Chapter 1

PREDICTING HUMAN LIMITS—THE SPECIAL RELATIONSHIP BETWEEN PHYSIOLOGY RESEARCH AND THE ARMY MISSION

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SUMMARY

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INTRODUCTION

The US Army has entered a new era of low-level persistent conflict. This changing operational environment is shaped by new threats and challenges, such as globalization, disaffected populations vulnerable to radical ideologies, catastrophic terrorist attacks, failed or failing states, competition for energy, and climate change and natural disasters.[1] The Army's modernization strategy to meet these challenges includes developing more agile protection of health and performance of the individual soldier. The soldier is the Army's most important military system (ie, "the soldier as a system"), as compared to other services with major platforms such as stealth fighters and destroyers. However, new technological complexity, the lethality of weapons systems, and rapid worldwide response capabilities make the performance of the individual soldier more critical to mission success than ever before. The near- and long-term health of individual soldiers is also potentially at risk from military technologies that can surpass operator capabilities and safety. Advances in warfighting technology and the changes in tactics and strategy that result from new capabilities make improved understanding of human limits critical to materiel and doctrine developers. The predictive models that provide developers and commanders access to critical physiological information are the subject of this book (Figure 1-1). No other agency or industry has a comparable need; thus, military needs have kept the Army at the forefront of human performance physiology. The continuously evolving threats drive more sophisticated predictive tools to improve selecting, training, monitoring, equipping, resting/recovering, and fueling the "soldier system" (Figure 1-2).

A good first sergeant has special skills in recognizing human performance limits, but a good physiological model can greatly extend leader intuitive abilities to assess the status and capabilities of his troops. For example, soldiers are protected from heat injury by predictive work/rest and hydration tables. These limits are based on computational modeling of heat strain from an enormous amount of data and findings from more than 50 years of experimentation (summarized in TB MED 507[2]). These predictions provide guidance appropriate to any ambient conditions and mission posture to prevent environmental heat injuries, while also limiting overconsumption of water that might produce hyponatremia. Military leaders and medical providers need such well-founded physiological models that go beyond any one individual's empirical experience. Even though every military leader has expertise acquired through careers in feeding, clothing, and training soldiers, the solution sets to these age-old issues are constantly improving with new technological and scientific breakthroughs. This knowledge base can be passed on to future generations, with constant improvement and enlargement of the predictive models. Technological advances in the ability to acquire, store, and manage vast amounts of physiological data are helping to close some of these centuries-old gaps in retaining and integrating the "lessons observed" so that predictive models will truly represent "lessons learned." These lessons can also be disseminated through decision support systems and through other new information technologies emerging in this new era of network-centric operations.[3]

Quantitation of biological relationships is at the heart of physiology. Classic examples of these defined relationships should be well known to students of physiology and are usually identified by the names of the creators (eg, the Siggaard-Andersen nomogram for acid-base balance, the Frank-Starling law of dynamic regulation of cardiac pumping, and the Åstrand-Ryhming prediction of maximal oxygen uptake from submaximal heart rate).[4] At the organismal level, these

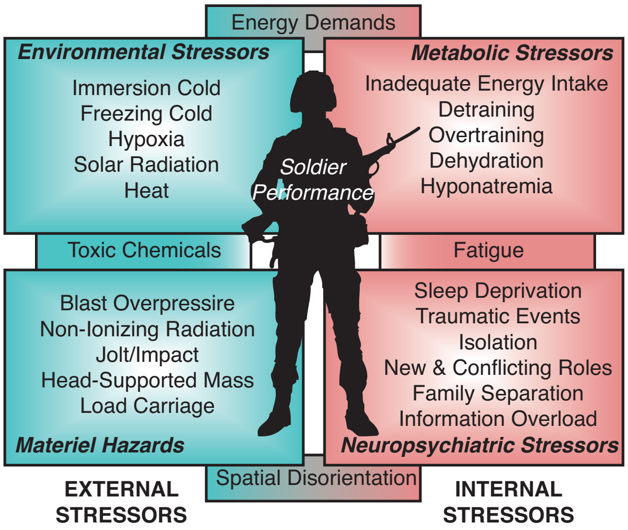


Fig. 1-1. Physiological stressors encountered by soldiers and marines affect health and performance. Human performance optimization involves strategies to sustain health and performance in the face of these stressors. Physiological modeling defining human tolerance limits and the effect of moderating factors provides scientifically based strategies to interventions that ultimately involve how we feed, rest, train, and equip individuals and teams. It is important to consider models that combine multiple stressors because individuals are rarely subjected to only one stressor at a time. The highlighted individual stressors are described in various chapters throughout this book.

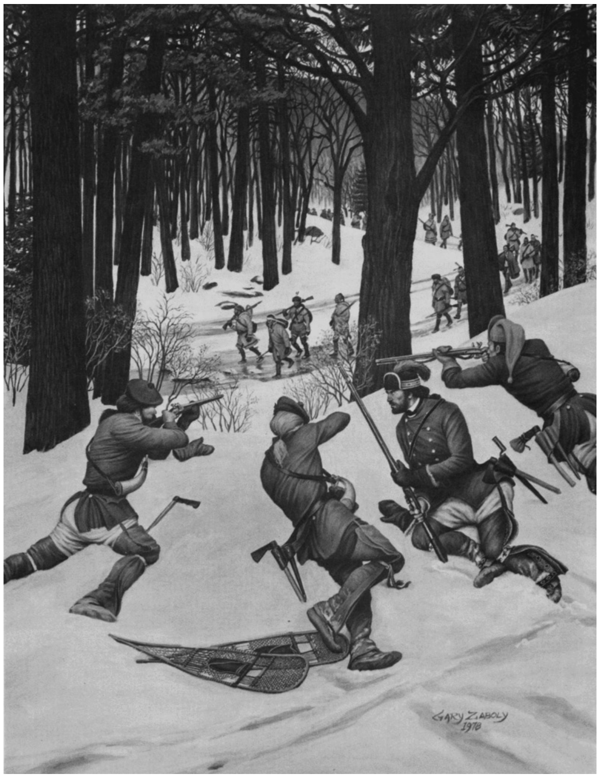


Fig. 1-2. Soldiers and marines today face many of the same physiological challenges presented to their counterparts in previous centuries. Today's technologically enabled warfighters should be better prepared and better protected because of the knowledge accumulated from experience and research on how to feed, rest, train, and equip individuals and teams. This knowledge is especially useful when assembled into predictive physiological models used to optimize mission planning and rehearsal, for virtual prototyping of equipment, and for decision support tools. (**a**) Roger's Rangers fought the Battle on Snowshoes in January 1757 against French, Chippewa, and Ottawa warriors. In similar environmental conditions, (**b**) US Marine Lance Corporal Harris C Bienn provides security for a simulated casualty evacuation during a 2009 winter training course at the Marine Corps Mountain Warfare Training Center in Bridgeport, California.
Painting: (a) Courtesy of Walking the Berkshires Web site, "Right Rangers, Wrong Fight," October 1, 2007, http://greensleeves.typepad.com/berkshires/2007/10/right-rangers-w.html.
Photograph: (b) Courtesy of the National Archives and Records Administration, Washington, DC.

models help to describe integrated biophysical and biochemical responses to stressors, such as exercise or hypoxia (Table 1-1).[5–23] In this volume, readers will find Army models, such as the INJURY model of blast injury risk, the US Army Research Institute of Environmental Medicine (USARIEM) heat strain model, and successors of the Walter Reed Army Institute of Research (WRAIR) sleep and performance model.

Military physiological models are the primary products of the Military Operational Medicine research program, wherein the findings of various laboratory and field studies are brought together in the form of useful algorithms, models, and simulations. Testing, refining, and validating these knowledge products comprise an additional step involving advanced development and engineering. This step has been typically neglected because there is no regulatory requirement for performance and preventive medicine predictions comparable to the US Food and Drug Administration's approval of products that influence medical treatment. Computational biology is the modern science that encompasses this form of advanced development that makes the Military Operational Medicine program's physiological and psychological research useful to Army customers. Computational biology is the interdisciplinary combination of mathematics, computer science, and life sciences. This chapter summarizes Army experiences and challenges in advancing physiological models developed through methods of computational biology.

HISTORY OF MILITARY PHYSIOLOGICAL MODELING

Predicting soldier performance has always been of great interest to military commanders. In earlier times, recruit selection was based on anecdotal experience and may have involved some test of strength or endurance, or typically a simple visual assessment of physical robustness and behavior. By the mid-1800s, objective measures of fitness were considered. Height was a key selection criteria as a surrogate measure for health and fitness.[24] During the Civil War, data were systematically collected by investigators who were interested in topics that are still relevant today, such as recruiting healthy and fit soldiers, sustaining

TABLE 1-1

KEY PHYSIOLOGY MODELS IN THE ARMY'S MILITARY OPERATIONAL MEDICINE RESEARCH PROGRAM

System Hazard	TRL	Inputs	Prediction [Key References]	Test System	Applications/Users
Blast overpressure (INJURY 8.0)	TRL 8—model in use by the Army	Pressure tracing from four sensors	Risk Assessment Code (based on lung injury) [Stuhmiller et al, 1996(1)]	Blast Test Device	CHPPM; Army Research Laboratory/Survivability and Lethality Directorate
Laser eye injury	TRL 7—findings used in ANSI standard	Frequency, wavelength, and duration	Retinal injury [Ness et al, 2000(2)]	Evaluation cards	CHPPM; ANSI standard
Thermal strain (SCENARIO, HSDA)	TRL 6—not yet generalized for export	Temperature, heart rate, fluid intake, activity, and clothing	Water requirements; work/rest cycle; and core body temperature [Kraning and Gonzalez, 1991(3); Moran et al, 1998(4)]	Heat strain monitor (includes model)	HHA, conducted at USARIEM
Head-supported equipment	TRL 5—some key design factors predicted	Equipment mass and center of mass	Neck fatigue and injury risk [Ashrafiuon et al, 1997(5)]	—	HHA, conducted at USAARL
Jolt/vibration	TRL 5—ANSI standard, but limited data	Vibration signatures	Fatigue [Cameron et al, 1998(6); Smith, 1995(7)]	—	HHA, conducted at USAARL
Inhaled toxic gases (TGAS 2.0)	TRL5—model predicts serious risk	Metabolic deficits, primarily oxygen delivery	Performance/escape [Stuhmiller and Stuhmiller, 2001,(8) 2005(9); Januszkiewicz et al, 1997(10)]	—	Survivability assessments, conducted at WRAIR
Radiofrequency radiation	TRL5—models can predict thermal risks	SAR	Body heat deposition [Adair and Berglund, 1992(11)]	—	HHA, conducted by CHPPM
Impulse noise	TRL5—models can predict eardrum rupture, but Army has inadequate predictor of hearing damage	Decibel exposure	Risk of eardrum rupture and permanent threshold shift in hearing [Chan et al, 2001(12); Stuhmiller, 1989(13)]	—	HHA, conducted by CHPPM

(**Table 1-1** *continues*)

Table 1-1 *continued*

System Hazard	TRL	Inputs	Prediction [Key References]	Test System	Applications/Users
Behind body armor effects (BABTA)	TRL5—new model that may eventually replace National Institute of Justice standard	Lethality of torso impact	Injury risk assessment [Stuhmiller, 2006(14)]	—	Materiel developer
Head impact and concussion (ANAM)	TRL5—thresholds of injury and reinjury risk have not been well defined	Neuropsychological testing	Neurocognitive impairments [Bleiberg et al, 2004(15); Warden et al, 2001(16)]	—	Medical personnel assessing return to duty and rehabilitation
Physical training enhancement/ injury (TOP 1.0)	TRL5—first version model in testing	Gender; training intensity, frequency, and duration; ground reaction forces	Physical performance/ physical injury [Stuhmiller et al, 2006(17)]	—	Military trainers
Sleep and performance (SAFTE)	TRL5—early version models in refinement	Sleep history; use of stimulants; scheduling of naps	Cognitive performance [Belenky et al, 2000(18); Hursh et al, 2004(19)]	—	Military planners, Army modeling, and simulation
Altitude ascent (ARMS)	TRL5—first version model in development	Acclimatization status; speed of ascent	Probability of AMS symptoms [Vann et al, 2005(20)]	—	Military planners, Army modeling, and simulation

Note: Except for the head impact/neuropsychological testing effort, all of these research model development programs have undergone scientific review at least once, and sometimes three or more times in external peer review site visits organized by the American Institute of Biological Sciences, in addition to review of the publications.

AMS: Acute mountain sickness; ANAM: Automated Neuropsychological Assessment Metric; ANSI: American National Standards Institute; ARMS: Altitude Readiness Management System; BABTA: Body Armor Blunt Trauma Assessment; CHPPM: US Army Center for Health Promotion and Preventive Medicine (now undergoing a name change with integration into the US Army Public Health Command); HHA: health hazard assessment; SAFTE: Sleep, Activity, Fatigue, and Task Effectiveness; SAR: specific absorption rate; TGAS: toxic gas assessment; TOP: Training, Overuse Injury, and Performance; TRL: technology readiness level; USAARL: US Army Aeromedical Research Laboratory; USARIEM: US Army Research Institute of Environmental Medicine; WRAIR: Walter Reed Army Institute of Research.

Data sources: (1) Stuhmiller JH, Ho KH, Vander Vorst MJ, Dodd KT, Fitzpatrick T, Mayorga M. A model of blast overpressure injury to the lung. *J Biomech*. 1996;29:227–234. (2) Ness JW, Zwick H, Stuck BE, et al. Retinal image motion during deliberate fixation: implications to laser safety for long duration viewing. *Health Phys*. 2000;78:131–142. (3) Kraning KK, Gonzalez RR. Physiological consequences of intermittent exercise during compensable and uncompensable heat stress. *J Appl Physiol*. 1991;71:2138–2145. (4) Moran DS, Shitzer A, Pandolf KB. A physiological strain index to evaluate heat stress. *Am J Physiol*. 1998;275:R129–R134. (5) Ashrafiuon H, Alem NM, McEntire BJ. Effects of weight and center of gravity location of head-supported devices on neck loading. *Aviat Space Environ Med*. 1997;68:915–922. (6) Cameron B, Morrison J, Robinson D, Roddan G, Springer M. *Development of a Standard for the Health Hazard Assessment of Mechanical Shock and Repeated Impact in Army Vehicles*. Fort Rucker, Ala: US Army Aeromedical Research Laboratory; 1998: 201 pp. Final Report. AD A339 243. (7) Smith SD. The effects of whole-body vibration on human biodynamic response. *J Gravit Physiol*. 1995;2:96–99. (8) Stuhmiller JH, Stuhmiller LM. An internal dose model for interspecies extrapolation of immediate incapacitation risk from inhalation of fire gases. *Inhal Toxicol*. 2001;14:929-957. (9) Stuhmiller JH, Stuhmiller LM. A mathematical model of ventilation response to inhaled carbon monoxide. *J Appl Physiol*. 2005;98:2033–2044. (10) Januszkiewicz AJ, Mundie TG, Dodd KT. Maximal exercise performance-impairing effects of simulated blast overpressure in sheep. *Toxicology*. 1997;121:51–63. (11) Adair ER, Berglund LG. Predicted thermophysiological responses of humans in MRI fields. *Ann NY Acad Sci*. 1992;649:188–200. (12) Chan PC, Ho KH, Kan KK, Stuhmiller JH, Mayorga MA. Evaluation of impulse noise criteria using human volunteer data. *J Acoust Soc Am*. 2001;110:1967–1975. (13) Stuhmiller JH. Use of modeling in predicting tympanic membrane rupture. *Ann Otol Rhinol Laryngol*. 1989;140(suppl):53–60. (14) Stuhmiller JH. *Mathematical Modeling in Support of Military Operational Medicine*. San Diego, Calif: Jaycor, Inc/L-3 Communications/Titan Corporation; 2006: 76 pp. Final Report DAMD17-00-C-0031. AD A458 419. (15) Bleiberg J, Cernich AN, Cameron K, et al. Duration of cognitive impairment after sports concussion. *Neurosurgery*. 2004;54:1073–1078. (16) Warden DL, Bleiberg J, Cameron KL, et al. Persistent prolongation of simple reaction time in sports concussion. *Neurology*. 2001;57:524–526. (17) Stuhmiller JH, Sih BL, Shen W, Amankwah K, Negus C. *Overuse Injury Assessment Model*. San Diego, Calif: Jaycor, Inc/Titan Corporation; 2006: 115 pp. Annual Report DAMD17-02-C-0073. AD A463 099. (18) Belenky G, Balkin TJ, Redmond DP, et al. Sustaining performance during continuous operations: the Army's Sleep Management System. In: Friedl KE, Lieberman H, Ryan DH, Bray GA, eds. *Countermeasures for Battlefield Stressors*. Baton Rouge, La: Louisiana State University Press; 2000: 197–205. (19) Hursh SR, Redmond DP, Johnson ML, et al. Fatigue models for applied research in warfighting. *Aviat Space Environ Med*. 2004;75(suppl 3):A54–A60. (20) Vann RD, Pollock NW, Pieper CF, et al. Statistical models of acute mountain sickness. *High Altitude Med Biol*. 2005;6:32–42.

endurance on road marches, preventing injuries, and reviewing recruitment and casualty statistics and associations.[25] The same questions are still being asked more than a century later, but, clearly, technological advances provide new options for the enduring problem set of soldier health and performance issues (see Figure 1-1). Although some soldier problems are new, and generated by our own technology, most of these new issues still fall into the same broad categories of research that have been pursued for generations. For example, information overload is a relatively recent information-age issue, but cognitive performance in the face of other psychological stressors (eg, sleep deprivation) has been formally investigated at least since the World War II era, with findings that are relevant to this new problem. Similarly, radiofrequency radiation is a modern technology problem, but body heating has been a relevant Army focus for many years. This highlights the fact that there are enduring research requirements for the Army, with new understanding and technology always providing greater advantage to the warfighter (see Figure 1-2).

Civil War and Early Physiological Models

During the Civil War, study teams were sent out to gather data at Union Army encampments that related body dimensions, nutrition, and nativity to physiological outcomes, such as spirometry measures, pulse, lifting strength, and general indicators of fitness for duty[25] (Figure 1-3). Along with other statistics on recruitment demographics and casualty rates, various analyses were conducted to develop predictors of success for recruitment standards and battlefield planning

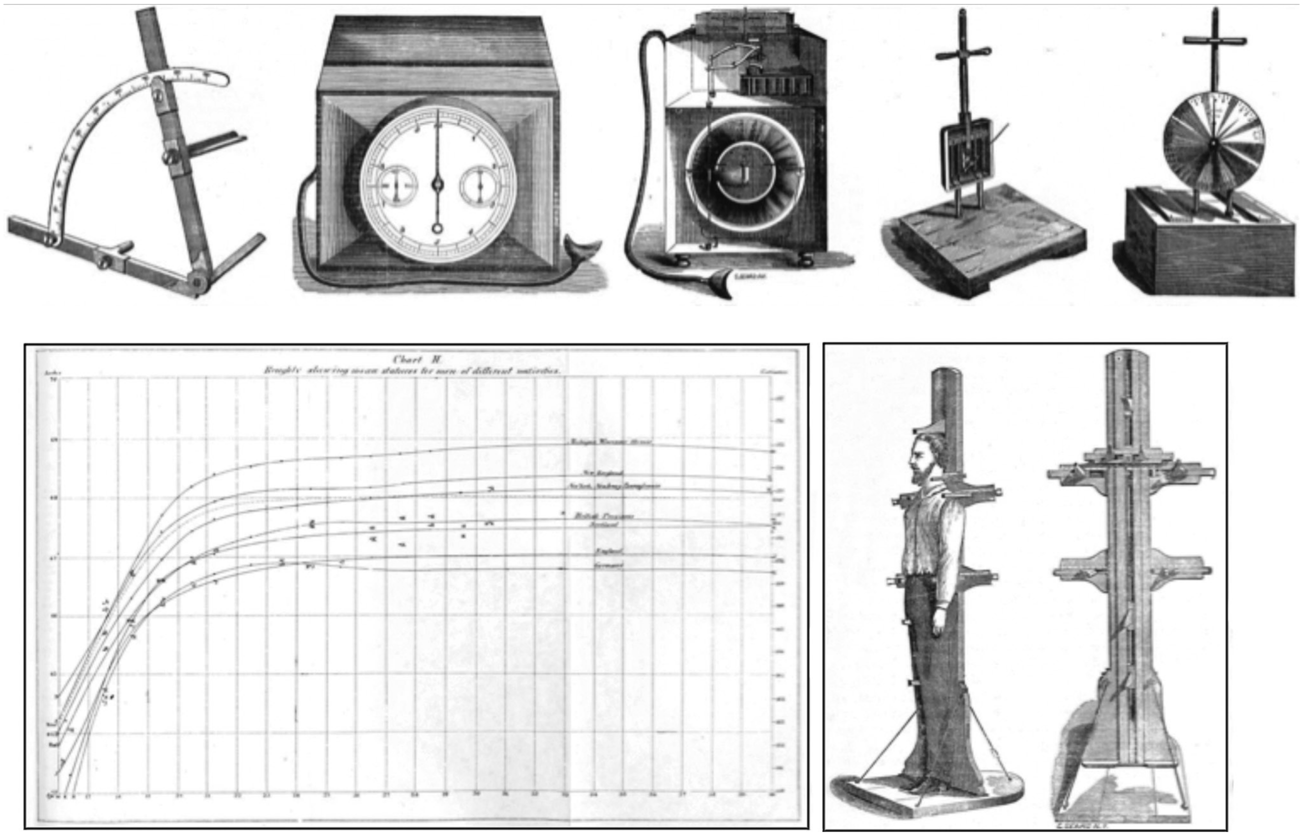


Fig. 1-3. Research teams were sent to Union camps to collect physiological data from a large sample of men during the Civil War. Test devices were constructed for a variety of measurements, such as the calipers for body breadths, spirometers for lung volume, and an upright lift device to measure strength performance (**top**). Twelve anthropometry “machines” were constructed, based on a device developed by an Edinburgh tailor, to efficiently collect a large number of measurements on each individual (**bottom right**). Much of these data were summarized by age and ethnicity, such as the graphical display of mean statures plotted by age, demonstrating the physical maturation in men for stature after age 21 (**bottom left**).
Illustrations: Adapted with permission from Gould BA. *Investigations in the Military and Anthropological Statistics of American Soldiers*. Cambridge, Mass: Riverside Press; 1869.

factors. Researchers also gathered data on road march performance and its relationship to food provisions (including coffee rations), topics that are frequently revisited today in Army research.[25–27] Unfortunately, the program had more ambitious objectives that were never realized because the secretary of war decided that research was not an important priority.

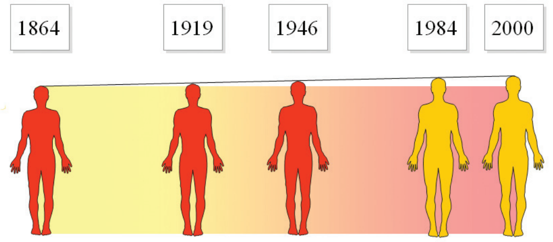
Gould[25] tested several new statistical approaches that describe normal height and weight relationships in humans based on this very large sample of healthy males, thus confirming Quetelet's observations that, in metric units, weight increases normally against height squared. Gould found that this did not work for adolescent soldiers in a growth phase up to age 21, but then held constant across older age categories. This relationship between height and weight (now referred to as body mass index) is used to calculate the Army weight-for-height screening tables used today in Army Regulation 600-9.[27a] Some of the Civil War data have been reused to assess body composition trends in young soldiers over time. This calculation of the average body fat of young soldiers in 1864 was not an application conceived of at the time, but was made possible because of the preservation of a well-defined data set (Figure 1-4).[24,28]

The struggle to preserve this unique data archive, as well as the challenges to productively analyze these measures from many thousands of Union soldiers, was articulated by Dr Benjamin Apthorp Gould (1869):

> These statistics greatly surpass in amount all that has been previously gathered on the same subjects, and it may be long before opportunity again offers for an equal collection of similar material. On the other hand, the proper reduction, elaboration, and discussion of this grand store of numerical data demands special training and peculiar gifts. No pains have been spared in their elaboration, and the enormous amount of work bestowed on the materials will be apparent only to those who are in some degree familiar with arithmetical computations. But the variety of topics is great; and medical and physiological knowledge of a high order is needed for eliciting such information as they may contain, as well as for deducing the best results.[25(p vi)]

Gould's plea for the unique importance of his data set has been a familiar refrain of scientists with their military data sets from deployments, large training studies, and experimental studies ever since.

In World War I, the seeds were planted for a new field of human nutrition science. A special commission of scientists was established to evaluate nutritional requirements for health and performance of soldiers.[29,30] This commission led to the formation of the National Research Council and today's Food and Nutrition Board in the Institute of Medicine. It was also the genesis of modern nutrition and metabolism research, which is now a credible scientific discipline. Detailed studies led by Major John R Murlin assessed 427 Army mess halls, representing 135,000 men, to determine that an average of 3,900 kcal were provided per man per day (including 131 g of protein and 134 g of fat), but only 3,600 kcal/day were consumed.[30] Additional studies considered the effects of season, duration in the camps, and strength performance of the men in relationship to food consumption to predict requirements for various circumstances. The Army research focus was heavily influenced by concepts of nutrition, genetics, and health that were popular at the start of the 20th century. One remarkable study examined health consequences of weight change using a longitudinal analysis of annual physical examination data. In this study, Reed and Love[31] defined a "cardiac type," reporting associations between weight gain and abdominal obesity with heart disease in Army officers. These important observations preceded the use of waist-hip ratio and abdominal fat as expressions for obesity-related diseases that gained prominence in the 1950s. Modern tools of genomics and proteomics provide us with new data handling and analytical challenges, with opportunities to revisit these old issues and move from predictions based on group membership to individual predictions for personalized medicine and individualized training and protective interventions.



Age	25.7	24.9	24.3	26.3	26.3
Ht (in)	67.2	67.7	68.4	68.6	69.6
BW (lb)	141	145	155	167	178
BF(%)	**16.9**	**15.7**	**14.4**	**17.3**	**17.0**
FFM (lb)	**117**	**122**	**133**	**138**	**148**

Fig. 1-4. Body composition of US male soldiers in various eras. These estimates are derived from large anthropometric data sets and the DoD body-fat (BF) model developed by Dr James Hodgdon at the Naval Health Research Center. For more than a century, the typical young male soldier has benefited from improved health and nutrition with an increase in height (Ht) and body weight (BW), primarily reflected in an increase in the fat free mass (FFM) component comprising bone and muscle. Relative body fat of active young men (17%) is similar between Civil War soldiers and soldiers in 2000.

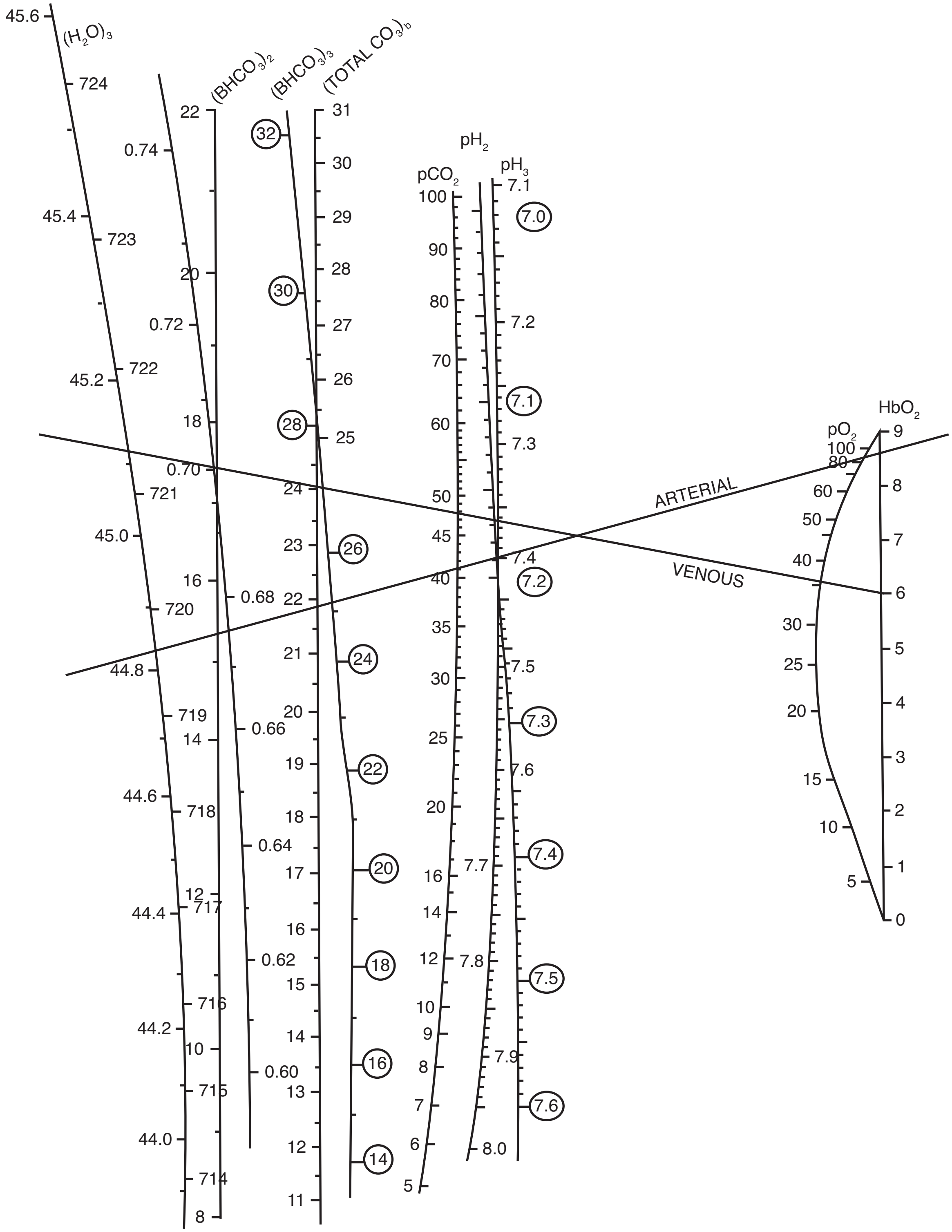


Fig. 1-5. Nomograms and slide rules are graphical analog computational devices that were common tools before the advent of electronic computers. Slide rules are general purpose computers, whereas nomograms are usually intended to perform a specific set of calculations. This nomogram for human blood was developed to combine known biochemical relationships, such as the oxygen dissociation curve, into a more complete model to describe more complex relationships. This was developed to make predictions about new studies conducted with men at altitude in the famous US medical research expeditions into the Andes. Illustration: Reproduced with permission from Dill DB, Edwards HT, Consolazio WV. Blood as a physicochemical system. XI. Man at rest. *J Biol Chem*. 1937;118:635–648.

In 1927, the Harvard Fatigue Laboratory was founded by Lawrence J Henderson and Elton Mayo as a research center for industrial physiology and psychology. Although the Army commitment to research on these problems rapidly waned after World War I, the work on occupational fitness standards; early occupational medicine standards, such as problems of inhaled gases in enclosed spaces (notably carbon monoxide); and responses to environmental stressors prepositioned the Harvard Fatigue Laboratory to deal with many important soldier problems in World War II.[32,33] In this precomputer era, "computational biology" took the form of nomograms. For example, blood-gas nomograms relating physicochemical characteristics, such as P50 and blood pH, were developed to provide useful mathematical predictions in respiratory metabolic assessments[34] (Figure 1-5). This was a sophisticated predecessor of the current TGAS (toxic gas assessment) model that relies on modern computing power to link these well-developed respiratory metabolic factors with more recent physiologically based pharmacokinetic modeling to predict the effects of inhaled toxic gases, especially if combined with other variables (eg, ventilation).[35]

World War II and the Harvard Fatigue Laboratory

Military physiology research reached maturity in World War II, with the mobilization of members of the Harvard Fatigue Laboratory (Cambridge, Mass) (Figure 1-6) to military research activities at the Army Climatic Research Laboratory (Lawrence, Mass), Bethesda Naval Medical Research Institute (Bethesda, Md), Fort Knox Armored Medical Research Laboratory (Fort Knox, Ky), Pensacola Navy School and Aeromedical Laboratory (Pensacola, Fla), and Wright Field Aero Medical Laboratory (Wright Field, Ohio). Some of the individuals from these laboratories later helped form the Army Chemical Corps Medical Laboratories (Aberdeen Proving Ground, Md), US Army Medical Research and Nutrition Laboratory (Denver, Colo), Quartermaster Army Medical Nutrition Laboratory (Chicago, Ill), and the Quartermaster Climatic Research Laboratory (Natick, Mass), each of which has spawned more recent successor efforts.[32] Today, the majority of integrated physiological research that relates to human performance limits are the primary mission of only one laboratory in the federal government: USARIEM (Natick, Mass).[36] Other laboratories that include some missions in this area are the US Army Aeromedical

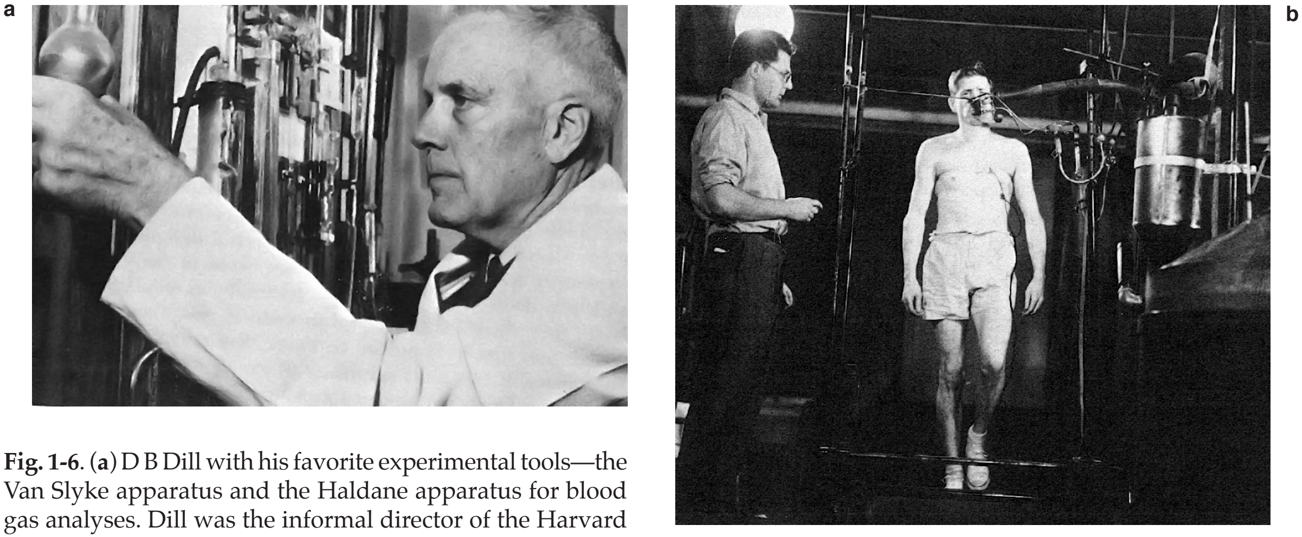


Fig. 1-6. (**a**) D B Dill with his favorite experimental tools—the Van Slyke apparatus and the Haldane apparatus for blood gas analyses. Dill was the informal director of the Harvard Fatigue Laboratory, mentoring many of the next generation of physiologists. One of these was his future son-in-law, Steve Horvath, founder of the Institute of Environmental Stress in Santa Barbara, the civilian parallel of the US Army Research Institute of Environmental Medicine. After World War II, Dill became the director of medical research for the US Army Chemical Research and Development Laboratory (1947–1961). Photograph: Horvath SM, Horvath EC. *The Harvard Fatigue Laboratory*. Upper Saddle River, NJ: Prentice-Hall; 1973. (**b**) Treadmill experiment at the Harvard Fatigue Laboratory in 1938. The subject is Sid Robinson, one of the two physiologists to receive their doctorate degree at the laboratory (the other was Steve Horvath). Robinson's work on physical fitness and age is still frequently cited today, as is his pioneering body of work on thermoregulation in exercise. The observer is R E Johnson, famous for his studies on nutrition metabolism and work with C Frank Consolazio, a later investigator at the Military Nutrition Laboratory in Denver. Photograph: Reproduced with permission from Horvath SM, Horvath EC. *The Harvard Fatigue Laboratory*. Upper Saddle River, NJ: Prentice-Hall; 1973.

Research Laboratory in Fort Rucker, Alabama (biodynamics models) and WRAIR in Forest Glen, Maryland (fatigue and performance models).

Wartime efforts included quick turnaround studies in nutrition, fitness, clothing and protection in hot and cold environments, and respiratory physiology.[32] Fatigue on long foot marches and during continuous operations was addressed, with countermeasures ranging from stimulants to nutritional supplements.[27,37] Amphetamines were extensively tested for use in military operations,[37] and these investigations of neurological factors associated with fatigue and fatigue interventions involving amphetamines provided insights that recent studies with more sophisticated methods confirm and extend. Fueling the soldier has always been an important consideration in sustaining performance. In World War II, the K ration was nutritionally complete, but was not eaten (even by hungry soldiers); thus, it was ineffective.[38] Ration studies examined macronutrient composition for optimal performance, exploring the use of high-fat rations and considering the importance of energy balance.[39,40] This led to modern studies by the Army to determine that carbohydrates are a preferred source of energy and still form the basis of current approaches to optimal composition of combat rations.[41,42] Predictions of the amount of work that an individual could accomplish relative to the caloric intake were developed from underfeeding studies during this era. These studies provided clear evidence of a ceiling effect produced by limited energy intake.[39] The Office of The Surgeon General contracted Ancel Keys and his group at the University of Minnesota to conduct the now famous Minnesota Starvation Study.[43] Fit young male volunteers for this study lost 24% of their body weight over 24 weeks and were then put on various refeeding regimens to determine the optimal recovery diet for returning prisoners of war and other starving populations. This study was published in two volumes, with the complete data set reutilized for metabolic modeling to this day.[44,45]

Environmental heat and cold exposures were significant factors in World War II, and extensive efforts to speed acclimation and improve soldier protection were investigated.[32] More sophisticated analyses and predictions of those same challenges are being conducted today.[46,47] Incorporation of accumulated data into thermal models provided early demonstrations of mathematical model approaches to predictive models for decision aids. This also preserved the key experimental results, even if data were not preserved. Physiological models that combined ambient conditions, clothing, etc, to predict heat strain were developed out of these data, with principles of the heat balance equation presented for the first time.[48,49] This provided a basis for current methods that have since been extensively expanded and redefined for biophysical evaluation of clothing, evaluation, and heat strain modeling, as described in Chapter 8. The thermal modeling and biophysical methods developed for assessment of clothing and personal equipment were a World War II success story and represent one of the most advanced military physiological modeling efforts today (Figure 1-7). This success is due, in part, to the close relationship between physiologists and materiel developers of personal protective equipment.

Although there was extensive evidence of health hazards and impaired operator performance in tanks, even in World War I, military systems were traditionally engineered with the operator as an afterthought. The Fort Knox Armored Medical Research Laboratory conducted a large series of tests in tanks to evaluate the risks from heat, impulse noise, toxic gases, and other factors.[50–53] These important findings were largely ignored. The problems were repeatedly demonstrated, including one event in which the senior officers attempted to fire 10 rounds from a Sherman tank with the hatches closed. However, they quit the test after firing four rounds because of the oppressive ammonia fumes.[54,55] To protect against exposure to heat and engine combustion products, vehicles were generally operated with all hatches open. Years later, systems such as the Bradley Fighting Vehicle were still being developed with an incomplete apprecia-

Fig. 1-7. Biophysical testing models, such as the copper foot, have been highly refined by the US Army for thermal insulating and vapor transmissibility properties of individual clothing. This copper foot at the USARIEM laboratory is being used to test a Norwegian boot.

Photograph: Courtesy of USARIEM, T Rice, Public Affairs Office.

tion for the human occupant and operators. In 1983, the Army Health Hazard Assessment program was instituted to address issues of operator safety and crew survivability starting at the earliest stages of planning of Army vehicles and equipment. This Army regulation drives the requirement for medical input with validated predictive physiological models and damage risk criteria.

Impulse noise was an issue from weapons and tunnel blasts in the Pacific Islands during World War II, addressed by goat studies in caves at Fort Knox (S M Horvath, personal communication, December 1982). This research was later refined with development of shock tubes for controlled blast exposures in a laboratory setting at Fort Knox.[56] Research to improve auditory protection with various forms of earplugs was conducted at the Fort Knox Armored Medical Research Laboratory, and other aspects were also considered, including burn risks from firing large weapons.[50–52] Today, impulse noise is an issue from new, high-powered weapons systems and has been addressed through an entire research program to protect against auditory and nonauditory effects of our own systems.

As the United States entered World War II, clothing became appreciated for its significant roles in protecting soldier health and enhancing survival. This, and nutrition research efforts, provided the major impetus for the Army's physiological research and modeling that continues today. In World War I, personal equipment was inadequate and too heavy. It was common practice for soldiers to discard clothing and equipment, because the standard individual load was about two thirds of the typical soldier's body weight.[57] Shoes were not waterproof, and 90% of the men suffered foot problems in the winter of 1917–1918.[57] These problems did not prompt much new development, and the US Army entered World War II still unprepared and with substantially the same inadequately designed cold weather uniforms and personal equipment, even for World War I conditions. A much wider range of conditions faced the American soldier in World War II, including, for example, dry heat in the north African desert, moist heat in the South Pacific, cold winters in Italy and western Europe, and damp cold in the Aleutians. In a remarkable move, borne out of wartime necessity, the Army established a multidisciplinary scientific team to deal with clothing issues. The group, modeled on the unique approach to practical problem-solving at the Harvard Fatigue Laboratory, included physicians, physiologists, textile experts, clothing design experts, and meteorologists. This was established as the Quartermaster Climatic Research Laboratory and later as USARIEM and Natick Labs. Much of the basic thermal modeling and studies in the protection against specific hazards were conducted at the Fort Knox Armored Medical Research Laboratory and later at the Pierce Laboratory (New Haven, Conn) at Yale University. This effort to study and predict the interaction of clothing, fatigue, and supplementary substances was guided by the National Research Council.[57] Tropical environmental problems were investigated by a team of preventive medicine specialists in the Panama Canal Department. Specialized clothing protection was investigated across multiple laboratories and with new technologies to enhance fire proofing, protection against chemical warfare agents, and even fabric weaves and chemical impregnation to protect against disease-bearing arthropods. Skin diseases, especially in hot climates, were an important cause of disability and lost duty time.[57] More than 90,000 cold injuries were reported in US troops during World War II, and much of this was attributable to inadequate supplies and training in their use.[57] At the end of the war, detailed anthropometric measures and photographic studies of a statistically derived sample of more than 100,000 male and 8,000 female soldiers were produced for future sizing and other studies.[58]

Ethical Considerations in Studies of Human Performance Limits

Ethical standards for the conductance of medical research have changed considerably in recent years. Greater awareness of what we do not understand and what constitutes misconduct in research has led to ever-improving human subject protections and regulatory safeguards. This obviously produces new challenges in conducting studies on the limits of healthy human tolerances, especially in the military environment where there is an even greater expectation of protection of healthy young men and women in an autocratic command structure (considered for research purposes as a special vulnerable population).[59,60] In a previous era, physiologists often first exposed themselves to new stressors and risks to observe these limits. The famous 40-40-40 Club of researchers at the Harvard Fatigue Laboratory included nude exposure to –40°C, ascent to 40,000-ft altitude, and 40-mile walks in 12 hours to study nutritional balance.[32] Military psychologists were among the first researchers to point lasers into their own eyes to acquire data on laser dazzle and performance effects. In the present, more enlightened research environment, safety of human subjects is of paramount importance, and even physiologists are protected in "self-testing" experiments and pilot experiments. This means that laboratory studies on tolerable limits will be stopped within a conservative safety margin of the lowest known or suspected amount of harmful exposures. For example, laboratory heat exposure studies are typically terminated before an individual's core temperature reaches 40°C, even though 40°C may be maintained with peak marathon running performance for more than 2 hours for some individuals.

There is greater caution today to respect what we may not know about health risks. A study that passed through multiple levels of ethical review more than a decade ago exposed young soldiers to small explosive detonations to determine new auditory protection standards. This was based on graded exposures leading up to temporary threshold shifts in hearing of 25 dB, from which every subject had full and rapid auditory recovery.[15] The most severe impairment noted in these subjects occurred in a single individual for whom baseline measures were obtained before he slipped out of his barracks to attend a rock concert; the impairment occurred without any experimental exposure. Nevertheless, it is doubtful that this study protocol would be approved today in light of new concerns (so far without supporting data, but also without assurance of safety) that impulse noise may have subtle effects on the brain, thus affecting mood and cognition. Similarly, studies of jolt and forces acting on the neck and laser eye exposures are carefully safeguarded, with exposures stopping within a conservative safety margin of the lowest known or suspected amount of harmful exposures. Therefore, the challenges of obtaining data for outcomes based on failure or approaching failure (eg, heat injury, hypothermia limits, muscle injury, etc) prevent direct laboratory-based validation of some models.

This means that more studies have to be designed around the discovery of basic principles that predict limits and models that interpolate and extrapolate biomedical data, supplemented by post-hoc observations of adverse outcomes from field data acquired in high-risk training and operations. Access to this kind of unique and interesting extreme of physiological performance in military training and operational missions is another reason that Army physiology has been in the forefront of performance modeling. Modeling existing data can improve efficiency and safety of new studies, thus helping to ensure the highest level of protection for human subjects with better predictions of limits and individual variability, as well as minimizing the suffering and use of laboratory animals.

USES OF PHYSIOLOGICAL MODELS

Physiological models are important for the Army, providing ways to organize bits of knowledge dispersed in journals and among subject matter experts; and to generate testable, verifiable, and, ultimately, validated predictions. These predictions of actual outcomes reduce costs, improve experimental control of conditions, improve safety, and provide rapid and repeatable testing to accelerate research and development and improve military decision-making. Predictive models serve several broad purposes, including the following:

- capture and generalize lessons learned to make these physiological discoveries more useful;
- produce predictions from complicated interactions that cannot be efficiently addressed by test matrices of all the relevant conditions;
- rapidly address new problems from a sophisticated and generalizable model;
- provide real-time sensor data fusion;
- enable virtual prototyping of new equipment or tasks, thus improving efficiency in the exploration of optimized designs; and
- identify key questions for hypothesis-driven research.

Models Help Institutionalize Science-based Policy

Lessons Learned to Prevent Physical Training Injuries

A family of thermal models has been used to ensure safe military training. These efforts originated from heat and cold physiology research in World War II. Computerized thermal strain models have been used by USARIEM to generate easily interpretable heat strain tables that are now widely used. These Army standards have been incorporated into national occupational standards.[61] New cold water immersion tables were constructed following the 1995 deaths of Ranger students in moderately cold water conditions in Florida.[62,63] These types of predictive models (ie, published table of training limits) are so important to the Army that they have become authoritative statements of policy that commanders are expected to follow. In this instance, physiological models have been used to make available the rules learned from many years of experiments and field data collection to improve safety Army-wide.

It is far more difficult to manage risks and enforce safety policies in the absence of validated models. For example, the Army has always contended with musculoskeletal injuries from excessive physical training and with fatigue-related mishaps resulting from inadequate restorative sleep. Even after decades of research to understand the predictive factors and appropriate interventions to reduce these, the rules learned about training injuries and fatigue[21,64] are only poorly imparted to new leaders. The solution to making this accumulated knowledge useful beyond a small group of subject matter experts in the Department of Defense (DoD) is to produce validated predictive models that can be queried when needed. New models of fatigue and performance are now being developed,[65] and the effort is reviewed in Chapter 3 of this volume.

The Training, Overuse Injury, and Performance model will help to institutionalize knowledge about physical training injury prevention.[20] Using extensive data sets on physical training injuries and expanding the qualitative rules summarized in TB MED 592 on prevention of physical training injuries, this model highlights the "cross-over point" wherein increased daily running mileage results in high injury rates and diminished training benefits.[66] One use of this overuse injury model is to help instructors plan recruit training schedules. Another application is to guide scientists to areas wherein work is needed to close gaps in our predictive capabilities. Model inputs include training regimen, characteristics of the individual(s), and physical training "dose" (biomechanical and physiological loadings). Model outputs predict performance enhancement, fatigue, and injury. The first version of this model for physical training and injury (Training, Overuse Injury, and Performance 1.0), which undergoes revisions as new data come available, reuses data from several large Army and Navy data sets from studies of metabolic responses of muscle and bone to create predictions about group outcomes.[20] A future iteration will attempt to refine the contributing factors to improve the accuracy of outcome predictions for individuals, not just groups.

Complexity Drives the Need for Models

Biomechanics of the Shoulder and Neck

Test and evaluation of every new product or strategy, of every new dietary supplement or technology, or of every combination of stressors encountered during deployment are simply impossible. More importantly, simple tests are usually not adequate for answering truly complex questions, and conclusions are not readily transferable to the next variation of the problem. Predictive models that grow with each new set of conditions or understanding of the underpinning physiological relationships should increasingly diminish the need and enhance the efficiency of costly and time-consuming testing. The Army maintains research capabilities to develop risk assessment tools that can then be handed off to users to conduct their own risk assessments (Figure 1-8). These tools continuously improve the ability of materiel developers to conduct virtual prototyping; the US Army Public Health Command and others to conduct health hazards and survivability assessments; and commanders and planners to implement safe and effective training, doctrine, and soldier management policies to optimize performance and readiness. The same laboratories may also use their capabilities to conduct expedient tests for an urgently needed piece of equipment or strategy.

For example, a new "bunker buster" armament for soldiers operating in urban terrain in Southwest Asia could not be fired by human testers because it exceeded an existing standard for permissible human exposure. The recoil force to the shoulder exceeded 70 ft-lbs, an old testing standard of uncertain derivation. The system had to be redesigned to reduce the recoil, causing delays in system fielding. New data were needed to provide quick field guidance on how this system should be used, particularly given the limited knowledge of actual human tolerances to firing this system by individuals of various sizes and strength, singly and repeatedly, and in various positions (eg, prone or standing). However, rather than embark on a major new effort to study and model the complex articulation of the shoulder and understand how recoil forces act on it, a single empirical study by USARIEM measured indicators of performance degradation and injury with repeated firing by soldiers.[66] The study included detailed assessment of injury, including magnetic resonance imaging of the shoulder, measures of edema, subjective assessments of soreness, biochemical markers of tissue damage, and markers of performance degradation (eg, changes in marksmanship accuracy). This test clearly demonstrated that the existing standard was conservative for these conditions; however, it could not address all of the important questions relevant to field use, such as health risks associated with firing position, repeated firings and fatigue, out-of-position firing, etc. This is an example of how core expertise in Army laboratories can be used to rapidly address a problem, but avoid the misstep of embarking on a major modeling effort for a relatively specialized problem in a resource-constrained environment.

In contrast to this expedient evaluation of shoulder recoil standards, a major modeling effort focused on understanding the forces placed on the human neck has been under way for more than a decade. Neck-related issues have become more important to

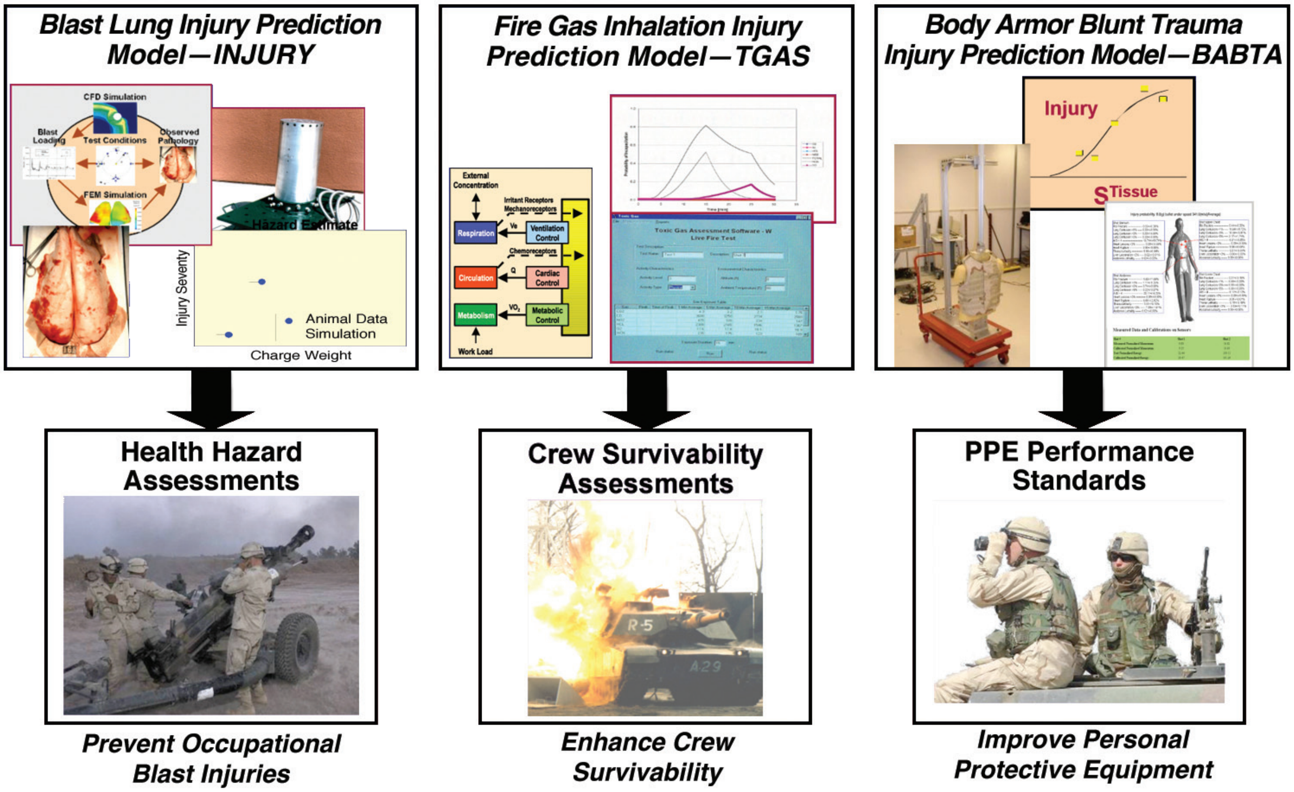


Fig. 1-8. Three examples of Army applications of medical research models that contribute to the safety of systems and better protection of teams and individuals. The blast injury model was developed for the Health Hazard Assessment process to determine safety of new high-powered weapons systems for the human operators. No such standards exist in the civilian community, but this model has found broad applications, including safety assessment of air bags in vehicles. The Toxic Gas Assessment Software (TGAS) model was developed for the Soldier Survivability Program to optimize military vehicle design and protection systems to protect crews against the effects of combinations of toxic fire gases. The Body Armor Blunt Trauma Assessment (BABTA) Injury Prediction model has been developed for the materiel developers of personal protective equipment (PPE) to improve the accuracy of the assessment of body armor effectiveness, permitting tradeoffs in flexibility and mass not previously possible.
CFD: computational fluid dynamics; FEM: finite element modeling.
Photographs: Courtesy of Michael J Leggieri, Jr, DoD Blast Injury Research Program.

the Army because of the increasing participation of women (with thinner and weaker necks, compared with most men) and because of the trend to add more technologies to head-supported equipment (eg, heads-up helmet displays, night vision goggles). DoD and the National Highway Traffic Safety Administration have evolved predictive models of both mannequin and human neck responses to external forces acting on the head.[9,67,68] Previous design criteria for head-worn devices have been estimated from what was tolerated by the typical young male, and not what was actually safe and tolerable for extended periods or what could be tolerated by the neck of an average female.[69] Injury risks have been related to dimensions and strength of the neck (eg, "giraffe necks" vs "bull necks"), but little is known about actual neck and spine damage that may be caused by single or accumulated jolts in vehicles running over rough terrain or from the shock of a parachute opening. Few neck-conditioning studies involving healthy individuals have been conducted,[70] in part because of the concern for the potential neck injury risk associated with neck strength-conditioning studies. Until new validated neck models are available, the neck will continue to be treated very conservatively. For example, neck stabilization is part of the standard of care for casualties who have received a helmet strike or penetrating head wound. This is apparently driven by caution, rather than based on any data that neck injury can actually occur as a result of the forces imparted by a bullet to the head in a survivable injury. Ultimately, the neck model needed by the DoD will assess muscle fatigue, degraded human performance (eg, head tracking), and risk of injury for various forces applied to the head with and without various masses.

Models Provide Rapid Solutions to New Needs

Problem Solving for Issues of Thermal Strain

Validated research models can rapidly generate answers to questions from commanders, materiel developers, or preventive medicine specialists. Usually, problems identified from the field demand immediate answers. The research response to write a research protocol and conduct some studies is not a satisfactory answer. The ability to respond in a timely manner comes from existing Army research programs in areas corresponding to critical physiological threats. For example, many of the practical decision support tools needed in the field can be rapidly generated from a primary research model. Many different types of applications have been produced on short notice using the research models for thermal strain prediction at USARIEM. The Ranger Training Brigade needed guidance for safe heat exposures during their standard distance runs and road marches. A simple slide rule was promptly generated from the heat strain decision aid model to provide run time limits for various ambient conditions. This quick turnaround application benefited from years of thermal physiology studies and modeling. Another problem, hyponatremia, emerged in recent years, leading to an assessment of maximum limits of water that should be prescribed for various heat, clothing, and workloads to prevent overhydration without incurring an increase in heat injury in susceptible individuals. The adequacy of the new guidance predicted from USARIEM heat models was tested in field studies at Army training sites to confirm the validity of the model predictions.[71]

Rapid applications from Army thermal models included the development of a cooling strategy for soldiers operating in high-mobility multipurpose wheeled vehicles (or "Humvees") in Iraq in the summertime. USARIEM models were used to predict thermal comfort and survivability in various cabin heat conditions, and estimates of the required cooling power to favorably shift these conditions within the constraints of the amount of cooling that could be practically achieved in these vehicles operating in high radiant heat conditions.[72] This information was used by the equipment developers at Natick Soldier Center (Natick, Mass) to modify a lightweight, water-cooled vest (or the Air Warrior Microclimate Cooling Garment) with rapid release for individual occupants in a vehicle. The Tank and Automotive Command used this design to produce a simple refit air conditioning system that would provide cooling to four occupants per vehicle. In 2004, this system was deployed in 5,000 high-mobility multipurpose wheeled vehicles in Iraq and proved to be a useful enhancement to soldier effectiveness. This project earned a Research and Development Collaboration Award in 2005 as an example of seamless interaction between biomedical research and materiel developers, and the systems went into widespread use. Other examples of successful quick response model applications are provided in Chapter 2.

Better Models Reduce Restrictions on Materiel Design Options

Impulse Noise and Laser Eye Exposure Standards

Development of new standards with a scientific basis almost always produces less conservative restrictions on materiel developers, because actual tolerance is refined from necessarily conservative initial limits. This should make easy friends between physiology modelers and materiel developers.[73] For example, new, high-powered weapons systems could not be fielded by the Army without impractical limitations to their use (eg, howitzers that must be fired with a 1,000-ft lanyard) until new studies produced data, criteria, and a test methodology for the evaluation of operator risks to nonauditory impulse noise (blast overpressure) injury (see Chapter 10 in this volume). In the absence of criteria for blast overpressure injury, an existing standard (MIL-STD 1474D) designed for acoustic hazards had been adopted. Through data collection and modeling effort, this acoustic standard was shown to be orders of magnitude more restrictive than a scientifically based model for nonauditory blast effects. Risks to hearing were also found to be overly conservative by at least an order of magnitude, based on controlled human blast exposures.[15] A similar phenomenon occurred with laser eye exposure thresholds when new research by the Army demonstrated constant motion of a nonanesthetized eye, even with a concerted effort to focus on a point.[6] This led to an order of magnitude increase in safe permissible exposure limits (ANSI Z136.1-2000) in the design and use of field range-finding devices and other Army laser applications.[6] Obviously, the reverse situation, with discovery of an unexpected hazard that produces new restrictions on materiel options, would be best made through a scientifically valid and relevant modeling effort and as early as possible in the development of a new system. Some modern technologies, such as directed energy (electromagnetic radiation and laser), pose new and very specific threats. Nevertheless, a basic scientific understanding of these technologies exists because of prior research, and the Army is positioned to avoid technological surprise. As an example, the effects of a new radiofrequency radiation weapon can be generally predicted from estimating energy deposition and heating in various tissues in the body.[14] Relatively few nonthermal bioeffects have been discovered over several decades of Army research in this area.[74] Thus, technical issues and potential threats are typically not completely new or surprising, and additional research can be quickly focused on any gaps in the existing knowledge base and models.

COMPUTATIONAL BIOLOGY

All Models Are Wrong, But Some Models Are Useful

Models are only approximations of the behavior of complex natural systems; but, despite the simplifying assumptions, they can be useful instruments if they provide a clear predictive advantage. A model will be more useful if it includes some estimate of the accuracy of the predictions. For example, a sleep and performance model is not particularly useful to a commander if it only highlights well-known associations between inadequate sleep and decreasing mental performance. Modeling must go far beyond statistical associations and use some of the modern techniques available, such as support vector machines.[75] Stochastic modeling and related approaches help to provide error estimates or probabilities associated with a prediction.[76,77] Both inter- and intraindividual variabilities need to be determined to provide estimates of the repeatability of the prediction and variation between individuals.[78] It will be even better if it has "learned its soldier" in a cybernetic type of individual process. Without baseline testing and individual response patterns, some predictions are of little value. Essentially all of the Army's current physiological models are based on group means; individual predictions are a future objective. For most outcomes, rate of change within individuals will be more predictive than group means and thresholds of change; this is a fundamental concept in systems biology and in new approaches to personalized medicine. Neuropsychological testing to predict mental readiness status is an example in which individual values provide information about change from an individual's usual performance in a much more helpful assessment than the information gained from comparison of a single assessment to group means.[79] Like physical fitness testing, the normal range is very wide, and thresholds of success are somewhat arbitrary. However, a dramatic change in individual performance on either physical or mental tests may indicate important changes in the individual's readiness status.

Other important examples of criterion selection include physical task performance. Selection for military occupations using a model that predicts strength capacity is grossly inadequate if strength is only one aspect of job performance, or if it is a unique requirement for task performance that can be accomplished through several strategies. Use of strength testing as the key determinant of suitability for certain Army jobs would predictably exclude most female soldiers from the job and would not identify individuals particularly suited to the tasks. Two decades of research on military occupational specialty job classifications by physical capabilities have concluded that the predictive criteria were wrong, or are certainly not valid today with improvements in task and equipment design, and strength is only one of many factors that play into job performance and safety.[80,81] In this book, the chapter on load carriage highlights the correlation between certain types of strength and successful load carriage performance; successful performance also includes not being injured during performance of the task.

Criterion Measures and Militarily Relevant Endpoints

Fatigue and Performance Models

A critical element of a model is the criterion measure or outcome against which it is developed. This determines a great deal about its validity and relevance in a particular application. Desired predictive endpoints of militarily relevant performance may not map easily to laboratory measures or even the outcomes that can be easily measured in the field. This is a special problem today for military performance research focused on domains of physical and mental capabilities. One difficulty in performance research is that the determinants of success on the battlefield also include unpredictable or intangible factors, such as coincidence and bravery.

Although psychomotor vigilance testing is the most reliable single laboratory measure that is exquisitely associated with sleep deprivation and sleep latency,[82] what this means is the prediction of mission success in a military operation is uncertain. This test can be cautiously generalized to military performance involving sustained concentration and appears to be a reasonable surrogate laboratory measure for high-order functioning. However, it would not be appropriate for the prediction of other domains, such as mood and motivation or marksmanship performance. Sleepy soldiers can continue to march effectively even if they score poorly on the Psychomotor Vigilance Test.[83] A research volunteer can rally long enough to do well on a test even when significantly fatigued, just as a soldier hearing a bullet pass his ear has a burst of adrenaline-stimulated alertness that does not reflect the probability of lapses in attention that might actually be better represented by the Psychomotor Vigilance Test or tests of sleep latency. In evaluation of the countermeasures to fatigue, delaying onset of sleep, high-dose caffeine, amphetamine, and modafinil all effectively sustain Psychomotor Vigilance Test performance while delaying sleep.[84] However, with increasing sleep restriction, there is also increasing impairment of some potentially important capabilities that are not reversed by stimulants, such as interpretation of nonverbal communication and complex emotions.[85] The countermeasures themselves can have effects on other aspects of higher cognitive function, including moral reasoning and humor appreciation and sleep recovery,[86] demonstrating the limitations of a performance model based on one key test outcome.

Mission failure outcomes may be a very different model and potentially less useful and generalizable. In sleep and performance modeling, occupational injuries have been modeled with respect to shifting work cycles. The likely outcome is a complex mix of time-of-day issues involving more than the human operator's state, but also changes in staffing, changed room lighting, and other human factors that also contribute to injuries. The result is a model that is not generalizable to anything except a prediction of injuries by time of day for the circumstances in which it was developed. Thus, it might be appealing to use fatigue models to predict accident rates instead of the intended performance status of the individual. However, this is not a logical extension of the model that has been developed, and a model based on accident rate outcomes has human performance as only one component of the prediction.[65]

Generalizability and Applicability

Body-Fat Standards/Personal Readiness Standards

The right endpoint measurement is not necessarily going to be the most sophisticated and accurate measurement obtainable. In an example using body-fat standards, techniques to predict a gold standard chemical model of the body do not provide the predictive value of an abdominal girth measurement technique obtained with a 50-cent tape measure. This is because it is specifically abdominal fat, not total body-fat assessment that best serves the intent of the Army's Weight Control Program. When the DoD was directed in 1980 to establish new standards to enhance fitness and prevent obesity, a new, practical prediction of body fat needed to be established.[87] The interim method using four skinfold thicknesses was difficult to implement because of observer training demands.[88,89] The previous standard based on weight-for-height standards described body size, but could not distinguish highly desirable big and lean (strong) recruits from undesirable big and fat recruits.[90] New guidelines called for an objective assessment of body fat to prevent obesity and improve military readiness, including improved physical fitness, military appearance, and health.[28] The 1980 expert panel recognized that abdominal girth was not only the most important predictor of excess fat, but also a highly suitable metric for the intended application of driving fitness habits (marker of overnutrition and underexercise), ensuring military appearance (potbellies are a main affront to military bearing), and reducing health risks (abdominal fat was already recognized as being key to obesity-related health consequences). The circumference equations developed by the DoD have been repeatedly validated across different populations using sophisticated three- and four-compartment models (Figure 1-9). The standard error of the estimate against these criterion measures is consistently around

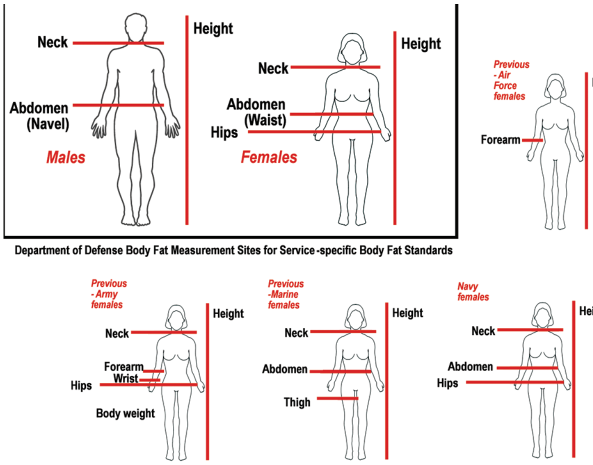


Fig. 1-9. Body fat prediction algorithms in the 1990s for women in the services ranged from too simplistic (Air Force) to overly fitted (Army) models before the DoD adopted a single most appropriate model developed by Dr James Hodgdon at the Naval Health Research Center. Each of the four military services had developed circumference-based body-fat predictive models after a 1980 report on fitness in the military services concluded that the post-Vietnam military needed new focus on overnutrition and underexercise, and lauded the US Marine Corps' first use of circumference-based body-fat estimates to enforce body-fat limits.

3% body fat; the reproducibility of the method is 1%; and the biological variability with normal ranges of hydrational changes, genetically determined fat deposition, etc, is at least several percentages of body fat. Thus, the criterion measure "calibrates" an abdominal measurement to body fat. Sophisticated methods of total body-fat estimation are less useful, accurately including fat located in genetically determined sites (eg, subcutaneous distribution to arms, back, and thighs) and locations that are less susceptible to environmental control (ie, exercise and nutrition). This was illustrated by a body composition study involving career male soldiers at the US Army Sergeants Major Academy (Fort Bliss, Tex). Comparison of body fat estimated by the abdominal circumference-based equation to dual-energy X-ray absorptiometry (a three-compartment model method) demonstrated a good correspondence up to the upper limit of acceptable male body fat and then plateaued to higher levels of dual-energy X-ray absorptiometry body fat, with nobody exceeding the Army standard by the circumference method.[28] This demonstrated the effect of environmental factors (eg, exercise and nutrition habits) on maintaining an abdominal fat "standard," even as age, genetics, and other less-controllable factors may produce changes in total body fat more accurately detected by sophisticated methods. This is an example in which *relevance* of the endpoint measurement (abdominal girth) is more important than *accuracy* of the originally targeted endpoint (precise total body fat).

Maturity of a Model—Testing in Realistic Environments

Technology Readiness Levels

The National Aeronautics and Space Administration (NASA) developed a rating scheme to categorize the level of research maturity known as technology readiness levels (TRLs). This came about because too many incompletely formed ideas were leaving the bench for actual use or advanced testing, with consequent problems and cost overruns when they did not meet expectations. TRLs have been adopted in Army research management. The modeling equivalents in the Army acquisition system are shown in Table 1-2. This is an important metric to apply to physiological models, because there are many commercial products dependent on models that have not been validated, wherein valid models have been misapplied and the models do not provide meaningful advantages. There is no trusted authority with a US Food and

TABLE 1-2

TECHNOLOGY READINESS LEVELS AND PHYSIOLOGICAL MODELING ANALOGS

Level	NASA Definition—Status of Research	Physiological Modeling Equivalent
3	Analytical and laboratory studies to determine and test separate elements of a technology	Qualitative relationships—conceptual exploration of qualitative factors important to a predictive model
4	"Low-fidelity" integration of components in the laboratory	Semiquantitative relationships—laboratory identification of rough quantitative relationships contributing to a physiological outcome
5	"High-fidelity" breadboard laboratory integration and testing in simulated environments	Quantitative relationships—mathematical and computer-working predictive model, version 1.0
6	"High-fidelity" testing in a relevant laboratory or simulated operational environment	Expansion and generalized testing model predictions against relevant human or surrogate data; peer review validation
7	Demonstration of an actual prototype in an operational environment	Testing model predictions in operational environment (actual use by intended operators); special panel review, ANSI, etc, field testing/experiment
8	Technology has been proven to work in final form and under expected conditions	Customer is using the model predictions with clear advantages to use
9	Product in use under mission conditions	Valid model has been institutionalized as the approved prediction model

ANSI: American National Standards Institute
NASA: National Aeronautics and Space Administration

Drug Administration–like function to regulate the commercialization of a physiological model that is not used for a medical decision (eg, sports watches that provide training heart rates, calorimeter/pedometers, body-fat measurement devices, fatigue and performance actigraphs and planning tools). Even for the Army, physiological models can easily find their way into major Army models and systems without any rigorous authentication.

The usefulness of TRLs can be illustrated in the development of soldier physiological status monitoring (PSM) systems. The original PSM concept developed in 1995 by Fred Hegge was intended to take information from noninvasive wearable sensors, conduct local sensor signal processing, connect to an executive processing unit on the soldier, and be transmitted to commanders or medics. This diagrammed concept is referred to as a TRL3—"still in the concept stage, without actually testing and prototypes." Studies with actigraphs to describe recent sleep history and models to associate this with laboratory performance predictions might score as a TRL4—"prototype testing." A TRL5 consisted of combining sensors (eg, actigraphy, core body temperature pills, and in-the-boot foot strike prototype monitors) to provide analyses of various fatigue and performance, thermal load and heat strain, and locomotory energy costs from a Norwegian Ranger training run that took place in 1997. The hardware system itself—that proved technically challenging in these field conditions because of broken wires, improper synchronization of data, and computer download failures—was a premature test of a system in a realistic field environment. A subsequent test in a concept exploration program used more refined systems with a squad of infantry soldiers operating in hot conditions at Fort Benning.[91] This test demonstrated other issues, such as sensor cross-talk between individuals. Another study with data collection from multiple sensors over 10 days on a squad of Marine officers in training highlighted other developmental gaps with data streaming and data storage protocols.[92] Individual physiological models continued to be developed in the laboratory (TRL6), and a new Army Technology Objective pursued an integrated and field-hardened hardware solution with soldier wearability testing (TRL6). At the end of the 30-month Army Technology Objective, a hardware system had been tested in limited field conditions, resolving frequency interference and other issues. Heat models using simplified and better predictive algorithms had been tested for retroactive identification of heat strain occurrences in actual soldier field data.[93,94] TRL7 has not been achieved for physiological monitoring systems and the predictive algorithms that make them useful. TRL7 requires a considerable investment and renewed focus on the prediction of specific outcomes. This current rating should clearly indicate that physiological monitoring is not ready for use on soldiers in an operational environment.[79,95] TRLs can be applied to the individual components, including hardware and models, as well as to the maturity of an overall system.

DATA MINING

Sociological Barriers to Data Sharing

It is a significant tragedy of the modern era that, within the relatively small circle of physiologists, data have not been routinely saved and distributed in useful forms that could be reutilized. This is especially important for data from studies that cannot be repeated because of the scope, cost, or unique opportunity. At last, both the sociological and technological barriers to data sharing are crumbling. Technological advances in information management are also making it easier to store and share data sets. Some journals, funding organizations, and regulatory agencies are beginning to require archiving of original data with access to others for examination and further analysis to protect against misinterpretation and fraud. Recognizing the importance of data sharing, the National Institutes of Health (NIH) have mandated the development of data-sharing plans in every major grant proposal. Recent policies on data sharing and guidelines for their implementation have been issued for all grant recipients:

> NIH reaffirms its support for the concept of data sharing. We believe that data sharing is essential for expedited translation of research results into knowledge, products, and procedures designed to improve human health. The NIH endorses the sharing of final research data to serve these and other important scientific goals. The NIH expects and supports the timely release and sharing of final research data from NIH-supported studies for use by other researchers.[96]

NIH has further defined the "timely release and sharing" of data to be no later than the acceptance for publication of the main findings from the final data set. Whereas initial investigators are expected to reap the "first and continuing" benefits of their data, there is no provision for "prolonged and exclusive use." There are many reasons given for not sharing data, but the culture has changed, and these reasons are no longer acceptable (see Table 1-3).[97]

TABLE 1-3

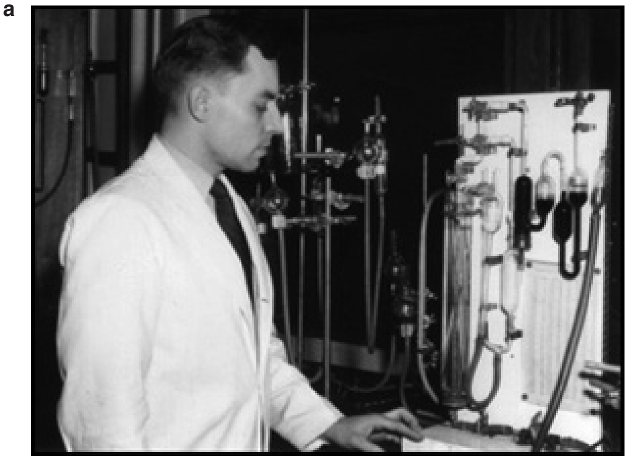
SOCIOLOGICAL BARRIERS TO DATA SHARING

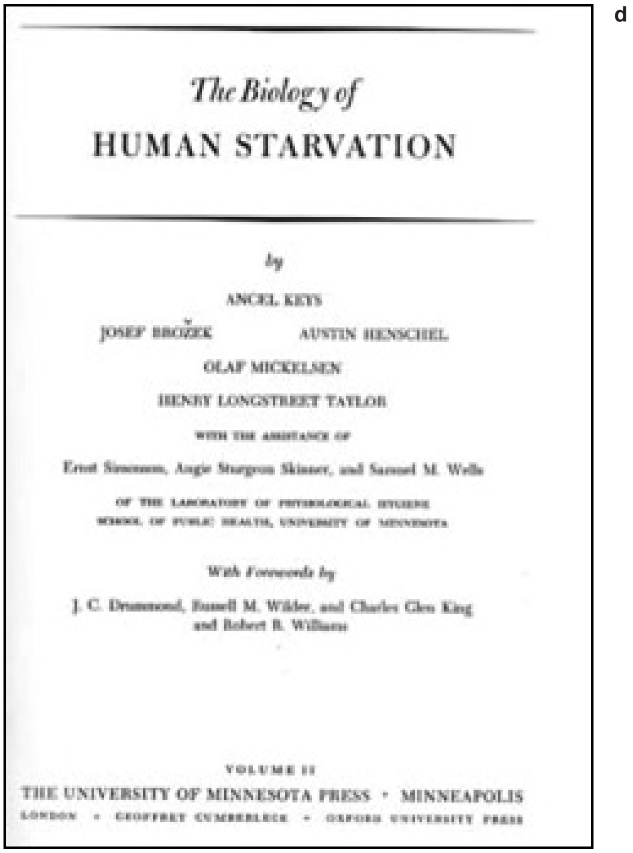
Common Reasons for Not Sharing Data	The New Reality
It's my data! I conceived the study and conducted the experiments.	Data reutilization is important to experimental efficiency, preventing unnecessary experiments and reducing costs and risks. It is government data if it was collected by an Army employee as part of his/her official duties.
I have not finished analyzing the data, and I still have more papers to publish.	Once the main papers are published, promptly sharing the data facilitates new research and should still bring credit to the original investigators and their subsequent papers.
Nobody else knows how to interpret these data properly.	An important challenge to making data available and useful is the adequate description of the relevant experimental conditions and variables. Journals and funding agencies are increasingly requesting fully documented data sets.
It is unethical to share the information for an analysis that was not described in the protocol approved by the Human Use Committee.	Data sets can be properly de-identified to protect the privacy of research volunteers and may have great value in analysis beyond the original hypothesis. This has been pioneered by federal agencies, such as the National Center for Health Statistics.
I'm afraid someone reanalyzing my data will come up with a different interpretation.	Testing new and alternative hypotheses is a cornerstone of science. It is important to encourage alternate interpretations and opinions.
Data yielded negative results and are of no use to anyone.	Well-designed, but negative, results are important to share, because the tendency to bury this data biases science. Making data available for an alternate use, including meta-analysis, may help salvage value from the study.
I cannot trust or understand data produced in another laboratory.	Sharing data sets is a good way to discover and resolve methodological differences.
It is a lot of work to assemble the data and information on the relevant conditions, protocol, etc, to help someone else.	The trend of using electronic laboratory notebooks, archiving protocols and data sets, and utilizing distributed computing technologies to enhance data sharing is making this easier.

Data source: Koslow SH. Should the neuroscience community make a paradigm shift to sharing primary data? *Nature Neurosci*. 2000;3:863–865.

Preserving and Distributing Data Sets

One classic experiment demonstrates how DoD-sponsored data have been effectively shared in the past. The Minnesota Starvation Study, highlighted earlier in this chapter, is famous not only because of the public attention elicited at the time the study occurred in 1945, but also because data were made available and have been repeatedly reused in metabolic studies (Figure 1-10).[43] Recently, these old data sets helped to (*a*) design and interpret studies of the health and performance effects of undernutrition in Ranger students,[39,98] (*b*) test coefficients in a metabolic model,[39,99] and (*c*) establish a new model of body composition balance.[45] These data sets were successfully shared in a precomputer era through a simple but elegant two-volume book set that clearly described the experiments and presented individual qualified data in a series of tables.[43] The report also interpreted the data, along with a comprehensive review of the rare literature, up to the time of the study. This form of data sharing (ie, publication of tables) worked well for a relatively small data set. The difference between science now and then is the amount of data that can be collected that may all be relevant to the production of a high-quality predictive model. It has been pointed out that the Human Genome Project could not have been undertaken if that massive amount of data on base pairs was to be published as a textbook.[100]





The Biology of
HUMAN STARVATION

by
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Fig. 1-10. (**a**) Ancel Keys in his laboratory at the University of Minnesota, where he and colleagues conducted the famous Minnesota Starvation Study for the Office of The Surgeon General in 1945. (**b**) Fit young men participating in this study lost 24% of their body weight over 24 weeks through energy restriction and were randomized to controlled refeeding regimens to determine how to best refeed returning prisoners of war and starving civilian populations. (**c, d**) Extensive physiological testing and psychological testing were conducted that produced a published data set that is still used to test new hypotheses and models today.
Photographs: Reproduced with permission from Keys A, Brozek J, Henschel A, Mickelsen O, Taylor HL. *The Biology of Human Starvation*. Minneapolis, Minn: University of Minnesota Press; 1950.

Publication of raw data is not well tolerated by modern journals. Consequently, collateral archives may not suffice for the complicated forms of data produced in modern studies. Data must be properly qualified and stored in a form that is accessible and useful to all. The Army has explored various computer routines to automatically process and store data in useful and retrievable forms.[17,94,101] Jaycor, Inc (San Diego, Calif) has experimented with data preservation that includes experimental context so that future investigators can access a data set with complete experimental context, methodology, and individual or summary data without having to go back to the original investigators. In one such important preservation effort, all of the important Army-funded blast data sets from more than a decade of animal and human experiments have been stored in a relational database that handles multiple formats.[17] This physiological data preservation effort has been extended to some other large Army data sets, such as a USARIEM boot biomechanics study. A recent effort retrieved and reutilized large epidemiological injury data sets from Army and Navy studies to develop a first prototype injury and fitness prediction model (Training, Overuse Injury, and Performance 1.0).[20]

Data sets have been developed for general purpose use and posted on the Internet. The National Center for Health Statistics conducts broad data collection efforts in national studies, such as the National Health and Nutrition Examination Survey, even though there is careful consideration regarding the types of hypotheses that will be addressed by data collection. These data are specifically intended to be shared with other researchers, and the de-identified data are publicly released as soon as they have been used to address key hypotheses advanced by various sponsoring agencies. The de-identification process has been carefully designed to ensure protection of volunteers. For example, unique characteristics, such as advanced age that might inadvertently single out an individual, are collapsed into larger categories. Similar protections against deductive disclosure of participant data in active duty military databases might include collapsing high ranks, such as general officers, years of service, older age, and other lower frequency characteristics.

Data enclaves are restricted data sets not openly shared beyond a group of investigators that agree to certain terms of data use. Recent NIH guidelines for implementation of data-sharing policies specify that data "should be made as widely and freely available as possible while safeguarding the privacy of participants, and protecting confidential and proprietary data." Data enclaves protect sharing of sensitive or proprietary information.[102] Military epidemiological data sets—such as the longitudinal Millenium Cohort Study (the military "Framingham" study),[103] the biennial survey of health behaviors in the DoD,[104] the Total Army Injury and Health Outcomes Database,[105] and the registry of Gulf War veterans[106,107]—are examples of data enclaves established to protect sensitive patient information protected by Health Insurance Portability and Accountability Act (HIPAA) regulations. A repository of DNA samples from research volunteers participating in various physical and environmental experiments, along with their phenotypic data, was established to study gene polymorphisms of interest.[108] This Environmental Medicine Genome Bank is an example of a potent capability for health modeling.[109,110] The Wound Data and Munitions Effectiveness Team database, representing comprehensive data on US military casualties in Vietnam between 1965 and 1967, has been coded and placed in an electronic format that can be queried.[111] Casualties from Iraq and Afghanistan are being summarized in the Joint Theater Trauma Registry database to provide important information on current practices and problems.[112,113] Like the Wound Data and Munitions Effectiveness Team, these data are also being combined with incident data for future analyses and modeling of protective equipment failures and monitoring of the effectiveness of improved safety equipment in the new Joint Trauma Analysis and Prevention of Injury in Combat program. Access to these data may require a simple data use agreement or involve extensive protocol development and approval, as well as appropriate security clearances.

The concept of a system of information analysis centers (IACs) has been explored by the DoD, recognizing the need for a "smart archive" and analytical cell within specialty areas.[114] The execution of this concept has had mixed success, with only a few centers serving their science communities well. The Defense Technical Information Center (DTIC) is the recognized archive for reports of all kinds from data collected under the auspices of the DoD, as well as related information, especially in technical reports from other countries. Many of the technical reports in DTIC are also made available outside of the DoD through the Commerce Department systems, such as the National Technical Information System. The IAC concept was intended to fall under the DTIC in various relevant configurations related to specialty areas. For example, IACs with relevance to physiological problem-solving included the Human Systems IAC, Chemical and Biological IAC, Modeling and Simulation IAC, and Survivability IAC. From the standpoint of physiological modeling, only the Survivability IAC (SURVIAC) has become specialized in data archiving, modeling support, or new syntheses of information.

Information Technology Solutions for Managing Massive Amounts of Data

Although physiological modeling still suffers from the relative paucity of data, remote physiological data monitoring and other new data collection systems will soon change this into a glut of raw data. It is likely that, in future deployments beyond the Iraq War, soldiers will be intensively monitored, and a vast amount of physiological data—along with contextual information regarding ambient conditions, equipment, and outcomes—will be harvested and available for modeling. This is actually a congressional mandate, following on the experience of the first Gulf War and the challenges associated with diagnosing illnesses from subjective medical symptoms and a dearth of location, treatment, and environmental exposure data for individuals. Gulf War illness issues have propelled the development of an effective and seamless electronic health record system between the Department of Veterans Affairs (VA) and DoD, as well as significant efforts to acquire and record individual deployment exposure data.

The need to save physiological data was clearly noted by Frederick Hegge, an Army psychologist concerned with developing metrics of cognitive function to assess performance status of soldiers in elaborate models and simulations. As the Director of the Military Operational Medicine research program, Hegge set out to recruit retiring senior scientists to gather and summarize existing data in their own areas of specialization so that they could be modeled by future researchers. Hegge was particularly frustrated by the lack of reutilization of important data sets, including the loss of virtually all information gathered in the P^2NBC^2 (Physiological and Psychological Effects of the Nuclear/Biological and Chemical Environment on Systems and Sustained Operations) studies, over which he had presided during the 1970–1980 time frame. This was an important human performance database developed in response to concerns about performance degradation with use of nerve agent protective equipment and prophylactic drugs.

To demonstrate his concept, Hegge helped to develop an approach using fuzzy logic and a breast cancer research data repository in the Defense Women's Health Research Program. This breast cancer decision assist system was designed to provide answers to users who typed queries into a terminal.[115] It provided the most up-to-date answer about the disease. The Army Medical Knowledge Engineering System was developed as a Java-based system with a back-end database, the software that accesses the database, and the connecting network server. The database was the heart of the system, requiring a one-time-only entry of new peer-reviewed study information that formed qualified "knowledge nuggets" or generic encapsulated knowledge objects.[115] As the database grew, the information became increasingly accurate and more precise. Because of its broad applications, this project was recognized with a Smithsonian-Computerworld Innovation Award and accepted into the Smithsonian Institution's permanent research collection of information technology.

Meta-analytical techniques provide a useful approach to deriving new knowledge from the summary results of separate studies, but there is greater power in analyzing all of the available data, including the individual data points from each study. The challenge is to access the complete data. This was illustrated in a project conducted for the Army's stress fracture research program. A vigorous attempt to obtain the original data from a large number of qualified data sets yielded only 25% of the data.[116,117] Even prospective attempts to preserve important data sets by collecting data from multiple experiments into single data sets have often proven to be monumental wastes of resources, with unmanageable data sets that could be analyzed by nobody. Oracle-based databases at the Institute of Environmental Stress (Santa Barbara, Calif) and at USARIEM were established to "blend" key data fields that were common in physiological studies at each of these organizations; both of these efforts failed to produce more than some large sample descriptive data.[118] Typically, the formal harvesting of data variables from very different studies has been a huge labor cost with little return. These data sets were not collected with a single hypothesis or goal in mind, and there is difficulty in matching even the same measurements collected in very different circumstances and for different purposes. New technologies for semantic interpretation using fuzzy logic and other artificial intelligence tools will eventually resolve these problems and make data reutilization an efficient and simple process.

New information management technologies will now make it possible to access the data from multiple studies without imposing additional demands on the investigator (eg, to reformat data, and to explain analytical methods and conditions of the studies).[119,120] This global grid approach to combining data into more powerful data sets will provide unprecedented efficiency and greatly enhance biological modeling. This has already been demonstrated in the neurosciences through the Biomedical Informatics Research Network, which uses the tools of grid networking, distributed computing, and "database federation."[100] The software that will make this a useful tool to physiological modelers is rapidly developing for the discovery and pooling of computational resources (eg, Globus, Condor-G, MPI, and Pegasus), as well as for the "middleware" that will integrate resources, applications, and security to simplify access for the user.[121] The future of military medicine depends on an efficient electronic medical record. Aggregation of electronic medical record data for hundreds and thousands of records in a "research data cube" will permit new healthcare modeling and outcomes research that should improve the quality of care and attenuate soaring medical costs. Creation of the data cube and future applications through grid technologies is a formidable challenge, considering the current problems in interoperability between DoD and the VA electronic databases for even seemingly simple issues. A major project following the first Gulf War failed in the attempt to efficiently combine the VA and DoD Gulf War illnesses data registries because of insurmountable differences in disease coding and other issues of comparability, including the way in which data were originally recorded.[122] Major technological advances in the past decade now put a new era of healthcare modeling within reach.

TRANSITIONING PREDICTIVE MODELS TO USE

Spiral Development

Data Fusion to Provide Real-Time Decision Support

Models developed for soldier performance limits have to be developed in an iterative process, wherein a first "best-available" version is constructed and utilized on a limited basis. This may be used in parallel with an existing standard for health hazards assessment to gain confidence in the validity of the model or to further refine the model. This is how the INJURY (blast overpressure) model was developed, with bioengineering modelers at Jaycor, Inc, using a developing model to make predictions that could be evaluated in subsequent animal experiments at the Army's blast test site in Albuquerque, New Mexico (now closed). Evolving models were similarly used to construct new experiments to examine the role of ventilation on exposure rates for various inhalation threats from "fire gases."[35] The iterative process may also be used to collect data (not available in real time) in actual field conditions to enhance the range of predictions to include actual limits of soldier performance that are not ethically or practically achievable in laboratory experiments. Physiological status monitoring is an example of this iterative process of collecting real field data with prototype sensor sets.

The current version of a prototype soldier-wearable physiological monitoring ensemble was developed in a 3-year effort at USARIEM (the PSM concept was retitled Warfighter Physiological Status Monitor [WPSM], to distinguish the DoD effort from a plethora of emerging commercial efforts), and perfectly reflects the process of spiral development of models and the systems on which the models operate. Originally just science fiction as a concept in Heinlein's *Starship Troopers*, this took hold as a feasible concept after Hegge brought together the key ingredients of computational biology, sensor technology, and the Infantry School's Dismounted Battlelabs. Simple physiological telemetry had been contemplated as a live-dead detector,[123,124] but Hegge introduced the concept of sensor data fusion (Hegge FW, collected briefings and summaries, unpublished data, 1997). The performance of a medic (or a leader) is not likely to be assisted, but more likely seriously degraded by the flow of raw heart rate data on a unit of instrumented soldiers. On the other hand, a medic's performance in detecting and aiding casualties, or even preventing impending environmental injuries, could be greatly enhanced by decision-assisted tools that use physiological sensor data to provide amber alert for predictions of impending injury, or red alert for a casualty-producing event (followed by early triage to assist the medic in prioritizing patients). Models and algorithms for sensor data fusion are critically important in the analysis of the massive amount of modern data streams that can be elaborated from physiological sensors. Hegge's expansive vision included wear-and-forget systems operating on extremely low ("flea") power, with local sensor signal processing, an executive hub with the physiology algorithms and databases, and some kind of communications link to other squad members, leaders, and medics. He further envisioned analyses that would include sensor data and contextual information (eg, ambient conditions and activities, recent signal trends, and individual soldier patterns and baseline information) (Figure 1-11).

Reed Hoyt, at USARIEM, pioneered many of the strategies to acquiring and managing data from wearable physiological sensors on soldiers.[94] A long series of experiments collecting data with experimental sensor systems included laboratory treadmill studies on energy expenditure predictions[125,126]; thermoregulatory monitoring in Ranger students[95,127]; and massive data acquisition efforts with Norwegian cadets in a week-long course with no food and sleep, a squad of soldiers at Fort Benning in a hot weather patrolling scenario,[91] a technology demonstration in the Infantry School's Dismounted Battlelab urban terrain test,[93]

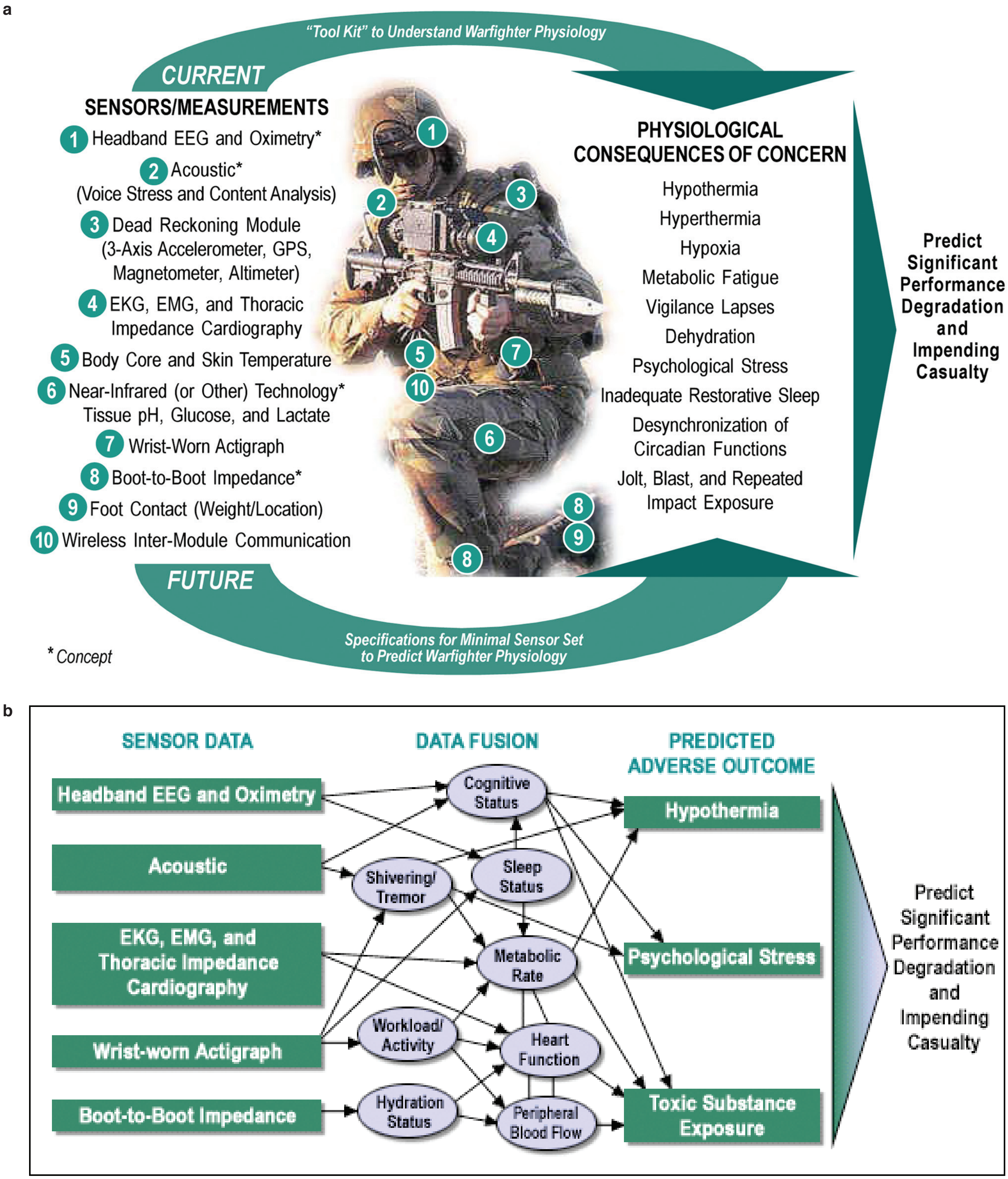

Fig. 1-11. The concept for Warfighter Physiological Status Monitoring. A suite of wearable sensors collect physiological data that are translated into actionable intelligence about the status of an individual (**a**). These data are processed through physiological models and interpreted in the context of the environment, mission, and individual (concept; **b**). In this simplified hypothetical example, intense shivering measured by a wrist-worn actigraph would be interpreted by other sensor data to distinguish between impending hypothermia, intense psychological response, or a neurotoxic chemical exposure.
EEG: electroencephalogram; EKG: electrocardiogram; EMG: electromyelogram; GPS: Global Positioning System.

and a group of Marine Corps officers in a field training exercise with unexpected snow conditions.[92] Each field study provided iterative advances to the management of data and the ruggedization of equipment. Colonel Beau Freund transformed the concept from a collection of physiological modeling efforts and commercial telemetry systems into a first comprehensive field-ruggedized prototype developed to interface properly to Army doctrine and equipment.[79] As the applications evolved during the development of this system, the inputs and outputs changed the modeling requirements. For example, heat strain predictions started with heart rate and impractical temperature pill data using a heat strain index analysis.[128] By the end of the development, through several iterations of models, heat strain predictions had moved completely away from reliance on temperature estimates.[129,130] This first version of WPSM has established specifications for soldier field monitoring and provided a system that can be used to collect new data on soldiers operating at physiological limits that are not obtainable in a laboratory or controlled field experiment.

Another example of this iterative field process is the development of Army-wide neuropsychological assessment (Figure 1-12). The goal, originally articulated by Hegge, is to develop task-embedded neuropsychological assessment tools and physiological markers to predict changes in mental status (eg, using measurements such as voice stress analysis, oculomotor patterns, pupillometry, slow eyelid closure, blood–brain flow changes, etc).[131] Current efforts are using a 20-minute version of the Automated Neuropsychological Assessment Metric (ANAM) to establish predeployment values for soldiers before deployment to Iraq and then to determine how these baselines should be used to assess soldiers following a concussive event. The reliability of the test system and the stability of the measurements and testing methods are known from a large series of studies, but a new iteration is required to determine thresholds for action, initially based on clinical experience and individual change. Eventually, these data will be modeled, perhaps in conjunction with other physiological measurements, to provide more robust and automatic interpretations.

Responsibilities to Maintain, Improve, and Supervise Use of a Model

To be useful, a model should be relevant, accurate, as simple as possible, understandable, predictive, testable, flexible to continuous updating/revision, and coherent with other models. These considerations are not necessarily foremost in the mind of a physiologist attempting to describe the important relationships in his/her data, but these are essential considerations in the elaboration of a model that will be useful to the Army. Along with these features, there must be consideration to continued technical support beyond the availability of the original producer. Open literature publication of the basis for models, as well as complete

Fig. 1-12. (**a**) Psychological testing in World War I at Camp Lee, Virginia, during an era when Major Yerkes and others pioneered testing of mental function and return-to-duty standards. Photograph: Courtesy of Robert M Yerkes. *The New World of Science—Its Development During the War*. New York, NY: The Century Co.; 1920: 358. (**b**) Contemporary neuropsychological testing with a computerized version of established paper and pencil tests in soldiers at Fort Campbell, Kentucky, before deployment into a war zone. In the past century, testing the brain, including cognitive functioning, has been slow to develop beyond laboratory and clinical settings. Modern technologies vastly expand the range of opportunities for brain function testing beyond computerized versions of ancient tests that were limited by paper and pencil and need to be developed for practical use in realistic mass testing.

reports on the lessons learned from their applications to Army problems, is an essential first step. Shoulder recoil standards are an example of legacy models that have had to be reinvestigated because of inadequate documentation of their origin. Complex research models, from which specific applications are derived (eg, the SCENARIO thermoregulatory model), are perpetuated through open literature publication, sharing with other researchers, and continued support to core capabilities for which the DoD may always have to maintain leadership. There is no Army agency responsible for biomedical model sustainment, although this could become a function of an IAC-like concept for human performance.

Models can be misused and inappropriately modified. There is usually no patent associated with the model that prevents legal remedies to misuse, even though failures associated with the misapplication may very well be ascribed to that "poor" Army model. The best way to avoid inadvertent problems with misuse is to ensure that subject matter experts, preferably the original developers, are involved in any modifications.

Some models need to be more fully developed and managed for broader use. The ANAM is an example in which there is general need for neuropsychological tools, including, for example, sports concussion batteries to determine return-to-play evaluative criteria, just as the Army has a need for return-to-duty criteria. The ANAM has been licensed by the Army to the University of Oklahoma, wherein further development, maintenance, and general commercial distribution can be effectively accomplished.[132] Commercial entities help to maintain and update products, including decision support tools, developed with government funding. This is an important product sustainment function typically specified in the terms of the grant agreement or through later licensing agreements.

The INJURY blast model has been maintained by Jaycor, Inc, the organization that developed the model through research contracts with the Army. The Army has no intrinsic capability to follow and maintain a model such as this for more than two decades of evolving applications. New requirements predictably emerge, and it is important to have a competent performer responsive to needs. As examples, the INJURY model was formally adopted by the USACHPPM (US Army Center for Health Promotion and Preventive) for health hazards assessment of blast overpressure, but further refinements to the automation of the process were required in the transition from experimental laboratory assessments at WRAIR to occupational evaluations at USACHPPM. When the INJURY model was applied to a novel type of explosive, thermobaric weapon, it was important to have experts who could evaluate new data against the data for which the model was originally developed.[133] When the Army needed a better science-based approach to evaluation of modern body armor concepts, the blast modeling experience to predict injury to lungs was a key factor in rapid adaptation of a torso finite elements model to address questions about the new behind-body armor. New interest in traumatic brain injury from blast exposures from improvised explosive devices has led to a call for a blast dosimeter, and the efficient development of a candidate system will again draw heavily on the institutional memory of available blast data, experiments, and modeling to produce a new predictive model of human blast exposure.

Validation, Verification, and Accreditation

The Army has a well-defined process of determining that an estimate produced by modeling and simulation meets acceptable thresholds of usefulness. This is referred to as validation, verification, and accreditation (VV&A). The intent of VV&A is to determine:

- if the model works as intended (*Did I build the thing right?*),
- if the model is realistic (*Did I build the right thing?*), and
- if the users' requirements have been met (*Should it be used?*), thus ensuring credible Army modeling and simulation (*Should it be trusted?*).

See the *VV&A Recommended Practices Guide*, available at www.amso.army.mil. The formal DoD definitions for the three processes (DoDI 5000.61)[134] include :

1. *Verification*: the process of determining that a model implementation and its associated data accurately represent the developer's description and specifications.
2. *Validation*: the process of determining the degree to which a model and its associated data provide an accurate representation of the real world from the perspective of the intended uses of the model.
3. *Accreditation*: official certification that a model, simulation, or federation of models and simulations and its associated data are acceptable for use for a specific purpose.

The Army recognizes that modeling and simulation is one approach to obtaining information for problem-solving or decision support—which saves development costs and provides many other advantages—if sufficient VV&A ensures correct program decisions from the modeling and simulation.

Physiological models have not been taken, traditionally, through the formal VV&A process used for other Army modeling and simulation. With increasing interest in the integration of physiological models as components of Army mission planning tools, with virtual prototyping models for military acquisition programs, there is increased pressure for scientific and military certification of the models.

Scientific validation of a biomedical model is an essential step to its approval for use. This includes peer-reviewed publication of the complete model, including its basis and assumptions. Peer review is a cornerstone of modern science; commercial proprietary models and related efforts that limit full disclosure are generally unacceptable because they cannot be fully evaluated. Peer-reviewed publication has been traditionally accepted as "validation" of physiological models. Even so, it does not always occur, and it is not required by any regulatory body. If it does occur, it still does not provide any confidence that the model has been run through its paces by anyone except the original developer. The new standard in physiological modeling journals is becoming one of full disclosure, with the capability for anyone to test the model—that means providing the data and the source code. Previously, models were published with statistical parameters defining their performance and with descriptions of their assumptions and development, but could only be challenged with new data and without full knowledge of the assumptions in the mathematical model.

Today, significant problems arise from commercially developed models with proprietary bases that are not disclosed and that rely on empirical testing to calibrate predictions to an outcome. Some of these have been aggressively marketed to the DoD. Because there is no regulation of predictive models unless they are specifically advertised for medical decision making or health claims, no testing is actually required. Thus, most commercial products available today for physiological monitoring of health and performance status (eg, sports watch programs or "wellness" monitors) are not transparent in their computational methods and need not have been tested or validated in any way.

In some cases, in recent years, the Army models have been subjected to panel peer review scrutiny. For example, the heat modeling was reviewed, but no final agreement on validity of this long-invested and commonly used method occurred. The blast injury model was reviewed by an external panel of experts before adoption by the Health Hazard Assessment Office as the Army blast injury assessment standard. Auditory models were similarly reviewed, and it was agreed that these needed further documentation, transparency to the rest of the critical research community, and validation. Numerous other reviews of Army models have been conducted in the past decade. Some models have been critically analyzed through expert consensus meetings. In 1959, a landmark review of body composition predictive models was held in conjunction with the National Academy of Sciences in Natick.[135] A more recent example is the intensive review and performance evaluation of the world's leading sleep and performance models, including the Army/DoD sleep model.[65] This consisted of a comparison of model performance using inputs from a data set that none of the researchers had previously seen. This workshop stimulated a new generation of more sophisticated sleep and performance modeling efforts.[136,137] Another form of expert consensus meeting is illustrated by the Pensacola 2001 Summit Meeting to review software development, applications, and predictive thresholds of a DoD neuropsychological assessment tool (ANAM).[138] This meeting put in motion the additional research and development of the tool that will now allow its application as a standard assessment tool of soldiers before deployment. For the most part, physiological models are a work in progress, and it is common to find models with no associated probabilities or validation statistics. Thus, all models must be viewed skeptically, and the starting assumption is that they have unknown reliability, reproducibility, and questionable thresholds for action.

Army Computational Biology Applications

The American public is generally unaware of the wide positive impact on daily life that is accrued from military medical research discoveries. Thus, hot weather guidance that is used worldwide to limit physical activities at temperature extremes and ensure adequate hydration to protect against heat injury was developed by the Army. This guidance was derived from studies by World War II–era physiologists of endurance limits in desert environments in Army tankers. More recent studies address hyponatremia and the need to set upper limits to fluid intake and the need to avoid overexuberant hydration in military settings. Navy research and modeling have led to dive tables that today protect divers worldwide. Using a similar concept of staging, Army models for ascent to altitude currently in development may eventually become the standard for mountaineers worldwide.[23] Laser pointer safety and vehicle jolt standards are derived from models of safe exposure limits that have been produced with significant contributions from Army researchers. The Department of Transportation has improved the safety of airbags in automobiles by modifying a blast injury model developed by the Army. Even the National School Lunch Program has links to Army research. Other specific military uses of physiological models include the following:

- health hazards assessment of new equipment based on predicted human tolerances (eg, thermal strain, TB MED 507, blast overpressure injury risk model, INJURY 8.0),
- survivability assessment for mission and equipment based on human performance limits (eg, performance predictions for defeated armor),
- training safety limits for environmental exposures (eg, safe limits for cold water immersion in high-intensity training, TB MED 508),
- medical standards for recruitment and retention (eg, body-fat prediction using the Hodgdon equations, DoD Instruction 1308.3, Army Regulation 600-9),
- readiness training optimization tools (eg, physical training planner that balances injury risk against training benefits, Transaction Online Processing System 1.0),
- mission planning tools (eg, performance predictions based on sleep and circadian rhythms, SAFTE [Sleep, Activity, Fatigue, and Task Effectiveness] model),
- real-time decision support tools (eg, readiness status and health risk warning system, Physiological Status Monitor),
- virtual prototyping of equipment and doctrine optimized to human physiology (eg, biomechanical optimization of load carriage), and
- hypothesis generator to pinpoint key research gaps (eg, ventilatory control and combined toxic gas modeling for enclosed spaces and fire gases).

Virtual Prototyping and Virtual Training Environments and Simulations

Virtual prototyping is a major component of the MANPRINT (Manpower and Personnel Integration) program. Not only will new equipment concepts be testable at the earliest stages for human factors and medical safety with effectiveness considerations, but also equipment can be designed based on models of human tolerances so that its design meets optimal specifications of human capabilities and needs. This is a very significant advance over earlier trial-and-error designs, which were sometimes brilliant engineering solutions, but so disconnected from human capabilities that special selection and training of the users were required; in some cases, significant injuries and performance inefficiencies were created by the equipment. Load carriage equipment is a simple example of this, with rucksacks that impeded performance of the average female, and anthropometric considerations—including optimal center of mass—made huge differences in performance capabilities. Today, load carriage models are used in combination with prototype equipment tests in biomechanical laboratory studies to produce the best possible load carriage equipment for soldiers (see Chapter 11).

An overarching goal of physiological modeling is to develop a complex family of research models, evolving from interlinked and poorly meshed “stovepipes” into the ultimate “total physiological human,” wherein models are syncytial and synergistic and include, for example, the following: (*a*) biodynamic models connecting brain, neck, thorax, spine, and weight-bearing lower extremities; (*b*) models integrated with predicting cognitive function based on neurobiology; and (*c*) models merged with brain, muscle, and bone metabolic models. These predictive models should make major contributions to larger Army simulations, including training programs with decision aids and teaching, virtual reality tools, and war games.[136] Dr James Stuhmiller, a longtime biomedical modeler, has articulated the current need to meet General Casey’s mission forecast[1]:

> Threats to the soldier are growing in nontraditional areas, such as acoustic, electromagnetic, ionizing radiation, chemical, and biological weapons. These threats have both a physical component (coupling of the external threat to the organs of the body) and a systemic effect (disruption of the normal protection and response functions). Although many of the physical interactions are known, they have never been combined with physiological response to produce a quantitative and predictive methodology.[136]

SUMMARY

The US Army has been a significant force in the advancement of the physiology of human performance, with specific and urgent needs that have called for practical problem-solving, real-life military training, and operational paradigms that test the limits of human tolerance and performance, and support for research and development in the interests of national security. In this century, the confluence of new computing technologies, the "convergence revolution" (mathematics and physical sciences coming to the assistance of the life sciences), and a new appreciation for the many military uses of physiological models and predictive decision support tools have the Army poised for even greater contributions. Current models have been largely data-driven; but with new computing resources and mathematical approaches, models can better incorporate and test physiological findings and move rapidly to a first principles quantitative physiology basis. This becomes especially important as human genome data are interpreted and used in human phenomics. The military gains advantage from this information through the ability to develop better human-centered materiel and systems, operational planning that more accurately predicts the human element in various courses of action, and decision support tools that make accurate group and individual predictions useful to commanders and clinicians. The Army is likely to continue to be the largest contributor to the knowledge of individual human performance limits.

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