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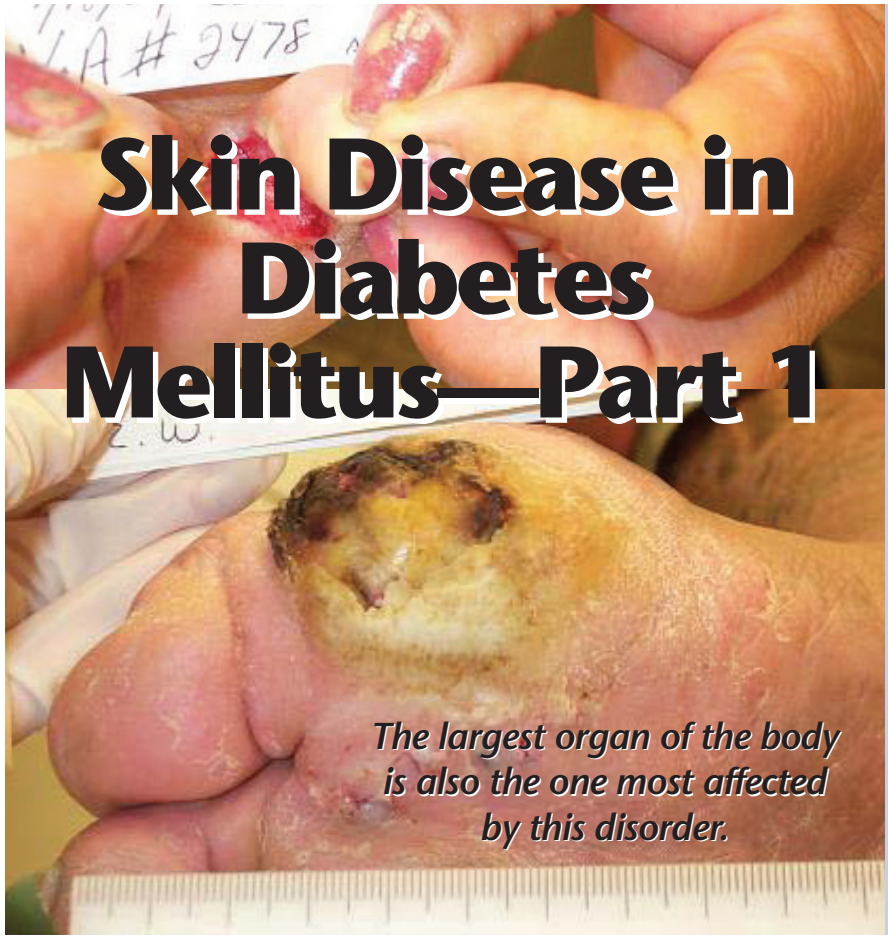

Skin Disease in Diabetes Mellitus—Part 1

Objectives

1. To clarify the dermatologic entities that podiatric physicians encounter.

2. To delineate the predominant biochemical causes of skin and nail changes in the diabetic and to understand the effects of abnormal glucose metabolism on the skin and nails.

3. To appreciate the diseases that have diabetes as a component and the dermatologic manifestations of those diseases.

4. To explain the bacteriological relationships between colonization, infection and the diabetic patient's host defenses.

5. To identify common diabetic foot infections.

6. To understand the role of antibiotics as they relate to opportunistic infection and superinfection in the diabetic patient.

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By Kenneth B. Rehm, DPM

Introduction

Diabetic patients presenting with lower extremity skin problems are among the most common occurrences that podiatric physicians encounter. Further, it is common knowledge that over one-half of all foot problems that people with diabetes present with include involvement of the skin and/or the toenails. This article is designed to clarify these dermatologic entities.

Diabetes mellitus has a significant effect on the skin and nails. Dermatologic manifestations in diabetes mellitus are universal, the prevalence approaching 100%. The findings range from the initial clini-

Continued on page 196

Diabetes Mellitus...

cal presentation to the expressions of long-term involvement, from commonplace to life-threatening complications. The clinical dermatological manifestation of the disease is directed in various ways but is thought to be universally influenced by the effect that the attachment of glucose to protein has on the structure and function of that protein. The increased cross-linking of collagen in diabetic patients is responsible for the fact that the skin is commonly thicker in diabetics than in non-diabetics (figure 14). Complex glycosylation end-products are thought to be responsible for the yellowing of the skin and nails (figures 11, 14).

Erythema of the face or the periungual tissues is thought to be a result of engorgement of the post-capillary venules in the papillary dermis secondary to the increased viscosity of blood due to stiff red blood cell membranes. An astute wound clinician is able to use these skin changes as a valid clinical indicator of the patient's current condition, as well as his/her past metabolic status and the control of his/her hyperglycemic state. Perceptive recognition of the subtleties of this clinical presentation is a valuable aid in the prevention and treatment of not only the devastating dermatological effects of the disease, but the complications of the disease in general.

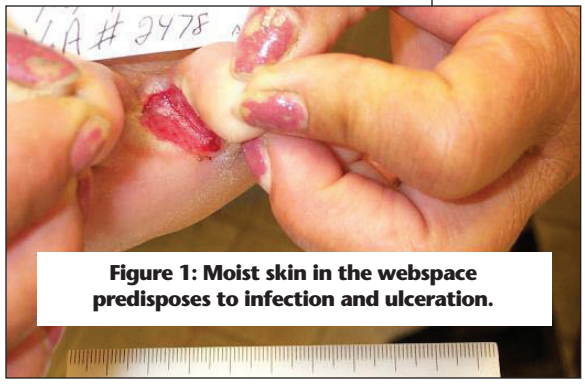

Figure 1: Moist skin in the webspace predisposes to infection and ulceration.

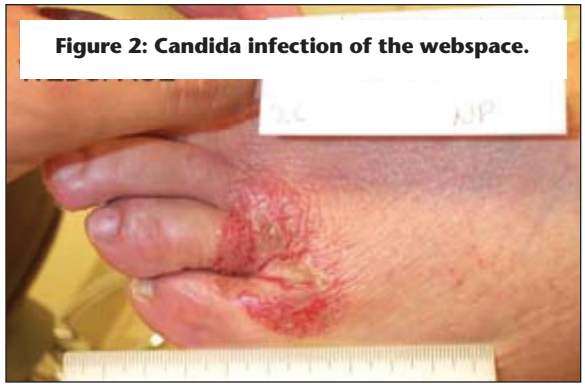

Figure 2: Candida infection of the webspace.

The Biochemistry of Dermatological Changes

The predominant biochemical cause of diabetic-related changes in the skin involves the attachment of the glucose molecule with many proteins, including hemoglobin. This is termed non-enzymatic glycosylation. The result of this union produces stable covalent products, which results in different physical and chemical properties than that of the original proteins. Most proteins evaluated seem to be involved in this process.

When glucose is in solution, it exists as a stable pyranose ring that is in equilibrium with the open chain aldehyde form. The NH2 group of the protein (either on the epsilon-amino group of the amino acid lysine or on the alpha-amino group of the N-terminal amino acid) combines with the double-bonded oxygen of the aldehyde, resulting in a Schiff base or aldimine. The Schiff base may reconfigure, resulting in the formation of a ketoamine.

Complex glycosylation end-products are thought to be responsible for the yellowing of the skin and nails.

Amador Rearrangement

This process is called the Amador rearrangement and the ketoamines are termed Amador products. The Amador products react with amino groups on other proteins to form glucose-derived intermolecular cross-links. This results in color changes of collagen that are confirmed by spectrophotometric measurement to correlate with diabetes-related complications. Among the advanced glycolysation end products that have been identified in the skin is a yellow imidazole compound and the amino acid pentosidine, which has been demonstrated to correlate with a score of diabetic complications. Non-enzymatic glycosylation of the red blood cell membrane is thought to cause stiffness in the erythrocyte of diabetics. Non-enzymatic glycosylation of collagen results in increased stiffness in collagen and resistance to normal enzymatic degradation.

Non-Enzymatic Glycosylation

To a minor extent, non-enzymatic glycosylation occurs at normal blood sugar levels and could be responsible for some of the mechanical changes of collagen and skin, which are characteristic of the aging process. This process, however, is apparently accelerated with diabetes mellitus and the resultant changes in solubility and tertiary structure of proteins could be responsible for many complications of the disease.

Clinically, non-enzymatic glycosylation results in alterations of the structural stability of the skin because of the change in the quality of the keratin and collagen formation (figures 3, 4, 7, 8, 14). These alterations predispose the diabetic to increased callus formation. Although keratin and collagen disturbances have been noted in diabetics that are normoglycemic, they are most commonly related to elevated blood glucose levels making the tissue rigid, inflexible, and more resistant to normal collagenase digestion. Such glycosylated keratin will build up easier and more abundantly as a result of repetitive pressures. It will not shed from the superficial layers of the foot and therefore builds up hyperkeratosis on the plantar walking surface and ultimately causes a plantar ulceration (figures 3, 12, 13). The most destructive lesion in the

Continued on page 197

skin of the diabetic is a neuropathic plantar ulceration.

One researcher describes several steps in the development of a neuropathic plantar ulceration in the diabetic foot.

1. The initial hyperkeratotic lesion (figure 13)
2. A weakening and breakdown of deeper tissues, with continued repetitive pressure (figure 4)
3. Eventual cavity formation that fills with blood (figure 15)
4. Enlargement to the point of rupturing forming an ulceration (figure 3)

Dermatologic Manifestations of Diseases Associated With Diabetes

It is important to realize that when a patient presents with diabetes and also a dermatologic problem, that problem may not be directly related to the diabetes but to another disease process. The following are examples of such diseases.

Maturity onset diabetes of youth syndrome may have an autosomal dominant inheritance pattern. This appears to be common in individuals from India and in Afro-Americans. The dermatologic association with this syndrome is facial flushing that is induced by chlorpropamide and alcohol, the combination found in sherry, among other alcohol-related substances. This flushing is significant in that it could be bothersome to the person, but even more important, it seems to be a marker for other diabetic complications.

Hemochromatosis

Hemochromatosis is often caused by an autosomal-recessive gene. Persons with this genetic syndrome often have insulin resistance and diabetes mellitus in association with manifestations of iron overload, such as bronzing of the skin. The sequelae of iron overload are preventable through simple phlebotomy. It is therefore important to screen all first-degree relatives of patients with hemochromatosis for abnormal iron metabolism by measuring transferring saturation and ferritin levels.

In a study of other skin manifestations of hemochromatosis, there was a high frequency of ichthyosis-like states and koilonychias, a condition characterized by a flattened nail that has concavities, also known as a spoon nail. An association with necrobiosis lipoidica and a black keratinous cyst has been reported.

Hemochromatosis is often caused by an autosomal-recessive gene.

Porphyria Cutanea Tarda

Porphyria cutanea tarda (PCT)is a common condition seen in diabetes mellitus. It is characterized dermatologically by photosensitivity on exposed areas and bullae on the dorsum of the hands. If bullae develop on exposed feet, it is reasonable to assume that this might be a manifestation of PCT. A feature of PCT is also hypertrichosis.

Myxedema

Myxedema, causing puffiness of the face and pre-tibial edema, can be associated with diabetes mellitus.

Lipid Abnormalities

Lipid abnormalities associated with diabetes can present a myriad of skin changes including those associated with lipodystrophy.

Acanthosis Nigricans

Acanthosis nigricans (AN) is characterized by velvety to verrucous-like hyperkeratotic, hyperpigmented plaques that are bilaterally symmetric (figure 5). These plaques are most commonly found on the neck, in the flexural areas and the axillae. The inconsistency of cutaneous involvement, however, is striking. The clinical presentation can vary from subtle hyperpigmented spots and papillary thickening that affect only a few areas to an aggressive, deeply pigmented verrucous process that could involve the entire integument including mucous membranes, palms and soles. Distinguishing this disorder from other verrucous-like lesions is the presence of hyperkeratosis, papillomatosis, areas of acanthosis that may alternate with areas of skin atrophy, and increased melanin in the basal epidermis as documented through the use of light microscopy. It is this author's experience that AN could be stimulated by the develop-

Continued on page 198

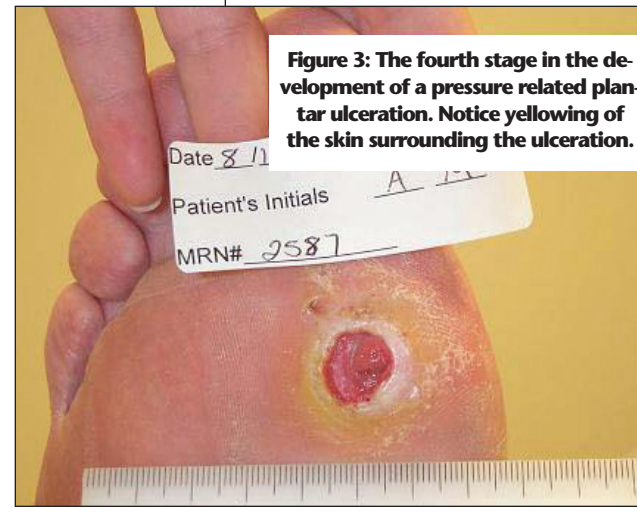

Figure 3: The fourth stage in the development of a pressure related plantar ulceration. Notice yellowing of the skin surrounding the ulceration.

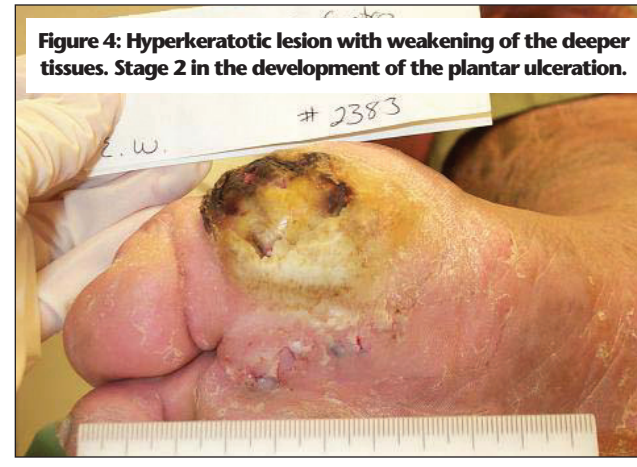

Figure 4: Hyperkeratotic lesion with weakening of the deeper tissues. Stage 2 in the development of the plantar ulceration.

ment of a plantar wound and involves the wound edges, and could interfere with its healing.

The relationship between insulin resistance and acanthosis nigricans is well established and especially clear. High plasma levels of insulin, stimulated by the non-responsive receptor sites, are thought to contribute to the development of AN. Many syndromes associated with AN have been linked to the presence of some form of insulin resistance.

These include the following:

1. Alström syndrome
2. Ataxia-telangiectasia
3. Bloom syndrome
4. Capozucco syndrome
5. Crouzon's disease (craniofacial dysostosis)
6. Lawrence-Seip syndrome (total lipodystrophy)
7. Leprechaunism
8. Prader-Willi syndrome
9. Rabson's syndrome
10. Rud's syndrome
11. Syndrome of acral hypertrophy and muscle cramps
12. Polycystic ovary disease (Stein-Leventhal syndrome)

Endocrine disorders associated with insulin resistance and acanthosis nigricans:

1. Acromegaly
2. Ovarian hyperthecosis
3. Addisonism
4. Cushing's Disease
5. Hypothyroidism
6. Pineal hyperplasia

The relationship between insulin resistance and acanthosis nigricans is well established.

Medications associated with acanthosis nigricans and possible insulin resistance:

1. Nicotinic Acid
2. Diethylstilbestrol
3. Glucocorticoids

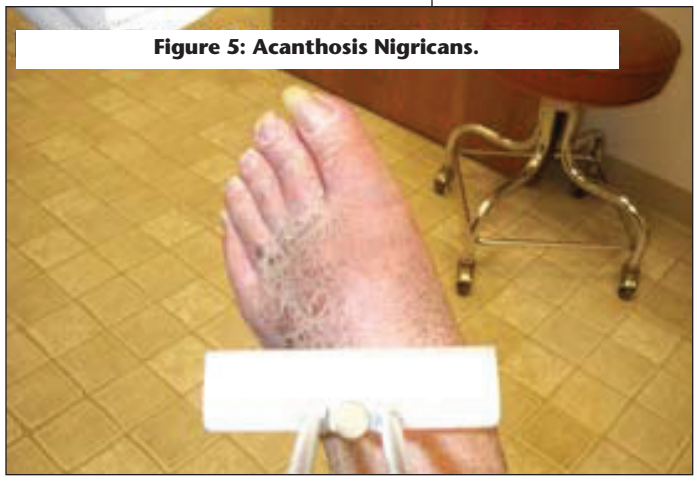

Figure 5: Acanthosis Nigricans.

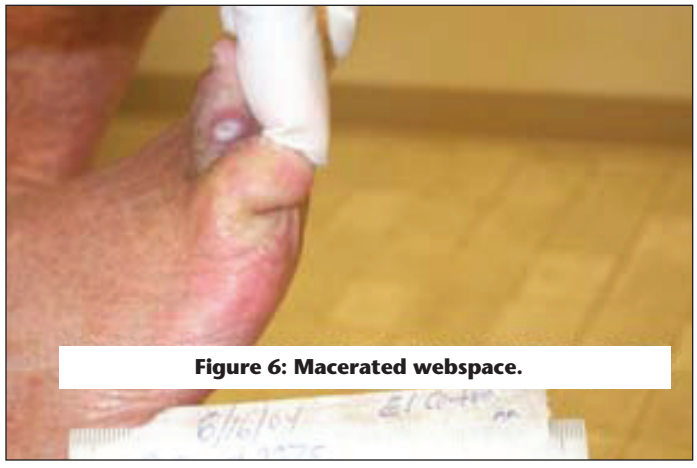

Figure 6: Macerated webspace.

Cutaneous Infections in Diabetes Mellitus

Bacteriology of the Skin

A discussion of infections of the diabetic foot must take into consideration two important pathogenic features: 1) the underlying metabolic disorder with its associated degenerative complications; and 2) the bacteriologic flora of the lower extremity. This discussion must consider the microbial ecology of the human skin and the relationships between colonization, infection and the diabetic patient's host defenses against infection.

Non-enzymatic glycosylation and its effect on skin characteristics and the effect that autonomic neuropathy has on the dryness and stiffness of the skin are important effects of the underlying metabolic disorder and participate in the susceptibility for infection (figure 8).

Variations in the bacterial flora of the lower extremity must be discussed to fully understand skin markers that relate to diabetic lower extremity infections. Different areas of the lower extremity are populated by different complex and changing bacterial and fungal flora. This is primarily due to these different environments, each of which predispose to different types of microbial colonization. On the dry portions of the lower leg and ankle, the flora is quite restricted (about 1000 bacteria per square centimeter) because of the physical and chemical conditions on the surface.

Microbial Growth and Survival

Microbial growth and survival are negatively influenced by the following factors. Lower environmental temperatures create a less than optimal environment needed for human pathogens to thrive. The presence of metabolic products of the skin (e.g., fatty acids) have direct antimicrobial chemical effects and predispose to extremes of pH (especially acidity) and ionicity on the skin surface. In addition, the relatively arid surface of the dorsum of the foot and the lower leg and ankle allows only those microbes resistant to drying able to thrive.

The increased density and the variety of organism species in the toe webs, which is even greater than that which is found in the axilla (where more than one million bacteria per square centimeter can be recovered) attest to the critical importance of moisture in bacterial and fungal growth. The toe webs typically are a nidus for the pres-

Continued on page 199

ence of Corynebacterium minutissimum, Pseudomonas, Herellea, Candida, nonlipophilic diphtheroids, and enterobacteria (figure 1). This contrasts markedly with the coccal and lipophilic diptheroid flora of the lower calf and ankle. When the feet are too moist they favor increased microbial density as well. In addition, this higher microbial density of the intertriginous areas results in a higher surface pH than anywhere else in the body because the urea and other nitrogenous substances are metabolized, resulting in ammonia formation. Normally, the low availability of carbohydrate substrates prevents acid production.

Skin pH

Since healthy skin has a slightly acid pH, a more alkaline pH on the skin surface, as is the case with increased microbial density and exposure to substances with an alkaline pH (such as many commercial cleansers and hand soaps) contributes to interruptions of skin integrity. Once the skin integrity is disturbed, a homeostatic repair mechanism is stimulated that causes the rapid repair of barrier function. Continued exposure to a high microbial load, alkaline substances, or continued exposure to unfavorable environmental factors will slow down repair by inhibiting normal skin acidity.

Interactive Flora

The significance of interacting flora is exemplified most on the skin of the toe webs, as is the case in many diabetics, where combined colonization by dermatophytes, Staphylococcus aureus, and Candida albicans intensifies itching and aggravates the inflammatory response(figure 1, 2, 6).

The low temperature of the distal lower extremity, especially in diabetics, has a significant effect on which microbial flora will affect it, since many of the common bacteria and fungi fail to grow at temperatures much below 37 degrees C and Mycobacterium marinum and the dermatophytes can flourish in areas where the temperature seldom exceeds 30 to 31 degrees C.

The toe webs typically are a nidus for the presence of Corynebacterium minutissimum, Pseudomonas, Herellea, Candida, nonlipophilic diphtheroids, and enterobacteria.

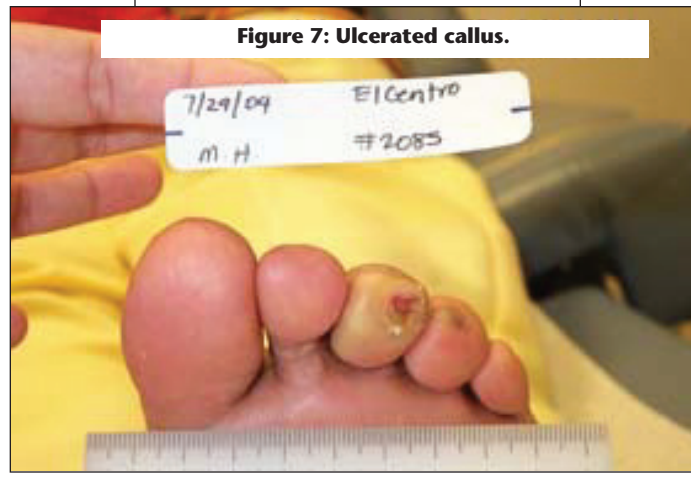

Figure 7: Ulcerated callus.

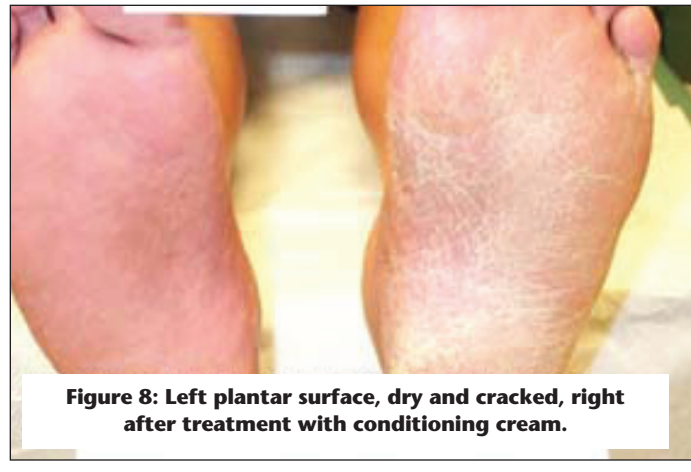

Figure 8: Left plantar surface, dry and cracked, right after treatment with conditioning cream.

Much of what is known about dermatophyte fungi on the skin comes from studies relating to patients with fungal infections and otherwise normal skin.

It is interesting to note that there can be dermatophytosis without clinical evidence of skin disease. In one study, foot scrapings from recruits demonstrated that 18.6% had colonization of one or more of three fungal species (Trichophyton mentagrophytes, T. rubrum, or Epidermophyton floccosum) without any clinical evidence of disease. Similarly, in one study of 100 generally well-controlled diabetics, 70 were found to have dermatophytosis of the inter-digital areas of the feet.

Environmental Factors

Weight bearing, body chemistry, poor circulation, trauma to the feet, and the environment that is created inside our shoes predispose a person with diabetes to certain bacteriological problems. The amount of fatty acids secreted by the sebaceous glands is less and this low fatty acid concentration may predispose the person to ringworm infection. If the feet are cool, too moist and contain more debris factors (dry skin, subungual debris, skin scaling) then dermatophyte and atypical mycobacterial infections become common-place. Interdigital dermatophytosis is a predisposing factor for the occurrence of bacterial infection because the resultant epidermal fissures and erosions create portals of entry for the pyogenic cocci, leading to cellulitis and "infectious" gangrene of the digits.

In the diabetic patient, even minor trauma can lead to stasis and ulceration, followed by penetration of potentially pathogenic skin fungi and bacterial and then by overt infection. If the

Continued on page 200

skin, especially on the plantar surface of the feet, loses its integrity, becomes dry, cracked, fissured and hard, the foot then is at increased risk for damage, sores, lesions, ulcers, and therefore all types of infections. Therefore, preventing the feet from becoming contaminated with debris, too wet or too dry, thereby maintaining the balance of proper lubrication, skin conditioning, and hygiene, becomes an essential part of preventing foot infection (figure 8).

Viruses

There is little information on the density or variety of viruses found on healthy skin, since they are difficult to identify in the absence of skin lesions. Virus replication would presumably be restricted to the deeper layers of the skin because viruses are obligate parasites of living cells, and there are no living cells in the upper layers of the skin. The viruses, however, that parasitize bacteria, called bacteriophages, must be present in significant numbers within the resident bacterial flora (e.g., S. aureus and cutaneous diphtheroids).

Predisposing Factors

Predisposing factors, such as metabolic derangements, faulty wound healing, neuropathy, vasculopathy and immunologic disturbances allow the person with diabetes to be more prone to foot infection than the non-diabetic. Among the defects in the host immune response associated with diabetes mellitus is an impairment of polymorphonuclear leukocyte function, including abnormalities of migration, phagocytosis, intracellular killing, and chemotaxis. Also, ketosis impairs leucocyte function. In addition, there is evidence that the cellular immune responses as well as monocyte and complement function are found to be reduced. The presence of these immodeficiencies appear to be correlated, at least in part, to adequate glycemic control.

Diabetic patients whose blood sugar is uncontrolled and who may be in ketosis are sometimes predisposed to a fungal infection called mucormycosis.

Other accompaniments of diabetes that predispose to infectious complications are poor granuloma formation and prolonged persistence of abscesses. Also, diabetic patients tend to have a higher carrier rate of Staphylococcus aureus on the skin. This virulent pathogen can become infectious when the protective skin barrier is broken. Trauma, various types of skin disorders discussed in this paper, as well as fungal skin and nail infections that disproportionately plaque the diabetic patient all create potential sites for bacterial invasion by the lesions that cause breaks in the protective skin barrier.

The etiology of gangrene in any part of the foot is often due to the infectious process.

A skin infection in a person with immunopathy, such as a diabetic, is potentially disastrous (figure 9). This morbidity is intensified by the unique anatomy of the foot. A skin infection can travel to the structures in the various compartments, tendon sheaths, and neurovascular bundles to favor its spread. These compartments are bound by rigid facial and bony structures, such that the edema and pressure of the infectious materials can cause an extreme elevation of compartment pressures, causing ischemic necrosis and possible gangrenous changes of these confined tissues. The etiology of gangrene in any part of the foot is often due to the infectious process.

Clinical Diagnosis

The clinical diagnosis of a foot infection is as important as the microbiologic presentation because all skin lesions are colonized with microorganisms; and infection of the skin, or cellulitis, requires the presence of purulent secretions or two or more signs or symptoms of inflammation (erythema, edema, and calor). Many patients, but not all, with sensory neuropathy do not report any pain with the infection. Infection should be suspected at the first appearance of a local foot problem, whether it is pain, swelling, ulceration, sinus tract formation, or crepitation.

Cellulitis may be accompanied by systemic signs and symptoms or metabolic disorder, such as severe hyperglycemia, ketosis, or azotemia. Infection should always be considered even when the local signs of cellulitis are less severe than might be expected. Benign appearing ulcerations with no outward signs of inflammation may be associated with underlying osteomyelitis. In addition, more than half of all patients with diabetic foot infections lack a fever, elevated white blood cell count, or elevated erythrocyte sedimentation rate. Therefore even though the clinical and/or the systemic signs and symptoms may be mild, the diabetic patient may be suffering from a potentially very serious infection. Always have a high index of suspicion.

Common Diabetic Foot Infections

There are several infections which can be of concern in persons with diabetes mellitus. There is controversy whether these are more common in the diabetic population; nevertheless, they are common and may be life and/or limb-threatening and are an important part of any discussion on skin disease in diabetes mellitus.

Candida Infections

The incidence of Candida infection in the hands and feet appears to be relatively the same in the diabetic and the non-diabetic population. When it does occur, its pre-

Continued on page 201

Diabetes Mellitus...

sentation may be influenced by the presence of diabetes. It usually presents in one of three ways in the diabetic patient.

Firstly, Candida causes paronychia, usually of the fingernails, but can occur on the toenails. It often begins at the unguilabia as erythema, edema, and separation of medial and lateral margins of the nail from the skin. Further infection of the yeast organism involves the proximal nail fold and subsequent separation of the nail from the cuticle. Moisture trapped in the defects created encourages further growth of yeast and repeated episodes of erythema and edema. A secondary bacterial infection can occur, as evidenced by a purulent discharge and pain, if the patient has adequate sensation. The diagnosis of a yeast infection can be established by performing a KOH preparation on extruded serous material.

Secondly, Candida infection can affect the web spaces of the hands and the feet. The space between the 3rd and 4th finger and between the 4th and 5th toes is most commonly affected (figure 2). Occlusion of the skin in these areas caused by apposing surfaces of the skin of the toes or fingers allows this area to retain moisture, and serves as a nidus for the growth of yeast. The increased sugars and their metabolic by-products further encourage its growth. Clinically, this infection appears as a white macerated patch of skin, often with central peeling. Candida infection of the toe web spaces is often mistaken for a dermatophyte infection, which can be differentiated by a KOH preparation.

Thirdly, Candida infection of the hands and feet can show up as an abnormality of the nail plate. This can literally be indistinguishable from a fungus infection of the nail and the only way to differentiate the two is to do a nail plate culture. These cultures are positive for Candida approximately five percent of the time. Even then, it is necessary to ascertain whether Candida is a contaminant or secondary to another causative organism.

The clinical presentation of nail yeast or fungus infection is the same. There is rarely primary involvement of live tissue, but the nail folds can become reactively inflamed, callused and secondarily infected with bacteria. There can be subungual debris and reactive hypertrophy of tissue. The nail plate becomes thickened, discolored with distal whitening or yellowing. The consistency can change and become powdery or brittle.

One must appreciate that the primary nail plate Candida infection does not pose a special risk in diabetics in and of itself. When the nail plate gets abnormally thickened and is able to cause a callused nail groove, or to become ingrown or to cause paronychia with a secondary bacterial infection, this poses a very significant risk for the person with loss of protective sensation and/or diabetes. This is especially true when one considers that persons with diabetes mellitus often suffer a compromised immune response (i.e., immunopathy).

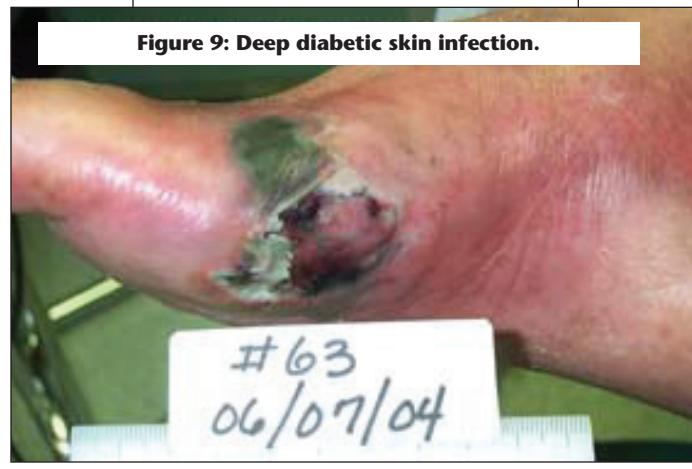

Figure 9: Deep diabetic skin infection.

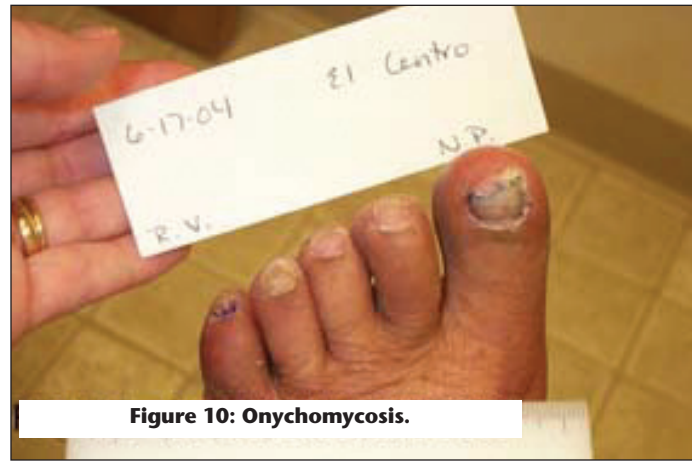

Figure 10: Onychomycosis.

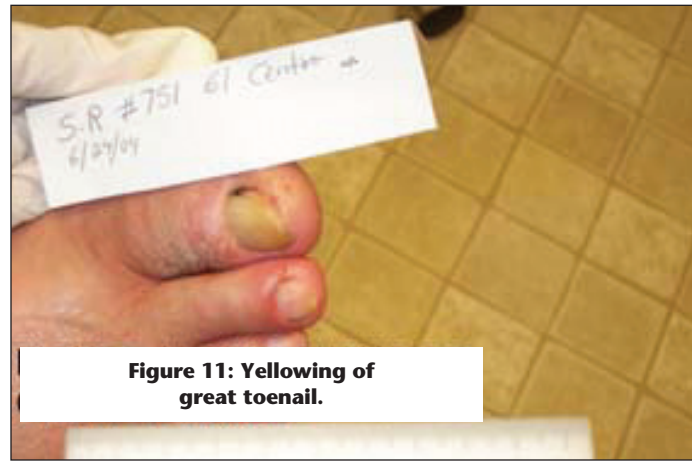

Figure 11: Yellowing of great toenail.

Mucormycosis Infections

Diabetic patients whose blood sugar is uncontrolled and who may be in ketosis are sometimes predisposed to a fungal infection called mucormycosis because of the decreased ability of their neutrophils to phagocytize and adhere to endothelial walls. Furthermore, the acidosis and hyperglycemia provide an excellent environment for this fungus to grow. The presence of systemic or local acidosis is an important risk factor for infection, no matter what causes the acidosis. Traumatized or ulcerated skin can be the site of involvement. Dermal infections frequently metastasize via the blood stream and spread

Continued on page 202

to the central nervous system.

This infection should be suspected when lower extremity ulcerations, post-traumatic or post-surgical wounds are not responding to treatment. The clinical picture is usually that of a typical fungal infection but may present with black crusting or purulence. The diagnosis, however, can be confirmed by culture and by the histologic demonstration of fungal elements invading vascular channels. Treatment consists of correction of acid-base imbalance, aggressive debridement of necrotic tissue, and intravenous amphotericin.

Pseudomonas Infection

The organism responsible for this infection is a gram-negative aerobic bacilli. The two most common pathogens in this species are Pseudomonas aeruginosa and P maltophilia and account for approximately 80 percent of opportunistic infections in the skin.

Pseudomonas species normally inhabit soil, water, and vegetation and can be isolated from the skin, throat, and stool of healthy persons. They often colonize hospital food, sinks, taps, mops, and respiratory equipment. Spread is from patient to patient via contact with fomites or by ingestion of contaminated food and water. The spread of Pseudomonas is best controlled by cleaning and disinfecting medical equipment. Resistance to infection of the host can be increased by avoiding excess moisture and by increasing the overall health and therefore the immune response of the host.

Often persons with onychomycosis of the toenails develop an uplifting of the nail plate from the nail bed. This is termed onycholysis. The space that results between the uplifted nail plate and the diseased nail plate is a nidus for colonization and potential infection with organisms of the Pseudomonas species. In a susceptible host, colonization and infection clinically result in a green discoloration of the area.

Pseudomonas may also cause web space infection on the feet, not unlike that due to dermatophytosis. The differential diagnosis also includes candidiasis. A Wood's lamp examination often yields a green fluorescence with Pseudomonas.

In wound patients, topical therapy of the area with antimicrobial agents such as silver sulfadiazine, coupled with surgical debridement, has markedly reduced sepsis. Soaks with dilute vinegar may eradicate superficial infection. With more significant infection, antibiotic susceptibility testing of clinical isolates is mandatory because of multiple antibiotic resistance. The combination of gentamicin and carbenicillin can be very effective in patients with acute P aeruginosa infections, but ciprofloxacin is often the treatment of choice.

Tinea pedis may present with extreme itching and pain, especially while walking, because of the scaling and blisters between the toes.

Figure 12: Destructive Neuropathic plantar ulceration.

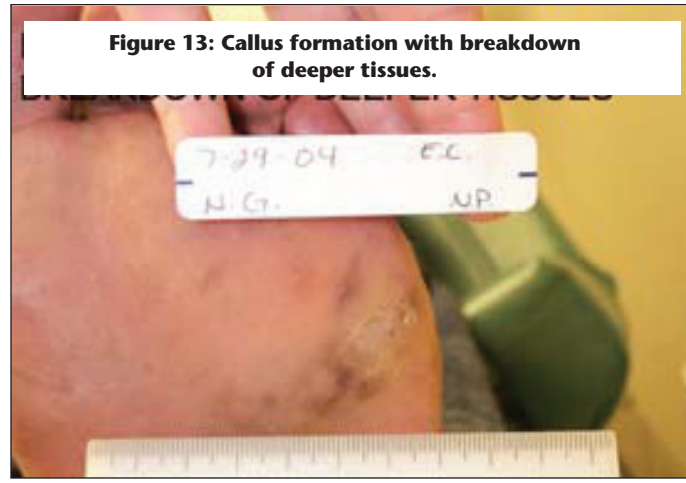

Figure 13: Callus formation with breakdown of deeper tissues.

Dermatophytosis

Dermatophytosis, also known as ringworm or tinea, is a superficial fungal infection of the skin, hair or nails. This group of superficial fungal infections is usually classified according to its location on the body. In the foot, dermatophytosis may present as infection of the toenails, called tinea unguium or onychomycosis or infection of the toe web space or the arch area of the foot, called tinea pedis (figure 10).

These disorders vary from mild inflammations to acute vesicular reactions. Although remissions and exacerbations are common, with effective treatment, the cure rate is very high. However, about 20 percent of all infected people develop chronic conditions. Tinea lesions vary in appearance and duration.

Tinea unguium or onychomycosis start at the tip of one or more nails. Fingernail infection is much less common. Inspection will reveal gradual thickening, discoloration and crumbling of the nail. Eventually, the nail may be completely destroyed. Tinea pedis may present with extreme itching and pain, especially while walking, because of the scaling and blisters between the toes.

Causes and Risk Factors of Dermatophytosis

Tinea infections result from several different

Continued on page 203

fungi. Transmission can occur directly through contact with infected lesions or indirectly through contact with contaminated articles such as shoes, towels or shower stalls. Another predisposing factor is the warm moist environment of the shoe, exacerbated by sweating and warm weather, which encourage fungus growth. Some of the fungi involved in these conditions primarily infect animals, but they may also be transmitted from animals to humans. Cats may have an infection, but may not be suspected until lesions appear on their owners.

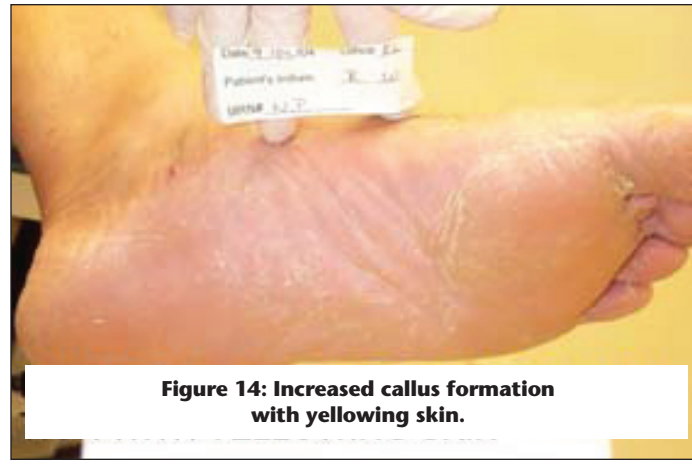

Figure 14: Increased callus formation with yellowing skin.

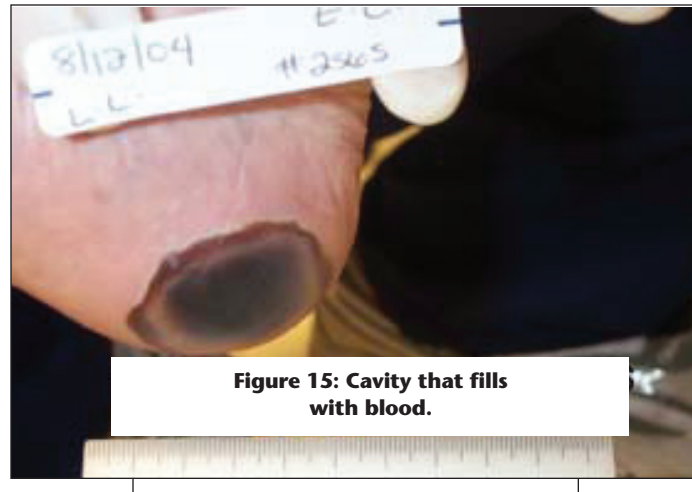

Figure 15: Cavity that fills with blood.

Diagnosis of Dermatophytosis

Diagnosis must rule out other possible causes of the signs and symptoms, which may include eczema, psoriasis, and contact dermatitis. A microscopic examination of some lesion scrapings usually confirms tinea infection. This is called a KOH (potassium hydroxide) preparation. Culture of the affected area, which may take weeks, may help identify the infecting organism.

Treatment of Dermatophytosis

Topical antifungal preparations should be effective in treating small, uncomplicated tinea infections of the skin. These include topical clotrimazole and miconazole (available over the counter) and terbinafine cream. Sometimes, oral antifungal medication may be required if the condition is severe. Medications may include griseofulvin, itraconazole, terbinafine and fluconazole. Corticosteroids may sometimes be used for the treatment of severely inflamed or widespread lesions, such as those that occasionally occur on the soles of the feet. Fungal infections involving the nails (onychomycosis) may require oral treatment as well, because the dermatophyte is found deep in the nail and nail bed.

Tinea versicolor may be treated with selenium sulfide lotion or ketoconazole shampoo. Occasionally, the question arises as to whether a concurrent bacterial infection is complicating a fungal infection. This situation most commonly occurs in persons who have an immunopathy, such as diabetics. The lesions usually resolve using oral antibiotics, along with the antifungal treatments instituted.

Prevention of Dermatophytosis

Nurturing the protective barrier of the skin by preventing excess moisture accumulation while keeping the skin conditioned and free from debris, scaling and cracking are first steps in preventing dermatophyte infections of the feet. Excess moisture in the skin favors the growth of fungi.

Cleaning the skin with a natural oil-based cleanser is important as it removes the debris that may contain contaminant fungus and that chokes and blocks the pores that are responsible for the secretions that favor an optimal pH of the skin. Avoid soaps with a high pH as they will dry the skin and eliminate its acid mantle protective layer on the surface. A slightly acidic ph (4-6) helps deter colonization by non-resident bacteria and other pathogens because these organisms can survive in a narrow pH range near neutral.

Dry the skin carefully after bathing and let it dry before dressing. Wear appropriate footwear that allows the skin to breath and prevent excess moisture retention. Socks that wick away excess moisture and leather shoes that can breathe are important tools in fungal infection protection.

Tinea Pedis

Tinea pedis should be aggressively managed in the person with diabetes mellitus and neurovascular compromise. Toe web space infection may cause fissuring and inflammation that might serve as a portal of entry for secondary bacterial infection in the immune-compromised, uncontrolled or neurovascularly compromised diabetic patient. It is important to note that the oxygen demand of the subsequent infection and inflammation may exceed the ability of the diabetic microcirculation, possibly leading to necrosis and gangrene.

Tinea pedis should be aggressively managed in the person with diabetes mellitus and neurovascular compromise.

Continued on page 204

Diabetes Mellitus...

Onychomycosis

Dermatophyte infection of the toenails (onychomycosis) should not be taken casually in the diabetic patient. Onychomycotic toenails become hard, brittle, deformed and thickened and can precipitate subungual and periungual debris, as well as incurvated, ingrown toenails. This, in turn can cause irritation, trauma, and infection of the tissues surrounding the toenail. Attentive hygienic and conditioning care and debridement of the toenails and surrounding skin is essential for preventing infection in this area. Recently, the FDA approved both itraconazole treatment (200 mg/day for one week a month for 4 months) and terbinafine (250 mg/day for 3 months) for the treatment of onychomycosis. These treatments pose no additional risk to the diabetic patient.

Bacterial, Opportunistic and Superinfection in the Compromised Host

Infections are risky in diabetics as they can cause necrosis of the tissues, edema, and ablation of local circulation, causing gangrene. Hyperglycemia and immunopathy predispose diabetics to infection. The signs of localized infection or cellulitis are redness (erythema), edema (swelling), calor (increase in temperature), pus (purulent drainage) and pain. Even in the patient with loss of sensation, pain can be perceived. The spread of infection is caused by the pressure of the purulence, sometimes causing as much as 25 pounds per square inch of pressure. The spreading erythema is a sign of spreading infection.

Non-pathogenic organisms can become colonized and progress to becoming infectious. This can occur in patients whose host defense mechanisms are compromised. In the hospital setting, they frequently occur as a result of colonization of antibiotic-resistant organisms. The use of catheters and mechanical devices are often the culprit in these types of infections.

Host Defense Mechanisms

Host defense mechanisms depend on the physiologic, anatomic and immunologic health of the body. These may be compromised or altered by disease, such as diabetes; trauma, such as ulcerations or injury; or by procedures and agents used for diagnosis and/or treatment, such as the indiscriminate use of antibiotics, immunosuppressive medications, or cytotoxic drugs. Host defense mechanisms can also be altered by age, burns, neoplasms, other metabolic disorders besides diabetes, irradiation, foreign bodies, corticosteroids, or diagnostic or therapeutic instrumentation.

When infections occur in this setting or if antimicrobial therapy alters the normal relationship between the human host and the microbe, this is often called an opportunistic infection. In these cases, the patient is predisposed to infection from endogenous microflora that is not pathogenic or from ordinary harmless, saprophytic organisms that are acquired by contact with other patients, hospital personnel, or even equipment such as catheters and various mechanical devices. The organisms involved may be bacteria, fungi, viruses, or other parasites, depending on the particular alteration in the host's defenses, and are often part of the normal flora of the skin surface and resistant to multiple antibiotics. These infections that result range from minor to fatal, and often pose serious challenges to the patient and the physician.

Antibiotics

Antibiotics, especially in the diabetic and others with impaired host defense mechanism, should be used with extreme caution. The reason is that they alter the normal microflora of the mucous membranes, GI tract and the skin and therefore then encourage colonization by new organisms. This colonization is harmless unless it results in invasion by indigenous or environmental organisms that have become resistant to the antibiotic being used. This is called superinfection and occurs mostly as a result of treatment with broad-spectrum antibiotics. Superinfections usually appear on the 4th or 5th day of therapy and may be responsible for conversion of a benign, self-limited disease into a very serious, prolonged or even fatal infection. The diagnosis of superinfection is certain only when the specimen is cultured from the blood, CSF, or fluid from a body cavity or deep wound.

It is logical that if nonpathogenic, normally benign organisms can cause such serious infections, then given the potentially immune compromised situation of a person with diabetes, pathogenic bacteria can wreak havoc as well. ■

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Dr. Rehm, board-certified in diabetic wound care, practices in San Diego, CA. He lectures nationally and offers seminars for podiatrists and other professionals. Dr. Rehm is Director of the Diabetic Foot and Wound Treatment Centers in San Diego, and a Fellow, American Professional Wound Care Association.

EXAMINATION

Continuing Medical Education

See answer sheet on page 207.

1) Which of the following statements are true?
- A) Dermatologic complications in diabetes are rare, but serious
- B) 30 % of all skin problems in diabetics put a patient at risk for serious ulceration
- C) Diabetic skin problems are usually life-threatening
- D) Dermatologic manifestations in diabetes mellitus are universal, the prevalence approaching 100%

2) The dermatologic manifestation of diabetes mellitus is universally influenced by which of the following?
- A) The attachment of glucose to protein
- B) The attachment of protein to insulin
- C) The attachment of protein to glucagon
- D) The attachment of collagen to insulin by-products

3) The skin is commonly thicker in diabetics because of:
- A) The increased lactic acid metabolism end-products
- B) The decrease in glycosylation end-products
- C) The increased cross-linking of collagen
- D) Engorgement of the post-capillary venules

4) Complex glycosylation end products have their greatest effect on which of the following?
- A) Erythema of the face
- B) Lower extremity post-traumatic fatty deposits
- C) Yellowing of the skin and nails
- D) Ketosis and glycemic control

5) Erythema of the periungual tissues is thought to be a result of all of the following except:
- A) Development of a functional sympathectomy in the cervical plexus
- B) Engorgement of the post-capillary venules
- C) Increased viscosity of the blood
- D) Stiff red blood cell membranes

6) The predominant biochemical cause of diabetic-related changes in the skin involves:
- A) Non-enzymatic lipoxidation
- B) Non-enzymatic glycosylation
- C) Enzymatic glucoxylation
- D) Covalent enzymatization

7) Color changes of collagen in diabetes-related complications involve all of the following except:
- A) NH2 group of the protein
- B) Schiff base
- C) Amador products
- D) Unstable pyruvate ring

8) Advanced glycosylation end-products that have been identified in the skin include:
- A) The amino acid pentosidine
- B) "Café au lait" imidazole compounds
- C) Glucose-loaded ketoaminic base
- D) Beta-amino group l-terminal amino acids

9) Which of the following is not true regarding non-enzymatic glycosylation:
- A) Causes increased stiffness of the red blood cell
- B) Causes decreased resistance to normal enzymatic degradation
- C) Causes increased stiffness in collagen
- D) Predisposes the diabetic to increased callus formation

10) The most destructive lesion in skin of the diabetic is
- A) A mosaic virus-related verruca
- B) Porokeratosis plantaris discreta
- C) Neuropathic plantar ulceration
- D) Heloma molle

11) Which is not part of the normal development of a neuropathic plantar ulceration in the diabetic foot?
- A) A deep puncture wound
- B) The initial hyperkeratotic lesion
- C) Weakening and breakdown of deeper cutaneous tissues
- D) Eventual cavity formation that fills with blood

12) The following are not diseases associated with diabetes mellitus:
- A) Hemochromatosis
- B) Porphyria cutanea tarda
- C) Wilson's disease
- D) Acanthosis nigricans

13) High plasma levels of insulin, stimulated by the non-responsive receptor sites, are linked to which of the following:
- A) Myxedema
- B) Primary lipidemias
- C) Cutaneous infections
- D) Leprechaunism

14) All of the following are associated with insulin resistance except:
- A) DHEA
- B) Glucocorticoids
- C) Diethystilbestrol
- D) Nicotinic acid

15) The microbial ecology of the human skin involves the following:
- A) Cutaneous levels of PABA in the granular layer of the epidermis

Continued on page 206

Continuing Medical Education

EXAMINATION

(cont'd)

B) Carotinization of the dermal epidermal junction
C) The relationship between colonization, infection and host defenses
D) Rapid epidermolysis of the basement membrane

16) Susceptibility for cutaneous infection involves all of the following except:
A) The ratio of melanocytes to total skin area
B) the dryness and stiffness of the skin
C) The underlying metabolic disorders
D) The effect of autonomic neuropathy

17) Which statement is true?
A) On the moist portion of the lower leg and ankle, the flora is quite restricted
B) Criteria for restricted flora requires 40,000 bacteria per square centimeter
C) Fatty acids in the skin have direct antimicrobial effects
D) When the feet are too moist they favor decreased microbial density

18) Higher microbial density of the intertriginous areas results in:
A) Decreased ammonia formation
B) Increased acid production
C) Higher surface pH
D) Prevention of the metabolism of urea

19) Which of the following is not true regarding Candida infection?
A) the incidence in the hands and feet appears to be relatively the same in the diabetic and the non-diabetic population
B) Candida can cause paronychia of the fingernails
C) Pilonidal cysts are often related to candida infection in the diabetic population
D) Candida often begins at the unguilabia as erythema, edema and separation of nail margins

20) All of the following are common causes of infections in the diabetic except:
A) H. pyloris
B) Mucormycosis
C) Pseudomonas
D) Dermatophytosis

See answer sheet on page 207.

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ENROLLMENT FORM & ANSWER SHEET (cont'd)

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Optimizing Wound Prevention and Healing (Donohue, Goss, LaVan, Weingarten, and Abboud)

Circle:

1.	A	B	C	D	11.	A	B	C	D
2.	A	B	C	D	12.	A	B	C	D
3.	A	B	C	D	13.	A	B	C	D
4.	A	B	C	D	14.	A	B	C	D
5.	A	B	C	D	15.	A	B	C	D
6.	A	B	C	D	16.	A	B	C	D
7.	A	B	C	D	17.	A	B	C	D
8.	A	B	C	D	18.	A	B	C	D
9.	A	B	C	D	19.	A	B	C	D
10.	A	B	C	D	20.	A	B	C	D

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_____

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_____ hours _____minutes

How well did this lesson achieve its educational objectives?

_____Very well _____Well

_____Somewhat _____Not at all

What overall grade would you assign this lesson?

A B C D

Degree_____

Additional comments and suggestions for future exams:

_____

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EXAM #12/04
Skin Disease in Diabetes Mellitus—Part 1 (Rehm)

Circle:

1.	A	B	C	D	11.	A	B	C	D
2.	A	B	C	D	12.	A	B	C	D
3.	A	B	C	D	13.	A	B	C	D
4.	A	B	C	D	14.	A	B	C	D
5.	A	B	C	D	15.	A	B	C	D
6.	A	B	C	D	16.	A	B	C	D
7.	A	B	C	D	17.	A	B	C	D
8.	A	B	C	D	18.	A	B	C	D
9.	A	B	C	D	19.	A	B	C	D
10.	A	B	C	D	20.	A	B	C	D

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_____Somewhat _____Not at all

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