Mesotherapy and Phosphatidylcholine Injections: Historical Clarification and Review

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BACKGROUND Mesotherapy was originally conceived in Europe as a method of utilizing cutaneous injections containing a mixture of compounds for the treatment of local medical and cosmetic conditions. Although mesotherapy was traditionally employed for pain relief, its cosmetic applications, particularly fat and cellulite removal, have recently received attention in the United States. Another treatment for localized fat reduction, which was popularized in Brazil and uses injections of phosphatidylcholine, has been erroneously considered synonymous with mesotherapy. Despite their attraction as purported ''fat-dissolving'' injections, the safety and efficacy of these novel cosmetic treatments remain ambiguous to most patients and physicians.

OBJECTIVE To distinguish mesotherapy from phosphatidylcholine injections by reviewing their history and the relevant experimental or clinical findings.

METHODS A comprehensive search of Medline indexed literature and conference proceedings.

RESULTS All the published studies evaluating the clinical efficacy of traditional mesotherapy currently originate from Europe. These reports focus primarily on musculoskeletal pain and vascular disease, rather than cosmetic applications. Although experimental data suggest that a number of traditional mesotherapy ingredients may theoretically reduce fat, these effects have not been supported in peer-reviewed studies. An increasing number of reports demonstrate that subcutaneous injections of a formula containing phosphatidylcholine combined with its emulsifier, deoxycholate, are effective in removing small collections of adipose tissue. Cell lysis, resulting from the detergent action of deoxycholate, may account for this clinical effect.

CONCLUSIONS Mesotherapy is distinct from a method of treating adipose tissue with subcutaneous injections of deoxycholate alone or in combination with phosphatidylcholine. Additional clinical and experimental studies are necessary to more definitively establish the safety and efficacy of these treatments.

Adam M. Rotunda, MD and Michael S. Kolodney, MD, PhD have indicated no significant interest with commercial supporters.

With the escalating demand for noninvasive cosmetic procedures,[1] injections intended to "dissolve fat" have attracted interest from physicians and the general public. These treatments are sometimes considered under the rubric of "mesotherapy," the subcutaneous injection of purportedly therapeutic mixtures for the treatment of numerous conditions, including fat and cellulite.[2–9] Several lay and peer-reviewed publications have reported that subcutaneous injections of phosphatidylcholine are efficacious in treating localized collections of fat.[10–30] A growing number of patients are receiving these treatments by health professionals who have attended mesotherapy conferences nationally and abroad. Most physicians familiar with mesotherapy have heard of the technique through discussions with their patients or colleagues, or the release of medical society policy statements[8,31] and reports in the popular press.[1–6,11,12] Despite their

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attraction as a novel cosmetic treatment, the safety and efficacy of these purported "fat-dissolving" treatments remain ambiguous to most patients and physicians.

Mesotherapy is the use of intra- or subcutaneous injections containing mixtures of compounds to treat local medical and cosmetic conditions. Localized therapy was hypothesized to avoid systemic adverse effects. Mesotherapy, also known as intradermotherapy, does not denote treatment of any particular condition; it simply describes a method of drug delivery. The composition of common mesotherapy formulations (Table 1) is selected and mixed in a "cocktail" (Table 2) before injection. What components are combined and in what proportions tends to be based on anecdotal reports or the physician's experience, rather than empirical data. A Medline search revealed a number of European studies describing mesotherapy's role in pain relief in

TABLE 1. Topical Ingredients used in Traditional Mesotherapy Cocktails, Categorized by Their Intended Role

Intended Role	*Ingredient*	*Class*
Analgesic		
Muscular	Orphenadrine, baclofen	Skeletal muscle relaxants, antispastics
	Diazepam	Benzodiazepine, muscle relaxant
Other soft tissue	Procaine, prilocaine, lidocaine	Anesthetics
Anti-inflammatory	Piroxicam, ketorolac	NSAIDs
Calcium deposition removal	Calcitonin	Hormone
	Ethylenediamine tetracetic acid (EDTA)	Heavy metal and mineral chelator
Circulatory stimulation	Pentoxifylline	Hemorrheologic
	Buflomedil	Vasodilator
	Coumarin	Anti-coagulant
	Artichoke, ginko biloba, melilotus, yohimbine, arnica	Herbs
Collagen rejuvenation	Tretinoin	Retinoid
Collagen remodeling, medication dispersion	Hyaluronidase, collagenase	Enzymes
Hair growth	Finesteride	5α-reductase inhibitor
	Minoxidil	Vasodilator
Immune stimulation	Vaccines	Bacterial proteins
	Interferon	Biologic
	Metronidazole	Antibiotic
Lipolysis	Aminophylline, theophylline, caffeine	Methylxanthines
	Isoproterenol	β-Agonist
	Ephedrine	Sympathomimetic amine
	Calcium pyruvate	Kreb's cycle metabolite
	Carnitine	Amino acid derivative
	Ma huang	Herb
	T3/T4, triiodothyroacetic acid (tiratricol)	Hormones, hormone metabolite
Metabolic and antioxidant support	Vitamins (biotin, pantothenic acid, C, E, A), minerals (Se, Zn, Cu, Mg, Cr), α-lipoic acid	Metabolic cofactors
	Melatonin	Hormone
Nausea reduction	Prochlorperazine	Antiemetic
Skin hydration, tightening, exfoliation	Hyaluronic acid	Glucosminoglycan
	Dimethylaminoethanol (DMAE)	Acetylcholine analog
	Silica	Mineral
	Glycolic acid	α-Hydroxy acid

TABLE 2. Common Mesotherapy Formulations Purported to Benefit Specific Conditions

Condition	*Formulation**
Alopecia	Minoxidil, finesteride, lidocaine, multivitamins, T3/T4 hormones
Cellulite	Pentoxiphylline; hyaluronidase or collagenase; carnitine; calcium pyruvate; aminophylline or caffeine; coumarin, artichoke, melilotus or ginko biloba
Facial rejuvenation	α-Lipoic acid, lidocaine, DMAE, multivitamins, hylauronic acid, tretinoin
Herpetic neuralgia	Lidocaine, acyclovir, corticosteroids
Muscle strain (chronic)	Lidocaine or procaine; piroxicam or ketorolac; diazepam or baclofen
Tendonitis (acute)	Lidocaine or procaine; piroxicam or ketorolac; calcitonin

*There are no standardized dosages or ingredients.

TABLE 3. Examples of Dermatologic and Other Medical Conditions Purported to Benefit using Mesotherapy

Dermatology	*Other Medical Conditions*
Acne	Allergies
Alopecia	Arthritis
Cellulite	Asthma
Eczema	Carpal tunnel syndrome
Hypertrophic or keloid scars	Cellulitis
Leg ulceration	Chronic fatigue
Photoaging: loss of skin elasticity, dyspigmentation, rhytides	Constipation
Pruritus	Degenerative disc disease
Psoriasis	Depression
Striae distensae (stretch mark's)	Fibromyalgia
Telangiectasias	Gout
Venous stasis	Headache
Vitiligo	Hearing loss
	Hemorrhoids
	Hepatitis
	Herpetic neuralgia
	Immune system deficiencies
	Insomnia
	Irritable bowel syndrome
	Lower back pain
	Lymphedema
	Obesity
	Osteophytes (''bone spurs'')
	Peripheral vascular disease
	Prostatitis
	Reflex sympathetic dystrophy
	Sports injuries (i.e., sprains, strains, tears, bursitis, tendonitis, plantar fasciitis, calcium deposits)
	Substance abuse
	Temporal-mandibular pain syndrome
	Tinnitis
	Vertigo

dental procedures,[32–36] cancer,[37] neuralgia,[38] arthritis,[39] and other musculoskeletal conditions,[40,41] and also vascular stasis.[42–44] Despite its traditional use for these conditions (Table 3), mesotherapy is most commonly employed today for the reduction of fat and cellulite, which may be described as the cutaneous dimpling of the thighs, buttocks, and hips seen predominantly in women.[9]

Phosphatidylcholine injections have recently become a popular treatment for localized fat removal.[2,3,11,18,19,23,24,27–30,45] A number of open-labeled, peer-reviewed clinical studies,[10,13,16,17,22,26,46] and recent abstract presentations[47–49] have demonstrated localized fat loss in multiple anatomic sites after subcutaneous injections of a formula containing phosphatidylcholine and its solvent, sodium deoxycholate.

Phosphatidylcholine is the predominant phospholipid component of cell membranes and a precursor to acetylcholine.[50] Oral

forms of phosphatidylcholine are sold in the United States as nutritional supplements marketed for the treatment of hyperlipidemia and cognitive dysfunction.[19,51,52] Intravenous preparations of phosphatidylcholine are manufactured and prescribed in Europe under the trade names of Lipostabil® and Essentiale® (Aventis Pharma, a subsidiary of Sanofi-Aventis Group, Paris, France) for cardiovascular conditions (angina, fat emboli, and hypercholesterolemia) and liver disease.[17,50,53] The phosphatidylcholine used in these formulations is also called polyunsaturated- or polyenylphosphatidylcholine to account for the unsaturated, soy-derived fatty acids from which it is derived. Oral and intravenous administration reduces serum triglycerides[54] and LDL cholesterol,[55,56] increases HDL cholesterol,[54–56] induces hepatic collagenase,[53,57] and protects against mitochondrial oxidation,[53,57] thus restoring damaged cellular phospholipids and reducing liver fibrosis and fat accumulation.

Some authors have theorized that the lipid-modulating effects of phosphatidylcholine in the blood and liver account for its lipolytic effects after subcutaneous injection.[10,13,15,22,26] However, this mechanism has never been demonstrated experimentally. Recent data demonstrate that the bile salt, sodium deoxycholate, previously thought to be an inert excipient used to solubilize phosphatidylcholine, may in fact account for the lipolytic activity of these treatments (discussed below).[17,58]

With increasing reports of efficacy using phosphatidylcholine and deoxycholate, these compounds are being indiscriminately injected with mesotherapy ingredients traditionally used to reduce fat. This crossover has led the media, patients, and physicians to assume that mesotherapy and phosphatidylcholine injections are synonymous. We aim to clarify these issues by briefly examining the history, clinical effects, and science that distinguish mesotherapy from phosphatidylcholine injections.

History

Mesotherapy

The use of cocaine for local pain management was initially reported by ophthalmologist Karl Koller (1857–1944) in 1884 after its discovery by chemist Albert Niemann (1834–1861).[59] In 1904, Alfred Einhorn discovered a nonaddictive anesthetic, procaine (Novocaine, from the Latin *novus*, meaning "new" cocaine). Albert Lemaire (1875–1933), a Belgian physician, relieved trigeminal neuralgia using local procaine injections, and later, René Leriche (1879–1955), a French surgeon, similarly injected procaine into sympathetic stellar ganglia and inflamed tendons.

In 1952, a French physician, Michel Pistor, administered procaine intravenously to an asthmatic patient, which had limited impact on his airway disease but purportedly improved his hearing (International Meso-Lipotherapy Seminar, Winnipeg, Canada, June 2004). With the intent of maximizing the local anesthetic and vasodilator effects of procaine,[60,61] Pistor employed multiple, local, superficial (3–5 mm deep) injections of the medication around patients' ears, which was later recognized as the original application of mesotherapy. Although hearing was not restored, temporal-mandibular joint pain syndrome, eczema, and tinnitus had improved in other patients receiving these injections. In 1953, Dr. Mario Lebel engineered a 3 mm needle that facilitated superficial, subcutaneous delivery of this medication. With his first publication of the technique in a local medical journal in 1958, Pistor coined the term *mésotherapy*, which can be strictly defined as treatment of the mesoderm, one of three primary germ layers in the early embryo that develops into connective tissue, muscle, and the circulatory system. Referring to the effects of localized procaine injections on a wide number of tissues, Pistor claimed, "the action on tissue originating from the mesoderm is so extensive that these treatments deserve the global name of mesotherapy"

TABLE 4. Traditional Mesotherapy Techniques

Technique	*Depth*	*Needle Length (mm)*	*Examples of Conditions Treated and Comments*
Intraepidermic (tremor)	Epidermis	4	Facial rejuvenation; very rapid superficial injections every 2 weeks, up to 10 treatments
Superficial intradermic (multipricking)	Dermis	4, 6	Cellulite; rapid injections, similar to purified protein derivative (PPD) wheal, 10 to 15 weekly treatments
Deep intradermic (point-per-point)	Dermis	4	Arthritis, tendonitis
Intrahypodermic	Subcutaneous	13	Lower back pain (musculoskeletal)

(International Meso-Lipotherapy Seminar, Winnipeg, Canada, June 2004).

Michel Pistor founded the French Society of Mesotherapy in 1964 and broadened mesotherapy to treat general medical, veterinary, and cosmetic conditions (primarily scars and venous stasis) (J. LeCoz, MD, written communication, November 4, 2004). In 1976, the First International Congress of Mesotherapy was established to promote the growing specialty. The unique, localized delivery of heterogenous mixtures of procaine, nonsteroidal anti-inflammatories (NSAIDS), vasodilators, and muscle relaxants into sites of musculoskeletal pain complemented traditional pain management at local hospitals and was used on professional athletes. In 1987, the French National Academy of Medicine acknowledged mesotherapy as an official specialty of medicine. Mesotherapy enjoyed its initial success in France, but widespread use throughout Europe followed as additional cosmetic applications were developed. There are approximately 15,000 mesotherapists in France and over 200 American physicians have visited France to learn the mesotherapy technique (J. LeCoz, MD, written communication, November 4, 2004). Depending upon the indication, each session may involve up to several hundred injections administered at various skin levels (Table 4) by syringe or specially engineered delivery guns (Figure 1).

Mesotherapy received its initial advance into the American consciousness when a popular American singer cited that mesotherapy (combined with a comprehensive diet and exercise routine), administered by the osteopathic physician, Dr. Lionel Bissoon, was responsible for her dramatically improved appearance.[2] "Wellness centers" and "medical spas" in the United States have embraced mesotherapy as a novel treatment for cellulite, fat loss, and photoaging. As mesotherapy is not a conventional medical technique taught in US medical schools and there are no federal or state regulations defining the scope and practice of mesotherapy, physicians and nonphysicians are learning mesother-

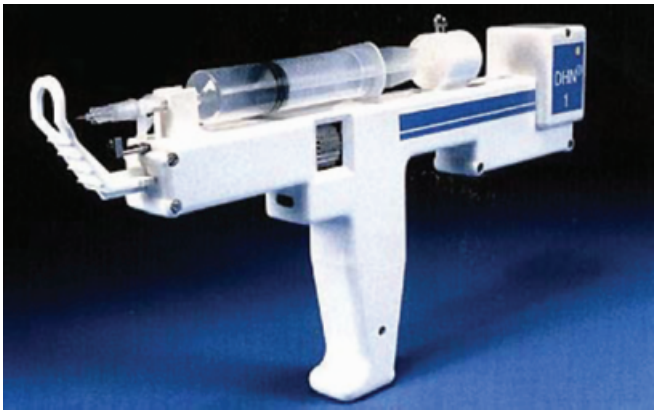

Figure 1. Prototypical mechanical mesotherapy delivery "gun." (Photograph courtesy of MesoUSA, New Jersey.)

TABLE 5. Studies Investigating the Injectable Phosphatidylcholine Formula for Localized Fat Loss

Author (Study Type)	*Methods*	*Outcome*
Maggiori[63] (case report)	Injection of a mixed polyunsaturated phospholipid preparation directly into the xanthelasmas of one patient	''Satisfactory'' results using a ''few drops'' whereas ''large volumes'' cause ''unpleasant local irritation''
Rittes[13] (open-label clinical trial)	30 patients injected with a total of 0.4 mL Lipostabil® (50 mg/mL phosphatidylcholine) under each eye every 15 days; most patients (22/30) had one or two treatments	All patients experience reduction of infraorbital fat herniation (no objective data reported); results persist after 2 years
Hexsel et al.[22] (open-label clinical trial)	213 patients (eight with HIV lipodystrophy) treated with 0.2 mL phosphatidylcholine (250 mg/mL, compounded) placed every 1.5 to 2 cm into lipomas, buffalo humps, chin, trunk, and extremities every 15 days for up to five treatments; 13 (non-HIV) patients had serum laboratory testing before, 48 hours and 2 weeks post-treatment after two treatments	''Vast majority'' of patients had reduction in fat thickness after up to five treatments; all buffalo hump patients report improvement, ''some'' with complete resolution after five treatments; no significant alterations in hepatic or lipid profiles
Rittes[26] (open-label clinical trial)	50 patients injected subcutaneously in the trunk, neck, and extremities with 5 mL of Lipostabil® (50 mg/mL phosphatidylcholine) distributed over 80 cm^2 surface area; 35/50 patients receive four treatments, the rest have one to two treatments, all spaced 15 days apart	Improvement occurs in ''all'' patients (no objective data); at 4-year follow-up, no recurrence in treated areas unless weight gained by patients
Ablon and Rotunda[16] (open-label clinical trial)	10 patients receive three to five infraorbital injections (seven patients had five injections, the rest had three or four injections) using 0.4 mL of a phosphatidylcholine formula (50 mg/mL, compounded) under each eye every 2 weeks	Physician-graded improvement of infraorbital fat herniation seen in 80% of patients, although 30% of patients self-reported minimal to no improvement. No persistent side effects (pain, erythema, edema) at 9-month (mean) follow-up
Rotunda et al.[17] (in vitro and in vivo experimental study)	Phosphatidylcholine formula (50 mg/mL, compounded), sodium deoxycholate (50 mg/mL), and positive/negative controls incubated in cell viability and cell lysis assays with human keratinocytes and porcine fat; histologic study of porcine tissue (skin, fat, muscle) after injection	Isolated deoxycholate component of the phosphatidylcholine formula produces cell lysis, loss of cell viability and histological disruption of tissue equivalent to the phosphatidylcholine formula and positive controls (laboratory detergents); nonspecific detergent effects on tissue suggests discretion be used when injecting clinically
Moy[25]* (case series)	Trunk, chin, and extremities injected with 0.5 mL/cm^2 of phosphatidylcholine formulation (50 mg/mL) for two treatments spaced monthly	Average decrease of 7.45 mm in subcutaneous fat thickness one month after last treatment
Asaadi et al.[64]* (double-blinded clinical trial)	100 patients were divided evenly into five treatment groups, each receive either a vasodilator (buflomedil), lipolytic (compounded phosphatidylcholine), homeopathic agents (carnitine and melilotus), equal combination of all medications, or placebo (normal saline). Each patient had 0.1 to 0.2 mL of solution injected every 1 to 2 cm into the thighs, waist and flank weekly for 5 weeks, then monthly for maximum of five months	18/20 of patients in combination group versus 14/20 patients in phosphatidylcholine group experienced at least a 2.5 cm decrease in thigh circumference; mean waist circumference decreased 4.2 cm in the combination group. No significant decrease in circumference or pinch testing in vasodilator, homeopathic, or saline groups. Patients lost two dress sizes in the combination group. No weight change experienced by any patients

TABLE 5. (Continued)

Author (Study Type)	*Methods*	*Outcome*
Rose and Morgan[65] (case report)	Histologic study of fat injected with a phosphatidylcholine formula	Mixed cell infiltrate, foam-laden macrophages and multinucleated giant cells in fat at one and 2 weeks after injection
Ablon[47]* (open-label clinical trial)	Forty-four patients were injected monthly with 0.8 mL of phosphatidylcholine (50 mg/mL) into the submental region for a total of five treatments, with a 6-month follow-up. Changes in submental fat were determined by physician grading (photography and skin caliper measurements) and patient grading (questionnaire) at baseline and at follow-up	All patients, each of whom completed five treatments, had ''significant'' degree of improvement. Progressive decrease in submental fat, evident by skin caliper measurements, and photography with each treatment. Side effects were transient edema, erythema, burning and paresthetsias at the injection site. No skin surface irregularities or systemic effects noted
Rullan and Hexsel[49]* (open-label clinical trial)	50 patients received one to three injections of a ''cocktail'' (phosphatidylcholine, aminophylline, carnitine, and lidocaine) in the jowls and submental region every 2 to 4 weeks. No more than 0.2 mL was delivered subcutaneously per 1 cm. Blinded photographic evaluation was performed before and after treatment	All patients had some degree of improvement: 50% had ''minor improvement,'' 40% had ''significant improvement,'' and 10% had ''dramatic improvement''; 85% of patients surveyed were satisfied and desired more treatments. Pain, edema, and erythema persisted hours to 10 days. Subcutaneous nodules developed in ''most patients'' and all resolved spontaneously
Bechara et al.[48]* (case series)	Lipomas injected directly with 0.3 to 1.0 mL of a phosphatidylcholine formulation in patients with familial benign lipomatosis. Surface area measured by ultrasound 6 weeks after last injection	Statistically significant (95% confidence interval) reduction of horizontally and vertically surface area measured by ultrasound (pretreatment, $278 \pm 140\,mm^2$; post-treatment, $140 \pm 85\,mm^2$)
Duncan and Hasengschwandtner[10] (case series and review of European experience)	Largest published review of anecdotal European phosphatidylcholine experience. Report also includes outcome of a series of 43 patients treated with up to 100 mL of phosphatidylcholine (maximum 2.5 g) per session every 4 to 8 weeks, for up to four treatments. Multiple anatomic sites (including chin, abdomen, buttocks, thighs) were injected subcutaneously with 0.4 mL phosphatidylcholine distributed every 1 to 1.5 cm. Outcome measured by unblinded skinfold and/or circumference measurements, patient questionnaires, and photography	Photographic results accompanying report demonstrate clinically apparent fat reduction on multiple sites. ''Dramatic improvement'' reported in 13 patients; 29 patients had ''mild to moderate improvement''; one patient was a nonresponder. ''Surprisingly good results'' of skin retraction in patients with skin laxity; no evidence of skin ''rippling, creases or local indentations.'' Itching, burning, erythema, swelling and bruising at the injection sites that persisted 3 to 10 days. With ''higher doses,'' side effects included nausea and diarrhea (number unspecified)

*Conference proceeding.

apy either at hands-on training courses or preceptorships abroad.

Phosphatidylcholine Injections

Intralesional phosphatidylcholine injections were first presented in 1988 at the 5th International Congress of Mesotherapy in Paris, France, as a treatment for xanthelasma in one patient.[62] Over the following decade, a number of physicians in France, Italy, and Brazil began using Lipostabil® and Essentiale® (formulated for intravenous use) off-label as subcutaneous injections to reduce localized collections of adipose tissue. A dermatologist from Brazil, Patricia Rittes, MD, is credited as the first physician to publish her experiences using injections of phosphatidylcholine for infraorbital fat pads[13] and other localized collections of fat.[26] Her techniques and findings have been replicated by a number of other investigators (Table 5). Injections of Lipostabil® or similar, compounded phosphatidylcholine preparations are marketed as minimally invasive (although less dramatic) alternatives to liposuction, or as postliposuction "touch-up" procedures.[22,25,26] These treatments are colloquially advertised as Lipodissolve, Lipotherapy, Lipolyse, Thinjection, Phospholipon, and Lipolight injections.

Medical-Legal

In January 2003, Anvisa, the Brazilian National Agency of Sanitary Monitoring, declared that Lipostabil® was not registered in Brazil for any medical or cosmetic purpose.[66] Aventis Pharma stated it had no plans to market the product as a fat treatment "due to absence of clinical studies for aesthetic conditions." In the United States, the Food and Drug Administration (FDA) issued a warning letter against the proprietors of an Internet website for marketing and distributing Lipostabil®.[67] The Centers for Disease Control and Prevention (CDC) recently reported that an unlicensed practitioner, who claimed to be a Columbian physician, was administering mesotherapy to patients from Virginia, the District of Columbia, and Maryland from his home.[68] According to this report, Virginia considers mesotherapy a medical procedure that should only be administered by a "licensed provider." What type of license is necessary was not specified. State and federal authorities are investigating this case as a result of a number of adverse cutaneous reactions that have been traced to these treatments (discussed below).

Rather than illegally importing Lipostabil® and Essentiale® into the United States,[19] physicians are purchasing phosphatidylcholine (with or without other mesotherapy components) from compounding pharmacies. The FDA does not look favorably upon compounding non-FDA–approved drugs, but is not able to ban their use as compounding pharmacies are primarily regulated by state enforcement agencies.[21] Several recent incidents have highlighted the controvery and risks associated with compounded medications, which are generally not tested by independent regulatory bodies and may potentially have inaccurate potencies or contaminants.[69–72] Reports of systemic effects after subcutaneous injections of these mixtures, and the potential conversion of phosphatidylcholine into toxic levels of its degradation product, lysophosphatidylcholine, highlight some concerns about using these uncontrolled substances (see "Safety"). Moreover, compounding phosphatidylcholine, a *nutritional* supplement not regulated by the FDA,[73] into a solution meant for subcutaneous injection has become a medical-legal "gray zone." The other element of this formulation, deoxycholate, a bile salt, has not been evaluated by the FDA for subcutaneous injection, although it has been approved for human use as a component of intravenous Amphotericin B (Fungizone®, Bristol Myers Squibb Co. New York, NY, USA).

Several mesotherapy components, such as aminophylline and pentoxyphylline, are approved for specific medical indications intravenously and orally. However, with the exception of local anesthetics, calcitonin, hyaluronidase, and collagenase, the FDA has not approved or granted orphan drug designation to other mesotherapy ingredients by subcutaneous delivery. According to the FDA,

when it comes to off-label uses, which is "…an indication not in the approved labeling," physicians "…have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects" as long as "…the intent is the practice of medicine."[74] Mesotherapy does not neatly fit into this definition. Although subcutaneous injection of most mesotherapy ingredients is not considered standard medical practice, medical insurance coverage varies depending on the company policy.

Safety

Mesotherapy

Traditional mesotherapy techniques and medications have been associated with atypical mycobacterial infections,[46,68,75–79] urticaria,[80,81] lichenoid drug eruptions,[82,83] and koebnerization of psoriasis.[84] Pain is typically minimal during and after the superficial injections. The injected sites may bleed transiently and exhibit signs of inflammation, which resolves in several days. Recent reports highlight the infrequent but potential risk of postinflammatory hyperpigmentation, ecchymoses, prolonged swelling and tenderness (persisting several months), ulceration, and hematoma formation.[84–86]

The CDC recently reported a series of 14 patients meeting the definition of "mesotherapy-associated skin reactions" after injections of "various substances (e.g., plant extracts from artichoke and thuja, liquid "graphites," and procaine)" into their torso and thighs.[68] One of seven cultured tissue samples was positive for an infectious agent (*My*-Mycobacteria chelonae) and four biopsies obtained from the injected sites revealed fat necrosis and inflammation. Patients recalled that the unlicensed practitioner withdrew the solution from a multidose vial, failed to "practice hand hygiene" or use gloves, and failed to clean their skin or the medication vials before injection. The CDC recommends that "…providers should adhere to recommended standard precautions, follow safe-injection practices with appropriate aseptic techniques, and inject only FDA-approved products that are prepared following guidelines to ensure sterility, as described in the FDA's good manufacturing practices."

The long-term local or systemic effects of subcutaneous placement of these mixtures are unknown at this time. With the continued practice of traditional mesotherapy by unscrupulous individuals, additional reports like these may be forthcoming.

Phosphatidylcholine Injections

Phosphatidylcholine injections are associated with immediate burning (typically lasting less than 30 minutes), erythema, transient urticaria, and variable degrees of pruritus. Erythema and a majority of the edema typically resolve within 2 days.[10,13,16,22,26] Patients may have localized tenderness and mild swelling lasting several weeks,[10,26,30] ecchymoses, and, rarely, hematomas.[22,26] Small, subcutaneous postinflammatory nodules at the injection site have been observed to spontaneously resolve within 1 month.[26,30] Injections placed too superficially may cause skin ulceration, and inadvertent injection into muscle has been observed to cause immediate pain lasting several days, but no persistent untoward clinical effects (R. Chubaty, MD, written communication, January 22, 2005).

Systemic effects of subcutaneous phosphatidylcholine in humans have not been adequately studied. Hexsel and colleagues[22] observed no significant alterations in lipid, liver, and renal profiles in 13 patients during and 2 weeks after two treatments with subcutaneous phosphatidylcholine injections. Several authors recommend that the total dose of phosphatidylcholine be limited to 2.5 g during each session to avoid nausea and abdominal pain,[10,11] although these symptoms have been observed with as little as 1.2 g of phosphatidylcholine (M. Braun, MD, written communications, December 4, 2004 and January 11, 2005). These symptoms are similar to the potential adverse effects of oral and intravenous Lipostabil®.[50–52] The appearance

of gastrointestinal side effects[10] as greater volumes of solution are administered confirm systemic effects that warrant apprehension until toxicity data are available.

A recent poster presentation by Paschoal and colleagues at the Brazilian Congress of Dermatologic Surgery in São Paulo has raised additional serious concerns about the potential side effects of phosphatidylcholine treatments.[11] In this report, six healthy pigs were administered ten 0.5 mL subcutaneous injections of phosphatidylcholine weekly (500 mg total) for 10 weeks, with six receiving a placebo. One pig died of cholestatic hepatitis. The five survivors developed mucousal bleeding, prostration, icterus, hematomas, petechiae, and skin ulceration 2 days after the last injection. It is not known how relevant these adverse reactions are to humans, as pigs hepatically metabolize phosphatidylcholine differently than humans,[11] and antibodies to a variety of liposome and phospholipids can be induced in animals.[87–89] Furthermore, heat and long-term storage can decompose phosphatidylcholine into lysophosphatidylcholine, which is known to cause hepatic cholestasis, enzyme elevation, and intravascular hemolysis.[90] The source and purity of the phosphatidylcholine used in this study was not disclosed, highlighting that until more safety data become available, physicians may be placing patients at unknown risks as they become reliant upon compounded formulations for these treatments.

Research

Mesotherapy

Mesotherapy has been used for tendonitis,[41] tendon calcification,[40] dental procedures,[32–35] cancer,[37] cervicobrachialgia,[38] arthritis,[39] lymphedema,[43] and venous stasis.[44] Of the two abstracts that were available in English, one demonstrated that naproxen, used locally in mucosal mesotherapy, was more effective than a classic (not specified) oral anti-inflammatory drug.[32] The other open-label trial reported complete pain resolution in 29 of the 31 patients receiving local ethylenediamine tetra-acetic acid (EDTA) injections for shoulder tendonitis.[40]

To date, there are no published clinical trials investigating the effect of traditional mesotherapy for cosmetic conditions. Amin and colleagues[91] recently presented a case series of 10 patients who received a total of 4 monthly facial mesotherapy treatments containing a multivitamin mixture suspended in a conjugated hyaluronic acid gel.[63] Aside from the deposition of smaller collagen fibrils on electron microscopy (suggesting new collagen production), blinded evaluation of clinical photography and histology (stained with mucin and hematoxylin and eosin) 2 months after the treatments did not reveal significant changes.

A recent review of experimental studies using common mesotherapy ingredients suggests a number of mechanisms, including lipolysis, connective tissue disruption, and enhanced circulation, which provide a plausible but thus far unsubstantiated basis for their use in treatments aimed at fat and cellulite reduction.[9] Numerous in vitro and in vivo studies have established a mechanism to explain why several mesotherapy compounds may be effective for fat loss. Methylxanthines (phosphodiesterase inhibitors), such as caffeine and aminophylline,[92–96] as well as thyroid hormones[62,94] and isoproterenol and other β-agonists[97–99] augment lipolytic responses in adipocytes. Lipolysis, however, is a transient metabolic state and differs from the permanent effects of apoptosis or fat cell ablation. It is unknown whether alterations in adipocyte volume by mesotherapy-induced β-adrenergic stimulation or inhibition of phosphodiesterase/adenosine pathways translate to clinically evident fat loss.[9]

Mesotherapy proponents claim that local pentoxifyiline, coumarin, and other herbs improve cellulite by "enhancing circulation and lymphatic drainage." While theoretically plausible (studies have documented circulation-enhancing effects after systemic administration of these compounds), effects on cellulite after localized injection are currently unsubstantiated. After 6 months of treatment, oral coumarin in

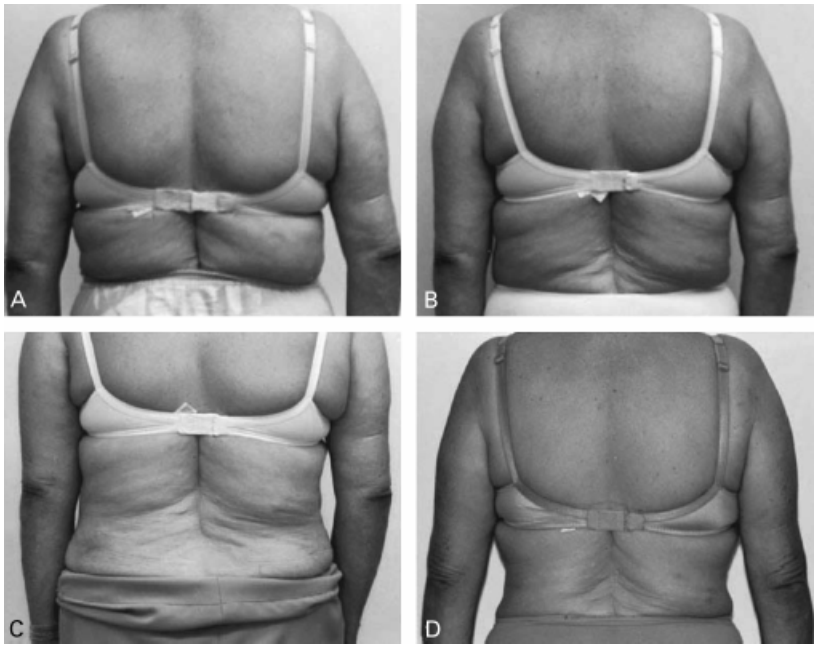

Figure 2. (A) A 57-year-old woman with local fat deposit because of cortisone use before procedure. (B) After two applications of phosphatidylcholine (30 days). (C) After four applications of phosphatidylcholine (60 days). (D) After eight applications of phosphatidylcholine (120 days). (Figure obtained with permission from Rittes PG, The use of phosphatidylcholine for correction of localized fat deposits, Aesth Plast Surg 2003 27; 315–18, Figure 2.)

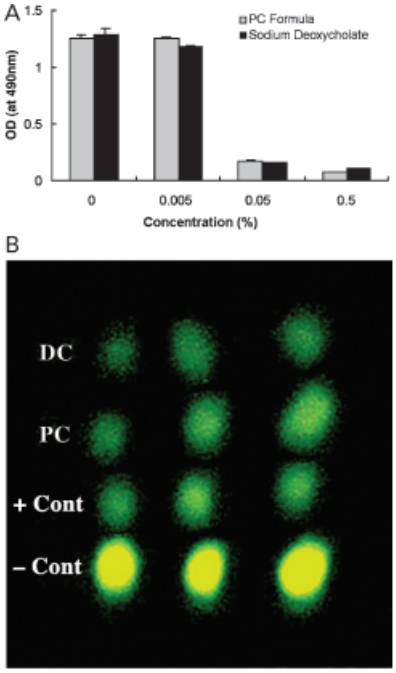

Figure 3. (A) MTS assay measuring viability of keratinocytes exposed to the phosphatidylcholine formula (gray) and sodium deoxycholate (black). Absorbance (OD) is directly related to cell viability. Increasing concentration of both compounds produces more cell death. (B) Calcien fluorescence in fat specimens (triplicates) treated with sodium deoxycholate (DC, 50 mg/mL), phosphatidylcholine formula (PC, 50 mg/mL phosphatidylcholine and 47.5 mg/mL sodium deoxycholate), Triton detergent (positive control, + Cont), and phosphate-buffered saline (negative control, −Cont). Loss of yellow-green fluorescence indicates cell lysis. (Figures obtained with permission from Rotunda et al., detergent effects of sodium deoxycholate are a major feature of an injectable phosphatidylcholine formula used for localized fat dissolution, Dermatol Surg 2004;30:1001–08)

patients with lower extremity and postmastectomy lymphedema caused softening, reduction in circumference, and increased mobility in the affected limbs.[72] Using a leg stasis animal model, intravenous coumarin increased venous and lymphatic flow,[100] and the isolated active component of coumarin, 7-hyroxycoumarin, increases coronary blood flow as a result of vasodilation.[98] Intravenous pentoxifyiline has been used to enhance graft survival in animal models.[99,101] The medications used in these studies were not administered subcutaneously, so whether the beneficial effects on circulation occur when given as mesotherapy is not established. Furthermore, the role of impaired circulation as a cause of cellulite is only speculative.[9]

Rigorous experimental studies investigating drug pharmacokinetics (absorption, distribution, and metabolism) after their subcutaneous placement and the clinical response of each isolated ingredient administered subcutaneously are necessary.

Phosphatidylcholine Injections

An emerging number of open-label studies have demonstrated mild to moderate loss of adipose tissue using subcutaneous injections of compounded or proprietary phophatidylcholine (Table 5 and Figure 2). Until there are double-blind, placebo-controlled studies to confirm these preliminary investigations, at the present time, it may be sensible to remain cautiously optimistic that this treatment may have some role as an noninvasive method of slowly eliminating localized fat.

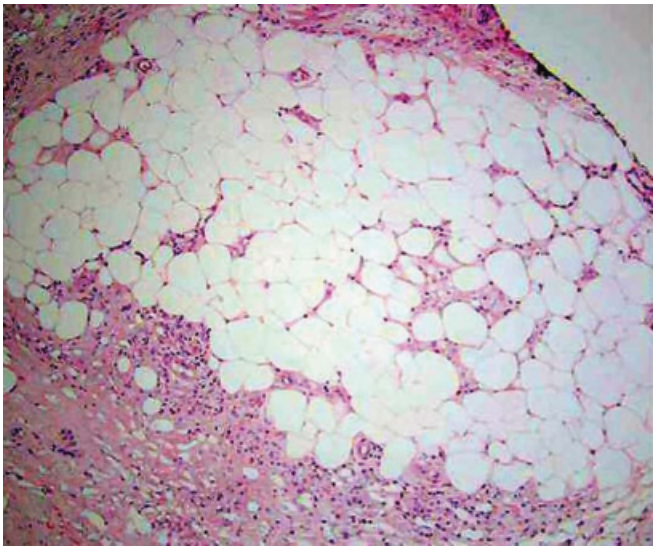

Figure 4. Microscopic findings of human fat, 1 week after injection with a phosphatidylcholine formula (50 mg/mL phosphatidylcholine and 21 mg/mL sodium deoxycholate) (hematoxylin and eosin, original magnification × 10). (Photograph courtesy of Paul T. Rose, MD.)

Recent laboratory investigations[17] demonstrate that sodium deoxycholate, a bile salt also used as a laboratory detergent,[102,103] was just as potent at causing adipocyte lysis and cell death as the complete phosphatidylcholine formula, which contains both phosphatidylcholine and deoxycholate (Figure 3). This bile salt is used to solubilize phosphatidylcholine by forming mixed micelles composed of phosphatidylcholine and deoxycholate.[102,104] It is common practice to combine intravenous medications with bile salts to improve their water solubility.[105,106] These findings suggest that sodium deoxycholate is the primary active ingredient in the phosphatidylchloline preparations. These findings have been translated clinically. We recently observed that lipomas reduce in area and may fragment after subcutaneous injections of deoxycholate alone, confirming that phosphatidylcholine is not necessary to produce fat reduction.[58]

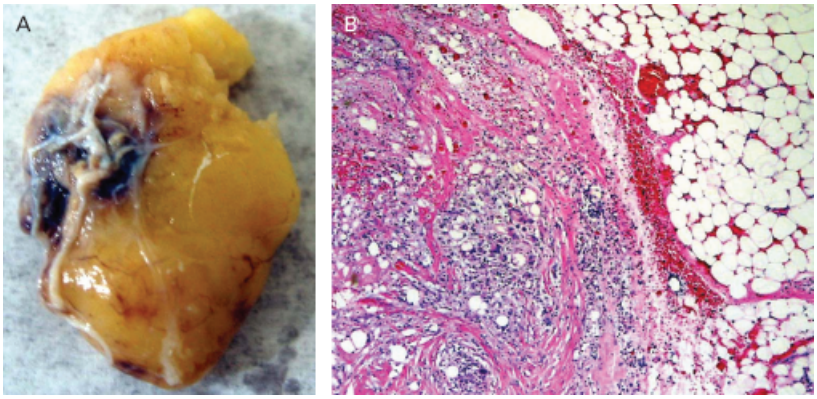

Figure 5. (A) Excised lipoma 2 days after injection with sodium deoxycholate (10 mg/mL) revealing a well-demarcated area of necrosis. (B) Microscopic findings demonstrating acute inflammation and necrosis (hematoxylin and eosin, original magnification × 10).

The effects of deoxycholate and the phosphatidylcholine formulation with deoxycholate are nonspecific, such that injection into tissue besides fat may cause necrosis. Human fat injected with a compounded phosphatidylcholine formulation results acutely in vacuolization of adipocytes and acute inflammation composed of a mixed cell infiltrate (Figure 4).[65] One month after injection, gross examination of excised fat demonstrates white nodules of fat necrosis and scar; histologically, there is evidence of adipocyte wall disruption, focal inflammation, and collagen deposition.[10] Isolated sodium deoxycholate (10 mg/mL) injected directly into lipomas causes visible and histologic evidence of necrosis (Figure 5), and ultrasonically confirmed reduction in size.[58] Clinical studies comparing the effects of phosphatidylcholine mixed with deoxycholate versus deoxycholate alone on fat are pending.

Conclusions

Mesotherapy and phosphatidylcholine injections are becoming increasingly common treatments

in the United States. Mesotherapy is a recognized therapeutic modality in Europe primarily for pain, but its efficacy for a number of other medical and cosmetic conditions has not been adequately evaluated in the English literature. Despite a number of anecdotal reports and experimental data suggesting that components of traditional mesotherapy formulations may be effective, there are presently no peer-reviewed clinical trials that critically evaluate the efficacy of these localized injections for medical or cosmetic applications.

Deoxycholate with or without phosphatidylcholine injections may potentially become a novel treatment for fat; however, physicians and patients should be cautious. Despite the concerning outcome of an isolated animal study, human experience with limited dosages has suggested that side effects are typically localized and transient. If double-blinded, controlled clinical trials support preliminary open label reports, these compounds may potentially become a novel, minimally invasive technique to reduce small collections of fat. Rigorous testing to confirm efficacy and long-term safety is crucial.

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References

1. American Society for Aesthetic Plastic Surgery. National plastic surgery statistics: cosmetic and reconstructive procedures trends (Internet). New York: American Society for Aesthetic Plastic Surgery, 2003. Available at: http://www.plasticsurgery.org/public_education//statistical-trends.cfm.
2. Bryant R. Controversial mesotherapy: could it be the next Botox? Derm Times 2004;25:1.
3. The American Society for Aesthetic Plastic Surgery. Fat-melting fad: too good to be true? (Internet). New York: American Society for Aesthetic Plastic Surgery, 2004. Available at: http://www.surgery.org/press/news-release.php?iid=387.
4. The American Society of Aesthetic Plastic Surgery. Cellulite: an update (Internet). New York: American Society for Aesthetic Plastic Surgery, 2004. Available at: http://www.surgery.org/press/news-release.php?iid=212#top.
5. Stahl L. Sound of success (Internet). New York: CBS News, 48 hours. Available at: http://www.cbsnews.com/stories/2003/04/28/48hours/main551361.shtml.
6. Leisenring A. Thinjections (Internet). New York: Elle, 2003. Available at: http://www.elle.com/article.asp?section_id=36&article_id=2694&page_number=1.
7. Rohrich RJ. Mesotherapy: what is it? Does it work? Plast Reconstr Surg 2005;115:1425.
8. Matarasso A, Pfeifer TM. Mesotherapy for body contouring. Plast Reconstr Surg 2005;115:1420–4.
9. Rotunda AM, Avram M.M., Avram A. Cellulite: is there a role for injectable? J Cosm Laser Ther 2005; 7:147–154.
10. Duncan DI, Hasengschwandtner F. Lipodissolve for subcutaneous fat reduction and skin retraction. Aesthet Surg J 2005;25:530–43.
11. Walsh N. Some would halt lipolysis tx pending safety data. Skin Allergy News 2004;35:26.
12. Clark J. PC injections may replace some surgery. Derm Times 2004;25:7.
13. Rittes PG. The use of phosphatidylcholine for correction of lower lid bulging due to prominent fat pads. Dermatol Surg 2001;27:391–2.
14. Serra M, Pereira F. Subcutaneous infiltration with phosphatidylcholine solution for treatment of "buffalo hump" and "fatty pads", 3rd International workship on the adverse drug reactions and lipodystrophy in HIV, Athens, Greece, October, 2001.
15. Young VL. Lipostabil: the effect of phosphatidylcholine on subcutaneous fat. Aesthet Surg J 2003;23:413–7.
16. Ablon G, Rotunda AM. Treatment of lower eyelid fat pads using phosphatidylcholine: clinical trial and review. Dermatol Surg 2004;30:422–7.
17. Rotunda AM, Suzuki H, Moy RL, Kolodney MS. Detergent effects of sodium deoxycholate are a major feature of an injectable phosphatidylcholine formulation used for localized fat dissolution. Dermatol Surg 2004;30:1001–8.
18. Bates B. "Fat dissolving" substance injects CCs of controversy. Skin Allergy News 2003;34:1.
19. Bauman LS. Phosphatidylcholine. Skin Allergy News 2003;34:1.
20. Bellman B. Phosphatidylcholine reaction. Skin Allergy News 2003;34:12.
21. Galson SK. Senate hearing on: federal and state role in pharmacy compounding and reconstitution: exploring the right mix to protect patients (Internet). Washington, DC: United States Food and Drug Administration, 2003. Available at: http://www.fda.gov/ola/2003/pharmacycompound1023.html.
22. Hexsel D, Serra M, Mazzuco R, Dal'Forno T, Zechmeister D. Phosphatidylcholine in the treatment of localized fat. J Drugs Dermatol 2003;2:511–8.
23. Gallegos D. Liposuction alternative targets fat cells. *Denver Post*, August 2, 2004.
24. KYW-TV. Health Alert: Lipostabil (Internet). Philadelphia, PA: CBS News, 2002. Available at: http://kyw.com/health/local_story_336152706.html.
25. Moy LS. Phosphatidylcholine injections. A study measuring decreased subcutaneous fat thickness. American Society for Dermatologic Surgery and the American Society of Mohs mocrographic surgery and cutaneous oncology combined annual meeting, San Diego, CA, September 30 to October 3, 2004.

26. Rittes PG. The use of phosphatidylcholine for correction of localized fat deposits. Aesthet Plast Surg 2003;27: 315–8.

27. The Saturday Morning Show. Burn fat away with an injection? (Internet). Boston, MA: CBS News, 2002. Available at: http://www.cbsnews.com/stories/2002/11/27/earlyshow/saturday/main531099. shtml.

28. American Society for Aesthetic Plastic Surgery. Liposuction (lipoplasty) without surgery update? (Internet). New York: The American Society for Aesthetic Plastic Surgery, 2004. Available at: http://surgery.org/press/news-release.php?iid= 370.

29. Toyama M. Next-gen liposuction (Internet). Tokyo, Japan: Time Europe, December, 2002. Available at: http://www.time.com/time/europe/magazine/printout/0,13155,901021216-395857,00.html.

30. Victor S. Phosphatidylcholine works. Skin Allergy News 2003;34:12.

31. American Society for Dermatologic Surgery. Emerging technology report: mesotherapy. Available at: http://www.asds-net.org/Media/PositionStatements/emerging_technology-mesotherapy.html.

32. Einholtz B, Maudet D, Bicheron M. Use of NHAI via mesotherapy in oral surgery. Actual Odontostomatol 1990;44: 285–98.

33. Medioni G. Orodental mesotherapy. Chir Dent Fr 1976;46:97–102.

34. Medioni G. Results of 6 years of treatment of painful periodontal episodes by mesotherapy. Chir Dent Fr 1980;50: 35–7.

35. Dalloz-Bourguignon A. A new therapy against pain: mesotherapy. J Belge Med Phys Rehabil 1979;2:230–4.

36. Pistor M. What is mesotherapy? Chir Dent Fr 1976;46:59–60.

37. Brule-Fermand S. Treatment of chronic cancer pain. Contribution of acupuncture, auriculotherapy and mestherapy. Soins 1993;39–40.

38. Palermo S, Riello R, Cammardella MP, et al. TENS + mesotherapy association in the therapy of cervico-brachialgia: preliminary data. Minerva Anestesiol 1991;57:1084–5.

39. De Ridder A, Driessens M, De Bruyne J, et al. Mesotherapy in abarticular rheumatism. Acta Belg Med Phys 1989;12:91–3.

40. Soncini G, Costantino C. The treatment of pathologic calcification of shoulder tendons with E.D.T.A. bisodum salt by mesotherapy. Acta Biomed Ateneo Parmense 1998;69: 133–8.

41. Menkes CJ, Laoussadi S, Kac-Ohana N, Lasserre O. Controlled trial of injectable diclofenac in mesotherapy for the treatment of tendinitis. Rev Rhum Mal Osteoartic 1990;57:589–91.

42. de Beir J, Bazon H. On the subject of mesotherapy. Chir Dent Fr 1984;54: 27–8.

43. Donini I, De Anna D, Carella G, et al. Mesotherapy in the treatment of lymphedema: histologic and ultrastructural observations. Chir Patol Sper 1982;30:25–34.

44. Gallo R. Mesotherapy in phlebology. Phlebologie 1980;33:153–6.

45. Sager S. New fat removal technique getting raves: is it safe? Does it work? (Internet). New York: CBS News, 2003. Available at: http://abclocal.go.com/wabc/news/wabc_020703_mesotherapy. html.

46. Marco-Bonnet J, Beylot-Barry M, Texier-Maugein J, et al. Mycobacterial bovis BCG cutaneous infections following mesotherapy: 2 cases. Ann Dermatol Venereol 2002;129:728–31.

47. Ablon G.. Preliminary experience with mesotherapy utilizing phosphatidylcholine. American Society for Dermatologic Surgery-American College of Mohs micrographic surgery and cutaneous oncology combined annual meeting, 2005.

48. Bechara FG, Sand M, Sand D, et al. Ultrasound controlled injection lipolysis of lipomas with phosphatidylcholine in patients with familial multiple lipomatosis. American Society for Dermatologic Surgery-American College of Mohs micrographic surgery and cutaneous oncology combined annual meeting, Atlanta, GA, October 27 to 30, 2005.

49. Rullan P, Hexsel D. Phosphatidylcholine injections for lipolysis of neck and jowls: 50 case presentation. American Society for Dermatologic Surgery-American College of Mohs micrographic surgery and cutaneous oncology combined annual meeting, October 27 to 31, 2005.

50. Lipostabil. Natterman international GMBH. Cologne, Germany: Natterman International, 1990, p. 9.

51. Physician's desk reference, 55th edition. Medical Economics Staff. Montvale, NJ: Thomas Healthcare, 2001.

52. Wood JL, Allison RG. Effects of consumption of choline and lecithin on neurological and cardiovascular systems. Fed Proc 1982;41:3015–21.

53. Lieber CS. New concepts of the pathogenesis of alcoholic liver disease lead to novel treatments. Curr Gastroenterol Rep 2004;6:60–5.

54. Kirsten R, Heintz B, Nelson K, et al. Polyenylphosphatidylcholine improves the lipoprotein profile in diabetic patients. Int J Clin Pharmacol Ther 1994;32:53–6.

55. Galli C, Tremoli E, Giani E, Maderna P, Gianfranceschi G, Sirtori CR. Oral polyunsaturated phosphatidylcholine reduces platelet lipid and cholesterol contents in healthy volunteers. Lipids 1985;20:561–6.

56. Tarkhovskaia TI, Khalilov EM, Fortinskaia ES, et al. Specificity of the effect of polyene phosphatidylcholine depending on the mode of administration and animal species. Biull Eksp Biol Med 1992;113:55–8.

57. Navder KP, Baraona E, Lieber CS. Polyenylphosphatidylcholine attenuates alcohol-induced fatty liver and hyperlipemia in rats. J Nutr 1997;127:1800–6.

58. Rotunda AM, Ablon G, Kolodney MS. Lipomas treated with subcutaneous injections of sodium deoxycholate. J Am Acad Dermatol 2005; 53:973–8.

59. Hersh EV. Local anesthetics. In: Fonseca RJ, editor Oral and maxillofacial surgery. Philadelphia, PA: WB Saunders, 2000:p. 58–78.

60. Ball C, Westhorpe R. Local anaesthetics —procaine (Novocaine, Ethocaine). Anaesth Intensive Care 2004;32:303.

61. Huang Y, Lau CW, Chan FL, Yao XQ. Contribution of nitric oxide and K + channel activation to vasorelaxation of isolated rat aorta induced by procaine. Eur J Pharmacol 1999;367:231–7.

62. Nedvidkova J, Haluzik M, Bartak V, et al. Changes of noradrenergic activity and lipolysis in the subcutaneous abdominal adipose tissue of hypo- and hyperthyroid patients: an in vivo mi-

crodialysis study. Ann NY Acad Sci 2004;1018:541–9.

63. Maggio S. Treatment of xanthelasma with phosphatidylcholine. 5th International meeting of mesotherapy, Paris, France, 1988.

64. Asaadi M, Salas AP, Motamedi B. Mesoplasty: a new approach to non-surgical liposculpture. American Society of Plastic Surgery, Philadelphia, PA, October 9 to 13, 2004.

65. Rose PT, Morgan M. Histological changes associated with mesotherapy for fat dissolution. J Cosmet Laser Ther 2005;7:17–9.

66. Anvisa (Brazil National Agency for Sanitary Monitioring). Resolution no30 (Internet). Brazil: D.O.U., 2003. Available at: http://www.e-legis.bvs.br/leisref/public/showAct.php?id=6847.

67. Center for Food Safety and Applied Nutrition. Warning letter for "Lipostabil" (Internet). Washington, DC: United States Food and Drug Administration, 2003. Available at: http://www.fda.gov/ora/about/enf_story/ch4/cfsan1.htm.

68. Centers for Disease Control and Prevention. Outbreak of mesotherapy-associated skin reactions—District of Columbia area, January-February 2005. Morb Mortal Wkly Rep 2005;54:1127–30.

69. Goldman MP. Sodium tetradecyl sulfate for sclerotherapy treatment of vein: is compounding pharmacy solution safe? Dermatol Surg 2004;30:1454–6.

70. Finn R. Compounding pharmacies get low marks in FDA tests. Skin Allergy News 2003;34:42.

71. Spenver J, Matthews AW. Stirring debate: as druggists mix customized brews, FDA raises alarm. *Wall St J*, February 27, 2004: Al, para. 5.

72. Casley-Smith JR, Morgan RG, Piller NB. Treatment of lymphedema of the arms and legs with 5,6-benzo-[alpha]-pyrone. N Engl J Med 1993;329:1158–63.

73. 103rd Congress. Dietary supplement health and education act of 1994 (Internet). Washington, DC: United States Food and Drug Administration, 1994. Available at: http://www.fda.gov/opacom/laws/dshea.html.

74. Office of Science Coordination and Communication. "Off-Label" and investigational use of marketed drugs, biologics, and medical devices (Internet). Washington, DC: United States Food and Drug Administration, 1998. Available at: http://www.fda.gov/oc/ohrt/irbs/offlabel. html.

75. Cooksey RC, de Waard JH, Yakrus MA, et al. Mycobacterium cosmeticum sp. nov., a novel rapidly growing species isolated from a cosmetic infection and from a mail salon. Int J Syst Evol Microbiol 2004;54:2385–91.

76. Nagore E, Ramos P, Botella-Estrada R, Ramos-Niguez JA, Sanmartin O, Castejon P. Cutaneous infection with Mycobacterium fortuitum after localized microinjections (mesotherapy) treated successfully with a triple drug regimen. Acta Derm Venereol 2001;81:291–3.

77. Paul C, Burguiere AM, Vincent V, Susbielle P, Bonvalet D, Dubertret L. BCG-induced mycobacterium infection induced by alternative medicine. Ann Dermatol Venereol 1997;124:710–2.

78. Bonafe JL, Grigorieff-Larrue N, Bauriaud R. Atypical cutaneous mycobacterium diseases. Results of a national survey. Ann Dermatol Venereol 1992;119:463–70.

79. Friedel J, Piemont Y, Truchetet F, Cattan E. Mesotherapy and cutaneous mycobacteriosis caused by *Mycobacterium fortuitum*: alternative medicine at risk. Ann Dermatol Venereol 1987;114:845–9.

80. Bessis D, Guilhou JJ, Guillot B. Localized urticaria pigmentosa triggered by mesotherapy. Dermatology 2004;209:343–4.

81. Urbani CE. Urticarial reaction to ethylenediamine in aminophylline following mesotherapy. Contact Dermatitis 1994;31:198–9.

82. Vaillant L, de Muret A, Muller C, Machet L, Lorette G. Lichenoid drug eruption after mesotherapy. Ann Dermatol Venereol 1992;119:936–7.

83. Grojean MF, Vaillant L. Lichenoid eruption caused by mesotherapy. Ann Med Interne 1995;146:365–6.

84. Rosina P, Chieregato C, Miccolis D, D'Onghia FS. Psoriasis and side-effects of mesotherapy. Int J Dermatol 2001;40:581–3.

85. Lee DP, Chang SE. Subcutaneous nodules showing fat necrosis owing to mesotherapy. Dermatol Surg 2005;31:250–1.

86. Brandao C, Fernandes N, Mesquita N, et al. Abdominal haematoma—a mesotherapy complication. Acta Derm Venereol 2005;85:446.

87. Swartz GM Jr., Gentry MK, Amende LM, Blanchette-Mackie EJ, Alving CR. Antibodies to cholesterol. Proc Natl Acad Sci USA 1988;85:1902–6.

88. Alving CR. Antibodies to liposomes, phospholipids and phosphate esters. Chem Phys Lipids 1986;40:303–14.

89. Wassef NM, Johnson SH, Graeber GM, et al. Anaphylactoid reactions mediated by autoantibodies to cholesterol in miniature pigs. J Immunol 1989;143:2990–5.

90. Teelmann K, Schlappi B, Schupbach M, Kistler A. Preclinical safety evaluation of intravenously administered mixed micelles. Arzneimittelforschung 1984;34:1517–23.

91. Amin S, Phelps RG, Goldberg DJ. Mesotherapy for facial skin rejuvenation: a clinical, histologic, and ultrastructure evaluation. American Society for Dermatologic Surgery—American College of Mohs micrographic surgery and cutaneous oncology combined annual meeting, October 27 to 31, 2005.

92. Tholon L, Neliat G, Chesne C, Saboureau D, Perrier E, Branka JE. An in vitro, ex vivo, and in vivo demonstration of the lipolytic effect of slimming liposomes: an unexpected alpha(2)-adrenergic antagonism. J Cosmet Sci 2002;53:209–18.

93. Scotini E, Carpenedo F, Fassina G. New derivatives of methyl-xanthines: effect of thiocaffeine thiotheophylline and 8-phenyltheophylline on lipolysis and on phosphodiesterase activities. Pharmacol Res Commun 1983;15:131–43.

94. Otto W, Taylor TG, York DA. Glycerol release in vitro from adipose tissue of obese (ob/ob) mice treated with thyroid hormones. J Endocrinol 1976;71:143–55.

95. Nencini P. Differences in the lipolytic and cyclic AMP accumulative action of noradrenaline-theophylline and norephedrine-theophylline. Arzneimittelforschung 1980;30:1080–2.

96. Matuszek M. Studies on antilipolytic activity of antipyretics. Part II. Influence of sodium salicylate, aminophenazone, and acetophenidin on lipolysis stimulated by noradrenaline and aminophylline in vitro. Pol J Pharmacol Pharm 1976;28:437–42.

97. Iwao N, Oshida Y, Sato Y. Regional difference in lipolysis caused by a beta-adrenergic agonist as determined by the microdialysis technique. Acta Physiol Scand 1997;161:481–7.

98. Baccard N, Mechiche H, Nazeyrollas P, et al. Effects of 7-hydroxycoumarin (umbelliferone) on isolated perfused and ischemic-reperfused rat heart. Arzneimittelforschung 2000;50: 890–6.

99. Karacaoglan N, Akbas H. Effect of parenteral pentoxifylline and topical nitroglycerin on skin flap survival. Otolaryngol Head Neck Surg 1999;120:272–4.

100. Borzeix MG, Angignard J, Dedieu F, Dupont JM, Miloradovich T, Leutenegger E. Effect of a combination of coumarin derivatives and rutoside on venous and lymphatic circulations during severe constriction of the caudal vena cava in rabbits. Arzneimittelforschung 1995;45:262–6.

101. Pickens JP, Rodman SM, Wetmore SJ. The effects of extended perioperative pentoxifylline on random skin flap survival. Am J Otolaryngol 1994;15: 358–69.

102. Jones MN. Surfactants in membrane solubilisation. Int J Pharm 1999;177:137–59.

103. le Maire M, Champeil P, Moller JV. Interaction of membrane proteins and lipids with solubilizing detergents. Biochim Biophys Acta 2000;1508: 86–111.

104. Durr M, Hager J, Lohr JP. Investigations on mixed micell and liposome preparations for parenteral use based on soya phosphatidylcholine. Eur J Pharmacol Biopharm 1994;40:147–56.

105. Wiedmann TS, Kamel L. Examination of the solubilization of drugs by bile salt micelles. J Pharm Sci 2002;91:1743–64.

106. Alkan-Onyuksel H, Ramakrishnan S, Chai HB, Pezzuto JM. A mixed micellar formulation suitable for the parenteral administration of taxol. Pharm Res 1994;11:206–12.

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