Welcome, and thanks for your interest in the science behind anti-aging skin therapy. We at Amway are excited for the opportunity to reach audiences who find this work as fascinating as we do. Certainly this is an exciting era for those of us who are committed to improving skin health—as well as for those of you dedicated to reporting on new developments in dermatology, health and beauty.

At Amway, we have had the privilege of benefiting from years of academic research dedicated to the science of skincare and, in particular, from work done at the University of Michigan, which has a long history of skin science. In the 1980s, the University first undertook studies of retinoids and their influence on the skin. In the decades since, the University of Michigan’s department of dermatology has brought together many thought-leaders in the field, leading to new discoveries and a better understanding of skin aging.

One of those thought-leaders, Dr. Gary Fisher, PhD, has spent many years working to understand the biology behind skin aging. Research in his lab has made great in-roads into the understanding of certain side effects that prevent many people from using products that most skincare experts believe to be the gold standard of anti-aging skin treatments. These treatments contain retinoids, which have marvelous anti-aging effects but which unfortunately can also cause significant side effects that limit their use. Fortunately, recent studies at the University of Michigan, drawing upon and alongside findings from cancer research efforts, has identified ways to minimize these side effects by directing retinoids to specific sites in the skin where they are most effective at fighting wrinkles and sagging, while minimizing irritation.

Given its widespread potential applications, the University of Michigan has patented the technology stemming from their findings. Recently, Amway licensed that technology from the University for use in our ARTISTRY exclusively from Amway anti-aging skincare products, which will soon be available globally. As a company, we look forward to seeing our work bringing benefits to people, especially women, worldwide.

Because skin and aging is a story that nearly anyone past their teenage years can relate to, we have developed this science writer’s guide to retinoids and anti-aging skincare, which we hope will be a one-stop resource for in-depth, timely information about aging skin, including the latest science behind the development of next-generation retinoid technologies. Kindly edited by Dr. Fisher, the guide features everything from a glossary of terms to the very latest scientific research findings. Perhaps most useful is a detailed list of references and sources for additional information about various aspects of the research and treatment of skin aging.

We hope you’ll find this guide useful for educating yourself and others about this popular topic.

Catherine Ehrenberger
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Ada, MI
INTRODUCTION

_Time may be a great healer, but it’s a lousy beautician._ –Author Unknown

_You can’t turn back the clock. But you can wind it up again._ –Bonnie Prudden

Throughout the ages, mankind has sought to thwart time’s effects on skin’s appearance. The first documented attempts reach as far back as the ancient Egyptians, who used olive leaves as an anti-aging remedy and kept detailed notes on the rejuvenating effects of everything from diet and exercise to treatments with herbs and minerals (Lanigan, 2009).

Thousands of years later, that same aspiration – to prolong the beauty of youth – lives on. Today’s efforts, fortunately, reap benefits from modern technology that the Egyptians lacked. Molecular biology, botany and modern chemistry are just a few of the disciplines that are helping researchers develop treatments to blunt the cosmetic effects of time.

Some of the most promising entries into the field of anti-aging skin creams are members of a class of compounds chemically related to vitamin A. These include vitamin A itself (also known as retinol) and its natural metabolites, retinaldehyde and retinoic acid as well as synthetic derivatives, collectively known as retinoids. Retinoid-based creams are currently considered by professionals to be the gold standard for topical treatments to improve the appearance of aged skin. For many people, however, retinoids can cause unwanted side effects that limit their use, namely a feeling of skin irritation that is accompanied by dryness, redness and flaking. Up to 90 percent of those undergoing retinoid therapy for aging skin experience this uncomfortable effect (Gilchrest, 1997), and many of those who do choose to end product use as a result.

Recent dermatological research has uncovered pathways that contribute to the unwanted side effects of retinoids. Additionally, compounds that have been studied for their healthful benefits have been shown to be useful inhibitors of the pathways that contribute to retinoid side effects. As such, the groundwork has been laid for new treatments that specifically target retinoids in the skin to their beneficial results while minimizing dryness, redness and flaking. This breakthrough will open the door for many more people worldwide to use retinoid-based creams to improve the appearance of fine lines and wrinkles.

This reporters’ handbook provides basic background on the effects of aging on the skin as well as the context needed for reporting on potential new treatments.
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BASICS OF THE SKIN

The skin is the largest organ in the human body, accounting for ~16 percent of total body weight, (Martini and Nath, 2009). It is a constant and dynamic interface between the body and its environment. It prevents harmful substances and microorganisms from entering the body and protects body tissues from injury. It also controls the loss of life-sustaining fluids such as blood and water, helps regulate body temperature through perspiration and protects from the sun’s damaging ultraviolet rays.

On a cosmetic level, the appearance of the skin is a reflection of health and a measure of age and beauty. The skin is the only organ continually exposed to the environment and on display for all to see (Fisher et al., 2008). In fact, skin changes are among the most visible signs of aging.

To understand aging, and anti-aging skincare, it is important to have a basic understanding of the structure of the skin. Every square centimeter of skin contains millions of cells and hundreds of sweat glands, oil glands, nerve endings and blood vessels. Skin can be divided into three distinct compartments (Figure 1): the epidermis, the dermis, and the subcutaneous tissue.

Epidermis

The upper compartment of the skin, the epidermis, forms a protective outer layer. About as thick as a sheet of paper (~0.1 mm) in most parts (Starr and McMillan, 2008), the epidermis has several layers of cells that are constantly flaking off and being renewed, thereby helping cuts and scrapes heal quickly. The main cells of the epidermis are keratinocytes, which produce keratin, a tough protein that is a basic component of hair, skin and nails and that helps create an intact, waterproof barrier.

The bottom layer of the epidermis, the stratum basale, consists of column-shaped cells that divide and push the cells above them into higher layers. As the cells move further and further up, they flatten and eventually die and shed off the skin surface. The top layer of the epidermis, the stratum corneum, is made up of the flat, dead cells, surrounded by a lipid matrix that helps create a protective barrier. Below the stratum corneum are several layers of viable epidermis, where the majority of maturing keratinocytes reside (McGrath et al., 2004).

Dermis

Below the epidermis is the skin layer most critical to the physiology of aging, the dermis. At least 20 times thicker than the epidermis, the dermis regulates body temperature and nourishes the epidermis. The dermis is made up of blood vessels, nerve endings, hair follicles, oil glands and connective tissue – changes in which are key to the formation of wrinkles.

The dermis is a type of connective tissue, which is primarily composed of extracellular matrix, a scaffolding network of fibers that are produced by dermal cells called fibroblasts and secreted into the tissue environment (Fisher et al., 2008). The most important types of matrix fibers in the dermis are collagen, which is strong and hard to stretch (Figures 2), and elastin. These fibers give the skin its strength and flexibility.
The dermis itself comprises two regions, each with its own arrangement of collagen fibers:

- The upper region, or **papillary dermis**, contains a thin arrangement of collagen fibers.
- The lower region, or **reticular dermis**, is thicker and made of thick collagen fibers that are arranged parallel to the surface of the skin. (McGrath et al., 2004). It is also the primary location of the elastin fibers.

**Collagen**

Collagen is the single most abundant protein in the animal kingdom. There are at least 16 types of collagen, but 80 to 90 percent of the collagen in the human body consists of types I, II and III (Lodish et al., 2000). Type I collagen is by far the most abundant component of human skin, accounting for more than 90 percent of its dry weight (Fisher et al., 2008).

The various collagens and the structures they form all serve the same purpose – to provide mechanical stability for the body.

Within connective tissues, most collagens are secreted by fibroblasts as an immature, soluble form known as **procollagen**. Once outside the cell, procollagens are processed into their insoluble mature state, which assembles into collagen’s prototypical networks.

Type I collagen in human skin is very stable, requiring about 30 years for full replacement (Verzijl et al., 2000). In part, this stability is due to the fact that only a few enzymes, known as **collagenases**, are able to initiate degradation of mature collagen, and only one or two of these are involved in the normal turnover of skin collagen. (Fisher et al., 2008)

The collagen network is organized and maintained by tension provided by fibroblasts. Age-related reduction in this tension is believed to be a driving force behind many of the changes in the appearance of aged skin. (Fisher et al., 2008)

**Elastin**

Interwoven with collagen fibers in the reticular dermis is a network of fibers that is at least five times more elastic than a rubber band of the same area. This fibrous network is mainly composed of the protein elastin. (Lodish et al., 2000)

**Subcutaneous tissue**

The fatty bottom layer of the skin, the subcutaneous tissue (also known as the **hypodermis**), is made up of connective tissue, blood vessels, and cells that store fat. This layer helps protect the body from injury and helps hold in body heat.
The various effects of aging in the skin are collectively caused by both internal and external factors. Most of these changes are related to environment, genetics, nutrition and other factors. The major environmental factor is sun exposure. Natural pigments found in the skin provide some protection against sun-induced skin damage, since fair-skinned people show more aging-related skin changes than do people with darker, more heavily pigmented skin.

Aging leads to a wide assortment of familiar and lesser known changes to the skin, including the following:

- The epidermis becomes thinner.
- The dermis becomes thinner.
- The blood vessels become more fragile, leading to bruising, bleeding under the skin and similar conditions.
- The number of pigment-containing melanocytes decreases, but the remaining melanocytes increase in size. Aging skin thus appears thinner, paler and translucent. Large pigmented spots (called age spots, liver spots, or lentigos) may appear in sun-exposed areas.
- Sebaceous glands produce less oil. Men experience a minimal decrease, usually after the age of 80. Women gradually produce less oil beginning after menopause, resulting in dryness and itchiness.
- The subcutaneous fat layer thins, reducing its normal insulation and padding. This thinning increases risk of skin injury and reduces the ability to maintain body temperature.
- The sweat glands produce less sweat, making it harder to keep cool and increasing risk for becoming overheated or developing heat stroke.
- Growths such as skin tags, warts and other blemishes are more common in older people.

Aging from intrinsic factors
Intrinsic or natural aging reflects changes in the function and appearance of skin that occur due to the passage of time. Although the precise causes of aging are not known, clearly genetics and metabolism play key roles in the biology of aging. A prominent theory of aging is that changes occur partially as a result of cumulative damage due to the formation of reactive oxygen species (ROS). These destructive molecules, which are created during normal cellular processes, damage cellular components including membranes, proteins and DNA.

Changes in growth factors and hormones, including estrogen, testosterone and insulin, also influence skin aging. Alterations in hormone levels with age are thought to lead to the early death of cells within the skin, reduced collagen levels and, conversely, more of the enzymes that degrade collagen. (Puizina-Ivi, 2008; Fisher et al., 2008)

Intrinsic aging manifests as thinning skin, loss of elasticity and deepening of normal expression lines. (Weiss et al., 1988)
Aging from extrinsic factors
As anyone who’s spent too many years in the sun has learned, external factors contribute heavily to the visible signs of aging. While physical and psychological stress, smoking, alcohol, poor nutrition and pollution all age the skin, the extrinsic factor that contributes the most (up to 80 percent) is ultraviolet (UV) irradiation from the sun.

UV irradiation-related aging is also known as photoaging. Photoaged skin is characterized by wrinkles, lack of firmness, uneven pigmentation, brown spots, and a leathery appearance. Photoaged skin is characterized by prominent changes in the dermal connective tissues – namely, fragmentation and loss of collagen and elastin. Changes in the amount and structure

Changes in skin connective tissues during aging
Changes to the connective tissues reduce the skin’s strength and elasticity. Sun-exposed areas of the skin often acquire a weather-beaten appearance common to farmers, sailors, and others who spend a large amount of time outdoors.

What accounts for these changes in the structure of the skin connective tissue during aging? Studies have shown that aged skin is associated with two events that directly affect the structure of the dermis:
• increased levels of collagenase activity (Figure 3), which lead to collagen degradation
• reduced production of new collagen (Figure 4)

Figure 3. Skin collagenase levels rise with age (modified from Varani, 2000).

Figure 4. Aged skin produces less new collagen (modified from Varani, 2000).
**Accumulation of abnormal and defective collagen**

Individual type I collagen molecules within a collagen fibril are cross-linked together by chemical bonds. Cross-linking is necessary for stabilization of collagen fibrils. The enzymes that normally break down collagen fibrils are not able to efficiently degrade cross-links, resulting in the build-up of collagen fragments within the extracellular matrix as skin ages. The fragments cannot be repaired or incorporated into newly made collagen fibrils, causing defects in the extracellular matrix (Figure 5). The defects weaken the structural and mechanical integrity of the dermis, impairing its function. Accumulation of fragmented collagen is thought to be a key reason for age-related changes in the skin’s appearance. (Fisher et al., 2008)

**Sunlight hastens collagen fragmentation**

While collagen fragmentation and its consequences for the skin apply to both photoaging and chronological aging, photoaging represents an acceleration of certain aspects of chronological aging. Acceleration occurs because UV irradiation both dampens collagen production and increases the activity of the enzymes that degrade collagen. Thus, UV irradiation, like chronological aging, shifts the balance towards net collagen degradation. Even moderate UV exposure, producing mild pinkness but no sunburn, causes hundred-fold increases in collagenase levels and reduces collagen production by about 80 percent. (Fisher et al., 2008)

These changes occur within 24 hours following a single acute exposure and then subside to normal during the following 48-72 hours. Daily minimal to moderate sun exposure, however, maintains collagenase levels and suppression of collagen production throughout the course of exposure. (Fisher et al., 2008)

Figure 5. Collagen fibrils (top) become fragmented (bottom) in the dermis of aged skin (modified from Fisher et al., 2008).
ANTI-AGING SKIN TREATMENTS

From the ancient Chinese and Egyptians to modern societies around the globe, the search for treatments that stop the march of time – or at least remove its boot prints on the skin – has been the holy grail of beauty.

Classically, the treatment of aging skin relied on the use of cosmetics, acid peels, collagen injections and surgical procedures. Although these often expensive procedures can improve appearance, they do not treat the underlying problem.

The emergence of retinoids
An important player in the skincare realm emerged about 40 years ago, when topical retinoids were first used for treating aging skin. Retinoids are a class of molecules chemically related to vitamin A and help regulate the growth of skin cells. Until the mid 1980s, retinoids were used solely to treat acne. (Griffiths et al., 1999) Currently, they are also used to treat psoriasis and skin cancer as well as improve the appearance of aging skin. (Rittié et al., 2006)

The breakthrough of retinoids into the anti-aging realm came in 1986, when the first human study with retinoic acid (also known as Retin-A®) for the treatment of aging skin was published (Klingman et al., 1986). Six to 12 months of treatment with daily topical application of 0.05% retinoic acid-containing cream produced more attractive, less wrinkled skin in older patients (Figure 6). Later double-blind, randomized, placebo-controlled studies revealed improvements in fine and coarse wrinkles, sallowness, skin looseness and hyperpigmentation. Most patients also developed a “rosy glow.” (Weiss et al., 1988)

The improvements seen in the skin after retinoid therapy were related mainly to changes in the dermis, especially in the connective tissues such as collagen and elastin. Some of the changes in skin cells that correlate with the clinical benefits of retinoic acid are listed below (Gilchrest, 1997; Fisher et al., 1997; Rittié et al., 2006):

• increased fibroblast proliferation
• decreased matrix degradation by collagenases
• increased collagen I synthesis by fibroblasts
• increased collagen I levels in the matrix of the dermis (Figure 7)
• increased collagen fibers at junction between epidermis and dermis
• improved collagen organization in dermis
• less structural damage to keratinocytes
• reduced level of the pigment melanin
• reduced inflammation around blood vessels in skin
• restoration of type I procollagen to levels approaching those in skin that has not been exposed to sun

Figure 6. The appearance of aged skin (left) is improved by retinoid acid treatment (right; modified from Griffiths, 1999).
Retinoid mechanism of action

For retinoids to affect skin cells they must bind to their receptors within the cell’s nucleus – the command center of the cell, where the genome lies. When bound to retinoic acid, the receptors find and activate specific genes in the cell nucleus. It is not clear, however, exactly which genes are responsible for the anti-aging effects of retinoids.

The retinoic acid-bound receptors can also interfere with the activation of enzymes that degrade collagen in the dermis. In this way, retinoic acid can reduce UV irradiation-induced photoaging via collagen degradation. (Fisher and Voorhees, 1996)

It is important to note the limitations of treatments with retinoic acid. Although approved for the treatment of photoaging, topical retinoic acid often induces skin irritation at application sites (discussed further below).

Entrance of retinol

The metabolic precursor of retinoic acid is vitamin A, called retinol. After application, retinol is converted within the skin into retinoic acid and thus has many of the same effects. As a result, retinol has become a common ingredient in many over the counter anti-aging products. (Kafi et al., 2007)

In a clinical trial, retinol lotion improved the appearance of naturally aged skin and was associated with increased levels of procollagen I (Figure 8). Retinol also increased the levels of glycosaminoglycan (GAG) in the epidermis of aged skin. GAGs are molecules that trap water in the skin, helping to plump up skin that has lost hydration. (Kafi et al., 2007)

Figure 7. Levels of collagen (pink) in aging skin cells (left) is increased by treatment with retinoids (right; modified from Griffiths et al., 1993).

Figure 8. Top, naturally aged skin (left) is improved (right) by treatment with retinol. Bottom, procollagen I (red) is increased (right) by treatment with retinol (modified from Kafi et al., 2007).
Side effects of retinoids and the epidermal growth factor receptor

Multiple studies suggest that up to 90 percent of patients treated with retinoids experience side effects in the treated areas, including redness, flaking and irritation, especially with long-term use. Collectively, these side effects are known as retinoid dermatitis. (Weiss et al., 1988; Gilchrest, 1997)

Researchers have investigated some the molecular pathways that lead to retinoid dermatitis. One major player that has been identified in this process is a protein that sits on the cell surface called the epidermal growth factor receptor (EGFR). When activated, EGFR initiates communication pathways within the cell that regulate genes controlling skin cell growth and survival. Epidermal cell growth is brought about by signaling proteins such as Erk1/2, which are activated in skin after treatment with retinoic acid (Figure 9). (Rittié et al., 2006)

Retinoid therapy causes cells in the lower epidermis to proliferate excessively, leading to a thickening of the epidermis (Figure 10) and more cells migrating towards the surface. A disproportionate number of cells arriving at the surface of the skin results in skin flaking, scaling and dryness. These side effects often deter patients from continued use of retinoid therapy. (Xiao et al., 1999)

The finding that dermatitis involves a pathway (EGFR) is important because it suggests that technologies that inhibit EGFR may dampen or eliminate retinoids’ side effects while not diminishing their capabilities to smooth wrinkles. Very recent results support this idea and may be an indication that such technologies are on the horizon.

Figure 9. Levels of Erk1/2 are increased by treatment with retinoids (Ritti et al., 2006).

Figure 10. Treatment of aged skin with retinoic acid causes the epidermis to thicken (top), a hallmark of dermatitis (Varani et al., 2001).
Inhibitors of dermatitis – drawing from cancer therapies

While moisturizers may be used in conjunction with retinoids to counteract dryness, they are generally insufficient to overcome all of the side effects associated with retinoid therapy. Fortuitously for skin-care experts, researchers have long been interested in identifying EGFR inhibitors, due to evidence that this receptor is linked to human cancers. For instance, abnormally high levels of EGFR have been found in lung, colorectal, pancreatic, ovarian, breast and prostate cancers. As a result, a wide variety of natural and synthetic compounds that inhibit EGFR’s ability to activate cell growth have been identified as candidate anti-cancer therapies. (Banerjee et al., 2008)

One promising anti-cancer therapy derives from a family of natural compounds known as isoflavones. These organic compounds found in soybean and related plants are associated with a reduced risk for breast and prostate cancers in Asian countries, where dietary soy intake is generally higher than in Western societies (Banerjee et al., 2008). Within soy extracts are three main forms of isoflavones: genistein, daidzein and glycine. Genistein itself has been shown to inhibit metastasis of human tumor cells and is a promising agent for patients with many different types of cancers (Pavese et al., 2010).

In 1998, a synthetic EGFR inhibitor was first shown to block hyperplasia in cultured human skin cells (Stoll and Elder, 1998). A 2004 study by researchers at the University of Michigan next demonstrated that soy extracts containing isoflavones also helped to prevent retinoid-induced dermatitis (Figure 11). Of the isoflavones in the soy extract, genistein was most effective at blocking epidermal cell proliferation. (Varani et al., 2004) Researchers then confirmed that topical application of genistein along with a retinoid reduced both keratinocyte proliferation and epidermal thickening (Figure 12). (Rittié et al., 2006)
FUTURE PROSPECTS FOR RETINOL TREATMENTS

The above findings support a scenario in which retinol, with its proven ability to improve the look of aging or photoaged skin, may be used in the future (Figure 14) alongside compounds that inhibit EGFR, to gain the anti-aging benefits while avoiding the side effects associated of retinol-based creams.

While generally designed for oral or IV-injected administration due to their development as cancer therapies, many previously identified EGFR inhibitors can also be used in a topically applied form. Since isoflavones such as genistein are relatively small (Figure 13) and can penetrate the skin when applied topically, they may be ideal additives to lotions, creams and gels for mitigating the side effects of retinol therapies. Non-isoflavone EGFR inhibitors may also prove useful.

In theory, topical EGFR inhibitor treatments to address the unwanted effects of retinoids may be used as a stand-alone product to be applied by the user as often as needed, either prior to, concomitant with, or following use of the retinoid. The inhibitor could also be added in combination with the retinoid into a single product. This type of combination treatment would specifically target the retinoid to its collagen/collagenase effects while blocking its EGFR effects that lead to dermatitis.

The advent of next-generation retinol technologies would be a major boon to would-be users worldwide who want to look younger without the unwelcome side effects of redness, flaking and irritation. Fewer side effects are expected to result in more consistent usage of the retinoid product and thus better results for younger-looking skin.

Figure 13. Chemical structure of genistein
Novel combination lotion improves look of aged skin without dermatitis.

Genistein seen to prevent dermatitis symptoms in people treated with RA.

Block in HB-EGF found to blunt epidermal cell hyperplasia.

RA found to improve photoaged skin.

RA first used to treat acne.

Soy first shown to inhibit RA-induced proliferation of keratinocytes.

First double-blind trial shows RA improved photoaged skin.

Retinoic acid (RA) first used to treat acne.

Retinol shown to improve naturally aged skin.

Figure 14. Milestones of retinoids in anti-aging skincare.
GLOSSARY

Collagen – Tough, fibrous protein that is a major component of extracellular matrix and connective tissue. The principal protein of the skin, tendons, cartilage and bone. (Alberts et al., 2002)

Collagenase – Any of a group of enzymes that degrade collagen. (Oxford, 1997)

Dermatitis – Inflammation of the skin. (Webster’s, 2001)

Dermis – Collagen-rich skin layer below the epidermis containing blood vessels, lymph vessels, sweat glands, nerve endings and hair follicles. (Oxford, 1997)

Elastin – Protein of the connective tissue that accounts for the elasticity of structures such as the skin, blood vessels, heart, lungs, intestines, tendons and ligaments. (Alberts et al., 2002)

Epidermal growth factor receptor (EGFR) – A cell-surface mediator of biological signals that control internal cellular growth and replication; EGFR is also involved in side effects of retinoid-based treatments. (Oxford, 1997)

Epidermis – The outermost layer of cells that make up the barrier of the skin. (Oxford, 1997)

Extracellular matrix – The layer consisting mainly of proteins and glycosaminoglycans that forms a sheet underlying cells such as epithelial cells. Substances within are produced by cells in the vicinity, especially fibroblasts. (Oxford, 1997)

Fibroblast – A common cell type found in connective tissue, including the dermis, that secretes collagen and other matrix molecules. (Alberts et al., 2002)

Glycosaminoglycans – Long, linear, highly charged polysaccharides mainly found linked to proteins in the extracellular matrix. (Alberts et al., 2002)

Hypodermis – See subcutaneous layer.

Isoflavones – A family of naturally occurring plant compounds that act as plant hormones. (Kaufman et al., 1997)

Keratinocyte – The main epidermal cell type, which produces keratin. (Oxford, 1997)

Melanocyte – A pigmented cell in the skin and eye that synthesizes and stores melanin. (Oxford, 1997)

Nucleus – The conspicuous structure within a cell that houses the chromosomes. (Oxford, 1997)

Papillary dermis – The uppermost layer of the dermis, intertwined with the epidermis, composed of fine, loosely arranged collagen fibers. (Marks et al., 2006)

Photoaging – The cumulative detrimental effects on skin, such as wrinkles or dark spots, that result from long-term exposure to UV sunlight. (Webster’s, 2001)

Procollagen – A helical protein that is the precursor of collagen. (Oxford, 1997)

Reactive oxygen species (ROS) – Molecules such as superoxide, hydrogen peroxide, and hydroxyl radical. At low levels, these molecules may function in normal cellular processes. At higher levels, however, they may damage important cellular components, such as DNA and RNA, and lead to cellular suicide. (Stadtman, 1992)

Reticular dermis – The lower layer of the dermis, beneath the papillary dermis, composed of thick, densely packed collagen fibers, and the primary location of dermal elastic fibers. (Marks et al., 2006)

Retinoic acid – Member of the vitamin A family, which mediates cellular growth and maturation programs. (Oxford, 1997)

Retinoids – Collective name for a class of compounds, natural or not, including retinoic acid and retinol. (Oxford, 1997)

Retinol – Predominant form of vitamin A in humans and precursor to retinoic acid. (Oxford, 1997)

Stratum basale – The deepest layer of the epidermis, consisting of dividing columnar cells that push the cells above them into higher layers. (Alberts et al., 2002)

Stratum corneum – The outermost layer of the epidermis, composed of flat, keratin-filled dead keratinocytes that have migrated from deeper layers of the epidermis. (Alberts et al., 2002)

Subcutaneous tissue – The deepest layer of the skin, containing connective tissue, sweat glands, blood vessels, and cells that store fat. (Alberts et al., 2002)
RESOURCES

Patient and professional education and information

American Academy of Dermatology (www.aad.org)
American Skincare & Cellulite Expert Association (www.ascea.org)
American Society of Dermatology (www.asd.org)
Asian Dermatological Society (www.medicine.org)
Australasian College of Dermatologists (www.dermcoll.asn.au)
China Dermatologist Association (www.cda.net.cn)
Dermatological Society of Thailand (www.dst.or.th)
European Society for Cosmetic and Aesthetic Dermatology (www.escad.org)
International Federation of Societies of Cosmetic Chemists (www ifscc.org)
International League of Dermatological Societies (www.web.ilds.org)
International Skin Care Nursing Group (www.isng.org)
International Society of Skin Pharmacology and Physiology (www.isp-society.org)
Japanese Dermatological Association (www.dermatol.or.jp)
Japanese Society for Investigative Dermatology (www.jsid.org)
Japanese Society for Pigment Cell Research (www.jspcr.jp)
Korean Dermatological Association (www.dermatol.or.kr)
Mayo Clinic (www.mayoclinic.com)
Medical Dermatology Society (www.meddermsociety.org)
National Institute of Health (www.nih.gov)
National Skin Care Institute (www.skincare.net.org)
Pacific Dermatological Association (www.pacificderm.org)
Philippine Society for Cosmetic Science (www.pscs.org.ph)
Primary Care Dermatology Society (www.pcds.org.uk)
Society for Investigative Dermatology (www.sidnet.org)
REFERENCES


