Melanoma

WHAT IS MELANOMA?

The Skin, Melanocytes, and Melanoma

Melanoma is the most lethal skin cancer, although it can often be cured if caught very early. To understand how melanomas form, it is useful to know something about the skin.

The Skin. The skin is the largest organ in the body and consists of layers.

- The outermost layer of the skin, the *epidermis*, is only about 20 cells deep, roughly as thick as a sheet of paper.
- The dermis ranges in thickness from one to four millimeters (about 1/32 to 1/8 inch). The dermis contains tiny blood and lymph vessels, which increase in number deeper in the skin.

Melanocytes. Between the epidermis and the dermis are a layer of cells called *melanocytes*, which produce a brown–black skin pigment called *melanin* that determines skin and hair coloring. Melanin also helps protect against the damaging rays of the sun.

Melanoma. Melanocytes give melanoma its name. As a person ages, melanocytes often proliferate, forming concentrated clusters that appear on the surface as small, dark, flat or dome–shaped spots, which are usually harmless moles or liver spots.

- When cell proliferation occurs in a controlled and contained manner, the resulting lesion is benign and is commonly referred to as a mole or *nevus*. Most adults have at least several dozen benign moles.

- Sometimes, however, pigment cells grow out of control and become a malignant and life–threatening melanoma.

Early detection of melanoma is critical because of the skin's unique anatomy. At first, melanoma cells grow sideways (laterally), and so are confined to the epidermis and to the top layers of the dermis. However, once they grow downward into the dermis, the cancer will come into contact with lymph and blood vessels. The thicker the melanoma, in fact, the greater the likelihood that it could spread through these vessels to distant sites. Removal of the lesion before it penetrates to the deeper layers of the skin is, therefore, crucial for achieving a cure.

Significant Features

People who regularly check moles on their skin may have a lower risk of developing advanced melanoma, but people should not panic over every skin irregularity. A physician should examine any suspicious lesion with one or more of the features discussed below or that changes noticeably in size, color, or shape. Itching, tenderness, scaling, bleeding, crusting, or sores can signal potentially cancerous changes in any mole.

A mnemonic device, ABCD, is used to describe several features that help to distinguish melanomas from noncancerous growths:

- *Asymmetry (A).* About half the time, a melanoma develops in an existing mole; in other cases, it arises as a new lesion that can resemble an ordinary mole. A noncancerous mole, however, is generally symmetric and circular in shape, while melanoma usually grows in an irregular, asymmetric fashion.
- *Border Irregularity (B).* Benign lesions generally have clearly defined borders that mark the boundary between mole and skin. A melanoma, in contrast, often has notched or indistinct borders that may signal ongoing growth and spread of the cancer.
- *Color Variation (C).* One of the earliest signs of melanoma may be the appearance of various colors within the lesion. Because melanomas arise within pigment–forming cells, they are often varicolored lesions of tan, dark brown, or black, reflecting the production of melanin pigment at different depths within the skin. Occasionally, lesions are flesh colored or surrounded by redness or lighter areas of depigmentation. Pink or red areas may result from inflammation of blood vessels within the skin; blue areas reflect pigment in the deeper layers of the skin; and white areas can arise from dead cancerous tissue.
- *Diameter (D).* A diameter of 6 millimeters or larger (about the size of a pencil eraser) is worrisome. Melanomas start out small; by the time a lesion has grown this large, other abnormalities will most likely be present. No matter what size, a physician should examine any suspicious lesion.

Growth Pattern

Melanomas tend to grow in stages:

- Most melanomas tend to be flat initially and spread laterally across the skin surface as they grow. At this early stage, which can last from one to five years or longer, removal of the growth has an excellent chance of curing the melanoma. Still, there is a chance that some of these melanomas are invasive and they should be treated aggressively.
- Lesions that become raised or dome−shaped over at least part of their surface indicate that downward growth has occurred. In some cases, this growth is very rapid, occurring over a period of weeks to months.

Any suspicious lesion should be checked immediately, particularly if it has grown quickly or is partially flat and partially raised.

Location

Common sites of melanoma in men are the head, neck, and trunk, and in women, the arms or legs. Any area of the skin may be affected, however, in either gender. Melanomas may not be noticed if they appear on areas that are difficult to examine, such as the scalp or the back. Less common sites for melanoma include the fingers, palms, soles of the feet, the genitals, lips, or under the fingernails or toenails. The presence of a dark lesion under the nail that runs into the adjoining skin and doesn't heal may signal melanoma. Rarely, melanomas appear in the mouth, in the iris of the eye, or in the retina at the back of the eye, where they may be detected during dental or eye examinations.

Specific Melanomas

Superficial Spreading Melanoma. Superficial spreading melanoma is the most common and most curable. It is flat, asymmetrical, unevenly colored, and usually grows outward across the surface of the skin.

Nodular Melanoma. Nodular melanoma appears as a fast−growing brown or black lump and its characteristics do not always fit the definitions described above. It is important to check for this type of melanoma, because it is associated with an outbreak of other tumors.

Lentigo Maligna. Lentigo maligna (sometimes called Hutchinson's freckle) usually occurs in elderly people and is marked by flat, mottled, tan−to−brown freckle−like spots with irregular borders. These lesions often appear on the face or other sun−exposed areas and typically enlarge slowly for five to fifteen years before cancer appears.

Acral Lentiginous Melanoma. Although rare, acral lentiginous melanoma is the most common melanoma among African and Asian populations. It commonly appears as a dark patch on the palms, soles, fingers, toes, under fingernails or toenails, or mucous membranes.

WHAT CAUSES MELANOMA?

Ultraviolet Radiation and Sunlight

The role of the sun cannot be overestimated as the most important cause of prematurely aging skin (called *photoaging*) and skin cancers. Overall, exposure to ultraviolet (referred to as UVA or UVB) radiation emanating from sunlight accounts for about 90% of the symptoms of premature skin aging, and most of these effects occur by age 20:

- Even small amounts of UV radiation trigger process leading to skin wrinkles.
- Long−term repetitive and cumulative exposure to sunlight appears to be responsible for the vast majority of undesirable consequences of aging skin, including basal cell and squamous cell carcinomas.
- Melanoma is more likely to be caused by intense exposure to sunlight in early life.

UVA and UVB Radiation. When sunlight penetrates the top layers of the skin, ultraviolet (referred to as UVA or UVB) radiation bombards the genetic material, *the DNA*, inside the skin cells and damages it.

- UVB is the primary agent in sunburning and primarily affects the outer skin layers. UVB is most intense at midday when sunlight is brightest.Slightly over 70% of the yearly UVB dose is received during the summer and only 28% is received during the remainder of the year.
- UVA penetrates more deeply and efficiently, however. UVA's intensity also tends to be less variable both during the day and throughout the year than UVB's. For example, only about half of the yearly UVA dose is received during the summer months and the balance is spread over the rest of the year. UVA is also not filtered through window glass (as UVB is).

Damaging Effects of UV Radiation. Both UVA and UVB rays cause damage, including genetic injury, wrinkles, lower immunity against infection, aging skin disorders, and cancer, although the mechanisms are not yet fully clear. The following are some ways in which cancer may develop and some defensive actions that the skin uses to defend itself against DNA damage.

- Oxidation and Antioxidants. The effects of UV radiation are implicated in the production of *oxidants*, also called free radicals. These are unstable molecules produced by normal chemical processes in the body that, in excess, can damage the body's cells and even alter their genetic material, contributing to the aging process and sometimes to cancer. The large surface area of the skin makes this organ a prime target for oxidants.
- Defective DNA Repair and Protective Enzymes. Some melanomas and other skin cancers are caused by a breakdown in the mechanisms that help repair DNA damage. This can occur from various causes including an inherited condition called xeroderma pigmentosum (XP). A number of enzymes in the skin help protect against this damage. One repair enzyme called T4 endonuclease 5 (T4N5) is, in fact, being investigated in lotions to protect against skin cancers.
- Breakdown of Immune Protection. Specific immune factors protect the skin, including white blood cells called T lymphocytes and specialized skin cells called Langerhans cells. Such immune factors attack developing cancer cells at the very earliest stages. Unfortunately, certain substances in the skin−−of note a chemical called urocanic acid−−suppress such immune factors when exposed to sunlight, setting the stage for skin cancers.

Defective Cell Death (Apoptosis). Apoptosis is the last defense of the immune system. It is a natural process of cell−suicide, which occurs when cells are very severely damaged. Apoptosis in the skin kills off cells harmed by UVA so that they do not turn cancerous. (The peeling after sunburn is the result of these dead skin cells.) In some cases, however, genetic mutations or other factors derail apoptosis. If this occurs, the cells can become immortal and continue to proliferate, resulting in skin cancers.

Genetic Factors

A number of genetic factors are being investigated for their role in melanomas, including inherited genes and genetic defects that are acquired from environmental assaults (particularly sunlight).

Mutations in Genes that Regulate Cell Growth. Noninherited mutations in a number of genes that inhibit tumor growth or other cell−protecting properties may account for cancerous changes in moles and for aggressive melanomas. The following are some examples.

- Important studies have now identified a mutation in the BRAF gene that appears to be the most common event in the process that leads to melanoma. Some researchers have observed mutations in 66% of malignant melanomas. Researchers hope that agents that block this gene may be a viable treatment path.
- P16 is a tumor suppressive gene that may be abnormal in some melanoma cases.
- Genetic mutations that regulate Ku70 and Ku80 proteins may disrupt processes that repair strands of DNA.
- Researchers are also studying mutations in a gene that encodes for a substance called epidermal growth factor (EGF). EGF plays a role in skin cell growth and wound healing, and may account for many sporadic (non−inherited) cases of melanoma.
- Of further interest are mutations in genes that regulate Fas proteins, which are involved in apoptosis, a natural process of cell self−destruction. When it goes awry in melanoma cells, proliferation can become rampant.

CDKN2A Mutations. Mutations in a genetic regulator called CDKN2A are the most common causes of inherited melanoma (which are still very uncommon). (Mutations in this gene also appear in non−inherited cases of melanoma.) Genetic tests are being developed for CDKN2A, although it is not clear if knowing the results of the test would benefit people carrying the gene.

Variations in the Melanocortin−1 Receptor Gene. One study found that the greater the number of variations from normal in a gene called the melanocortin−1 receptor gene, the greater the risk for melanoma. The gene plays an important role in determining if a person has red hair, fair skin, and sensitivity to UV radiation. Interestingly, people who had olive and darker skin and who carried one or more variations of the gene had a *higher* than average risk for melanoma.

Aging

Aging may weaken the body's ability to fend off impending cancers, including melanomas. As a person ages, they lose specialized immune cells in the skin (Langerhans cells) that are thought to be responsible for eliminating skin cancers at the very earliest stage when only one or two cancer cells are present. The number of these immune cells decreases with age, possibly setting the stage for skin cancers to take root and thrive in later life.

WHAT ARE THE RISK FACTORS FOR MELANOMA?

General Statistics

In the US, the incidence of melanoma is rising more rapidly than any other cancer. During the 1970's, the incidence of melanoma rose by about 6% a year. On a positive note, since the early 1980's this has slowed to an increase of 3% a year. At this time, men have a lifetime risk for melanoma of 1.75% and women of 1.23%. In 2003, some 54,200 Americans will develop melanoma−−about 29,900 men and 24,300 women.

An estimated 7,600 Americans are expected to die from it this year, 4,700 men and 2,900 women. Survival rates have been improving, however, and the increase in melanomas has occurred principally with thin, less aggressive forms of the disease. Some experts believe this is due to the increased awareness from effective public programs and earlier diagnosis.

Age and Gender

Melanoma in Adults. Melanoma is most common in people over 40 and the incidence increases significantly as people get older. Before age 40, melanomas are slightly more common in women than men, but after age 40 men are more often affected. Men are also more likely to have invasive and fatal melanoma than are women, although some research suggests that the higher rates are only because men fail to seek a diagnosis of suspicious skin changes before they become dangerous. The rate in women levels off somewhat between age 45 and 60; researchers speculate that menopause could have some sort of protective effect during those years.

Melanoma in Children. Melanoma is rare in children under age 10. Among children ages 10 to 14 the incidence is only 0.3 per 100,000 and between ages 14 and 19, it is still very rare, 1.3 per 100,000. Parents, then, should not be unduly alarmed by every minor skin imperfection in their children. Nevertheless, melanoma is as serious in children as in adults and early detection is still critical.

People at Higher Risk for Melanoma from Intense Exposure to Sunlight and Ultraviolet Radiation

Ethnic Groups and Complexion. People with light skin, blue, gray, or green eyes, red or blond hair, and lots of freckles are at highest risk than people with other skin types for developing melanoma. The risk increases for those who are easily sunburned and rarely tan, particularly if they live close to the equator where sunlight is most intense. Darker ethnic groups or those with swarthy complexions are not immune, however.

Experts have devised a classification system for skin phototypes (SPTs) based on the sensitivity to sunlight. It ranges from SPT I (lightest skin plus other factors) to IV (darkest skin). [*See Table*] Tanning and Sunburn Risk People with skin types I and II are at highest risk for photoaging skin diseases, including cancer. It should be noted, however, that premature aging from sunlight can affect people of all skin shades.

People Exposed to Intermittent Intense Sunburns. Whereas some skin cancers, such as squamous cell and basal cell carcinomas, are associated with cumulative lifetime exposure to the sun, melanoma is more often linked to intermittent intense exposure to sunlight, particularly during childhood and adolescence. Cancer typically arises many years later.

Fortunately, many parents are now taking effective steps to protect their children, although experts worry that they are relying too much sunscreen and less on other protective measures. Adolescents, however, are at special risk for sun−related cancers because, according to a 2002 study, the majority fails to take protective measures when out in the sun. According to the study, boys are less likely to use sunscreen than girls, but girls have more sunburns and use tanning salons more often. Adults who work indoors and experience the occasional weekend sunburn may also be at increased danger.

Interestingly, a number of studies report that *continuous* exposure to sunlight during adolescence or adulthood may be protective.

Exposure to Tanning Parlors. Tanning beds and parlors have been possibly linked to a higher incidence of nonmelanoma skin cancers, though the link to melanoma remains unknown.

Tanning and Sunburn Risk

Skin Type	Tanning and Burning Risk
I	Always burns, never tans, sensitive to sun exposure.
II	Burns easily, tans minimally.
III	Burns moderately, tans gradually to light brown.
IV	Burns minimally, always tans well to moderately brown.
V	Rarely burns, tans profusely to dark.
VI	Never burns, deeply pigmented, least sensitive.

Personal or Family History of Melanoma

Individuals who have been diagnosed with melanoma are at increased risk for a second primary melanoma. According to one 2003 study, the risk over time for developing a second melanoma is 1% in the first year after diagnosis, 2.1% at five years, 3.2% at 10 years, and 5.3% at 20 years. The risk is especially higher in older men and in those with first melanomas on the upper body and face.

People with family members who have or had melanoma should also be considered at high risk and examined on a regular basis.

Other Skin Conditions That Increase the Risk for Melanoma

Nonmelanoma Skin Cancers. Nonmelanoma skin cancers, including basal and squamous cell carcinomas, increase the risk of dying from other cancers, including melanoma itself, lung cancer, non−Hodgkin's lymphoma, bladder cancer, and leukemia as well as testicular and prostate cancers (in men) and breast cancer (in women). [For more information *see* the *Well−Connected* Report #20 *Aging Skin: Blemishes and Nonmelanoma Skin Cancers*.]

Moles (Nevi) and Other Dark Blemishes. Any mole (called *a nevus*) or other blemish that seems new, changing, or unusual in any way should raise suspicion, but one should not be alarmed by every rash or bump. Benign (noncancerous) moles (*nevi*) typically have the following characteristics:

- Benign moles generally remain small with clearly defined, regular borders and uniform coloration. Some have a regular stippled or net−like pattern of pigmentation, however, and may even resemble early melanoma.
- They typically first appear during childhood, puberty, or young adulthood. They may naturally grow, darken, or increase in number at certain times of life, such as adolescence or pregnancy.

Some specific moles or dark blemishes that either resemble melanomas, are risk factors for melanoma, or both include the following:

- Freckles. Freckles typically appear in children on sun−exposed areas and are usually evenly brown or tan. The more freckles a person develops as a child, the greater the risk for melanoma in adulthood.
- Liver Spots. Liver spots are usually evenly brown or tan sun−induced lesions that are universal signs of aging. Occurring most noticeably on the hands and face, these harmless blemishes tend to enlarge and darken over time.
- Dysplastic (or Atypical) Nevi. About 30% of the population has moles called dysplastic nevi, or atypical moles. They are larger than ordinary moles (most are 5 mm across, about the size of a pencil eraser, or larger), have irregular borders, and are various shades or colors. Individuals who have dysplastic nevi plus a family history of melanoma (a syndrome known as FAMM) are at a high risk for developing melanoma at an early age (younger than 40) and often develop subsequent melanomas at additional locations. The risk for those with atypical moles and no family history of melanoma is less clear.
- Blue Nevus. The blue nevus is a benign mole that may easily be mistaken for melanoma. It is a blue−black, smooth, raised nodule and commonly occurs on the buttocks, hands, or feet.
- Spindle Cell (Spitz) Nevus. Children may develop a benign lesion called a spindle cell (or Spitz) nevus. The mole is firm, raised, and pink or reddish−brown. It may be smooth or scaly and usually appears on the face, particularly the cheeks. It is not harmful, but it may be difficult to differentiate from a melanoma, even for experts.
- Congenital Nevi (Birthmarks). Whenever possible, very large birthmarks should be removed during infancy. Those known as giant congenital nevi are more than eight inches across and are major risk factors for melanoma. In such cases, cancer usually appears by age 10. Medium−sized congenital nevi do not appear to increase the risk for melanoma. Experts disagree, however, about whether small birthmarks need to be removed. Parents are advised to watch any birthmark for changes.

The more moles one has the higher the risk that one of them will become cancerous, although the danger is still very small. A 2003 study estimated that the risk for a single mole to develop into melanoma by age 80 is 1 in 3164 in men and 1 in 10,800 for women. (The risk is higher, however, with atypical moles. One study of people with melanoma indicated that the presence of even one atypical mole doubled the normal risk and having 10 or more increased the chance 12−fold.) Any moles should be watched for changes, particularly in people with fair skin and other risk factors. However, simply having them should not cause alarm.

Psoriasis and Its Treatments. Psoriasis increases the risk for squamous cell carcinoma, but studies conflict on whether it has any effect on melanoma. One study, in fact, reported a *lower risk*. Nevertheless, there is some evidence that long−term treatment for psoriasis using UVA radiation (PUVA) may increase the risk for melanoma. In one study,

there was a significantly higher risk even with relatively few treatments. In one study, invasive melanoma had occurred in 2.8% of patients 15 or more years after the initial treatment. [For more information *see* the *Well−Connected* Report #87 *Psoriasis*.]

Non−Skin Medical Conditions

- *Non−Hodgkin's Lymphoma.* Survivors of either non−Hodgkin's lymphoma or melanoma face a higher risk for the other malignancy. These may have common causes, such as exposure to UV radiation or shared genetic factors.
- *Immunosuppressed Patients.* Individuals whose immune systems are suppressed because of certain medications, organ transplantation, or specific medical conditions such as AIDS are also at risk. (Melanoma has also developed in patients who received heart transplants from donors who had the disease.)
- *Endometriosis.* Endometriosis may put women with this condition at higher risk for melanoma, although more research is needed to confirm this.

Geographic Location

Australia has the highest melanoma rate in the world. In the US the incidence is highest in California, Florida, and Texas. The disease is by no means limited to such sunny states and countries, however. In general, the risks are highest in regions where the population tends to be blonde and fair−skinned. Norway, for example, has had the highest rate of melanoma in Europe, and rates are soaring in the UK, particularly among men, perhaps because Britons are increasingly vacationing in sunny climates.

Other Forms of Radiation Exposure

Occupational exposure to radiation, such as in health−care or industrial settings, may increase the risk for melanoma. Airline pilots, too, are at increased risk for melanoma. It is uncertain, however, whether this higher risk is from excessive exposure to ionizing radiation at high altitudes or because they have more opportunity to spend time in sunny regions. Experts disagree over whether frequent flyers are also at increased jeopardy.

HOW SERIOUS IS MELANOMA?

Melanoma presents a case of extremes. If detected while it is still local (called melanoma in situ), the five−year survival rate is over 95%. And, fortunately, about 80% of melanomas are diagnosed in this early stage.

If the cancer is more advanced, however, survival drops below 60%. Its deadly nature is due to the spread of cancerous melanoma cells to other parts of the body. Cancer cells that spread in this fashion are known as metastases and are very difficult to treat. Melanoma cells usually spread first via lymph vessels (channels that carry immune system cells and fluids to the lymph nodes) or glands. Melanoma cells can also spread via blood vessels to various organs, causing metastatic tumors in the liver, lungs, brain, or other sites.

In general, after patients are treated for melanoma, the longer they remain free of cancer recurrence following treatment, the better the chance of remaining disease−free. However, relapses are not uncommon in those whose initial melanoma was large. (Current research suggests that even many local melanomas may be more dangerous than previously thought. Even after small melanomas have been completely removed, patients must be monitored for recurrence.)

Anyone who has recovered from melanoma should be especially strict about adhering to preventive guidelines and remain vigilant for suspicious lesions, since the risk for developing a new melanoma is increased even if the first one was successfully cured. Such relapses may occur years after the original diagnosis.

HOW CAN MELANOMA BE PREVENTED?

Public Programs

Australia and Scotland have reported improved survival rates from melanoma after aggressive detection and prevention programs were started. In addition to encouraging regular self−examination, such programs include eliminating the sales tax on sunscreens, discouraging suntans and midday sports, and planting trees and placing canopies over children's playgrounds.

Self−Examinations for General Population

Anyone with risk factors for this cancer should be vigilant and check the entire body every month or so. Some experts have defined three specific areas for locating melanomas:

- Areas visible to anyone, such as the arms or face. (About 60% of melanomas are found here.)

- Areas usually covered with clothing and visible only to the patients or their partners. (About 34% of melanomas are detected in these areas.)
- Hidden areas usually found by health professionals (scalp, buttock folds, oral cavity.) About 6% are found here, but they also most likely to be more advanced and dangerous. Partners are useful in checking these areas. (A hair dryer to separate hair is useful for examining examine the scalp.)

Experts suggest drawing a map of the body indicating locations of moles, areas of discoloration, lumps, or other blemishes. Whenever a person conducts a self−examination, the map is checked for new lesions, lumps, or moles and for changes in shape, color, and size.

Professional Examination for High−Risk Individuals

Some experts recommend regular full−body screening by a trained health professional in high−risk individuals, which include people with personal or family history of melanoma and individuals with atypical nevi (irregular moles that are also larger than normal).

Such people should protect themselves from overexposure to sunlight and have a medical examination of the entire skin surface every three to 12 months, with the frequency depending on risk factors. Doctors may take photographs of any moles at each visit and compare them with previous photos for any changes. A self−examination should be performed every two months.

Routine screening for everyone does not appear to save many additional lives. In any case, individuals who are worried about any suspicious areas should see a dermatologist or be sure their primary care physician is able to recognize skin cancers.

Examinations for Patients Previously Treated for Melanoma. People who have had melanoma and been treated successfully are at risk for recurrence or a second primary melanoma. Based on recurrence rates by cancer stage [see *Staging,* below], a team of researchers suggested the following guidelines for being reexamined by the physician after treatment:

- Stage I patients: Annual examinations.
- Stage II patients: Every six months for years one and two and annually thereafter.
- Stage III patients: Every three months for the first year, every four months for year two, and every six months for years three to five.

All patients should be checked annually from the sixth year onward. These are guidelines only and may be modified, depending on individual patient characteristics. Some studies also indicate that regular screening of family members of people with melanoma could prevent a number of serious cases.

General Guidelines for Avoiding the Sun and UV Radiation

The best way to prevent skin damage in any case is to avoid episodes of excessive sun exposure. The following are some specific guidelines:

- Use sunscreens that block out both UVA and UVB radiation. *However, do not rely on them only for sun protection.* Also wear protective clothing and sunglasses.
- Avoid exposure particularly during the hours of 10 AM to 4 PM when sunlight pours down 80% of its daily UV dose.
- Avoid reflective surfaces, such as water, sand, concrete, and white−painted areas. (Clouds and haze are *not* protective and in some cases may intensify UVB rays.)
- Ultraviolet intensity depends on the *angle* of the sun, not heat or brightness. So the dangers are greater the closer to the summer−start date. For example, in the Northern Hemisphere, UV intensity in April (two months before summer starts) is equal to that in August (two months after summer begins).
- The higher the altitude the quicker one sunburns. (One study suggested, for example, that an average complexion burns at six minutes at 11,000 feet at noon compared to 25 minutes at sea level in a temperate climate.)
- Avoid sun lamp, and tanning beds or salons. They provide mostly high−output UVA rays. Some experts believe that 15 to 30 minutes at a tanning salon are as dangerous as a day spent in the sun. People should not be misled by advertising claims of "safe" tanning or promotions offering unlimited tanning.

Sunscreens. The use of sunscreens is complex and everyone should understand how and when to use them. The bottom line is *not* that people should avoid sunscreens or sunblocks, but that they should always use them in combination with other sun−protective measures. [*See Box* Sunscreen Guidelines.]

Protective Clothing. Wearing sun−protective clothing is extremely important and protects even better than sunscreens. Special clothing is now available for blocking UV rays and is rated using SPF ratings or a system called the UPF (ultraviolet protection factor) index, with 50 UPF being the highest. (According to one study, this is a very reliable

indicator of protection.) The clothing is expensive, however. The following are some tips for anyone:

- Everyone, including children, should wear hats with wide brims. (Even wearing a hat, however, may not be fully protective against skin cancers on the head and neck.)
- People should look for loosely fitted, unbleached, tightly woven fabrics. The tighter the weave the more protective the garment.
- Washing clothes over and over improves UPF by drawing fabrics together during shrinkage. An easy way to assess protection is simply to hold the garment up to a window or lamp and see how much light comes through. The less the better.
- Everyone over age one should wear sunglasses that block all UVA and UVB rays when in the sun.

Chemical Tanners

Some research suggests that melanin and dihydroxyacetone (DHA), the active ingredients in many self−tanning lotions, may help filter out UVA and UVB radiation and so be protective. More research is underway.

Role of Fats

One study indicated that people who reduced their intake of fat to 20% of their daily diet were significantly less likely than those on a high−fat diet to develop actinic keratosis, a common aging skin disorder that can also be a precursor to nonmelanoma skin cancer. Low−fat diets, however, appear to have no effect on basal cell carcinoma. In fact, some studies have suggested that certain fatty acids, such as those found in monounsaturated fats (e.g., olive and canola oils) or fish oils, may help protect the skin against sun−related diseases.

Antioxidants and other Natural Substances

Antioxidants are substances that act as scavengers of free radicals, mopping up unstable particles that, in excess, can damage the basic structure of cells, including their genetic material (DNA). Nevertheless, it is not yet known whether antioxidants can effectively protect against cancer, heart disease, premature aging, and other maladies. Among the most well−known antioxidants for the skin are vitamins C and E, and coenzyme Q10 (CoQ10).

Antioxidants are substances that act as scavengers of oxygen−free radicals, the unstable particles that can damage cells and which are implicated in sun damage and even skin cancers. Antioxidants in the skin are depleted when exposed to sunlight and must be replaced. The antioxidants studied for skin protection include vitamins A, C, E, selenium, coenzyme Q10 (CoQ10), and alpha−lipoic acid.

Topical Antioxidants. Although there are wide claims about the benefits of antioxidants for wrinkles when used in skin creams, to date, only vitamins E and C and selenium applied topically have been proven to have any benefits for reducing sun damage in the skin. Even with these antioxidants, however most available brands contain very low concentrations of them. In addition, they are also not well absorbed and they have a short−term effect. New delivery techniques, however, may prove to offset some of these problems.

- Vitamin E. Studies suggest that topical vitamin E, particularly alpha tocopherol (a form of vitamin E) cream decreased skin roughness, length of facial lines, and wrinkle depth. Studies on mice have also reported reductions in UV−induced skin cancer with its use.
- Vitamin C, or ascorbic acid. This is a very potent antioxidant and most studies on the effects of antioxidants on the skin have used this vitamin. In laboratory studies, large amounts reduced skin swelling and protected immune factors from sunlight. It may even promote collagen production. Vitamin C by itself is unstable, but products that solve the delivery problem are now available (e.g., Cellex−C, Avon's Anew Formula C Treatment Capsules, and others).
- Selenium in the form of L−selenomethionine has protected against sun damage and even delayed skin cancer in animal studies. It is not known if such benefits apply to people.

Oral Antioxidants. One small study found that taking a combination of vitamins oral C and E supplements may help reduce sunburn reactions, although the protection is much less than from sunscreens. (Taking the vitamins singly does not appear to have the same effect.)

Other Natural Substances. The following natural substances have antioxidant properties and are being tried for sun−protection:

- Both green and black tea and ginger appear to have properties that may provide some protection against skin cancers and photoaging. A 2001 study using extracts of topical green tea suggested that it might protect against ultraviolet damage. More research is warranted. Green tea skin care products are now available, but their

quality is unregulated.
- The substance silymarin, found in the milk thistle family (which includes artichokes), may inhibit UVB−promoted cancers in animals.
- In one interesting study, eating garlic protected animals very effectively against UVB damage by interfering with urocanic acid in the skin. Whether these results may be applied to humans, and what quantities of garlic might be beneficial, is still unknown.

Warning Note: A wide range of herbal products−−both oral and topical−−may contribute to dermatological problems. Some Chinese herbal creams have been found to contain corticosteroids, and some may contain mercury or arsenic contaminants have been reported in some Ayurvedic therapies. In addition, a number of oral herbal remedies used for medical or emotional conditions may produce irritation in reaction to sunlight (photosensitivity). The include but are not limited to St. John's Wort, kava, and yohimbe.

Experimental Agents

Ointments that Prevent Skin Cancers on a Molecular Level. Of interest are studies suggesting the compounds that target genetic mechanisms in the skin may prove to be beneficial ingredients in topical products (e.g., creams, lotions) that prevent skin cancers on a molecular level. They include the cytokine interleukin−12 and an enzyme called T4 endonuclease 5 (T4N5).

Specific Cholesterol−Lowering Drugs. Some interesting but preliminary reports suggest that specific cholesterol−lowering medications, including the popular drug lovastatin (Mevacor) and Apomine (a drug originally developed to treat high cholesterol) may have some benefits for preventing or even treating melanoma. Further research is needed, however, to determine if there is indeed a link between cholesterol and melanoma and if these and similar medications actually help prevent the disease.

Sunscreen Guidelines

In choosing a sunscreen, look at the ingredients. Preparations that help block UV radiation are sometimes classified as sunscreens or sunblocks according to the substances they contain. In general, sunscreens contain organic formulas and sunblocks inorganic formulas. However, the term sunblock is used less and less as sunscreens increasingly contain both kinds of ingredients:

- *Organic* formulas contain UV−filtering chemicals such as octocrylene, octyl salicylate, homosalate, and octyl methoxycinnamate (block UVB), avobenzone−Parsol 1789 (blocks UVA), cinoxate, ethylhexyl p−methoxycinnamate (blocks UVB and small amounts of UVA), oxybenzone, benzophenone−3 (blocks UVA/UVB). People should look for a wide−spectrum sunscreen that contains combinations of these ingredients and filter both UVA and UVB. Of note: para−amino benzoic acid (PABA), once a popular ingredient, is now used infrequently. It is not known if they have the same effects. PABA may actually *break down* in the presence of UV exposure and release harmful oxidants. And many people have an allergic reaction to it. Some products contain PABA derivatives, such as padimate O or octyl dimethyl PABA.
- *Inorganic* formulas contain the UV−blocking pigments zinc oxide or titanium dioxide. Zinc and titanium oxides lie on top of the skin and are not absorbed. They prevent nearly all UVA and UVB rays from reaching the skin. Older sunblocks are white, pasty, and unattractive, but current products use so−called microfine oxides, either zinc (Z−Cote) or titanium. They are transparent and nearly as protective as the older types. Microfine zinc oxide may be more protective and less pasty−colored than microfine titanium oxide.

Inexpensive products work as well as expensive ones with the same ingredients. Unfortunately, there are still no standards for sunscreens, and even those claiming UVA protection may offer very little. In one study, the average UVA protection from a wide range of brands was only 23%. In fact, the average protection on brands not making the claim was 37%!

Organic formulas and inorganic microfine oxides do not protect against *visible* light, which is a problem for people who have light−sensitive skin conditions, including actinic prurigo, porphyria, and chronic actinic dermatitis. Inorganic sunscreens that protect against visible light and are still cosmetically acceptable are now available in Europe, but not yet in the US.

Calculating the SPF

The sun protection factor (SPF) on all sunscreen labels is a ratio based on the amount of UVB (not UVA) radiation required to turn sunscreen− or sunblock−treated skin red compared to non−treated skin. For instance, people who sunburn in five minutes and who want to stay in the sun for 150 minutes might use an SPF 30. The formula would be: 30 (the SPF number) times five (minutes to burn) = 150 minutes in the sun.

Protection offered by sunscreens may be classified as follows:

- Minimal: SPF 2 to 11
- Moderate: SPF 12 through 29.
- High: 30+. (Although some sunscreens claim SPFs higher than 30, the added protection at such higher levels is insignificant.)

SPF Levels by Age Group

Certain groups should have higher or lower SPFs depending on age and other factors:

- Although sunscreens are safe in most toddlers and children, they should not be the first and only lines of defense. In fact, experts are worrying that by relying too much on sunscreen and not providing other protective measures, parents may actually be increasing their children's risk for melanoma. All young children should be well covered with clothing, sunglasses, and hats as the first line of defense against sunburn. Children should be kept out of the sun during peak sunlight periods. Sunscreens should not be used on babies younger than six months without consulting a physician.
- Older children and adults (even those with darker skin) benefit from using SPFs of 15 and over. Some experts recommend that most people should use SPF 30 on the face and 15 on the body.
- Adults who burn easily instead of tanning and anyone with risk factors for skin cancer should use at least SPF 30.

Timing and Amount of Application

Sunscreen or sunblock should be applied liberally as follows:

- Adults should include sunscreen with a daily skin regimen, even if going outdoors for only a short time.
- Apply a large amount to all exposed areas, including ears and feet. To achieve protection as indicated by the sunscreen's SPF, experts recommend half a teaspoon each for the head, neck, and each arm and a teaspoon each for the chest area, the back, and each leg.
- Apply initially 30 minutes before venturing outdoors for best results. (This allows time for the sunscreen to be absorbed. Then reapply every 15 to 30 minutes while being in the sunlight.
- Also reapply each time after exercise or swimming. (Choose a waterproof or water−resistant formula even if activities don't include swimming. Waterproof formulas last for about 40 minutes in the water, whereas water−resistant formulas last half as long.)
- Insect repellents reduce sunscreen SPFs by up to one−third. Use higher SPFs and very liberal application when applying both.

Possible Hazards of Sunscreens, Sun Avoidance, or Both

When used generously and appropriately, sunscreen products and sun avoidance help reduce the severity of many aging skin disorders, including squamous cell cancers. There are certain concerns, however.

Sunscreen Use May Not Protect Against Basal Cell and Melanoma Cancers−and May Even Increase the Risk. Although sunscreens help prevent squamous cell carcinomas and other skin disorders, sunscreens do not appear to provide protection against melanoma and some basal cell cancers. In fact, some studies have reported a *higher* association with sunscreen use and these skin malignancies, though not all studies report such negative results.

The reasons for this possible increased risk are unclear, though some theories include the following:

- Until recently, many sunscreens blocked only or predominantly UVB rays and not UVA, the more deeply penetrating rays now known to be especially dangerous. Studies then may not have reflected the effects of the broad−spectrum sunscreens now available, which block both UVA and UVB.
- People who apply sunscreens may feel safe and stay out longer during high sun−exposure hours than is safe. Even if a person doesn't sunburn, UVA rays can still penetrate the skin and do harm.
- People may not put on enough sunscreen. In fact, according to a 2002 study, people generally apply only 20% to 60% of the recommended amount, which can provide significantly less protection than the given SPF.(Of note, a 2003 study reported that when applied at the recommended amount, a broad−screen sunscreen prevents DNA damage from UV exposure. However, omitting it even once resulted in significant cell injury.)

Sunscreens Use May Increase the Risk for Health Problems Related to Sunlight Deficiencies. There is some major concern that underexposure to sunlight, due to the use of sunscreens or sun−avoidance measures, may produce other health problems, such as the following:

- Vitamin D Deficiency. Vitamin D is found in foods, but it is primarily manufactured a chemical reaction to ultraviolet B sunlight.

Vigorous sun−protection measures, then, may increase a person's risk for developing vitamin D deficiency. Vitamin D is important for prevention of rickets and osteoporosis and some cancers, including melanoma. People who need to avoid sunlight and whose diet is low in foods that contain vitamin D should check with their physician about taking supplements. People with darker skin are at higher risk for deficiencies from sun protection than those with whiter skin. (Note: vitamin D is toxic in high doses.)

- Other Cancers. Although sunlight is implicated in skin cancers, it is also associated with lower risks for breast, prostate, ovarian, and colon cancers. Some protection against these cancers may be related to vitamin D production by sunlight.
- Depression. Many people suffer from SAD (seasonal affective disorder), a form of depression that generally occurs in winter and is associated with exposure to less sunlight.

The bottom line is that some sunlight is important and even necessary for a healthful and high−quality life. Some experts recommend that adults may benefit from daily moderate tanning (20 to 30 maximum minutes of exposure during lower−risk hours) over a number of days to slowly build up pigment in the skin.

HOW IS MELANOMA DIAGNOSED AND ITS PROGNOSIS DETERMINED?

Identifying the Melanoma

An experienced physician should first rule out benign conditions that resemble melanoma, such as a noncancerous mole called a melanocytic nevi. In rare instances, a melanoma will be difficult to detect. For example, an uncommon form of melanomas called a myxoid melanoma may be mistaken for a benign skin disorder known as a myxoid fibrohistiocytic lesion. Another opinion from a second pathologist, computerized image processing, or advanced staining techniques may help to confirm the diagnosis.

Some doctors now employ dermoscopy (also called dermatoscopy or epiluminescence microscopy), which uses a hand−held scope−like device that enhances the suspected lesion. It is still not clear if such devices are any better than the naked eye of a trained professional. Of interest, however, was a 2002 study suggesting that it was very useful in identifying possible melanomas in suspicious nail abnormalities and therefore avoiding many painful biopsies in this area.

A recently developed Australian device (the Solarscan) may improve detection. It is shaped like a hair dryer and takes an image of the suspicious lesion; it then reads the image and compares it with a databank of melanoma images to help determine if it is cancerous. It can also store the image of lesion and compare it for changes with later images taken at subsequent check ups.

Biopsy

Biopsy of the Melanoma. Melanoma is diagnosed by biopsy (excision) of suspicious lesions. With this procedure, the physician will anesthetize the area around the lesion and, depending on size and site, remove all or part of it. The biopsy specimen will be sent to a lab for analysis, where a pathologist will take thin slices of the lesion and examine the cell structure under a microscope. If melanoma is found, it will be staged and its depth and probability of spreading will be assessed. [*See Box* Staging Melanoma.]

- Melanomas less than 4 mm thick suggest Stage I or II cancers, and the next step is to attempt to determine if they have spread or are likely to spread to the lymph nodes.
- Melanomas that are over 4 mm thick indicated later stages. In such cases, the lymph nodes are sometimes removed to attempt to prevent the cancer from spreading, although about 70% of these melanomas have already metastasized (spread).

Sentinel Lymph Node (SLN) Biopsy. When Stage I and II melanomas metastasize, they most often spread first to nearby lymph nodes. A procedure called sentinel lymph node (SLN) biopsy helps determine whether lymph nodes might be involved and how far it may have spread. SLN biopsy is now recommended for cancers that are thicker than 1 mm (millimeter) and generally unnecessary for those thinner than 0.75 mm (unless they are ulcerated). Although some evidence suggests this procedure may improve survival, no clinical trials have proven to date that this procedure improves the prognosis in melanoma.

This procedure involves the following:

- A tiny amount of a tracer, either a radioactively labeled substance (radioisotope) or a blue dye, is injected into the tumor site.
- These substances then flow via the lymphatic system into the so−called *sentinel node*. This is the first lymph node to which any cancer would spread.
- The sentinel lymph node and possibly one or two others are then removed and biopsied.

The results of the biopsy can help physicians decide whether to remove other lymph nodes or not. The choices are not always clear cut, however:

- If the sentinel node and others shows signs of cancer then the nearby lymph nodes are removed.
- If they do not, particularly in Stage I, then it is highly likely that the remainder of the lymph nodes will be cancer free and further surgery becomes unnecessary.

Controversy exists over the best approach for patients with Stage II cancers when the sentinel node test has found no evidence of cancer. These melanomas are usually between 1 mm and 4 mm thick, and tumors at this stage carry a risk for sending microscopic cancer cells out into the lymph system unnoticed. In such cases, removal of lymph nodes would probably have no impact on survival.

Biologic markers in blood tests may also prove to identify microscopic cancers if sentinel node biopsy results are uncertain [*see below*].

Secondary Tests

If melanoma has been diagnosed, the physician will perform others tests to see if the cancer has spread. They typically include the following:

- A chest x−ray.
- Blood tests that show high levels of lactate dehydrogenase suggest metastasis.
- Blood tests to assess liver function and other factors to help determine specific sites where the cancer may have spread.
- Advanced imaging techniques, such as computed tomography (CT) or positron emission tomography (PET), may also be used. PET is particularly accurate. One study reported that PET was able to diagnose melanoma that had spread even when other tests, including CT, did not. PET can also be very accurate for identifying recurrent melanomas.

Biologic Markers for Metastasis

Researchers are continually looking for other biologic factors, or markers, that would indicate whether the cancer had metastasized (even if sentinel node biopsies are negative). They also might suggest the severity of the cancer, which would help determine whether treatments should be more or less aggressive. A number of proteins and other factors detected in blood tests are showing promise as markers for microscopic metastasis. Examples include antibodies to MART−1, Melan−A, tyrosinase, and microphthalmia transcription factor (Mitf). Combinations of some of these factors may improve detection rates.

Risk Factors for Determining Prognosis

To reach a prognosis, other factors in addition to staging must be considered such as gender, age, and location of the melanoma. All cases are unique, however, and the presence of any of these factors should not discourage people from seeking all possible treatment options.

- Age. Patients older than 50 generally have the worst prognosis, perhaps because they tend to wait to see the doctor and thus have the thickest lesions.
- Gender. Although women and men fare equally well in the first two years after diagnosis, women appear to do a bit better after that time, particularly younger women. Prepubescent girls have a poorer prognosis than boys do (although it is very rare in children). This suggests, but does not prove, that estrogen may have some protective properties. The difference in gender may simply be due to women giving more attention to their skin.
- Melanoma Characteristics. Thick melanomas, those that are ulcerated (in which skin layers over the tumor appear indistinct on pathologic examination), and those that have invaded blood vessels tend to have a worse prognosis.
- Original Site. Patients with melanomas that arise within preexisting moles may fare better than those with new lesions. Some studies indicate that melanomas furthest away from the trunk, particularly the feet, were associated with poorer survival, but this may be because such areas are less likely to be observed and so such melanomas tend to be diagnosed at a late stage.
- Metastasis. Survival rates are worse if the cancer has spread, particularly to the gastrointestinal tract, liver, or lung. In any case, the more sites that the cancer has spread to, the poorer the prognosis.
- Regression. In some people, melanomas spontaneously stop growing for a time and may actually shrink in size, which is a favorable sign.

Staging Melanomas

If melanoma is diagnosed, health professionals have devised various methods for staging (assessing the severity of) the cancer. This report now uses the new staging system recommended by American Joint Committee on Cancer, which should improve the precision of predicting outcome and determining treatments. The stages use the following abbreviations:

- T = tumor. T is followed by a number to indicate thickness.
- N = node. N is followed by numbers to indicate the number of lymph nodes involved.
- M = metastasis.

In addition a stage will include whether the melanoma is *ulcerated* or not, an indication of severity. Ulceration is determined if skin layers over the tumor appear indistinct under the microscope.

In general, the thicker the lesion and the farther the cancer has spread, the higher the assigned stage. The higher the stage, the worse the long−term outlook.

The earliest melanomas, which do not penetrate beneath the surface of the skin and are known as melanoma in situ, are highly curable and are called stage 0 or not given a stage. Others are staged as follows:

Stage I. Cure rates are excellent, 80% to 100%, with surgical removal, since they are least likely to have spread

- Stage 1A. Tumor has not spread to the nodes. It is less than 1 mm and is not ulcerated.
- Stage IB. Tumor has not spread to the nodes. It is less than 1 mm, but is ulcerated, or the tumor is between 1.01 and 2 mm but is not ulcerated.

Stage II. Melanomas can be cured, but the success rate (60% to 80% five−year survival) lags behind that of Stage I because a small number of cancer cells may have escaped from the original lesion and seeded distant sites. In addition to surgery, other forms of therapy may be recommended.

- Stage IIA. Tumor has not spread to the nodes. It is between 1.01 and 2 mm and is ulcerated, or it is 2.01 to 4 mm without ulceration.
- Stage IIB. Tumor has not spread to the nodes. It is between 2.01 and 4 mm and is ulcerated or greater than 4 mm without ulceration.

Stage III. Patients have a 30% to 70% five−year survival.

- Stage IIIA. Tumor has spread to 1 node and it is up to 4 mm without ulceration. Sentinel biopsy has detected microscopic evidence of tumor cells in the node (micrometastasis).
- Stage IIIB. Tumor is up to 4 mm without ulceration and has spread to one node or there is evidence of micrometastasis in two nodes.
- Stage IIIC. Tumor is any thickness and ulceration may or may not be present. It has spread to 2 or 3 nodes. Additional "satellite" melanomas on the skin more than 2 cm (about an inch) from the original lesion may be present; these are sometimes called "metastases in transit."

HOW IS MELANOMA TREATED?

Treatment depends on various factors, including the following:

- The site of the original lesion.
- The stage of the cancer.
- The patient's age and general health.

Treatment options include the following:

- Surgery is performed at every stage to remove the melanoma cancer cells.
- Melanoma that has spread to lymph nodes or additional nearby sites usually requires additional forms of treatment including chemotherapy, immunotherapy, and radiation therapy.
- Advanced melanoma that has spread to distant sites often cannot be cured, although surgical removal of metastatic tumors may provide some benefit by easing pain, increasing the general quality of life, and lengthening survival. Patients should seek to enter clinical trials, studies that examine new immunotherapies (vaccines, cytokines), gene therapies, chemotherapy combinations, or other treatments.

Surgery

Surgery is the primary treatment for all stages of melanoma.

Removal of the Melanoma. Some or all of the melanoma is often been removed during the biopsy. If cancerous tissue still remains after a diagnosis of melanoma, a surgeon will cut away additional tissue from the surrounding area to remove any stray cancer cells.

Mohs micrographic surgery was developed to allow meticulous surgical removal of skin tissue. This procedure involves the following:

- Very thin layers are removed one at time, with each layer examined immediately under a microscope.
- When the layers are shown to be cancer free, the surgery is complete.

Because the physician needs to be certain that all cancer cells are removed, in some cases the surgical area required is very wide and requires plastic surgical techniques. The amount of tissue removed depends on the size, depth, and degree of invasion:

- Stage I lesions that are less than one millimeter deep require the smallest excisions, usually about one centimeter (2/5 inch) off each side and downward from the original lesion.
- For melanomas up to 4 mm thick, a margin of 2 cm (almost an inch) appears to be safe.
- Thicker lesions require wider excisions.

It used to be customary to remove a large area, regardless of the stage of cancer. This potentially disfiguring approach has been abandoned because studies have shown that excising wider margins does not improve survival. Nevertheless, sometimes skin grafts may need to be taken from other body sites to help cover the wound.

Of note: recurrence rates are very high with lentigo maligna (LM) after conservative surgery. Although this is a very slowly progressive condition, LM can develop into melanoma. Most of these lesions appear on the face and neck, so extensive surgery can be disfiguring. Patients should discuss with their physician carefully staged surgery to remove all diseased tissue with as little cosmetic harm as possible.

Lymph Node Removal. If there is evidence that melanoma has spread to nearby lymph nodes but has not spread beyond, removing them may improve local disease control and might even improve survival in selected patients, although this is an ongoing area of investigation. At this time, Australian guidelines recommend lymph node removal only for patients younger than 60 years of age with 1 to 4 mm thick primary melanomas on the trunk. [*See* Biopsy *under* How Is Melanoma Diagnosed and Its Prognosis Determined?]

Surgery for Metastatic Melanoma. In some cases, surgical removal of distant tumors may be possible and prolong survival, since often in melanoma the cancer spreads first only to a single site, such as the lung or the brain.

Cryosurgery. Cryosurgery freezes skin tissue and destroys it. This procedure is not useful for most melanomas, but it might have some value in specific situations. For example, it may be effective for smaller melanomas in the eye, a location that is difficult to treat with traditional surgery. It may be useful to eliminate residual cancer cells after standard surgery for lentigo maligna melanomas, an atypical form of melanoma that has a wide surface and is difficult to treat.

Chemotherapy

Chemotherapy is often used to treat recurrent or metastatic melanomas. The drugs are not intended as a cure but can prolong life and improve its quality.

Drugs Used. The following are some of the agents used to treat melanoma. They may be used alone or in combination under specific situations.

- Methylating agents, which impair the ability of cancer cells to divide, include dacarbazine (DTIC), temozolomide (TMZ), and procarbazine. To date, dacarbazine is the only drug approved for melanoma. Temozolomide, an oral drug, may be comparable and improve quality of life. Because it can cross the blood–brain barrier (unlike dacarbazine), temozolomide is showing promise in preventing metastasis to the brain. It may also have some benefits in treating cancers that have already spread to the brain.
- Nitrosoureas, which include carmustine (BCNU) and lomustine (CCNU) are often used.
- Taxanes, such as docetaxel (Taxotere) and paclitaxel (Taxol), are showing some low–level activity against melanoma. Docetaxel is being studied in combination with other drugs.

Many other drugs and combinations used to boost drug effectiveness or minimize toxicity are under study. They include, vincristine, vinblastine, cisplatin, and tamoxifen.

Side Effects. Side effects occur with all chemotherapeutic drugs. They are more severe with higher doses and increase over the course of treatment.

Common side effects include the following:

- Nausea and vomiting. Drugs known as serotonin antagonists, especially ondansetron (Zofran), can relieve these side effects in nearly all patients given moderate drugs and most patients who take more powerful drugs. In one study, a combination of dexamethasone (a corticosteroid) with ondansetron taken within 24 hours of chemotherapy achieved either a major or complete reduction in nausea and vomiting.
- Diarrhea.
- Temporary hair loss.
- Weight loss.
- Fatigue.
- Anemia. Erythropoetin stimulates red blood cell production and can help reduce or prevent this side effect. It is available as epoetin alfa (Epogen, Procrit) and darbepoetin alfa (Aranesp). Aranesp persists longer in the blood than epoetin alfa and so requires fewer injections.
- Depression.

Serious short– and long–term complications can also occur and may vary depending on the specific agents used. They include the following:

- Increased chance for infection from suppression of the immune system.
- Severe drops in white blood cells (*neutropenia*). Certain agents, such as taxanes, pose a higher risk for this than other chemotherapeutic drugs. White blood cell count may be improved with the addition of a drug called granulocyte colony–stimulating factor (either filgrastim or lenograstim).
- Liver and kidney damage.
- Abnormal blood clotting (*thrombocytopenia*).
- Allergic reaction.
- Menstrual abnormalities and infertility in women. A natural hormone medication called a gonadotropin–releasing hormone analogue that puts women in a temporary pre–pubescent state during chemotherapy may preserve fertility in some women.
- Rarely, secondary cancers such as leukemia.
- Problems in concentration, motor function, and memory, which may be long–term.

Benefits of Chemotherapy. About 20% of cancers shrink in response to one or more of these drugs, but the effects last only between three and six months. If the tumors completely disappear, the cancer may stay in remission much longer, but in virtually all cases it returns.

Chemotherapeutic Regional Perfusion

Chemotherapeutic regional perfusion (also called isolated limb perfusion) allows the administration of very high–dose chemotherapy. It is often used effectively for metastasized or recurrent melanoma that occurs on the arm or leg. (It does not appear to be useful for preventing metastasis after a first occurrence of melanoma in one of these locations.)

This technique involves the following:

- The blood supply to the limb with melanoma is temporarily interrupted using a tourniquet and then rechanneled through a heart–lung machine.
- Anticancer drugs (usually with the drug melphalan alone or in combination with other drugs) are added to the blood in doses up to ten times the standard doses.
- The blood is then heated to enhance the drug's potency.
- The chemo–infused blood is then sent directly to the melanoma site, minimizing the likelihood of drug toxicity.
- Adverse effects occur in less than 1% of cases and include the following:
- Severe problems in the treated limb; in rare cases amputation is needed.
- Drug leakage into the general blood stream. This can severely reduce white blood cells and lead to serious infection.

Other treatments being explored include combinations of melphalan with immunotherapy drugs, notably interferon and tumor necrosis factor. Complete response rates as high as 90% have been reported in some patients, but more research is needed to verify the safety and effectiveness of this treatment.

In addition to arms and legs, perfusion techniques have been tested for the pelvis, head, neck, skin of the breast, and even the abdomen.

Immunotherapy

Immunotherapy uses drugs to boost the patient's own immune system. This treatment was developed after experts observed that in some melanoma patients, the tumor temporarily stopped growing and shrank, apparently in response to a very effective natural immune response. This phenomenon is very rare, though it appears more often in melanoma than in other cancers. Adjuvant immunotherapy (used after surgery) is proving to be helpful in melanoma patients at

high risk of recurrence.

Cytokines. Specific powerful immune factors called cytokines, particularly those known as interferons, are being used to develop therapies for metastatic melanoma. These agents are typically administered with chemotherapy agents, with other immunotherapies, or both. (If cytokines are prescribed as single−agent therapy they are ineffective at lower doses while at higher, effective doses they become very toxic.) The results of one 2002 report, for example, reported that adding interferons and interleukins to chemotherapy doubled the five−year survival for advanced melanoma, from 5% to 10%. Side effects are greater with this approach but they are manageable. A number of other cytokines and combinations are being investigated.

- Interferon alpha−2b (Intron) is a genetically engineered agent (called a recombinant drug). It is given by injection and is the only FDA approved immunotherapy for late stage melanoma. Although a 2002 analysis of eight studies reported no overall survival benefits, specific patients may benefit and different schedules, doses, or combinations with other agents may still prove to have advantages. The most common side effects are fatigue, depression, and flu−like symptoms, which can be severe. (Starting an antidepressant, such as paroxetine (Paxil), several weeks before interferon therapy may help prevent depression.) Some patients have reported eye problems in the retina.
- Different forms of interferons, such a long−acting formulation called pegylated interferon and natural human interferon are under investigation. In one 2002 study of patients with Stage IIB or III melanoma who were first treated with two rounds of dacarbazine chemotherapy, low−dose natural interferon led to five−year relapse−free survival in 42%, compared to only 17% in those who did not receive any adjuvant interferon immunotherapy.
- Interleukin−2 (Proleukin) is a hormone−like substance that stimulates the growth of cancer−fighting white blood cells. High−dose interleukin−2 has obtained regression of metastatic melanoma in 15% to 17% of patients. The drug, which is injected, can have significant side effects, including very low blood pressure, heart rhythm abnormalities, severe infections, and shortness of breath, but they are manageable and nearly always reversible.
- Another injectable cytokine under study is granulocyte−macrophage colony stimulating factor (GM−CSF, Leukine, Sargramostim), which boosts production of immune cells in the blood and bone marrow. An inhaled form of the drug is also being tested for melanoma that has spread to the lungs.

There is some concern that these treatments may actually produce substances called reactive oxygen species (ROS), which in turn *inactivate* immune cells that fight cancer. Histamine (Maxamine) is a powerful inhibitor of ROS, and researchers are testing it in combination with interleukin−2 cytokine therapy. In one study, the added benefits of histamine were modest except in patients with liver metastatic; in these patients, survival improved by 129 days, which was significant.

T−Cell Therapy. Some promising work uses T−cell therapy, which involves extracting white cells called tumor−infiltrating lymphocytes (TILs) from the patient's tumors. Specific TILs from this batch are then expanded. The selected TILs target specific molecules in the melanoma cells. In one study, patients were given chemotherapy that depleted their own lymphocytes, and the specially prepared TILs were then reinfused back into the patients. In the small study, 10 out of 13 patients had a substantial response with two patients experiencing over 95% tumor regression. There were significant adverse effects and not all patients benefited. Still, the study suggested a promising path for additional research.

Vaccine Immunotherapy. Vaccine immunotherapy uses melanoma−associated cells to serve as antigens (foreign proteins that antibodies in the immune system specifically seek out and attack). Part of the problem in developing a vaccine is that scientists are still unsure exactly which antigens are most likely to elicit an immune response that effectively kills cancer cells. Furthermore, antigens that are effective in one person may not be effective in another.

Many vaccines are now in advanced stages of development. Some are promising, but to date, none has yet emerged as an important weapon in treating advanced melanoma.

Some vaccines employ one or a few antigens (so−called monovalent vaccines); others consist of a "cocktail" of antigens (so−called polyvalent vaccines), which may be more likely to contain the right antigen targets.

Vaccines are often enhanced by substances or procedures called adjuvants (e.g., SAF−M, viruses, dendritic cells) to further boost effectiveness.

Most use one of two basic approaches, autologous and allogeneic, or a combination of the two (called a hybrid):

- Autologous vaccines are made from the patient's own cancer cells or parts of them. This produces a very specific immune response that can target the patient's cancer precisely. Some, such as Oncophage (HSPPC−96) and M−Vax, are showing promise in early trials and are undergoing additional testing. One problem with the autologous approach is that there is no way to scientifically assess outcome or even guarantee repeated success since each vaccine is unique to the individual patient. This approach is also appropriate only for select patients.

- Allogeneic vaccines purify and use antigens that may be derived from proteins from tumor cells, genetic material, or even bacteria. Such antigens are anchored on melanoma cells and stimulate an immune attack by powerful antibodies. A number of investigative vaccines (e.g., Melacine, Canvaxin) use multiple antigens (called allogeneic polyvalent vaccines) to reduce the risk for eventual tumor resistance to a single antigen. Studies are suggesting that the polyvalent vaccines may improve long−term survival rates in some patients. For example, Canvaxin achieved five year survival rates of 39% compared to 20% for unvaccinated patients. It is not yet clear if they are superior to high−dose interferon, but research continues.

Unlike chemotherapy, in which the drugs directly attack the tumor and shrinkage occurs quickly, the use of vaccines requires the body to build up its own defenses. It can take months before beneficial effects occur, but when they do, tumor reduction is much more lasting than with chemotherapy. Vaccines also seem to have fewer side effects than interleukin and interferon.

Antisense Compounds. Of interest is therapy that employs *antisense* compounds, which can prevent defective cancer genes from being translated into proteins that cause abnormal cell proliferation. Compounds are being investigated for use against mutations in bcl−xL and bcl−2 genes that block *apoptosis,* a natural process by which cells self−destruct and so do not become cancerous. A 2000 study using a combination of dacarbazine with oblimersen (G3139, Genasense), an antisense agent that turns off bcl−2 produced, achieved complete remission in one patient and partial responses in 43%. Late phase trials are in process.

Monoclonal Antibodies (MAb). Antibodies are natural substances produced by immune cells that home in and destroy cancer cells. Scientists are identifying specific antibodies that may attack melanoma cells and cloning them to create monoclonal antibodies. MAbs have shown promise for other cancers and are now being tested for melanoma, often in combination with vaccines and other forms of immunotherapy.

Other Experimental Therapies

Tetracyclines. Chemically modified tetracyclines, a common antibiotic, have been shown to modify metalloproteinase, an enzyme in the skin that promotes skin cancers, including melanoma.

Anti−Angiogenesis Agents. A number of trials are studying agents that block *angiogenesis*, which is the formation of new blood vessels. A tumor can fuel its own growth with angiogenesis. Thalidomide (Thalomid) is one of the most important anti−angiogenesis agents under investigation for melanoma. This agent had gained notoriety in the 1960s because of devastating birth defects in the children of women who took it during pregnancy. It not only has anti−angiogenic activity but also other anti−tumor effects when given concurrently with chemotherapy (e.g., temozolomide, dacarbazine). Several studies indicate that some cases of advanced melanoma may respond to thalidomide. A thalidomide derivative (Revimid) and Endostatin, another anti−angiogenesis drug, is also undergoing testing.

Herpes Virus. In a small study in five patients, injection of a modified version of the herpes virus (HSV1716) into metastatic melanomas caused cancerous cells, but not nearby healthy tissue, to die.

Radiation

In general, radiation is used to help relieve pain and discomfort caused by cancer that has spread or recurred. Radiation is not used as often for treating melanoma as it is for other forms of cancer because melanoma cells tend to be more resistant to its effects. It may be useful in some cases, however.

- In some patients with tumors less than 3 cm deep, however, radiation may help slow down metastasis when combined with a super−heating process using microwaves.
- Brachytherapy, in which radioactive seeds are implanted close to the tumor, has also been used with success for melanoma of the eye.
- Lentigo maligna may sometimes be treated successfully with specific radiation treatments called soft, or Grenz, x−rays.
- Radiotherapy using a so−called gamma knife (very focused gamma radiation) is also effective for cancer that has metastasized to the brain, in some cases halting the growth and, in rare situations, even eliminating it.

WHERE ELSE CAN HELP BE FOUND FOR PEOPLE WITH MELANOMA?

The Skin Cancer Foundation (www.skincancer.org). Call (800−SKIN−490).

American Academy of Dermatology (www.aad.org). Call (847−330−0050).

American Society for Dermatologic Surgery (www.asds−net.org).

American Cancer Society (www.cancer.org). Call (800−ACS−2345).

American Society for Dermatologic Surgery (www.asds−net.org). Call (847−965−0090).

National Cancer Institute (www.cancernet.nci.nih.gov).

Clinical trials for melanoma can be found at (www.clinicaltrials.gov).

Centers for Disease Control and Prevention (www.cdc.gov/nccdphp/dcpc/nscpep/skin.htm). Call (888−842−6355).

National Comprehensive Cancer Network (www.nccn.org). Call (215−728−4788).

American Society for Clinical Oncology (www.asco.org). Call (703−299−0150).

The Environmental Protection Agency provides information on the UV Index (www.epa.gov/sunwise/overview.html). Call (202−564−9361).

Melanoma Patients' Information Page (www.mpip.org).

Sponsored site affiliated with American Academy of Dermatology (www.skincarephysicians.com/melanomanet/index.html)

University of Pennsylvania sponsors a cancer site at (www.oncolink.com).

Find a list of cancer trials at (www.cancer.gov/clinicaltrials).

Find a dermatologist at (www.aad.org/findaderm_intro.html).

The following two companies offer sun−protective clothing. Our editors have not reviewed their products. Other companies also offer similar products.

Sun Precautions (www.solumbra.com). Call (800−882−7860).

Sun Protective Clothing (www.sunprotectiveclothing.com). Call (800−353−8778).

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