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14. ABSTRACT Special Congressional Interest funds appropriated for diabetes ambulatory monitoring have supported dual use research in the "Technologies for Metabolic Monitoring" program, managed by the Military Operational Medicine Research Program (USAMRMC). The U.S. Army Research Institute of Environmental Medicine (USARIEM) integrates new knowledge and technology developed from the program into metabolic research and monitoring applications for soldiers. The Diabetes Technology Society has been a key forum for dissemination of DoD interests and research results, at the annual Fall meetings and in a Military Metabolic Monitoring section of Diabetes Technology and Therapeutics. Papers feature DoD-supported research, accompanied by editorials that highlight dual military and clinical uses of the research to promote a broader interest in technology solutions for both applications. This report includes reprints of eight MMM editorials that appeared in the journal (2004-2005). Topics include IGF1 monitoring, advanced technology, hyperspectral imaging, accelerometry, foot-strike monitoring, ConA-based sensors, lactate sensors, and tissue responses to implants.					
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2003

Volume 5, Number 3

Nindl BC, Kellogg MD, Khosravi MJ, Diamandi A, Alemany JA, Pietila DM, Young AJ, Montain SJ. Measurement of insulin-like growth factor-I during military operational stress via a filter paper blood spot assay. *Diabetes Technology and Therapeutics* 5(3):455-462.

Friedl KE. Insulin-like growth factor-I - a metabolic marker representing quality of life? *Diabetes Technology and Therapeutics* 5(3):463-465.

Volume 5, Number 4

Vigersky RA, Hanson E, McDonough E, Rapp T, Pajak J, Galen RS. A wireless diabetes management and communication system. *Diabetes Technology and Therapeutics* 5(4):695-702.

Friedl KE. Military diabetes and advanced technologies research. *Diabetes Technology and Therapeutics* 5(4):703-4.

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Gillies R, Freeman JE, Cancio LC, Brand D, Hopmeier M, Mansfield JR. Friedl KE. Systemic effects of shock and resuscitation monitored by visible hyperspectral imaging. *Diabetes Technology and Therapeutics* 5(5):847-856.

Friedl KE. Signs of illness: When will technology provide greater advantage than the practiced eye of the clinician (or the military commander)? *Diabetes Technology and Therapeutics* 5(5):857-9.

Volume 5, Number 6

Chen KY, Acra SA, Majchrzak K, Donahue CL, Baker L, Clemens L, Sun M, Buchowski MS. Predicting energy expenditure of physical activity using hip- and wrist-worn accelerometers. *Diabetes Technology and Therapeutics* 5(6):1023-1034.

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2004

Volume 6, Number 1

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Volume 6, Number 4 [REVIEW ARTICLE]

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Volume 6, Number 5 [REVIEW ARTICLE]

Friedl KE. Can You Be Large and not Obese? The Distinction Between Body Weight, Body Fat, and Abdominal Fat in Occupational Standards. *Diabetes Technology and Therapeutics* 6(5):732-749.

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Analysis

Insulin-Like Growth Factor-I—A Metabolic Marker Representing Quality of Life?

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IT MAY NOT BE SO REMARKABLE to some human metabolism researchers that insulin-like growth factor-I (IGF-I) is emerging as a truly important regulator that may be central to aging and health. IGF-I provides a key mechanistic link between health habits involving exercise and diet and numerous health outcome benefits that are highly relevant to diabetic patients as well as the healthy aging population. As such, this could represent a generalized marker of quality of life. As examples, osteoporosis and neurodegenerative diseases are two problems of the elderly that show promise for risk reduction through exercise and dietary habits. The importance of IGF-I in the regulation of bone density has been well demonstrated, including recent studies with an IGF-I knockout mouse strain.¹ Similar anti-apoptotic actions of IGF-I on dopaminergic cells may explain a neuroprotective effect of exercise on brain cells,^{2,3} and there is evidence that the observed exercise induction of neurogenesis is mediated through IGF-I.^{4,5} Recombinant IGF-I has even been considered in the treatment of osteoporosis and neurodegenerative diseases.^{6,7} The benefits of exercise and macronutrient dietary influences on IGF-I and these outcomes of bone and brain function are being further assessed in ongoing Department of Defense-supported studies.

Health habits such as physical activity, weight management, and dietary intake are emphasized in the U.S. military because these factors are believed to be important for military readiness (the "go to war" status of soldiers). The goal of enforcing these habits is to ensure that soldiers are as prepared as possible to accomplish demanding tasks in adverse environments through enhanced physical and mental endurance, decreased injury and illness susceptibility, and greater resilience and recovery potential. This includes health benefits associated with weight management and prevention of Type II diabetes and physical activity that provides benefits to glucose tolerance and other aspects of metabolic efficiency. These same fitness habits that ensure that soldiers are combat-ready are also likely to produce lasting health benefits that will carry beyond their period of national service and into old age. IGF-I is one promising outcome measure for military studies on the refinement of medical fitness standards as well as physical training and nutrition policies. For example, detection of high rates of bone remodeling during the rapid training-up phase that occurs for new recruits and for reservists in a military mobilization could provide a simple approach to determining when a period of rest from intensive training might reduce musculoskeletal injury

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risks. IGF-I (and its principal binding protein, IGFBP-3) might also be useful in monitoring health benefits accrued from a weight loss training program, providing positive feedback to overweight patients on their diminishing risks for atherosclerosis, impaired glucose tolerance, and bone fracture risk.⁷⁻¹¹ The level of stimulation of IGF-I in response to exercise is related to training status,¹² and IGF-I has also been associated with sarcopenia in the elderly, suggesting its usefulness as an indicator of exercise fitness and response.

In this issue of *DT&T*, Nindl et al.¹³ describe the application of a practical filter paper blood spot method for circulating IGF-I monitoring that can be used in the most challenging field environments. In young Marines participating in an 8-day grueling field training exercise, blood IGF-I levels declined by half in both the filter paper blood spot and standard serum assay methods. Although the blood spot method produces concentrations that are less than half of the serum measurement, there was good agreement on the relative magnitude of changes, suggesting that this experimental method is a useful approach to field metabolic studies where frequent venipunctures are not practical. This blood spot method allows a practical follow-up to military studies in the last decade (discussed by Nindl et al.¹³), where blood glucose levels declined by 20%, and serum insulin and IGF-I each declined by 50% within the first 4 weeks of an intensive training course. The availability of this new blood sample collection method may permit some new discoveries in our understanding of near-term metabolic regulation with respect to diet and exercise programs.

Although IGF-I might be useful in long-term epidemiological studies or longitudinal comparisons, a hormone that is so susceptible to acute exercise and diet will be less reliable in prediction of individual factors that are much slower to change such as bone density or brain region volumes. Clearly, like any other useful biochemical marker such as high-density lipoprotein-cholesterol, the conditions under which the sample is collected will require some control or at least careful annotation of recent exercise and dietary practices. The method tested by Nindl et al.¹³ will also need to be care-

fully validated in a variety of other conditions where there may be significant alterations in the levels of binding proteins and bioavailable IGF-1, including diabetes.

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Analysis

Military Diabetes and Advanced Technologies Research

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CURRENTLY, SERVICE MEMBERS who develop diabetes are likely to be medically discharged or retired. Crude rates of Type I and Type II diabetes in the military population are 1.9 per 1,000 person-years, comparable to rates for the age-matched U.S. population and demonstrating the same increase with age.¹ However, the rise in Type II diabetes in the U.S. population associated with the obesity epidemic includes a significant number of young men and women who could otherwise qualify for military service. This becomes a national security issue as diabetes reduces the pool of qualified recruits, in addition to significant losses of highly trained soldiers diagnosed later in their careers. Although the Department of Defense is not likely to become a major force in diabetes research, there will be important "dual use" benefits from the solutions developed for urgent defense applications. In fact, Army researchers have been periodically asked by Congressman George Nethercutt, a champion of diabetes research, to explain what is being done to make it possible for diabetics to serve on active duty with the military. Diabetes care stands to be one of the beneficiaries of medical information technologies that are being vigorously exploited by the military. This is demonstrated in this month's issue of *Diabetes Technology & Therapeutics* by Colonel Robert Vigersky, M.D. from the Diabetes Institute at the Walter Reed Army Medical Center (WRAMC) and his colleagues from the Telemedicine and Advanced Technologies Re-

search Center (TATRC).² Their article highlights several critical features of a useful patient care system: elegant simplicity, patient empowerment, open software architecture, solid scientific underpinning, and rigorous validation with user assessment (in progress).

This article also raises several topics pertinent to Department of Defense medical research including: research in personal digital assistant (PDA) health applications, nutrition and exercise physiological modeling, and monitoring and treatment expert systems. Currently, there are many projects to develop military PDA applications, and every soldier may soon be equipped with some form of personal handheld computer. A whole division at the TATRC at Fort Detrick, MD, is specialized in military medical use of PDAs (<http://www.tatrc.org/>). Another PDA-based initiative is currently in development under the Small Business Innovative Research program (<http://www.acq.osd.mil/sadbu/sbir/>) to provide highly customized training and nutrition guidance to service members. These "personal fitness assistants" will help individuals maintain military fat and fitness standards; these standards are intended to ensure fit and healthy soldiers who are ready to deploy anywhere in the world on short notice. Prevention of Type II diabetes may be a near-term benefit of helping soldiers maintain physical activity and good nutrition habits throughout their careers. An attempted giant step involves modeling of glucose levels with an ambitious first-principles model

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(DYNUMO) being developed by the Natick Soldier Center.³ The goal of this project is to optimize soldier bioenergetics with customized nutrient requirement predictions. This is important, as soldiers typically consume only about 75% of their actual energy requirements in field settings, and both physical and mental performances are substantially improved with timely supplementation of carbohydrates.⁴ Nobody has yet evaluated continuous glucose measurements in soldiers operating in field conditions, or in combination with periodic mental performance assessments. Undoubtedly, such studies will lead to some new discoveries on the normal range and resilience of human responses. A PDA application for neuropsychological testing is currently being developed by Army and Navy researchers and has been tested with U.S. soldiers in Bosnia. Instead of using a blood glucose measurement, it may eventually be useful to titrate interventions against functional measures such as some critical cognitive test, with all of this integrated through a future many-layered version of the diabetes management and communication system (DMCS) concept of Vigersky et al.² to predict precise carbohydrate energy and insulin needs.

Where is this all headed? The Department of Defense is working hard to implement global medical information transfer with standard platforms such as the Theater Medical Informatics Program (TMIP) and Composite Health Care System (CHCS). Before long, the information flow may extend from physiological sensors (including glucose sensors) on soldiers, to records on their electronic dogtags [e.g., the Personal Information Carrier (PIC)] or entered from a medic's PDA [e.g., Battlefield Medical Information System (BMIST)], all the way up to the central databases. This kind of system will provide real-time monitoring of changes in health status, alerting the Army to the status of individual soldiers and to evolving threats on the battlefield. In longer-range concepts for the Objective Force Warrior, the technology-en-

abled ground soldier of the future, physiological monitors will one day automatically activate infusion of specific drugs in a Food and Drug Administration-approved closed circuit monitoring, diagnostic, and treatment system for the individual soldier (<http://www.natick.army.mil/soldier/WSIT/index.htm>). Diabetics with infusion pumps and semi-invasive glucose monitors are likely to be early leaders in the demonstration of these reliable closed-loop physiologically driven systems. And, someday soon we may have some impressive results to show Congressman Nethercutt and the diabetes community through work that may be led by the WRAMC Diabetes Institute. It's not hard to imagine a future variant of the DMCS coupled with a glucose sensor predicting optimal physical and cognitive performance of the future soldier.

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Analysis

Signs of Illness: When Will Technology Provide Greater Advantage Than the Practiced Eye of the Clinician (or the Military Commander)?

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INFORMATION THAT CAN BE GAINED from examining the skin or measured unobtrusively from the surface of the skin is an obvious starting point for noninvasive monitoring that may eventually become part of a standard system such as a smart "wear-and-forget" t-shirt. Earlier generations of physicians who relied on observational skills without technology have found useful information in the feel, taste, smell, appearance, and turgor of the skin. Temperature, wettedness, roughness, saltiness of a child's forehead, a scent of ketones, color and mottling, and rebound of a skin fold could all contribute to a diagnosis. Current technologies also allow us to measure noninvasively below the skin for important functional indicators such as nerve conduction velocity, subdermal concentrations of specific analytes, and hydration. Peripheral circulatory changes have already been monitored with semi-invasive methods; for example, "arterialization" with heating of a small portion of skin is the basis of transcutaneous oxygen sensing in neonatal monitoring and has also been tested in emergency patients for shock and hypoxia.^{1,2} Hyperspectral imaging is a new technology that maps regional changes in tissue perfusion based on the differential absorption of light by oxy- and deoxyhemoglobin at the surface of the

skin. This method has recently been used to assess regional tissue viability.³ In this issue of *DT&T*, Gillies et al.⁴ have demonstrated a unique application of hyperspectral imaging to assess systemic status, with detection of patterns of skin perfusion to provide objective information on mottling as well as overall changes in oxygenation. In this pilot study, mottling was detected during hemorrhagic shock but did not occur in post-contusion shock (blunt trauma lung injury), even though overall oxygenation was reduced in both conditions.

Hyperspectral imaging should now be tested in a variety of conditions as part of a research toolkit of sensors for studies where cutaneous blood flow may play importantly in a diagnosis and in tracking treatment. This research team, with Department of Defense (DoD) funding, is taking the critical next step distinguishing serious conditions that are characterized by a reduction in skin perfusion such as severe hypoglycemia, hypothermia, and hemorrhagic shock. Until the studies have been done that include hyperspectral imaging sensors along with other sensors in the research toolkit, the actual usefulness cannot be fully realized. Diagnostic algorithms could be further strengthened by other information such as heart rate

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and context information such as ambient conditions, meals and recent activity, and specific knowledge of the individual being monitored. This paper by Gillies et al.⁴ suggests a new tool that may be particularly useful for remote monitoring, important for soldiers operating away from their main units or enshrouded in chemical protective suits, astronauts on extended voyages, and young diabetics on the playground.

This leveraging of new technology is the crux of DoD research efforts in Warfighter Physiological Status Monitoring (WPSM), as well as the goal of the Technology for Metabolic Monitoring (TMM) special interest program that has been sponsored by the Juvenile Diabetes Research Foundation. The common goal of these programs is to provide early warning and predictions of impending changes for decision assist (e.g., impending performance failure to a commander or early warning to the parent of a diabetic child). The concept is to monitor individuals at risk using a minimal set of sensors that together provide all the information needed for specificity and enough redundancy for high reliability of the assessment. These sensors will also "learn" the individual's normal

responses in the context of various external challenges ("green light") (Fig. 1). Detection of a critical event or crossing a physiological threshold will trigger an automatic "911" signal for electronic notification of emergency services ("red light") (Fig. 1). The software will move into a medic mode, providing early triage information, feedback on the effectiveness of resuscitation efforts, and help to monitor the patient through evacuation to a medical treatment facility. Eventually, predictive algorithms will warn of impending risks when there is still time to intervene such as a warning signal to diabetics about the near-term need for glucose or insulin, or to a soldier who is becoming dehydrated ("amber light"); monitoring and predicting changes in this phase of active physiological compensation may take longer to develop as it is far more difficult than detection of a frank casualty.

The two greatest challenges to the development of this system include identification of the right set of sensors and development of the machine interpretation of these data ("sensor data fusion"). Moving to a messy field environment where sand, dust and dirt, and sweat, as well as ambient temperature and light changes, may

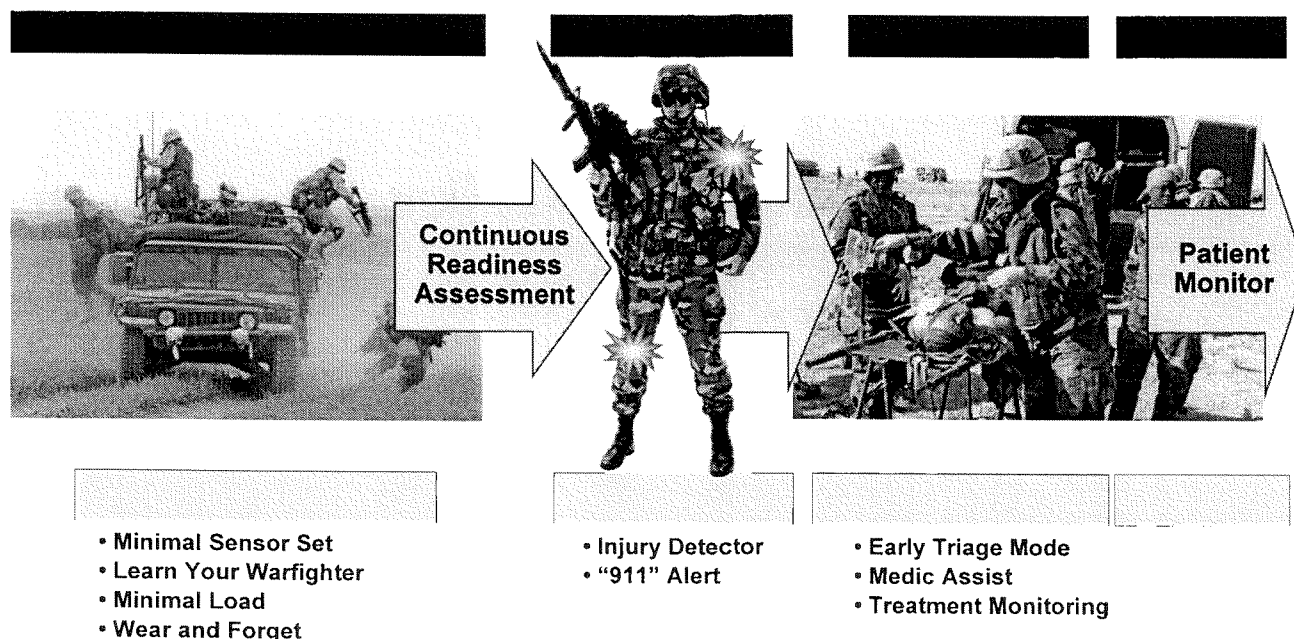


FIG. 1. The concept for progression of monitoring includes correct classification of normal physiological activation in healthy individuals ("green") to detection of a casualty-producing event or critical condition ("red"), early triage, and subsequent monitoring of resuscitation and transportation responses.

disrupt the stability of the measurement, which is also a large step that challenges many technologies. The effects produced by differences in skin pigmentation need to also be carefully evaluated. Development of the sensors is important, but even more challenging is the useful interpretation of the combined sensor signals and converting their data into useful knowledge. The goal of these efforts is to use technology to provide a substantial advantage to commanders and patients and not to provide an expensive and complex substitute for common sense and good training.⁵ However, even after many years of clinical telemetry sensor development, there is still relatively little progress on useful interpretation of the signals. This is the challenge to enterprising technologists.

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Analysis

Actigraphy as Metabolic Ethography: Measuring Patterns of Physical Activity and Energy Expenditure

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TO BETTER UNDERSTAND the relationship between physical activity and metabolic regulation, we need new measurement tools that are accurate, inexpensive, available, and untethered to a laboratory setting. Actigraphy, the continuous measurements of motion amplitude and frequency from body-worn accelerometers, has been actively investigated for applications in the measurement of patterns of voluntary activity. In this issue of *Diabetes Technology & Therapeutics*, Chen et al.¹ have described the combined use of two accelerometers, mounted on the hip and the wrist, to accurately predict energy expenditure of physical activity across a range of activity levels in a sample of overweight women. Not only does this approach provide the energy expenditure associated with activity (EE_{act}), it can also provide EE_{act} patterns throughout the day. David Marlowe, a former military social psychologist, used to say that life involves motion, and a technology such as actigraphy that quantifies human motion can be used to describe behavior, providing an important tool for ethographers. We may finally have an accurate and practical tool for describing EE_{act} patterns for individuals with respect to meal timing and medication, and for a variety of physical and emotional states, providing a tool for medical ethnographers interested in their patients' behaviors. Such a method for gathering accurate data could revolutionize our understanding of the role of physical activity and energy balance

in health and disease, especially for weight management.

The gold standard for total energy expenditure is still a calorimeter. This group at Vanderbilt is well known for the refined precision of their special metabolic chamber that has a force transducer instrumented in the floor.² This chamber was used as the reference method in this study. An alternative method that allows us to step outside of the laboratory measures the differential elimination of stable isotopes using deuterated ^{18}O water. This doubly labeled water method provides precise measurements of energy expenditure in free-ranging subjects, but requires careful attention to natural variations in isotope enrichment in the ambient environments, careful handling of specimens, and costly and time-consuming analyses. Nevertheless, this has been a breakthrough technology in military field studies, allowing us to understand energy balance for healthy individuals operating in extreme environments.³ Unfortunately, the greatest problem in metabolic studies has been the worldwide shortage of ^{18}O enriched to the concentrations needed for this research, and this method only provides energy expenditures in 24–48-h periods. A third method to obtaining estimates of EE_{act} involves more pedestrian and practical methodology developed before doubly labeled water techniques were available, such as continuous heart rate monitoring. Despite the large sacrifices in accuracy, esti-

mations of EE_{act} from heart rate have been used to address some important hypotheses on nutritional status and work capacity, such as the studies by Gerry Spurr and colleagues that demonstrated a ceiling effect on energy expenditure in undernourished Colombian schoolchildren compared with their better-fed peers,⁴ that might find parallels in poorly regulated diabetics.

Wrist-worn actigraphy has been used in many military studies to quantify sleep patterns in field settings, demonstrating how robust these systems are even in the harsh environments of Army Ranger training.⁵ However, the hopes that a single wrist-worn actigraph could provide adequate measures of energy expenditure⁶ have not been fulfilled because measurement of upper body movement provides an even less complete representation of overall activity than measurement of only lower body and trunk movements as described in a previous paper by Chen and Sun.⁷ The combination of these two accelerometer signals is clearly advantageous in predictive accuracy. These physical methods will always have some limitations associated with changes in metabolic activity (post-exercise oxygen consumption phase, thermic effects of feeding, etc.), but even some of these currently missed variations may be correctable with further sensor inputs such as heart rate changes. The Army has also explored piggyback applications of accelerometry that would capitalize on planned soldier systems such as an inertial navigation device, the Dead Reckoning Module, built into future soldier equipment. This three-axis accelerometer is intended to provide backup to the global positioning system but can also provide remote detection of traumatic events involving the individual soldier and, if adequately coupled to the body, may provide more detailed activity and metabolic data.⁸

The energy cost of physical activity (i.e., that portion of energy expenditure beyond resting energy expenditure) is of great interest to the military as well as to specific patient populations. For the military, physical fitness and body fat standards are strictly enforced across all ranks in order to motivate regular physical activity habits. This is intended to optimize individual health and ability to meet the de-

mands of combat that may be called for on short notice and without time to train up. Current studies are focused on energy balance in soldiers to assist them with weight management and good fitness habits. New recommendations that support and expand these current research efforts were provided by the Institute of Medicine's Committee on Military Nutrition Research earlier this year⁹ (see <http://books.nap.edu/books/0309089964/html/index.html>). Physical activity is also a first-line treatment for specific illnesses, ranging from fibromyalgia (a chronic multisymptom illness with some symptom features shared by returning Gulf War veterans with undiagnosed illnesses) to diabetes and obesity. Actigraphic systems such as that described by Chen et al.¹ may provide important solutions to assist individuals in meeting military standards or following medical treatments. For example, wear-and-forget actigraphy systems built into waistbands and wrist watches could be used in conjunction with Internet-based weight management systems, automatically downloading daily activity and prescribing adjustments to diet and activity levels to meet desired weight management or therapeutic goals. Even more important may be the analyses of patterns of low and high activity that will explain variations in energy balance. These variations might include periods of sedentary activities involving TV viewing and computer time, energy costs associated with simple choices such as taking the stairs versus riding an escalator, and frequently overlooked differences in behavioral efficiencies such as the exclusively purposeful movements observed in semi-starvation that saves energy compared with the extreme fidgeting (non-exercise activity thermogenesis) of some individuals that ensures they remain thin even if well-fed. With a current Army-funded grant, Chen and his colleagues are now exploring other modes of actigraphy to predict EE_{act} with even higher accuracy and to provide additional information that classifies types of physical activity throughout the day.

These new tools for research and patient care are needed to help combat the continuing rise of obesity and its medical sequelae. In the next issue of *Diabetes Technology & Therapeutics*, the discussion will further expand this theme of

automatic measurements of EE_{act} with the introduction of a paper on foot-ground contact pedometry that is being pioneered for use in a soldier "smart boot." Ultimately, through the pioneering efforts of Chen and others, we should have an unobtrusive smart system that will provide useful information back to the individual or physician that can predict and prescribe near-term adjustments to activity and nutrition, and perhaps even provide more informed insulin dosing for diabetics. This calls for many more experiments to interpret and model these sensor data.

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Analysis

Bioenergetics of Animal Locomotion: Lessons for Expedient Monitoring in Human Fitness and Weight Management

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BASIC PRINCIPLES of animal physiology can provide valuable insights to complex systems. Such is the case with foot-ground contact time (T_c) and bioenergetics. Modeling energy costs of human movement is complicated, requiring articulated models to account for biomechanical efficiencies, elastic elements that cyclically store and release energy, and the various groups and types of muscles appropriate to the type of locomotion. However, overarching principles governing the metabolic cost moving a body mass through space and time suggest total mass (body weight and load weight) and T_c (the time during each step that the foot is in contact with the ground) present a much simpler solution to estimating the energy costs of locomotion. Reed Hoyt and Peter Weyand applied an empirical observation that the metabolic cost of walking or running varied as a function of the ratio of body weight (W_b) and T_c to estimate the metabolic costs of walking or running (M_{loco}).¹ In this issue of *DT&T*,² the T_c technique for estimation of M_{loco} has undergone further validation for use in free-ranging humans moving over level ground at different speeds. For an extra challenge, these tests involved Marines carrying backpack loads in rigorous training.

The idea for this measurement approach came from studies at Harvard University's Concord Field Station in Bedford, MA, where

cross-species studies seek to improve our understanding of the principles of biomechanics and bioenergetics from the cell and tissue level to whole organisms. Energy expenditure and locomotor mechanics have been measured for terrestrial birds, mammals, and even some reptiles with a wide variety of locomotory strategies, ranging from tiny kangaroo rats running on a treadmill to trotting elephants accompanied by a golf cart modified to collect gas expired from the elephant's trunk. All of the animals tested fall in on a single curve relating mass, T_c , and energy expenditure; locomotion is more economical with increasing mass of various species, no matter how ungainly some larger creatures may seem.³ The Concord Field Station investigators observed that the same size dependence they initially quantified for the rate of metabolic energy expenditure also applied to the rates at which the different-sized animals completed their strides. For example, at equivalent speeds such as the trot-gallop transition where the relative proportions of the contact and aerial portions of the stride are the same, the per-stride costs of the large and small creatures are also the same. This observation raised the possibility that the greater mass-specific metabolic rates of smaller animals might be a direct function of the shorter periods of their strides. The Concord Field Station crew considered the likely candidate to be the con-

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tact portion of the stride during which ground force must be applied to support the body's weight. Subsequent investigation demonstrated this was indeed the case. Regardless of the animal's size or speed, mass-specific metabolic rates are a constant multiple of the inverse period of foot-ground contact that the investigators used to estimate the rate of ground force application.⁴ This led to the understanding that on level ground, the primary metabolic costs are those required for the muscles to support body weight.⁵ The T_c method is increasingly accepted,⁶ and is well suited to field application because the equation requires only two inputs: body weight and T_c ($M_{loco} = Wb/T_c \times \text{Constant}$).

The actual measurement device first devised by Hoyt and co-workers measured T_c using force-sensitive resistors under the toe and heel and was validated with treadmill walking and running.⁷ Field tests of the prototype hardware were disheartening. The initial conceptions required an imprint of each soldiers' foot so that special insoles could be constructed to house an inside-the-boot monitor. A collaborative field trial was conducted with Norwegian cadets going through an extreme endurance course. Wires to the connectors broke, data downloads failed, and the inserts proved to be an irritant to the subjects. These technical problems were solved without international incident, and eventually led to the accelerometric outside-the-boot lace-up prototype footstrike monitor. This has since been used in a variety of military physiological monitoring studies along with other sensors such as the wrist-worn actigraph to complement sleep/wake history in studies such as one of senior military leaders involved in high-intensity military planning activities, and another study involving a squad of infantry soldiers in a field training exercise.⁸

In this latest validation test by Hoyt et al.,² activity periods were classified into categories of locomotion that determined the method of energy estimation. The metabolic cost of running and walking were estimated from total weight and the time between the detection of heel strike and toe off (foot down/foot up). Slow walk was detected by a heel strike with no detectable toe off, with energy costs esti-

mated from some assumptions about T_c . Shuffle [or "non-exercise activity thermogenesis" (NEAT)] periods were detected by accelerometer activity without discernible heel or toe activity, with energy costs estimated as the metabolic cost of standing. Rest was when no accelerometer activity was present and no additional energy costs beyond resting metabolic rate (RMR) were estimated. These estimates were summed to estimate total M_{loco} . Comparisons were made to total daily energy expenditure (TDEE) measured using doubly labeled water (DLW) ($^2\text{H}_2^{18}\text{O}$). To do this, the investigators had to estimate the missing components of TDEE that are not estimated from M_{loco} , including RMR and thermic effects of food (TEF). Although follow-up studies are certainly needed, and a number of assumptions were required to make this comparison, the results were quite good with the mean error in TDEE between T_c and DLW estimated at 12%. This was a highly active group with relatively little sleep time, and average energy expenditure of 15.3 MJ/day (3,670 kcal/day) over the 50-h period of their exercise. This also included average carried weights of 30 kg (also factored into the total mass for T_c computations).

There are numerous gadgets now marketed for energy expenditure measurements with a variety of uses and usefulness. One should clearly distinguish the components of metabolic costs that the methods attempt to measure. Portable calorimeters that have a breathing apparatus and a backpack gas analyzer provide estimates of total energy expenditure, including those components associated with locomotion. These have been used to assess metabolic costs associated with various typical soldier tasks such as carrying stretchers and carrying backpack loads in various types of constricting clothing, etc. This method is estimated to provide accuracy within 5% alongside of treadmill testing for $\text{VO}_{2\text{max}}$.⁹ Heart rate, calibrated to the individual, provides some reasonable estimates of total energy expenditure in discrete time periods but can be unreliable in largely sedentary populations. Both calorimetry and heart rate reflect something about overall metabolic rate, combining RMR, TEF, NEAT, and energy costs of activity (including locomotion). Pedometry, accelerometry, and T_c

measurement each provide estimates of metabolic costs associated with body motion. The type of activity captured obviously depends on the location of the sensors. Standard pedometry, in which only a step count is recorded, is one of the least reliable of energy measurement methods and provides more value as a motivational tool for patient exercise than a useful energy measurement device. However, accelerometer-based pedometers capable of reliably recording time series data over days appear to be scientifically useful.¹⁰ Accelerometry has been used primarily on wrists and hips to estimate overall body motion energy expenditure and may work best in combination, as described in the last issue of *DT&T*.¹¹ Compared with measures of oxygen uptake in a laboratory, commercially available accelerometers have been reported to have errors averaging 10–20%; much better accuracy was reported by Chen et al.,¹¹ who used multiple accelerometers. The T_c method provides an alternate path to accurately estimate muscle force generation and M_{loco} , making it potentially more accurate for measurement of this specific component; upper body motion captured by multiple accelerometers or heart rate techniques is not measured with this approach. There is great value in assessing weight-bearing exercise, as the most important component of fitness and weight management programs, as well as for specific exercise objectives such as stimulating bone mineral accretion. As Hoyt et al.² point out, this may also provide a novel approach to estimating NEAT, a potentially important factor in weight management.

In future developments, if high-tech accelerometer-based pedometers capable of recording data over days could be coupled with a tri-axial accelerometers or supersensitive altimeters to detect movement up or down inclines, including ladders and stairs, this might resolve some variability expected from work on uneven surfaces. Technologies that put the sensor back inside the shoe to measure regional pressures on the foot ("pedobarography") may also provide very useful information for noninvasive monitoring of energetics of locomotion, with a complete picture of type of activity as well as ground reaction forces involved.

The research effort on locomotion continues with Department of Defense-supported research in Peter Weyand's lab at Rice University. One hope is that this type of research will provide a basis for a non-running test of fitness that could be applied both to the military and to patients with diabetes, providing a simple and accurate method to assess overall changes in physical fitness levels. As an example, Weyand, Hoyt, and colleagues recently reported that combining T_c with heart rate monitoring produced accurate estimates of maximal aerobic power.¹² It would be useful to know if changes in T_c and heart rate relationships over periods of stable monitoring taken weeks or months apart could reflect changes in fitness levels, or if acute alterations during military field operations might provide an index of thermal or dehydration. Providing noninvasive "smart shoe" technologies that provide feed back about energy expenditure as well as improvements in fitness could encourage soldiers and patients with diabetes to engage in physical training programs.

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Analysis

Novel Biosensors for Long-Term *In Vivo* Physiological Monitoring

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RELIABLE LONG-TERM MONITORING of the metabolic status of individual soldiers and diabetic patients alike is a key goal of the Army's Technologies for Metabolic Monitoring (TMM) research program (see <http://www.momrp.org/tmm.jsp>). The TMM program is a partnership between the Juvenile Diabetes Research Foundation and a consortium of federal agencies working with the U.S. Army. Central to this effort is the investigation of novel biosensors that couple a biologically active compound with a signal transducer. Studies currently underway are considering approaches to *in vivo* measurement of glucose variously based on the physical expansion of hydrogels, competitive binding to lectins, nanoparticle-borne glucose sensing systems, and simultaneous measurement of glucose and lactate with enzyme-based probes. Other relevant studies are considering approaches to overcome biofouling issues for implanted sensors. The sum total of these and other research efforts in the field is intended to provide a family of metabolic monitoring technologies that advance us to highly reliable and precise long-term monitoring systems.

In this issue of *DT&T*, Ralph Ballerstadt and his colleagues¹ report further investigations of the applicability of a biosensor based on concanavalin A (Con A). Con A is a sugar-binding protein (lectin) obtained from jack bean (*Canavalis ensiformis*) seeds that has a specific binding affinity for glucose and mannose. In this

device, glucose competes for Con A binding sites with fluorescently labeled dextran (polymerized glucose). In this reversible reaction, glucose crosses a semipermeable membrane housing that contains the immobilized Con A and fluorophore complex. Excitatory wavelengths from an external laser diode generate a fluorescent signal for the detector. The signal is modulated by fluorescence resonance energy transfer, which is sensitive to molecule distances and well suited to detecting fast changes in glucose binding to Con A. This technology provides greater specificity for glucose and reduces interference from other plasma components.² Ballerstadt et al.¹ have optimized the choice of fluorescent dyes and other conditions in the sensor, improving response time and sensitivity over those in previous studies.^{3,4} Most importantly, they have demonstrated the stability and reusability of this sensor configuration over months of repeated glucose fluctuations. An important next step is to demonstrate biostability with *in vivo* testing, where membrane degradation and other biofouling issues have previously held up implantable sensors that had appeared to be quite promising on the basis of *in vitro* performance. This constitutes a first-generation biosensor, with future generational advances eliminating the need for a semipermeable membrane with the biomolecule attached to the transducer, and eventually directly linked to the signal production through microelectronics.⁵

Unlike glucose oxidase-based sensors, the Con A sensor does not depend on local oxygen tension and appears to have great stability at normal body temperatures. The reusability and stability features make it potentially useful for long-term implantation in systems ranging from a tattoo injected under the skin,⁶ to even longer-term use of immobilized Con A in a special intraocular lens following cataract surgery in patients with diabetes.⁷ The initial concept of a minimally invasive sensor that can be slipped under the skin and easily removed several months later should be immediately useful in exploring the significance of glucose fluctuations with respect to health outcomes, as well as the effectiveness of various interventions. The availability of this research tool will quickly determine the value of long-term continuous monitoring. This tool should also help advance public health policy, associating excursions in glucose regulation over months and years with changes in personal fitness and dietary habits, insulin regulation, and indicators of long-term health risk. Ultimately, the most important application may be in providing patient feedback and training for optimal monitoring points that may be more important than continuous or daily integrated glucose concentrations. For soldiers in the field, the same monitoring technologies will have parallel applications in feedback and training to normal limits and appropriate interventions to sustain mental and physical endurance in the future Ground Soldier System (2010+).

Con A has a variety of established *in vitro* laboratory uses, notably as a probe in studies of surface carbohydrates in cells, as a controlled mitogenic stimulus in lymphocytes *in vitro*, and for laboratory purification of compounds with sugar moieties. Con A is known for its hemagglutinating activity. Although another well-known lectin derived from castor beans, ricin, is a highly potent toxin investigated as a biological threat agent, lectins are not all toxic and occur in common foods, including most beans. The toxicity of Con A, in the concentrations being considered for implantable sensors, appears to be far lower than that of glucose oxidase already being used in probes in humans. Ballerstadt et al.¹ highlight a study that indi-

cates the absence of toxicity of this lectin in mice exposed to concentrations 10 times higher over a 30-day period.⁸ Further demonstration of the integrity of the probes, where the immobilized Con A is reliably contained long term *in vivo*, will add to the safety data. There is every reason to believe that Con A-based devices can offer a safe and viable option for implanted sensors.

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Analysis

The Promise of Lactic Acid Monitoring in Ambulatory Individuals

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LACTATE MEASUREMENTS in clinical practice and experimental studies are challenging because of whole-blood metabolism that increases levels far more rapidly than the loss of glucose. Direct lactate sensing technologies have been actively pursued by critical care specialists, exercise physiologists, and food technologists for their respective applications for more than a decade, and the methods are maturing. The capability to obtain lactate measurements over weeks or months is also important to understanding glucose counterregulatory responses for soldiers in the field and individuals with diabetes in their normal activities.

In this issue of *DT&T*, Ward et al.¹ provide a human *in vivo* monitoring approach to combined lactate and glucose sensing that promises to be more responsive and practical than currently available options. The goal is to produce a completely implantable telemetered sensor. This is one of several projects on lactate monitoring funded by the U.S. Army in a competitive solicitation offered through the Technologies for Metabolic Monitoring research program (see <http://www.momrp.org/tmm.jsp>). The sensing method for lactate and glucose uses the typical amperometric detection of hydrogen peroxide after conversion of the analyte of interest by an immobilized oxidoreductase enzyme. Because of the proximity of the sensors, it was important to demonstrate low crosstalk with peroxide from one

reaction registering in the other sensor. Previous tests of this subcutaneous probe in animals demonstrated good stability of the immobilized enzyme for at least a month, but the investigators also discovered that the extent of crosslinking in the immobilization with glutaraldehyde may affect sensitivity and response time, perhaps through protein conformational restrictions. This study suggests approaches to optimization of the sensor. Further miniaturization can be compared with this baseline for crosstalk issues and other challenges; carbon nanotubes fabricated with glucose and lactate oxidase immobilized on glassy carbon electrodes have already been described,² and very small probes are a near-term possibility.

The concept of direct lactate sensors are not new³; Ward et al.¹ have nevertheless helped to advance the arrival of practical subcutaneous measurements. Biofouling issues still complicate the development of *in vivo* biosensors, and have driven currently available techniques down the path of ultrafiltration, microdialysis, and open flow interfaces, introducing other problems such as management of tiny samples and delays in response time additional to the sensor response. The utility of previous studies with amperometric enzyme-based lactate sensors has already been demonstrated in physiological studies. For example, Gfrerer and colleagues at Graz University of Technology (Graz, Austria) conducted laboratory bicy-

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cle exercise studies with continuous flow sampling through a heparin-coated single-lumen system, establishing maximal levels of 14 mmol/L that matched well to other methods of analysis.⁴ Cespuglio's group at INSERM in Lyon, France have used a lactate biosensor coated with lactate oxidase and cellulose acetate to measure cortical lactate in free-moving rats, demonstrating large circadian changes in lactate synchronized with light-dark cycles and stages of sleep.⁵ The way forward is equally exciting. Looger et al.⁶ have described an approach to computational design of a "designer" soluble receptor for lactate with the highest possible selectivity and affinity based on engineered protein structure and function relationships. The eventual goal would be to connect a custom-built protein receptor into synthetic cellular transduction pathways regulating gene expression, with some measurable output, or perhaps even a closed-loop regulatory response. Whatever form they will take, future-generation biosensors will build on what we can learn now about monitoring physiology.

At the November 2003 meeting of the Diabetes Technology Society meeting, a special session on lactate monitoring summarized the state of knowledge in lactic acid physiology. The session included clinical applications, new concepts of metabolic physiology, and specific environmental and exercise considerations, as well as a presentation by Ken Ward on his earlier evaluation of dual-analyte sensors that led to his current sensor configuration. Thomas Pieber reviewed the clinical applications that are currently pushing the technology for continuous lactate probes in emergency vehicles and critical care units, focused on conditions of impaired oxygen delivery and tissue perfusion, such as shock, sepsis, and cardiac failure. Lactate levels rise dramatically because of acute renal failure in shock, decreased hepatic clearance, and reduced gas exchange in acquired respiratory failure, making severe lactic acidosis a common metabolic marker of important prognostic value. Michael Donoghue presented data on the specialized but highly relevant occupational risk of heat injury faced by soldiers, emergency workers, and miners, where the combination of physical exertion in the heat

producing metabolic acidosis may signal serious compromises ranging from acute dehydration to rhabdomyolysis.⁷ There is a clear market demand for an effective continuous lactate monitor in critical care medicine. This will serve the soldier in future physiological status monitoring systems to trigger immediate interventions in remote battlefield locations. More sobering, but important to saving would-be rescuers from unnecessary risks, is the potential use of extraordinarily high lactate values combined with other sensor readings to suggest positive signs of death, so that a very high probability indication of death could be used to gauge the risk of a rescue operation.

Onset of blood lactate accumulation is a traditional marker of fitness training and limits of endurance performance for an individual, used to monitoring training progress in swimmers and other athletes. Higher lactate tolerance with lower lactate accumulation per unit of work reflects a higher training status and is related in part to higher gluconeogenesis in trained individuals. Bruce Gladden reviewed the data that associate acute lactic acid changes with performance declines from overtraining (excessive training with inadequate rest and metabolic recovery).⁸ Although still not providing a biochemical measure with prognostic value, this suggests an area of research that will benefit from new metabolic monitoring technologies. His critical view of lactate as something more than a marker of hypoxia has been informed, along with the rest of the current generation of physiologists, by George Brooks' lactate shuttle hypothesis. In this symposium, Dr. Brooks presented the importance of lactate as a normal substrate in oxidative metabolism.⁹ This concept has altered views that elevated lactate is a limiter of performance and a marker of impending performance failure in healthy individuals. It may have particular importance in the brain, although it is not clear how much lactate can be utilized as a substrate and replace glucose as an energy source for neurons. Thus, the rise in lactate following hypoglycemia in patients with diabetes may be a beneficial response, indicating an adequate alternate support to cerebral metabolism. This is suggested in studies where counterregulatory and symptomatic responses are reduced by increases in

blood lactate following hypoglycemia episodes.¹⁰

In the near future, continuous monitoring of lactate in free-living individuals may provide one of the few critical biochemical markers of metabolic status that, depending on the relevant contextual information, e.g., diabetes history, ambient temperature, exercise conditions, provides a key prognostic indicator of an impending casualty requiring immediate attention, or signals appropriate physiological responses to an exertional or hypoglycemic threat.

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Analysis

Corticosteroid Modulation of Tissue Responses to Implanted Sensors

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IN VIVO GLUCOSE MONITORING has been remarkably influenced by the technological barriers surrounding the use of implantable sensors. This impasse has stimulated alternate paths ranging from methods to bring the analytes to a noninvasive sensor [e.g., GlucoWatch G2[®] Biographer (Cygnus, Inc., Redwood City, CA)] or to measure the analytes in secretory products (e.g., biochemical assessments of lacrimal secretions), or even to find functional outcomes reflecting metabolic status (e.g., nerve conduction). While each of these will likely find important applications, they do not replace the need to go deep with direct measurements. The key limiter in implantable sensors has been host defense responses to the foreign body challenge. These responses range from chemical attack on the integrity of the implanted sensor itself, to attempted anatomical isolation of the sensor through fluid accumulation and fibrous encapsulation, to maladaptive responses of inflammation and even carcinogenesis. If external wires are eliminated in autonomous systems that are independently powered for transmission or that can be passively queried, at least some of the problems associated with routes of infection and continuous movement and irritation can be eliminated. Although biosensors are relative newcomers in implantable technology, these are

clearly not new problems to medical science, with substantial precedent in the development of other types of xenobiotic implants such as intravascular stents and valves, prosthetic bone implants, slow drug release systems such as Norplant[®] (Wyeth Pharmaceuticals, Madison, NJ), and brain and heart electrical stimulators. The current challenge with biosensors is to obtain optimal control of tissue responses to an implant to obtain a stable and long-lasting tissue interface for rapid and accurate sampling in tissue or blood.

In this issue of *Diabetes Technology & Therapeutics*, Diane Burgess and her colleagues present new data on tissue responses to a drug-doped biocompatible material intended as a device coating. The significant advance is the demonstration of an effective process for steroid doping of the material that permits a consistent drug release that controls local tissue responses.¹ This overcomes previously identified difficulties in providing a consistent rate of drug release starting at the time of surgical implantation.² Poly(vinyl alcohol) (PVA) hydrogels have desirable properties of biocompatibility and high stability in fabrication processes, and this team previously demonstrated glucose permeability that makes this suitable for use as a glucose sensor coating. In this study, the integration of dexamethasone-loaded

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poly(lactic-co-glycolic) acid (PLGA) microspheres with the hydrogel was shown to provide prompt and stable release of dexamethasone into the local tissue with very small amounts detected in circulation over a 1-month period. The inflammatory response produced by the hydrogel was essentially abolished with the dexamethasone-treated coatings.

Previous glucose sensor studies have highlighted the problems associated with fibrotic encapsulation; while some of these capsules are well vascularized and may provide stable readings for several months, this is an inconsistent response.³ A more serious problem is the delayed sensor response that may be caused by surrounding fluid masses, with response times reduced by about 2 h as glucose levels decline.⁴ Systemically administered dexamethasone is highly effective in reducing the thickness of tissue reactions around an implant, presumably through inhibition of macrophage activity, including secretion of growth factors (e.g., interleukin-1, tumor necrosis factor, platelet-activating factor, and platelet-derived growth factor),⁵ but clearly a potent corticosteroid produces iatrogenic responses in blood glucose regulation and would especially be a problem for a patient with diabetes.⁶ Localized release of the drug may be the right answer, but it will have to be demonstrated that there is no artifact in the measurements produced even by this amount of drug. Yet to be considered by the research community is the optimal corticosteroid (or other compound) that will provide the specifically desired moderation of tissue responses, with minimal systemic effects or artifactual disruption of the local metabolic environment and sensor measurement. "Designer" corticosteroids have been planned for desired effects, synthesized, and characterized for specifically desired properties. For example, one compound was conceived as a potent anti-inflammatory agent that would rapidly metabolize to cortic acid with minimal corticoid activity as it enters systemic circulation.⁷ In rat studies, the compound had superb anti-inflammatory actions with more potent granuloma inhibition than prednisolone but with no effects on thymus weight or plasma corticosterone concentrations.

A completely different approach to consider

is stimulation of the vascularization around an implant. Ken Ward and his associates specifically tested this in a study with vascular endothelial growth factor (VEGF) reported in an issue of *DT&T* earlier this year.⁸ Within the same animals, glucose sensors closest to the slow release of VEGF (via osmotic minipumps) maintained the best response with lower lag time in response to glucose infusions. This suggests that even with a fibrotic response, angiogenic factors may greatly enhance implanted sensor function. The same group has also shown that angiogenic responses can be promoted simply by the surface properties of an implant, with greater porosity generating a better vascularization.⁹

Perhaps a future approach will include a sophisticated regimen of timed release drugs appropriate to the stage of healing, first with control of the acute inflammatory responses to reduce the size of the fibrotic capsule perhaps with a corticosteroid, followed by a treatment that enhances and maintains a generous vascular connection with a VEGF-like compound. The military has been faced with a related issue in the treatment of laser eye injury in soldiers, where aggressive treatment with prednisone, the standard of care, is believed to reduce later scar size in the retina, but it may also prevent revitalization of the injured tissue.¹⁰ There is evidence that corticosteroids not only inhibit inflammation, but also specifically prevent angiogenesis.¹¹ The ultimate solution probably will not be a complicated drug regimen timed to the phase of injury but rather a treatment that targets more fundamental mechanisms of tissue responses.¹²

Solutions to this sensor implant problem will clearly find a wide range of applications. One important application for the military could be personal identification systems (and even "black box" recorders of individual soldiers) that maintain a current metabolic status and history of an individual.¹³ Radar tag technology used to track nuclear missiles through passive scanning of a wide area could also be used to track missing soldiers or downed pilots hiding in enemy territory where location, identification, and a current medical status could be provided through a simple continuous-reading embedded chip. This is the same radar tag tech-

nology that is being piloted by Sandia National Laboratories (Albuquerque, NM) for passive friend-foe detection systems. The Defense Department has a research initiative on Personnel Recovery Extraction Survivability aided by Smart-Sensors (PRESS) that is intended to provide real-time combat survivor location and tracking. A key addition to the current efforts would be a glucose measurement that would provide critical information on medical status.

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