Joint Meeting of the Skin Diseases Interagency Coordinating Committee and the Diabetes Mellitus Interagency Coordinating Committee

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National Institutes of Health
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Conference Room G
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Dr. Saul Malozowski, Executive Secretary of the Diabetes Mellitus Interagency Coordinating Committee (DMICC) and Senior Advisor for Clinical Trials and Diabetes Translation, Division of Diabetes, Endocrinology, and Metabolic Diseases (DDEM), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) opened the joint meeting with the Skin Diseases Interagency Coordinating Committee (SDICC). After apologizing for the small size of the room due to the number of meetings being held at Natcher this day, Dr. Malozowski announced the topic of the joint meeting was wound healing and introduced Dr. Stephen J. Katz, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), lead agency for SDICC.

Dr. Katz welcomed the attendees and assured them that "It is not the size of the room that matters. It is the interactions that count." He explained that the interagency committees are composed of members from other institutes and agencies of the Federal Government with a focus in a particular area, as well as voluntary organizations particularly concerned about each of these areas. Dr. Katz stated that NIAMS has an interagency working group on bone and one on lupus. Quarterly, and sometimes semiannually or annually, each of the lead National Institutes of Health (NIH) institutes, such as NIDDK or NIAMS, holds meetings. At these meetings, not only do the institutes come together but it affords them an opportunity to get together with the Centers for Disease Control and Prevention (CDC), other U.S. Department of Health and Human Services (DHHS) agencies, the Department of Defense (DoD), the Veterans Health Administration (VHA), and whoever else has a role in addressing the problem on the agenda. Thus the Federal agencies are doing things collectively, not redundantly or at odds with one another.

Dr. Katz pointed out that this seemed an opportune time to have a combined meeting with NIDDK and NIAMS because both are focused on and have an interest in wound healing, particularly in chronic wounds. He added that diabetes is the paradigm for many of the models that are used, both in humans and in animals. Dr. Katz thanked Dr. Alan Moshell and Ms. Geraldine Pollen from the NIAMS; Dr. Malozowski and Dr. Judy Fradkin, Director, DDEM, from the NIDDK; and Mr. Iain MacKenzie of the Hill Group for helping to put the joint meeting together.

According to Dr. Katz, as a consequence of a similar meeting in 1993, opportunities were identified and a request for applications (RFA) focused on wound healing was issued by NIAMS and supported by NIDDK. The RFA received a tremendous response. An important thing to note was that the RFA was sponsored by many groups, not only the NIAMS and NIDDK, but also by the National Institute of Nursing Research (NINR), National Institute on Aging (NIA), and National Institute of Child Health and Human Development (NICHD). He emphasized that there are many opportunities at NIH and many institutes that are particularly interested in this area. Over the past 10 years, NIAMS has trebled its investments in wound healing research to close to $11 million. Most of the focus is on basic research, although in the last few years, as some of those in the audience would know, there also has been a focus on clinical studies, particularly on gene therapy.

Dr. Katz stressed that the hope for a meeting like the current one was to focus on what the opportunities are, what other agencies are doing, and try to identify opportunities and gap areas for future action. For a long time, SDICC tried to develop or encourage guidelines for a standard of care against which new therapies should be compared. Dr. Katz noted this is not a simple problem, but one that, if the Federal agencies do not deal with it, whatever the responsibilities are, it will not get done. He concluded by saying that he looked forward to hearing the day's presentations and discussions.

Before introducing Dr. Spiegel, Dr. Malozowski also thanked Dr. Moshell and stated that without his assistance, it would have been very difficult to put the agenda together for the meeting.

Dr. Spiegel reinforced Dr. Katz's statement regarding this being an excellent opportunity for their two institutes to join with representatives of other institutes and agencies to discuss wound healing, a topic of great significance in and of itself, but particularly in relationship to diabetes. In addition to adding his thanks to those who put the meeting together, Dr. Spiegel wanted to underscore that the meeting typifies a reinvigorated spirit of collaboration among particular NIH institutes around the issues of diabetes complications. He said that diabetes is really a trans-NIH disease. In the area of complications, there are a variety of issues, such as a particular interest in wound healing in type 1 and type 2 diabetes, that bring together the various NIH institutes and centers, including, among others, the National Institute of Neurological Disorders and Stroke (NINDS); the National Heart, Lung, and Blood Institute (NHLBI); the National Eye Institute (NEI); obviously the life cycle institutes, both NIA and NICHD; and NINR. He assured the group that NIDDK intends to support research in wound healing in a collaborative way. Such support will range from basic mechanistic research in which NIDDK is spearheading new initiatives—for example, in angiogenesis, which underlies many diabetes complications and with animal models under NIDDK's Animal Models of Diabetes Complications Consortium—through the translational area and, ultimately, to direct clinical testing in human subjects.

Dr. Spiegel added that, as many of those present knew, a special funding pool was legislated by Congress for type 1 diabetes. For fiscal years 2004 to 2008, funding is at $150 million a year for type 1 diabetes-related issues. For those who are interested, there is a special area on the NIDDK website (www.niddk.nih.gov) listing the many trans-NIH initiatives that have been created with these funds. He stated that he also was looking forward to the day's presentations and discussions.

From the speakers' presentations and the discussions on the epidemiology of diabetic foot ulcers, pathways to development of foot ulcers and the need for offloading, what has been learned from data on foot ulcers that would contribute to future clinical trial designs, clinical protocols for treating diabetic foot ulcers, and adjunctive therapies for foot ulcers, the following key opportunities and recommendations were identified for possible future action.

- Agree on a definition for diabetic foot ulcer.
- Identify consistent ICD codes for diabetic foot ulcers and other lower limb conditions to enhance data collection and further collaborative research.
- Issue a mandate to treat diabetic foot ulcers before complications develop.
- Establish the goal of reducing amputations related to diabetic foot ulcers to less than 10 percent.
- Establish as part of the standard of care for diabetes patients that their feet be examined at each office visit.
- Establish aggressive debridement and offloading as the standard of care for diabetic foot ulcers.
- Use a simple test to measure neuropathy (i.e., lack of sensation) in diabetic patients.
- Use the presence of neuropathy as a surrogate marker for the endpoint of ulceration in clinical trials.

- Establish surrogate markers, such as size, grade, and duration of wound, based on current FDA data, as predictors of healing to conduct phase 1 and 2 clinical trials of shorter duration and without the endpoint of complete healing.
- Design more efficient clinical trials based on epidemiologic studies and tools.
- Require offloading, preferably using an instant total contact cast, for all treatment groups in clinical trials testing new therapies for chronic wounds.
- Investigate further the refractory subset of patients who do not heal as expected and find ways to reverse the reasons for this refractory subset.
- Recognize the importance of the foot and the impressive work being done by making 2005 "the Year of the Foot" with the goal of implementing meaningful strategies in diabetic foot ulcer care.
- Organize a consensus conference to discuss diabetic foot ulcer issues such as guidelines for improved primary care and clinical practices.

Citing the late Dr. Paul Brand's statement that "Pain is God's greatest gift to mankind," the group agreed that neuropathy resulting in lack of pain was seen as a major contributor to the development of foot ulcers in persons with diabetes and to the non-compliance with offloading devices that are essential to healing. Other prominent risk factors are peripheral vascular disease, past history of neuropathic foot ulcers, microvascular complications, elderly patients living alone, foot deformity, and unilateral amputees.

Topics of particular interest were photographing, measuring, and grading of the diabetic foot ulcer on a patient's chart; the need to work with a multi-discipline team in treating the person with a diabetic foot ulcer; investigating factors contributing to chronicity in diabetic foot ulcers such as unresponsive or senescent cells present either in the wound or in the callous around the wound, a proteolytic or inflammatory environment, deficient or unavailable growth factors, or bacterial interference and therapies to address these; the use of adjunctive therapies such as platelet-derived growth factors, bilayered living skin constructs, dressings to remove or change the proteolytic environment, other anti-inflammatory agents, and removal of bacterial interference; the possibility of a biochemical assay of fluid from a wound to predict healing; recognizing and addressing the presence of stress and depression in the diabetic patient and its effect on compliance with prevention and therapies and with healing; use of sterile maggots as a debriding agent and honey or heat as healing therapies; encouraging the CDC to provide regular surveillance data from all the surveys being conducted annually, including VHA and DoD data; providing information to primary care providers and patients on NIH websites regarding standards of care, wound treatment therapies, and expectations for healing; suggestions for clinical trials and other studies; and the availability of various funding mechanisms from the NIH to further research in wound care.

The following sections detail the presentations and discussions leading to the above recommendations.

Epidemiology of Diabetic Foot Ulcers

Dr. Malozowski introduced Dr. Gayle Reiber, Veterans Administration (VA) Career Scientist and Professor, Health Services and Epidemiology, University of Washington, Seattle, who has spent 15 years of her career on the epidemiology of diabetic foot ulcers.

Dr. Reiber outlined five topics for her presentation: (1) a consensus definition for foot ulcers; (2) CDC foot ulcer history findings; (3) updated risk factors for foot ulcers; (4) current national foot ulcer data; and (5) issues for epidemiologists.

Definition of Foot Ulcers. Dr. Reiber adapted her definition from a Lazarus definition published in 1994 by inserting the italicized phrase: A foot ulcer is "a cutaneous defect extending into the dermis or subcutaneous tissue that does not undergo self-repair in a timely and orderly manner *within 4 weeks of onset*." When physicians see a foot ulcer, they know it is a foot ulcer, but some of these lesions are on the periphery. They don't heal. They are deep. Dr. Reiber stated that foot ulcers need to be better classified and offered her definition to aid the future collaborative endeavors of the group.

BRFSS History of Foot Ulcers. Dr. Reiber praised the Behavioral Risk Factor Survey (BRFSS) efforts in collecting nationwide information on risks. (See Centers for Disease Control and Prevention's (CDC's) online newsletter, Morbidity and Mortality Weekly Report (MMRW), November 14, 2003, at www.cdc.gov/mmwr.)With an annual budget of approximately $12.5 million dollars, it is the world's largest telephone survey. Each year a relevant core question is, "Do you have diabetes?" More detailed diabetes information varies annually. Between the years 2000 and 2002, 44 different States and the District of Columbia put an extended module on the BRFSS and asked, "Have you ever have any sores or irritations on your feet that took over 4 weeks to heal?" There was an unusually good response rate for a telephone survey of close to 58 percent. The CDC adjusted the data for age, sex, race, and ethnic background. Significant results related to foot ulcers in those diagnosed with diabetes included the following:

- There is a history of foot ulcers in 12 percent of adults with diabetes.
- There was an increase in annual foot examinations from 56 percent to 62 percent between 1995 and 2002.
- Duration of diabetes, smoking, and insulin use each increase significantly risk.
- People at increased risk also include those who are obese and those who are not married or cohabitating, which has been shown in a number of studies.
- There was a significant protective effect with age in those over 64-years-old.
- Surprisingly, based on race and ethnicity, blacks had a protective effect and Hispanics' odds were a little higher, but not significantly higher.
- There was no significant difference between men and women (p value = 0.2).

Dr. Reiber cited several BRFSS limitations. The survey does not cover people in institutions such as nursing homes or hospitals. Participants self-report and there is no consistent definition of foot ulcer, so persons are often confused about whether they have had a foot ulcer or a less severe lesion. Persons must have a land line telephone (not a cell phone only or no phone) to be included in the survey. Finally, possibly because of confounding for a number of variables that could not be analyzed in the data set, several risk factors did not reach statistical significance.

Another CDC finding cited by Dr. Reiber was that the number of people with diagnosed diabetes increased between the years 1980 and 2001 (National Health Survey Data from the CDC Division of Diabetes Translation). As diabetes increases, physicians can expect to see more foot ulcers. Dr. Ramsey (Ramsey, SD, Newton K, Blough D, McCulloch DK, Reiber, GE, and Wagner, EH. Incidence Outcomes and Cost of Foot Ulcers in Patients With Diabetes. *Diabetes Care* 1999, 33:282-387) and Dr. Moss (Moss, SE, Klein, R, and Klein, BEK. The Prevalence and Incidence of Lower Extremity Amputations in a Diabetic Population. *Arch Intern Med* 1992, 152:610-616) reported that the incidence or onset of new foot ulcers is about 2 to 2.5 percent in the diabetic population. Dr. Ramsey looked at the Group Health population in Seattle; Dr. Moss, the Wisconsin population. Dr. Moss reported a 10 percent prevalence.

Risk Factors for Foot Ulcers. Dr. Reiber pointed out that, whenever measured, neuropathy is uniform across studies, which makes it a highly important risk factor. Dr. Reiber referred the audience to the following reference for more information: Reiber, G.E. and Ledoux, W.R. 2002. Epidemiology of Diabetic Foot Ulcers and Amputations: Evidence for Prevention. In *The Evidence Base for Diabetes Care*, edited by Williams, R., Herman, W. Kinmonth, A.-L., and Wareham, N.J. John Wiley & Sons, Ltd. Other independent risk factors are ankle arm index (AAI) and transcutaneous oxygen tension ($TcPO_2$), two different components of the circulation; prior ulcer (typically 60 percent of those presenting with foot ulcer); peripheral vascular disease (PVD); prior lower extremity amputation (LEA); and increased HbA1c.

Based on U.S. population sample data from the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2000, prevalence of insensate feet is about 2-fold greater in people with diabetes and prevalence of insensate feet plus peripheral neuropathy (PN) symptoms is about 3-fold higher in people with diabetes than in those who are not. Peripheral artery disease (PAD) is 2-fold higher and if all the different lower extremity diseases are combined, they also are 2-fold higher in the population with diabetes compared to those without diabetes. Dr. Reiber remarked that it is really quite astounding the different ways that PN is measured and reported in studies. Measures that are used are signs, symptoms, nerve conduction abnormalities, and composite definitions. Depending on whether a definition like nerve conduction deficit or whether sensory examination reflex is used, there is a 73-fold difference in prevalence of neuropathy. However, despite the fact that it is reported very differently, neuropathy consistently shows up. In the type 1 Diabetes Control and Complications Trial (DCCT) baseline information, the gold standard was a 2.1 prevalence. A study done by Partanen (Partanen et al., *New England Journal of Medicine*, 1995) reported an 8.3 percent prevalence of neuropathy at baseline and 42 percent at 10 years in persons with type 2 diabetes.

New Outpatient and Inpatient Data. Along with standardizing a definition for foot ulcers, Dr. Reiber recommended that it would be valuable for researchers in Government agencies to use the same ICD-9 codes for foot ulcer conditions and amputations in order to share and compare data and better understand the findings. Among the many different ICD codes used for foot ulcers, the most common one is the 707 code. This is “ulcers for lower limbs except for decubitus” and that is about 55 percent of foot ulcers, with osteomyelitis, cellulitis, and abscess being among the conditions that make up the rest.

The VA, which has information on all individuals who come in for outpatient and inpatient care, does not use ICD codes for foot ulcers. They have their own list that includes varicose ulcers and lower leg conditions that are not foot ulcers. Also, since the denominator is veterans who are usually older males, the VA rates are much higher than those in the U.S. population as a whole. In the VA data, 9.4 percent of those in the youngest age group (0-44) had foot ulcers, 17.2 percent of persons in the 45-64 age group had foot ulcers, whereas those 65 and older dropped to 15 percent. Combining the VA’s 115,000 episodes in 2001 with the 184,000 discharges reported in HCUP, for a total of 299,000 episodes in persons with diabetes, rates were 2.4 percent in the 45-64 age group, 2.8 percent in the 65-74 age group, and 3.3 percent in those over 75, showing an increase with age. Comparing 1993 to 1997 data with that from 2001, Dr. Reiber noted that there was very little change. She also provided VA and HCUP 2001 data on amputations in 55,000 persons as indicative of the prevalence of foot ulcers since 84 percent of amputations are preceded by a foot ulcer.

Epidemiology Issues. In conclusion, Dr. Reiber asked the group to consider the following requests:

- Agree on a definition for foot ulcer.
- Agree on ICD codes for foot ulcers and other lower limb conditions to further collaborative research.
- Encourage the CDC to provide regular surveillance data from all the surveys being conducted annually, including VA and DoD data.
- Recognize the importance of the foot and the impressive work being done by making 2005 "the Year of the Foot" with the goal of implementing meaningful strategies in diabetic foot ulcer care.

Pathways to Foot Ulcers and the Need for Offloading

Dr. Malozowski introduced the next speaker, Dr. Andrew J.M. Boulton, Visiting Professor of Medicine, University of Miami, Professor of Medicine, University of Manchester, and Consultant Physician, Manchester Royal Infirmary, Manchester, United Kingdom

Dr. Boulton said he left Miami 10 days ago and had been in Rumania for World Diabetes Day and then Eastern Germany and England and Ireland. Given this travel and his presentation for today, he wryly assumed this made him a specialist as defined by his sponsor when he was a medical student: "A specialist is someone who comes from a long way away and brings slides." He added that in 2005, the World Diabetes Day indeed will be focused on the foot.

Pathways to Foot Ulcers. Dr. Boulton presented a number of studies that illustrated the pathways to foot ulcers. He also put neuropathy first on his list of risk factors, noting that, in research done in combination with Dr. Reiber, this was the most important component cause, although neuropathy alone will not lead to ulceration. Other factors are peripheral vascular disease, past history of neuropathic foot ulcers (with a recurrence rate in studies of between 40 and 60 percent a year), microvascular complications, elderly patients living alone, foot deformity, and unilateral amputees, who are obviously at great risk.

Dr. Boulton showed slides illustrating that to some extent "Nothing is new in medicine." In the 1880s, Dr. Pryce, a surgeon from Dr. Boulton's hometown of Nottingham, looked at a series of patients and published in *Lancet* in 1887 the statements: "Diabetes itself may play an active part in the causation of perforating ulcers….And it is abundantly evident that the actual cause of the perforating ulcers was a peripheral nerve degeneration." He also quoted the late Dr. Paul Brand who said "Pain [is] God's greatest gift to mankind." Dr. Brand, who passed away in July 2003, was the noted physician who described in leprosy the association between insensitivity and foot ulcers, rather than the cause of the ulcers being the infection itself. Dr. Boulton stressed that the importance of pain is something we forget. He stated that not having sensation really summarizes many of the problems seen in the diabetic foot in 2003, with regard both to pathways and offloading.

The United Kingdom Prospective Diabetes Study (UKPDS) study of 5,000 patients indicated that 11 percent of patients have significant neuropathy at diagnosis of type 2 diabetes. At Dr. Boulton's center, which participated in the UKPDS, neuropathy was possibly asymptomatic in up to 50 percent of patients. He reported that in population-based community studies of 811 older patients (mean age of 65 years) with type 2 diabetes, probably over half have risk factors for foot ulceration, 42 percent have clinical evidence of significant neuropathy, and 11 percent have peripheral vascular disease (see Kumar et al., 1994; UKPDS, 1998).

When Dr. Boulton moved to Manchester in 1988 and opened the new diabetes center, there were no longitudinal studies proving that neuropathy is a major risk factor for foot ulcers. At the new center, neuropathy was assessed by a simple semi-qualitative measure—by vibration dysfunction measured by biothesiometer, a handheld vibration device that has a gradiated reading of 0 to 50, the higher the reading the more severe the sensory loss. The center's 469 patients, who all received education, were followed for 5 years. Those with vibration perception less than 15 were considered to have no neuropathy; those over 25 had undoubted neuropathy. The risk per patient per year of developing foot ulcers went from 0.7 percent in those with no clinical neuropathy and then increased 7-fold to almost 1 in 20 in those who had neuropathy (see Young et al., *Diabetes Care* 1994; 17:557).

In a larger multicenter European and North American study with 1,035 patients, published in 1998 (Abbott et al. *Diabetes Care* 1998:21:1071), the entry criteria were a diagnosis of diabetes, no history of foot ulcers, definite risk measured by a vibration perception of more than 25 volts, and no evidence of vascular disease. The patients received standardized education and three monthly visits to the podiatrist. Yet, the annual incidence of foot ulcers in these patients was even higher than what had been reported earlier—7.2 percent. This study also showed that the foot ulcer risk increased significantly with an increment grade rise in vibration perception threshold (VPT)—5.6 percent per volt VPT.

Another Manchester study that Dr. Boulton thought was important in terms of surrogate endpoints for use in clinical trials, enrolled 169 patients and 22 controls with a spectrum of neuropathic deficits and followed them for 6 years (see Carrington et al. *Diabetes Care* 2002;25:2010-2015). Thirty-seven percent developed ulcers, 11 percent received amputations, and 18 percent died. The best predictor of the endpoint of neuropathy was motor nerve conduction velocity (MNCV) in the peroneal nerve. Dr. Boulton called this the missing link, because this is electrophysiology where the speed of nerve conduction can be directly measured in the patient, not a psychophysical test, and highly reproducible, with a low coefficient of variation. Dr. Boulton's group had previously shown that MNCV correlates very well with structural abnormality in the sural nerve and is a predictor of clinical neuropathy. He noted that it is also a predictor of mortality, as is foot ulcers, which might explain the rather lower prevalence in the study Dr. Reiber cited of patients over 75, because these are the survivors. Dr. Boulton emphasized that the Manchester group's prospective study confirmed MNCV as a predictor of the endpoint of insensate foot ulceration and indicated that electrophysiology is the best surrogate endpoint for use in clinical trials, which is important because agents are needed to teach diabetic neuropathy.

Dr. Boulton commented that researchers in the United Kingdom have the advantage in conducting population-based research. The government funded his University of Manchester group's North West Diabetes Foot Care Study (NWDFCS), an ongoing population-based prospective study of 16,000 patients in six health-care districts to see what can be used in clinical practice as a predictor of foot ulcers. All known patients with diabetes were selected from general practitioner records. (An earlier study of just under 10,000 patients was published previously (see Abbott et al., *Diabetic Med* 2002;19:377)). In clinical practice, most providers have a tendon hammer, a tuning fork, a pin, and so on, so a very simple test can be done by trained research nurses and podiatrists in all the patients wherever they are seen, either at their homes, in primary care, or in secondary care. Dr. Boulton stressed that sophisticated equipment is not needed to identify the at-risk foot. There are simple tests that are applicable anywhere, such as in Romania where they often do not have sophisticated equipment.

For the NWDFCS, a simple neuropathy disability composite score was used with three sensory modalities—a vibrating 128 Hz tuning forks over the apex of the hallux, pin-prick ("can you feel the difference between sharp and blunt") on the dorsal distal hallux, just proximal to the great toe's nail, and similarly, hot-cold rods. If the patient cannot feel the vibrating 128 Hz tuning fork, or cannot distinguish the pin-prick, or cannot tell the difference between hot or cold, the score is one. Any hesitation, any suggestion of abnormality, the score moves towards abnormality, or a one. So if the patient has to think

whether or not he/she feels a tuning fork on the hallux, then that is abnormal. Delay is abnormal. So that's a maximum score of three abnormalities per foot or six altogether. Next ankle reflex, which is a good predictor, is tested. Normal is zero; if absent, the score is two, and if present on reinforcement, that scores a one. So the maximum score is 3 from the first test and 2 from the ankle test for a possible total of 5 per leg or 10 for both legs. Dr. Boulton repeated that this is a very simple procedure that can be done quickly in clinical practice; in fact, more quickly than it takes to describe it.

In the earlier NWDFCS, the 9,710 patients were seen in their homes, given a half-hour one-on-one education session that was appropriate to their identified level of risk, and followed for 2 years. They developed 291 ulcers, with a higher rate in males, which is a uniform finding in Western countries. The best single predictor of risk for foot ulcers was the very simple neuropathy disability score that Dr. Boulton had just described and had assured the audience was applicable in clinical practice anywhere in the world. At less than 6, the patient had a 1 percent annual risk of developing an ulcer. At 6 or more, there was a 6-fold increase in risk.

In a joint study with Dr. Reiber (Reiber, Vileikyte et al., *Diabetes Care* 1999;22:157-162), the two groups looked at approximately 155 incident ulcers, and using a Rothamn model, identified key components leading to the ulceration. In the pathway to ulcers, the most important component cause was neuropathy. Four out of five patients had significant neuropathy. The critical triad most commonly seen (present in 63 percent of patients with foot ulcers) was neuropathy, deformity (commonly clawing of the toes, prominence of the metatarsal heads), and trauma (often caused by inappropriate footwear). More than 80 percent of these ulcers were potentially preventable. The pathway again began with lack of pain. Asked about their feet, patients replied "I feel great" because of sensory loss. These were patients with a baseline pathology of neuropathy, along with the rest of the triad, deformity and trauma. Dr. Boulton stated that it is the job of practicing physicians, nurses, podiatrists, or other healthcare providers, to prevent these three events coming together in the same individual.

Other studies conducted over the 10-year period from the 1980s to the 1990s and referred to by Dr. Boulton also indicated the importance of foot pressure abnormalities and loads under the neuropathic foot (Boulton et al. *Diabetes Care* and *Diabetic Medicine* 1983, 1984, 1985, 1986; Veves et al. *Diabetologia* 1992;35:660-664; Murray et al. *Diabetic Medicine*1996;13:979-982) These studies showed high foot pressures are associated with first and recurrent ulcers, foot pressure abnormalities occur early in diabetic neuropathy, high foot pressures are a predictor of ulcers, and the presence of callous or of hard skin under the metatarsal heads is associated with high pressure and is a predictor of ulcers.

Need for Offloading. Dr. Boulton observed that a number of factors are known to enhance wound healing, so the job of physicians is to try to correct the underlying condition. He noted that today providers are controlling infection; providing vascular reconstruction through distal bypasses and angioplasty for patients with severely compromised peripheral circulation; and helping patients with their glycemic control, at least in the short-term, although the long-term is still a challenge. However, they have failed miserably at offloading. When asked "What dressing should I use?" Dr. Boulton would reply, "It's not what you put on the ulcer that matters. It's what you take off it." He recommends aggressive debridement. Dead tissue, the callous, needs to be removed. In a clinical trial of platelet-derived growth factors (PDGFs) and a placebo, Dr. Boulton noted that where 100 percent debridement was performed at every office visit, there was more rapid healing (Steed et al., *J AM Coll Surg* 1996;183:61-64). Secondly, pressure must be removed.

Dr. Boulton listed a variety of devices that have been used over the years to remove pressure, including an outcast boot, a sort of crow-walker, half-shoe, special shoes, orthoses, bed rest, a wheelchair, crutches—none of which work. When asked "How can the patient be so silly? They've got this huge hole in their foot and they're walking on it? Why?" he replies, "Because we don't appreciate what it is not to have sensation." As Dr. Paul Brand taught with regard to leprosy, *pain is God's greatest gift to mankind*. Lack of pain results in a foot ulcer. If a patient's foot does not hurt, he/she will follow the physicians' offloading instructions to stay in bed or in a wheelchair or use crutches for a day or two, but that is all. Dr. Boulton pointed out that we live in a very strong, lay-driven, symptom-driven society. When patients go to the doctor with pain, treatment is given and they usually get better. But a patient does not go to the doctor and say, "Look, I can't feel under my feet." Medical schools do not teach how to take care of people who have lost sensation. So patients get out of bed and throw their crutches away.

The best tools for the foot ulcer patient, according to Dr. Boulton, are the removable cast walker and the total contact cast (TCC), which has many advantages. The TCC enforces adherence (compliance), shortens stride length, decreases cadence, reduces activity, and reduces peak pressures equal to that of a removable cast walker. He cited two major trials: Mueller et al., 1989, that compared the TCC with standard treatment, and Armstrong et al., *Diabetes Care*, 2001, that compared the TCC with a removable cast walker and a half shoe. At every stage, there was more healing in the total contact cast group. Even though the pressure offloading effect of the TCC and the removable cast walker is equal, the removable cast walker performed much less well.

In another study to try to understand the superior performance of the TCC over the removable cast walker, Dr. Boulton described activity patterns in patients with diabetic plantar foot ulcers. Patients were given a removable cast walker to wear, told that wearing the device was very important in all activities day and night, and told they would be monitored 24x7 with a pedometer or accelerometer, which they wore. Another accelerometer was placed inside the cast walker, without their knowledge, so their activity level with or without the cast walker could be monitored. The removable cast walker is, indeed, removable. Less than 30 percent of the footsteps taken per day by patients in the study included wearing the cast walker.

Dr. Boulton said there are, however, disadvantages to the TCC as the gold standard because, when casting an insensitive foot, it is possible to cause damage such as a new ulcer. In addition, using the TCC requires a lot of time, equipment, and new removable casts. Patients must return every week to be checked and have the cast replaced, so the cost is high. In place of the TCC, he suggested an "instant total contact cast" using the DH walker, which offloads as well as the TCC, and can be made irremovable by wrapping it in a Scotchcast. This creates a device that can be used every week. The patient can come back, have the inexpensive outer cast cut off, the HR removed, get the wound looked at, have the wound treated and debrided, and get the same HR cast put back on and rewrapped with one band of cast. The result is a significant cost-saving.

Addressing the question of why trials of removable devices are so disappointing, Dr. Boulton described an event some years ago, in the United Kingdom's National Health Service, where patients were provided free footwear. Only 20 percent of patients reported that they wore it regularly. In a trial with the standard DH walker, it was worn for only 28 percent of daily activity. Despite all good intentions, offloading devices are not used. If they can be removed, they will be. He proceeded to describe two current key trials. One is a randomized trial in Miami testing the TCC versus the instant total contact cast based on the hypothesis that the healing rates of the two should be the same. To date, this appears to be so with 35 patients. A second trial in Tucson testing the instant TCC with a removable cast walker is based on the hypothesis that healing with the instant TCC should be faster.

Dr. Boulton strongly recommended a paradigm shift in conducting studies of new therapies for neuropathic foot ulcers. To date, most of these studies have not attended to offloading. This factor probably explains the very disappointing results of many new modalities that are being put out in the community, such as growth factors, artificial skin, and so on. He stated there is no doubt that the huge confounding variable is pressure. Patients are walking on the wounds. Hence, they are not responding in either the placebo or treatment groups. Dr. Boulton proposed that all future trials of therapies for plantar neuropathic ulcers should have standardized offloading in all treatment groups. He believes support for his proposal will be forthcoming in a paper published by Dr. Albert Piaggesi of Pisa, Italy, in November 2003 in *Diabetes Care*. Dr. Piaggesi's group conducted a randomized trial of patients with chronic plantar foot ulcers in Pisa, Italy. Patients with chronic foot ulcers were randomized to a TCC for 20 days followed by an ulcerectomy or to an ulcerectomy at baseline. Comparing histological changes between the two groups, Dr. Piaggesi found that the group who had the ulcerectomy on day 1 had much more chronic inflammation with fibrosis, less angiogenesis, and more inflammation. Those who were casted for 3 weeks prior to the ulcerectomy had more evidence of angiogenesis and granulation, more like an acute wound. Dr. Boulton deemed this a very important study showing that pressure not only has a direct effect on the ulcer, but also appears to support the chronic inflammation. Prolonged repetitive pressure appears to contribute to the chronicity of diabetic foot ulcers. After pressure release, the diabetic foot ulcer in many ways resembled an acute wound.

Dr. Boulton offered the following summary conclusions, which he suggested would be discussed further during the meeting:

- Wound healing in diabetes is impaired.
- Multiple factors have shown to be impaired in diabetic wound healing.
- Cellular differences have been noted between acute and chronic wound healing.
- Failure to offload pressure from plantar neuropathic ulcers is a major contributory factor in ulcer chronicity and may explain disappointing results for potentially exciting new treatments.

To illustrate the truth of one of the aphorisms of Professor J. A. Lindsay of Belfast in Northern Ireland that Dr. Boulton thought was applicable to the diabetic foot, he quoted Dr. Brand again. Professor Lindsay had said in the early 20th century "For one mistake made for not knowing, ten mistakes are made for not looking." When Dr. Brand was invited to address the American College of Surgeons more than 20 years ago, a surgeon asked him, "What's the most important thing that we can do to reduce amputations in diabetes?" The audience was expecting to hear about some new ultimate device or test such as a CT scan. But Dr. Brand replied, "Take the patient's shoes and socks off every time you see them and look at their feet." Dr. Boulton recommended that all remember this.

Clinical Trial Design: Lessons Learned From 20,000 Foot Ulcers

In introducing the next speaker, Dr. David Margolis, Associate Professor of Dermatology and Epidemiology, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, Dr. Malozowski commented that the number of foot ulcers had probably increased since the topic was first discussed.

Dr. Margolis agreed that the number is always changing. He opened his presentation on data that has been used for the past 3 to 4 years in designing clinical trials by crediting a few of the many collaborators he had worked with at the Center for Clinical Epidemiology and Biostatistics: Drs. Jesse Berlin, Ole Hoffstad, and Lynne Taylor who had been intricately related to the studies that would be presented, and also Drs. Jill Knauss, Jonathan Kantor, Joel Gelfand, and Brian Strom. The particular data set that

Dr. Margolis would be talking about was from Curative Health Services (CHS), which had funded his first exploratory look at the data set with an unrestricted grant in 1998 and 1999. CHS is a medical management system that has been in existence for about 12 or 13 years, during which time they have managed more than 150 centers in the United States, with centers entering and exiting the system. Currently CHS manages approximately 90 centers. Dr. Margolis added that he had also received funding from both NIDDK (DK 59154) and NIAMS (AR 02212 and AR 44695). The focus of his presentation would be on the not-so-positive success rates seen in clinical trials of diabetic neuropathic foot ulcers. These success rates are that only 30 to 40 percent of the patients will heal in about 20 weeks. As suggested by Dr. Boulton, these poor success rates may certainly have to do with lack of offloading. These success rates were used when products such as growth factors (of which only one has been approved) and cell-based therapies (of which two have been approved for diabetic neuropathic foot ulcers) were conducted.

Dr. Margolis remarked that today a fair number of studies are being done in 12 weeks rather than the previous 20-week standard. Again, about 25 percent of the patients will heal at 12 weeks, and about a third will heal at 20 weeks. Given these results, Dr. Margolis' group addressed the CHS database of information from their wound care centers with the question: Are there issues with foot ulcer healing that clinically would be easy to examine and use to make predictive or prognostic estimates of who is going to do well?

Patients in the various CHS-managed centers are treated by similar algorithms, which means that Curative goes to the centers and tries to educate physicians, nurses, and other healthcare providers about how diabetic foot ulcers and other ulcers should be treated. CHS has also maintained a database during most of their 12 years on the results of basic patient information and assessments that CHS required. Initially the database was used to assess center performance and suggest ways to improve it. Because of the long-term existence of the database, there are more than 20,000 individuals with diabetic neuropathic foot ulcers within the data set.

The first thing Dr. Margolis' group did with the CHS data set was to try to take information from the data set and find people that truly had diabetic neuropathic foot ulcers, meaning they had diabetes, had a foot ulcer, and primarily had neuropathy and did not have significant arterial disease. Different schemes were tried in order to extract the information on patients. First, they looked at the diagnostic codes used, which differ from ICD 9 codes. They then actually pulled charts to see if patients had certain attributes and created constructs and criterion that patients needed to have to confirm the diagnostic assessment that they had made from the codes.

Dr. Margolis reported that in one of the earliest studies covering patients seen between 1988 and 1997, based on conditions possessed by the patient, they could correctly code a person in the database as having a diabetic neuropathic foot ulcer about 93 percent of the time, as verified by the patient's chart. Dr. Margolis stated that the positive predictive values derived from these early studies are very good for making clinical decisions based on large administrative databases.

One of the classical, analytic epidemiology assessments his group did initially was look at events they knew were well coded in the database, such as sex, age, prior ulcers, number of ulcers, age and size of ulcer, and grade of ulcer, and try to see whether or not these attributes were good predictors of an individual's likelihood of healing at 20 weeks. For example, grade was predictive. Wounds were described using a grading and staging system from grade 1 to grade 6 that was similar to other grading systems in use, with the biggest difference being that the CHS system has been used with more than 20,000 individuals, not just a few hundred, and it has been used in more than 150 different centers by probably close to 500 different healthcare providers. If one goes back and looks at clinical trials that have been done, the vast majority, if not all the clinical trials, certainly the ones that have gone to the Food and

Drug Administration (FDA) and been used in their clinical application, involve grade 1 or grade 2, not these higher grade, wounds. Another predictive issue, especially with venous leg ulcers, was that the older or larger a wound was, the less likely it was to heal.

From a health service perspective, an issue that was important to Dr. Margolis was that regardless of the type of regression analysis done, whether fixed effects modeling or random effects modeling or GEE-based (generalized estimating equations) models, they were unable to show any center-based effect. This means that the usual concern in designing large, multicenter clinical trials about the different centers applying the protocols somewhat differently and thus creating important center-based effects on how therapies work did not happen in this case. Whether this is due to everybody in this large system being easy to educate, all getting the message, and all doing the same thing or everybody being uneducable and doing an equally bad job is unknown. However, they were all fairly equal in these multiple centers throughout multiple different states.

Dr. Margolis' Center then considered not only individual risk factors for healing, but groups of factors. This can be important in designing a clinical trial because of the inclusion and exclusion criteria used for patients, which one would assume might cause different rates of healing in different types of patients. Fairly complicated models or fairly simple mathematical models were used in this analysis. In all cases, the analysts had a fairly reasonable ability to discriminate. Dr. Margolis explained that what an area under the ROC curve (AROC) of 0.70 basically means is that given two patients, about 70 percent of the time it is possible, using this model, to correctly differentiate who will heal and who will not 20 weeks later. Another assessment used was the Brier score.

Dr. Margolis pointed out that using these prognostic models is still fairly complex for the average physician, because it requires adding up risk factors and making other statements, which can be confusing. However, his group generated a prediction chart with dichotomized risk factors for diabetic neuropathy foot ulcers. On this chart, they selected points they thought were important in terms of discrimination such as the area, age, and grade of the wound. A patient could either have a risk factor or not have risk factor. Again, this is important in designing a clinical trial because the designer can determine how well the control arm is going to do based on simple risk factors. Thus, a trial could be designed in which it is predictable that two-thirds or one-third or all patients will heal based on their initial risk factors and the inclusion and exclusion criteria used. This selection of criteria is very important when comparing different trials or different results.

An important factor in a clinical trial is being able to recruit patients. Because the CHS system is large and diverse, it is feasible to use its data to generalize to patients in the general population and to those who are likely to participate in a clinical trial. Using the data from the large CHS system, it is possible to create good prediction models that discriminate well and are well calibrated. Applying these models, it is possible to create cohorts of study subjects who are more or less likely to heal with standard therapy, which is critically important in a randomized clinical trial. This information enables the designer to create more honest power calculations. In the CHS group, there was minimal center effect, which is also important for power calculations. This may be more important from a health services perspective in terms of understanding who is going to do well in different systems and who is not. The one problem Dr. Margolis had with the data set was that some of the information is not digitally coded, it is free text. For example, wound location information combines free text with a computer-ready variable. Thus, it can be determined that 80 percent of the wounds are forefoot wounds, but identifying wound location in individual patients is not necessarily known. With new funding, the group hopes to resolve this problem and others by properly coding the variables.

In funding the database analysis project, Curative originally had wanted the university's Center to evaluate a proprietary product that they had that was called platelet releasate, which they no longer sell, and determine whether or not patients who received their platelet releasate were more likely to heal. One of the different components in the platelet releasate was PDGF, which is also the active component in one FDA approved cytokine. The Center did a propensity score study. This was done about 4 or 5 years ago just as propensity score studies were being accepted. There are now multiple studies like this. What is done in a propensity score study is try to determine why someone was selected for treatment and thus model selection bias.

For the Curative patients, multiple groups were created with relative risks and the effects on healing examined. There was an approximately 14 to 60 percent increased likelihood that an individual was going to heal when they received platelet releasate, depending on which propensity category they were in. The important result of this study, according to Dr. Margolis, was that as his group was able to know the propensity categories better, they realized that these closely paralleled the severity indices that they had developed earlier for these relative risk factors. The patients in groups one and two were all patients who had wounds that were just a few centimeters, were young wounds, and were early grade wounds of two or less, which actually were the same as the patients who were in the randomized PDGF pivotal trials as well. An interesting point is that the propensity score of about 24 percent was not all that different from the 30 percent severity index in some of the PDGF pivotal trials. What to Dr. Margolis was more interesting was that patients who were not included in randomized clinical trials because their wounds were more severe may actually have benefited more from the system, but they were not studied. Again, in designing a randomized clinical trial using cytokines or other cell substitutes, based on this information, it would be important to think carefully about what patients to include and exclude.

The next thing that Dr. Margolis' group began to do with the CHS data was to evaluate whether or not there had been a change in healing rates over time. This was of interest to them because around this time period (1998-1999) is when the new therapies came out and others would also want to know if patients were not only healing but healing faster with the new therapies. Looking at the Curative system in the early years, about a third of the patients healed. If you looked at it in the later years, about half of the patients healed. However, most of this improvement occurred well before any new therapy existed. In fact, looking at the data in greater detail shows that the percentage of patients with good prognostic signs just increased over the years. Patients were presenting with smaller, lower grade wounds of less duration. The change in healing rates and the percentage of easier to heal wounds are mirror images. The data suggests that more of these patients were being attracted to the centers and they were receiving better treatment, even before the new products became available. On the other hand, using the prognostic categories defined earlier, the evidence is that there was little change in healing rates over time for those with wounds in the most severe prognostic categories.

Dr. Margolis identified a major adverse event as another issue to be addressed when designing a clinical trial. Adverse events are of concern in clinical trials, especially in terms of how products are going to work in the future. Certainly, death is the worst adverse event that can occur in a clinical trial for a device or drug, but amputation is the worst commonly seen in a diabetes foot study. According to the CDC website (www.cdc.gov/diabetes), there has recently been a decrease in amputation rates among diabetics. This is true for all diabetics, not just those with pure neuropathy, and that may be part of the difference. However, as Dr. Reiber stated in her presentation, the CDC has also shown that there has been a rapid increase in the number of patients with diabetes, and it may well be that our definition of diabetes has changed over the years. Therefore, if one looks at the same data adjusted for the population-at-large, there has been little or no change in the amputation rate.

Dr. Margolis next presented amputation rates within the Curative system for patients with diabetic neuropathic foot ulcers who have participated in clinical trials. In general, those with significant arterial disease were excluded from trials. Within the Curative system, about 6.7 percent of the patients with diabetic neuropathic foot ulcers had an amputation within 20 weeks of care. Dr. Margolis stated that what is interesting is that almost 50 percent of these people had minor amputations such as a toe or a ray. This distinction is important because there has been much discussion in the last 5 years about the huge difference between a minor amputation and a major amputation, those that are trans-tibial or higher, in terms of rehabilitation potential and in terms of the likelihood that the patient will have additional problems. Another interesting point is that the only risk factor that is really predictive of who will have an amputation is grade. About 62 percent of those who had an amputation had a grade greater than 2.

Another factor of importance to designing a clinical trial noted by Dr. Margolis was when the amputations occur. About 45 percent of them occur within the first 4 weeks of care. This is important because many of the clinical trials that are done in wound care generally have a 2- to 4-week washout period during which patients are followed before enrolling them. Therefore, the likelihood is that it will be known that an amputation will occur before the patient is formally enrolled; however, a fair number of people will continue to have the possibility of having an amputation even years out.

Dr. Margolis also mentioned another aside that may not have to do with clinical trial management, but is interesting from a health services point of view, is that in the Curative system, the rate of amputation for a diabetic neuropathic foot ulcer really has not changed much in about 10 years. What has changed is the percentage of amputations that are minor. There were almost no minor amputations early on, whereas today the vast majority are minor amputations.

To summarize, Dr. Margolis noted that, from the large database of patients with diabetic foot ulcers, the following factors have been learned that would be useful in designing a clinical trial:

- Likelihood of finding a patient with a diabetic neuropathic foot ulcer that has various wound characteristics (e.g., size, age, and grade).
- Use of different aspects to effect inclusion/exclusion criteria and outcome (rate of healing).
- Awareness that rate of healing has changed over time, but sudden adverse events do occur, although most happen in the beginning of a trial.

Surrogate markers were the final item that Dr. Margolis wished to discuss regarding what has been learned about designing clinical trials. Information might be acquired from the CHS database to indicate how long a study needed to be. Most of the studies in the database were 20 weeks long, which is a very long period of time and resulted in very expensive studies. More recently many studies have been 12 weeks long. In determining appropriate study length, Dr. Margolis suggested that it would be very nice to have a surrogate marker, something that early on would determine if the wound was going to heal. He cited the following FDA definition for a surrogate marker: A surrogate endpoint as defined by Temple is "a laboratory measurement or a physical sign used as a substitute for a clinically meaningful that measures directly how a patient feels, functions or survives." Standard surrogate markers today include blood pressure lowering to prevent cardiovascular disease, lipid lowering to prevent cardiovascular disease, and so forth.

To answer the question "Is there something that we can use that would allow us to do a shorter study and still be able to say that a product might actually be beneficial?", Dr. Margolis' group looked for potential surrogates occurring at 2, 4, and 6 weeks for a 12-week care study or at 2, 4, 6, and 8 weeks for a 20-week care study. He presented the results at 4 weeks looking at a 20-week study from a first pass through the CHS data set and looking at healing rate changes. More elaborate studies are planned for the future. In two groups of a total of about 28,000 patients, a healed group and an unhealed group, there were expected

differences in terms of the duration and size of the wounds. However, the average log healing rate for those who healed in the first 4 weeks was 0.062, whereas for those who did not heal, their average log healing rate was 0.007. There is a 10-fold difference between the two numbers. According to Dr. Margolis, this indicates that it is possible to do a fairly small early study and find broad differences between the healing rates very early on that are predictive of what is going to happen later on.

For those who live in a dichotomous world and want to see how this reflects what is ultimately going to happen, Dr. Margolis said to take these rates and try to maximize differences between sensitivity and specificity using AROC curves. If the threshold for the log rate is passed, about 70 percent of the time one can actually predict at the 4^{th} week of care who is going to heal and who is not going to heal at the 20^{th} week, which is good for a surrogate. Dr. Margolis was not suggesting that the ultimate goal of healing be replaced in a clinical trial, but that for an earlier phase study, such as a phase 1 or phase 2, where the goal is to get information on whether or not it is worthwhile to pursue a large study, it would be valuable to be able to determine that about 70 percent of the time the trial's premise will be correct at just 4 weeks.

Dr. Margolis summarized what has been learned so far: First, that it is fairly easy to distinguish between hard and easy to heal wounds, which will have important implications for the size of the study and for comparing studies. To compare two studies, one must first determine whether or not the patients were the same. Second, early information in the growth factor studies indicates that there might have been a more profound difference and more patients might have been helped if the focus had been on the harder to heal wounds. Third, there are very minimal center effects. This was true looking at three or four different studies. This fact has important implications for sample size calculations as well, especially if there is an important interest in center-based effects, based on some of the information Dr. Boulton discussed. For example, there could be profound differences in terms of how centers interpret offloading and how they encourage their patients to use offloading. Fourth, there is a year-based effect in the easy-to-heal wound; therefore it is necessary to be very careful about using uncontrolled clinical trial information from 2003 and comparing it against data from 1996. Fifth, amputations are unlikely adverse effects, but they do occur and they tend to be minor. That is important in terms of the consent form and in terms of how patients are counseled. It is also necessary to realize that there are going to be some amputations in almost any clinical trial. Lastly, it may be possible to use surrogates based on the change in the size of the wound, at least for the early stages of drug development.

Dr. Margolis made the following suggestions for the future of clinical trials:

- It would be possible to do cluster randomized trials with the prediction models and the surrogate models to see how they might impact practice. Predicting how patients may do with the therapy may actually influence physicians' and other healthcare providers' standards of care.
- It is possible to create analyses, using data and models, of the impact of subject selection strategies on clinical trial feasibility, including the impact on patient recruitment, the size of trials, how expensive the trials are going to be, and the likelihood of finding differences.
- It may be possible to go through the database, depending on funding sources, to find better surrogates than just area changes.
- It should be possible, from using this information, to design clinical trials based on how patients are going to do, with a more profound understanding of whether or not they are going to succeed or not succeed, and thus improve sample size calculations.

Brief Discussion. Dr. Kurt Stromberg of the FDA's Division of Therapeutic Proteins, Office of Biotechnology Products, asked Dr. Margolis if he thought that the surrogate of reduction in wound size as a therapy model to shorten studies would be more meaningful if it were derived from 200 patients in randomized controlled trials versus non-randomized control data from 20,000 patients.

Dr. Margolis answered that in previous work his group had found very similar surrogates using data sets from companies that did earlier studies and looking at their control arms. He had never been given the opportunity to look at treatment arms. Part of the problem with the surrogate is that one does not know how the treatment is working through the surrogate. Certainly the treatment could be working late through the surrogate, in which case the effect will not be captured, or it could be working in an entirely different mechanism, something that emphasizes the surrogate in an odd way. All this previous work was based on status therapy. The data is not very different. What is better about the current work is that, with 20,000 people, the precision of the data is much better, In terms of doing some of the other analyses, like looking for cutpoints within that and trying to determine sensitivity and specificity, the other data sets just were not large enough to do that adequately.

Dr. Margolis added that they had done analyses involving a few thousand patients as opposed to 28,000, but that was not really a randomized trial, it was a cohort, one arm of a randomized study. To evaluate how the surrogate worked in the treatment, again it is a cohort. The two groups cannot be compared. If the question is, "Would it be worthwhile to go back and take the randomized clinical trial data that showed an effect and see whether or not the effect could have been seen at 4 weeks," that would be a randomized situation, and that would be interesting."

Dr. Malozowski, asked Dr. Stromberg, if, given the fact that the information is available at the FDA from many product studies that have been done and given the fact it is not important what product was used, would it be possible to access the data blindly to assess whether these surrogate endpoints are valid or not.

Dr. Stromberg replied that this is proprietary information that the FDA cannot reveal. It would have to be done through the companies themselves. Hopefully, they might be encouraged to release what is antique data because in the end this would benefit them if it enabled shorter trials.

Dr. Margolis agreed with Dr. Stromberg, but pointed out that it had been extremely difficult to obtain even the control arm data from the companies he had dealt with for his meta-analyses and there were severe restrictions on what data was available to him and on how he could use it. None of the companies were willing to give him longitudinal data. He only could obtain data on first visits and on outcomes. Dr. Margolis asked Dr. Stromberg, if he thought the companies were more likely to cooperate with Federal agencies.

Dr. Stromberg questioned where the pressure point was to encourage individual companies to mobilize information that would be useful to the country as a whole.

Dr. Malozowski, related that when he was at the FDA looking at postprandial glucose changes, although they had access to proprietary data, companies would not discuss outcomes related to glucose control measured by HbA1c, so his office looked at data from five different products and came to a conclusion that was shared with the American Diabetes Association at an appropriate time without releasing what products were involved. Internally, the data was presented as being from products a, b, c, d, and e and they were able to determine whether or not there was a relationship to glucose control. Dr. Malozowski suggested that similar exercises could be done by others internally looking at other proprietary data on wound healing.

Dr. Stromberg commented that typically, the FDA has the data since it is the agency that must request the data analyses and also the agency that must decide if shorter trials for a device or drug would be acceptable. The FDA is interested in the treatment arm, as is everyone else. The agency could mobilize a position in-house to deal with the data they have without necessarily having to publish it or release it. They could use the data to reach a conclusion that they believed was satisfactory.

Dr. Margolis repeated that he was not suggesting that the surrogate be a replacement for a pivotal study, but that it be used in earlier phase studies. He offered to work with the FDA to accomplish that goal.

Clinical Protocols for Treatment of Inpatients and Outpatients With Diabetic Foot Ulcers

Following a brief break, Dr. Malozowski introduced Dr. Harold Brem, Director, Wound Healing Program, Mount Sinai School of Medicine, New York.

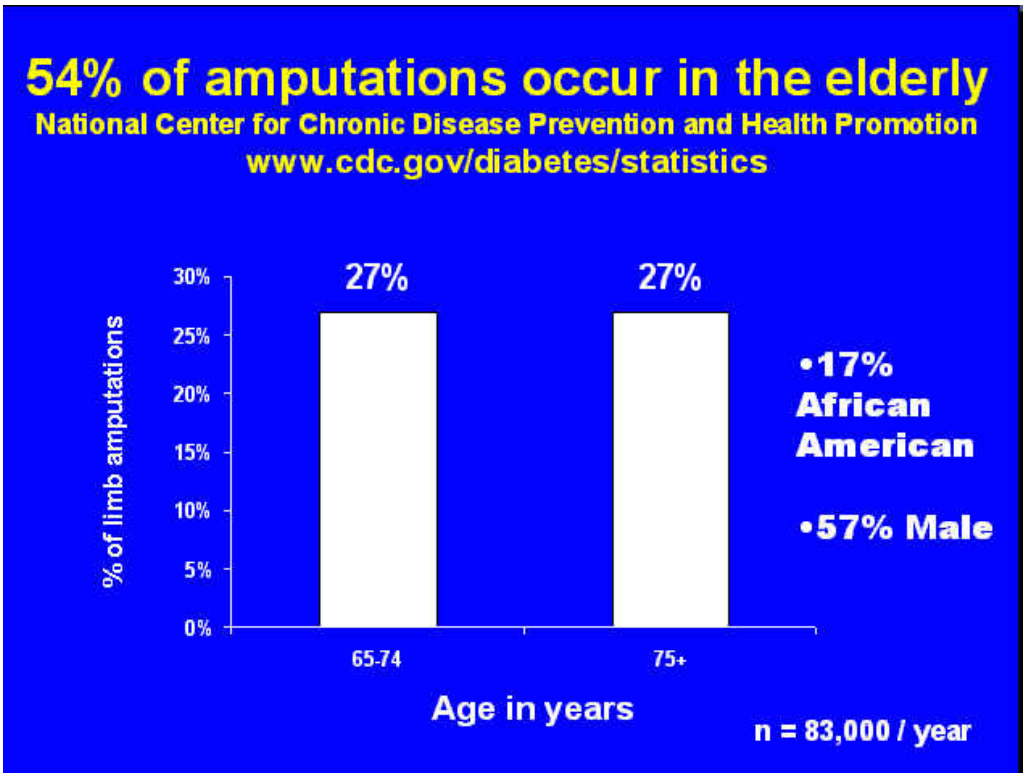
Dr. Brem expressed his appreciation to Dr. Moshell and Dr. Malozowski for laying the groundwork for this meeting and creating a true interdisciplinary environment to discuss care for persons with diabetes and foot ulcers. Dr. Brem also acknowledged Dr. Hyde's and Dr. Abraham's generosity with their time over the last 5 years, which demonstrated to him the substantial support system the NIH had in place for clinicians and researchers. He also thanked NIDDK, the American Diabetes Association, and the United Spinal Association for their assistance in funding his research.

Need for Establishing a Standard of Care and Standard Protocol. Dr. Brem stressed that there needeeds to be a focus on decreasing amputations in patients with diabetes. He believes that it is important to establish a foundation of expectation, both in and outside the hospital, on the part of the physician, the nurse, and the patient with diabetes who suffers from related wounds. Accomplishing the goal of decreasing amputations also requires the use of a standardized protocol, regardless of who is being treated or where they are being treated. Dr. Brem emphasized that the most important paradigm is that ***patients who do not have either ischemia or osteomyelitis should be expected to heal all of their wounds and always avoid amputation, if the protocol is strictly followed***. What is not known is the timeframe in which each of these patients will heal.

Dr. Brem said that he would focus today's presentation on such questions as:

What is the standard of care?
What is the data?
What should be the focus of future directions?

Extent of Amputation Rate in the Elderly. Dr. Brem noted that the problem of foot ulcers is particularly critical in the elderly. Dr. Brem said that aging in and of itself does not necessarily impair wound healing. What is not known at this time, is whether aging when combined with diabetes has a synergistically negative effect on healing and thereby results in the high amputation rate in the elderly (Slide 1). An alternative hypothesis is that the protocol of standard of care is not applied to the elderly immediately on first observation of the ulcer because more attention is placed on other co-morbidities.



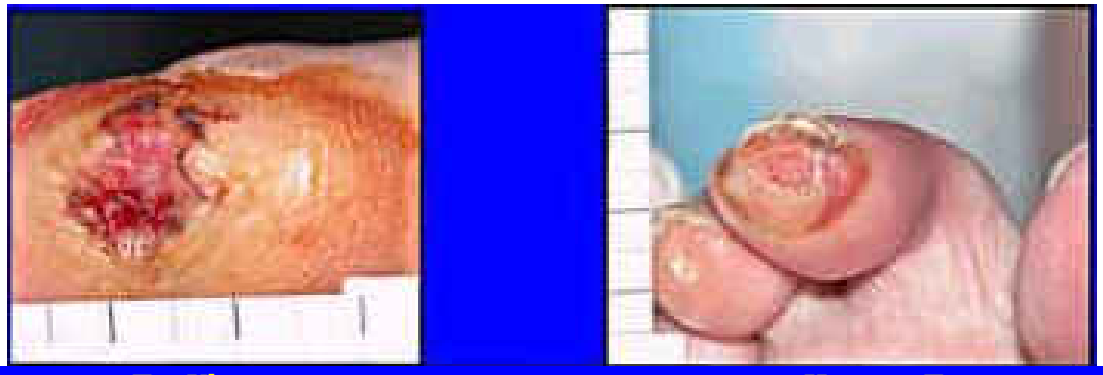
Slide 1 (summarized from CDC Website)

Clinician's Approach. Dr. Brem posited that clinicians who see a patient with hypertension, early breast carcinoma, or a one-millimeter melanoma expect the patient to be cured in a relatively short period of time regardless of comorbidities, based on the patient's ability to follow strict-well-established protocols. Dr. Brem stressed that there is no reason for clinicians not to treat patients with diabetes who have a foot ulcer with the same level of care. In 2003, the data clearly suggests that in the absence of osteomyelitis or ischemia, patients who strictly adhere to a well-established protocol should be expected to heal.

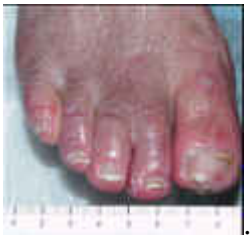
Dr. Brem presented slides of a small portion of a typical day's patient population at the Mount Sinai Wound Healing Program. He said these patients are representative of those at most wound centers. The patients were being treated for foot wounds varying in severity and underlying conditions and comorbidities. Dr. Brem stressed that the importance of the variety in clinical presentations being shown was that the protocol (which he would be describing later) was the same for each of them.

In defining a foot ulcer, Dr. Brem said it is any break in the skin of the foot of a person with diabetes; although the most common definition is of a neuropathic plantar foot ulcer, this definition should be expanded. He emphasized that the pathogenesis and sometimes the treatment would differ based on the etiology, location, duration, underlying bony abnormalities, and many other variables of the foot ulcer.

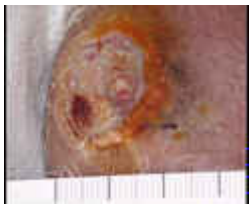
Indicating a patient with a toe ulcer and a hammer toe (Slide 2), Dr. Brem explained that the hammer toe must be corrected if the patient's ulcer is to be expected to heal and stay healed. A patient with a foot ulcer often may have fungal nails, as shown in Slide 3. For the ulcer to heal, a combination of topical and/or systemic therapy may be necessary in addition to mechanical debridement or cutting of the nails. Significantly more investigation must be done on fungal nails.



Slide 2



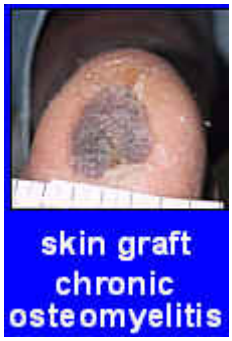
Slide 3



Slide 4

Dr. Brem explained that another issue in diabetic foot ulcer treatment is treating bacteria that often delay healing. For example, the wound shown in Slide 4 does not appear infected but the wound is not healing (i.e., contracting and epithelializing) because of methicillin-resistant Staphylococcus Aureus. Clinicians often wait until there is cellulitis or drainage to treat a neuropathic foot ulcer. He said that this was a mistake because often the wound is infected, but the inflammatory response is suppressed in the neuropathic foot ulcer.

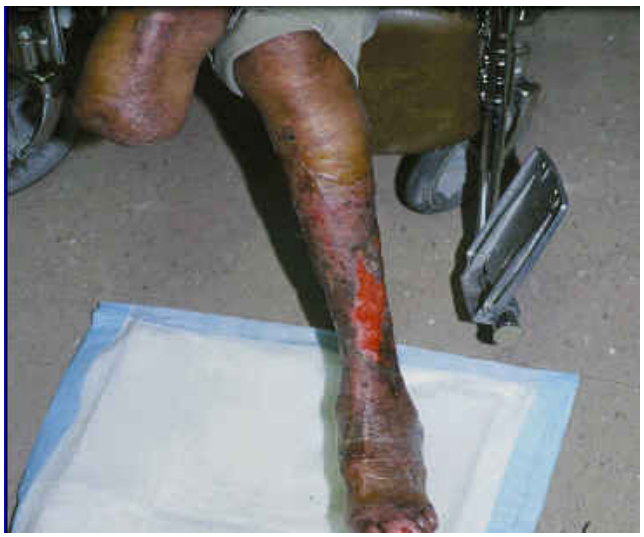
As Dr. Boulton had described earlier, Dr. Brem said that the type of off-loading for a diabetic foot ulcer is often dependent on its anatomical location in the foot. For example, the off-loading used for the heel ulcer is completely different from the off-loading used for the plantar foot ulcer.



Slide 5

Another example of the diversity of conditions seen in these patients, is a patient with chronic osteomyelitis, who underwent an autologous skin graft (which Dr. Brem feels is usually a mistake) (see Slide 5). Almost no publications demonstrate the efficacy of such a graft. In this patient's case, the ulcer was tiny, but drainage was significant. Dr. Brem noted that any drainage is unexpected and is a clinical symptom that must be rectified.

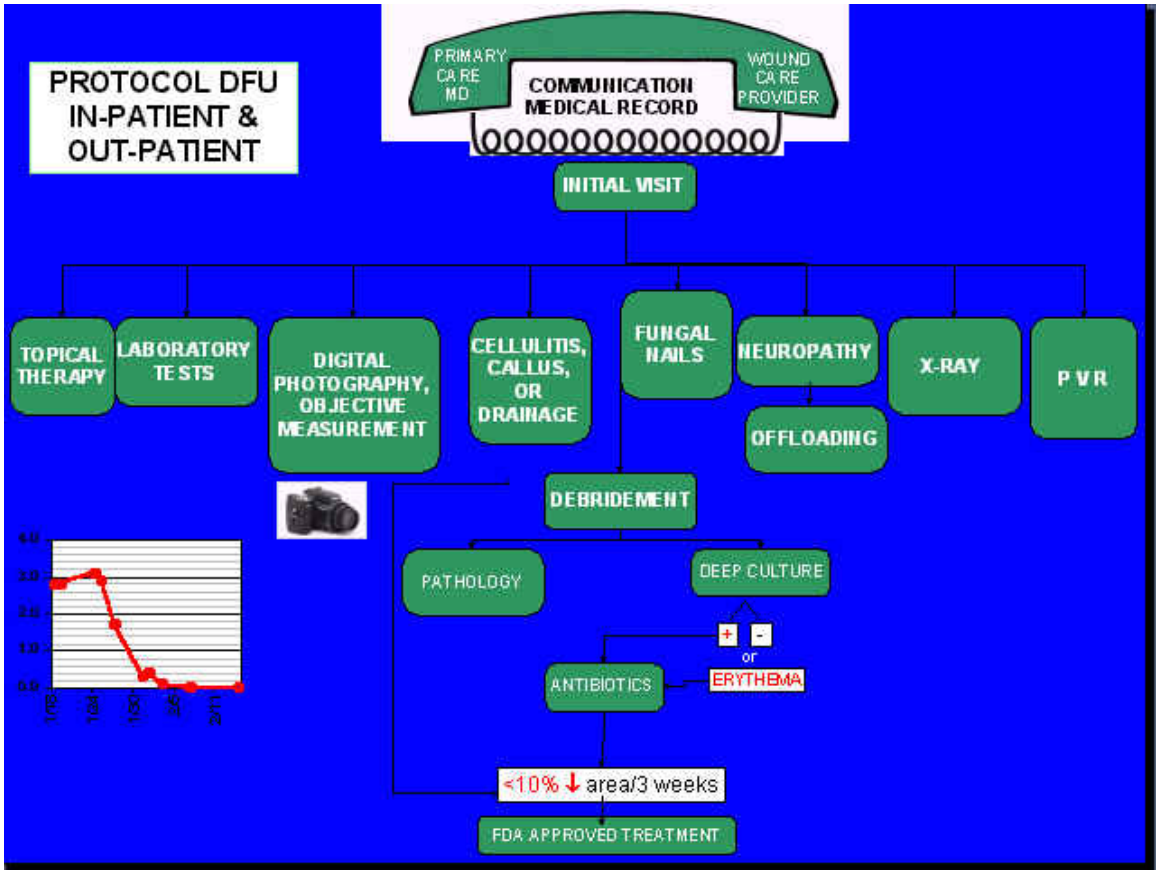
Another unfortunate example of the lack of early treatment is seen in Slide 6. This patient had his right leg amputated; essentially because of a faulty diagnosis. The patient was diabetic and diagnosed with PVD (peripheral vascular disease). The assumption made at the time of diagnosis was, "He has diabetes, so he has PVD," implying a lack of adequate blood supply in the patient. In actuality, the patient had a good blood supply. Dr. Brem said the actual diagnosis should have been diabetes with a venous ulcer, which is in essence a simple wound to treat, if treated on first observation.



Slide 6

Recommended Standard Protocol. Dr. Brem stressed that the heterogeneity of the foot ulcer mandates a need for a standard protocol. All patients, regardless of type of complication or comorbidity, should be treated with the same protocol. As illustrated in slide 7, the following is the protocol used for all patients at the Mount Sinai Wound Healing Program:

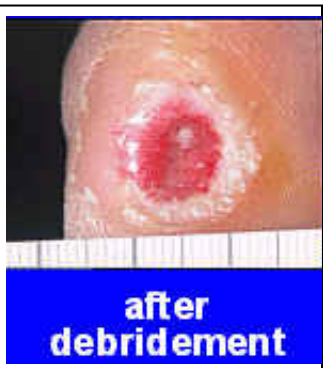
- Photograph the wound.
- Measure the wound using planimetry.
- Objectively evaluate the limbs for ischemia.
- Rule out osteomyelitis.
- Debride the wound sharply.
- Provide moist wound healing.
- Offload the foot.
- Eliminate cellulitis, infection, callus and drainage.
- Expect any wound without osteomyelitis or ischemia to heal.



Slide 7

Debridement. Dr. Brem emphasized that debridement must be performed sharply, as another measure to prevent amputation and accelerate healing. When the wound is debrided, the pathologist should examine all specimens. The wound should be debrided to the outer edge of the hyperkeratotic tissue (see Slide 8).

Debridement can sometimes be worrisome to the patient, who may fear that amputation may be inevitable, since the appearance of the wound and its concomitant infection is frightening. Dr. Brem said, that the patient should be reassured that mechanical debridement is a necessary part of treatment, because it will clean out local bacterial contamination and infection and prevent the possibility of amputation and/or osteomyelitis (See Dr. Boulton's and Dr. Kirsner's presentations for additional data).



Slide 8

Additionally, the physician treating a diabetic foot ulcer should contact the patient's primary care physician to ascertain the patient's current medications—in particular, ACE inhibitors—the patient's glucose control, the ability of the patient to manage offloading, and other information related to the treatment of the wound. This contact should include sharing with the primary care physician the treatment regimen for the patient's diabetic foot ulcer. The protocol also should include measurement of pain and quality of life.

If the wound heals less than 10 percent over a 3-week period after debridement, Dr. Brem recommended that an FDA-approved biological treatment be considered. He urged elimination of the concept of a non-healing wound. Dr. Brem insisted that if the initial treatment is appropriate and performed at onset, the term "non-healing wound" need not enter one's vocabulary.

Dr. Brem noted that the question of clinical involvement and staffing also enters into a discussion about care for the diabetic foot ulcer patient. Included in the range of clinicians and staff for patient care that the physician treating the patient should integrate are the following: internist, radiologist, pathologist, physiatrist, physical therapist, occupational therapist, podiatrist, dermatologist, anesthesiologist (e.g., pain control), podiatrist, diabetologist, psychiatrist and nurses. There may also be a need for a neurologist, if neuropathy is a symptom. Dr. Brem stressed that all these clinicians should be aware of the possibility of a referral from the treating physician for a patient with a diabetic foot ulcer. To better assist the patient, each clinician ideally should be familiar with the protocol practiced by the others in this expanded circle of healthcare providers.

Focus for Future Practices and Research. From the experience with his wound center's patients in the program as well as from his staff's clinical studies and experimental work, Dr. Brem offered the following suggestions for future practices and research:

- Determine a rate of healing for these patients. Based on the wound and its complications, does the wound appear to be one that will heal in 3 months? Six months? Eight months?
- Prove, by strictly practicing a standard protocol, that the amputation rate for these patients can realistically be less than 10 percent, including those with ischemia and osteomyelitis.
- Study separately the healing of wounds of patients with diabetes who do not have a diabetic foot ulcer.
- Develop angiogenesis stimulators for use in the healing of wounds.
- Develop better delivery systems for growth factors—VEGF, bFGF, EGF, GMCSF and PDGF-BB.
- Study the cell populations of patients with diabetes to observe specific changes at the cellular level with treatment by growth factors, noting changes in angiogenesis and related indicators of healing.
- Focus on outcomes with the purpose of changing the standard of care (Dr. Brem suggested this would be a particularly important area for the NIH, CDC, and the FDA.)
- Post on the NIH/NIDDK/NIAMS websites additional information regarding the expectation in healing diabetic foot ulcers, the work funded by the various institutes, and additional patient and provider information regarding available treatment modalities for this condition—specifically offloading. (Dr. Brem noted that the sites currently provide information on foot care, but very little on the care of wounds.)
- Create a Federal mandate to solve the problem of the diabetic foot ulcer, as has been done for numerous other diseases.

Regarding the last bullet, Dr. Brem emphasized that the mandate should go hand in hand with an official standard of care that would directly address the issue of why a patient under the care of one physician suffers amputation, while another with the exact same condition receives appropriate treatment and heals.

As an example of the overall goal that he proposed, Dr. Brem presented a slide of a patient who healed in 4 weeks, representing the expected standard of care from following the protocol described (see slide 9).

Slide 9

Dr. Brem concluded by saying that he looked forward to a time when amputations will have substantially decreased and perhaps have been all but eliminated for the patient with a diabetic foot ulcer. He recommended that a consensus conference to address standard of care and a standardized protocol for these conditions be organized.

Adjunctive Therapy for Diabetic Foot Ulcers: Current and Future Approaches

Dr. Malozowski introduced the final speaker prior to the discussion period, Dr. Robert Kirsner, Associate Professor, Department of Dermatology and Cutaneous Surgery, Department of Epidemiology and Public Health, University of Miami School of Medicine.

Dr. Kirsner disclosed that in discussing therapeutic approaches he would be talking about some proprietary products of companies with whom he had worked. In presenting these adjunctive therapies and looking towards the future, Dr. Kirsner said he preferred Yogi Berra's statement that "You can observe a lot by watching" to the more pessimistic quote from Sir William Osler that "Half of us are blind, few of us feel, and we all are deaf."

Today, Dr. Kirsner said that the group had learned, from what Dr. Margolis eloquently spoke about and what others had observed, that current practices were not very successful at treating diabetic foot ulcers. According to the outcomes from clinical trials, between 24 and 31 percent of patients are healed between 12 and 20 weeks (*Diabetes Care* 1999 May;22(5);692-5). Some may say, "Well, that's a select population of difficult-to-heal patients." Dr. Margolis also described how patients from a large database are treated in practice. Only between 30 and 50 percent of these patients' diabetic foot ulcers healed in 32 weeks (*Diabetes Care* 2001;24;483-8). Dr. Boulton spoke on the importance of offloading and Dr. Brem emphasized debridement as a standard of care. Given all this information, Dr. Kirsner said that the question: remains "Why aren't we achieving the outcomes?" Is the answer something simple or not? Is it

because of poor compliance with the methodologies by patients or clinicians? Or is something else going on? Is there a refractory subset of patients that just will not respond to this modality?

In responding to the questions he had raised and the subject of the refractory subset, Dr. Kirsner first referred to Dr. Margolis' presentation and the research literature on baseline predictors such as the size, depth, and duration of an ulcer (Margolis et al. *Diabetes Care* 2002;25:1835-9; Margolis et al. *Arch Dem* 2000;136:1531-5); healing rates or surrogate outcomes predictive of healing such as a wound being on a certain wound-healing trajectory (Robson MC, Hill DP, Woodske ME, Steed DL *Arch Surg* 2000;135:773-7) or decreasing in size over a certain period of time (Kantor J, Margolis DJ *Br J Derm* 2001;142:960-4); and the value of dichotomizing patients into healers and non-healers to look at why patients who are not going to heal do not heal.

Next, Dr. Kirsner offered proposed mechanisms—unresponsive or senescent cells present either in the wound or in the callous around the wound, a proteolytic or inflammatory environment, deficient or unavailable growth factors, or bacterial interference—as being responsible for chronicity in diabetic foot ulcers. Some of these mechanisms also are true for other chronic wounds such as abuse ulcers or pressure ulcers. He then presented current and future modalities that have been applied to address each of these mechanisms.

Cellular Senescence. Cells that are older differ from young cells in that they are less likely to undergo apoptosis, they do not grow as well, and they produce certain matrix proteins. Dr. Kirsner illustrated this difference with an example: using a platelet-derived growth factor as stimulus, his slide showed that, while fibroblasts taken from acute wounds and fibroblasts taken from a dermis responded well, those taken from chronic wounds did not and the longer the fibroblasts were in the wound bed, the less responsive they were to stimuli (Agren et al. *J Invest Dermatol* 1999). This information correlates with the idea of duration of ulcer being predictive of healing, along with the concept of *in vitro* senescence.

A number of companies have addressed the idea that cells are perhaps abnormal in a chronic wound by delivering non-senescent cells to diabetic foot ulcers to stimulate the senescent cells or provide new cells to stimulate healing. The first FDA-approved product based on this concept was Apligraf®, which is a bilayered living skin construct with neonatal fibroblasts placed in bovine type 1 collagen and then neonatal keratinocytes grown on top of it. A second product is a dermal construct, where neonatal fibroblasts are placed on an absorbable suture material, and in culture those fibroblasts produce a neodermis. These allogeneic cells, whether in Apligraf® or Dermagraft®, were applied to diabetic foot ulcers. In the pivotal trial that led to Apligraf's® FDA approval, patients who received the product plus good wound care were 2.1 times more likely to heal than patients who received good wound care alone (*Diabetes Care* 2001;24:290-5). The results were similar for Dermagraft®; patients who received the product were 1.7 times more likely to heal than patients who received standard care (*Diabetes Care* 2003;26:1701-5). Future skin constructs include OrCel™, another bilayered cellular matrix that is different because it is cryopreserved, making it more of an off-the-shelf product that can be kept in the clinician's office. It also is grown differently. Although bilayered, it is simultaneously cultured fibroblast and keratinocyte, so the culture time is somewhat shorter. It has been suggested that perhaps this epidermis, which is not mature, may provide greater stimulation than perhaps a mature epidermis. Looking at the concept of these tissue-engineered skins—because the products are not present for a very long time in that they are allogeneic materials—one sees that their main function is to provide growth factor stimulation to the previously non-healing wound. In OrCel™, there is a large variety of growth factors produced by the product (including IL-1b, KGF-1, M-CSF, TGF-a, and TNF-a) compared to the growth factors present in normal acute wounds treated by standard of care only. In a small 12-week pilot study done in patients with diabetic foot ulcers, greater healing was found in patients who received standard of care plus OrCel™ compared to standard of care alone (http://www.ortecinternational.com/~johncapa/technology/orcel/31).

Inflammatory Environment. The second concept presented by Dr. Kirsner of why wounds in patients with diabetes may not heal is the presence of a environment which is not conducive to healing. Unlike patients with acute wounds who go through the three phases of healing in a normal fashion, patients with non-healing diabetic foot ulcers may remain in the inflammatory phase and therefore not progress normally. There is data in other chronic wound situations indicating this chronic inflammation may be the case. Investigators have studied cytokine levels and mitogenic activity, comparing both healing ulcers and non-healing ulcers (Trangrove NJ, Bielefeldt-Ohmann H, Stacy MC *Wound Rep Reg* 2000). They found that there is an increased level of inflammatory cytokines in non-healing ulcers compared to healing ulcers. The importance of this is that the pro-inflammatory cytokines (such as Interleukin-1, tumor necrosis factor-alpha) stimulate the production of a proteolytic environment—specifically, some of the matrix metalloproteinases (MMPs)—and in addition, they inhibit some of the natural inhibitors of these metalloproteinases, the TIMPs (tissue-derived inhibitors of metalloproteinases) (Ito et al. *Fed Euro Bio Chem Sci* 1990;269:93-95; Murphy et al. *Ann NY Acad Sci* 1994;732:31-41). Dr. Kirsner said the problem with this scenario is that a coordinated expression is needed of both MMPs and TIMPs to result in normal healing (*Plast Reconstr Surg* 2000;108:236). Not only are proteinases elevated in chronic wound fluid and inhibitors lowered, but in fact the inhibitors are inactivated, resulting in an imbalance of the proteinases and inhibitors. Investigators recently studied this and found that the higher the ratio of MMP-9 (one of the proteinases) with their inhibitor (TIMP-1), the less likely this was to correlate with healing (*Wound Repair Regen* 2002;10:26-37). This means there exists a possible biochemical assay to predict healing. Acute wound fluid placed on cells causes them to grow. Contrarily, fluid from chronic wounds placed on fibroblasts in culture does not cause them to grow. In fact, it induces senescence. Therefore, one thing the future may hold is a way to test fluid from a wound, with a litmus-like test, and predict whether or not the wound is going to heal.

Dr. Kirsner explained that other investigators have proposed that another way to approach this chronic wound fluid that is inhibitory is to heat it (Park HY, Shon K, Phillips T: *Wounds* 1998;10:189-192). In the non-heated chronic wound fluid, the cell growth is low. As the temperature is raised just a few degrees, the cells grow faster. One company has come up with a product called Warm-Up that does this using a temperature control unit, an AC adaptor, a noncontact wound cover, and a warming card. They conducted a randomized trial of 20 patients and found that 70 percent of the wounds treated with the device healed after 12 weeks compared to a control group where 40 percent healed (*J Foot Ankle Surg* 2003;42:30-5).

Researchers at the University of Virginia thought about the proteinases in a different way. They crafted a gauze that selectively absorbs elastase, one of the destructive proteinases found in chronic wound fluid (Edwards JV, Yager DR, Cohen IK et al: *Wound Repair Regen* 2001;9:50-58). Another company has specifically manufactured a product that, according to them, absorbs liquid and physically binds and activates matrix metalloproteases. Each of these products is based on removing or changing the proteolytic environment. According to Dr. Kirsner, over the next few years, a number of additional anti-inflammatory agents will probably be seen. At least two are currently in clinical investigation. One is an agonist of adenosine receptors, which is an anti-inflammatory that is in early trials for the diabetic foot ulcer (Montesinos et al. *J Exp Med* 1997). Another anti-inflammatory agent, lactoferrin, is also in human trials for diabetic foot ulcers (Engelmayer et al. *Wounds* 2003).

Other investigations are underway to reverse the proteolytic environment, one of which is the topical use of doxycycline. Doxycycline is used systemically in a number of specialties (dentistry, rheumatology, vascular disease) specifically to reverse proteases. A group from the University of Florida has shown that increasing doses of doxycycline reduces TNF-alpha in a dose-dependent way and reduces the proteolytic environment. A small trial of patients that received the doxycycline topically has done quite well (Chin et al. *Wounds* 2003). A larger trial is ongoing.

Bacterial Interference. Dr. Kirsner stated there is a long-standing paradigm that bacterial count is paramount to non-healing of wounds, that once there is greater than perhaps 10^5 organisms, the wound is infected. However, he added, some people in wound healing have felt that there may be something else happening, that the bacterial count is not leading to a frank cellulitis, but perhaps just causing ulcers to be non-healing. Although the number of bacteria is an attractive concept, Dr. Kirsner suggested that if he raised the issue of beta-hemolytic streptococcus, some persons would say "That's different." Therefore, maybe virulence of the organism is important. If he asked, "What about an AIDS patient?" again some would say "They're different. They're immunosuppressed." This raises the question "Are diabetics immunosuppressed?" They may be. Dr. Kirsner suggested that perhaps a better way to determine whether a patient is infected or has an increased bacterial burden that may lead to a poor healing wound might be to consider several critical variables affecting the wound: amount of necrotic tissue, number of organisms, bacterial virulence, and patient's immune response. He noted that the formula would then be:

$$\text{Infection} = \frac{\text{dose of bacteria x virulence}}{\text{host resistance}}$$

Dr. Kirsner continued by remarking that in addition to sheer numbers, perhaps quality or the type of bacteria may be causing the wound not to heal, or possibly something new that has been suggested—the formation of biofilms. With regard to quality, better agents and more agents are needed for MRSA because unfortunately patients with chronic wounds have a lot of MRSA. Dr. Kirsner cited two studies that associated the presence of MRSA with longer healing times in a large percentage of patients, 40 percent of whom had MRSA in their wounds (Kac et al. *Arch Dermatol* 2000;136:735-9; Tentolouris et al. *Diabet Med* 1999;16:787-71).

Dr. Kirsner explained that biofilms have been implicated in many chronic microbacterial diseases. The characteristics that make biofilms special are that they adhere tightly to biologic and non-biologic surfaces and they form a polysaccharide matrix that makes them resistant to conventional therapy. In special circumstances, free-floating or planktonic bacteria form a biofilm, and these biofilms have recently been found in chronic non-healing ulcers. The future holds new ways to handle these biofilms: maybe enzymes will address the polysaccharide matrix or physical modalities (ultrasound, ultraviolet light, electrical stimulation) may be used to break up biofilms and remove the bacterial interference.

Deficient and/or Unavailable Growth Factors. Dr. Kirsner said that, because of some of the factors in a chronic wound, particularly proteases (perhaps bacteria), some investigators feel platelet-derived growth factor is very useful, but it would be even better if delivered in a better way. He mentioned that Dr. Margolis had spoken of the FDA-approved recombinant platelet-derived growth factor (becaplermin) that had shown a moderate improvement in healing in its pivotal trial (Weiman TJ, Smiell JM, Su Y: *Diabetes Care* 1998;21:822-7). At the University of Pennsylvania, Dr. Margolis and others are planning, but have not begun, a study in gene therapy, delivering platelet-derived growth factor through a gene construct in an effort to stimulate the healing of diabetic and neuropathic foot ulcers (Margolis DJ, Cromblehome T, Herlyn M: *Wound Rep Regen* 2000;8:480). As recently as this year, *Diabetes Care* reported that epidermal growth factor had a significant healing rate of 95 percent at 12 weeks in a dose-dependent fashion when given in a randomized study of 61 patients with diabetic foot ulcers (*Diabetes Care* 2003;26:1856-61). Dr. Kirsner added that it is possible that other growth factors are on the horizon for diabetic foot ulcers.

Nerves and Enzymes. Dr. Kirsner reported that, in addition to the importance of sensory neuropathy and the results of a loss of protective sensation described by Dr. Boulton, other researchers have thought about diabetic neuropathy in a different way, as the loss of pro-healing cytokines. He noted that fetal wound healing is a model for the importance of nerves in healing. If wounded, a fetus does not scar. Many theories have been suggested as to why fetuses have scarless healing. Perhaps the difference is in the types of transforming growth factor beta, differences in collagen, or differences in the environment. Recently it has been suggested that neural stimulation is important for scarless fetal healing. The reason for this is that in studies involving fetal lambs, when different types of wounds were placed in the limbs, one of which was de-enervated and the other left intact, it was found that the limb that was de-enervated had slower healing and had scarring as opposed to the limb that had enervation intact, thus suggesting the importance of nerves in healing (*Plast Reconstr Surg* 2000 January;105(1):140-47).

Other investigators have found that fewer nerves are present in the epidermis and papillary dermis of patients with diabetes. This is also true in diabetic murine models, which had significantly fewer epidermal nerves, and the fewer nerves correlated with increased healing times in mice with diabetes (Gibran NS, Jang YC, Greenhaigh DG, Muffley LA, Underwood RA, Usui ML, Larsen J, Smith DG, Bunnett N, Ansel JC, Olerud JE *J Surg Res* 2002;108:122-28). This has resulted in the concept that in hyperglycemia or diabetes, there are less nerves and thus less of the factors that nerves elicit to speed healing (Spenny ML, Muangman P, Sullivan SR, Bunnett NW, Ansel JC, Olerud, JE, Gibran NS: *Wound Repair & Regen 2002 Sep-Oct*;10(5):295-301).

Dr. Kirsner explained that in addition to fewer nerves in the skin of those with diabetes, there are also more enzymes that break down some of the proteins that may speed healing. In the animal model for diabetes, the db/db mouse, there is greater endopeptidase activity in diabetic mice than there are in normal mice. Similarly, in patients with diabetes, there is a higher level of the protease that breaks down some of those products that nerves release compared to controls (Antezana, MA, Sullivan, SR, Usui ML, Gibran NS, Spenny ML, Larsen JA, Bunnett JC, Olerud JE *J of Invest Dermatol* 2002;119:1400-04).

Fewer nerves and more enzymes may lead to delayed or non-healing in diabetics. Dr. Kirsner reported that it has been suggested that, given this situation, perhaps providing something that the nerves elicit, such as substance P, might speed healing. At least in one study in animals, substance P shortened the time to closure in animal models of diabetes (Gibran NS, Jang YC, Isik FF, Greenhaigh DG, Muffley LA, Underwood RA, Usui ML, Larsen J, Smith DG, Bunnett N, Ansel JC, Olerud JE *J Surg Res* 2002;108:122-28).

Future of Diabetic Complications. Dr. Kirsner summarized that future research needs and opportunities were certainly to prevent, to regenerate, and to treat diabetic complications. In addition to neuropathy, there is vascular insufficiency that may cause disease directly or through neuropathy. Dr. Kirsner cited in a slide a number of efforts at gene therapy for peripheral vascular disease (PVD). The importance of the PVD studies for neuropathy is that some products such as vascular endothelial growth factor (VEGF) are now being examined for diabetic neuropathic ulcers. Thus information gained from PVD is being applied in another setting.

Returning to the refractory subset, Dr. Kirsner said he had presented several ways to reverse non-healing of chronic diabetic foot ulcers—eliminate unresponsive and/or senescent cells, alter the proteolytic/inflammatory environment, supply and protect deficient and/or unavailable growth factors, and remove bacterial interference.

Another issue Dr. Kirsner wished to address was standard of care and, regardless of whether poor compliance is by patients or clinicians, how therapeutic adjuvants to the standard of care, particularly debridement and offloading, can lead to better outcomes. As Dr. Boulton mentioned, patients are just not wearing their removable offloading devices. There are many reasons for this, but Dr. Kirsner feels it is important to understand the stress involved in patients with diabetes and their level of depression, factors that may lead to poor compliance. Dr. Kirsner therefore posed the question "If patients' ulcers are debrided properly and healing occurs, perhaps by using a contact cast, or Dr. Boulton's instant contact cast, is there any benefit in speeding healing in patients who may heal anyway?" He answered that he thought there was because there would also be fewer complications such as osteomyelitis and amputations, better quality of life, and less cost to society.

Dr. Kirsner's next question was "Do any of the adjuvant therapies speed acute wound healing?" To respond he described two studies done in Miami. One was a randomized trial of platelet-derived growth factor compared to standard of care, which was bacitracin ointment. Patients had acute wounds created on their inner arms. One group received the standard of care, and the other group received the platelet-derived growth factor (rhPDGF-BB gel (Regranex®)). There was faster healing in those wounds that received platelet-derived growth factor (92.9 percent by day 22 and 100 percent by day 24) compared to the antibiotic ointment (50 percent and 57 percent, respectively) (Cohen M, Ealgstein WH *J Am Acad Dermatol* 2001;45:857-62). In another study of acute wounds using tissue-engineered skin, the Apligraf® product, compared to autologous skin, compared to the standard of care, which was a film dressing, the tissue-engineered skin behaved similarly to the patient's own skin, both of which healed faster than the film dressing in a statistically significant way (Muhart M, McFalls S, Kirsner RS et al. *Arch Derm* 1999;135:913-18; Muhart M, McFalls S, Kirsner RS et al. *Lancet* 1997;350:1142).

In conclusion Dr. Kirsner stated that he feels the key adjuvants to the standard of care, which are debridement and offloading, are the mainstay of treatment. Therefore, it is critical to address issues of poor compliance. It is also highly important to investigate further the refractory subset and ways to reverse the reasons for this refractory subset.

Discussion

Dr. Malozowski opened the meeting to questions and discussions.

Dr. Steven Kravitz, Executive Director, American Professional Wound Care Association**,** with a membership of 1,200 U.S. clinicians, commented on Dr. Reiber's recommendation for a consensus in use of ICD-9 codes for diabetic foot ulcers that it is probably easier to try to get physicians practicing in the VA to code in a similar manner than to get agreement among physicians participating in large clinical studies across the country. Dr. Kravitz added that one of the problems is the way billing is done in the United States. Since Medicare is interpreted by different carriers, billing is generally based on how the carriers interpret it, and thus physicians in Pennsylvania code their bills differently and those in New York or elsewhere. A national coding system is needed to eliminate these geographical biases. The question has been discussed within his association and is considered a problem.

Referring to the fact that CDC uses a particular code and other agencies use other codes, Dr. Malozowski asked "What are the barriers to implementing a universal system and how can we overcome these barriers?"

Dr. Reiber suggested that the easiest way to deal with the situation is to discuss it among one's colleagues. For example, in presenting a set of preferred codes, one might ask others to consider these or justify use of other wound codes for reimbursement. She thought that asking the Government agencies to resolve this might become too complicated.

Dr. Brem agreed that the concept was valuable although difficult to implement. The persons doing billing, for instance, cannot simply look at a photograph and determine the correct code. Dr. Brem felt, however, it was important to work with the VA and with the Centers for Medicare & Medicaid Services (CMS) on the definitions and the modifiers. Once these are standardized by CMS, as for example"707.16 diabetic foot ulcer breaking the skin," then there will be a financial incentive for those seeking reimbursement to follow that coding system in order to be compliant with CMS

Dr. Margolis said that he thought part of Dr. Reiber's concern was in regard to looking at a data set and seeing the distinction, for example, between a foot ulcer and a venous leg ulcer in a person with diabetes. The codes are important not only at the healthcare provider level but also when being interpreted at the larger database level. For example, diabetes with venous leg ulcers as a 454 code is very different than a 707 code for a foot ulcer code with diabetes. Thus, relying on these codes alone can cause major differences between epidemiologic studies done by one person versus another. The best way, according to Dr. Margolis, is to pick code algorithms and then go back to the patients' charts and see if you find what you expect to find. The new Health Insurance Portability and Accountability Act (HIPPA) regulations make this more difficult to do.

Dr. Gilman Grave, Chief, Endocrinology, Nutrition, and Growth Branch, National Institute of Child Health and Human Development (NICHD), raised a different issue. He expressed his surprise that Dr. Stanley Cohen's work on epidermal growth factor (EGF) that NICHD has been supporting for nearly 25 years, is just now being used with diabetic ulcers. (Dr. Cohen, Professor Emeritus at Vanderbilt University, received the Nobel Prize for Physiology of Medicine for his work on EGF and its receptor, tyrosine kinase, which paved the way for all of the following receptor kinase research.) Dr. Grave thought that the use of VEGF had been an established standard of care for years to cure ulcers.

Dr. Kirsner responded that EGF was the first growth factor to be studied and shown to speed healing in humans. This study was in patients without diabetes and had their donor site wounds treated with EGF in a silver sulfadiazine base compared with the base alone and was published in the *New England Journal of*

Medicine in 1989 by the group out of Vanderbilt. However, their work was not then reproduced. Next, studies were done based on whether there was a rationale for using epidermal growth factor for deeper wounds, for full-thickness wounds, but the pressure ulcers and venous ulcers that were studied did not heal faster in a statistically significant way. Other growth factors then became more popular, such as platelet derived growth factor, which probably has been studied the most.

Dr. Brem noted that a new trial using EGF was reported in *Diabetes Care* in 2003. What they did differently from the earlier trial with deep wounds was to use better delivery systems and the results were very promising.

Dr. Kirsner commented that the *Annals of Internal Medicine* recently reported a randomized trial of 36 non-diabetic patients who received nerve growth factor or placebo plus standard care for pressure ulcers on the feet present for less than 1month duration. Those receiving the nerve growth factor had better healing rates and a greater reduction in wound size. Dr. Reiber added that the patients, however, were only followed for 6 weeks.

Dr. Brem asked if it were possible to achieve consensus on clinical trial standards, such as length of trial, that could be established by FDA based on epidemiological information such as that provided by Dr. Margolis. Such standards would certainly be cost-effective. Dr. Stromberg replied that current consensus on the endpoint is one of complete closure, which has not been shown to be achieved in a short-term trial.

Dr. Boulton pointed out again that the new therapies, including growth factors, have probably only shown minor results because of lack of control for offloading. Researchers he has spoken to about this are reluctant to include offloading because they believe the ulcer will heal without the offloading, which can be difficult, expensive, and time-consuming to accomplish. Dr. Boulton still considers offloading the confounding variable that, if included and controlled, would produce better success rates, and emphasized studies are needed to investigate this hypothesis. He added that another factor that needs to be addressed, as Dr. Kirsner had mentioned, is the depression that is common in patients with diabetic neuropathy. Even those who experience no pain, suffer from troubling unsteadiness, a major symptom that is rarely assessed. The impact of the psychological aspects in these patients was demonstrated by the Ohio group, headed by Dr. Ron Glaser, who showed very clearly that pro-inflammatory cytokines are much higher in patients with depression. Classic studies in dental students also found that, at the times of stress at final exams, healing rates were half what they were during vacation periods.

Dr. Stromberg agreed that data on the effect of offloading in controlling outcomes could be important information to present to sponsors of clinical trials, possibly as a requirement.

The use of honey as a wound therapy was raised as a possibility for a controlled trial. Apparently honey's carbohydrates exert osmotic forces that break open the bacteria's walls. Another alternate therapy, raised by Dr. Moshell, was the use of sterile maggots. Dr. Boulton said that maggots are used widely all over the world. The concept arose during the American Civil War from observing that soldiers who survived loss of their legs also had these wounds infected with maggots. There has been extensive experience in the United Kingdom in using maggots in refractory patients with neuro-ischemic ulcers who had distal vascular disease without possibility of a bypass. These living chemical factories make enzymes that are bacteriostatic. There also is uncontrolled evidence suggesting they are useful in getting rid of MRSA. They have several advantages: they are less expensive than antibiotics or surgery and they work 24x7. A controlled trial in the Ukraine showed faster healing with wounds treated with maggots, but the comparison method was not a good one. Dr. Boulton recommended that larva therapy or biosurgery—for a more acceptable term—is an area in need of controlled data to support the anecdotal experience with this therapy.

Dr. Kirsner agreed that many view it as a viable therapy but those who do not wondered if it were possible to extract the enzymes the maggots secrete and use them as a potent debriding agent. Several participants suggested this was might be one of the clinical trial areas, among other areas that are likely to be commercially non-viable, that the DMICC and SDICC might sponsor.

Dr. Judith Fradkin, Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, NIDDK, said she would be talking later about such initiatives and opportunities for support, such as R01 trials, and urged those present to submit proposals. Dr. Stromberg wanted those present in the wound healing community to know that NIH supports efforts other than basic research and seconded Dr. Fradkin's suggestion that they submit proposals for clinical trials of new therapies to enhance the field.

Dr. Fradkin noted that several researchers present were in fact being supported by NIDDK for other than basic research. She added that there also are opportunities for follow-up studies in patients who were formally enrolled in large clinical trials enrolled in clinical trials and there are certainly unanswered epidemiological questions that could be addressed in these populations. One example is the Epidemiology of Diabetes Interventions and Complications (EDIC), which is the follow-on to the Diabetes Control and Complications Trial (DCCT) and has 1,400 subjects for whom comprehensive data has been collected over the past 20 years—their blood pressure, their lipids, their inflammatory states, everything that could be measured. ACCORD (Action to Control Cardiovascular Risk in Diabetes), a clinical trial co-sponsored by NIDDK and the National Heart, Lung, and Blood Institute (NHLBI) is currently enrolling 10,000 type 2 patients being randomized to various levels of glucose, blood pressure, lipids, and controls. Dr. Fradkin asked the participants to suggest epidemiological ideas and methods that could be pursued with these populations for whom there exists or will exist extensive relevant data.

Dr. Margolis contributed that there are hundreds of questions that could be addressed via these populations. Most of what is known about the natural history of the onset of foot ulcers is really based on either small series or large databases. Some of the small series are quite large, like the VA groups; however the EDIC and proposed ACCORD groups offer relatively large, virgin populations on which there is extensive data that could provide more information than can be currently obtained from databases or past surveys. This is invaluable.

Dr. Fradkin pointed out that the data from these studies provide a potential opportunity to characterize people in a standardized way versus relying on the range of codes currently being used and their attendant problems. On the other hand, it is a smaller sample size than what is available in the huge, national databases. She added that obviously funds are limited for these studies, but the EDIC group is, in fact, developing their protocol for the next period of follow-up, and she thought they would welcome suggestions for measurements or other attributes that could be incorporated into EDIC. They have been working with Dr. Eva Feldman, Department of Neurology, University of Michigan, about a more extensive neuropathy component, possibly including nerve conduction. Dr. Fradkin emphasized that suggestions from those present would be very much welcomed.

When asked how long patients are followed, Dr. Fradkin replied that EDIC has been following them for 20 years. The next 5- to 10-year period is now under discussion. Patients are seen twice a year. EDIC has 1,400 patients for whom every conceivable measurement has been made, including coronary CT scans. Their vascular status is characterized and all sorts of markers of inflammatory mediators and so forth have been collected.

Dr. Malozowski added that the same will be true for ACCORD's 10,000 diabetes patients in multi-centers across the United States and Canada. Over 3,000 have been recruited at the rate of about 80 per week.

Dr. Fradkin went on to say there are potential opportunities for add-on studies at relatively low additional cost, which could answer some of the remaining questions. It would also be good to figure out a standardized approach to the foot so that the two studies could be compared across each other—EDIC's type 1 diabetes patients versus ACCORD's type 2 patients. To apply, those interested should submit a proposal stating the nature of the examination to be conducted and what the hypothesis would be. Dr. Fradkin would be very willing to bring such a proposal to the EDIC chairs, Dr. David Nathan and Dr. Malozowski, and also to Dr. Peter Savage, Director, Division of Epidemiology and Clinical Applications, NHLBI, for ACCORD.

Dr. Brem asked if it would be possible to photograph the feet of these patients and measure their wounds, if present, with a ruler. This could resolve coding problems. All of the process data would be irrefutably standardized. Dr. Fradkin replied that she could see no reason why the feet could not be photographed; they are photographing the retina. Dr. Malozowski commented that it would be less complicated to photograph the feet.

Dr. Moshell said that, in terms of not reinventing the wheel, there is a dermatologic component of NHANES run by the National Center for Health Statistics (NCHS) based on digital photography for photographing skin. The bottom of the foot is not part of that digital photography, but the equipment and the techniques are in place. If anybody wanted to do that, Dr. Moshell offered to put them in contact with the appropriate persons at NCHS who are doing this. Dr. Kravitz added that digital photography is very inexpensive today. The American Professional Wound Care Association's website has 10 guidelines for clinicians to use with almost any digital camera. Dr. Fradkin cautioned that the hypotheses, the questions to be addressed, and the study design need to be identified and a proposal submitted prior to asking for photographing of the patients.

Dr. Kravitz introduced the separate issues of access and cost with regard to adjuvant therapies. Medicare recently approved venous compression stockings for people with venous stasis ulcers. Dr. Kravitz strongly suggested that it would be more cost-effective, given the $40,000 noted in one report to heal a foot ulcer, for Medicare to approve the compression stockings for patients with venous stasis *before* an ulcer occurs. He noted there continues to be a frustrating disconnect between cost containment and practical care to decrease morbidity. Dr. Brem agreed that overall cost would be dramatically reduced by taking existing knowledge and establishing standards of care, including offloading.

In response to a question from Dr. Malozowski regarding why patients do not use the offloading device—is it a matter of aesthetics or discomfort—Dr. Boulton responded that it is because they have no pain perception and they think that as long as they are at home, they do not need it. In a previous study, it was shown with activity monitoring, that patients with foot ulcers are more active at home and less active out-of-doors, whereas patients with neuropathy and no foot ulcers are more active out-of-doors and less active at home. In foot ulcer patients with no sensation of pain, even though 75 percent of their activity is around the home, they wear the device as one would wear a shoe out in the rain. They see the dangers as being outside. There is some data to suggest that they take it off at home because they perceive the familiarity of the surroundings—the carpet, the lack of foreign objects on the floor—as safe. However, the problem with an insensate foot ulcer is that there is no safe zone. Just those few steps to the bathroom each night are the most dangerous steps. The only device that works is an irremovable cast walker. Again, it is a matter of perception. The patient thinks that if something hurts, rest it. If it does not hurt, it cannot be all that bad.

Dr. Kravitz commented that these psychological aspects are correct. A person feels just as "normal" as he/she was a couple of months earlier, and now there is the hassle of wearing this device wherever he/she goes. So, the patient takes it off for "just 5 minutes" and, unfortunately, loses the healing effects of the last 4 weeks.

Dr. Reiber observed that patients who have their first diabetic foot ulcer tend to be more compliant, more likely to offload, than they are with subsequent foot ulcers. It seems in subsequent foot ulcers, they think, "I've been through it before. Nothing bad will happen." Dr. Boulton agreed with this observation that was also seen by Dr. Paul Brand in leprosy. He said the most useful time for education is at the time of the first foot ulcer. Dr. Brand once showed a cartoon of a patient with the first ulcer falling over the edge of the cliff: at this stage the patient responds well to education and can be "pulled back" from the edge of the cliff.

Dr. Malozowski commented that another perception problem is that the foot is not seen as an item of great appeal. Treating a foot ulcer is not neurosurgery. The importance of the foot ulcer in limiting activity and affecting quality of life is not recognized. He stressed that this meeting is important in raising awareness of this. Dr. Boulton agreed that people have always been more interested in treating eyes or kidneys and have the attitude that one can ignore the foot. However, this is beginning to change. In looking at the number of papers published on the diabetic foot as a proportion on all papers on diabetes from Medline, from about 0.7 percent of all papers in 1980, it is now about 4 to 5 percent, up five-fold. Part of the reason for the change is health economics.

In reply to Dr. Myrlene Staten's (Senior Advisor, Diabetes Translational Research, Division of Diabetes, Endocrinology and Metabolic Diseases, NIDDK) query about the distribution of severity in the 20,000 patients with diabetes and foot ulcers, Dr. Margolis said that about 45 percent of the patients were grade 2 or less, with about 18 percent without major risk factors, another 18 percent having a larger wound, and another 18 percent having one of longer duration but still grade 2 or less. Dr. Staten responded that meant that more than half are at the more severe grades. They have osteomyelitis or exposed tendons.
Dr. Margolis answered that there were very few patients in the highest grade however. What is being seen over time is that most of the patients are in the earlier grades and more and more of these patients are being seen. There are, however, patients with grade 3, 4, 5, and 6 ulcers.

Dr. Malozowski stated that Dr. Margolis' slide on Prediction With Dichotomized Risk Factors for DNFU presented important, relevant information to power a study. It indicates how many patients are needed at each level to show whether or not healing rates will progress from one stage to another. Dr. Margolis said the slide would be published in December 2003 (*Am J Med* 2003;115:627-631).

Dr. Leonard Pogach, VA National Program Director for Diabetes, asked Dr. Margolis if there was any data on the psychosocial determinants predicting what type of people would come to the wound care centers.

Dr. Margolis replied that, although such information might be collected and might exist, it would not be in the database. He added that because he was somewhat surprised to find that the healing rates changed over time and had heard a tape of Dr. Vinicor's speech at the ADA meeting in 2002, he had sought an explanation for the results he was seeing. He proposed that possible reasons for the increased healing rates may be that people were coming to the centers sooner or more physicians were looking at the foot than in the past. Perhaps patients are becoming more empowered through the messages issued by the foundations on the importance of the foot in diabetes and the need to see a doctor if one has a wound on the foot.

Ongoing Brief Overview of Planned Activities

Representatives of DMICC member agencies presented overviews of their current and future activities related to diabetic foot ulcers. Dr. Malozowski introduced the first presenter, Dr. Kurt Stromberg of the FDA's Division of Therapeutic Proteins, Office of Biotechnology Products, Office of Pharmaceutical Science (OPS), Center for Drug Evaluation and Research (CDER).

Food and Drug Administration

Dr. Stromberg stated that, as discussed earlier, there are only a handful of approved products for treating diabetic foot ulcers. There are several approved non-interactive, wound healing dressings, but these are actually products for wound management, not treatment of diabetic wounds. There also are various approved debriding agents, but these are for chronic wounds and most of them are "grandfather-approved." Given this situation, Dr. Stromberg said that it was important to ask the question "Why are there so few approved treatments?"

As emphasized by the speakers, diabetic foot ulcers are a multifactorial problem and therefore, treatment needs to be multifactorial. However, treatments tend to be single. Dr. Stromberg suggested that the FDA might help address this problem by trying to speed up clinical trials to provide more incentive for variability in types of treatments. For example, instead of a trial for one growth factor, there might be a sequential application for a number of growth factors to try to duplicate the healing process.

Dr. Stromberg explained that, whereas, complete healing and the longer trial is appropriate for the pivotal trial to actually determine effectiveness and efficacy, at the earlier stages perhaps several of the surrogate endpoints could be used to enable more trials to be carried out. Although FDA has data that might enable use of these surrogate endpoints, such as reduction in wound size as a predictor of healing, there is no vehicle or person available to analyze the data. Dr. Stromberg recommended that perhaps this is where NIH can make a major contribution by funding such analyses. The FDA would ensure that the data being looked at remains anonymous. He believed such analyses would result in developing the necessary epidemiology to support identification of surrogate markers for clinical endpoints, which he saw as an important objective resulting from today's meeting.

In summarizing FDA's current planned activities, Dr. Stromberg said there are no new devices, in the approval or trial stage. They are being investigated. There is a tri-center clinical focus group on wounds that developed a guideline in 1991 that will be presented to the Dermatological Diseases Advisory Committee in the spring of 2004. The guideline has been available for 2 years; a version was published in June 2001 to guide development of wound healing products. There was a meeting recently of the Anti-Infective Drugs Advisory Committee, but they did not achieve a consensus on the required outcome for diabetic foot infections. Dr. Stromberg expressed concern over the problem of the increasing obesity of the population and its association with diabetic foot ulcers and the necessity this creates for development of effective treatments.

National Institute of Diabetes and Digestive and Kidney Diseases, NIH

Dr. Malozowski presented Dr. Judith Fradkin, Director, Division of Diabetes, Endocrinology, and Metabolic Diseases (DDEM), NIDDK.

Dr. Fradkin said that when the special funding for type 1 diabetes was first received in 1998, diabetic foot disease and diabetic neuropathy were immediately identified as two understudied areas. NIDDK issued a series of requests for applications (RFA's), mostly R01s, in conjunction with the National Institute of Neurological Disorders and Stroke (NINDS) and other partners to stimulate research in this area. These include DK 98-009, Pathogenesis and Therapy of Complications of Diabetes ($6.7 million); NS 99-005, Neurologic Complications of Diabetes ($2.2 million); NS 00-002, Neurobiology of Diabetes ($4 million) and DK 01-006, Gene Therapy Approaches for Diabetes and Its Complications ($2 million). In addition, using regular NIDDK funds, the Institute issued an RFA specifically for diabetic foot disease, which resulted in funding for some of those present (DK 00-009, New Therapies for Diabetic Foot Disease, $1.5 million). Dr. Fradkin expressed pleasure in hearing today how the work supported through that RFA has come to fruition.

Dr. Fradkin noted that for several years the National Diabetes Education Program (NDEP), headed by Joanne Gallivan, and the Diabetes Clearinghouse, led by Kathy Kranzfelder, has supported an ongoing campaign called “Feet Can Last a Lifetime” that was done in partnership with voluntary organizations (American Diabetes Association, Juvenile Diabetes Foundation, American Association of Diabetes Educators, and orthopedic and podiatric societies) and other components of the U.S. Department of Health and Human Services (CDC, the Indian Health Service, HCFA now CMS, the Health Resources and Services Administration, and the VA). More than 20,000 kits have been distributed to healthcare providers, and they are now in their third production cycle. Each of the kits contains monofilaments and instructions for foot exams, stickers to put on patients’ charts to identify people who are high-risk, information about getting reimbursement for patient care, and patient education materials for people with high-risk feet. The kits also include posters to put up in the providers’ offices telling people with diabetes to take off their shoes, because, in busy practices, if people do not take off their shoes, their feet probably will not be looked at.

Dr. Fradkin agreed with Dr. Brem that NIDDK’s focus had largely been on prevention of foot ulcers, not treatment. As diabetologists, NIDDK knows about preventive care for people at risk of foot ulcers, but patients are referred to other specialists for treatment. However, she assured Dr. Brem that his recommendations had been heard by the NDEP and Clearinghouse directors. She also asked that those present contribute to helping NIDDK develop materials to specify a standard of care, such as emphasizing the importance of offloading.

Next Dr. Fradkin introduced Dr. Myrlene Staten, Senior Advisor, Diabetes Translational Research, DDEM, who is responsible for NIDDK’s bench-to-bedside translational initiatives, including a special program for those who have an idea for a new drug or new agent that might be effective but is potentially not something that would be developed by pharmaceutical companies. The program provides resources rather than financial support to help develop the product such as preclinical testing, development of agents, and so forth. At the other end of the spectrum are projects to take findings from clinical trials that have been shown to be effective in diabetes prevention and control of complications and to develop trials to show how these procedures can be more cost-effectively or more efficiently applied in clinical practice. This is research-to-practice translation. There is an ongoing program announcement that has all the advantages of a regular program announcement (PA) and an RFA in that it has three receipt dates a year, but it is reviewed by a special study section the way an RFA is reviewed. It is specifically reviewed with regard to clinical interest in improving patient care. For example, this PA could be used to develop an approach that had been shown in trials to work, such as offloading, and develop a method for applying the

approach in providers' practice in the community. Dr. Fradkin encouraged those present to look at that solicitation and to talk to Dr. Staten if interested in applying for funding under it.

There is also an RFA using special type 1 funds for a bench-to-bedside program that moves a protocol from the pilot and feasibility phase, with demonstrated milestones, into a larger clinical trial. This is available for any area of research relevant to type 1 diabetes. The next receipt date for that is February 20, 2004. There is an innovative partner solicitation, for which the due date has passed, that Dr. Fradkin said NIDDK is considering re-issuing. This solicitation is a mechanism that allows researchers working on diabetes to further their research by bringing in a collaborator who does not currently do research on diabetes but who has some special talent such as bioengineering that would be relevant.

Finally, this year NIDDK has a special small business innovative research (SBIR) solicitation focused on developing new therapies for type 1 diabetes. This includes complications. Dr. Fradkin commented that many of those present had ideas that could be commercially viable, ranging from new products for offloading to biologicals that might be developed working with a small business. The due date for this solicitation is February 20, 2004. She added that all the initiatives she had discussed can be found on the NIDDK website (www.niddk.nih.gov) under "What's New?"

Future plans, according to Dr. Fradkin, include working with the Juvenile Diabetes Research Foundation (JDRF) and the Department of Defense (DoD) to develop, through DoD's Defense Advanced Research Projects Administration (DARPA) program, a project to improve wound healing focused on battlefields. (DARPA is high-risk, intensive deployment of resources program to develop a specified application driven by a pre-defined outcome. Projects usually have a lifetime of 3-5 years and a large budget of $5-10 million.) NIDDK and JDRF are talking with DoD about how their project might be directed toward applications relevant to diabetes. Also, NIDDK has been coordinating with the National Cancer Institute and JDRF to interest angiogenesis researchers in moving into the area of diabetes. A large workshop is planned for 2004 that will probably be followed by a research solicitation.

To investigate participation in any of these initiatives, most of which are trans-NIH, Dr. Fradkin urged those present to contact Dr. Staten for translational projects and Dr. Teresa Jones, Program Director for Diabetes Complications, DDEM, who is taking over administration of these grant programs from Dr. Kristin Abraham, who will now head up the Diabetes Centers Program.

A NINDS member commented that her Institute has been partnering with JDRF and NIDDK on diabetic neuropathy solicitations. She added that they may not be ready to issue another similar RFA at this time, but might consider one to address the multifactorial nature of diabetic foot ulcers, particularly the lack of sensation that occurs sub-clinically early on prior to the infection and also the age relationships.

Dr. Reiber suggested that primary care provider education is needed to give them information and guidelines about what they can do prior to referring their patient to a wound specialist. Dr. Fradkin responded that that is, in fact, the goal of the "Feet Can Last a Lifetime" campaign, to have these primary care providers look at the diabetic patient's feet, identify who is at high-risk, and then give the patient prevention information. NDEP also has a working group of providers in various sub-specialties, including podiatrists, who have been helping develop materials with regard to the diabetic foot. Dr. Malozowski added that the group's recommendations will be used in reviewing and evaluating a document the group is developing. In response to Dr. Reiber's concern that the primary care provider not only know about prevention but also what questions to ask when the ulcer is present, Dr. Fradkin welcomed partnership with those present in developing appropriate materials.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Dr. Malozowski turned the podium over to Dr. Alan Moshell, Director, Skin Diseases Branch, DMICC representative from NIAMS, and cosponsor of today's meeting.

Dr. Moshell pointed out that NIAMS, as a small institute, supports the broad area of chronic wound healing research, not diabetic foot ulcers specifically. Chronic wounds were the subject of a number of Skin Disease Interagency Coordinating Committee meetings in the early 1990s, which resulted in a workshop in January 1993, followed by an RFA and a subsequent program announcement. In the 2 years after issuance of the RFA, NIAMS' wound healing portfolio continued to grow until in 2003 it is approximately $11 million. This included in the past a free-standing clinical trials planning grant. Dr. Margolis was successful in obtaining a NIAMS contract solicitation. NIAMS is now part of the general NIH clinical trials planning grant mechanism announced a few months ago.

Dr. Moshell noted that there is an R01 application in-house for review for a clinical trial that includes the use of sterile maggots. He asked if those present thought such a therapy, if found successful in a U.S. clinical trial, would be widely applicable in clinical use in the United States. Dr. Brem said that his colleagues' opinions are to use what is there. In real life, however, Dr. Brem's opinion is that the therapy would not be used if other options are available. Only centers that do not have other options available to them would use the therapy. Others present thought it would be used if found effective in a clinical trial. Dr. Stromberg said that historically, the FDA could support such a licensed product; it was done with heart patients in the 1930s. It is not inherently impossible, but it is an education problem. Dr. Margolis said that they might be adopted as standard therapy if it were demonstrated that they were successful as a permanent debriding agent. However, earlier studies indicated that diabetic foot ulcer patients had to be constantly debrided and decallousified when the maggot therapy was used, so there would be no clinical advantage then to using it for diabetic foot ulcers. It might be useful for pressure ulcers or arterial wounds. Dr. Boulton responded that they are being used in the United Kingdom and he believed they were also being used widely in the United States. Dr. David Armstrong is using them at the VA in Miami, but not for simple neuropathic foot ulcers. For those, aggressive debridement and offloading are the therapy used and most of the wounds heal. Larvae therapy is reserved and is very useful for neuroischemic wounds that can be painful to debride, in which there is not a lot of callous but a lot of slough that is very difficult to remove, even surgically. Dr. Boulton added that his experience is anecdotal, but there was a clinical trial in the Ukraine that was presented in 2000 and an abstract published. Under the right conditions, it is a useful therapy.

Dr. Moshell continued that historically, some of NIAMS manpower activities have been to stimulate epidemiology within skin disease, including chronic wounds, and again Dr. Margolis has been one of the researchers participating in this. In terms of current and future plans, the NIAMS portfolio is predominantly basic research in wound healing, but there has been some movement toward clinical and translational research. There is a Small Grants Program announcement with resources, called a PAR (a program announcement for which special referral guidelines apply), that sets aside money and has receipt deadlines three times a year. A separate committee reviews these.

NIAMS also has a high-risk RFA, which is for individuals who either have been previously funded by NIAMS and who are now looking at a different kind of work, or for individuals who are established investigators who have not been doing research in NIAMS diseases but now want to do work in these diseases. This is an annual RFA with a January deadline. Although NIAMS now participates in the NIH-wide clinical trials planning grant mechanism, they will separately review these. There is a broad range of roadmap initiatives that Dr. Zerhouni, Director, NIH, announced, all of which are essentially NIH-wide mechanisms. Several have to do with epidemiology, clinical trials and translational research.

In conclusion, Dr. Moshell brought up the subject of a consensus development conference, a type of conference that the NIH conducts several times a year. In order to hold a consensus development conference, the scientific literature must have established that there is an intervention—diagnostic, preventive, or therapeutic—that is not widely accepted in the medical community, that if it were accepted and widely applied, would improve the health of the U.S. population. Dr. Moshell asked if those present felt that the wound healing community was at the stage where such a situation existed for a standard of care for diabetic foot ulcers or other chronic ulcers and that the literature could establish this for a panel of experts outside the wound healing community. If so, he assumed the FDA would recognize this and adopt it as a standard of care for controls in wound healing clinical trials.

Dr. Reiber responded that there are two therapies well-supported by the literature that are beneficial in treating diabetic foot ulcers and associated with better outcomes—debridement and offloading—and both are highly underutilized, particularly by the primary care community. She stressed that it would be wonderful to get that message out.

Dr. Pogach expressed the opinion that, at least from the VA and DoD standpoint, standards should not be derived from consensus conferences. Standards, measures, and guidelines should be the result of a rigorous review of the scientific evidence. He concurred with Dr. Reiber's statement that the interventions would be based on well-developed randomized clinical trials, even though there are always knowledge gaps in emerging therapies, and a consensus conference could be productive at this time. He emphasized, however, that any standard should be based on uncontroversial evidence from clinical trials, not from a consensus conference.

Dr. Moshell explained that consensus development conferences do not establish standards. They basically confirm that the literature shows that a certain practice has been established to be more effective than what is generally being used in the community and therefore should be brought to the attention of the practicing medical community and brought into greater use. Then, it is up to the FDA to decide where to go from there. Dr. Kravitz noted it is simply a matter of communicating to the general practice community that there are guidelines that have been established, published, and are well accepted and should be implemented in daily practice.

Dr. Margolis stated that although he believes debridement works, the data supporting its efficacy is incomplete. He recommended that a well-done study be conducted to definitely prove the effectiveness of debridement in healing diabetic foot ulcers. Dr. Brem said that a good reason for a consensus conference is to address such issues. He felt a consensus conference would result in agreement to substantially reduce amputations by debridement or other therapies. That would be a valuable outcome.

In response to Dr. Moshell's question about if there was better literature to support offloading. Dr. Boulton answered that there was a recent Cochrane Update that reported controlled trial data on offloading, but there is a need for larger trials. Dr. Brem thought no one would argue the value of offloading; the discussion would be on which type should be used. Another result of a consensus conference might be agreement on outcome, which patients can be expected to heal. This would at least provide a goal.

As a result of the discussion, Dr. Moshell concluded that most of the researchers present would be willing to participate in trying to hold a consensus conference on diabetic foot ulcers.

Veterans Health Administration

Dr. Malozowski next introduced Dr. Leonard Pogach, National Program Director for Diabetes, to present a summary of the VA's Preservation, Amputation, Care, and Treatment (PACT) Program.

Dr. Pogach noted that the VA has achieved increasing recognition as a national system of care within the United States. The agency has been improving outcomes compared to the private sector and trying to decrease disparities. He mentioned that there was actually a public law passed in 1992 (P.L. 102-405, Veterans Medical Programs Amendments) that emphasized the importance of quality amputation care. It identified veterans with amputations as a special disability group and chartered the Special Advisory Committee on Prosthetics and Special Disabilities to oversee the VA. That led to the formation of the PACT program in 1993, developed to meet the changing needs of veterans and to proactively identify and treat veterans at risk for amputations, usually as the result of neuropathy and peripheral vascular disease. Such amputations have decreased but with the increasing casualties in Iraq, now attention is focused on traumatic amputations.

The Undersecretary has issued a series of PACT directives. These are unfunded mandates, which leave medical centers to assume the costs and direction to carry them out. The first established the program and directed each medical center to establish a care system. In 1996, the directive tied the program explicitly to performance measures, and in 2001, the reissued directive called for improved performance measures and the development of high-risk registries within the VA.

Guidelines for foot exams for sensation and pulses were implemented in 1997, and in 1999, if a patient was screened by the primary care provider and considered high risk, the provider referred the patient to a podiatrist. Each quarter, every facility in the network receives foot care measure feedback on their performance from the Office of Quality and Performance. There is very little variation in ratings from facility to facility, less so than in the private sector. Although the program has been a diabetes quality improvement project measure and has been a part of the national quality improvement alliance measure since 1997, Dr. Pogach was not aware of any other agencies aside from the VA and the Indian Health Service that report, use, or publish these performance measures on a national basis. Doing so might help in terms of prevention.

Dr. Pogach commented that after patients are referred to a podiatrist, the foot care programs at individual VAs do differ widely, reflecting the lack of an evidence-based standard of care from which to impose guidelines and performance measures within the agency.

The data Dr. Pogach presented on amputation rates had not yet been reviewed and approved for distribution outside the agency. He said that hopefully it would be soon. Although the VA began collecting outpatient data in 1997, when the definition of diabetes changed, the agency relies on cross-sectional data on age-standardized amputation rates for patients from 1999 on, rather than depend on the reliability of the 1997-1998 databases. Clearly, as stated by earlier speakers, there has been a decrease in overall amputation rates, major amputations, and moderate amputation rates in persons with diabetes treated at the VA. The number of amputations is remaining relatively constant, though there is a shift from the ratio of major to moderate amputations. The amputation rates for persons without diabetes are very small in number. Eighty percent of the amputations at the VA are performed on individual veterans who have diabetes. VA data will be merged with Medicare data to determine total amputation rates. About 70 percent of VA patients with diabetes are also Medicare enrollees. If a patient comes in for diabetes medicine or a patient visit, the patient is counted as a clinical user, although the person may be receiving the majority of his/her care in other healthcare systems. This can cause denominator effects in the data.

Dr. Pogach next described the VA's future plans. As a result of the external evaluation of the VA PACT Program in 2002, the Undersecretary felt it was time to further evaluate amputations and re-amputation rates using more rigorous methodologies. The Undersecretary also established a multi-disciplinary panel to develop data elements and performance measures, improve data accuracy and completeness, and strengthen the PACT foot care programs nationwide.

Current VA action plans are to identify unmet patient care needs, identify knowledge gaps in terms of what facilities need and what providers need, and then develop strategies to fulfill these needs. The Amputation Care Advisory Group (ACAG) is multi-disciplinary, both among disciplines and among headquarters offices. In defining how the program is to be measured, the ACAG looks at process measures (screening, risk assessment, referral), patient-centered measures (foot care behaviors, unmet needs), and outcome measures (ulcer rates in addition to amputation rates, functional status, patient satisfaction). Since the VA is a provider system, not a payer system, all the data have to be actionable. There are always competing needs; however, with better data collection and better feedback, the medical center division directors will be able to support better foot care initiatives.

Dr. Pogach remarked that he had been energized by today's comments from the speakers and attendees. One thing the VA can do is look at their guidelines again based on the emerging better data in foot care. He assured the group that the VA would welcome being a part of the greater community in reviewing and discussing a standard of care. Fortunately, the VA is very much a learning laboratory these days and has funding available, especially for implementation strategies. In conclusion, Dr. Pogach referred the audience to the VA website (www.oqp.med.va.gov/cpg/cpg.htm) to look at some of the agency's performance measures and guidelines.

National Institute of General Medical Sciences

Dr. Malozowski presented the final speaker, Dr. Richard A. Ikeda, Program Director, Pharmacology, Physiology, and Biological Chemistry Division, NIGMS.

Dr. Ikeda explained that the National Institute of General Medical Sciences is a little different from the organ- and disease-specific institutes at NIH, in that it is the basic science institute. Its mission is to fund research in the basic sciences of life processes, projects ranging from chemical molecules that mimic an enzyme mechanism to small-scale clinical studies with burn patients or trauma patients. In 2003, the NIGMS budget was $1.8 billion. Because NIGMS emphasizes small investigator-initiated research, it supports about 10 percent of all the research grants that are granted by the NIH. NIGMS also has a very large training component in its mission and thus supports about 45 percent of all the predoctoral trainees at the NIH and 28 percent of all trainees in general who are supported by the NIH. NIGMS also has a medical mission to support research into diseases or trauma that involves multiple organs or multiple diseases. Traditionally, this has led to research in trauma, burns, and wound healing.

The majority of NIGMS grants are R01 investigator-initiated projects, P01 program grants requiring more resources and collaborative interactions, and T32 training mechanisms. Dr. Ikeda noted that problems in wound healing are likely to be P01 grants, but encouraged those present to look at R01s as individuals, as well as the P01s, and to consider a T32 to establish a pre- or postdoctoral training program in wound healing. Because of the emphasis on investigator-initiated projects, there are fewer opportunities at NIGMS for targeted programs, set-asides, centers, and large awards. These are used sparingly to support new areas of research, emerging technologies, areas that are becoming important but are underutilized, projects that require extensive collaborations and data sharing, or research spanning disciplines that have not previously worked together.

Dr. Ikeda presented the following NIGMS current initiatives relevant to wound healing: PA 03-100, Exploratory Studies for High-Risk/High-Impact Research; PAR 02-092, Research Centers in Trauma, Burn, and Perioperative Injury; and PA 03-047, Research on Microbial Biofilms. He encouraged those present to contact him if they were interested in any of these announcements or had suggestions for other initiatives relevant to diabetic foot ulcers. He suggested that they "push the envelope" in pursuing areas of investigation, such as stem cell research.

Centers for Disease Control and Prevention

Dr. Frank Vinicor, Director of the CDC Division of Diabetes Translation, was unable to attend the meeting but forwarded a handout on the CDC's current surveillance, epidemiology, and programmatic activities and referred the audience to the November 14, 2003, MMWR article on the CDC website. As mentioned by the meeting's speakers, CDC is documenting preventive behaviors by professionals through NHANES and BRFSS. These surveys show that foot examination rates are slowly increasing, and amputations among persons with diabetes are not increasing, but have remained stable over the past 2 to 3 years. This data is based on discharge diagnosis and not to increased outpatient procedures. NHANES has expanded the data relevant to diabetic foot ulcers. The Healthy People 2010 objective relevant to foot disease among persons with diabetes was refined to include evidence about foot ulcers. In addition to the article cited above, MMWR, in collaboration with the Indian Health Service, published data on rates of amputations among American Indians. Manuscripts are pending regarding initial documentation of preventive care practices and rates of lower extremity amputations (LEA) within the Translating Research Into Action for Diabetes (TRIAD) project. CDC has included LEA preventive care practices as a required "intermediate indicator" of impact of its State-based Diabetes Prevention and Control Programs. This is consistent with PARTS (Performance Assessment Review Tool) and Office of Management and Budget outcome assessments. The CDC has assisted with the development and finalization of a Pharmacists, Podiatrists, Optometrists, and Dental Professionals (PPOD) Primer for NDEP partners. Along with the American Podiatric Medical Association, CDC has also collaborated with CMS to develop policies for reimbursement of diabetic foot examinations based on neuropathy, not just vasculopathy.

Dr. Malozowski closed the meeting at 1:15 p.m. with a final request to contact him with suggestions for subjects for future meetings. He announced that the next DMICC meeting would be on diabetes and obesity.