superficial and deep dermo-hypodermal tissue, stretched by excess of adipose tissue, with a particular increase of the “steatomeric” fat situated in the splittings of the bands. There is no stasis of interstitial liquid, which can be associated with being overweight. The orange-peel appearance is caused by connective tissue stretching due to excess of fat tissue.

Principal symptoms:
- No pain
- No edema
- No sense of periodic swelling
- No intestinal disbiosis but swelling of the epigastric region
- Compact skin

Differential diagnosis:
- Lipedema
- Launoise–Bensaude syndrome

Fleboside is an Italian product recorded as an antiedema drug and a capillary protector mostly used intravenously. It is a pharmacological product constituted by troserutine and carbamazocromo.
Barraquer–Simmons syndrome
Localized adiposity
Systemic multiple lipomatosis
Lipomatosis
Lipodystrophy

Diagnostic examinations (first level):
- Videocapillaroscopy (good vascularization of the capillary ones)
- Echography (plotted compact connective in horizontal normal position)
- Thermography (normal temperature stadium T0)
- Blood examinations (endocrine-thyroid study)
- Thyroid echography

Diagnostic examinations (second level):
- Nuclear magnetic resonance
- Biopsy

THERAPEUTIC PROTOCOL (60 DAYS)

Phase 1 (20 Days)
- Systemic medical therapy: Cellulase Gold®: 3 cps per day.
  - Local medical therapy: None.
  - Physical therapy: Endermologie®—two sessions per week (liporeduction action).
  - Surgical therapy: None.
  - Other therapy: Controlled amino acid diet.
  - After 20 days: Check up by the physician.

Phase 2 (40 Days): Basic Scheme of Treatment that May Vary Based on the Individual Patient
- Systemic medical therapy: Cellulase Gold®: 2 cps per day.
  - Local medical therapy: Occasional carboxytherapy 50 cc /zone.
  - Physical therapy: Endermologie®—two sessions per week (remodeling and recovering action) (seven days after surgery).
  - Surgical therapy: Liposculpture.
  - Other therapy: Controlled amino acid diet (20 days after intervention).
  - Other therapies: None.
  - After 60 days: Check up and maintenance therapy.

INTERSTITIAL CELLULITE (LIPEDEMA)

The pathophysiology is characterized by a dermo-hypodermal tissue with edema of the thigh and superficial adipose tissue typically seen in young women. The orange-peel skin is caused by connective tissue stretching from edema and fat tissue.

Principal symptoms:
- No pain
- Edema to the thigh and not to the leg or foot
Beginning of cellulite formation in the thigh and calf
Formation of orange-peel of adipoedematous in compact tissue
Sense of periodic swelling
Intestinal disbiosis (hypogastric swelling)
Sense of swelling of the hands

Differential diagnosis:
- Localized adiposity
- Dercum syndrome
- Barraquer–Simmons syndrome
- Adipoedematous cellulite (no Stemmer sign implies absence of edema of the foot)

Diagnostic examinations (first level):
- Videocapillaroscopy (good vascularization of the capillaries)
- Echography (moderate presence of liquid and adipose fabric with connective horizontal and hyperechogenic fibers)
- Thermography (middle temperatures stadium T0–T1)
- Blood examinations (hormonology, endocrinology, glycemic state, and oxidative stress)

Diagnostic examinations (second level):
- Pain test
- Pelvic echography
- Lymphoscintigraphy
- Measurement of circumferences

THERAPEUTIC PROTOCOL (60 DAYS)

Phase 1 (20 Days)
- Systemic medical therapy: Cellulase Gold®: 2 cps per day + Legapass®d: 10 drops in the evening.
- Local medical therapy: Occasional mesotherapy with benzopirone.
- Physical therapy: Endermologie®—two sessions per week (action of linfodrenante–liporiducente).
- Surgical therapy: None.
- Other therapy: Amino acid and alkaline controlled diet.
- After 20 days: Check up by the physician.

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This phytotherapeutic drug (Legapass®) can be used as an epato-intestinal cleansing agent to help the elimination of toxins. It is a natural product sold by the German company Pascoe and by the Italian company Named.
Phase 2 (40 Days): Basic Scheme of Treatment that May Vary Based on the Individual Patient

- Systemic medical therapy: Cellulase Gold®: 2 cps per day + Legapass®: 10 drops in the evening.
- Local medical therapy: Mesotherapy (aminophylline and physiological solution or phlebothropic drug alcalinized).
- Physical therapy: Endermologie®—one or two sessions per week (lymph draining and liporeductive action).
- Surgical therapy: Possible liposculpture.
- Other therapy: Alcalinizing and antioxidants drugs: Physical activity (not involving weights), walking, sun, and sea are recommended for this type of cellulite. Other local therapy can be thermal baths with carbonat-gassosus water at 37° to 39°C.
- After 60 days: Check up and maintenance therapy.

FIBROUS CELLULITE

The physiopathologic aspect is characterized by a cutaneous and subcutaneous tissue with loss of water and loss of adipose tissue. It presents, particularly, with fibrous connective tissue, various nodules of adipose tissue with sclerotic capsule.

The orange-peel skin is coarse and is caused by the retraction of the connective tissue fibers and not from an excess of liquid or plotted adipose.

Principal symptoms:

- Pain
- No edema—coarse granularity
- Presence of cellulite mostly in the anterior region
- Intestinal disbiosis (hypogastric swelling)
- Heaviness in the legs—articular pain
- Disturbance to the digestive process (bitter mouth, flatulence)

Differential diagnosis:

- Localized adiposity
- Advanced Dercum syndrome
- Systemic multiple lipomatosis
- Advanced lymphedema

Diagnostic examinations (first level):

- Videocapillaroscopy (scarce vascularization of the capillaries)
- Echography (adipose nodules, sclerosis of the connective unorganized fibers)
- Thermography (low temperatures stadium T3/T4)
- Blood examinations (metabolic picture, oxidative stress, nutritional balance)
- Lymphoscintigraphy
- Laser Doppler
Pain test
Light reflection rheography

Diagnostic examinations (second level):
- Mineralometria ossea computerizzata (MOC, computerized bone mineralometry), a nuclear study for osteoporosis
- Nuclear magnetic resonance

THERAPEUTIC PROTOCOL (60 DAYS)

Phase 1 (20 Days)
- Systemic medical therapy: Cellulase Gold\textsuperscript{e}: 2 cps per day.
- Local medical therapy: Mesotherapy with pentoxiphiline.
- Physical therapy: Endermologie\textsuperscript{e}—two sessions per week (vascularizing and recovering action).
- Surgical therapy: None.
- Other therapy: Alkalinized antioxidant diet.
- After 20 days: Check up by the physician.

Phase 2 (40 Days): Basic Scheme of Treatment that May Vary Based on the Individual Patient
- Systemic medical therapy: Vascularys\textsuperscript{f}: 2 cps per day + Lyndiaral\textsuperscript{f}: 20 drops × 2.
- Local medical therapy: Carboxytherapy (50 cc per leg introduced in the subcutaneous layer by little drops of gas) (two session per week).
- Physical therapy: Endermologie\textsuperscript{e}—two sessions per week (vascularizing and recovering action).
- Surgical therapy: None.
- Other therapy: Alkalinized and antioxidant nutrition. Walking, physical activity, sun, and sea are recommended for this type of cellulite. Other local therapy can be thermal baths with carbonat-gassosus water to 37°C.
- After 60 days: Check up and maintenance therapy.

\textsuperscript{e}The phytotherapeutic drug (Vascularys\textsuperscript{e}) can be used as basic treatment of the forms of cellulitic syndromes characterized by veno-lymphatic alterations because it provides an increase in metabolic and functional activity of the local interstitial matrix and microvascular system. This product is sold under the trademark Vascularys\textsuperscript{e} by Medestea Internazionale, Turin, Italy, and is composed of Bioflavonoids expressed as polyphenols (\textit{Vitis vinifera}), fatty acids (EPA, DHA, \textit{y}-linolenic acid, etc.), Vitamin E, \textit{Ginkgo biloba}, Ruscus, Melilotus, and Centella.

\textsuperscript{f}The phytotherapeutic drug (Lyndiaral\textsuperscript{f}) (33–35) can be used as basic treatment for the forms of edematous cellulitic syndromes. It is characterized by a typical lymphocinetic action and provides an increase in metabolic activity and an improvement in the elimination of the lymphatic toxins. This product is sold under the trademark Lyndiaral\textsuperscript{f} by the German company Pascoe and the Italian company Named.
SUMMARY

The classification of cellulite is important in planning a precise therapeutic strategy, both medical and surgical. Currently, a common definition of cellulite does not exist (36). The attempt to classify according to the scheme BIMED–TCD, following the indications and the experiences of the classification CEAP, can improve the diagnosis and treatment.

Although many of the recommended treatments are not approved by the U.S. Food and Drug Administration, the recommended therapies and medicines are part of the pharmacopoeia approved by the European sanitary legislation. Recommended treatments have been studied for the described indications (36–40).
REFERENCES

8

Medical Treatment of Cellulite

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■ INTRODUCTION

Medical therapies include drug administration. Thus, the author suggests prescribing
generic equivalents whenever possible; trade names should be used only for drugs of proven
therapeutic efficacy ascertained in one’s own experience and through scientific research.

Medical treatments of cellulitic pathologies should start with a cycle involving function
regulation: stimulating microcirculation, lymphatic drainage, lipolysis, and antioxidant action.

Drugs derived from herbs, such as phytodrugs, an important element for prevention
and treatment of cellulite, are also recommended. Be reminded that the quality of phyto-
drugs varies widely: perfect extraction, titration, and association of substances and vita-
mins are required. In the treatment of veno-lymphatic and cellulitic pathologies, Ginkgo
biloba, ruscus, centella, and benzopyrene derivatives are used, among others.

In phytotherapy, the active ingredient is not the extract itself but one or more sub-
stances present inside the extract in a certain concentration.

In a phytotherapeutic extract, many differences in the concentration of the active
substances, as high as 200/300 times, may be found. Accordingly, the activity and the
price of different types of the same plant extracts vary dramatically.

Cellasene® (Argentina) or Cellulase Gold® (U.S.A.) is an oral medication based on
grape seed bioflavonoids, G. biloba, centella, melilotus, fucus, fish oil, and borage oil. It is
a phytotherapeutic agent of proven activity on skin microcirculation that reduces subcuta-
aneous adipose panniculum thickness, and subsequently reduces thigh and flank circumfer-
ence (1). In addition, it relieves lower limb cramps, paresthesias, heaviness, and pains of
microcirculatory origin. It is indicated for the treatment of the aesthetic pathology “cellu-
lite” (in particular connective tissue, edematous, and interstitial cellulite).

Based on the results of epidemiologic studies, we include the use of polyphenols as
medical therapy.

■ Polyphenols (leukoanthocyanins) are the most powerful known antioxidants (activity
50 times higher than that of vitamin E).
■ Leukoanthocyanins protect capillaries and vessel wall fibers (2).
In pharmacological studies, leukoanthocyanins show good pharmacological bioavailability in oral administration and also show trophism toward the cardiovascular system and tissues rich in glycosaminoglycans (such as artery walls and microcirculation) (3).

Based on biochemical and pharmacological studies, we conclude that *Vitis vinifera* leukoanthocyanin is effective for preventing and treating vascular disorders and all conditions involving vascular structure–interstitial matrix relationships (4,5).

**G. BILOBA EXTRACTS**

Some of the active principles of *G. biloba* have the property of increasing blood perfusion, both at a central and peripheral level. This dynamic activity on vessels increases volume and speed of local blood flow, acting particularly on small arteries and prearteriole capillaries.

Recent studies demonstrate that the active principles of *G. biloba* have high vaso-motor effects, increase blood flow, and have significant antioxidant effects (6). They also extend the effects of endothelial-derived relaxing factor, a substance that contributes to vasodilatation in microcirculation (7).

**PURIFIED ASIATIC CENTELLA: TRITERPENES AS PHYTOSOMES**

The therapeutic activity of centella has been known for a long time. It is used for its activity on skin healing. Research studies support its action on lymphatic drainage and highlight the plant extract’s stimulating effect on collagen production (8). The plant’s active substances are called triterpenic fractions. A careful and complex purification process of centella extract yields a content of madecassic acid (30%), asiatic acid (30%), and asiaticoside (40%). These substances are well described from a toxicological point of view: the main activity site is the fibroblast.

Triterpenes accelerate lysine and proline (two fundamental amino acids in collagen structure) metabolism, increase tropocollagen synthesis, and stimulate connective tissue mucopolysaccharide exchange (9). Since 1983, many scientific studies have proven the effectiveness of triterpenic fractions from asiatic centella in preventing and treating cellulite. Clinical, histological, and instrumental studies reported that 70% of the treated patients showed an improvement in tissue trophism and connective vascular stimulation.

To improve pharmacodynamics and biological activity of asiatic acid, madecassic acid, and asiaticoside, the triterpenic fraction is exposed to a chemical reaction with soy phospholipidic extracts, which yields a chemical complex called phytosome. The lipophilic fraction (soy phospholipid) of the complex increases the active interaction of ingredients, and cholic acid emulsifies and captures substances that are then carried through the portal circuit to the liver. The complex has proved its nontoxicity and shows better and faster absorption than the free form.

**MELILLOTUS OFFICINALIS EXTRACT**

Diverse active components such as melilotin, melilotic acid, and melilotoside, and some P-vitamin–like flavonoids proved effective in increasing capillary resistance, reducing
vascular permeability, favoring venous return, and increasing lymphatic return. These activities had been demonstrated in animals (10). Clinical studies on pharmacological and toxicological effects of melilotus extract report that it is an effective element for the prevention and treatment of pathologies in which capillary permeability and lymphatic circulation are altered (11,12).

**FUCUS VESCICULOSUS EXTRACT**

*F. vesciculosus* extract helps restore an appropriate lipidic catabolism in the subcutaneous tissue. The chemical structure of the extract is composed of some polysaccharides and also bromine and iodine, the latter being bound to the extract protein fraction (organic combination). As many pharmacokinetic studies have proven, this organic combination provides ready bioavailability of iodine content (13,14).

The phytocomplex iodine content represents the active fraction of the extract. Based on pharmacological and clinical data, it is possible to assert that fucus extract has a metabolic and rebalancing action on subcutaneous fat, without altering thyroid metabolism.

These pharmacological, pharmacodynamic, clinical, and toxicological properties aided in the development of Cellasene® and Cellulase Gold®.

The “Gold” in Cellulase Gold® is the addition of *Ruscus aculeatus*, whose active principles are fundamental to increasing the activity of microveins. Recaptacell™ is a natural mixture that favors cellular membrane fluidity to keep cell membranes younger. Recaptacell™ has borage oil, polycosanoles, lipoic acid, orange oil, *Piper nigrum*, folic acid, and vitamins E and B6 (15).

All of these allow Cellulase Gold® to have a complete and synergic activity.

| **Vitis vinifera** | Capillary microcircle |
| **Centella asiatica** | Protection of collagen fibers |
| **Ruscus aculeatus** | Collagen synthesis |
| Horse chestnut (*Melilotus*) | Connective tissue protection |
| **Fucus vesiculosus** | Microarterial |
| **Ginkgo biloba** | Lymphatic reflux |
| Policosanoles | Tissue catabolism |
| | Lipolysis |
| | Younger cell membranes |

Fluidifying membranes mean:

1. Activating intracellular and extracellular exchanges in areas where cellular and tissue exchange is considerably compromised;
2. Disposing of metabolic toxins;
3. Transforming deposited “fats” into metabolic energy and consequently reducing adipose accumulations; and
4. Ensuring connective tissue elasticity.
ABSTRACTS OF STUDIES IN CELLASENE®

Report on the Clinical and Experimental Trial: Cellasene
Dermatological Center, San Mateo Polyclinic, University of Pavia
(Director: Prof. G. Rabbiosi)

The prospective study was carried out from December 1999 to February 2000 at San Mateo Polyclinic. Twenty-five healthy female patients were selected. The mean age was 33. They were receiving no treatment for cellulite when the study started (neither cosmetic treatment nor physical therapy). Cellasene was administered thus: two tablets daily orally for two months (one tablet in the morning and one in the afternoon).

The following investigations were performed:

I. Examination of body weight: no variations in body weight were observed.
II. Assessment of arterial pressure: half point decrease in systolic and diastolic pressures was observed.
III. Circumference measurements: decrease in hip, thigh, and ankle circumferences was observed.
IV. Skin plication: significant reduction in skin thickness (12.58%) was seen.
V. Doppler laser flowmetry: high increase (28.1%) in blood flow rate at microcirculatory level after eight weeks of Cellasene® administration was observed.
VI. Ultrasound: through Dermascan 5.87% reduction in subcutaneous tissue thickness was observed.
VII. Thermography with computerized thermograph: increase in temperature after Cellasene® administration (+1.75%) was observed.
VIII. Blood tests
   a. T3, T4, and TSH: No changes were observed.
   b. Fibrinogen and kPTT: Mild increase was seen.
   c. Cholesterol, HDL, LDL, and triglycerides: No changes were observed.
IX. Assessment of anti–free-radical capability
   a. Lipoperoxidase
      1. A significant reduction of lipid peroxide was seen in nonsmokers, and was even more pronounced in smokers. Cellasene® has a potent antioxidant activity that protects lipidic membranes from free-radical damage.
   b. Assessment of total antioxidant capability
      1. Plasma antioxidant capability increased 11.70% after eight weeks of Cellasene® administration. Hence, the product increases antioxidant and protective capabilities of the body.
X. Assessment of tolerance
   a. All patients showed an optimum tolerance and no secondary effects were observed.

Logically, a double-blind study with a placebo is needed to complete the trial. Therefore, the same research team carried out the following trial.

Report on Clinical and Experimental Trial:
Cellasene® vs. Placebo

Fifteen patients were selected. The mean age was 30.92. This trial covered the same period of time. The following investigations were performed:
I. Examination of body weight: No variations were seen.
II. Assessment of arterial pressure: No changes were observed.
III. Circumference measurements:
   a. Hip: No changes were seen.
   b. Thigh: No changes were seen.
   c. Ankle: No changes were seen.
IV. Plication: No reduction in subcutaneous thickness was seen.
V. Doppler laser flowmetry: No increase in subcutaneous tissue microcirculation speed was seen.
VI. Ultrasound: No variations in subcutaneous adipose tissue thickness were seen.
VII. Thermography: No temperature changes were observed.
VIII. Assessment of tolerance: All cases showed good tolerance and no secondary effects as compared with the placebo group.

The Dermatologic Center, San Mateo Polyclinic,
University of Pavia, Italy

This clinical and instrumental third trial was carried out on 25 women. Two tablets of Cellassene® were administered in the morning and two tablets in the afternoon (total: four tablets) daily during eight weeks. The mean age was 38. Volunteers were taking no other medication; they were not using creams or any other anticellulite product or treatment. During the trial period, diets and exercise were suspended.

The following investigations were performed:

I. Measurement of local diameter
   a. Significant reduction (statistically measurable) in hip, thigh, and ankle circumferences.
II. Plication
   a. Subcutaneous fold decrease.
III. Ultrasound
   a. Important reduction in subcutaneous tissue thickness.
IV. Doppler laser flowmetry
   a. A significant increase in subcutaneous tissue microcirculation was observed after eight weeks of four tablets per day Cellasene® administration (Fig. 1).

NEW RESEARCH ABOUT THE USE OF CELLASENE® OR CELLULASE GOLD®

Randomized, Placebo-Controlled, Double-Blind Clinical Study on Efficacy of a Multifunctional Phytotherapeutic Product in the Treatment of So-Called Cellulite (15)

The general objective of the trial was to evaluate the effect of administration of two different dietary supplements or phytotherapeutic products using a number of parameters commonly acknowledged as being correlated to cellulite and to evaluate possible differences in clinical results in relation to the different formulae (1).
Cellulite is a widely used term to indicate a common condition afflicting women, i.e., fat-lobular hypertrophy, localized mainly on the thighs and buttocks. Despite the fact that several physiopathologic factors have been proposed for localized fat-lobular hypertrophy, the arena seems to be limited to vascular damage and lobular hypertrophy. These two components are known as the possible targets of many different plant extracts, which may play an important role in influencing and reducing vascular damage and lobular hypertrophy.

Leibaschoff et al.: Non-Invasive Assessment of the Effectiveness of Cellasene® in Patients with Edematous Fibrosclerotic Panniculopathy (Cellulitis): A Double-Blind Prospective Study (16)

A clinical and instrumental study was carried out to determine the effect of a phytotherapeutic flavonoid agent based on seed extracts of *V. vinifera*, *G. biloba*, asiatic centella, melilotus (*Mellilotus officinalis*), fucus (*F. vesiculosus*), fish oil, and borage oil (Cellasene®). The study was aimed at determining the activity on microcirculation and lipedema in patients affected by edematous fibrosclerotic panniculopathy. The study had a prospective, longitudinal, and double-blind design. A group of 37 female patients with cellulitis was investigated. The main noninvasive instrumental methods used were the echo-Doppler
and the videomicroscopy with digital image processing. Medication was administered to the patients orally for 60 days. The patients were divided into three groups: the first received the medication containing all active elements, the second received the active medication deprived of *F. vesiculosus* content, and the control group received a placebo. Clinical results showed an improvement in symptoms and signs in the first group that received the active medication. The echo-Doppler study showed an improvement in lipedema conditions in the patients who received the active medication. Videocapillaroscopy with digital image processing detected a $43 \pm 5\%$ benefit in vertical capillary density. The conclusion was that this phytotherapeutic medication shows activity on microcirculation and lipedema in patients with edematous fibrosclerotic panniculopathy cellulite (Fig. 2).

On day 0, there were microhemorrhagias that disappeared after 60 days of use of Cellulase<sup>R</sup>. In the digital image, the increase in the number of capillaries is seen (Fig. 3).

**M. Gasparotti (Italy)**

We would like to emphasize that in our experience in liposuction we have constantly obtained the reduction of the circumference of both buttock and thigh by having the patients wear a special postop garment designed and patented for us. These results are due to the lymphatic and venous micromassage produced by two layers of the garment during the first month postop. Interstitial edema drainage is stimulated and subdermic capillary microcirculation is increased, inducing an improvement of the so-called cellulite. Moreover, the same circumferential reduction on buttocks and thighs has been enhanced lately by administering two softgel capsules or daily administration of Cellulase Gold<sup>R</sup> for

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**Figure 2**

Effect of Cellasene<sup>R</sup> on the microcirculation and lipedema in patients with edematous fibrosclerotic panniculopathy cellulite.
Figure 3
In the left panel, a big hypoechogenic region between the epidermis and the aponeurosis (edema) measuring 1.44 cm is seen. In the right panel, the edema is shown to have diminished; there is a decrease of 1.00 cm in lipedema after 20 days of use of Cellasene®.

Figure 4
Liposhape™ using the technique proposed by Prof. M. Gasparotti.
Figure 5
Before and after liposurgery, Cellulase Gold\textsuperscript{R}, \textsuperscript{TM} and Liposhape\textsuperscript{TM}. \textit{Source:} Photo courtesy of M. Gasparotti.

Figure 6
The effects of Cellulase Gold\textsuperscript{R} and Lipopanthy\textsuperscript{TM} after four months. \textit{Source:} Photo courtesy of M. Gasparotti.
a period of 60 days prior to superficial liposculpture, and continuing for two month after the surgery.

Cellulase Gold® is a membrane flow activator and a dietary supplement based on *C. asiatica*, Bladderwrack, *M. officinalis*, *G. biloba*, *R. aculeatus*, bioflavonoids, and Recapta-cell™. It increases the cell membrane fluidity for a better intracellular–extracellular exchange, stimulates microcirculation, activates the anti–free-radical defences, contrasts vessel permeability and enhances drainage of the excess of fluids in the tissue.

As a result, the use of Cellulase Gold® helps the transformation of fatty deposits into metabolic energy, prevents the fibrous and sclerotic conditions of the connective tissue, and helps reduce volumes and circumferences. In our opinion, the use of Cellulase Gold® appears to optimize the outcome of three-dimensional liposuction and increases overall patient compliance (Fig. 4–6) (17).
REFERENCES

All of the conventional physical stimulation systems used in cosmetic medicine such as laser, ultrasound (US), transcutaneous electrical nerve stimulation (TENS), and magnetic fields share one common characteristic, i.e., they are unfocused. This means that they all emit large amounts of energy in different ways in a repetitive fashion, following logical but preestablished patterns.

With lasers, this energy takes the form of consistent light, while magnetotherapy uses electromagnetic waves. US relies on sound waves, while TENS uses electrical stimulation. These types of emissions share one characteristic. They are not suited to the requirements of correction. They are therefore quantitatively and qualitatively unfocused. They are used because they are backed by medical tradition, but unfortunately they produce very few truly satisfying results in the correction of blemishes. Beautytek® encompasses the biological requirements that are unrecognized by conventional therapies. Time after time, day after day our bodies require a whole range of different corrections. The instruments and methods used in conventional physical therapies emit energies of different types and characteristics in an imprecise way. This means that they have an unpredictable effect on biological structures.

The most important information system in living biological systems is the neuronal network. Biological systems have many ways of transferring information, but the most important is probably via the neuronal network. Advances made in neurophysiological research mean that we can now measure the chemical activity that occurs in individual cells or in groups of cells. Many of the functions of the neuronal and muscle cells are chemical in nature. Nonetheless, these functions produce changes in the electrical field, which can be monitored using electrodes. The so-called electrical potentials help neurophysiologists to study cell function by directly measuring the chemical potential relating to ion concentrations. These phenomena can be detected using special transducers such as selective electrodes.

The source of the electrical signal is the individual neuronal or muscular cell. However, such cells do not function alone; they function in large groups. The cumulative effects of such cellular activity result in the generation of an electrical field that propagates...
in the conduction volume, which consists of various types of tissues. Thus, the activity of
the muscle or certain neuronal networks can be indirectly improved by applying electrodes
to the skin. This type of information is not simple to collect, and the electrodes must be
properly positioned on the skin. Even then, it is very difficult to analyze the information
process involved. The results of all of the neuronal and muscular activity in unknown
anatomical sites are transmitted using a homogenous medium. The electrical signals moni-
tored on the surface of the skin are of enormous clinical and physiological importance.
Electroencephalograms, electrocardiograms, electromyograms, and other signals are
already being used in clinical medicine to measure the activity of muscular and neuronal
systems. The way in which the information supplied by these systems is interpreted is
based principally on statistical experience built up over the years. The plasma cell mem-
brane is a medium that separates the intercellular fluids from the extracellular ones. These
two types of fluids have different ions concentrations, and the membrane has different
levels of permeability for the different ions dissolved in the solution. A membrane potential
is generated by the ion transfer, principally as a function of diffusion mechanisms. If
we take into consideration the effects of the three main ions alone, potassium, sodium, and
chlorine, we obtain the membrane potential via the following equation:

\[ E = \ln R T \left[ \frac{P_{X}[K^+] + P_{Na}[Na^+] + P_{Cl}[Cl^-]}{P_{Na}[Na^+] + P_{Cl}[Cl^-]} \right] \]

where \( R, T \) and \( F \) are the universal gas constant, the absolute temperature, and Faraday’s
constant, respectively; \( P_X \) is the permeability of the remaining membrane to \( X \) ions and \( X_o \)
and \( X_i \) are the concentrations of \( X \) ions in the extracellular and intracellular fluids. The
remaining membrane potential calculated in this way is approximately 80 mV; the interior
of the cell becomes negative in relation to the exterior.

Some membranes have different levels of excitability. When the membrane is excited
by an electrical or mechanical signal or by a chemical stimulus, its permeability changes in
relation to the ion transfer. These changes in turn cause an increase in the remaining
potentials of the membrane, which become positive for a short period of time and then,
when the membrane changes its sign, return to the resting potential.

The type and duration of the action potential differs from one cell type to another.
The membrane only becomes excited when the stimulus exceeds a threshold level of
around 20 mV. Once this threshold has been exceeded and the action potential appears,
there is also a change in the sensitivity of the threshold. After the potential has been acti-
\vated, there is a period of time (approximately 1 or 2 msec) during which the threshold
becomes infinite. This period is called the period of total refractoriness during which no
new action potential can be activated. The threshold thus returns to its nominal value
in accordance with the computation of the decay function. The period during which the
threshold falls to its normal level is known as the relative refractoriness period. In that per-
iod, a new action potential can be activated by a stimulus that is sufficiently large to cross
the relatively high threshold.

The source of electrical signals is the action potential generated by individual
neurons and muscle fibers.

The current density generated by the membrane activity can give rise to a change in
the surrounding medium. The surrounding tissue in which the current change took place is
called the conduction volume. In many clinical and neurophysiological applications, we
can monitor the conduction volume field but not the bioelectrical sources that generate it.
This is definitely the case when electrodes are attached to the skin to monitor the electrical activity of the heart and brain. It is therefore extremely important to be able to precisely deduce the underlying bioelectric source producing the conduction volume activity.

This operation involves a very complex computation, especially if the characteristics of the biological medium are taken into consideration.

Mathematical models of flow fields of currents in the conduction volumes have been developed with varying degrees of success.

Beautytek creates a loop—a closed circuit—with the area to be stimulated. If, for example, the two electrodes are situated in a position that will permit a reading of the system in an inflamed area, the machine performs a very fast physiochemical analysis of the tissue once the circuit is closed. Using a series of algorithms, Beautytek reads and interprets the physiochemical situation and then makes the necessary correction. Even as the correction is being made, the system is already moving to the next reading so that the closed system ensures that the machine can take hold of the tissue and bring it to a different physiochemical state of equilibrium. Because the system’s algorithms are aimed at bringing about tissue equilibrium, the electronic system cannot cause any damage even though the goal is to bring about a biological change. Once a state of equilibrium has been reached in the area of the tissue under examination, the machine stops the treatment, so it cannot overstimulate or understimulate it. The stimulation is always by definition the level required to reach equilibrium.

Instant by instant, several hundred times a second, the machine takes readings, interprets the data, and makes a correction. Then it starts from the beginning again with a reading of the tissue modifications obtained, calculates, and corrects once again. It intervenes in a cyclical and interactive fashion so that the tissue is forced to modify itself and all of its physiochemical compensation systems and to establish a new equilibrium.

Thus, the polarization of the chemical–physical constituents of the tissue is modified; this is an expression of the chain of overlaps of substances commonly involved in biological and bioelectric processes.
INTRODUCTION

Cellulite is the unsightly skin dimpling that is frequently found on the thighs and buttocks of women. Approximately 85% of post-adolescent women have some degree of cellulite (1–3). Many allegedly successful cosmetic and medical treatments show little effect in improving cellulite, and none of them has been shown to cause its complete disappearance. The anatomy and pathophysiology of cellulite are poorly understood. A review of the literature demonstrates a paucity of studies to validate currently popular theories and treatments. However, a thorough understanding of cellulite pathophysiology is necessary for successful treatment modalities to be developed. Until this is clearly delineated, accepting a less-than-ideal outcome from treatment of this unwanted skin condition will continue to be necessary.

This chapter describes the role of topical agents in reducing the appearance of cellulite. The effect of supplementary aids, such as occlusive garments, will be addressed as well. The various therapies are presented with a focus on how the therapy addresses current concepts of the origin and nature of cellulite.
DEFINITION AND NATURE OF CELLULITE

The term “cellulite” is used in modern times to describe the dimpled or puckered skin of the posterior and lateral thighs and buttocks seen in both trim and overweight women. The appearance is often described as resembling the surface of an orange peel or that of cottage cheese. The condition is best described by Goldman as a normal physiologic state in post-adolescent women, which maximizes adipose retention to ensure adequate caloric availability for pregnancy and lactation (4). Adipose tissue is also essential for nutrition, energy, support, protection, and thermal insulation (5).

At the histological level, cellulite is the result of localized adipose deposits and edema within the subcutaneous tissue. In women, fascial bands of connective tissue are oriented longitudinally and extend from the dermis to the deep fascia. These bands form fibrous septa, which segregate fat into channels resembling a “down quilt” or mattress, and the subcutaneous fat is projected superficially into the reticular and papillary dermis. As the fat layer expands, the perpendicular connective tissue remains fixed and anchored to the underlying tissue, creating a superficial puckered appearance of the skin (5–8). Fatty acids are then believed to be modified through peroxidation by free radicals. These events are thought to contribute to the worsening of local microcirculation by disrupting venous and lymphatic drainage. This skin phenomenon is rarely found in men because the connective tissue in males is not normally arranged vertically, but rather in a crisscrossing pattern that is gender-typical for the skin of the thighs and buttocks (5,7).

PATHOPHYSIOLOGIC MECHANISMS OF CELLULITE FORMATION

Hormones, specifically estrogens and androgens, are thought to influence the formation of cellulite. Estrogen is known to stimulate lipogenesis and inhibit lipolysis, resulting in adipocyte hypertrophy (9). This may explain the onset of cellulite at puberty, the condition being more prevalent in females, and the exacerbation of cellulite with pregnancy, nursing, menstruation, and estrogen therapy (oral contraceptive use and hormone replacement) (9). The opposite seems true for men. From the limited number of studies involving men, it is hypothesized that the combination of gender-specific soft tissue histology at the cellulite-prone anatomic sites, with a relatively lower circulating estrogen level, may be responsible for the lower incidence of cellulite in males (10,11). Although not proven, it is possible that circulating androgens may have an inhibitory effect on cellulite development by contributing to a different pattern of adipose tissue storage (that is, more on the trunk than on the buttocks and thighs).

Adipose tissue is very vascular, leading to the theory that cellulite may worsen in predisposed areas where circulation and lymphatic drainage have been decreased, possibly due to local injury or inflammation. In response to impairment of microvascular circulation, there is increased microedema within the subcutaneous fat layer, causing further stress on surrounding connective tissue fibers and on the accentuation of skin irregularities (2,4). Many of the currently accepted cellulite therapies target deficiencies in lymphatic drainage and microvascular circulation. The lipids within adipocytes are derived from plasma-circulating lipoproteins. In a dynamic process, the stored fat is hydrolyzed and eliminated again to the plasma as free fatty acids and glycerol. Various enzymes including
insulin and cyclic adenosine monophosphate (cAMP) participate in this process. In particular, triglyceride lipase is very important in the promotion of lipolysis. This enzyme is activated by adenylyl cyclase stimulation by means of an antagonist effect. This inhibitory process causes triacylglycerol hydrolysis and releases free fatty acids and glycerol into the interstitial space and plasma.

On the surface of adipocytes, there are receptors that promote the storage of fat and lipogenesis, such as neuropeptide Y and peptide YY. Conversely, other surface receptors promote the elimination of fat and lipolysis, such as β1 and β2. Manipulation of these surface enzymes by topical medications is a new mechanism by which cellulite development can be controlled.

### TOPICAL MANAGEMENT

When using topical treatments to reduce the appearance of cellulite, the concentration and pharmacokinetics of the active drugs as well as the nature of the vehicle must be considered. Vehicles can be in the form of gels, ointments, foams, creams, and lotions, all of which aim to efficiently deliver active product to the skin. Factors that affect the clinical response to treatment are: (i) the interaction of the drug with the vehicle and the skin, (ii) the method by which the drug is applied, and (iii) other biological and environmental factors (12–14). The main barrier to drug penetration is the stratum corneum, the cornified outermost layer of the epidermis. Formulations for topical use may include “skin enhancers,” which significantly increase cutaneous penetration when included in the formulation. Skin enhancers can be common solvents (water, alcohol, and methyl alkyl sulfoxide) or surfactants. They may also be phospholipid molecules called phytosomes, which, when attached to the active drug, increase their lipid solubility. A novel percutaneous delivery system utilizes liposomes, which are specially designed lipid vesicles that are filled with active medication (15,16). Topical anticellulite preparations can be divided into four major groups according to their proposed mechanism of action (Table 1).

1. **Agents that increase microvascular flow.**
   This includes most of the active ingredients in cellulite treatments. They are included to increase microvascular flow and lymphatic drainage, which is thought to play a role in cellulite pathogenesis.

2. **Agents that reduce lipogenesis and promote lipolysis.**
   With the goal of reducing the size and volume of adipocytes, decreased tension on surrounding connective tissue is thought to decrease the clinical appearance of puckering.

3. **Agents that restore the normal structure of the dermal and subcutaneous tissue.**
   By thickening the dermis or preventing fat herniation into superficial tissue, the appearance of cellulite may be reduced.

4. **Agents that prevent or destroy free-radical formation.**
   It is believed that free radicals modify free fatty acids by peroxidation, contributing to the availability of lipids for cellulite formation. Free radicals may also damage elements of the microcirculation, further assisting cellulite development.

The following discussion summarizes the current knowledge of individual and combination topical therapies used to reduce cellulite.
Agents that increase microvascular flow

Drugs that act on the microcirculation of the skin, include the ivy and Indian chestnut vegetable extracts, which are rich in saponins, *Ginkgo biloba*, and rutin, which contain bioflavonoids. These compounds decrease capillary hyperpermeability and increase venous tone by stimulation of proline hydroxylase and inhibition of prostaglandin E₂. These agents also decrease platelet aggregation, thereby inhibiting microthrombus formation. Studies using oscillometry, Duplex ultrasound, hemodynamic methods, and capillaroscopy have demonstrated that *G. biloba* extract is anti-edematous and improves venous return and arterial circulation (17,18). This is accomplished by decreasing capillary hyperpermeability and is employed as an active agent in many topical anticellulite formulations.

*G. biloba* is a member of the Ginkgoaceae family. The leaf extracts contain substances such as flavonoids (quercetin, campherol epicathecol derivates, etc.), biflavones (ginkgetin), and terpenes (ginkgolide B) among others (19). *G. biloba* is used in the treatment of cellulite due to its several effects on peripheral circulation, such as reducing blood

<table>
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<th>Table 1</th>
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<td>Topical Therapies for Cellulite, Based on Proposed Mechanism of Action</td>
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### Agents that increase microvascular flow

- Ivy
- Indian or horse chestnut (*Aesculus hippocastanum*)
- *Ginkgo biloba*
- Rutin
- Pentoxyphylline
- Butcher’s broom (*Ruscus aculeatus*)
- Asiatic centella
- Silicium
- Choititol or artichoke (*Cynara scolymus*)
- Common ivy (*Hedera helix*)
- Ground ivy (*Glechoma hederaceae*)
- Sweet clover (*Melilotus officinalis*)
- Red grapes (*Vitis vinifera*)
- Papaya (*Carica papaya*)
- Pineapple (*Ananas sativus, Ananas comosus*)

### Agents that reduce lipogenesis and promote lipolysis

- Methylxanthines (theobromine, caffeine, aminophylline, theophylline)
- Beta-adrenergic agonists (isoproterenol, adrenaline)
- Alpha-adrenergic antagonists (yohimbine, piperoxan, phentolamine, dihydroergotamine)

### Agents that restore the normal structure of the dermal and subcutaneous tissue

- Retinol (vitamin A)
- Ascorbic acid (vitamin C)
- Bladderwrack (*Fucus vesiculosus*)

### Agents that prevent or destroy free-radical formation

- Alpha-tocopherol (vitamin E)
- Ascorbic acid (vitamin C)
- *Ginkgo biloba*
- Red grapes (*Vitis vinifera*)

### AGENTS THAT INCREASE MICROVASCULAR FLOW

Drugs that act on the microcirculation of the skin, include the ivy and Indian chestnut vegetable extracts, which are rich in saponins, *Ginkgo biloba*, and rutin, which contain bioflavonoids. These compounds decrease capillary hyperpermeability and increase venous tone by stimulation of proline hydroxylase and inhibition of prostaglandin E₂. These agents also decrease platelet aggregation, thereby inhibiting microthrombus formation. Studies using oscillometry, Duplex ultrasound, hemodynamic methods, and capillaroscopy have demonstrated that *G. biloba* extract is anti-edematous and improves venous return and arterial circulation (17,18). This is accomplished by decreasing capillary hyperpermeability and is employed as an active agent in many topical anticellulite formulations.

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viscosity. The terpenes, especially ginkgolide B, inhibit the platelet-activating factor. They increment red blood cell deformability, diminish vascular permeability, and improve vascular wall tonus. All these actions improve the microcirculation. The methylxanthine “pentoxyfylline” improves microcirculatory perfusion through its effect on hematological factors such as erythrocyte shape, platelet aggregation, and plasma fibrinogen concentration. It also has immunomodulatory activity. It has been utilized for peripheral vascular disease treatment with significant benefit. For the treatment of cellulite (20), it has been used transdermally with other drugs, making its evaluation difficult.

Butcher’s broom (R. aculeatus) is a potent venous vasoconstrictor and has the ability to decrease edema. It acts as an alpha-adrenergic receptor agonist of the smooth muscle of veins and therefore reduces vascular permeability. The main active ingredients are saponins, ruscogenin, and neororuscogenina (21).

Asiatic centella extract, both topically and systemically, has been used for treating cellulite and has been demonstrated through capillaroscopy to have an effect on the microcirculation in patients with chronic venous insufficiency, who were treated for venous ulcers (22). Chemically consisting of 40% asiaticosideo, 30% madecassic acid, and 30% Asiatic acid, topical and systemic Asiatic centella have been shown to be harmless by toxicity tests. Asiatic centella also acts in vitro on fibroblasts, stimulating collagen and mucopolysaccharide synthesis. This compound also acts as an anti-inflammatory agent, which may be beneficial in protecting dermal and subcutaneous structures from inflammatory cell injury (19).

Silicium is a structural element of connective tissue, which regulates and normalizes cellular metabolism and cellular division. In the microcirculation, it modifies venous capillary and lymphatic permeability and, in the fatty tissue, it stimulates cAMP synthesis as well as triglyceride hydrolysis, likely activating adenylcyclase in the cellular membrane (23). For this reason, it has been used in topical cellulite treatment products.

Chofitol or artichoke (Cynara scolymus) is a member of Arteraceae family, and it is found in northern Mediterranean soil. Its principal active chemical constituents are numerous enzymes, cynarin, ascorbic acid, caffeoylquinic acid derivates, and flavonoids. It has an antiedematous and diuretic effect, as well as a stimulating effect on the circulation (19).

Common ivy (Hedera helix) is a phytomedicine that grows in places with rich soil, sun, or shade. The parts of the plant used are dried leaves and stems. The leaves have flavonoids such as rutosid and rutinosid, and saponins such as hederin, hederacosid, and hederagenin (19,24). The fruits have saponins, especially hederin, and the trunk has gomoresins and saponins. All saponins improve venous and lymphatic drainage and reduce edema. One of these compounds, hederin, also has an analgesic and anti-inflammatory effect. It has vasoconstrictive and antiexudative properties and can also reduce capillary permeability. It increases circulation and therefore assists drainage of the infiltrated tissue and reduces inflammation.

Ground ivy (Glechoma hederacea) is from the Lamiaceae family and is also used in antcellulite treatment. The main constituents are flavonoids, triterpenoids, and phenolic acids. It grows in moist soil in Europe, especially the Caucasus, and in North America (19). Both types are used in concentrations of 2%.

Indian or horse chestnut (Aesculus hippocastanum) belongs to the Hippocastanaceae family. The seeds and the shells are used in the elaboration of the standard extract (25). The active ingredients contained in the seeds are triterpenoid saponins, such as escin and aesculin, and flavones, coumarins, and tannins (25), with anti-inflammatory and anti-edematous properties (26). Escin is the principal component of horse chestnut, and it has the capacity to reduce lysosomatic enzyme activity by up to 30%, probably by stabilizing
the cholesterol content of the lysosome membranes, thus reducing enzyme release and
capillary permeability. The recommended concentration is 1% to 3%.

Sweet clover (Melilotus officinalis) is a plant from the Fabaceae family. The active
ingredient is contained in the flowers and leaves. One of the components of this botanical
extract is coumarin, which reduces lymphatic edema and diminishes capillary permeability
(27). It is usually recommended to patients with chronic venous insufficiency and lymphatic
congestion—conditions that are believed to be associated with cellulite. The recom-
mended concentration is 2% to 5% (27).

Red grapes (Vitis vinifera) have procyanidins that increase the permeability of
lymphatic and microarterial vessels (27). In topical products, the essential oil is used at
a concentration of 2% to 7% (27).

The fruits and leaves of papaya (Carica papaya) and pineapple (Ananas sativus, Ana-
nas comosus) have anti-inflammatory and anti-edematous effects (28). They contain the
proteolytic enzymes papain and bromelain, respectively. These plants are originally from
tropical America and were introduced to southern Florida. The recommended concentra-
tion is 2% to 5%. Extracts from the fruits and leaves of pineapple (A. sativus, A. comosus)
may be associated with the so-called “pineapple itch,” a contact dermatitis due to a mite
that infests pineapple plantations (29).

AGENTS THAT REDUCE LIPOGENESIS AND
PROMOTE LIPOLYSIS

Drugs that have a lipolytic effect on adipose tissue include the methylxanthines (theobromine,
caffeine, aminophylline, and theophylline). These act through phosphodiesterase inhibition
and are the most common active ingredients in commercial anticellulite formulations (30).
The most useful and safest methylxanthine is caffeine, normally used at a concentration of
1% to 2%. It offers good skin penetration and is therefore rapidly absorbed, leading to rapid
action. Caffeine acts directly on adipocytes, promoting lipolysis through the inhibition of
phosphodiesterase by augmentation of cAMP (31). All methylxanthines activate the enzyme
triglyceride lipase and transform triglycerides into free acids and glycerol. Caffeine also has a
stimulating effect on the cutaneous microcirculation. Table 1 lists botanical sources of methyl-

xanthines, extracts of which are very common in anticellulite agents.

Beta-adrenergic agonists such as isoproterenol and adrenaline, and alpha-adrenergic
agonists such as yohimbine, piperoxan, phentolamine, and dihydroergotamine have
also shown the ability to cause lipolysis. In vitro studies have shown that both the methyl-
xanthines and the beta-adrenergic agonists stimulate lipolysis and a reduction in adipocyte
size through an increase in cAMP inhibition of phosphodiesterase (32,33).

Greenway and Bray demonstrated a statistically significant reduction in the anthropo-
metric measurement of the medial thigh by a double-blind placebo-controlled study,
which utilized topical isoproterenol (a beta-adrenergic agonist), aminophylline (a methyl-
xanthine with phosphodiesterase inhibitory properties), and yohimbine (an alpha-adrenergic
agonist) (34). The reduction in thigh measurement was greatest when all active
drugs were used together, three to five times a week for four weeks’ duration. Of the results
obtained when the three agents were used separately, the best results were obtained with use
of aminophylline.

The effects of methylxanthines can be enhanced by coenzyme A and the amino acid
l-carnitine (23). These agents work by stimulating the mobilization and destruction of free
fatty acids and inducing their active transport through the membranes of the mitochondria. This is important because free fatty acids may cause saturation of the system, leading to negative feedback of lipolysis. Also, the mobilization and destruction process of free fatty acids generates adenosine triphosphate, which increases lipase activity, enhancing hydrolytic breakdown of triglycerides.

Yohimbe (Corynanth yohimbe, Pausinystalia yohimbe, and Rauwolfia serpentine) and alpha yohimbe are alkaloid derivatives extracted from the leaves, shell, and roots of Rubiaceas and Apocynaceas (19). They are adrenergic blockers capable of stimulating the catabolism of fat due to the presence of alkaloids that act directly on the fat cells (19).

**AGENTS THAT RESTORE THE NORMAL STRUCTURE OF THE DERMAL AND SUBCUTANEOUS TISSUE**

Retinol (vitamin A) and the retinoids have been evaluated for their effectiveness in the treatment of cellulite. Topical retinoic acid and related vitamin A derivatives have been used to stimulate circulation, decrease the size of adipocytes, and increase collagen deposition in the dermis (9,35). Based on the capacity of all-trans-retinoic acid (tretinoin) to promote the synthesis of glycosaminoglycans in normal skin and increase the deposition of collagen in the photodamaged dermis, Kligman et al. proposed the use of topical retinol to improve cellulite (35). The premise for its use in cellulite treatment is that topical retinol can be used to increase the thickness and firmness of the dermis, disguising the effect of the superficial fat histologically present immediately beneath it. The use of retinol was proposed instead of tretinoin due to its better tolerability and the evidence that retinol is metabolized to retinoic acid in the skin. In the study by Kligman et al., 19 patients completed a study of retinol 0.3% versus placebo applied to opposite lateral thighs twice daily for six months’ duration. Of the 19 patients, twelve demonstrated greater clinical improvement on the actively treated side on clinical evaluation and laser Doppler velocimetry.

Pierard-Franchimont et al. demonstrated that topical retinol treatment might improve the tensile properties of skin in a beneficial way for cellulite care (36). In a randomized, placebo-controlled study combining the use of retinol with gentle massage, skin elasticity was increased by 10.7% while viscosity was decreased by 15.8% at retinol-treated sites. The main retinol-related change consisted of a two- to fivefold increase in the number of factor XIIIa + dendrocytes both in the dermis and in the fibrous strands of the hypodermis. This is all indicative of increased skin firmness and smoothened appearance of the surface. In addition, some topical ingredients such as vitamin C may help by stabilizing collagen and/or stimulating collagen deposition (3,4,9).

Bladderwrack (Fucus vesiculosus) is a brown marine algae that contains sulfated polysaccharides, iodine compounds, and alginic acid. It is reported to produce contraction of the dermal connective tissue through the increased expression of integrin molecules (19). Increasing dermal density is the likely mechanism by which this agent improves cellulite. It also has a stimulating effect on vascular flow.

**AGENTS THAT PREVENT OR DESTROY FREE-RADICAL FORMATION**

Vitamins such as ascorbic acid and vitamin E may work as antioxidants, protecting dermal and subcutaneous cell membranes from free-radical toxicity. This, in turn, may prevent
and allow for repair of fat herniation. Also, vitamins may improve microcirculation, the impairment of which may be an etiological factor in cellulite formation. *G. biloba* also has flavonoids that act as antioxidants and anti-inflammatory agents (19). Red grapes (*V. vinifera*) are rich in tannins that are antioxidants that diminish lipid peroxidation (27).

**COMBINATION AGENTS**

It is likely that the future of topical cellulite therapy will consist of agents that contain multiple active ingredients. In addition to providing different mechanisms of action directed toward the same goal of reducing cellulite, the different constituents may work synergistically to yield results better than those obtained when each component is used alone. Unfortunately, there are very few good studies in the literature that document the use of these combination products.

Bertin et al. performed a double-blind evaluation of an anticellulite product and showed it to be more effective than placebo in reducing cellulite (37). This product combines retinol with a microencapsulated time-release mechanism to treat cellulite. The compound contains caffeine to stimulate the lipolysis and prevent fat accumulation, esculolide to improve local microcirculation, Asiatic centella as an anti-inflammatory agent, and l-carnitine to stimulate free fatty acid transport and breakdown. Efficacy parameters included cellulite appearance before and after treatment, histology, cutaneous flowmetry, and skin mechanical characteristics. As mentioned, retinol has been shown to increase dermal thickness. The product also contains ruscogenine, which inhibits elastase activity, allowing recovery of extracellular matrix integrity that contributes to the thickening of the dermis and the masking of cellulite.

In a recent multicenter, randomized, placebo-controlled trial involving the testing of a combination anticellulite cream, subjects applied cream on a nightly basis with occlusion on the posterolateral region of one of the thighs. Overall, 62% (21/34) noticed an improvement in their cellulite, with 62% (13/21) reporting greater improvement in the thigh that was treated with the active product. The average measured decrease in thigh circumference was 1.9 cm (range: 0.1–4.5 cm) with active product, and 1.3 cm (range: 0.1–3.0 cm) with placebo. Upon review of the pre- and poststudy photographs, dermatologist evaluators found thighs treated with active product to show greater improvement than thighs treated with placebo in 68% of subjects. This product contained several active ingredients including caffeine, green tea extract, black pepper seed extract, citrus extract, ginger root extract, cinnamon bark extract, and capsicum annum resin (41).

A novel agent named “Bio-actif” consists of a compound containing neuropeptide Y and peptide YY (38). These agents are known to participate in the metabolism of fat with lipogenic effects on adipocytes. Bio-actif is a topical gel of these neuropeptides, combined with green tea, ivy, aloe vera, wheat protein, and other agents, and has shown to decrease fat herniation responsible for the appearance of cellulite.

**EXTERNAL AIDS TO TOPICAL THERAPY**

Supplemental techniques such as massage and fomentation have been shown to assist in topical medication delivery into the skin and further reduce the appearance of cellulite (36). Goldman describes the use of a synthetic bioceramic-coated neoprene
garment to stimulate lymphatic and vascular flow that assisted in improving cellulite (4). This is depicted in Figure 1.

Recently, a double-blinded, randomized, placebo-controlled trial examined the effect of this garment for the treatment of cellulite (39). In this study, 17 subjects were evaluated for cellulite reduction using an anticellulite cream and occlusive garment on only one thigh. Four weeks later, 76% of subjects noticed an improvement in their cellulite, with 54% reporting greater improvement in the thigh that was subjected to garment occlusion. Average thigh circumference reduction was 1.3 cm in the occluded thigh, and 1.1 cm in the nonoccluded thigh. The evaluators who were dermatologists found an overall improvement in cellulite in 65% of treated legs with occlusion and 59% of treated legs without occlusion. Furthermore, the evaluators found the occluded thighs to show greater improvement than the nonoccluded thighs in 65% of subjects. This study demonstrated that although the results obtained from its use are modest, occlusion by compression garments is beneficial in assisting topical agents to improve cellulite. In addition to potentiating topical drug delivery through occlusion, the warmth created by the garment likely improves microcirculation, which may be an etiological factor in cellulite development.

Figure 1
Bioceramic-coated neoprene shorts, worn after topical application of an anticellulite product to the posterior and lateral regions of the thighs to provide greater penetration into the skin by occlusion.
ADVERSE EVENTS

Physicians need to be informed about the great range in efficacy among purported treatments for cellulite, if for no other reason than to avoid untested products. Sainio et al. investigated 32 anticellulite products, mostly botanicals and emollients, each containing an average of 22 ingredients (3). It was found that one-fourth of the substances used have been shown to cause allergy, including isothiazolinones and dibromogluaronitrile. This indicates that despite the fact that most topical cellulite therapies are acceptably safe to many consumers, the risk of adverse events should be taken into account. There are some reports in the literature, of cases of hypersensitivity to ginkgo contained in anticellulite products(3). There are also citings of allergic reactions in patients who used topical products containing ivy (3). The leaves of this plant are considered poisonous when ingested, because they contain arsenic oxide. Hypersensitivity has been reported in users of products containing escin, the principal component of horse chestnut (40). Cases of contact dermatitis on the hands have been reported, resulting from squeezing the fruit to obtain the juice, which contains several acids such as oxalic, malic, tartaric, and racemic (29).

CONCLUSION

The multifactorial etiology and nature of cellulite make it a particularly difficult condition to treat. To better serve patients, the search for a complete cure for cellulite should be avoided. Rather, the aim of treatment should be to minimize the physical aspects of cellulite and prevent its progression by safe, cost-effective means. Topical treatments may improve the appearance of cellulite and represent a reasonable, affordable modality to reduce the severity of this unwanted condition. It is reasonable to speculate that many of these products may also have a role as a preventive measure. The supplemental use of external aids such as compressive bandages or garments to combine the effects of compression and enhanced penetration of topical agents has shown to be useful.
REFERENCES

The Role of Endermologie® in Treatment of Cellulite

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INTRODUCTION

Endermologie®, a treatment method patented by Louis Paul Guitay (LPG System, Nice, France), constitutes a true revolution in the field of physical therapy, both for clinical applications and aesthetics (1). This technique represents a revolution both in principle and in practical application of massage by maximizing the traditional techniques of the physiotherapist. Endermologie® is performed with unique equipment and various protocols for different pathologies.

The equipment consists of a patented tool, the Cellu M6™, produced by LPG System in different versions (the most recent version, introduced in 2002, is the KeyModule), which allows stretching the skin in various directions (Fig. 1). Using only compressed air, it aids in the performance of various physiotherapeutic maneuvers such as pumping, draining, and stimulating the vascular system (Fig. 2).

The first maneuver is directed to muscles and tendons; the second is mostly directed to lipodermal tissues. These maneuvers favor the emptying of the venous and lymphatic systems with the manual techniques described by Casley-Smith, Foldi, and Leduc (2–4). The fingers of the physiotherapist can perform maneuvers of grazing, pinching, slurring, compression, and rotation of the tissues, in addition to the classic “paper-roller,” characterized by movements of compression and rotation that exploits the elastic return of the tissue and also stimulates fibroblastic function. The Cellu M6™ and Endermologie® treatments enhance the execution of the same maneuvers and operations performed with the fingers. It is therefore possible to perform stretching and traction at the same time.

The aspiration system of the machine lifts the skin and subcutaneous tissue inside the motorized handpiece as the operator works, rolling up and moving the handpiece in the desired directions. The equipment software allows the operator to perform “compression–rotation” or “rhythmic compression–rotation” maneuvers, allowing the therapist an endless range of therapeutic maneuvers to treat various pathologies or different phases of a complex pathology. Such characteristics increase the indications and potential fields of application.
Figure 1
The Cellu M6™ instrument for Endermologie®.

Figure 2
There are two different instruments for Endermologie® treatments, the newer instrument provides more activities.
To understand the concept and role of this complex medical methodology, it is necessary to describe the scientific principles and practical bases of some methods such as massage and lymphatic drainage by focusing on the fundamental principles of anatomy and physiology of the dermoepidermal tissues.

**ANATOMY AND PHYSIOLOGY**

Skin and subcutaneous tissue are represented by a grouping of specialized cells into appropriate functional systems:

- Epithelial
- Connective
- Muscular
- Nervous
- Bony

The epithelial tissue provides a functional barrier between the external surface of the body and the underlying tissues, and is characterized by the abilities of secretion, transportation, and absorption.

**EPIDERMIS**

The skin is composed of epidermis and dermis. The epidermis is a stratified scaly epithelium separated from the dermis by a basal membrane, and is constituted by five layers. Starting from the most superficial, the following layers are observed: basal layer, thorny layer, grainy layer, shiny layer, and horny layer. This section of skin draws nourishment from the papillary layer (at the level of the dermoepidermal junction). The permeability and the sturdiness of the epidermis depends on the keratinocytes, cells that produce keratin, while the color depends on the melanocytes.

The defenses and immunity of the skin depend on the Langerhans cells. As epidermal cells move from the deep layer to the superficial layer, the cells become keratinized with consequent modification in form, structure, and chemical composition of the cells themselves. The cells that die also form an impermeable and resistant external barrier.

**DERMIS**

The dermis is composed of connective tissue with fibroblasts, adipocytes, and macrophages in a groundwork of collagen, elastic, and reticular fibers. The deep layer of the dermis is called the reticular layer; the more superficial layer is the papillary layer.

The reticular layer is the principal fibrous layer of the dermis, and is formed from fibers that withstand traction in various directions.

The elastic and collagen fibers are aligned in various directions and form the planes of cleavage or the cutaneous lines of tension that constitute the fundamental parameters for surgical incisions. When the dermis is submitted to tension, a series of “stretching stripes” become visible through the epidermis, i.e., stretch marks. The papillary layer takes its name from the papillae that characterize it, and the “undulations” or “prominences” extending from it into the epidermis. These papillae contain many blood vessels that reach
the epidermis, bringing nourishment, removing by-products, and contributing to the regu-
lation of body temperature. The dermal–epidermal barrier is not an isolated organ
because it also comes functionally into contact with the bones and the underlying muscles
through the lipodermal tissue.

LIPODERMA

The lipoderm fulfills the role of connection, support, regulation of body temperature, and
padding. This layer is composed of connective tissue, with thin collagen and elastic fibers.
The principal cells constituting it are fibroblasts and macrophages. Adipose tissue makes
up over half the volume and has the functional role of regulation based upon endocrine-
metabolic effects from receptors for insulin and estrogenic hormones (Fig. 3).

The Connective Tissue

The connective tissue is the center of important metabolic exchanges among many differ-
ent cellular structures. The connective cells are specialized in the production of the typical
elements that compose the extracellular matrix and they can be generically divided as:

1. -blasts, the elements that they “create,”
2. -cites, the elements that they “preserve,” and
3. -clasts, the elements that they “demolish.”
It is by this fascinating and intelligent synergism among creation, maintenance, and demolition that the connective tissue maintains the whole bodily structure with various and diversified functions. The extracellular matrix that contains these structures and cells, the so-called interstice, is comprised of three principal components:

1. The base, made of nonfibrous proteins, vital elements, and other molecules.
2. The fluid substance of the base.
3. The protein fibers that constitute the connective tissue and are present in the interstice, i.e., collagen and reticular and elastic fibers.

Collagen is the most common protein present in the human body. It represents approximately 6% of the body weight. The molecules of collagen appear microscopically as small ropes composed of three chains of glycine, lysine, and proline. Because of this structure, collagen is very tenacious and flexible but at the same time relatively inelastic.

The cells responsible for the production of collagen are the “fibroblasts,” appearing as fusiform or starry cells on histological examination. They produce elastin and collagen when they are submitted to traction and stretching, playing a fundamental role in the plasticity and reparation of the connective tissue. The typical fibroblast produces filaments that anchor the cell to the membrane of the adiposities and lymphatic cells that constitute the first microscopic lymphatic streets. These filaments have an important role, provoking reactions to different stimuli, such as cicatrization or structural morphologic regeneration.

Reticular fibers are fibers of collagen very thin and very short that branch as a network. They are different from collagen fibers microscopically, both in their structure and in their function. Elastin is a protein that is able to return to its original form after being extended, conferring notable elasticity to the tissue. The molecules of elastin form a net woven so that it extends throughout the whole tissue. The synthesis of elastin considerably decreases with age, so the fibers lose their elasticity and become fragile.

In the extracellular matrix, we can also distinguish two other nonprotein macromolecules with important functions: (1) hyaluronic acid, present in great quantity in the connective tissue and composed of long-chain polysaccharides composed of units of disaccharides that repeat and confer stringiness to the tissues, and (2) proteoglycans, formed by proteins and polysaccharides with the ability to trap a great deal of water, which confers notable elasticity and hydration to the tissues.

The different types of connective tissue meld into one another, and the points of transition cannot be precisely defined. The three principal categories are connective tissue with an extracellular matrix composed of mostly fluid with both protein fibers and substance of base, and composed primarily of protein fibers.

The latter identifies a tissue essentially composed of protein fibers that can subsequently be classified as fibrous tissue.

In fibrous connective tissue, the fibrous protein component of the matrix predominates and is divided into wavy reticular or dense tissue. In wavy reticular tissue, the protein fibers form a net with spaces filled with interstitial fluid, fixing the skin to the lipoderma and the fascia. The principal protein fibers composing it are collagen, reticular fibers, and elastin, and cells like fibroblasts, macrophages, and lymphocytes.

In the dense connective tissue, the protein fibers fill the extracellular space almost entirely. It is composed of fibroblasts and is divided into regular connective fabric and irregular connective fabric. In regular connective fabric, the fibers lie in the same direction,
thus conferring to the tissue the same notable resistance to stretching in the direction of the
orientation of the fibers (as we can find again in tendons and ligaments). In irregular con-
nective fabric, the fibers are in an irregular network, as we find again in the deeper and
resistant portion of the dermis.

The special connective tissue also contains two subgroups: the adipose tissue (consti-
tuted by adipocytes, which are cells containing great quantities of lipids and a small quan-
tity of reticular matrix) and the reticular tissue (characterized by a net of reticular fibers
from different cells). Fat tissue has very important functions in our body, providing insula-
tion and protection, apart from being an important source of energy. In fact, a lipid calorie
occupies less space than a protein or carbohydrate. The reticular tissue constitutes the
structure of lymphatic tissue, bone marrow, and the liver.

The Interstitial Matrix

This constitutes and represents the true inside “sea,” where all the exchanges and all the
vital cellular regulations happen, where life begins and chronic illnesses and degenerative
changes such as the processes of aging occur. This substance permeate every space and is
found as a solution or gel.

ADIPOSE TISSUE AND LIPODERMA

Adipose tissue is, very probably, the most important tissue in the body. It is a form of con-
nective tissue with energetic formation and regulatory functions (5–9). The representat-
ive cell of this tissue is the adipocyte whose principal role is to maintain a reserve of fat, in addi-
tion to acting as mechanical protection and assisting with thermoregulation. The adipocyte
measures from 10 to 150 μm in diameter. Its membrane has two different types of receptors:
(1) alpha 2, antilipoelastic and lipogenetic receptors, that favor the storage of fat; and (2)
beta 2, lipoclastic receptors, which stimulate lipolysis and the use of energy.

The quantity of adipocytes varies among individuals and also among regions of the
body. The variability is based on genetics (10,11). The lipodermis is a cellular tissue that is
found between the dermis and superficial fascia. It is composed of fibrous septa that con-
tain adipose lobules with adipocytes that measure from 0.5 to 1 μm. The lobules are sepa-
rate from elastic connective tissue. Blood vessels and nerves are within the septa that run
from the deep aspect of the dermis to the superficial muscular fascia.

Above the muscular fascia is a pillow of fat called parallel fat; its principal character-
istic is reactivity to food or caloric intake, constituting an important cause of obesity.
Some regions of the body possess subfacial fat that is referred to as steatomery. It is
slightly sensitive to caloric intake and insulin. To be able to lose 1 kg of steatometric fat,
one must lose 6 kg of systemic fat. Inside the abdomen another type of fat, intravisceral
fat, also responds quickly to caloric intake.

Adipose tissue is connected to the endocrine system through hormones that act on
the metabolism of the fats. They are divided into two groups:

1. Lipoclastic hormones [catecholamine, adrenaline, glucagons, adrenocorticotropic
   hormone (ACTH), thyroid stimulating hormone (TSH), and thyroid hormones]
2. Lipogenetic hormones (insulin and sex hormones; in particular, estrogens)
Endermologie® acts on the skin and subcutaneous tissue, connective tissue, fat tissue, and the arteriolar, venous, and lymphatic microcirculation (12,13).

THE SUPERFICIAL FASCIA

Surgeons and anatomists have often ignored or denied the importance of the superficial fascia of the body. For example, the anatomical layer on which liposuction or liposculpture is performed is really the superficial fascia, sometimes considered to be a systemic bandage or the superficial fascial system. An interesting anatomical and histological examination of the inferior limbs has shown the presence of the superficial fascia to be responsible for numerous aesthetic alterations of the skin surface (14).

The depressions and elevations of the contours of the body are explained from the anatomy of the superficial fascia and from its relationships with the skin, fat, and musculoskeletal system. The study of anatomy and the understanding of physiopathological exchanges of the superficial fascial system are the basis for surgical correction of the silhouette, and, above all, the basis for recovery in osteopathic therapies.

Moretti, Schapira, and Kaplan performed a study on 20 patients, 10 males and 10 females, that involved withdrawing a “lozenge” of tissue, 20 cm in length and 4 cm in width, from the area along the side and the knee. Their anatomical study found the presence of a net of connective tissue that extends from the subdermal plane to the muscular aponeurosis (15). It is really this net that constitutes the true superficial band, and it is formed from various horizontal septa of collagen and elastic fibers separated by fat lobules and always crossed vertically by septa-type fibers. At the subdermal level, the presence of the superficial fascia also constitutes a connection with the deep dermis with bigger fibrous septa woven among them in such a way that it provokes the separation of adipose tissue in small compartments that organize the superficial adipose tissue in a classic honeycomb structure. This structural configuration constitutes the bundle-dermal system, which is of great functional importance.

Even if, anatomically, a real plane of separation is not observed between the superficial muscular fascia and the connective fibers of the deep dermis, we can deduce that, functionally and histologically, the continuous imbrications of fibers collectively constitute this hypodermic superficial fascia.

In thin patients, the superficial band is well delineated and of a whitish color. In obese patients, the great quantity of adipose tissue stretches the superficial fascia and attenuates the end, making it difficult to be recognized. The connective and elastic fibers are diluted in the fat fabric, and this can explain the error of some studies that cast doubts on the existence of this superficial band. Without doubt, in the facial zone over the iliac crest in men, it appears as a deep band that is not found in the female sex. Instead, in women, the fibrous band appears with the muscular aponeurosis at a level of the subgluteous that constitutes the base for the adipose tissue situated in this zone. This difference explains the difference in the contour of the gluteus between the two sexes.

The skin, the superficial fascia, and the superficial fat must be considered as a system of protection and functional support. Thisfunctional unity constitutes the support of the adipose fabric and helps to prevent the abnormal location of this fabric in other anatomical regions. The traction and stretching of the superficial facial band and the superficial muscular fascia with Endermologie® are essential in the treatment.
MASSAGE

Massage is an art as well as a therapeutic action, comprised of a feeling between the hands of the operator and the tissues of the patient, which must not be traumatized but instead revascularized, stimulated, and cleansed. A well-done massage relaxes the body and the mind to increase the skin temperature with stimulation of the microcirculation, which favors intercellular exchange. A global massage of the body can have a sedative action and, at the same time, stimulate the nervous system. A massage should not be violent or prolonged to avoid provoking lymphatic congestion.

MANUAL LYMPHATIC DRAINAGE

Lymphatic drainage is a physical method to reduce the stasis of lymphatic fluid and toxic substances in the tissues. Lymphatic drainage is not traumatic, but a gentle massaging technique. Manual lymphatic drainage has its scientific basis in the study and teachings of Foldi (16) and Leduc (17). It deals with a series of grazing and compressions on the lymphatic system to improve lymphatic flow. In the technique of Vodder, lymphatic drainage becomes less physical and more aesthetic in nature. Periodic cycles of manual lymphatic drainage are recommended by Vodder, primarily to keep the tissues free from lymphatic congestion. We believe that manual lymphatic drainage performed with the hands is the only method that gives acceptable results.

THE TECHNIQUE “ENDERMOLOGIE”

HISTORY AND PRINCIPLES

Our experience with the LPG-system began in 1996. The French engineer Louis Paul Guitay developed a system to help in the treatment of fibrosis. He developed this based on a violent trauma that resembled the movement performed by his therapist’s fingers, including additional effects. Sophisticated software allows for possible phases of continuous and sequential aspiration with mobilization of the tissues, offering the therapist an endless range of possibilities for interventions appropriate for various pathologies. It began as a true revolution in physiotherapy and today scientific research has confirmed the effectiveness of this method. This revolution has also given birth to an important professional team formed by doctor/surgeon and physiotherapist, a union that is important in the fields of phlebolymphology.

What Is Endermologie®–Cellu M6®?

Endermologie®–Cellu M6® is patented equipment that works with two motorized rollers with a vacuum suction between them and with varying programs to lift the skin by reaching the deepest structures (Fig. 4).

The hands of the therapist are helped by the integrated action of this equipment, allowing one to make the same physiotherapy maneuvers enriched by stretching the cutaneous fabrics and enabling one to work with deeper layers. The effect is mainly the
stimulation of the metabolism, the vascularization with lymphatic drain, and a purification through manual lymphatic drainage.

To ensure proper treatment, one must:

1. Make the correct diagnosis, to apply the therapy or the suitable program, and
2. Have qualified personnel, to perform the therapy.

MECHANISM OF ACTION

Endermologie performs five complementary actions that allow treatment of different types of tissue:

1. Mobilization of the tissues that characterize the different structures with consequent activation of the arteriolar microcirculation;
2. Traction of the connective tissue with exercise of the skin;
3. Activation of the reflected arcs and stimulation of fibrous banding;
4. Neurometabolic regulation with metabolic activation;
5. Rhythmic compression of the tissues with lymph drainage.

Together, the stretching and the rhythmic compression of connective tissue activate fat lobules to cause their shrinkage with stretching of the fibrous septae (Fig. 5).

The mechanical stimulations act on the following mechanoreceptors:

1. Corpuscles of Meissner that are sensitive to the light stimulations with activation of the fibroblasts.
2. Corpuscles of Water–Pacini that are found in the deep dermis and in the lipoderma. They are sensitive to deep pressure of the skin and vibration. They stimulate the activity of the fibroblasts.
3. Corpuscles of Golgi that are sensitive to light pressure. They stimulate fibroblasts and the regeneration of collagen and connective tissues.
4. Corpuscles of Merkel that are situated in the epidermis and are sensitive to vibrations and light pressure. They act on cellular metabolic activity.
The hyperdistension of the subcutaneous tissue will activate the specific receptors to free substances such as the bradykinin, histamine, serotonin, and catecholamines. These act on the beta-adrenergic receptors and activate the adenocyclase resulting in an increase in the adenosine monophosphate (AMP) and thus an increase in tissue AMP. This in turn stimulates protein kinase that activates intra-adipocytic lipase with hydrolytic action on the triglycerides of the fat cells. Two actions can be hypothesized here.

One of these involves a light treatment that stimulates the Golgi complexes to provoke:

1. vascularization
2. stimulation of the receptors—lipoclasis
3. stimulation of the fibroblasts—restructuring connective tissue

Thus, the stimulation of the beta-adrenergic receptors occurs with

1. lipolytic action
2. increased tissue AMP
3. hydrolytic intrafat action
4. restructuring of connective tissue

The other action involves the strongest and deepest treatment, with stimulation of the Pacini corpuscles, provokes liberation of bradykinin, histamine, serotonin, and catecholamine with

1. increased free radicals
2. alteration matrix
3. phlogosis
4. fibrosis

Then we have a direct action on cicatrization rather than on the restructuring.

Figure 5
Using Endermologie*, we can reduce the typical alterations of the skin and subcutaneous layer, such as fibrose, lipovascularization, lymphatic stasis, increase of free radicals, and alteration of the extracellular matrix.
Treatment Phase

The physician and operator act as a team. The actual procedure can be performed by the physiotherapist or osteopath, according to the diagnosis by the physician specialized in phlebology in the case of pathologies of the venolymphatic system, or by the dermatologist or cosmetic surgeon in the case of burns or scars that introduce fibrous retractions.

The various phases of application are as follows:

1. vascularizing phase, to reactivate the cutaneous microcirculation.
2. drainage phase, to drain the lymphatic stagnation.
3. stimulation phase, to stimulate the fibroblasts and the interstitial neurophysiologic systems.
4. invigorating phase, to stimulate the skin.
5. exercise phase (in which the patient actively performs isometric contractions, as instructed by the operator), to produce tissue and muscle tonification.
6. visceral phase (always with the cooperation of the patient along with specific maneuvers), to stimulate abdominal visceral activities.

INDICATIONS

PHLEBOLYMPHLOGY

This treatment enhances the possibilities offered by traditional manual lymphatic drainage, overcoming the traditional concept of “emptying of the lymphatic vessels” with the concept of metabolic stimulation. Unlike the traditional therapies, performing the lymphatic drainage with Endermologie® allows one to possibly reduce the necessity for high compression of stockings or elastic bandages. This means that the mechanism of action of treatment includes activation of the autonomous nervous system and the interstitial connective tissue (18–21).

PLASTIC AND AESTHETIC SURGERY

The method here is a natural complement of liposculpture, recovering and remodeling the fat tissue and decreasing complications (irregularities). In addition, Endermologie® will decrease the incidence of seromas, edemas, and alterations of the skin (fibrosis and asymmetries) (22–26).

CELLULITIC SYNDROMES

Cellulite and Endermologie®

As discussed in previous chapters, cellulite is a condition comprising various pathological expressions of vascular and/or degenerative alterations of the connective tissue or interstitial matrix, often in partnership with lipotrophy of the muscular tissue. Cellulite should not be confused with obesity. Obesity is the condition when the fat tissue exceeds the normal level by 30%, while cellulite is a transformation and an alteration of subcutaneous interstitial tissues (27–37).
In addition to aesthetic alterations, various subjective symptoms exist including cramps, pain to the touch, heaviness, livedo reticularis, edemas, and tiredness. Such symptoms represent important diagnostic signs for the various cellulitic pathologies that are classified in the following five fundamental groups (38–40).

**Edematous Cellulite.** It is characterized by orange-peel skin provoked by the stretching of the connective fibers because of an excess of liquid. The principal symptoms are pain, edematous plasticity, sense of periodic swelling, and edema of the ankle.

**Adipose Cellulite.** It is characterized by skin stretched by an excess of adipose tissue, with particular increase of the “steatometric fat.” There are no imbibitions of interstitial liquid, which is associated with being overweight. Orange-peel skin is caused by the stretching of connective tissue because of an excess of fat tissue. The principal symptoms are no pain, no edema, and no sense of periodic swelling.

**Interstitial Cellulite.** It is a typical lipedema, which is characterized by the superficial tissue of the thigh being imbibed with fluid and the presence of superficial adipose tissue, and is characteristically seen in young subjects. Orange-peel skin is caused by the stretching of connective tissue owing to edema and fat tissue.

The principal symptoms are pain and edema on the thigh, but not on the leg or foot. There is often a sense of swelling on the hands (41–45).

**Fibrous Cellulite.** From the pathophysiologic point of view, it is characterized by dehydration of the cutaneous and fibrous connective tissue and presence of fat, along with the development of nodules of adipose tissue surrounded by a sclerotic capsule. The skin has an orange-peel appearance and is coarse, caused by the retraction of connective tissue fibers. The principal symptom is pain without edema.

**Localized Adiposity.** They are lipomatosi and localized adipositi present in subcutaneous tissue or in the splitting of the superficial fascia. Their anatomic, physiologic, and pathologic evidence are completely different from the cellulite. The surgeon will proceed to eliminate the localized adiposity through excision or liposculpture. The therapist will begin treatment with lymphatic drainage that aids in recovery.

### Method

Endermologie® is ideal in the treatment of the different forms of cellulite, but precise protocols of technique are necessary (46). Three fundamental rules to provide correct treatment are: no pain, no persistent vascularization, and fluidity of the massage technique used by the operator. The therapist should not provide a strong traction with the rollers. On the contrary, the effect of the technique should be like fluid sliding on the body garment. Another important rule is to position the machinery at the foot of the table on the left. Positioning the Cellu M6™ in this manner allows the operator to use both hands to massage the patient in a superior–inferior direction (Fig. 6).

All the necessary maneuvers are performed, with slow movements in the descending phase, respecting the tissues and favoring the lifting and tonification. The manipulation of
We have various protocols for the treatments of different pathologies.

Endermologie is the typical basic treatment for lymphatic diseases of the legs and for lipodystrophy or cellulite syndromes.
Figure 8
Before and after 7 sessions.

Figure 9
Another case after 6 and 12 sessions of LPG treatment. The biopsy shows the interesting result with new life of the papillary layer of the skin. Abbreviation: LPG, Louis Paul Guitay.
the head must be compared to a painter’s brush that has to cover the whole surface of the body within every treatment session.

In patients with predominant venolymphatic stasis, it is necessary to begin the treatment from the abdomen, treating it in such a way as to prepare the lymphatic vessels to drain from the whole body as well as stimulate the muscular fascia, perivisceral fascia (kidney and peritoneum), and the suspensor ligaments of the colon and liver.

The standard time of treatment applicable to most cases is 35 minutes. More time may be devoted to subjects who are notably overweight, where it is necessary to work on a single part of the body. Whatever the constitution and problem, it is always best to treat the whole body (Figs. 7–9).

Endermologie treatment aims to bring plasticity, elasticity, and compactness to the skin and subcutaneous tissue, thanks to the stimulation of connective tissue. The variations of technique follow the clinical indications and are described in Chapter 7.

CONCLUSIONS

The Endermologie–LPG System is certainly not a panacea for all the pathologies, but it is a real revolution in the field of the physical medicine and of physiotherapy and aesthetic physiotherapy (47). The method consists of not only a massage but also a treatment—massage to perform a local stimulation with local result, a treatment to perform a systemic and local stimulation with systemic and local results.

The use of Endermologie never focuses on the execution of a massage or a lymphatic drainage but on the execution of a treatment that results in the metabolic recovery and the stimulation of connective tissue. When compared with manual lymphatic drainage, Endermologie has created a revolution and is appropriate for cellulitic syndromes.

Endermologie is a natural complement to cosmetic and plastic surgery in the treatment of lipodystrophy and cellulite as well as various forms of edema and lipolymphedema (48,49). With Endermologie, for the first time a particularly active treatment in the activation of fibroblasts and the metabolism of the interstitial matrix is available (50).
REFERENCES

The Use of TriActive™ in the Treatment of Cellulite

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MECHANISM

TriActive™ (Deka, Florence, Italy), as the name implies, has three major weapons in our battle against cellulite (Fig. 1). These three mechanisms, contact coolant, massage, and diode lasers, work together to restore the body’s normal homeostatic environment. The contact cooling system decreases edema by causing an initial vasoconstriction followed by a compensatory vasodilatation, allowing the pooled fluid to remobilize. The rhythmic massage counteracts circulatory stasis again mobilizing fluids by stimulating lymphatic drainage. The TriActive™ device is equipped with six 808 nm diode lasers that work directly on the endothelial cells coating vascular walls, stimulating arterial, venous, and lymphatic flow as well as neovascularization.

REVIEW OF CELLULITE

Cellulite is caused by the swelling of individual adipocytes with increased fat storage, resulting in the obstruction of vascular and lymphatic flow. The resultant edema causes the ensuing fibrosis, which gives the much-dreaded cellulitic appearance. The TriActive™ mechanism is based upon this hypothesis. The TriActive™ device improves the circulatory system, decreasing the edema that may be present. In addition, the massage stretches the connective tissue, smoothing the interface between the dermis and epidermis.

PARAMETERS

The parameters of the TriActive™ system can be manipulated to optimize patient results and are detailed in the following. The intensity of the rhythmic massage can be controlled by the
frequency and duty cycle. The frequency (in Hz) measures the number of aspirations per second. The duty cycle is the percentage of time the aspiration is active between one aspiration and the next. For example, a duty cycle of 70% indicates that the aspiration is active 70% of the time between two aspirations. Thus, by manipulating the duty cycle, one can increase or decrease the intensity of the massage. Andrea Pelosi, a physiotherapist, developed standardized protocols to treat patients with either a gynecoid or an android/male habitus. The gynecoid protocol will be detailed in this chapter as most patients are treated with this protocol.

**INITIAL STUDIES**

The experimental studies in Europe regarding the efficacy of TriActive™ were conducted by Nicola Zerbinati. Ten patients were enrolled and each treated with 20-minute sessions three times a week. Clinical observations, circumference of the thighs and hips, plicometry,
skin elasticity, and thermography were recorded. All patients showed an increase in skin tone and a reduction in the circumference of the areas treated.

■ OTHER USES

The TriActive™ device has been used before, during, and after other surgical procedures including liposuction and abdominoplasty. Robert A. Weiss, associate professor of dermatology at Johns Hopkins School of Medicine, uses TriActive™ during liposculpture operations. He believes that the use of this device helps evenly distribute the anesthetic fluid in the treatment areas. Although not scientifically proven, it is also believed that diode lasers penetrate the fat cells and assist their ability to rupture. TriActive™ can also be used after liposuction to improve results. We have found that the use of TriActive™ in conjunction with liposuction improves cosmetic results and noted a marked improvement in irregularities when TriActive™ is performed after liposculpture. We believe that the TriActive™ device is able to target and improve dystrophic adipose cells.

■ CONTRAINDICATIONS

There are several contraindications to using the TriActive™ device, including pregnancy, active skin infections, asthma, bronchitis, inflammatory/irritable bowel syndrome, heart failure, hyperthyroidism, hypotension, carotid sinus syndrome, and tumors.

■ PROTOCOL

Treatment of the body consists of an intensive phase of 12 to 15 treatment sessions that last 30 minutes each and are carried out two to three times per week. Once this intensive phase of treatment is finished, the maintenance phase consists of one to two treatments per month. A separate protocol exists for gynecoid and android women. However, only the gynecoid protocol will be reviewed as it is the most frequently used. Each phase should be repeated three times, unless otherwise noted. Any area to be treated should be free of any lotions and sunscreens. In the initial phase, the abdominal and inguinal lymph nodes are treated. This is followed by the digestive phase used to stimulate the digestive system. The subsequent draining phase involves transverse movements from the inner knees and continues until the entire thigh is completed. The supine treatment is completed by re-treating the inguinal lymph nodes. The patient is then placed in a prone position and the initial phase is repeated with the stimulation of the posterior inguinal lymph nodes. The drain phase is also repeated. A transverse motion should be carried out from the distal thigh to the proximal thigh and followed by a longitudinal motion, first on the thigh (starting from the distal part) and then on the lower leg (starting from the final part) for two or three passages. Transversal and linear movements on the buttocks must be performed.

Draining action is performed on the lymph nodes in the region between the groin and the inner thigh.

To reactivate the vascular pump of the foot, the handpiece is passed over the sole of the foot in a transverse manner, starting from the heel; two to four aspirations are carried out at each point, taking more time on the heel.
Final lymph node drainage includes first draining the lymph nodes of the region between the groin and the inner thigh, and then draining the lymph nodes of the popliteus cavum.
To tone the buttocks, the patient is repositioned in the supine position and the abdominal and inguinal lymph nodes are re-treated.
Andrea Pelosi conducted a study subsequent to that by Nicola Zerbinati using the above protocol, which he had designed and perfected.
We performed a study to evaluate the combination of active and passive mechanisms in the treatment of cellulite.
Subjects consisted of 11 female patients, all of whom had cellulite on the thighs and/or hips. The group had an average age of 37.2 ± 8.4 years, an average BMI of 22.76 (normal to overweight range), and an average starting body fat percentage of 21.67, measured by electrical impedance.
Prior to treatment (T0), subjects were weighed and height measured to determine BMI. A tape measure was used to measure the circumference of the patient’s hip and thigh. Photographs were taken using standardized lighting, including anterior, lateral, and posterior views of treatment areas.
Each patient underwent twice weekly treatments using the TriActive™ device (Cynosure, Inc., Westford, Massachusetts, U.S.A.) for a total of 10 treatments over a five week period (Fig. 1). The lower body, hips, and thighs were treated according to manufacturer’s instructions for 25–30 minutes, using circular motions with the handpiece held perpendicular to the skin. Throughout the treatment period, any side effects were noted. Measurements and photographs were taken at treatments 5 (T5) and 10 (T10).
Measurements at T5 and T10 were compared to T0 to determine if there were changes in subject BMI or limb circumference. T0 and T10 photographs were compared by three blinded graders to determine subjective improvement, which was graded as none (0), mild (1), moderate (2), good (3), or excellent (4).
Post-treatment, the BMI averaged 22.91 at T5 and 22.79 at T10. Percent body fat measured 21.00 at T5 and 21.35 at T10 (Table 1).
All subjects (100%) exhibited observable improvement in cellulite following 10 treatments (Fig. 2). Blinded evaluation of pre- (T0) and post-treatment (T10) photos yielded an average improvement of 1.67 or moderate improvement (Fig. 3).
Average hip circumference measured 100.62 cm at T0, 100.56 at T5, and 99.35 at T10, an average reduction of 1.21 cm (Fig. 4). Average thigh circumference measured 50.80 cm at T0, 50.53 at T5, and 49.97 at T10, an average reduction of 0.83 cm (Fig. 5).

<table>
<thead>
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<th>Table 1</th>
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<tr>
<td><strong>Average BMI and Percent Body Fat Prior to and Following 10 TriActive™ Treatments</strong></td>
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<tr>
<td><strong>BMI</strong></td>
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<tr>
<td>Pre-treatment (T0)</td>
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<tr>
<td>T5</td>
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<tr>
<td>Post-treatment (T10)</td>
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Abbreviation: BMI, body mass index.
Figure 2
Percent of subjects with observed improvement by grade and overall average improvement score.

Figure 3
Cellulite before (A) and following (B) 10 treatments.
All subjects found the treatment to be pleasant. Often, patients fell asleep during the treatment sessions. There were no adverse effects reported throughout the study.

The TriActive™ device proved to decrease hip and thigh circumference. In addition, blinded evaluators found improvement in appearance of cellulite in all subjects. Treatment

**Figure 4**
Hip circumference measured over the course of treatment.

**Figure 5**
Thigh circumference measured over the course of treatment.
was progressive, with an improvement in cellulite over the course of the procedures. It is anticipated that additional procedures may further improve outcomes. Improvements in appearance included reduction in the appearance of skin dimpling, improvement in the overall contour of the limb, and improvement in overall skin texture. Patients enjoyed the procedure and found it to be relaxing, with no side effects.

There was no significant change in either BMI or percent body fat. This suggests that observed improvement were due to the action of the TriActive™ device. It also suggests that the TriActive™ device provides localized treatment, without an apparent systemic effect on the body.

Many patients are interested in treatments that improve the appearance of cellulite. We have found that the TriActive™ device offers a unique and unmatched combination of low energy irradiation, contact cooling, and dynamic suction massage to treat this unpleasant condition of the skin and subcutaneous tissue, leading to improvement in the appearance of cellulite.
INTRODUCTION

“Carboxytherapy” is the therapeutic use of carbon dioxide (CO₂) in its gaseous state, either by transcutaneous or subcutaneous injection.

This therapy was first performed in Argentina (1) and later in France, in the thermal waters station of Royat, near Clermont Ferrand (2). There, a group of cardiologists from the hospital of Clermont Ferrand began to treat patients with peripheral organic and functional arteriopathies (atherosclerotic, Buerger’s disease, Raynaud’s disease, etc.). In 1953, the cardiologist Jean Baptiste Romuef published a paper about his 20 years of experience in using subcutaneous injections of CO₂ for treatments (3). Later, the Parisian cardiologist Jerome Berthier, along with Luigi Parassoni from Gaillard A, started to apply it in patients with cellulite (4).

Until 1983, 402,000 patients had been treated in Royat. By 1994, 20,000 patients were treated per year. The large number of patients confirms the popularity and perhaps the efficacy of this therapeutic method.

CO₂ is an odorless, colorless gas, first discovered by Van Helmont in 1648. The clinical use of CO₂ is not new. Many years ago in France, Clermont Ferrand used thermal CO₂ (CO₂ 99.4%, N 0.558%, and O₂ 0.021%, plus argon, xenon, and krypton traces) for treating lower limb peripheral arteriopathies, especially the obliterating ones (5).

When administered subcutaneously, CO₂ immediately diffuses at the cutaneous and muscular microcirculatory level. After the administration of 200 cc of CO₂ in the subcutaneous thigh tissue of a canine, CO₂ is detected in the femoral venous blood in approximately 5 minutes, with a maximum time lag of 30 minutes. This demonstrates the ability of CO₂ to diffuse across fasciae and reach the underlying muscles (6). Most of the gas is eliminated through the lungs (expiration), while a smaller portion is converted into carbonic acid in tissues and is eliminated through the kidneys.

At the vascular level, CO₂ increases vascular tone and produces active microcirculatory vasodilatation. CO₂-induced vasodilatation results from the direct action of CO₂ on arteriole smooth-muscle cells (7).

In addition, this promotes Bohr’s effect, a mechanism that allows the transfer of tissue CO₂ to the lungs and lung O₂ to tissues through the oxyhemoglobin dissociation...
curve. When administered through an external route, CO₂ promotes this mechanism, resulting in a higher tissue oxygenation and neoangiogenesis (Fig. 1).

![Figure 1](image)

_Figure 1_
Change in oxygenation and neoangiogenesis after administration of CO₂.

Although it is toxic when inhaled (10% in air may cause asphyxia), subcutaneous or intra-abdominal administration of CO₂ has not shown any toxic effects, even at high doses (2–10 L). It differs from other gases because no nitrogen embolisms arise, unlike those that occur in oxygen–ozone therapy.

**INDICATIONS**

I. Cosmetic medicine  
   a. Cellulite (8)  
   b. Localized adipose tissue (as a coadjuvant)  
   c. Skin grafts (pre- and postoperatively) (Fig. 2)  
II. Cosmetic surgery  
   a. Pre- and postliposculpture (Fig. 3) (9)  
III. Angiology  
   a. Organic or functional peripheral arteriopathies (10)  
   b. Microangiopathies (atherosclerotic, diabetic, etc.) (Fig. 4) (11)  
IV. Rheumatology  
   a. Autoimmune arthritis  
   b. Degenerative osteoarthritis  
   c. Acute arthritides (epicondylitis, periarthrhritis, etc.)  
V. Urology  
   a. Erectile dysfunction, associated with microangiopathies
Figure 2
Before and after CO₂ treatments to correct skin graft surgery.

Figure 3
Before and after CO₂ treatments to improve liposculpture results.
VI. Dermatology
   a. Psoriasis
   b. Ulcers associated with microangiopathies (varicose, diabetic, etc.)

   Lipodystrophy and cellulite are pathologies in which the microcirculatory disorders resulting in interstitial edema constitute triggering factors that also support the pathological process. Because subcutaneous CO₂ improves capillary blood flow and reduces stasis, carboxytherapy contributes to the restoration of microvascular-tissue unit exchanges.

   On administration through the percutaneous as well as subcutaneous routes, CO₂ causes the vasodilation of subcutaneous microcirculation, expressed by an increase of blood flow and the opening of “virtual” capillaries that normally are closed. This seems to occur from dilatation of arteriole smooth-muscle cells (12), with an increase in tissue CO₂ that is maintained for a certain posttherapy period (Fig. 5) (13).

   The formation of increased vascularity after treatment leads to the following question: Is it an actual “opening” of capillaries or neoangiogenesis? Certainly, CO₂ activity at the interstitial level and the activity of neurophysiological mediators demand further research. In fact, there are many extremely interesting hypotheses to consider.

   Although, in the case of cellulite and lipolymphedema, carboxytherapy shows an effective activity, its use in localized adiposity is rather perplexing. Cellulite and lipolymphedema show microvascular alterations (stasis microangiopathy) (14) and histomorphological disorders (adipocyte aggregation and fibrosis) that do not appear in localized adiposity. Above all, localized adiposity does not show the typical signs of vasculo-connective cellulite disease, such as hypothermia, granuliform sensation under deep palpation, etc. From the
microcirculatory point of view, vascular areas are present because of compression of the capillaries by the adipose tissue, while capillary stasis is not evident. This explains why carboxytherapy is not indicated for the treatment of localized adiposity, though it may be used when this pathology evolves toward lipolymphedema or liposclerosis (Fig. 6).

In this case, the use of carboxytherapy is supported by the idea that an increase in blood flow in precapillary arterioles enhances lipolysis, owing to α and β fiber stimulation. It must be remembered that such fibers have antilipolytic and lipolytic activity according to the area in which they are located. The concept of localized adiposity is often misunderstood. This was also evident in treatments for systemic multiple lipomatosis (15) in which, in combination with surgery, a reduction in adipose masses was observed. In fact, such masses do not constitute localized adiposity, and are manifestations of hypertrophic lipodystrophy, an entity that is very different from localized adiposity in terms of histology and physiopathology. Hence, it is evident that carboxytherapy has good results, both in terms of clinical manifestations and histology (16,17).

**TREATMENT METHOD**

I. Equipment
   a. Allows CO₂ administration in a controlled manner: flow velocity, injection time, total volume, and monitoring of administration dose percentage.
   b. The gas in the canister is administered under sterile conditions, at 2 kg/cm² pressure.
   c. Needle 27 or 30 G (Figs. 7 and 8).
Videocapillaroscopy with optical probe (VCOP) to follow the actions of CO₂ can be used. Until now, the absence of clinical parameters and instruments, for semiologic characterization and differential diagnosis limited the treatment investigations to inspection and palpation.

The instrumental help of VCOP allows diagnostic classification, which corresponds to the histomorphological alterations and anatomotopography of the adipose tissue (fatty) to be made. This was achieved with simultaneous biopsies in a study accomplished by the Plastic and Reconstructive Surgery Cathedra of the University of Sienna, headed by

Figure 6
Before and after CO₂ treatment for localized adiposity.
Dr. Prof. D’Aniello. This linkage of the morphologic and biologic diagnoses allows us also to evaluate evolutionary purposes and prognoses.

The VCOP is a noninvasive method that analyzes capillaries in both the static and dynamic forms, which, on combining with the process of digital imaging, transforms the qualitative to quantitative characteristics (Fig. 9) (18).

After administration of subcutaneous CO₂, there is an increase in vertical capillaries (black points) and transverse capillaries (Fig. 10).

**CONTRAINDICATIONS**

- Recent or acute myocardial infarction
- Unstable angina
- Congestive heart failure
- Severe high blood pressure
- Acute thrombophlebitis
- Gangrene
- Localized infections
- Epilepsy
- Respiratory failure
- Renal failure
- Pregnancy
Figure 8
Subcutaneous administration of CO$_2$.

Figure 9
Videocapillaroscopy before the use of CO$_2$. 
SIDE EFFECTS

- Fleeting, burning, or oppressive pain, at the injection site, related to flow velocity and patient’s threshold
- Limb heaviness sensation, related to dose and treatment evolution
- Rubor and calor at the injection site
- Ecchymosis
- Subcutaneous crepitations, of variable duration (no longer than 30 minutes)

PROTOCOL FOR CARBOXYTHERAPY IN CELLULITE

I. Subcutaneous injection are given at variable volumes between 100 and 200 cc per limb. Initial flow may vary between 10 and 50 cc/min (19).
II. Injections not exceeding 30 or 50 cc per injection per area are recommended.
III. It is advisable to make punctures in different directions (downward–upward and upward–downward) with a 27 or 30 G needle.
IV. The area is divided into four to six quadrants per limb.
V. Therapy is started at low flow, 10 to 50 cc/min.
VI. Therapy is accompanied by manual massage (finger are moved as if playing a piano, playing over subcutaneous emphysematous areas) to contribute to gas diffusion, to control emphysema, and to reduce patient’s possible discomfort.
VII. Frequency of sessions
   1. Daily
      a. Ideal for patients staying at thermal centers or patients receiving one-week treatment. Generally, two or three cycles per year are suggested.

Figure 10
Videocapillaroscopy after use of CO₂.
2. Two or three sessions per week
   a. It has a more widespread frequency and is the most recommended, particu-
      larly if symptoms and an important microcirculatory stasis are present. Also
      used for achieving lipolytic effects (to reduce localized obesities).

Figure 11
(A) Each intersection of lines is the point to inject the CO$_2$. (B) Before and after 8 sessions of CO$_2$,
300 cc in each leg.
3. One session per week  
a. This is an alternative for patients with aesthetic problems showing no symptoms. At least 15 to 20 sessions should be performed.

It must be remembered that carboxytherapy’s most important activity is microcirculatory stimulation, which becomes evident from the first application, and that its effect depends directly on the amount of gas injected into the subcutaneous tissue (Figs. 11–13).

■ CONCLUSIONS

Carboxytherapy:

- is a valid therapeutic method of easy application;
- has no significant or adverse side effects; and
- can possibly be associated with other types of therapy (20).
Figure 13
Before and after CO₂ therapy.
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Surgical Treatment

A: Lipoplasty, Vibro-Assisted Liposuction, Lipofilling, and Ultrasonic Hydroliposuction

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LIPOPLASTY

Medical therapy may precede surgical treatment when weight reduction is necessary, which consists of low-calorie, balanced, high-protein diets. Physical therapeutic and pharmacological methods may also be useful to reduce localized adiposity.

The treatments to reduce localized adipose tissue volume excess should include local lipolysis stimulation. Comprehensive treatments (e.g., high-protein diet plus Endermologie® and mesotherapy) lead to fat loss in overweight body areas without loss of muscle-cutaneous tone. Inadequate diets and gastric bypass or stapling operations may cause generalized weight loss, ultimately intensifying a poor metabolic state. With generalized weight reduction, loss of adipose tissue from the breast and face occurs, while localized areas with adiposity remain almost unaltered leading to subsequent worsening of the patient’s psychoemotional condition.

Lipolytic treatments may offer good results only in hypertrophic adiposities or in the initial treatment of mixed adiposities because of the particular tendency of the adipocyte to keep a constant volume. Lipolytic treatments reduce the volume of the fat cells, but do not destroy the cells (lipoclasis). Many lipoclastic treatments have been proposed, but only carboxytherapy and Ceccarelli’s external ultrasound lipoclasis (lipoclastic treatment), the latter to a lesser degree, show real clinical results.

Among lipoclastic methods that cause tissue damage at the adipose cell/lobule level and decrease volume excess, liposuction—today known as liposculpture or lipoplasty because it is aimed at body contour remodeling—is effective. In other words, it is targeted at the remaining fat, at its specific location, and at the treatment of the pathology, rather than at generalized fat reduction.
HISTORICAL BACKGROUND

In 1921, the French surgeon Dujarrier tried to remove adipose tissue from the internal area of a dancer’s knee by means of an obstetric curet. The limb was later amputated because of an ensuing infection (1). In 1964, the German surgeon Schruder tried to repeat the same operation using a different technique (1). Thus, “lipeoxeresis” was born, although physicians were unwilling to accept it because it frequently resulted in lymphorrhea and cutaneous unevenness. Some years later in 1974 in Rome, the Italian surgeon Arpad Fisher and his son Giorgio developed a new technique called “liposculpture,” that included the use of blunt cannulae and a liposuction device (2). In 1978, Drs. Meyer and Kesserling reported a liposuction technique that used a sharp cannula connected to a 0.5-atmosphere suction device.

Liposculpture is a modeling of the contours, a real artistic job of architecture bound to restore the juvenile and harmonic forms of the face or body by working with the hypodermic fatty tissues. — Pierre Fournier

But it was only in 1977 that liposculpture became popularized when the distinguished French surgeon Illouz first submitted a new technique of his own, based on a cannula similar to Fisher’s, to an international cosmetic surgery conference. Tunnels were excavated at different adipose tissue levels after injecting a hypotonic solution (3). However, it was the French physician Fournier who first coined the term “lipoplasty” for his “dry” fat suction technique (meaning that no previous hypotonic infiltration was applied) that enabled contour remodeling (4).

Since 1980, “liposculpture” and “lipoplasty” became widespread around the world. Research papers were submitted to major cosmetic and plastic surgery journals and scientific conferences. The Italian physician Marco Gasparotti, who developed superficial—or
first-generation—liposculpture, which consists of an extremely accurate use of liposculpture and lipoplasty, later improved these techniques. By removing deep fat from certain skin areas, this method enables body contour remodeling (5).

Left: Before liposculpture; right: after liposculpture. Source: Courtesy of Prof. Marco Gasparotti.

A discussion of the development of liposculpture is not complete, however, without Dr. Jeffrey Klein’s research work. He developed tumescent anesthesia and thus set a landmark in lipoplasty (6). There was previous research on local anesthesia by the Russian physician Vinieschewky (1916), who studied hydraulic tissue preparation, and other works on local anesthesia applied to large volumes carried out in the United States during the 1930s and 1950s. Dr. Klein’s revolution allowed lipoplasty to be carried out on outpatients under local anesthesia, entailing little blood loss.

In his attempts to reduce blood loss and postsurgical trauma, Dr. Pierre Fournier showed, in 1985, that fat might be extracted through single-use syringes. By using hypodermic needles, cylinders of fat tissue may be extracted and adipocytes may be saved and later reinjected into a different area (this technique was later named “lipofilling”) (4).

Finally, Dr. Michele Zocchi developed ultrasonic liposculpture (second-generation liposculpture), and submitted his first reports on this technique in his papers on the selective cavitation effects of ultrasound for adipose tissue lysis (7). Later on, in 1992, a specific device was introduced. Carried out by competent professionals, this method enables the controlled extirpation of great amounts of adipose tissue and also allows skin retraction.
Tumescent anesthesia and Fournier’s syringe technique.

Types of cannulas.
Unfortunately, complications derived from irresponsible use of ultrasound devices have limited their use to experts only, with optimal results (8).

Since 1997, we have presented a third-generation liposculpture technique. According to our first tentative definition, it may be called pneumo-assisted vibratory liposculpture (reciprocating automatic liposculpture). It consists of a handle, weighing hardly 300 g, connected at one end to the operating room compressed air equipment or to a nitrogen cylinder and, at the other end, to a small surgical suction tube. Modern vibratory cannulae working at low frequencies are also in available—energy is provided by electric power, the device may be easily transported, and a wider range of cannulae sizes is available. In every case, operation time is reduced, the surgeon’s effort is diminished by 40%, and the postoperative period is improved. All this indicates that vibratory cannulae involve a positive advance in lipoplasty.

The combined action of the cannula causes fat tissue rupture and homogenization, and simultaneous suction. This is the methodology used nowadays—applying a 2 mm to 4 mm cannula—to treat lymphedema and lipolymphedema (9). This technique is easily learned and has few adverse effects even when operations are not carried out by experts.

The powered lipoplasty device, the vibratory cannula, has introduced a new electrical power system. It is provided with a higher number of cannulae that contribute to tumescent anesthesia. It includes cannulae of several sizes and different headstocks. The surgeon’s effort is reduced by about 45% and the operation time shortened by about 35% to 40%. The striking fact is that postsurgical recovery is faster, edema is minimized, and hematomas are very rare. Postsurgical pain also decreases (10).

Dr. Michelle Zocchi was a visionary man of science, a genuine researcher, and an insightful observer who noticed the advantages of ultrasound and their potential contribution to lipoplasty. Ultrasonic liposculpture carried out through devices such as solid titanium ultrasonic probes enables selective destruction of fatty cells with no damage to venous and lymphatic vessels or fibers (11,12).
Drs. Leibaschoff and Ciucci have carried out direct and radioisotope lympho-
graphies that demonstrate conclusively this selective destruction, as well as Tazi and
Schefflan’s videofibroscopies (13).

In 1992, Dr. Giorgio Fischer developed orthostatic liposculpture. He designed an
orthostatic couch that lets the physician operate and control liposculpture while the patient
is in a standing position. No risk is involved and the operation is performed while the force
of gravity exerts its action. Thus, a more convenient aesthetic result may be attained (2).
Almost simultaneously, Dr. Marco Gasparotti reported his superficial liposculpture methodology, which enables better skin retraction and a smooth, homogeneous, cutaneous surface. This technique requires a thorough knowledge of topographic anatomy, because it is carried out with blunt minicannulae (2–3 mm in diameter) that should be applied superficially through quick and accurate movements (14).

In 1993, Jeffrey Klein made yet another contribution by using 2-mm microcannulae of various lengths in tumescent liposculpture. By working through multiple entry orifices, he achieved excellent results and the patient’s recovery was very quick (15).

Advantages of microcannulae are:

- less pain
- more accuracy
- greater finesse
- superficial liposuction
- more complete removal
- easier penetration
- microincisions
- no sutures
- accelerated healing
- less elbow trauma
In 1996, the Sylberg method or external ultrasound-assisted lipoplasty (UAL) was introduced. It is based on an external fixed power ultrasound source having special characteristics. Ultrasound is applied on areas that have already received tumescent anesthesia, and liposuction is carried out according to the rules of the art. According to the author
and Dr. Rosenberg’s reports, the tumescent solution is evenly distributed, and the activity of ultrasound on fat tissue may be seen through fibroscopic studies. The adipose tissue is fragmented, thus facilitating extraction through minicannulae (3–4 mm) (16).

Today we have a new machine for internal ultrasonic liposculpture; the VASER\textsuperscript{*} is the safest machine to work with in ultrasonic lipoplasty, with all the advantages of the ultrasonic machine (17).
VASER®-pulsed ultrasound is a relatively recent device, which utilizes ultrasound energy to emulsify fat tissue. The main differences from previous ultrasound technologies (i.e., UAL) concern safety issues. Owing to the excessive ultrasound energy delivered by first- and second- generation UAL devices, a series of complications arose including seroma, cutaneous burn, skin necrosis, and dysesthesia. The initial enthusiasm for UAL decreased due to the complication rate and the cost of equipment.

In 2001, VASER® appeared on the U.S. market as a new device delivering nearly half the ultrasound energy in comparison with the older machines. The shape and design of the new solid titanium probes increased the efficiency of the system.

Superficial UAL allows (through minimal skin incisions) the utilization of 2.2 mm solid titanium probes to fully undermine the subcutaneous tissue, thus allowing excellent skin retraction. Deeper planes are treated with 2.9 mm or 3.7 mm probes for faster emulsification. Grooved probes increase efficiency of the system. Three alarms control the system and prevent mistakes (18). It is thought that the complication rate has dropped virtually to zero with the present device.
Drs. Di Giuseppe and Leibaschoff demonstrate lipoplasty with VASER®.

Before and after VASER®. Source: Courtesy of Alberto Di Giuseppe, M.D.
Lipoplasty has a threefold target: aesthetics, functionality, and restoration. But only surgeons properly trained in liposculpture may achieve this target. Lipoplasty is a surgical technique performed through mini-incisions. Thin tools, a few millimeters in diameter, are used under tumescent local anesthesia. Operations should be performed by surgeons who have experience in this field, under the control of anesthetists or cardiologists specialized in surgical monitoring.

**DEFINITION**

Some specialists define liposculpture as a technique for fat tissue extirpation using blunt 2 mm to 5 mm cannulae. Suction may be carried out with 20 cc or 60 cc syringes or through minicannulae (2–4 mm) with suction equipments (1 atm). The name “liposuction” is used for the same technique carried out for fat removal using suction equipment with larger cannulae.

Fournier said that “liposculpture is the technique that uses disposable syringes to aspirate localized fat deposits and, if necessary, reinject it where needed (19).”

We personally believe that the term “lipoplasty” is all inclusive, and that the term “lipoplasty liposculpture” includes all surgical, medical, or rehabilitative therapeutic practices. It is sheer nonsense to assume that results are guaranteed after surgical procedures. The lack of comprehensive treatments is precisely what caused dissatisfaction in most patients submitted to liposuction some years ago.

We define “lipofilling” as the method of reinjection at different locations of the adipose tissue previously extracted through liposculpture and subsequently washed with physiologic salt solution to preserve adipocyte integrity (20).
We define autologous tissue “implanting” (“autolipofilling”) as the method that employs fat tissue extracted through liposculpture and submitted to adipocyte lysis. After subsequent decanting, it is possible to obtain a compact tissular extract corresponding to the support structure of the adipocyte.

**FAT TISSUE VASCULARIZATION**

It is important to recall adipose tissue vascularization. There are three vascular networks laid horizontally and separated by different structures within the space between the muscular aponeurosis and the capillary dermis.

From deep to superficial levels, we may find:

- the musculoaponeurotic vascular network
- the superficial fascia vascular network
- the dermic subpapillary vascular network

There are also perforating vessels across the deep fatty tissues that have no ramifications. They connect to the superficial fascia through communicating branches that constitute a wide network from which small communicating vessels emerge and reach the capillary dermis for skin irrigation. It has been demonstrated that the adipose tissue blood flow varies according to the nutritional status and body weight, and that it increases in fasting conditions.

**AREOLAR FAT**

It is located on the superficial fascia and is crossed by small perforating vessels for skin irrigation. It is adipose tissue affected by the liposclerosis process, causing the typical peau d’orange condition, related to deep skin layers. At the abdominal wall level, the thickness ranges from 0.8 cm to 2.1 cm in slim individuals, and from 1.5 cm to 2.5 cm in obese individuals. It corresponds to a safety fascia that should be preserved during liposuction and liposculpture; hence, surgical operations should never alter it.

**DEEP FAT**

Deep fat is located under the superficial fat, separated by the superficial fascia. The biggest blood vessels and lymphatic vessels may be found at this level. Fat excess, altering body contour and corresponding to different steatomeries, is located at this level, where fat may suffer hypertrophy in the event of general weight increase. Its thickness may range from an average of 0.5 cm in normal individuals to 4 cm or 5 cm in obese individuals. This is the fatty tissue that should be removed through liposuction and liposculpture.

It is important to remember that adipose tissue is not only a reserve tissue but also has an important hormonal function: autocrine regulation, paracrine regulation, and endocrine regulation (21).

**PATIENT SELECTION**

Liposculpture sometimes may be carried out under local anesthesia and as an ambulatory procedure because of its characteristics as a less aggressive method. A wide variety of
patients may be submitted to it. In each case, the following rules should be observed in order to prevent future complications or the patient’s disappointment:

- Liposculpture is a technique aimed at localized adiposity, but it is not a slimming technique. Hence, patient selection as well as the study of body contours and steatomeric areas is essential.
- No more than 3000 cc of tumescent anesthesia solution should be used.
- Maximal dose of lidocaine should be 50 mg/kg.
- A maximum of 3 L of fat should be extracted.
- No more than 25% of the body surface should be treated.
- Mega-liposculpture should be avoided. If aspirating more than 5000 mL of fat, one should follow the recommendations of the American Academy of Cosmetic Surgery (22,23).
- It is particularly indicated in patients showing good trophism and good cutaneous elasticity.
- The technique should not be applied to patients with a history of blood dyscrasia; renal, hepatic, or cardiac affections; hypertension; diabetes; and those suspected of having psychic disorders.
- Patients with general obesity showing clear signs of muscular or cutaneous flaccidity may be treated. It must always be kept in mind that an association of methods will be necessary in rehabilitation.

**PRESURGICAL VISIT**

First the physician should have a long conversation with the patient to understand the real motivation for the visit, the referral, the patient’s knowledge of the technique, and especially the expectations and fantasies about the results. It is very important to ascertain what the patient expects as the possible outcomes of the operation. Then, the patient should be examined naked to detect examination areas and get a general impression of body and proportions assess possible outcomes according to body harmony.

The examination should be carried out with the patient in a standing position and in different decubitus positions. In fact, we should remember that the fat tissue mass has its own mobility and changes according to different positions.

The patient should be required to contract different muscle groups in order to distinguish muscular flaccidity from “false culotte de cheval,” to differentiate rectus abdomicus dehiscence or flaccidity from swelled or dilated abdomen, and thus define the appropriate indications and techniques.

The history of previous treatments such as iontophoresis, electrolipolysis, and mesotherapy should be investigated, as well as all methods that might have changed fatty tissue characteristics: drugs or other therapies such as ozone therapy or masotherapy. We should examine skin quality and muscle group tonicity. Then we must provide our impression, suggest indications, and give advice on possible risks.

In the event that intervention is possible or indicated, we should provide a brochure with complete information on the methodology and techniques to be used, including details on the anesthesia and possible sensations to be experienced by the patient during the operation. We should explain the method in detail, how the fat is extracted, the instruments used, and the risks and possible outcomes of the intervention. Two photographs in each position should be taken with an instant camera. One of each pair will be modified,
drawing different body contours in black ink to serve as a real estimate of the possible outcome according to our personal view and experience. A digital camera and image editing software may also be used, but it is advisable to warn the patient that the results predicted by computer are impossible to reproduce exactly.

Real “cullote de cheval” does not change with the contraction of the gluteus muscle.

The difference when the patient contracts the gluteus muscle.
Big lipodystrophy. The patient was informed about the possibilities of a second procedure and the use of additional postoperative treatments.

Same patient after 2 months of ultrasonic liposuction.
Factors in determining safety of liposuction include:

- the number of areas treated
- volume of supranatant fat removed
- percent of body fat removed
- ratio of body weight to the weight of fat removed
- dosage (mg/kg) of lidocaine
- volume of intravascular fluid infused
- duration of surgical procedure

It should be remembered that in many cases there is a gap between the fantasies of the patient and the real medical possibilities. This may lead to discontent, disappointment, and complaints, and also legal procedures. The patient should be informed that immediate and late postoperative periods are not identical. Specific care for each period and the possible limitations in each should be remarked on.

Once explanations are given, all elements should be assessed and the indicated technique described again. If necessary, the patient may take some photographs home to come to a decision in private or with her family.

In the event of a favorable decision, routine laboratory tests, protein and albumin content (lidocaine carrier), coagulation tests, cardiovascular surgical risk assessment, and hepatitis and HIV tests should be required. Other factors to be investigated include possible allergies to substances—especially to anesthetic drugs and skin disinfectants—and history of previous surgery, type of incision, and formation of keloids.

**DETAILED PHYSICAL EXAMINATION**

- abdomen: hernias, scars, and diastasis
- skin alterations

Retractions and bumps.
varicose veins and hemorrhage
- edema
- retractions and bumps
- flaccidity

**PRESCRIPTIONS**

Aspirin administration should be discontinued at least seven days before the operation to avoid coagulation disorders. The use of all other unnecessary drugs should also be suspended 1 week prior to the operation.

Broad-spectrum antibiotics should be prescribed, such as ciprofloxacin 500 mg, 1 g/day for 5 days after the operation. If necessary, an analgesic or a nonsteroidal anti-inflammatory drug (diclofenac potassium) may also be prescribed.

Exercise and sports should be interrupted at least for 2 weeks, but the patient must walk every day after the liposculpture (1 mile per day the first week after the second day); and also avoid sun exposure of treated areas for approximately 15 days.

Care during immediate and late postoperative periods is very important. When lipoplasty is finished, bimodal compression with absorbent pads is fundamental, because it contributes to the patient’s comfort and to a uniform skin and cellular subcutaneous tissue retraction. This is accompanied by adequate compression and a supporting binder. After 24 hours, the pads are removed and replaced by a supporting noncompressive binder (hence allowing lymphatic precollector functioning). In case of lower limb surgery, the patient should start wearing graduated compression stockings (15 mmHg) 1 week after the operation.

Immediate physical therapy consists of manual lymphatic drainage, 1 and 3 MHz external ultrasound, and magnetotherapy for 1 week. Then, subdermal therapy and carboxytherapy are introduced or continued.
**POSTOPERATIVE SCHEME**

- **Day 1:** The patient is advised bed rest. Mobilization must be only with bimodal elasto-compression using absorbent pads and compression and supporting binder.
- **Day 2:** The patient may start moving about. Wound healing is checked. Elastocompression is applied using a light compression binder. Bandages are removed. The patient may walk. Manual lymphatic drainage is performed.
- **Day 3:** Treated areas and the wounds are examined. The patient undergoes lymphatic drainage, external ultrasound 3 MHz, and magnetotherapy. In the event of hematoma formation, medical phlebotonics and specific local therapies are prescribed. The patient may shower with due precautions taken to protect the treated areas.
- **Day 4–7:** Same procedures as in day 3 are performed, followed by diet therapy.
- **Day 15:** Subdermal therapy is started aimed at connective tissue restructuring.
- **Day 21:** This therapy may now be associated with carboxytherapy.

Patients should be reminded that the best results may be observed only after some months (today we know that the first result will be at 4 months and the second at 14 months) (24).

Subdermal therapy with Endermologie® (liquid petroleum gas) or TriActive® (DEKA) associated with microcirculation cleansing and stimulant oral therapy (Cellulase Gold®) has an added value in a successful surgical intervention.

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![Liposhape™ compression garment.](image)
CONCLUSION

Safety is the state of being free from danger and exempt from harm. The foremost ethical principle of medicine is “primum non nocere”—first, do no harm. In lipoplasty, this principle is paraphrased by the statement “excessive liposuction is unsafe and therefore unethical.”
C: Vibro-Assisted Liposuction

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**INTRODUCTION**

The dream of the aesthetic surgeon has always been body improvement, because aging cannot be prevented. But all their efforts result in scars, the unavoidable traces of the knife. Adipose tissue and its various compositions as well as distributions, represents the main structure producing the body silhouette. But in the past, surgical attempts to reduce or remove excess fat have been limited by scars.

In September 1976, report of the first revolutionary operation that allowed the removal of fat while limiting trauma and scars was published: liposuction was born (25,26). This methodology underwent various evolutions (19,27–29), allowing it to be used for different pathologies (30–32) or for lymphedema, lipedema, or lipolymphedema (33,34).

Localized adiposity means physiological or pathological accumulation of fat tissue in a specific body area. Lipodystrophy means a pathologic condition affecting the supporting tissue as well as the subcutaneous adipose tissue, characterized by various circulatory and metabolic damages.

Essentially, we use liposculpture for any particular type of pathology such as localized adiposity, adipose cellulite, and adipose lipodystrophy.
LIPOPLASTY

Liposculpture or lipoplasty defines a surgical strategy of body contouring for withdrawing the localized adiposity. With this therapeutic strategy, the body can be shaped by decreasing the adipose tissue. At the same time the microcirculation is enhanced, allowing better venous and lymphatic return, improving metabolism, decreasing interstitial toxicosis, and improving venous and lymphatic drainage. Lipoplasty uses various methodologies of liposuction and lipolymphosuction.

LIPOLYMPHOSUCTION

The use of liposuction has already been adopted with success (35) in the traditional method with the utilization of 3 to 4 mm cannulae linked to a mechanical suction pump. Surgery can be performed under local or general anesthesia, sucking up even small quantities of adipose tissue by the way of a moss-pointed cannula (Mercedes type) with one or two holes at the top. Cannulae are connected to a device expressing a power of 0.8 atm. In a particular area, such as the ankle or knee, the canalization technique can be used; that is, the creation of channels under the skin using small cannulae (diameter, 2–4 mm). This is performed under local anesthesia through 2 or 3 mm incisions.

Cannulae are not connected to a suction device; it is only the movement of the cannula that induces the cellular disruption and channel formation. The adipocyte disruption is not induced by suction but essentially by the backward–forward motion of the cannula. The created channels will help the adhesion of subcutaneous tissue to skin. The adipocyte contains collagen. Thus, its disruption leads to collagen exposure into the extracellular matrix, which is useful in the postoperative healing phase.

With the introduction of ultrasound-assisted liposculpture and the patented vibro-assisted method Microaire® the possibilities have been multiplied (36,37). The benefits obtained from the reduction of interstitial pressure due to the adipocyte decrease is characterized by an improvement in microcirculation (arterial and lymphovenular) and tissue metabolism.

The reduction in adipocyte number and size prevents the evolution of the adipose tissue and lipodystrophic pathology. A consequence of adipocyte reduction is the systemic slimming and improvement of systemic metabolism related to the improvement in insulin metabolism. All this is intensified by the use of Endermologie® and/or TriActive® in the rehabilitation postsurgery phase. An important application for liposuction is also the treatment of lymphedema and particularly, lipolymphedema. Lipolymphosuction allows the reduction of lymphedema and can be performed on the ankle, knee, and/or calf.

THE VIBRO-ASSISTED METHOD

The vibratory pneumo-assisted liposculpture (also called reciprocal automatic liposculpture according to the U.S. patented Microaire® method) is a methodology that consists of a 300 g device linked to compressed air from the surgery room or a nitrogen bottle, and to a 2 to 3 mm cannula connected to a vacuum device. The PAD100-Microaire system allows vibrations of the cannula tip, 2 mm transversely and 4 mm vertically, inducing rupture
and homogenization of fat, which is simultaneously aspirated. Heat production and veno-
lymphatic tissue trauma are avoided because backward–forward motions are not necessary
as in traditional liposuction; a little movement is sufficient. Such a method, with a 1.8 to
2.4 mm cannula, is used in the treatment of lymphedema and lipolymphedema, particularly at the level of ankle, calf, or arm. This methodology is extremely useful given
its easy use and its rare side effects (38,39).
As early as 1893 (Neuber), there have been publications that discuss lipoinjection or fat transfer (40). In the book by C. Willi (1926), photography was first used to show before and after results of lipoinjection in the face.

Bircoll, in 1982, first reported the use of autologous fat from liposuction for contouring and filling defects (41). Of the wide variety of injection methods aimed at enlarging the volume of soft tissues of the face and the body offered by specialists over the last decade, lipofilling attracts the ever-growing attention of aesthetic surgeons and dermatologists all over the world.

Adipose tissue is the main energy store of our body and is associated with several hormone receptors. Autologous fat is thus an important source of material to fill lacking areas (42). It is also a strong stimulus for restructuring and metabolic regeneration. An autologous fat graft is always followed by a noticeable improvement in trophism and skin conditions. Following the work of Giorgio Fisher, Pierre Fournier, Y.G. Illouz, Sydney Coleman, Chajchir Abel, Newman Julius, and Roger Amar, we know today the importance of fat transfer and lipoinjections (20,41,43–46).

Regarding the classical variants, they consist of obtaining fat by means of liposuction with thin cannulae, separation of fat from the ballast by centrifugation or washing with or without a special solution, and administration of this fatty suspension under the skin or

Felman’s cannula for lipoinjection. Source: Courtesy of KMI.
into the muscle by means of a thick-diameter injection needle or a blunt cannula. Methods for preserving the obtained adipose implant, aimed at delayed additional use, are also proposed.

Our own experience confirms these conclusions: fat tissue may be successfully reimplanted in depressions derived from liposuction, heat, or trauma, in order to restore an aesthetic contour and stimulate tissue restructuring.

Indications are:

- smoothing of facial wrinkles and fold,
- improvement of the congenital contours of the face and body, as well as those induced by involutional alterations and soft-tissue ptosis, and
- removal of individual defects such as cicatrices following acne, hypotrophy of posttraumatic and postoperative scars, leveling of roughness after a failed liposuction, as well as those induced by the so-called cellulite.

We infiltrate tissues with a solution of any known local anesthetic without other components that may influence the cellular membrane of adipose cells (e.g., 0.1% lidocaine solution).

The volume of the administered solution should be two to four times as large as in the traditional liposuction. It is very important to administer the solution suprafascially, under the fatty layer from which fat procurement occurs.

Doing so provides not only anesthesia, but also pushes the fat closer to the skin and its packing, thus making it possible, with the help of the cannula, to easily obtain the fatty implant in the form of a pole with minimal injury to the adipocytes, because there is no mechanical, toxic, or osmotic effect. In addition, the blood vessels are compressed, with the lumen decreasing and practically no bleeding.

Then, through a 5 mm or smaller cutaneous cut in a barely visible place, the donor fatty tissue is taken into a 20 or 50 mL syringe by means of a cannula with reciprocating movement.

However, to treat small facial wrinkles and striae, the collagenous and membranous portion may be used after centrifugation and sedimentation. In other words, tissue itself is used as a collagen or hyaluronic acid implant. Association of the tissue with hyaluronic
acid itself may be useful since fat implants potentiate the hydrophilic action of this acid, causing an enduring physiological edema (47,48).

Careful attention should be paid to sterilization and to the technique for collecting and reimplanting adipose tissue. Excessive tissue trauma should be avoided and care should be taken to prevent potentially dangerous infections. Despite its simplicity, lipofilling is a surgical operation that requires an accurate technique. The administration of antibiotics is recommended by some to prevent any chance of infection.

**LIFTING**

When the amount of tissue is excessive or when important structural alterations are detected, surgical intervention is required to restore functionality and outer appearance. As cellulite itself is a disease with various manifestations that require functional and aesthetic recovery, every act of cosmetic surgery should be targeted at maintaining, improving, or restoring functionality. Similar to medical consultation or physical therapy, surgery should start from an accurate diagnosis and a carefully orientated therapeutic inquiry. Aesthetic recovery naturally derives from an accurate diagnosis and appropriate therapy. Thus, we may say that, strictly speaking, aesthetic surgery does not exist (neither does aesthetic medicine): cosmetic surgery (which is a better definition) is characterized mainly by the patient’s motivations. However, aesthetical pathologies certainly exist; there are some visible diseases that usually require medical, surgical, or physiotherapeutic treatment plus aesthetic/cosmetic complements.

Plastic and aesthetic surgery is not precisely the last resort; neither is it a therapy suitable only for the important problems derived from cellulite. Many aesthetic problems may
be solved through small and early surgical interventions. We refer, for example, to small medial thigh liftings carried out through vertical incisions on the pubis that enable skin rotation, thus reducing tissue excess in the medial thigh. Limited abdomen miniliftings (inferior partial abdominoplasty) may also be useful since they enable cutaneous stratum repositioning after liposuction. The same is true for soft gluteal lifting, which restores loose tissues to their original position and improves the cellulite pathology at the back of the thigh, thus offering an image of a longer and slender limb plus more tonic and higher glutei.

## LIPOSHIFTING

Internal fat mobilization or liposhifting has proved to be an excellent method for the correction of postliposuction imperfections as well as for the redistribution of unaesthetic fat cumulus. Blugerman has introduced a new instrument that facilitates the production of fat micrografts in perfect condition to be internally moved to the area to be filled. Internal lipomobilization reduces fat trauma during suction and injection and also prevents contact with air, reducing the risk of dehydration and contamination. The new instrument, in its reusable as well as disposable presentation, is called the Micro Graft® fat cutter and is available in three different models for use in different body areas.
The Micro Graft® cannula.

Source: Courtesy of KMI.
E: Ultrasonic Hydrolipoclasis
(External Ultrasound)

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Ultrasonics is a branch of physics that studies the properties of ultrasonic waves, the necessary media for their generation and development, their numerous physical, chemical, and biological effects, and their applications in research, technology, and medicine.

Wavelengths \( (L) \) depend on frequency \( (f) \) and also on the value of the velocity of propagation \( (V) \) of elastic waves in the considered medium, according to the following ratio:

\[
L = \frac{V}{f}
\]

\( V \) varies according to the medium, from a thousand to some hundreds of meters per second; the highest values are produced with longitudinal waves in solid media, and the lowest values are produced in gaseous media.

\( L \) ranges from values in decimeters for the ultrasound lower limit to values in microns for the upper limit.

Most of the ultrasound effects are due to the specific properties of these waves. There are two essential properties, both related to high frequency: 1) Because of the relatively small value of \( L \), ultrasound has quasioptical properties, in the sense that propagation is produced under conditions and modes close to geometric optics. 2) The radiation intensity obtained with ultrasound is greater than that obtained with audible frequencies.

Intensity \((W/cm^2)\) is, in fact, proportional to the frequency squared; provided that frequency is sufficiently increased, the intensity of radiation may be very high, even with very small amplitudes of vibration.

In the study of the various ultrasound effects, the absorption coefficient \( a \) should often be considered. The \( a \) value varies according to the aggregation state of the medium in which propagation takes place (usually high in gases) and, in general, it is directly proportional to the frequency squared.

Under the most unfavorable conditions (high-frequency ultrasound and gaseous medium), the useful distance reached with substantial intensity by ultrasonic radiations emitted from a generator is normally very short. Every oscillating mechanical system vibrating at frequencies higher than the audibility limit may represent, at least in principle, an artificial source of ultrasound.
According to the kind of energy used to drive them (electrical or mechanical), artificial sources may be grouped into two classes. The first class comprises electrically driven ultrasound sources, and it consists almost exclusively of electromechanical transducers suitable for irradiating high-frequency elastic vibrations. The most commonly used transducers are piezoelectric, electrostriction, and magnetostriction transducers. Most of the transducers employed as ultrasound sources are used under resonance conditions in order that the irradiated ultrasound power and the transducer electromechanical efficiency (the relationship between the irradiated ultrasound power and the input electric power) have the highest possible values.

Under these conditions, every transducer can irradiate ultrasound of only one frequency, that of resonance. Sources not specifically used for ultrasound and analogous to those used for audible frequencies can irradiate ultrasound of any frequency within a certain range.

The piezoelectric sources are made up of a crystal (quartz, tourmaline, and others) that, through the activity of an alternating field, begins to vibrate and radiates elastic waves into the surrounding environment.

The electrostriction sources are made up of a dielectric (barium titanate ceramic) that, through the activity of an alternating field, begins to vibrate, as is the case with the piezoelectric crystals.

The barium titanate transducers may be treated to maintain the necessary polarization permanently: the transducer, however, should be used at temperatures below 70°C (158°F).

By way of compensation, the acquired properties are so intense (effects are approximately 100 times greater than in the case of quartz, according to the voltage applied) that it is possible to irradiate plane ultrasonic waves of an intensity of up to 100 W/cm² higher than those obtained with any piezoelectric transducer. Besides their great sensitivity, another advantage of barium titanate transducers is the possibility of shaping them, in order to obtain a concentration of irradiated power in relatively limited areas and, thus, particularly high intensities.

The efficiency of piezoelectric or electrostriction ultrasound sources greatly depends on the mode of coupling them to the medium which the source irradiates and, thus, on the features of the support used to guarantee the implied conditions. If one side of the transducer is coupled to an elastic medium and the other side points to an empty cavity, the irradiated power in the medium is four times greater than that obtained when both sides of the plate are coupled to the propagation medium, depending on the excitation voltage. Unilateral irradiation is obtained when the active side is coupled to a liquid or solid medium and the other one is in contact with the air. In fact, gases have a very low acoustic impedance.

The magnetostriction ultrasound sources use the deformation present in ferromagnetic materials under the activity of a magnetic field. There are nickel or permadur (49% Fe, 49% Cu, and 2% Va alloy) and ferrite (NiO, ZnO, and Fe₂O₃ mixture) magnetostriction transducers.

If there is a periodically varying component in the field, the magnetostriction core begins to vibrate. The magnetostriction cores are also used in resonance conditions. The magnetostriction ultrasound sources are made up of a magnetostriction core around which there is an excitation coil driven by the electric signals generated of the same
frequency as the mechanical resonance of the transducer. Magnetostriction transducers can irradiate relatively low-frequency ultrasound (not higher than 200 kHz) with an intensity of up to about 30 W/cm².

The second class of ultrasound sources comprises mechanically driven generators, by means of a compressor, a pump, or a motor. This class groups generators emitting sound power of some kW, necessary for specific ultrasound uses. Ultrasound reception is carried out through magnetostriction or piezoelectric receivers that profit from the reciprocity of magnetostriction and piezoelectric transducers.

In addition, condenser microphones may be employed, working up to 100,000 Hz. Optical devices are used for the development. They allow the observation and photography of stationary ultrasonic waves in gases and liquids. These waves act as a diffraction grating of the luminous monochromatic radiation that goes through the device.

In addition, ultrasound may be developed by devices based on the variations of electric resistivity of thin conductors overheated by the ultrasound itself, variations which are due to temperature modifications. Elastic ultrasonic waves propagate similar to luminous radiations. In other words, they exhibit reflection and refraction phenomena when interposed obstacles are big in comparison to the wavelength of the incident ultrasound radiation.

On the other hand, interference and diffraction phenomena occur when the dimensions of obstacles or openings are similar to the wavelength.

Ultrasound also has quite different properties linked to the high energy transmitted by radiation, proportional to approximately the frequency squared.

A power of around 30 kW and a sound intensity of around 5 kW/cm² have been observed. Under such conditions, temperature rise of about 20 cm in the medium, cavitations, and liquid are obtained.

In addition, ultrasound causes liquid luminescence besides mechanical and chemical effects, depending on the medium.

The use of ultrasound has now become particularly important in the study of the sea: to reveal the presence of varied obstacles through the sonar, to outline the bottom of the sea, and gather information on its stratigraphic composition through the echo technique (echo-sounding), and as a means of subaquatic telecommunication. Ultrasound has been developed as a technique to search and localize faults in mechanical and manufactured pieces. Ultrasound is used for the measurement of propagation constants (velocity of sound, absorption, etc.) and related parameters (elastic constants) in solid, liquid, and gaseous media within a wide temperature range.

Echo or resonance techniques or the interferometric method are used for this purpose. These serve as a refined means for the physical research of the structural properties of matter. The applications of ultrasound in diagnosis, in which reflex signals (or transmitted signals) are employed across tissues, are based on the quasioptical properties of ultrasound.

It is easy to generate very intense ultrasonic waves. This enables their use to cause modifications and effects of a varied nature (physical, chemical, and biological) in the treated medium. All these effects are due to strong mechanical stress linked to elastic waves of high intensity and their respective thermic effects. When the irradiated medium is a liquid and ultrasound intensity is enough to cause cavitation, cavitation seems to play a determining role in the modifications induced by the treatment. The proper use of treatment requires an adequate selection of the ultrasound intensity.
CAVITATION

This is a phenomenon that takes place in liquids when submitted to strong depression. When the absolute pressure turns lower than the liquid vapor pressure, a violent development of vapor in the form of small bubbles takes place. At the same time (due to the effect of Henry’s law), a separation of water–dissolved air is produced. Cavitation can occur in a tube with a neck in which an increase in velocity means a decrease in pressure (Bernoulli’s theorem).

Cavitation may occur toward the tips of the buckets of jet hydraulic turbine runners or pumps and on the blades of sea propellers. The rapid formation and destruction of vapor bubbles give rise to a rapid series of collisions, subjecting the metal walls to intense stress and causing great corrosion. It has been demonstrated that the pressure originated from bubble bursting can achieve, in situ, 1000 atm (explaining the strong corrosion). The following formula of the cavitation number describes the cavitation phenomenon:

\[ n = \frac{P_a + P_s + P_v}{(d/2) \times V^2} \]

where \( P_a \), \( P_s \), and \( P_v \) are pressure at the free surface of fluid, hydrostatic pressure at the considered point, and vapor pressure, respectively; \( d \) is fluid density and \( V \) is velocity of undisturbed fluids.

The tendency of fluids to cavitate depends inversely on their intensity and velocity of movement, and directly on the pressures applied.

BIOLOGICAL EFFECTS

The effects of ultrasound on biological materials can be classified into micromechanical, thermic, or those causing cavitations.

The micromechanical unidirectional effects cause, through direct action, displacement of intracellular organic molecules with frequent diffusion into the extracellular space, rupture of macromolecular chromosomes, molecule conglomerates originating from the rupture of intermolecular bonds, modification in protein spatial structure, formation of free radicals, denaturation of cell membrane components, and electrochemical modifications in cell surface.

Ultrasonic waves can be compared to a strong wind striking biological materials with power proportional to ultrasound intensity. This wind causes, depending on its strength, displacements, ruptures, and variations in the shape of biological molecules. The mechanical drive may cause displacement of macromolecules out of their normal cell compartments and, thus, disorders in cell function.

Biological functions of macromolecules are conditioned by their presence in the site of reaction. When mechanical waves achieve enough strength, macromolecule flexion and even rupture can occur with its consequent functional loss. Formation of highly reactive oxygen free radicals is another mechanism involved in the damage of surrounding biological structures. The most common process of ultrasound micromechanical activity is protein denaturation.
From a stereochemical viewpoint, proteins are made up of primary, secondary, and tertiary structures. Primary structures are possible thanks to peptide bonds—covalent bonds requiring high energy supply to be split. On the other hand, the remaining structures are possible thanks to weak bonds (polar, or hydrogen) requiring a certain spatial closeness of the constituent groups.

Because they are weak bonds, weak energy is enough to split them and to separate the constituent chemical groups. Spatial distance hinders, then, the new formation of the same bonds. This causes serious functional damage because it is precisely due to secondary and tertiary structures that proteins form active loci. Thus, cell functions are blocked.

The thermic effects of ultrasound are attributable to the so-called Joule effect. The mechanical waves of ultrasound cause molecular movements that increase the kinetic energy of molecules: according to Joule's law, the potential energy of electric charges in movement is partly ceded under the form of heat. This causes the temperature of biological materials to increase, and when the physiological value of 37°C (98.6°F) is exceeded, protein denaturation may begin and the resulting loss of cell function may take place.

Cavitation occurs in liquids subjected to ultrasound at frequencies higher than 900 kHz. This determines the formation of vapor and air bubbles inside the liquids; a real explosion of these microbubbles is produced damaging the surrounding structures.

For cavitation to occur, tissues require ultrasound intensities 1000 times higher than liquids. However, it must be considered that the human body is made up of 60% water and has anatomical cavities (cerebral ventricles, heart, great vessels, gall bladder, and urinary bladder) with liquid contents.

It is known that the application of ultrasound on biological materials soaked in water causes notable damage. This damage does not occur through the cavitation of biological materials, but through the explosion of the microbubbles produced by the cavitation of the water present.

Water infiltration in tissues and the subsequent application of ultrasound cause water cavitation, microbubble formation and explosion, and rupture of surrounding biological materials.

It is understood that the more delicate structures (endothelial cells, adipose cells, etc.) will be damaged more easily than the more resistant structures (connective, bone, etc).

Ultrasonic hydrolipoclasia (ILCUS) is employed to cause volumetric reduction of tissues made up of structures highly sensitive to the mechanical damage resulting from the microbubble explosions caused by cavitation. Indications should be limited to the nonsurgical treatment of lipomas and to the treatment of localized adiposities as an alternative to liposuction. In ILCUS, the frequency used is 3 MHz.

Because of the inverse relation between ultrasound frequency and penetration, its beam activity is limited to the more superficial strata of the body. In addition, cavitation of the infiltrated liquid absorbs quite a large amount of energy so that the ultrasound power that penetrates beneath becomes irrelevant. In any case, treatment of anatomical areas close to or above organs or parenchyma that could be damaged by ultrasound requires special attention.

Regarding the cosmetic treatment of localized adiposities, it should be remembered that the ILCUS is a traditional treatment that acts by damaging the structures present in the excessive adipose tissue, with damage proportional to the sensitivity of biological materials. A precise diagnosis is required when planning ILCUS in patients with cellulite.
TECHNIQUE

PATIENT PREPARATION

The localized adiposity area is demarcated with a dermatographic pen and areas are demarcated symmetrically on both sides of the body. The thickness of adipose tissue is measured with a 7.5 MHz linear sound echograph to select the needle length (liquid should be infiltrated in the lower third of the thickness situated between the hyperechogenic line of deep dermis and the hyperechogenic line of muscular fascia). The treatment areas are carefully disinfected.

SOLUTION PREPARATION

Sterile physiological saline, local anesthetic 1%, and sodium bicarbonate 10 mEQ/mL are used. In a single-use 20 cc syringe, 0.5 cc of local anesthetic (lidocaine 2% or carbocaine 2%) to mitigate pain from nerve ending compression after liquid infiltration is introduced, together with 0.5 cc of sodium bicarbonate to buffer pH variations responsible for the burning sensation at the moment of injection, and 19 cc of physiological saline (sodium chloride 0.9%).

INFILTRATION

The needles mounted on the plate are placed on the demarcated and disinfected area and 2 cc of the solution is slowly injected. The needles are then removed and the treated area is
covered with a cotton wool and disinfectant. The operation is repeated until all the treatment area has been covered. The dressing that covers the wounds should be disinfected and sprayed.

ULTRASOUND APPLICATION

Conductor gel is spread on the treated area and ultrasound emission equipment is turned on at a 3 MHz frequency. Emission is selected in continuous mode and power is turned to maximum (state-of-the-art equipment enables us to exceed 5 W/cm²). The ultrasound emission probe is applied on the skin of the infiltrated area that is covered with gel, the timer of the equipment is set for a time period determined by the number of punctures of the multi-injector multiplied by two [e.g., 10 punctures (10 needles) in the multi-injector require a 20-minute time period], and emission is initiated. The ultrasound probe is moved slowly in order to cover the whole infiltrated area, going over the area again and again until the end of the time period. The operation is repeated on the contralateral side. To finish the treatment, the gel is removed and the treated areas are disinfected once again.
A 5-needle mesotherapy single-use circular plate is mounted to the syringe; 30 G 6 mm long needles are mounted to the plate.

FREQUENCY OF TREATMENT

The adipocyte rupture resulting from treatment causes triglycerides to come out of the fragmented intra-adipocyte vacuoles. At this point, triglycerides are collected by the lymphatic and venous return systems and enter the greater circulation.

Most of the triglycerides are eliminated through the kidneys, and a part reaches the liver where it is conjugated into lipoproteins. To enable a full elimination of the reactive edema, it is recommended that sessions are repeated at 15- to 20-day intervals (shorter intervals, if manual lymphatic drainage is performed).

SIDE EFFECTS

Almost none.
Ultrasound before and after ultrasonic hydrolipoclasis.

Before and after ultrasonic hydrolipoclasis.
REFERENCES


Subcision®

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■ INTRODUCTION

Subcision® is a simple surgical technique, originally described by Orentreich and Orentreich (1), in which subcutaneous fibrous septa are cut; this both diminishes the traction exerted on the skin and creates hematomas which in turn promotes the formation of new connective tissue. Therefore, it acts as an autologous and physiologic filler (2). In 1997, Hexsel and Mazzuco described the effectiveness of Subcision® for the treatment of cellulite (Figs. 1 and 2) and in 2000, presented a detailed step-by-step guide to the procedure, based on the use of Subcision® in 232 female patients (3).

■ INDICATIONS AND MECHANISMS OF ACTION

Subcision® can be used in the treatment of all conditions where subcutaneous septa pull on the skin surface. These include wrinkles and folds and depressed scars and lesions (4), in addition to cellulite (2). Subcision can also be used to correct other skin relief alterations, such as those that appear after liposuction (Figs. 3 and 4), and depressed areas caused by tissue loss such as posttraumatic or that due to inflammatory diseases, in addition to the donor areas of fat grafts (1,3) on the face and body (4).

Subcision is useful in treating grade two and three cellulitis in which the lesions are visible when the patient is in the standing position with a relaxed gluteus muscle (Fig. 1) (3). Two mechanisms of action were initially described by Orentreich and Orentreich: the cutting of subcutaneous fibrous septa, which releases the tension exerted on the skin, and the formation of new connective tissue, which results from the creation of hematomas (1). The surgical movements cut the septa and the nearby vessels, giving rise to hematomas. The size of the hematomas depends on the size of the cut vessels, extension of the treated lesion, postoperative care, and the integrity of the blood coagulation mechanisms. These aspects directly determine the proportion of the filling effect in the treated area (3).
Figure 1
62-year-old female presenting with cellulite on the buttocks.

Figure 2
Same patient as in Figure 1, one month after Subcision®.
the treatment of cellulite, a third mechanism of action is involved: the redistribution of the traction and tension forces between fat lobes, which contributes to the improvement of the relief of the treated areas.

The number of the Subcision treatments necessary to correct a defect depends on the size, depth, and location of the defect, as well as on the degree (or quantity) of new collagen formation. Most cases can be treated by one or two procedures, with a minimum interval of two months between them.
CONTRAINDICATIONS FOR SUBCISION®

Orentreich and Orentreich described the following contraindications for Subcision® (1), divided into two categories:

1. Absolute: Active infection in, or immediately adjacent to, the area to be treated as well as in the case of scars like “ice pick” acne scars.
2. Relative: Coagulation disorders, atrophic scars, and history of hypertrophic scars or keloids.

Hexsel and Mazzuco, using this technique to treat larger areas, described other contraindications such as the use of medicines or the existence of diseases that may interfere with blood coagulation or with anesthetics and medicines that can alter the expected or desired postoperative evolution (3).

PREOPERATIVE CONSULTATION

For Subcision®, previous medical evaluation is important, not only for adequate patient selection but also for the preparation for the procedure.

The preoperative care is basically the same as that for any other outpatient surgical procedure. Some additional items should be checked: the tendency to develop keloids or allergic reactions to the medicines that patients will be taking.

Anticoagulant agents, drugs that interfere with platelet aggregation, beta-blockers, immunosuppressor agents, neuroleptic agents, oral isotretinoin, and iron should be avoided. These, as well as cigarette smoking, are relative contraindications to the procedure.

Laboratory exams should include a coagulogram and any other exam required according to the patient’s needs (2,3).

Prophylactic antibiotic therapy with Ciprofloxacin 500 mg is recommended twice a day.

SURGICAL TECHNIQUE

The surgical procedure includes the following steps:

1. Skin marking: All skin relief depressions should be marked prior to the procedure. This should be done while observing the patient standing in an upright position, with relaxed muscles (Fig. 5) (3). The light source should be perpendicular to the skin surface, to enable better observation of the skin relief alterations (5). Slight lesions, such as those evident only when the muscles are contracted, should be avoided due to the risk of producing dermal depressions (2,3). To avoid the creation of large hematomas, their organization, and the formation of extensive dissection planes and the complications that may arise as a result of these situations (6), it is recommended that lesions up to 3 cm in diameter or parts of larger lesions not exceeding this measurement be chosen (3).

2. Antisepsis: Antisepsis should be rigorous and widespread, in the surgical area (2). The most frequently used antiseptic is iodized alcohol, and in patients who are allergic to iodine, chlorexidine can be used. It is recommended that the procedure be carried out in an antiseptic room and that sterile fields are used.
3. **Anesthesia:** Local anesthesia is given with the patient lying down (Fig. 6). The needle should be inserted 1 to 2 cm beneath the marked skin and the anesthetic injected while withdrawing the needle, into the subcutaneous level. Upon completing the injection, an anesthetic button is left at the site where the Subcision\textsuperscript{®} needle will be placed. General anesthesia and nerve blocks are not recommended. Two percent lidocaine with epinephrine (1) or norepinephrine, in the ratio 1:200,000, can be used for small areas (2). Tumescent anesthesia is used when there are many depressions (7) although, as this infiltrates the fat, it may reduce the bed for the hematoma and bleeding. The recommended dose of 2% lidocaine with vasoconstrictor is from 7.0 mg/kg (8), and the dose of lidocaine per session should not exceed 500 mg (8). The number of lesions treatable in a single session depends on the dose of anesthetic available, calculated according to the patient’s body weight (9,10). The total anesthetic dose described as safe for lidocaine with vasoconstrictor should not exceed 500 mg (8,11) or 7.0 mg/kg (6).

4. **Cutting the subcutaneous septa:** Following maximum vasoconstriction, apparent as paleness and piloerection, the procedure can begin. A BD Nokor\textsuperscript{TM} 18G\textsuperscript{3} is preferred, because it has a cutting blade at the point. Other alternatives are the use of a special scalpel, with the same cutting blade at the point, or a normal or three-beveled needle, as described by Orentreich and Orentreich (1). The needle should be inserted about 1.5 cm beneath the lesion to be treated, at the point where the anesthetic button was previously placed (Fig. 7). The insertion should be made at an angle of 45\textdegree{} to 90\textdegree{} to the skin surface and then, at a depth of 1 to 2 cm from the skin surface, the needle should be positioned parallel to the epidermis, with the cutting edge to the left against
the septum. The septa are cut on the backstroke of the needle, while maintaining the blade traction against the septa, thus releasing the tension exerted on the skin. This cutting technique allows a precise cut with a minimum of tissue damage, which ensures better postoperative results. A slight pinch test on the treated lesion is useful because it reveals any areas that remain retracted by septa (3,5).

5. Compression: Following cutting the septa, vigorous compression is required in the treated area for 5 to 10 minutes, sufficient time for the process of coagulation to begin, permitting hemostasis and control of the size of the hematomas. The use of sand bags is recommended; they should weigh approximately 5 kg, be made from a washable material, and be wrapped in sterile fabric (3). Such bags produce a more uniform and efficacious compression than that achieved manually.

6. Dressings: The treated areas are covered with sterile adhesive bandages and given additional compression with dressings and compressive clothing (elastic pants or shorts) that should be worn for 30 days.

The patient receives the following postoperative instructions:

- Use analgesics for the first 48 hours; this period can be extended if pain persists. Acetaminophen at a dose of 750 mg every six hours is recommended.
- Continue use of the antibiotic until the third day.
Perform physical exercises only after the third week.
Use compressive clothing for 30 days.

THE POSTOPERATIVE PERIOD

The first postoperative evaluation should be made after 72 hours, when the dressings are changed and the use of the antibiotic discontinued (3). Hematomas and hemosiderosis are expected in all patients during this period. The hematomas should follow a normal evolution of spontaneous reabsorption over a period varying from 10 to 20 days. Hemosiderosis may persist for several months and is directly proportional to the absorption of iron present in the extravasated red blood cells. Other complications may arise as a result of this procedure and they are listed below.

COMPLICATIONS

According to Orentreich and Orentreich (1), the following complications may arise; they are rare and easily dealt with:

1. Hematomas and ecchymosis (Fig. 8)
2. Erythema, edema, and localized sensitivity
3. Infection

Figure 7
A gentle pinch test is performed to find residual septa pulling the skin surface.
4. Alterations to the consistency of the treated area
5. Alterations to the color of the skin in the treated area
6. Suboptimal response
7. Excessive response
8. Keloid scars

In fact, complications arising from the use of Subcision® (5) for the treatment of cellulite are rare, owing to the safety of the method and the fact that regions of the anatomy commonly treated are free of vital structures and large blood vessels.

Other complications include:

1. Hemosiderosis: This occurs due to the extravasation of the red blood cells and the deposit of hemosiderin, a pigment that contains iron, and the resulting degradation of the hemoglobin, (12) giving the skin a chestnut pigmentation (Fig. 9). It occurs in all treated patients to varying degrees and resolution occurs spontaneously within 2 to 12 months.
2. Organized hematomas: This may occur in some treated areas, but usually clear up spontaneously in a period from one to three months, although they can be treated with intralesional corticosteroids. They are usually painful and hard to the touch.
3. False excess response: This is characterized by a raised area of skin at the treated area, appearing as a herniation of the skin and fat (Fig. 10). This does not respond well to corticoid injections and may be due to bad technique (e.g., Subcision® in extensive areas or excessively superficial) or a lack of postoperative care such as not using compressive clothing for 30 days following the procedure. Favorable results can be obtained with the use of liposuction in the affected area.
Figure 9
Hemosiderosis one month after Subcision®.

Figure 10
False excess response after Subcision®.
CONCLUSIONS

Subcision® is a simple, effective (Figs. 11 and 12), low-cost surgical method for the treatment of advanced cellulite.

Figure 11
Cellulite on the buttocks before treatment.

Figure 12
Same patient as in Figure 11, after two Subcision® treatments.
It is a precise surgical procedure, in which the septa that retain the skin are cut, and the resulting traction and tension forces are redistributed among the fat lobules in the treated area, giving an immediate improvement to the skin surface.

Complications are rare and easily treated. The production of new connective tissue from the hematomas occurs in two to five weeks and normally persists for a considerable time in the correction of the treated defect. The results are technique dependent and are usually long lasting (3).
REFERENCES


Mesotherapy in the Treatment of Cellulite

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A BRIEF HISTORY

The idea of treating a pathology using the intradermal (ID) or subcutaneous route is not new. This method has also been used with great effect in the treatment of visceral pain, with the injection of an anesthetic with lidocaine and distilled water into painful areas. In dermatology, ID injection has traditionally been used for the treatment of alopecia, keloids, scars, and other conditions for many years.

The French physician Pistor brought together these experiments with his own pioneering work, expanded them, and began to work with this technique on a regular basis with a large number of patients. It all began in his country surgery in the village of Bray-lu (France), where the favorable response of a deaf patient to procaine injection led Dr. Pistor to inquire further into the properties of this drug, when injected intradermically in the vicinity of the affected auditory organ. He broadened his pathologic investigations, moved to Paris, and in 1958, presented the first publication on the subject, wherein he proposed the name “mesotherapy” for this procedure. In 1964, his professor and friend, the medical surgeon Lebel, invented the small needle that carries his name and recommended the creation of The French Society of Mesotherapy, which Pistor started that same year (1).

THE CONCEPT

Mesotherapy is a simple therapeutic concept in which the principle is to approximate the medicine to the location of the disease using minimal doses applied intradermically into the region. The word mesotherapy derives from the Greek meso (medium or middle) and therapy (treatment). In this case, the word meso refers to the mesoderm, which is the embryonic middle layer located between the ectoderm and endoderm. This middle layer
originates all the connective tissue that forms the dermis and it is into this layer that the medicine is injected when mesotherapy is used.

According to Dr. Pistor, mesotherapy is an allopathic, light, parenteral, polyvalent, and regionalized medicine.

- Allopathic: because the medicines used form part of the official pharmacological range.
- Light: because the doses used are always low compared to those habitually used in traditional medicine.
- Parenteral: because intradermic or subcutaneous injections are performed with active drugs while using procaine as a vehicle.
- Polyvalent: because of its efficacy in multiple diseases involving distinct specialties.
- Regionalized: because mesotherapy is performed in the vicinity of the lesion.

ACTION MECHANISM OF MESOTHERAPY

PISTORIAN REFLEX THEORY

While the action mechanism of this therapeutic technique is not totally explained, there are a number of theories.

Dr. Pistor alleges that the direct pharmacological action of the drugs administered locally or regionally is not sufficient to explain the results obtained in pathologies in which the ethiopathogenic base is located in deep organs. He advances the possibility that the skin might be a projection of different internal locations of deep organs, over/on which an authentic map or plan can be designed as in acupuncture. His observations suggest the existence of a correlation between a pathology and its cutaneous representation. According to this reflex theory, mesotherapy interrupts the visceral–medullar–cerebral path at the lateral-medullar level (where the vegetative system is connected to the cerebral–spinal system) by means of inhibitory stimuli originating at the dermal level. These dermal inhibitory stimuli are both mechanical (provoked by the needle) and physiochemical–pharmacological (due to the medicines administered through the needle). Definitively, this represents a localized “shock” that has repercussions on the lateral-medullar sympathetic center. Studies analyzed by Lichwitz in his 1929 thesis showed that depending on the substance injected at the dermal level, vegetative, medullar, and cerebral reactions are produced that may be accompanied by an action at the visceral level. According to this concept, mesotherapy, with few chemical products and small doses, is capable of producing significant results (2).

BICHERON’S MICROCIRCULATORY THEORY

The drugs administered locally or regionally produce a stimulating effect on the local microcirculation that is altered by the lesion. A diseased organ, tendon, or articulation leads to microcirculatory vascular damage that further worsens the problem in question. This theory on the role of microcirculation has been confirmed by thermographic studies that reveal alterations before and after the treatment. This explains how mesotherapy acts in such diverse pathologies as cephalgias, rachialgia, degenerative osteoarticular disease, vascular acrosyndromes, or cellulite. However, the ID use of vasodilators represents a risk factor for cutaneous, iatrogenic harm related to the appearance of hematomas and lesions caused by microbacteria.
MESODERMIC THEORY
According to its creator, mesotherapy is the treatment of the connective tissue that has its origin in the mesoderm. The mesoderm gives origin to various tissues: skin, bone, and cartilage among others.

The mesodermic theory can be explained by the actions of three units:

1. **The microcirculatory unit**: It consists of small capillary and venous spaces that ensure blood interchange as well as the transport of the secretions from the connective tissue cells and the medications introduced via the mesoderm.
2. **The neural-vegetative unit**: Owing to the elements of the sympathetic system that exist in the dermis, it is possible to achieve the regulation of the nervous system.
3. **The immunological aspect unit**: The connective tissue generates defined defense zones with specialized cells (plasmocytes and mastocytes) to react to the penetration of a product through the skin. This explains the influence of mesotherapy on the immunological system.

THIRD CIRCULATION THEORY
The interstitial compartment is known as the third circulation, the first being the blood circulation and the second, the lymphatic system. The interstitial compartment or third circulation is the chosen area for mesotherapy. There may be a process, perhaps mediated by procaine with its membrane-stabilizing action, which in some way retards the passage of medicines to the lymphatic and venous capillaries. These would dissolve through the interstitial space to the deepest tissues, reaching the target site in high concentrations, without loss due to absorption by vessels.

In this way, mesotherapeutic infiltration would have a therapeutic effect even with minimal medicinal doses. It can be seen how, with distinct perspectives, the authorities on mesotherapy have tried to explain this phenomenon.

■ BENEFITS AND ADVANTAGES OF THE METHOD

1. **Elevation of the therapeutic rate**: However great the impact and therapeutic efficiency may be on the local or regional (in situ) affections, this therapeutic method treats the disease locally.
2. **Reduction of the required doses**: Owing to the pharmacokinetic film that permits the potentization of the active agents, it is possible to administer efficient allopathic microdoses. The quantity of medicine administered is greatly inferior to that habitually used in conventional medicine.
3. **Reduction of iatrogenic and side effects**: This is achieved as a result of the global reduction in the doses of drugs and also by the suppression of the unwanted plasma peaks that occur with other methods or routes.
4. **Fewer therapeutic sessions**: Because of the basic principles of this method, the difference in the number of therapeutic interventions and, consequently, the shortening of the treatment period is very accentuated (3).
MATERIALS AND TECHNIQUES

Every year new materials appear—from the most simple to the most sophisticated. Some of these are destined to facilitate the injections and others propose pointless objectives. Whatever the method of injection used, ID therapy consists of two successive stages:

1. Preparation of the cutaneous surface prior to injection and
2. Penetration of a small quantity of the active agent.

SKIN ANTISEPSIS

ID treatment requires numerous injections. Therefore, more than in any other situation, care should be taken to ensure correct antisepsis of the skin. The risk of cutaneous complications from atypical microbacteria, particularly the acid–alcohol resistant “Mycobacterium fortuitum,” demands that the surfaces be cleaned with iodized alcohol.

MANUAL TECHNIQUES

It is always possible to perform all the injections manually—assisted techniques do not dispense with the necessity for having a good knowledge of the manual techniques. For many years, ID injection techniques relied upon the use of multi-injectors that distribute the contents of the syringes (more or less homogeneously) with the aid of five needles in line (linear multi-injector), or from 7 to 18 needles (small or large circular multi-injectors). The necessity to change all the needles once they have been used, together with the difficulty in cleaning the multi-injector and the problem caused by the formation of oxide particles on the body of the device following sterilization, led to the abandonment of the use of such devices (4).

Equipment

Needles and syringes appropriate for mesotherapy are used.

Syringes. For the manual method, 5mL syringes are used and 10mL syringes for the Den Hub® and DHN2® injectors.

Needles. The ideal needle should measure no more than 2 or 3 mm with a short bevel in order to reach the dermis with greater accuracy. It should be coupled to the syringe to avoid dislodgement during use.

Injection Techniques

The depth of the injection can be modified using three different techniques.

Pimples. The needle is placed at a tangent to the skin, with the bevel turned up. A small quantity of the medicine is impelled to form a superficial pimple.

Superficial Injections. The needle is inserted at an angle of approximately 30° and a single drop of the medicine is deposited at a depth of 3 mm. This is a “hit–by-hit/step-by-step” technique that has two variants:
1. Injections to the spine, vascular axes, members, and abdomen are always performed while maintaining constant pressure on the plunger of the syringe. The injection is applied at a depth of 0 to 3 mm, while a small quantity of the mixture is lost on the surface of the skin.

2. Injections into cellulite are performed separately, hit-by-hit/step-by-step with the aim of avoiding puncturing of the superficial vessels that are so commonly found in the disease vicinity (5).

**GENERAL INDICATIONS FOR MESOTHERAPY**

Mesotherapy can be used in various tissues and for various diseases.

- osteoporosis
- arthritis
- lumbago
- sports injuries/ailments
- other injuries/ailments

**MESOTHERAPY IN CELLULITE**

Cellulite is one of woman’s greatest enemies, and is one of the most common complaints presented at aesthetic clinics, followed by localized fat and stretch marks among others. It affects around 90% of postadolescent women, and is more common in Caucasians. Owing to the multiplicity of treatment options offered in advertisements, it is important to highlight the necessity of finding a specialized professional to receive appropriate guidance on the ideal treatment for each case.

The greatest single cause of cellulite is the presence of female hormones associated with family predisposition. The hormone favors the retention of liquid and the accumulation of fat in certain regions of the body, mainly the buttocks, thighs, and belly. This retention impedes tissue exchange and with time, the problem worsens, favoring the formation of nodules and depressions, giving the skin an “orange peel” appearance. Other factors that contribute to the appearance of cellulite are obesity, weight gain (although cellulite also occurs in slim people), orthopedic problems, bad diet, sedentarism, stress, the use of certain medications (like oral corticosteroids), clothing (tight clothes), and high heels.

Intradermic therapy: This is a technique in which medicaments are administered into the dermis, aimed at correcting skin alterations. The application is performed exclusively by a doctor, who gives multiple injections into the affected area, using short, delicate needles (6).

**SIDE EFFECTS**

**Pain**

Pain is, chronologically speaking, the first unwanted effect that is present during a session of mesotherapy; this, we accept, is a result of the way in which the medicaments are administered. Aware of this fact, the first mesotherapists with Pistor at the head, chose to
use multi-injector devices (that permit multiple injections to be performed, with the sensation of only a single painful jab); this gave the patient an acceptable degree of comfort. Others preferred to use ethylene chloride sprays in order to reduce the pain of the jab. We prefer to use “distraction” techniques.

The mesotherapeutic act ruptures the skin and therefore causes pain due to the jab. This pain can be greater or lesser, depending on the needle that is used—the classic mesotherapy needle has a thickness of 27G to 30G. When manual techniques are used, the introduction of the needle should be made in a single quick shot. When the injection is very painful, the needle is withdrawn without injecting anything.

The liquid that is injected should also be taken into consideration, not only with regard to its pH, preferably between 5 and 8 so as not to overload the physiological sealing systems, but also with regard to its viscosity, the volume administered per unit in the meso injection, the speed with which it is injected, and the depth of the injection. Bicarbonate of soda or ammonium chloride may be used to buffer the acid or base solutions, with the aim of bringing the pH as close as possible to the physiological level of 7.4. A not excessively large dose (e.g., 1/20 cc), administered very quickly into the dermis–epidermis level would lead to pain because of the sharp distortion to the algogen receptor elements; however, larger volumes can be administered without pain using mesoperfusion and/or mesoinjections at the level of the dermal reticulum.

From the anatomical point of view, the hands and feet, internal surface of the muscle and knee, bosom, etc. are painful injection areas, while some dorsal zones, the cranium, and certain areas are practically painless if we follow a good technique. This can only be achieved with practice.

It is a good idea to distract the patient during the session; it is also good custom to maintain an entertaining conversation. During the menstrual period, some patients who do not normally complain of pain may make some complaints that coincide with their state of algogenic perception.

**Cutaneous Necrosis**

Cutaneous necrosis, along with anaphylactic shock, is the most feared iatrogenic outcome, with the greatest number of legal medical implications. This problem can have two different etiologies: one, a chemical or pharmacological type, the other a biological type. Chemical type necrosis results from vascular damage caused by drugs having a vasoconstrictor action or by excessively dense or irritant excipients. It is known that some “aine” class anesthetic agents cannot be injected without prior dilution because of the risk of forming high concentrations of mucopolysaccharide depolymerizers, especially in the presence of hematomas.

Chemical necrosis is treated with the use of cicatrizants/healing products. Biological necrosis is more serious. It results from the accumulation of errors on the part of the practitioner that lead to veritable catastrophes. The initial lesion is delayed; it appears several weeks after the mesotherapy session. At the beginning, it has the aspect of erythematous pimples that evolve to the point of ulceration and the presence of pus. It begins in the region of the injections, but later may appear at some distance from the injection site. Histologically speaking, this represents a tuberculoid granuloma that affects all layers of the skin, with significant infiltration of histiocytes, lymphocytes, plasmocytes, and giant cells that surround the zone of caseation. Treatment is difficult and slow (7).
COMPLICATIONS (8–45)

Allergic reaction to mesotherapy. Source: Courtesy of Dr. H. Gancedo.

Abscesses from mesotherapy. Source: Courtesy of Dr. H. Gancedo.
USES FOR MESOTHERAPY

FAT LOSS
For those patients seeking fat loss, mesotherapy is a good treatment for losing localized fat; it is not a treatment for weight loss. With its action on adrenergic receptors, lypolytic action is improved and alpha-2 receptors are blocked (antilypolytic). This allows for modification of the biology of the fat cell by blocking the signals for fat accumulation, simultaneously triggering the release of stored fat.

The desired area of treatment can be patient specific, targeting the most problematic areas. Additionally, a complete dietary and nutrient evaluation will help maintain weight loss goals (40).

CELLULITE REDUCTION
Cellulite affects the majority of women over the age of 15 (after menarche). It is caused by an alteration in the matrix that affects microcirculation in subcutaneous tissue and dermis and eventually changes fat cell metabolism. Mesotherapy treatment is targeted to improve microcirculation, strengthen connective tissues, and dissolve excess fat (41–43).

FACE AND NECK REJUVENATION WITH MESOLIFT
Aging, sagging, and wrinkling of the skin occur from accumulation of fat, loss of skin elasticity, and excessive free-radical damage. Using antioxidants and amino acids, mesotherapy can reduce fat from under the neck, decrease free radical damage, and tighten loose skin. Mesotherapy effects include the rejuvenation of face, eyelids, and neck, but only when performed along with a comprehensive treatment including skin care, use of fillers, toxins, threads, and exfoliation (10).

How many treatments are required before one sees results? It depends on the patient’s body. Some patients require four to five treatments before beginning to see results while others may need more (12–17).
FOUR ESSENTIAL QUESTIONS THAT EXPLAIN THE MESOTHERAPY TECHNIQUE

WHAT IS MESOTHERAPY?

Mesotherapy consists of the introduction of drugs into the superficial subcutaneous skin (46). The injections use minimal amounts of drugs as a complement to routine clinical procedures (47,48). The amount of the injection is determined by the proximity of the injection site to the site of the pathology.

The different theories that have been proposed to explain the activity mechanisms of mesotherapy are as follows:

- Dr. Pistor talks about reflex theory—the interruption of the visceral spinal tract when ID medication is administered (46).
- Dr. Bicheron talks about microcirculation stimulation (49).
- Dr. Dalloz Bourquinon believes the effect is due to activation of the microcirculatory, neuro-vegetative, and immunologic competing units (50).
- Dr. Didier Mrejen believes that all body organs have representation on the skin and has developed a skin map indicating their places of origin (8).
- Dr. Multedo says that superficial administration of procaine produces a block in the Na–K pump, with the spread of medication through the extracellular space (9).
- Dr. Gancedo believes that when the administration is superficial, there is greater spread and the effect is deeper. For better diffusion, the injections must be given at several points in parallel lines, without space in between. The depth of injection has to be 1 mm from the skin (10).
- Dr. Ballesteros has coined the phrase “energetic mesotherapy” (11,12).
- Dr. Kaplan combines multiple concepts and uses radiomarkers showing that the more superficial the injection, the more extensive the diffusion (10).

WHY ARE DRUGS INJECTED INTO THE SKIN?

Drugs are injected into the skin in mesotherapy because treatment is applied at or closest to the disease.

WHAT DRUGS ARE USED?

Drugs that are used intravenously, intramuscularly, subcutaneously, or intradermically are also suitable for use in mesotherapy (51). Therefore, drugs prepared in oily substances should not be administered, except those that have a content of propylene glycol in their formulation, which does not exceed a 20% concentration when diluted.

All products must be water soluble, isotonic, and not cause nodules, abscesses, or necrosis at the site of injection. Injected products should not be allergenic.

Because drugs are applied at the site of the pathologic condition, drug concentrations are higher in comparison to that obtained by other administration routes. Thus, greater therapeutic effects are achieved (52). The ID route is widely used by dermatologists for the administration of active drugs in specific disease states, for example, corticosteroids in the treatment of psoriasis.
CRITERIA FOR USE OF MEDICINES

The choice of a pharmacologically active substance for percutaneous administration is made following preestablished criteria such as compatibility, specific physical-chemical characteristics, and recognized efficacy. It is important to remember that the introduction of medicines intradermically confers properties that are specific to this form of administration and that, beside the pharmacological actions pertaining to the active agents, other unforeseen effects may be observed, as well as the retardation and extension of the dose-effect relationship.

One of the most transcendental aspects of these methodologies is the selection criteria of the drugs and their combinations; consequently, there are ten commandments to be followed when making this choice; i.e., the drug should be:

1. water soluble and never dissolved in an oil-based solution
2. isotonic with suitable pH
3. perfectly tolerated at the subepidermal tissue level
4. integrated to the receptor tissue medium
5. nonallergenic
6. physically and chemically compatible
7. of recognized efficacy
8. physiologically synergic
9. free of any antagonistic action
10. particularly recommended for each particular case.

WHICH DRUGS SHOULD BE USED AND HOW SHOULD THEY BE ADMINISTERED?

CONCERNS REGARDING THE CHOICE OF DRUG COMBINATIONS

- individual action of each drug (pharmacogenic)
- necessity to avoid the use of drugs that precipitate when combined
- combinations should be compatible with each other as well as soluble in water (18)

SUBSTANCE USED

The pharmacologically active agents cited in the literature act on the adipose tissue, connective tissue, or microcirculation, and can be used transdermally. Those that act on the adipose tissue have a lipolytic effect—metilxantines (theophylline, aminophylline, caffeine, etc.) that inhibit phosphodiesterases. In vitro studies show that alpha-adrenergic antagonists and metilxantines (beta agonist) stimulate lipolysis and the reduction in the size of the adipocytes, through an increase in cyclic intracellular adenosine monophosphate (AMP) and the inhibition of phosphodiesterase. In a double-blind placebo study that used topical agents containing a beta antagonist, a metilxantine, and an alpha antagonist, there was shown to be a statistically significant reduction in the anthropometric measurement of the mid-thigh, of $1.33 \pm 1.12$ cm, with $p < 0.001$. This reduction was greater when the three active agents were used together, three to five times a week for four weeks. When used separately, the drug with which the best results were obtained was aminophylline (a phosphodiesterase inhibitor). No
side effects were observed and the statistical analysis was done using Student's $t$-test for paired observations.

With regard to systemic effects, caffeine used topically showed minimal general distribution. The serum rates obtained following repeated applications of a 5% hydroalcoholized gel were lower than those obtained with the ingestion of a cup of coffee.

Coenzyme A and the amino acid L-carnitine enhance the effects of the metilxantines by stimulating the mobilization and destruction of free fatty acids, introducing their active transport through the mitochondrial membrane (the excess of free fatty acids can saturate the system, leading to a negative feedback of the lipolysis). Moreover, this process releases ATP, which augments the efficacy of the lipase, facilitating the hydrolysis of the triglycerides.

Of the active agents that act on the connective tissue, those that are most studied are the silicium salts and Asian centella. Silicon is a structural element of connective tissues, which regulates and normalizes the cellular metabolism and cellular division. Studies on fibroblast cultures have shown that silates (groups of hydrogen and silicon compounds, analogs of hydrocarbons) promote the formation of bridges between the hydroxylated amino acids of the elastic fibers and the collagen, protecting the fibers from nonenzymatic glycosylation, reducing its rate of degradation. It acts as a coenzyme in the synthesis of the macromolecules of the interstitial matrix and reorganizes the structural glycoproteins and proteoglycans of the fundamental substances by stimulating the grouping of the polar amino acids and normalizing their hydrophilic capacity. In the microcirculation, it modifies the venous capillary and lymphatic permeability, and in the adipose tissue it stimulates the synthesis of the cyclic AMP and the hydrolysis of triglycerides, probably through an action mechanism on the cellular membrane, which activates adenylcyclase.

Extract of Asian centella is of vegetable origin and its chemical constituents are asiaticoside (40%), madecassic acid (30%), and asiatic acid (30%) triterpenic derivates that act on fibroblasts, stimulating the synthesis of collagen and mucopolysaccharides. Histological studies on epidermal cell cultures demonstrated the stimulus of the keratinization process by the asiaticoside. With topical and systemic use, action at a microcirculatory level was observed, with improvement in the perfusion of the lower members demonstrated using capillaroscopy in patients with chronic venous insufficiency. Asiaticoside is also used in the treatment of chronic venous ulcers.

Extract of Asian centella has been used systemically in a number of studies on cellulite. Analysis of the results is hampered by the varied methodologies and different, nonstandard evaluation criteria, as well as the absence of control in the majority of studies.

The active agents that act on the microcirculation include the vegetable extracts of ivy and Indian chestnut that are rich in saponins, and *Ginkgo biloba* and rutin that contain bioflavinoids. These act by reducing the capillary hyperpermeability and increasing the venous tone, by stimulating proline hydrolysis, and by inhibition of prostaglandins. They also reduce platelet aggregation, inhibiting the formation of microthrombi. Experimental studies (analyzed using oscillosmetry, thermometry, “Doppler,” hemodynamic methods, and capillaroscopy) show that the extract of *G. biloba* is antiedematous (by reduction of the capillary hyperpermeability) and improves the venous return and arterial circulation.

Pentoxifylline is a metilxantine that improves perfusion in the microcirculation, through its effect on the hemorrheological characteristics, such as erythrocyte deformation, platelet aggregation, and fibrinogenic plasma concentration. It also has an immunomodulating and trophic action on the connective tissue. It has been used in the treatment of peripheral vascular diseases (chronic venous insufficiency, stasis ulcer, etc.), with significant results (53).
ADMINISTRATION

Drugs are administered into the most superficial skin layers, a few millimeters under the skin surface, along with a deeper administration into spaces close to aponeuroses, giving way to an administration cylinder when mesotherapy needles are removed (54).

Drug biodistribution in superficial skin layers is slower than in deep layers where diffusion is more rapid and drugs have both general and local effects. Absorption occurs through blood and lymphatic vessels (55). This allows the administration of minimal amounts of active medications.

RECEPTORS

The minimal drug amounts in contact with peripheral receptors directly increase therapeutic effects. Results depend on the activation of the largest amount of receptors for disease control. Substance diffusion increases with increasing depth of delivery (13).

The administration of anesthetics in the treatment area retards the absorption of the injected drugs and allows them to diffuse deeper into the connective tissue, thus arriving at the desired site of treatment in higher concentrations without dilution. Without the application of anesthetics, the drugs may be absorbed. Because of this effect, the authors do not perform this therapy without the use of procaine or lidocaine (14,15).

METHOD OF APPLICATION

1. Introduction of the needle perpendicular to the skin for a depth of 2 to 6 mm.
2. Injection of 0.1 to 0.3 mL of the medication, applied symmetrically with a separation distance of 0.5 cm.
   a. Face—the distance between each puncture is 0.5 cm.
   b. Body—the distance between each puncture is 2 cm.
3. Weekly injections.
4. Pharmacology determined by the physician.
5. Quantity injected determined by the physician (16).

PROCEDURE

- The drugs are applied with the patient lying down. The area to be treated is mapped in each session.
- The patient is positioned to present the best angle for application, which must always be perpendicular to the skin.
- Injections are administered at multiple points very close, 2 to 4 mm, in parallel lines using a 4-mm needle and regular pressure (Napage technique). The angle of the needle should be 30° to 60° (17).
- The drugs are introduced smoothly with a regular interval between each dose.
- Care is taken to respect the locations of the vascular and nervous systems to diminish the possibility of hematoma formation. This technique is the most effective of all (overall in cellulite).
- In the Napage technique, a stimulation is produced that in turn activates the lymphatic circulation.
MATERIALS REQUIRED (19)
- disposable syringes (1–10 cc)
- disposable needles (27–30 G 1/2 in.)
- disposable Lebel's needles 4 mm
- multiple syringes
- manual or automatic “guns” syringes

Manual Application Equipment

*Syringe, hand, and needle:* Manual application is the most simple and is recommended for the trained operator. Success is based on the combination of the hand of the operator, the selected syringe, and the chosen needle. The smallest possible combination of syringe and needle is chosen that can contain the required number of injections.

Mechanical Equipment

- Den Hub
- Pneumatic injectors: Mesalyse
Electrical Equipment

Electronic injectors: DHN1, DHN2, DHN3, DHN4, and Dermotherap mesogun

Pistor Gun

Pistor developed a very light, somewhat noisy multinozzle injector made of plastic, with the capacity to regulate the depth of the needle from 1 mm onward. However, these injectors report the loss of infiltrate from one-thirds to two-thirds of the total volume. This unit can function in manual or automatic mode. It has the advantage of its lesser price and the disadvantages of the loss of the drug and the noise. There are now new electronic guns that do not waste drugs.

The following are important points in mesotherapy (20,21):

- Diffusion and distribution of the medicine is slower through the mesotract than through rest of the parenteral tracts.
Diffusion does not depend on the anatomical puncture location but on a perfect mesoexecution technique.

- Speed of diffusion is inversely proportional to the molecular weight of the medicine used.
- Mixtures of medications are avoided.
- If you do not have experience it is better to use one drug at a time, plus procaine 2%.
- Small amounts are injected at many points.
- One session per week is recommended.
- One or two sessions per month are recommended for maintenance.
- Intradermic superficial levels (4 mm) of injections are given.
- Please do not use enzymes in aesthetic mesotherapy.

Drugs for use in cellulite mesotherapy (22):

- Benzopirone > lymphokinetic action
- Pentoxifylline > hemorrheologic action
- Theophylline > lipolytic action
- TRIAC > lipolytic action
- Caffeine > lipolytic action
- Carnitine > lipolytic action
- *Cynara scolymus* > lower lipolytic action
- Monomethyl Silanol > action over the connective tissue
- Yohimbine > action over the alpha-2 adrenergic receptors
- Buflomedil > vasodilatation
- Procaine > anesthetic and more
- Phentolamine > action over the alpha-2 adrenergic receptors

**DRUGS AND PRODUCTS USED IN MESOTHERAPY**

**DISINFECTANTS**

There are many disinfectants that can be used on the skin, such as chlorhexidine, chloride of benzalconio, alcohol, ether, etc. However, it is preferable to use an alcoholic solution of Betadine (1%, colorless) prior to the mesotherapy due to its powerful action on bacteria, virus, and the majority of the fungus. Subsequent to the treatment session, it is advisable to clean the skin with 70% ethyl alcohol.

**AESCULUS (23)**

This homeopathic drug has the property of vitamin P, and normally affects the degree of capillary and membrane permeability. It contains escin with a high activity in microvascularization, antiedema, and anti-inflammatory processes.

**CONJOCTYL (SALICYLATE OF MONOMETILSILANOTRIOL) (24)**

Silicon is an element in the structure of elastic connective tissue. It enters the makeup of the macromolecules that form the woven connective tissue: elastin, collagen, proteoglycan, and glycoprotein. Regarding its structure, it possesses increased lipolytic action over theophylline, aminophylline, and caffeine.
It inhibits the formation of free radicals. A reduction in the destruction is produced by elastin and collagen, with limitations to the destruction of connective tissue and its sclerosis. It reorganizes the lipids in the cell membrane, thus increasing its resistance to peroxide damage.

CHOFITOL: (EXTRACT OF ALCACHOFA—C SCOLYMUS) (25)

**Actions**
- increases the volume of bile secreted
- antitoxic function of the liver
- glycogenic function of the liver
- metabolism of the lipids
- metabolism of cholesterol

**Indications:**
- phytotherapy to stimulate biliary function
- symptomatic processing of the dyspeptic changes
- excess blood urea; complementary processing of urinary lithiasis
- hypercholesterolemia
- cellulite

MELILOTUS-RUTÓSIDO (26)

It has a pH of 6.4 and is used in the treatment of lymphatic or venous pathology. It has an antispasmodic effect on the smooth muscle fibers of the lymphatic system and the capillaries, thus diminishing permeability and increasing vascular resistance.
PROCAINE

It is best known for its anesthetic property. It is three to four times less powerful than cocaine. Procaine is used in mesotherapy in the form of chlorhydrate of procaine, 1% to 2%, with a molecular weight of 272.8 and a pH between 5 and 6 (27).

Actions

- Local: has a short-term anesthetic effect due to the stabilization action of the membranes that oppose ionic transmembrane migration.
- Cardiovascular system: antiarrhythmic and vasodilator.
- Autonomous nervous system: with a strong dose, procaine produces effects due to inhibition of ganglion receivers.
- Muscular system: reduction of the muscular activity and hypotony of the striated muscle fibers, and causes spasm of smooth muscle fibers (28,29).
- Respiratory system: with small doses, acceleration of the rhythm and increase of respiratory amplitude, and with a strong dose, depression of the respiratory center.
- Red blood cells: improves their deformability to aid their passage through the microcirculation (30).

Precautions

- Dosage of procaine should be advised by a physician, since an overdose may result in complications such as agitation, delirium, trembling or lack of motor coordination, and drowsiness.
- It has absolute incompatibility with sulfonamide treatment.
- It should never be administered in patients with a history of epilepsy.

In case of collapse, an injection of caffeine must be administered immediately.

Secondary Effects

- exceptional allergic dermatitis
- asthma
- anaphylactic shock
- muscle paralysis
- nausea, vomiting, and irritability
- agitation

BUFLOMEDIL

It opens the precapillary sphincter, improving microcirculation (31).

CAFFEINE

With regard to lipid deposits, it is well known that caffeine causes an increase in the intracellular concentration of cyclic AMP (acid adenosin-5-monophosphoric cyclic) and has immediate consequences on the lipid metabolism of adipose tissues, thus increasing the levels of the cyclic AMP (32).
The activated protein kinase is responsible for the activation of lipase. The activation of the lipase into the fat cell lipase hormone promotes hydrolysis of triglycerides “in situ,” giving rise to the corresponding formation of glycerol and fatty acids. The role of caffeine in mesotherapy is lipolytic.

**L-CARNITINE**

L-carnitine, “the decorative molecule of fat,” is an amino acid that constitutes an essential cofactor in the metabolism of fatty acids acting to diminish triglycerides and of total cholesterol by improving lipid metabolism (33).

**Indications**

- Cellulite: the lack of L-carnitine impedes fat transport. This accumulation of fat is translated exteriorly as orange skin presentation and cellulite.
- The more L-carnitine individuals have, the more their fat cells burn and, consequently, this makes the individuals thin and creates more energy along with an improved resistance to cold and exhaustion.

**PHENTOLAMINE**

It blocks alpha-2 adrenergic receptors. It is used for lipolysis and vasodilatation (34).

**GINKGO BILOBA**

It is used in mesotherapy for tissue regeneration. It antagonizes the free production of free radicals, lipoperoxidation of the cell membrane, and oxidation of proteins and nucleic acids (35).

**MESOGLYCANS**

They are complex macromolecules composed of a polypeptide chain (protein) called glycosaminoglycan, a mucopolysaccharidic acid. They are dynamic components that intervene in biological processes of the cell, such as proliferation, recognition, and differentiation. Thus, they reestablish the epidermal cells by stimulation, and at the same time are capable of increasing the metabolism of the components of connective tissues, which leads to a recovery of normal functions of the skin (10).

**PENTOXIFYLLINE**

Pentoxifylline intensifies blood perfusion, improves the microcirculation, and favors lipolysis by the inhibition of phosphodiesterase; it restores the cyclic AMP. It is contraindicated in patients with a myocardial infarction (36).

**THEOPHYLLINE**

Theophylline promotes lipolysis by inhibition of the enzyme phosphodiesterase. To this is added the effects created by cyclic AMP. Together they intervene in the metabolic step that transforms the triglycerides in glycerol and fat-free acids (37,38).
TRIAC
When administered locally, it possesses lipolytic action and lacks systemic action, except for its power of stimulating the formation of T3-autoantibodies (39). It leads to an increase in fat catabolism. It is used in the treatment of cellulite and hypercholesterolemia caused by a deficiency of thyroid hormones.

YOHIMBINE
Yohimbine produces a short-term blockade of alpha-2 adrenergic receptors in adiposities. It also has lipolytic and vasodilatory actions. It has an anesthetic action on sensory nerve endings. It is an antidiuretic, improves orthostatic hypotension, increases the heart rate and lowers blood pressure by vasodilatation. It possesses aphrodisiac properties over that of strychnine; therefore while strychnine enlarges all the vessels, yohimbine only acts on pelvic vessels. It is used as a sexual stimulant in impotence, in painful menstruations with low blood flow or amenorrhea, and in prostatic hypertrophy.

<table>
<thead>
<tr>
<th>MESOTHERAPY FOR CELLULITE AND OBESITY</th>
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<tbody>
<tr>
<td>Product</td>
</tr>
<tr>
<td>Benzopirone</td>
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<tr>
<td>Pentoxifylline</td>
</tr>
<tr>
<td>Theophylline</td>
</tr>
<tr>
<td>Triac</td>
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<tr>
<td>Caffeine</td>
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<tr>
<td>Carnitine</td>
</tr>
<tr>
<td>Extract of Cynara scolymus</td>
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<tr>
<td>Salicylate of monometilsilanotriol</td>
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<tr>
<td>Yohimbine</td>
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<tr>
<td>Buflomedil</td>
</tr>
<tr>
<td>Procaine</td>
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<tr>
<td>Lidocaine</td>
</tr>
</tbody>
</table>

Complementary treatments: 5.5 25 U

Extract of Melilotus 200mg
Rutin sulfate de sodium 50mg
Naftidrofuril 40mg
Nicotinato de Xantanol 250mg
Extract of Cynara 150mg
Procaine 1%
Distilled water c.s.p 18 cc

VENOTROPIC MESOTHERAPY

<table>
<thead>
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<th>Product</th>
<th>Conc.</th>
<th>pH</th>
<th>U</th>
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<td>Fentolamine</td>
<td>100mg</td>
<td>6</td>
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</tr>
</tbody>
</table>
**NO-NEEDLE MESOTHERAPY™**

This is a device (with FDA clearance II) that uses the combination of all viable technologies: electrotherapy with three specialized waveforms in sequence, laser with two diode laser wavelengths, and an active conductive gel. The device has preprogrammed treatment protocols and utilizes a new technique of molecule delivery called Aquaphoresis™. Aquaporins are a family of specialized proteins that reside in the membranes of cells and control the inflow and outflow of water.
CONCLUSION

The results obtained in aesthetic medicine when using mesotherapy are very good. After completing a series of treatments, generally over a two- or three-month period of time, patients notice an improvement in skin quality with less dimpling of the skin, and a reduction in the localized fat deposits.

DIFFERENCES BETWEEN THE RESULTS OF MESOTHERAPY AND LIPOSCULPTURE

Mesotherapy and liposculpture are two different techniques, and both can be used in localized adipocyte treatment. Mesotherapy is a noninvasive technique and can be used in improving connective tissue, the elasticity of the skin, the microcirculation, and also diminishing the volume of the fat cells without destroying them (lypolytic action).

Following liposculpture, local fat loss is permanent; with mesotherapy, the results are temporary and less dramatic.

In localized fat areas, the best results are obtained by using mesotherapy to repair skin elasticity, improve the microcirculation, and diminish the fat cell volume. Liposculpture is then used to destroy the fat cells, reducing the localized fatty area.
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Manual Lymphatic Drainage

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Manual lymphatic drainage (MLD) is an essential complementary therapy for cellulite disease. It should be gentle and nontraumatic in order to provide improved tissue metabolic homeostasis. MLD follows Foldi’s, Leduc and Caplan’s, and Ciucci’s teachings (1–3).

It consists of a series of gentle touches and compressions over specific lymphatic system sites aimed at emptying congested ganglia and improving lymphatic flow by removing lymph from tissues. Curri (4) has shown that MLD combined with a simultaneous application of a cream with phytodrugs brings about a significant improvement.

MLD can be included in classical large surface massage methods. Close examination reveals that MLD is more difficult because it involves manual techniques that are not used in classical massage.

MLD consists of four different techniques:

1. **Stationary circles technique**: In this technique, the fingers are placed flat on the skin and moved in the same place as stationary circles. Each of these circles is performed with a smooth increase of pressure and a smooth decrease of pressure into the tissue.
2. **Pump technique**: In this technique, the palms face downward. The thumb and fingers move together in the same direction, moving the skin in oval circles.
3. **Scoop technique**: In this technique, the palm is facing upward. Vodder describes the movement as a giving motion.
4. **Rotary technique**: This technique is used on relatively flat areas of the body and consists of various individual movements.

Proper MLD consists of a combination of round or oval, small or large, and deep or shallow circular movements; it:

1. Stimulates the microcirculation, improving edema and cellular nutrition
2. Requires only thirty to forty minutes of treatment
3. Does not cause pain
4. Does not cause redness of skin
5. Does not require the use of creams—it is important to remember that MLD does not use creams, only the hands
6. Mobilizes the lymph
7. Moves lymph and high protein from the interstitium into the small lymphatic vessels
8. Requires applying lighter pressure for softer tissues (Fig. 1).

Figure 1
Maneuvers of MLD in the legs (A–C) and in the arms (D) after mastectomy for breast cancer. Abbreviation: MLD, manual lymphatic drainage.
The Vodder method of MLD is a technique used to stimulate the movement of fluids in the tissues (5). The gentle, rhythmic, pumping massage movements follow the direction of lymph flow and produce rapid results. This massage technique is focused on tissue and lymphatic detoxification and is proposed as an important means of preventing cellulite recurrence (6).

MLD periodic cycles are recommended to maintain tissues free of lymph stasis. With the introduction of endermology, the device itself carries out drainage and promotes secondary detoxification, connective tissue stimulation, and a neurophysiologic response. It reduces the need for compression garments in the treatment of lymphedema. The bimonthly or monthly inclusion of Vodder’s MLD may be extremely useful for cosmetic as well as medical purposes.
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The Role of Dermoelectroporation

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INTRODUCTION

Dermoelectroporation is a treatment method that enables absorption of active substances (normally they are ionic drug solutions) using equipment that generate electric pulses allowing the opening of cellular “electric gates” and promoting the passage of substances through the epidermis. In 1970, a group of American dermatologists discovered that by applying an intense electrical impulse for a short time at an adequate wavelength, a change in polarization of the cellular membrane occurred, which could be used to promote a kind of cellular “pulsation.” In fact, after the initial pulse, the polarity is slowly reversed, avoiding electrolysis, and this opens intercellular channels through which substances can pass. Once they are formed, these channels stay open for a relatively long time—several seconds.

This method was named “electroporation” and was used, with special techniques, in the transdermic treatment of melanomas. Electroporation with high voltage is the only system that can introduce substances of high molecular weight transdermally. Over 4000 published scientific reports demonstrate the actions and possible uses of the method (9).

Despite the very similar name, “dermoelectroporation” is different, because this new method works with lower voltages in comparison to “electroporation.” In the apparatus used for medical and aesthetic purposes (Transderm Ionto® by Mattioli Engineering, Florence, Italy), dermoelectroporation treatment is applied by a discharge given by an electric inductor charged at a controlled current value and then discharged with a typical kind of reversible exponential voltage wave.

Why does the new method work well only after dermabrasion of the horny layer? The answer can be that the high voltage in classical electroporation produces only partly poration of the horny layer and partly poration of the dermis (with the residual energy after having perforated the horny layer).

Dermoelectroporation eliminates the need for high voltage because the epidermal horny layer is eliminated with microdermabrasion and so the voltage necessary to porate the dermis is lower.

It works like high voltage electroporation, however, replacing the dangerous and hardly controllable effect of high voltage on the horny layer with the safer microdermabrasion. Less energy is used to open channels in the dermis.
**TRANSDERM® METHOD**

This technique enables transdermal absorption using an apparatus that generates electrical pulses that are able to open “intercellular gates” used for the passage of substances of suitable dimension. For this author, it is the apparatus of choice for reaching our clinical and aesthetical goals. The electrical activity of electroporation is given by a discharge sent by an electric inductor loaded with current, which is able to produce discharge tensions up to 100 V and therefore unload with a reversing exponential waveform. When in contact with the skin, an intense ion flux develops that allows a direct charge to the skin in a value proportional to the voltage applied. In this way, a temporary perturbation of the normal value of the potential of the cellular membrane occurs and this determines the increase in the permeability. This situation remains for a limited time, because of the mechanisms of electrolytic conductivity and the potential of the membrane to regain its equilibrium state. The technical innovation of the instrument is in the employment of a transformer to control the current and, therefore, the ion flux (1–8).

The Transderm® instrument realizes a sequence of impulses of opposite polarity so that electrolysis of the electrodes and the drug solution is avoided. Dermoelectroporation controls the average pulse value by providing a continuous reversed polarity current. Varying the pulse shape according to the skin’s specific electrical impedance promotes the transdermal delivery of drugs as in classical iontophoresis, despite the fact that the average current is zero. Moreover, macromolecules are transdermally delivered from an iontophoretic device.

The absence of a temporary pH change allows the use of microdermabrasion before dermoelectroporation application. Pretreatment with microdermabrasion promotes the transdermal delivery rate and ensures repeatability as a result of the standardization of the thickness and permeability of the stratum corneum. The pulse shapes operate at a much lower energy and penetrate even under high skin-impedance conditions.

**CHARACTERISTIC FEATURES**

The classical electroporation equipment basically works on the principle of capacitor discharge. A capacitor is charged to a value of some hundred volts and then discharged on the tissue to be electroporated. If the load is purely resistive, the voltage waveform obtained is an exponential decay curve. The maximum peak current occurs at the beginning of the discharge and the value is given by the ratio, charge voltage/load resistance. Unfortunately, the living skin has a significant capacitance in parallel to the resistive load. This means that at the beginning of the discharge the resulting current is very high for a short period of time until the skin capacitance is charged to a value close to the voltage of the electroporation capacitor; then the exponential current decay curve occurs.

Moreover, the skin impedance and the resulting current are functions of several variables—skin condition, pressure of the electrode on the skin, moisture, stratum corneum thickness, etc. This occurs despite the fact that the current in the in vivo application is a critical parameter, because skin damage occurs when the current density is too high. The electric circuit based on the capacitor is intrinsically unsafe because the peak value current is unpredictable. Strict international rules limit the maximum current density
applicable to the skin and this limits the practical application of classical electroporation. For this reason the authors experimented with a different type of circuit that is intrinsically safe, verifying if transdermal transport of molecules and macromolecules occurs as in classical electroporation despite the limited density of current. The circuit uses an inductor instead of a capacitor as a means to store energy and obtain a pulse with exponential decay equivalent to the one obtained by the circuit based on a capacitor. The circuit with the inductor is able to deliver a pure resistance with the same waveform of the circuit based on the capacitor. The advantage occurs when the load is a resistance in parallel with a capacitance as in the living skin. In this case, at the beginning of the discharge, the value of the current is the maximum value during the pulse.

The current waveform is an exponential decay curve. The voltage waveform is variable and depends on the characteristics of the load. The parameters chosen are 2 mA, maximum peak pulse current of 5 mA (value at the beginning of the discharge), and a drug-soaked electrode surface of 3.6 cm². Such values are capable on a 20 kΩ load to generate a peak voltage value of 200 V.

To maximize the effect and add an iontophoretic transport mechanism, the pulses have been grouped in bursts at a frequency of 2200 Hz. The burst is composed of a sequence of negative and positive symmetric pulses and no direct current is applied. Burst duration and time between bursts is 10 msec. To avoid the stimulation of muscles under the electrode area, a novel electrode geometry has been chosen. The return electrodes are designed around the active electrode soaked with the ionic substance to be transdermally delivered. In this way the current flows only inside the dermis and no current flows into the muscles under the skin.

### POSSIBLE USES

Our experience is particularly on the face, where we have had good results using a protocol called “bioresurfacing.” This signifies a treatment procedure aimed at rejuvenating the face through a nonsurgical, “soft,” outpatient treatment (9–11). The treatment requires bimonthly or monthly sessions—a total of four to eight—of a procedure consisting first of superficial microdermabrasion intended for the removal of the corneus layer and for vascularization. These crystals are then used with a manual massage to promote further mechanical smoothing of the skin. Immediately afterwards, active substances such as collagen, hyaluronic acid, amino acids, and elastin or, better, their precursors are introduced by means of the dermoelectroporation treatment as previously described. Cellulite requires integrated treatments according to the various pathologies described below.

### DERMEOELECTROPORATION TREATMENT

In aesthetic pathologies characterized by skin irregularities and dystrophies, such as acne, wrinkles, stretch marks, and sagging of the skin, treatment with dermoelectroporation is preceded by a surface microdermabrasion treatment performed by a system using corundum powder crystals (aluminum oxide in a sterile, disposable package), which produces a process of removal of the corneous layer with simultaneous vascularization of the tissue by
mechanical stimulation (light suction–light pressure–dermabrasion). When the dermabrasi-
on treatment requires deeper effects that may cause pain, a session of dermoelectropora-
tion treatment is used first to introduce an anesthetic (2% lidocaine without epinephrine).

The treatment is aimed at improving the outer appearance by stimulating reconstitu-
tion of a new collagen and matrix tissue. The several stages in attaining this end are as follows:

1. Lymphatic drainage and vascularization performed with Endermologie.
2. Skin smoothing performed by very superficial microdermabrasion with corundum
   powder crystals (Ultraceel Transderm by Mattioli Engineering). After being made
   aseptic by means of nonalcoholic detergents, the skin is smoothed without being
   traumatized. At the end of the session, the crystals remaining on the skin are used to
   perform a final “gommage” with the fingers, and then the skin is washed with a physi-
   ological solution.
3. Electric and pharmacologic stimulation, using dermoelectroporation treatment with
   Transderm. Over the clean skin a sterile gauze pad is applied and on it is poured a
   sterile solution of glycerin, proline, lysine, and glycoaminoglycan (the precursors of
   collagen, elastin, and hyaluronic acid) whose transdermal introduction is helped by
   the dermoelectroporation treatment. The procedure usually lasts for five minutes per
   area until the substances are absorbed. At this point, the skin is washed with a physio-
   logical solution and a soothing treatment is performed.
4. Soothing action, performed by applying compresses of cold water and soothing sub-
   stances after applying a cream (in our practice we use Biafin or Biolenil Medestea as
   soothing substances).

The treatment is usually performed once or twice a week for about 10 to 15 times,
and then a maintenance treatment is performed every three weeks.

■ CLINICAL STUDY

Professors Agree and Kinnon, at the University in Florence, produced experimental
studies that have shown the passage of bovine collagen type I (a big molecule of
0.8 μm) in rodent skin using the Transderm methodology (Fig. 1) (12,13).

This photo shows a section of rat cutis after this treatment. The surface of the skin
appears phosphorescent, and in the dermis, one can observe many molecules of fluorescent
collagen extending from the superficial dermis till the lipodermic layer. It is interesting to
note that the molecules enter precise zones of the skin using the channels—“the watery
electropores.” The large molecules, such as the collagen, have not been altered.

Figures 2 and 3 show the large molecule of bovine collagen to be unaltered, as the
placebo test shows the validity of the experimentation.

This test shows the effect of this methodology in introducing substances such as
bovine collagen or elastin into the dermis and lipodermal layer using dermoelectric pora-
tion. In another part of the study, the test shows that using only microdermabrasion or
only dermoelectroporation does not produce this result, confirming the importance of
integrated treatment.

Biologically active drugs and macromolecules such as peptide drugs, proteins, oligo-
nucleotides, and glycosaminoglicans are characterized by a short biological half-life and
scarce bioavailability; such characteristics make it difficult to employ therapeutic strategies
Figure 1
Section of skin of an experimental rat after treatment by Transderm\textsuperscript{\textregistered} (\times 150). The skin surface appears uniformly covered by fluorescent. Numerous molecules of fluorescent collagen are observable from the outermost part to the inner part of the dermis.

Figure 2
Microscopic extension of many molecules of bovine collagen type 1 fluorescent (0.8 micron).
other than parenteral ones. In this experimental study, the authors have used a new type of dermoelectroporation, which involves the application of pulsed electric fields with Transderm®. Moreover, they have analyzed the transdermal delivery of biologically active molecules in vivo. The advantage of using pulsed electric fields as opposed to continuous ones is that there is a significant reduction in the degradation of the molecules to be transported as a result of the electrolytic phenomena.

The study was divided into three parts: (1) microscopic analysis of skin tissue after the application of the electric field; (2) qualitative analysis of transdermal delivery of a protein macromolecule (collagen type I); and (3) quantitative analysis of transdermal delivery of lidocaine.

The study demonstrates that dermoelectroporation can be used for transdermal delivery of biologically active molecules, which in our case is represented by a large protein macromolecule (collagen) and by an anesthetic (lidocaine) (14–19).

European dermoelectroporation applications (Fig. 4), after two years of experience in controlled experimental and clinical studies, demonstrate activity in:

- photo damage
- postacne scar
- hyperpigmentation
- cellulite
- sports medicine
- rheumatology
- anti-inflammatory and analgesic therapy
- phlebology
- photo aging

Figure 3
Section of rat cutis not treated (×150). The surface of the skin appears uniform and fluorescent but, in the dermis, there is no observation of any fluorescent molecules.
CONCLUSIONS

Certainly, dermoelectroporation is not the panacea for cellulite, but is a valid weapon, particularly for the treatment of fibrous cellulite in difficult areas, such as the posterior area of the thigh and buttock, and for painful cellulite (20–22).

ACKNOWLEDGMENT

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Lipodissolve for Body Sculpting

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INTRODUCTION

Lipodissolve involves an injection into adipose tissue to dissolve fat. This treatment slowly breaks down fatty deposits with subcutaneous injections of an adipocyte-dissolving formula. While it is in its infancy in North America, it has been practiced in Europe and South America for over 10 years. Despite the fact that lipodissolve injectors outside the United States tout its benefits based on their favorable experiences, there exists a considerable amount of healthy skepticism in the American cosmetic medical community concerning this procedure. This is mainly due to the paucity of scientific literature demonstrating the histopathology, mechanism of action, and detailed measurable clinical results. This is similar to the situation that pioneering practitioners using Botox® for cosmetic purposes found themselves in during the early 1990s.

Lipodissolve injections are suitable for nonobese patients with localized fat accumulation, which cannot be reduced with appropriate diet or sincere efforts at exercise. Lipodissolve injections do not result in weight loss; lipodissolve injections modify body contours. The ideal patient has a body mass index (BMI) of less than 25. Lipodissolve is not a substitute for liposuction; it is an alternative to liposuction for smaller areas of fat accumulation in a patient who prefers a less invasive procedure. It is the author’s opinion that liposuction is a more cost-effective and efficient procedure than lipodissolve for larger fatty deposits.

The active ingredients of the lipodissolve formula are a mixture of phosphatidylcholine (PC), a natural substance derived from soybean lecithin, and deoxycholate (DC), a bile salt. Aventis Pharma (part of the Sanofi-Aventis Group, Paris, France), which is the third largest pharmaceutical company in the world, markets a PC/DC preparation under the trade names Lipostabil® and Essentielle® in Europe (primarily Germany and Italy), Russia, and South America. The Lipostabil® brand contains 5% PC (50 mg/mL) and 4.75% DC (47.5 mg/mL) with 0.9% benzoyl alcohol and saline. Lipostabil® is not sold in the United States or Canada.
PHOSPHATIDYLCHOLINE (PC)

PC is an essential phospholipid, which comprises 40% of the human cell membrane. PC is commonly known as lecithin, and the commercial preparations of purified PC are derived from soybean lecithin, rather than egg yolk. PC is composed of choline, phosphate, and two fatty acids (Fig. 1). One end is polar, the other nonpolar. This is the primary constituent of the bilipid cell membrane.

Figure 1
Phosphatidylcholine.

PC is involved in the regulation of lipid metabolism (1,2), and is marketed by Aventis as an injectable intravenous infusion to lower cholesterol and triglycerides, under the name...
Lipostabil\textsuperscript{\textregistered}. Lipostabil\textsuperscript{\textregistered} is also used in the treatment of hepatitis (3–5) and cardiovascular atheromatous diseases in Europe and Russia (2,6).

The known ability of oral and intravenous PC to reduce systemic triglycerides and cholesterol eventually led to its use as a subcutaneous injection in an attempt to decrease fatty deposits (Fig. 2). The first published trial of using Lipostabil\textsuperscript{\textregistered} as a subcutaneous injection was in 1988 by the Italian physician Sergio Maggiori in the treatment of xanthelasma (7).

Subsequently, Lipostabil\textsuperscript{\textregistered} was reported as being used for a successful office-based procedure for fat dissolution of the “buffalo hump” (AIDS lipodystrophy) at an HIV symposium in Athens, Greece, in 2001 (8). Brazilian dermatologist Marcio Serra described the substantial reduction of buffalo humps in two HIV patients injected on five occasions every two weeks with 200 mg of PC. Local side effects of erythema and edema were reported to resolve over three to four days (8).

In 1999, Brazilian dermatologist Dr. Patricia Rittes reported the injection of PC into the small fat pads in the lower eyelid area at the 54th Brazilian Dermatology Congress (9). The first paper published in an English peer-reviewed journal concerning PC use for localized fat dissolution was by Rittes in 2001 (9). Rittes has performed this office procedure thousands of times since 1999. Rittes’ paper in Dermatologic Surgery describes the injection in 30 patients (22 females, 8 males, ages 30–70) at 15-day intervals up to four times in each of the three infraorbital fat pads (9). Cosmetic improvement was reported in all patients, with local side effects of erythema and edema for up to three days. Follow-up was for two years with no recurrences. This paper gives the total dose of PC per infraorbital eye pad (PC 20 mg), but does not report the exact technique. Dr. Rittes has described her injection technique at many medical seminars, and it is detailed in Figure 2.

This work was reproduced by American physicians Ablon and Rotunda in 2003 (10). Ten patients (seven women and three men, ages 42–71) were injected at 14-day intervals up to five times using the Rittes’ technique. Immediate local side effects were mild burning, erythema, and edema. Dr. Rotunda reported that 6 of 10 patients

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**Figure 2**

Hasengschwandtner’s injection technique for Lipostabil\textsuperscript{\textregistered}. Note that each injection point is equidistant and spaced 2 cm apart. The injection pattern should resemble the five sides of a die. Each point represents 20 mg of PC injected to a depth of 6–13 mm. (More superficial injection will affect the dermis and can cause necrosis.) Rittes injects twice as much PC in each site, and the sites are spaced further apart.
had moderate-to-significant improvement with no significant side effects during the 6- to 10-month period of follow-up (10).

Dr. Rittes published a second article describing injections of PC 40 mg per injection site into areas of fatty accumulation other than infraorbital fat pads in 50 patients (40 female and 10 male, ages 25–60) every 15 days up to four times (11). 40 mg PC was injected every 2 to 3 cm using a 30 G 1/2 in. needle into the fatty deposit. A total dose of 250 mg PC was injected uniformly over an 80 cm² area. Various areas of the body with fatty accumulation were chosen. Before and after photographs were taken, but no measurements. Cosmetic improvement was reported in all patients, with fat reduction and improvement in body contour with the loss of a roll of fat. In the discussion, Dr. Rittes reports no return of fat in four years of follow-up, but exact numbers are not given. Local side effects of burning pain, erythema, and edema are again described. Subcutaneous nodules that disappeared within 30 days are mentioned. No lipoatrophy occurred. Rittes found the treatment safe and effective (11).

Brazilian dermatologists Hexsel and Serra reported injections of 10 mg PC per injection point in 213 patients every 15 days up to five times (12). 10 mg PC was injected every 2 cm using a 30 G 1 in. needle at a depth of 1 to 2 cm. A maximum of 500 mg of PC was injected at any one session. The 213-patient group included eight HIV patients who were treated for buffalo humps at 30-day intervals. By the fifth session, 80% to 100% remission or “considerable improvement” was reported. Local side effects included transitory pain at the site of injection, erythema, and edema. No systemic adverse reactions were observed. Thirteen patients underwent pre- and postprocedure liver and renal-function testing. There were no significant alterations in laboratory parameters. Hexsel and Serra reported the treatment as safe, effective, and low cost, as well as being much simpler compared to surgical liposuction.

Unfortunately, these have all been open-label clinical studies. Owing to the immediate erythema and edema that occur following injection of PC, it would be difficult to
design a double-blind study. The studies also have not shown any histopathology concerning the mechanism of action of the PC. Measurements are lacking, although some very good “before” and “after” photographs are shown in the papers discussed. Only Hexasel and Serra reported any laboratory data in 13 of 213 patients (12).

**DEOXYCHOLATE (DEOXYCHOLIC ACID)**

DC is a bile acid found in human bile and has a primary detergent effect in the emulsification of fats in our diet (Fig. 4). DC is also widely used as a laboratory reagent to solubilize cell membrane proteins because of its detergent effects. Detergents have had various uses in medications for many years, especially as sclerosing agents for sclerotherapy injections. A specific example of DC as a detergent is in the solubilization of amphotericin B. Amphoterin B is insoluble in water; the presence of sodium deoxycholate in the formulation solubilizes amphotericin B during reconstitution with sterile water, providing a colloidal dispersion of the drug for intravenous injection.

A major criticism of the lipodissolve treatment is that there have not been any histopathological data on the PC/DC formula injected into adipose tissues until recently (24). The Lipostabil® formulation contains almost equal amounts of PC (50 mg/mL) and DC (47.5 mg/mL).

Rotunda et al. (13) published their findings in *Dermatologic Surgery* in 2004, describing a loss of cell viability with cell-membrane lysis and disruption of fat and muscle architecture in porcine cell cultures and tissue specimens treated with PC/DC and DC alone. As mentioned previously, DC is a detergent that is used to emulsify and solubilize compounds that are insoluble in water, such as injectable amphotericin. Rotunda et al. showed that injecting the bile salt DC alone produced similar effects as the combination PC/DC Lipostabil® formulation, suggesting that DC is an active ingredient. They were unable to test PC in isolation, because PC is not soluble in aqueous saline solution by itself. DC is used to increase the solubility of PC.
Histology of the porcine skin did not show any changes in the epidermis, dermis, or adnexal structures after injection of PC/DC. There was a concentration-dependent increase in cell lysis in both the PC/DC- and DC-treated cell cultures. Muscle cell viability was also compromised on injecting into porcine muscle, indicating the critical importance of limiting PC injections to adipose tissue and avoiding any underlying muscle. Rotunda et al. summarized the effect of the PC/DC formula as a detergent action causing nonspecific lysis of cell membranes with a brisk inflammatory response and subsequent adipocyte necrosis, similar to the conclusions drawn by Rose and Morgan (24).

**AVAILABILITY OF LIPOSTABIL® IN THE UNITED STATES AND CANADA**

At this writing, Aventis has no plans to market Lipostabil® in the United States or Canada (personal communication with the manufacturer). Thus, it has not gone through the FDA regulatory process, and its use is therefore illegal in the United States (14). In a letter written to warn a U.S. importer of Libostabil® , an official of the FDA wrote,

If a drug is marketed as an injectable product, it does not qualify as a dietary supplement since it is not intended for ingestion as set forth in section 210(ff)(2)(A)(i) of the Federal Food, Drug, and Cosmetic Act (the Act).

Based on the route of administration (i.e., injectable) of this product and the claims made for the product to affect the structure or function of the body, it is a “drug” within the meaning of section 201(g) of the Act. Moreover, the product is a “new drug” [section 201(p) of the Act] because there is no substantial evidence that the product is generally recognized as safe and effective for its intended use.

Since the product is a “new drug” it may not be marketed in the United States without an approved new drug application [section 505(a) of the Act]. In addition, in accordance with section 503(b)(1) of the Act, injectables other than insulin may not be sold directly to consumers (14).

However, since the principal constituents of Libostabil® are PC, derived from soybean lecithin, and the bile salt DC, the ingredients are readily available to compounding pharmacies in the United States and Canada. Therefore, a physician can order these substances to be mixed to any specification. Because the route of administration is parenteral, and claims are being made that these substances will dissolve fat, the FDA would consider the entire process to be the practice of medicine with the simple administration of a drug falling under the duties of responsibility and judgement of the physician.

In view of the fact that injectables cannot be sold directly to consumers (other than insulin), a licensed physician can write a prescription instructing a compounding pharmacy to make the formula to dissolve fat. The physician then takes the responsibility for the administration and safety of the prescribed treatment, as is the case with any other medical treatment. It is the author’s hope that these rules will prevent nonmedical personnel from injecting PC/DC formulations as previously occurred in Brazil. Due to the widespread popularity of Lipostabil® in Brazil, this formula was being injected in beauty salons, gymnasiums, and spas by nonmedical individuals, which alarmed Aventis Pharma.

Aventis notified the Brazilian health authority, the Brazilian National Agency of Sanitary Monitoring (Anvisa). Aventis Pharma, Brazil issued a notice stating that
it does not market the product in Brazil and has no plans to do so. When Anvisa investigated the widespread unauthorized use of Aventis’ Lipostabil® (fosfatidicolin) to reduce fat, it found two Internet companies distributing Lipostabil® in Brazil. This led to the banning of Lipostabil® at the national level in Brazil in January, 2003, with the intent that nonmedical people would have difficulty purchasing and administering it outside a physician’s direct control (15). Some North American physicians have incorrectly quoted the banning of Lipostabil® in Brazil as “evidence” that Lipostabil® must be inherently unsafe.

### CONTRAINDICATIONS FOR LIPODISSOLVE INJECTIONS

The following factors are contraindications for lipodissolve injections:
1. Pregnancy and breast-feeding
2. Being a minor
3. Diabetes with microangiopathy
4. Serious cardiac, liver, or renal disease
5. Serious obesity
6. Acute/chronic infections
7. Blood dyscrasia (warfarin/ASA/NSAIDS/vitamin E/hemophiliac)
8. Allergy to any ingredients, especially soy
9. Having unrealistic expectations

### SIDE EFFECTS OF LIPODISSOLVE INJECTIONS

#### LOCAL SIDE EFFECTS (IN THE INJECTED AREA)

For a few days:
1. Pain 100%
2. Swelling 100%
3. Sensitivity to touch 100%
4. Pruritis 100%
5. Erythema 100% (Figs. 5 and 6)
6. Ecchymosis, occasionally
7. Hematoma rarely

For a few weeks:
8. Nodules and “dents” which will eventually disappear
9. Skin necrosis, ulceration, infection (very rare)

#### SYSTEMIC SIDE EFFECTS (CHOLINERGIC)

These are more common with higher doses.
1. Nausea
2. Perspiration
3. Diarrhea
4. Altered taste sensation/salivation
5. Cardiac arrhythmia (reported with intravenous PC)
Figure 5
Post-treatment erythema.

Figure 6
Immediate post-treatment erythema.
DOSAGES AND TECHNIQUES FOR LIPODISSOLVE INJECTIONS

Toxicity studies have been done with PC (International Journal of Toxicology, 2001). The maximum nonlethal subcutaneous dose of PC for mouse, rat, and rabbit was 1000, 4000, and 10,000 mg/kg, respectively (16). Different doses of PC to dissolve localized fat are used by various experts.

Dr. Franz Hasengschwandtner (Founder and Director of Network-Lipolysis at www.network-lipodissolve.com and Chairman of the Austrian Society for Lipodissolve) uses a maximum of 2500 mg PC per session. He spaces his sessions four to six weeks apart. He injects 0.4 mL of 50 mg/mL Lipostabil per injection site (20 mg of PC) approximately 2 cm apart to a depth of 13 mm into fatty pads (Fig. 3).

Dr. Patricia Rittes (world’s foremost specialist on lipodissolve with over 26,000 cases in Brazil—www.prittes.com.br) injects 0.8 mL of 50 mg/mL PC per injection site (40 mg of PC) approximately 4 to 6 cm apart to a depth of 13 mm. A typical injection pattern would involve six injections of 0.8 mL each in an area of about 80 cm². This area corresponds roughly to a 4 × 4 in. gauze (10 × 10 cm) and would require about 250 mg of PC. Rittes limits her total injection dose to 500 mg per session.

Dr. Hasengschwandtner is performing more injections closer together using half the PC that Dr. Rittes uses for each injection site. Her injection technique involves injecting more PC into each site, but using fewer injections that are spaced further apart. It may be that there is less pronounced nodulation with smaller amounts injected into more sites.

The nodulation following PC injection is a direct result of fat necrosis, and it makes intuitive sense to limit the volume of injection into any one point, although the optimal amount to inject in any one point is unclear. The author uses 20 mg of PC injected into one point. The author also limits his initial total dose of PC to 1000 mg to observe patient response and to minimize the chance of any systemic side effects. This is an office-based, elective cosmetic procedure, and patients choosing this treatment do not want any “down-time” with excessive pain, swelling, or complications.

GENERAL CONSIDERATIONS FOR LIPODISSOLVE INJECTIONS

First, a proper medical history should be taken to determine if the patient has any contraindications or unrealistic expectations. The ideal patients for lipodissolve therapy are individuals who do not wish to pursue surgical liposuction because they have relatively small fat deposits. A patient with smaller areas of fat accumulation would very likely have a BMI less than 27.

Following the consultation, measurements should be made with standard reference points. For example, if the plan is to treat the “love handles” at the sides of the waist, a measurement is taken at this area using a tape. The distance from the symphysis pubis or umbilicus is measured so that the identical measurement can be taken weeks later. The loss of fat is gradual, and the patient may not notice any signs other than loose fitting clothing. It is invaluable to show the patient that they lost several centimeters in their standard measurement at a subsequent visit. It is not absolutely necessary to have the patient’s height and weight, but it can be useful to demonstrate a body contour improvement to a patient without the loss of any weight. Furthermore, if patients gain weight they will lose the body
contour improvement, similar to gaining weight after liposuction. The remaining adipocytes simply swell because they store more fat, and the fatty deposit reappears. A pretreatment recording of the weight can therefore be useful to defend the effectiveness of the therapy.

Patients are photographed using a tripod, standard positions, and neutral background. Some areas are difficult to measure with a tape; so good photographs can be invaluable.

The skin must be disinfected prior to any injections and also after the injections before massaging the skin to spread the material. A potential complication is infection, and this is obviously related to the absence of good aseptic techniques (17–19).

The injection sites are marked with a surgical marking pen with the patient standing. Injections should not be performed below the knee due to muscle proximity. Rotunda et al. demonstrated muscle necrosis with PC/DC injections into porcine muscle (13). There is no need to stop ASA or NSAIDS, although there may be more bruising with the injections.

The first session may be limited to 500 mg PC to observe the patient’s response. This is an outpatient, cosmetic, office-based procedure chosen by a patient who wishes to avoid liposuction. It would be unwise to subject this inexperienced individual to undue pain, swelling, and erythema by injecting multiple sites. By beginning conservatively, the practitioner can gauge this new patient’s tolerance for more injections. For future visits, one can then consider the maximum dose of PC = 2500 mg per session spread over multiple areas. A concentration stronger than PC 50 mg/mL should not be used, because all of the published scientific literature report the use of this concentration of PC (8–12).

Injection sites are marked about 2 to 3 cm apart (one finger breadth) on skin that has been prepared with a good disinfectant. Using a 30 G needle, 20 mg of PC is injected into each location at a depth of 6 to 13 mm into localized fat. Injections should not be given at the exact point marked with the surgical marking pen, to avoid tattooing the skin.

Superficial skin ulcerations have been reported when injecting PC more superficially than 6 mm. Therefore, injections must be made at a depth of at least 6 mm. Sessions should be spaced three to six weeks apart, never closer than two weeks apart. The author routinely waits until any nodulation has disappeared or has markedly diminished before injecting again.

Diet and exercise following this treatment appear to enhance results, but these are not critical to success. However, it makes sense that the body will metabolize the emulsified residue more efficiently if the patient is in a slightly negative or neutral caloric intake, rather than gaining weight. Gaining weight will not enhance the dissolution of any fatty areas or improve body contours, even following liposuction.

Hypothyroidism (may be subclinical) and beta-blockers may diminish results. If patients fail to obtain satisfactory results following lipodissolve treatments, their thyroid status should be checked.

Injections are repeated two to five times in a given area and liposuction is considered if the fourth injection session did not accomplish anything.

LIPODISSOLVE FORMULAE FOR FAT PAD DISSOLUTION

Most compounding pharmacies in the United States will produce PC at a concentration of 100 mg/mL. The content of DC in the formulation varies considerably with different pharmacies, ranging from 21 to 42 mg/mL (20,21). The 42 mg/mL concentration of DC is closest to the Lipostabil® brand by Aventis, which contains DC 47.5 mg/mL.
The following formula assume one is starting with PC 100 mg/mL concentration and diluting it 50/50 with lidocaine 1%.

- Dr. Rittes uses 0.8 mL of 50 mg/mL PC = 40 mg PC per shot.
- Dr. Hasengschwandtner uses 0.4 mL of 50 mg/mL PC = 20 mg PC per shot.

The author has decided to use Dr. Hasengschwandtner’s dose, which also necessitates twice the injections closer together than Dr. Rittes’.

Maximum PC per session = 2500 mg PC total.

At 20 mg PC per shot, the maximum dose that can be given is 2500/20 = 125 maximum shots in one session.

If PC is purchased as 100 mg/mL, then an injection of 0.2 mL (20 mg) of PC is equal to Dr. Hasengschwandtner’s dose of PC.

The author injects 0.2 mL of PC in each shot.

**LIDOCAINE**

With injections of pure PC 50 mg/mL into the fat, patients report pain on a scale of 8 of 10 versus 2 of 10 with the addition of lidocaine (personal clinical experience). Therefore, it appears useful to add lidocaine to the injections. Furthermore, French mesotherapists have always claimed that lidocaine or procaine enhance the effects of various mesotherapy cocktails used for cellulite reduction (personal communication).

The maximum safe dose for lidocaine (or marcaine) in an adult is 400 mg according to the package insert. It seems prudent to use 250 mg as the maximum to improve this margin of safety. Alternatively, one can use marcaine 0.5% instead, but it is six times the cost of lidocaine.

- Lidocaine 250 mg/125 shots = 2 mg per shot.
- Lidocaine 1% = 10 mg/mL; therefore, 2 mg of lidocaine 1% = 0.2 mL lidocaine.

The author injects 0.2 mL of lidocaine in each shot.

The author injects a total of 0.4 mL with each injection point which consists of 20 mg PC and 2 mg of lidocaine.

The daily solution for injection is made up by mixing equal volumes of PC 100 mg/mL and lidocaine 1%. This dilutes the PC by 50%, down to 50 mg/mL. Therefore, a 5 mL syringe will contain 250 mg (50 mg/mL × 5 mL) PC. The maximum that should be injected is 10 syringes of this solution. It is strongly recommended to start with two to four syringes as a maximum dose (500–1000 mg PC).

**Note:** If one adds other medications to PC, the solution must be used within 24 hours. It is not known if a mixture of PC with other drugs is stable for longer periods. Many practitioners are routinely adding l-carnitine, aminophylline, collagenase, and hyaluronidase to their PC syringes. Thus, examples of alternative formulae mixed in a 5 cc syringe for injection are:

- 2 cc PC 100 mg/mL
- 1 cc Collagenase 1000 U/mL
- 1 cc l-Carnitine 250 mg/mL
- 1 cc Lidocaine 1%
HOW TO MAKE LIPODISSOLVE SOLUTION IN THE OFFICE

Most compounding pharmacies make up 50 mL bottles of PC 100 mg/mL. One can order only 25 mL of PC in the sterile 50 mL bottle, and then fill the bottle as follows:

- PC @ 100 mg/mL (2500 mg) = 25 mL
- Lidocaine 1% (250 mg) = 25 mL
- Total = 50 mL solution

This 50 mL solution can be drawn up into ten 5 mL syringes. This is the maximum amount that any one patient should receive in one session.

This formula was designed so that 0.4 mL can be injected with each injection, which is up to two lines on a 5 mL BD syringe. One 5 mL syringe will allow the physician to inject 12 points, with a tiny amount left over for a 13th shot.

Some practitioners will prefer a 3 mL syringe based on the size of their hand. If a 3 mL syringe is used there will be 150 mg of PC in each syringe. In this case, a conservative starting dose would be $3/3 = 150$ mg PC.

PROCEDURE FOR INJECTING LIPODISSOLVE INTO FATTY PADS

1. Patient consultation, signed informed consent, photographs, and measurements are taken.
2. The skin is cleaned with a good skin disinfectant. The author uses Techni-Care® Surgical Scrub as it is gentle on the skin and has a high efficacy (22). It can be purchased at http://www.caretechlabs.com.
3. The solution is made up consisting of equal volumes of PC 100 mg/mL and lidocaine 1%.
4. The solution is drawn into 3 or 5 mL syringes (5 mL = 250 mg PC).
5. A surgical marking pen is used to draw the points of injection over the localized fatty deposit. The points should be about 2 to 3 cm apart.
6. The number of points are counted. The patient is informed that the injections will be made beside the points so that ink does not go in. About 13 points can be injected with one 5 mL syringe with 0.4 mL per injection site. Remember, the most that should ever be injected is 2500 mg of PC in total, or about 130 injection points.
7. A 30 G 1/2 in. needle is used. The needle is changed after every one to two injections because it gets dull. Injections are made next to the points that are marked to a depth of 13 mm into the fatty deposits to avoid tattooing the skin with ink. A 6 mm needle may also be used.
8. A Zimmer cooler, ice, or vibration is used to decrease the pain of injections.
9. The skin is wiped again with Techni-Care® or isopropanol to remove the surgical marking pen marks and to help spread the PC in the skin.
10. The patient is given instructions and an analgesic prescription if necessary.

TYPICAL INJECTION PATTERN USING A 5 ML SYRINGE (FIG. 3)

Dr. Rittes’ technique for lipodissolve is to inject 0.8 mL of PC 50 mg/mL solution (40 mg PC into each injection point) into six sites spread over about 80 cm².
LIPODISSOLVE FOR INFRAORBITAL FAT PADS (RITTES’ TECHNIQUE)

The globe of the eye is gently pressed. Bulging of the three infraorbital fat pads under the eye is observed. Three injections are given to a depth of about 6 mm, perpendicular to the skin into the middle of each infraorbital fat bulge.

I. PC 50 mg/mL is used. In a 1 mL syringe, 0.8 mL (40 mg PC) is drawn up to treat both infraorbital fat pads.

II. A 30 G 1/2 in. needle is used. The needle is inserted only half way (about 6 mm) into the fat pad (not the eyeball!) perpendicular to the skin.

III. A total of 0.4 mL (20 mg) is used per eye, injected carefully into three sites as in Figure 4.
   a. Lateral fat pad 0.1 mL
   b. Middle fat pad 0.2 mL
   c. Nasal fat pad 0.1 mL
   d. Total per eye 0.4 mL

IV. The patient is asked to try to avoid ice packs or NSAIDS for eye swelling and is advised to sleep with the head elevated on three pillows for two days following treatment to reduce swelling around the eyes.

V. Intervals of at least two weeks must be given between treatments for the skin to tighten.

VI. A total of two to four injection sessions are needed. It may take six months to achieve optimal results.

■ CLINICAL EXAMPLES OF LIPODISSOLVE THERAPY

Figures 7 and 8 demonstrate the injection techniques. Figure 9 depicts a 53-year-old female patient wearing pants that were previously snug fitting, standing six weeks following one lipodissolve session using 750 mg of PC spread out over the suprapubic fat with about 40 injections. Table 1 details her measurements. This patient lost 2.5 in. (6 cm) from her waistline following only one treatment. Nodules resolved by week 6. Note the posttreatment swelling, which added 3 in. to her waistline measurement in the first two weeks following treatment.

Figures 10 through 16 show other popularly requested areas for lipodissolve treatments: the posterior arm fat, the fatty rolls beneath the posterior bra strap, the abdomen, the gluteal fold, and the neck.

■ LIPODISSOLVE SUMMARY: SIMPLE INJECTIONS FOR FAT REDUCTION

Lipodissolve is an injectable technique that specifically targets localized fat and indurated cellulite deposits. The ideal patient has a BMI less than 25. The patient may also have cellulite, stretch marks, and flaccid skin. The treatment slowly dissolves the deposits with injections of a fat-dissolving substance called PC, a natural substance derived from soybean lecithin. PC makes up 40% of our cell membranes, and is found throughout our bodies. The
Figure 7
Waistline lipodissolve.

Figure 8
Waistline lipodissolve.
body naturally eliminates the residue after a lipodissolve session over the following three to four weeks. Side effects can include mild swelling, bruising, discomfort, or itching.

Treatment typically involves a series of injections, administered in a clinical setting, at the target area(s) over several weeks. On average, one to four treatments, with 14- to 42-day intervals between them, are required to achieve the desired results. No global protocols have been established.

Over the past five years, doctors in South America and Europe have successfully used the lipodissolve procedure on thousands of patients. The areas that respond best to lipodissolve treatment in those who are not excessively overweight are certain stubborn

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**Example of abdominal lipodissolve results:**

53 year old female, waist = 36"
PPC dose 750 mg spread over 40 injections
Day 1: 37"
Day 3: 39"
Day 5: 38"
Day 14: 36"
Day 28: 35"
Day 35: 34"
Day 42: 33.5"

![Figure 9](image)

*After one treatment, a 2.5 inch waist loss.*
Figure 10
Upper arm fat pad.

Figure 11
Fat pads below bra strap.
fat deposits that resist further reduction after diet and exercise. These include the lower eyelids or tear bags, double chins, the abdomen, love handles, and backs of arms, thighs, saddlebags, knees, and wings (the area on the back, just beside the armpits). Lipodissolve has also been shown to improve and smooth out the skin.

In fact, lipodissolve is now being used to help improve cosmetic irregularities that can occur following liposuction. Liposuction does not improve cellulite; it has been shown only to improve the skin texture in cellulite.

Long-term side effects in lipodissolve applications are unknown at present. However, no long-term adverse effects have been reported from any physicians who have been administering these injections for almost a decade now in areas outside of North America. Lipodissolve injections should be administered under medical supervision. People who are pregnant, morbidly obese, diabetic, suffering certain diagnosed illnesses, or allergic to the product should not have lipodissolve injections.

Further clinical studies must be done to enhance our scientific knowledge of this promising therapy. It should not be discarded simply because the exact mechanism of action or optimal dose is unknown (23). Allopathic medical practitioners have been injecting cortisone for decades at different depths for a variety of inflammatory conditions, but the exact mechanism of action, optimal dose, and interval of injections for a given inflammatory condition in a specific location has never been scientifically proven. This does not mean that cortisone injections should be abandoned; rather caution is advised when using this substance until the careful practitioner gathers clinical experience and confidence with its use. Spending time with a medical practitioner experienced with the use of the injectable substance is invaluable for observing injection technique and clinical practice. The same can be said for lipodissolve therapy at the present time.
Figure 13
Infraumbilical fat paunch.
Figure 14A
Central abdominal paunch.

Figure 14B
Zimmer cooler for analgesia.
Figure 14C
Immediate post-treatment erythema.

Figure 15A
Gluteal fold enhancement.
Figure 15B
Lipodissolve treatment.

Figure 16
Submental fat pad.
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