

“Treatment” Cosmetics: Hype or Help?

COSMETICS alleged to achieve drug-like effects, such as the repair of sun damage and reversal of aging, add a new wrinkle to skin care, according to presentations at the annual meeting of the American Academy of Dermatology (AAD) in Orlando, Fla, in March, and interviews with government and industry experts. Debate continues on how well these products work, whether substances that behave like drugs should be marketed as cosmetics, and whether they are safe for long-term use.

These new cosmetics have been dubbed “cosmeceuticals,” a term the Food and Drug Administration (FDA) does not recognize, John Bailey, PhD, director of the FDA’s Office of Cosmetics and Colors, said in an interview. Cosmetics are defined by law as products not intended to affect the body’s structure or functions, and drugs are defined as products that do so.

While several dermatologists noted in their presentations at the AAD meeting that even water affects the skin’s structure and function, the legal distinction between a cosmetic and a drug hinges not on the ingredients in a product but on the claims made for it. A product said to make skin look younger is a cosmetic, Bailey said, while the identical product, if alleged to reverse aging, would be regulated as a drug. Manufacturers of cosmetics, unlike those of drugs, are not required to demonstrate safety and efficacy, or to obtain premarket approval.

A key concern to regulators, Bailey said, is whether the effects of a product are temporary or sustained, subtle or more profound. Dividing lines, he acknowledged, often are not clear. The so-called treatment cosmetics fall into this gray area. Following are some of the most frequently encountered.

Hydroxy Acid Products

These include cleansers, moisturizers, toners, masks, age-spot removers, and other preparations, and exemplify the is-

suues raised above. Hydroxy acids are botanical substances that induce mild inflammation and accelerate exfoliation with little or no burning or stinging, said Paul Lazar, MD, emeritus clinical professor of dermatology at Northwestern University Medical School, Chicago, Ill. “A little inflammation isn’t bad. It improves skin coloring and evens skin tone,” said Lazar, who served for many years as director of the American Medical Association’s Committee on Cosmetics and Cutaneous Health. “A little edema,” he noted, “puffs out fine wrinkles.” But concerns remain, he said, about whether chronic low-grade irritation has adverse lasting effects, such as increasing blood vessel dilation, whether the acids harm the skin’s barrier functions, and how much they increase sun sensitivity.

The most widely used of these chemicals are the alpha-hydroxy acids (AHAs). Beta-hydroxy acid, better known as salicylic acid, long a part of the dermatologist’s acne-treatment armamentarium, is a newer addition to cosmetic products, as are combination-hydroxy acids and polyhydroxy acids.

The concentration of hydroxy acids in a product is directly related to its potential to cause peeling and irritation, said Zoe Draelos, MD, clinical associate professor of dermatology at Bowman Gray School of Medicine, Winston-Salem, NC, and chair of an AAD symposium on innovations in cosmetic dermatology. But concentration is not the only factor, she said, as preparations can be changed by buffering or through neutralization. Low concentrations, such as 1% AHAs, have been shown to alter the pH of the outer 3 layers of the stratum corneum, she said, while the higher concentrations available in some cosmetic products, such as 10% AHAs, have been shown to affect the pH of the stratum corneum 10 to 20 layers deep. Application of a glycolic acid preparation to the skin, she said, has been reported to yield a 2.4% concentration in the stratum corneum, an 11.6% concen-

tration in the epidermis, and an 8.6% concentration in the dermis. “This degree of biological activity,” she said, “does not fit with the current definition of cosmetics” (*Skin Aging*. 1998;6:45-47).

The safety of glycolic acid and other AHA ingredients has been investigated by the Cosmetic Ingredient Review Board, an independent panel of physicians and other scientists with no financial ties to the cosmetic industry, for the Cosmetic, Toiletry, and Fragrance Association (CTFA), the industry’s trade organization in Washington, DC. The review board concluded that AHAs were safe for use by consumers at a concentration less than 10% and at a pH of 3.5 or greater, and also for brief, discontinuous use in salons when applied by trained professionals in a concentration no greater than 30% and at a pH of no less than 3.0, followed by thorough rinsing of the skin. The reviewers did not examine the medical uses of AHAs at higher concentrations.

The review board also found that use of AHAs increased sun sensitivity by 13% overall but in some persons by as much as 50%, a finding that raises concern about accelerated photoaging and elevated risk of skin cancer. The reviewers, said Gerald McEwen, PhD, CTFA vice president for science, concluded that formulating some products differently—adding a sunscreen with a sun protection factor of 2, for example—could eliminate the added sun sensitivity. They also recommended that people who use these preparations be advised to use daily sun protection, including sunscreens and protective clothing (*Int J Toxicol*. In press).

The FDA, according to Bailey, “is not as convinced as the industry that the problem can be solved this easily.” The FDA has referred AHAs to the National Toxicology Program for a study of phototoxicity, a process that will take several years. The same concerns about possible long-term effects apply to beta-

hydroxy and other hydroxy acid products. In the meantime, Bailey said, the FDA may provide guidelines to the industry or regulations for safe use but has not yet made a decision on this matter.

Along with hydroxy acids, other new cosmetic ingredients alleged to provide therapeutic benefits include the following.

Vitamins C and E

Ascorbic acid (vitamin C) and vitamin E function as antioxidants when consumed orally. Some manufacturers have added them to moisturizers and other products, saying they serve as scavengers of sunlight-induced free radicals even when applied topically. "This is a bit of a jump," cautioned Bailey. Whether vitamins C and E serve as active ingredients or simply as marketing ingredients, Bailey said, is not yet clear. "Vitamins may not cause any harm when used topically," he noted, "but their benefit, if any, is not well established."

Botanical Additives

These include such substances as extracts of aloe vera and green tea. While so-called natural ingredients have high consumer appeal and are promoted as having low potential for adverse reactions, they also vary considerably from batch to batch, by site of origin, and in manner of processing. Few safety data exist for most of these substances. High on the FDA's list of current concerns is wild yam extract, purported to have estrogenic activity and, when applied topically, to increase skin thickness and decrease fine wrinkling, much as topical estrogens are said to do. According to McEwen, the Cosmetic Ingredient Review Board is embarking on a study of wild yam extract.

Retinol (Vitamin A Alcohol)

This substance, added to moisturizers, serves as a humectant, attracting

water to plump up the epidermis. Topical retinol also is alleged to convert in the skin to retinoic acid, a biologically active agent that shrinks sebaceous glands and unclogs follicles, and is used to treat acne, fine wrinkling, and mottled hyperpigmentation. If used regularly, cosmetic retinol products may help prevent actinic keratoses and other age-related skin damage, said Nia Terezakis, MD, clinical professor of dermatology, Tulane University School of Medicine, New Orleans, La, at the AAD symposium on innovations in cosmetic dermatology. But prescription retinoic acid (tretinoin), she said, is more effective.

Retinoids rebuild the skin's collagen infrastructure, Terezakis said, and thus may provide improvements that persist after they are discontinued. This effect contrasts with that of the hydroxy acids, which, she said, benefit skin only as long as they are used. Serial photographs of some of her patients who have used topical retinoids for 5 to 10 years, she said, suggest that the benefit may be cumulative. The appearance of skin in most persons would be improved, Terezakis asserted, if they were to use retinoids consistently from their teen years onward.

\$30 Billion Annually

Americans spend \$30 billion on cosmetics annually. The average American adult, Bailey said, uses 10 to 12 cosmetic products daily, including soaps. Some 85 manufacturers of cosmetics staffed commercial exhibits at the AAD meeting, deluging dermatologists with samples and literature on product formulation and efficacy. Some exhibitors wore white coats, promoting their products by linking them with familiar, positive medical imagery. Exhibitors included private-label brands that some dermatologists, and others, such as facial plastic surgeons, dispense in their offices, with their own name on the package.

Lazar, who heads the AAD's ethics committee, said AAD guidelines require dermatologists who dispense cosmetics in their offices to tell patients if they own stock in the company that makes the products they are selling, not to charge inflated prices, and, if products are prescription items, to give patients copies of the prescriptions so that they may fill them elsewhere if desired.

Given the widespread use of all types of cosmetics, adverse reactions are few. "As now formulated and when used according to directions," Bailey said, "these products are by and large very safe." He termed the likelihood of an acute serious reaction "very remote." But most studies of cosmetics, he stressed, have only short-term safety end points. More than 5000 ingredients are used in cosmetics, and for most of them, no long-term safety data exist, alone or in combination.

Physicians will find a list of cosmetics associated with adverse reactions on the FDA Web page on the Internet at www.fda.gov and may report adverse reactions to their local FDA office, listed in the blue pages of their local phone directory. If there is a need for follow-up, Bailey said, it will be at the local level.

Recent budget reductions have cut the FDA's cosmetics program about 50%. Consequently, research to find or anticipate problems will suffer, Bailey said, asserting that his office "is working hard to preserve consumer safety and public health aspects."

Skin treatment products, Terezakis said in an interview, already have changed the way women use cosmetics. "Their skin looks so good," she asserted, "that they don't need to hide it." Changes in recreational activities also favor a more natural look, she said, adding, "Women can't go into an exercise class wearing lots of cosmetics."

—by Lynne Lamberg,
JAMA contributor

Trial Suggests Change in Transfusion Strategy

A RESTRICTIVE blood transfusion strategy significantly reduces 30-day all-cause mortality in critically ill patients compared with a liberal blood transfusion strategy, according to new data from the first prospective, randomized trial to examine the use of both strategies in intensive care units.

The multicenter Canadian trial known as TRICC, for Transfusion Requirements in Critical Care, found that mortality was 24% in the liberal transfusion group compared with 18% in the restrictive trans-

fusion group, an absolute difference of 6%. In the liberal group, 101 patients died, and in the restrictive group, 77 patients died. The trial was conducted in 25 critical care units throughout Canada, with 420 patients randomized to the liberal transfusion group and 428 patients allocated to the restrictive group.

"That means, on average, 1 life was saved for every 17 patients transfused with the restrictive strategy," said Paul C. Hebert, MD, principal investigator of the trial and associate professor of medi-

cine and epidemiology at the University of Ottawa in Ontario.

Hebert said 52% fewer transfusions were given in the restrictive group compared with the liberal group. "Transfusion was avoided in 33% of the patients in the restrictive group," he emphasized.

The bottom line is "less transfusion is better than more transfusion," he said, noting that "no patient in the trial ever did better when transfused more."

Hebert made the first presentation of the study findings in March at the 18th

International Symposium on Intensive Care and Emergency Medicine, held in Brussels, Belgium. The meeting drew more than 3000 intensive care physicians from throughout Europe and North America. A full analysis of the trial, including subgroup analysis, is being completed.

Immediate Practice Change

"These data are sufficiently compelling that we will have to revise our transfusion strategy," said symposium chair Jean-Louis Vincent, MD, clinical director of the department of intensive care at Erasme Hospital, Free University of Brussels, in Belgium. "We will decrease the amount of blood being transfused in our critically ill patients, and we are planning to change the practice in our hospital immediately," he said.

Vincent said, "This is the first time we have had a prospective evaluation of blood transfusion and a well-conducted and scientific study." He noted that some articles in the literature have proposed that transfusion may have deleterious effects, but it has been difficult to separate the effects of the severity of the disease process and the amount of the transfusion.

Enrollment in the Canadian study, funded by the Medical Research Council of Canada, began in 1994 and was completed in 1997. During this period, 6285 patients in 25 critical care units were screened. Of those who met the criteria and gave informed consent, 838 were randomized into 2 groups with comparable patient characteristics. The patients' average age was 58 years, with slightly more men than women in both groups. The Acute Physiology and Chronic Health Evaluation (APACHE) II score at baseline was about 21. The length of hospital stay was 35 days, and the stay in the intensive care unit was 11 days in both groups.

The hemoglobin levels of patients randomized to the restrictive arm of the trial were maintained at between 70 g/L and 90 g/L, with a transfusion trigger at 70 g/L. Hemoglobin levels of patients allocated to the liberal transfusion strategy were maintained at between 100 g/L and 120 g/L, with a transfusion trigger at 100 g/L. Physicians participating in the trial used allogeneic red blood cell transfusion and were asked to transfuse red blood cells 1 unit at a time and to measure hemoglobin concentrations after administration of each unit.

"We managed to significantly reduce exposure to blood in the patients without harm," Hebert said. "The restrictive strategy is superior to the liberal strategy."

Based on the study findings to date, Hebert's recommendation to critical care physicians is "consider transfusing less." He advised adopting a transfusion policy with a trigger at 70 g/L and maintaining patients who are seriously ill at hemoglobin levels between 70 g/L and 90 g/L. However, he stopped short of recommending this strategy for the subgroup of patients with ischemic heart disease.

Red Cells in ICUs

In a conference round table report entitled "Tissue Oxygenation in Acute Medicine," William Sibbald, MD, assistant dean, academic network and clinical evaluations, at the University of Western Ontario, London, Ontario, raised a number of issues about red blood cell transfusion in intensive care departments.

"We're concerned about the effects of storage on the efficacy of blood," Sibbald said. "We're concerned that the longer blood has been stored, the less efficacious it is."

He suggested that free hemoglobin in stored blood may aggravate the sepsis

syndrome and said, "We are aware there is free hemoglobin in old blood that we transfuse into our patients." He also suggested that there may be a problem with leukocytes in stored blood, which may aggravate an inflammatory response syndrome.

Sibbald questioned the safety profile of stored blood and challenged the medical community to determine whether the red blood cells in stored blood effectively deliver oxygen to tissue.

Hebert hypothesized that one of the major determinants of outcome in transfusion is the shelf life of the blood stored in hospitals. He pointed out that many countries, including Canada and the United States, originally established policies on the shelf life of blood based on cell survival studies that "have nothing to do with whether the blood product is efficacious." He said the efficacy of the product can be based only on oxygen delivery. Currently, the shelf life of blood in Canadian hospitals is about 35 days, said Hebert.

From a health policy perspective, a change in the shelf life of blood would raise overwhelming issues and a radical change in how the product is used, he said. Restricting the shelf life of blood to 15 days would challenge the Canadian, US, and European blood systems, leading to major changes in collecting, processing, and delivering blood.

"For my critically ill patients, when a transfusion is required I want units of fresh blood," Hebert maintained.

In the TRICC study, data were collected on the age of every unit of blood transfused. Hebert is now planning to do a separate analysis comparing the effect of old blood vs new blood, a topic he considers a "hot new issue."

—by Pat Phillips,
JAMA contributor

"Blood Soup" and Bear Exams Acquaint Kids With Hospitals

BOSTON, Mass, with many of the best and best-known hospitals in the United States, has taken steps to make sure its citizens become aware of them early.

At a special event in March called Children and Hospitals Day, the Children's Museum of Boston and a local affiliate of the Association for the Care of Children's Health (based in Mt Royal, NJ), aided by dozens of volunteer local health care professionals, gave young visitors and their parents a chance to learn about medical equipment and procedures and general health practices.

Even the smallest could watch the favorite stuffed animals that accompanied them—or ones "adopted" for the day from a museum menagerie—get "check-ups" from cooperative physicians in the Teddy Bear Clinic, while their more sanguine older siblings used unique ingredients to make "blood soup," thereby learning about the composition of that vital substance.

Musical productions entitled "Let's Get Moving" (on fitness and well-being) and "Blue Plate Special" (featuring food and healthy eating) entertained muse-

umgoers, while wannabe physicians could try on caps, gloves, masks, and shoe covers—without having to scrub! Other events included making casts for fingers, constructing collages of such materials as Band-Aids, cotton balls, and tongue depressors, learning about good oral hygiene, and exploring an ambulance.

An annual spring event for the past 10 years, Children and Hospitals Day is designed, according to Darlene Salvatore, a Child Life specialist at Children's Hospital in Boston, "to help children learn about hospitals in a nonthreatening



Lynne Lamberg

Arin Greene, MD, a surgical resident at Beth Israel Deaconess Medical Center in Boston, performs a careful check-up at the Teddy Bear Clinic at the museum event. Children saw x-rays of bears who had "swallowed" Lego pieces and learned from the x-rays that all bears have their hearts in the right place.



Lynne Lamberg

Ronald Minter, MD, director of pediatric anesthesiology at the Massachusetts Eye and Ear Infirmary (MEEI), Boston, demonstrates operating room procedures at the Children's Museum of Boston on Children and Hospitals Day. Assisting him is Milagros Lopez-Ramirez, MEEI's director of Child Life. At MEEI, parents are invited to be in the operating room while their child falls asleep and are encouraged to be present when the child wakes up.

way," as well as to promote good attitudes about health and nutrition. Salvatore was coordinator of this year's event with Milagros Lopez-Ramirez, director of Child Life at Massachusetts Eye and Ear Infirmary. While the museum venue may be unique, Salvatore said, the event is one of many celebrations of an annual Children and Health Care Week sponsored throughout the United States by the Association for the Care of Children's Health. The association is an international, multidisciplinary

group of parents and professionals in diverse fields "promoting family-centered care, policies, and practices that are responsive to the unique developmental and psychosocial needs of children and youth and their families."

In other areas of the country where, as Salvatore put it, "physicians are beginning to appreciate the importance of children's psychosocial understanding of going to the hospital," recognition has taken various forms. Usually, she said, hospitals hold some sort of festive event

within the institution, such as the Pancake Breakfast and Teddy Bear Clinic featured at St Francis Hospital Medical Center in Hartford, Conn, or a tea party or the like.

What is exciting about the Boston approach, she added, is to have so many dedicated people working together entirely on a volunteer basis to try to make going to the hospital a far less frightening experience than they themselves may remember.—by Lynne Lamberg, *JAMA* contributor, and Marsha F. Goldsmith

Miscellanea Medica

Lois T. Ellison, MD, Medical College of Georgia, Augusta, has received the 1998 Will Ross Medal, the highest award of the American Lung Association.

Robert Gallo, MD, University of Maryland at Baltimore, and **Luc Montagnier, MD**, Queens College, Flushing, NY, and Pasteur Institute, Paris, France, have been awarded the \$100 000 Tenth Annual Warren Alpert Foundation Prize for their discovery of the human immunodeficiency virus.

William D. Bloomer, MD, Northwestern University Medical School, Chicago, Ill, has been awarded the Gold Medal of the American College of Radiation Oncology.

The 20th annual General Motors Cancer Research Foundation Awards have been presented to the following scientists: **H. Rodney Withers, PhD, DSc**, University of California, Los Angeles,

has received the Charles F. Kettering Medal; **Suzanne Cory, PhD**, Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia, and **Stanley J. Korsmeyer, MD**, Washington University School of Medicine and Howard Hughes Medical Institute, St Louis, Mo, were awarded the Charles S. Mott Medal; and **H. Robert Horvitz, PhD**, Howard Hughes Medical Institute, Massachusetts Institute of Technology, Cambridge, has received the Alfred P. Sloan Medal.

Edward M. Copeland, III, MD, University of Florida College of Medicine, Gainesville, has become president of the Society of Surgical Oncology. **Glenn D. Steele, Jr, MD**, University of Chicago Pritzker School of Medicine, Chicago, Ill, is president-elect.

Peter V. Scoles, MD, Case Western Reserve University School of Medicine, Cleveland, Ohio, has been appointed

deputy vice president, Division of Evaluation Programs, of the National Board of Medical Examiners, Philadelphia, Pa.

Philip W. Majerus, MD, Washington University School of Medicine, St Louis, Mo, has received the eighth annual Bristol-Myers Squibb Award for Distinguished Achievement in Cardiovascular/Metabolic Research.

Louis R. Caplan, MD, Beth Israel Deaconess Medical Center, Boston, Mass, has received the 1998 **C. Miller Fisher, MD**, Award. It was presented by Dr Fisher, for whom it is named, at the American Heart Association's Second Annual Stroke Awareness Luncheon, in Boston.

Editor's Note: Miscellanea Medica normally appears in the Medical News & Perspectives section several times each month. Items submitted for consideration should be sent to Marsha F. Goldsmith, editor, Medical News & Perspectives.