

SOMATIC CONSEQUENCES  
AND  
SYMPTOMATIC RESPONSES  
TO  
STRESS:

DIRECTIONS FOR FUTURE RESEARCH

June 26<sup>th</sup> - 28<sup>th</sup>, 1998

The Bethesda Hyatt  
Bethesda, Maryland

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Department of Psychiatry  
F. Edward Hébert School of Medicine  
Uniformed Services University of the Health Sciences  
Bethesda, Maryland 20814-4799

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This volume is an edited transcript of the Conference, "Somatic Consequences and Symptomatic Responses to Stress: Directions for Future Research." The Conference assembled scientists with expertise across many fields in order to bring a multidisciplinary approach to understanding somatic consequences of stress.

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Department of Psychiatry  
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Uniformed Services University of the Health Sciences  
Bethesda, Maryland 20814-4799

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## Preface

This conference was held as part of a research project, *Stress and Arousal Symptoms Expressed in Individuals and Groups - Persian Gulf War Symptoms as a Paradigm*. The grant was funded by the United States Army Medical Research and Materiel Command.

The conference was assembled renowned scientists with expertise across many fields in order to bring a multidisciplinary approach to understanding somatic consequences of stress. Its major goal was to develop suggestions for future research that integrates stress and its effects from the cellular to the sociocultural levels.

The meeting was co-chaired by Drs. David Marlowe and Ann Norwood, respectively, the Senior Scientist and Principal Investigator of the project. Ms. Laura Casoni and Mr. Adam Kaplan were Research Assistants on the grant. The conference was held at the Bethesda Hyatt on June 26<sup>th</sup> - 28<sup>th</sup>, 1998.

This volume represents a transcript of the conference that has been edited for ease of reading and clarity.



## Conference Participants

Robert Ader, Ph.D.  
Department of Psychiatry  
University of Rochester School of Medicine/Dentistry  
Rochester, NY 14642

Nancy L. Bakalar, M.D.  
Clinical and Program Policy  
Skyline 5, Suite 601  
5111 Leesburg Pike  
Falls Church, VA 22041-3206

Paul Black, M.D.  
Boston University School of Medicine  
Department of Microbiology  
Room L504D  
80 East Concord Street  
Boston, MA 02218

Etzel Cardeña, Ph.D.  
Department of Psychiatry  
Uniformed Services University of the Health Sciences  
4301 Jones Bridge Road  
Bethesda, MD 20814-4799

Bruce Dohrenwend, Ph.D.  
Columbia University  
Social Psychiatry Research Unit  
100 Haven Avenue, Tower 3-19E  
New York, NY 10032

Charles Engel, Jr. M.D., M.P.H.  
Department of Psychiatry  
Uniformed Services University of the Health Sciences  
4301 Jones Bridge Road  
Bethesda, MD 20814-4799

Kai Erikson, Ph.D.  
Department of Sociology  
Yale University  
140 Prospect (Office)  
P.O. Box 208265  
New Haven, CT 06520-8265

John A. Fairbank, Ph.D.  
Department of Psychology & Behavioral Sciences  
Duke University Medical Center  
905 West Main Street, Ste. 22  
Durham, NC 27710

Karl Friedl, Ph.D.  
HQ USAMRMC  
ATTN: MCMR-PLC  
504 Scott Street  
Ft. Detrick MD 21702-5012

Timothy R. Gerrity, Ph.D.  
Office of Research and Development  
Veterans Health Administration  
US Department of Veterans Affairs  
Washington, DC 20420

Ronald Glaser, Ph.D.  
Office of Research and Graduate Education  
Ohio State University Medical Center  
2175 Graves Hall  
Columbus, OH 43210

Bonnie Green, Ph.D.  
Georgetown University  
Department of Psychiatry  
310 Kober-Gogan Hall  
Washington DC 20007

Samuel B. Guze, M.D.  
Washington University School of Medicine  
4940 Children's Place  
St. Louis, MO 63110

Frederick W. Hegge, Ph.D.  
844 West Central Avenue  
Davidsonville, MD 21035

Harry C. Holloway, M.D.  
Department of Psychiatry  
Uniformed Services University of the Health Sciences  
4301 Jones Bridge Road  
Bethesda, MD 20814-4799

Janice Kiecolt-Glaser, Ph.D.  
Department of Psychiatry  
Ohio State University  
School of Medicine  
1670 Upham Drive  
Columbus, OH 43210

Laurence J. Kirmayer, M.D.  
Division of Social & Transcultural Psychiatry  
McGill University  
1033 Pine Avenue West  
Montreal, Quebec H3A 1A1

David H. Marlowe, Ph.D.  
Department of Psychiatry  
Uniformed Services University of the Health Sciences  
4301 Jones Bridge Road  
Bethesda, MD 20814-4799

Grant Marshall, Ph.D.  
Health Sciences  
RAND Corporation  
1700 Main Street  
Santa Monica, CA 90407

John Mason, M.D.  
Yale University School of Medicine  
VA Medical Center 116A  
West Haven, CT 06516

James L. Meyerhoff, M.D.  
Department of Neuroendocrinology  
Walter Reed Army Institute of Research  
Division of the Neurosciences  
Washington, DC 20307-5100

Benjamin H. Natelson, M.D.  
Fatigue Research Center (127A)  
VAMC  
385 Tremont Avenue  
East Orange, NJ 07018

Ann E. Norwood, M.D.  
Department of Psychiatry  
Uniformed Services University of the Health Sciences  
4301 Jones Bridge Road  
Bethesda, MD 20814-4799

Paula P. Schnurr, Ph.D.  
National Center for PTSD (116A)  
VA Medical Center  
215 North Main Street  
White River Junction, VT 05009

Robert J. Ursano, M.D.  
Department of Psychiatry  
Uniformed Services University of the Health Sciences  
4301 Jones Bridge Road  
Bethesda, MD 20814-4799

#### **Research Assistants**

Laura Casoni  
Adam Kaplan

**DR. MARLOWE:** I think we will begin now.

There are a couple of issues that Ann would like to bring up with you. One is about the fact that the proceedings are being taped.

**DR. NORWOOD:** Irene Gray, sitting at the back, is with Neal Gross transcription. We'll send around a consent form agreeing to be transcribed to all of you.

Our plan is to make this, as we usually do, into an edited transcript that we'll be sending along with our final report to the Research Command. The whole goal of the grant is to provide the Army Research Command with a set of research suggestions for future exploration and understanding of issues, such as the Gulf War Syndrome.

So I don't think you'll see any excerpts of this on CNN or in *Time* magazine. Chuck was hoping for the *National Inquirer*.

It probably will end up as a Defense Technical Information Center report. We'll be happy to send you, the participants here, what comes out of it.

We try to edit it so that it's easy to read, and also if someone says something that they may not particularly want out in public, we also are sensitive to that.

So does anyone have any questions about that particular --

**DR. MARLOWE:** Well, there's one other thing. Irene requested that there be no cross-conversations at the same time because it makes it hard for the transcribers. I told her we would try, but I doubt that we would be very successful.

(Laughter.)

**DR. MARLOWE:** We will live with what we have. Just a couple of other things. Dr. Ahern cannot make it, unfortunately, due to the storms. He couldn't get out of Boston, and so he won't be joining us. I'm sorry. He was recommended as a substitute by Dr. Barsky and had worked on many of the same issues, and I think the issues of amplification and -- their effects that Barsky has worked on are really of significance and perhaps importance to what we're trying to do here, and it's unfortunate that he won't be able to make it.

We do not know what has happened to Dr. Kirmayer. Dr. Kirmayer has worked with and was recommended by Dr. Kleinman, who was in China, and for those of you who know Kleinman's work, he's both a psychiatrist and anthropologist. He's at Harvard Medical School now. He has done some of the most pertinent research dealing with the entire concept of the cultural shaping of what he calls the illness narrative and the way in which this tends to control the kinds of symptoms that are presented by patient to physician and by patient to society at large. I do hope that Dr. Kirmayer can show up.

Once again, let me welcome you all and simply state that it's a great pleasure to have you all here. We still have a couple of strays who haven't come, but I think it's important that we begin.

What we'd like to begin with is to ask each of you to talk for five to ten minutes about the pattern of the research you've been doing and the directions it's been going in and the directions you think it should go in in order to best grasp the kinds of issues that you construe as of major importance in what you're doing.

Let me introduce -- I think some of you know -- Dr. Ben Natelson, who has just arrived.

(Laughter.)

**DR. MARLOWE:** And if you and Jim Meyerhoff will sit down, we'll begin.

(Laughter.)

**DR. NATELSON:** Yes, sir. Sorry about that.

**PARTICIPANT:** You're our first speaker, by the way.

(Laughter.)

**DR. MARLOWE:** With that, what I would like to do, I'll just begin at my right. If each of you would introduce him or herself and talk for five to ten minutes max., again, about the work you've been doing, its pattern, where it's going, and where you would like to see it go.

Part of what we are concerned with, let me emphasize again, is trying to conceptualize future research ranging from the animal to the epidemiological that may help us get a handle on the whole issue of how stress produces somatic and other symptoms.

With that, let me begin with you, Grant.

**DR. MARSHALL:** My name is Grant Marshall. I'm a psychologist from the Rand Corporation, and with late appearances, I'm not quite up yet. So I had hoped to not have to do anything but sit here like a vegetable until about noon or something.

For the past year, I have been working on a report looking at the potential role of stress as a factor in Gulf War illnesses, and we're very nearly completing our report. Most of my work to date has been looking at how people cope with various traumatic life experiences, and the Gulf War work fits into that. We've just been looking particularly at the link between emotional stress and physical illness and somatization in particular, and hoping to see if I can get some ideas from some of you who have worked more on the hard sciences end of things to see how I can integrate your work into the work I've been doing, which has been focusing on psychological symptoms following exposure to trauma.

**DR. MARLOWE:** Thank you, Grant.

**DR. GERRITY:** My name's Tim Gerrity. I am Special Assistant Chief Research and Development Officer in the Department of Veterans' Affairs and have as one of my primary responsibilities to carry out on a day-to-day basis the coordination of research across DOD, VA, and HHS on Gulf War veterans' illnesses research.

I'm here today both in that capacity, but as well as one who, I think, wants to both learn and hopefully be able to contribute some to the discussion today because we have this responsibility of guiding the future research on Gulf War veterans' illnesses. We are going to also have the responsibility for carrying out a similar role in guiding the research agenda for health research related to future deployments as a result of a strategic plan developed out of the Office of Science and Technology Policy, National Science and Technology Council, which will be release within the next one to two weeks out of the Office of the President.

And if at some point during the day you'd be interested in hearing a little bit about that, I'd be happy to share some of that with you, specifically in this area of research.

I think, speaking for VA, this is an extremely important area of research, and I think that it expands well beyond issues of military deployments and touches the entire human race, if you will. I think advances in this field will have major impacts in the way we view somatic illnesses and how we approach treating and caring for those individuals who are experiencing stress and manifesting symptoms that could be a direct outcome of that experience.

So I think this is a very exciting time right now in this particular area of science as we move from -- I won't say "move from" -- but move toward a greater understanding of the basic mechanisms of the central nervous system and peripheral nervous system, where we are able to bring to bear some of the tools of technology to expand our understanding. Hopefully, I would like somewhere down the road to be able to dispel this persistent cultural notion of a mind-body split. Unfortunately this leads to our Persian Gulf veterans viewing a suggestion that stress could be a significant cause of their illnesses as somehow demeaning them and, I would say in reference to your talk last night, David, actually suggesting that we are telling them that they are cowards.

So I think that this is an exciting time. I'm glad to be here as a part of it.

**DR. MARLOWE:** Bruce.

**DR. DOHRENWEND:** Yeah. Well, when I heard about having ten minutes, I thought I'd better put down some things that I could hand out.

**DR. MARLOWE:** Name first, Bruce.

**DR. DOHRENWEND:** Bruce Dohrenwend.

**DR. MARLOWE:** Thank you.

**DR. DOHRENWEND:** So if I could just pass this brief.

I'm trained as a social psychologist, and my field is psychiatric epidemiology. My interest is in the role of adversity and stress in psychopathology, very broad, which is why I thought I'd better have a handout.

To say a little bit about what I mean by adversity, I mean very much what the dictionary means, Webster's. The adjective "adverse" is defined as acting against or in contrary direction and more personally as opposed to one's interests. The noun "adversity" refers to a calamitous or disastrous experience, whose synonym is misfortune. The misfortune is grave or persistent and is distinguished from mishap, which applies to a trivial instance of bad luck.

Events in extreme situations, such as military combat and natural disasters and events such as child abuse and neglect, rape, physical illnesses, and injuries, or even unemployment, marital separation, divorce, in more usual situations can be important manifestations of adversity.

I think that there are some general dimensions of stressful events. Those that seem most important to me are on the second page there of your handout. Certainly -- positive, negative, involving gain or loss; what I call fatefulness, the extent to which the occurrence of the event is outside the control of the individual and unaffected by his or her behavior. The other extreme is what Constance Hyman calls "stress generational behavior." The extreme would be culpable conduct in producing the event, the legal term "culpable conduct," which the individual's behavior is heavily involved in the occurrence of the event.

Predictability of occurrence, whether most people would think that it was expectable that the event could be anticipated.

Magnitude defined in terms of changes in the usual activities of most individuals who experience the event.

Centrality, the relation of these activities, these changed activities, to the important goals of the individual. In extreme situations involving life threat, centrality is self-defined. It couldn't be more central to the goals of the individual.

Physical impact, the likelihood that the changes the individual undergoes would be physically exhausting for most individuals who experience the event.

Note that in addition to these general dimensions there are important dimensions that are specific to particular categories of events. For example, traditional legitimate events in military combat situations and illegitimate nontraditional events, such as participation in atrocities.

I think there's a great deal that we'll need to do or has to be done to expand this notion of specific dimensions with regard to such things as the Gulf War, a whole host of events, Three Mile Island, just the specific characteristics of these events, especially with regard to socially defined threats. Who defines them? And major issues of trust in relation to who defines these events socially.

There are some comments that I would like to make about these characteristics. I think that all of them are involved in extreme form in prolonged exposure to severe combat situations. They're negative. Certainly some of the events in combat situations are fateful. Some are certainly highly predictable. They change the usual activities of individuals. They're highly central and involve a life threat and are highly likely to be exhausting physically.

So you have a situation where these characteristics, the negative ends of them or the fatefulness end, are maximums, and with regard to the Marlowe-Norwood memo, I would argue that extremes of exposure under such situations, contrary to what's in their memo, are sufficient to produce the onset of the psychopathology involved in what's now called and defined as post traumatic stress disorder certainly as now defined, that it's one month duration, three months for acute, and so on.

Note that I emphasize onset, and I think I can support this from the epidemiologic literature of research on combat.

So sufficient for onset at the extreme. However, course is quite another matter. A number of other factors are involved in course, and I think that could use some discussion.

With regard to events in more usual situations, various of these characteristics are involved or not involved in different degrees and combinations, not in the full strength that you observe them in severe events and extreme situations.

Now, note that most current approaches to measuring major events over the life course, a checklist approach, are simply inadequate with regard to operationalizing these dimensions. Much more labor intensive procedures are required.

Without these kinds of measures, we lack another thing that's called for in the Marlowe-Norwood heuristic paper, and that's an epidemiology of major events over the life course in general population samples or military population samples. We simply don't have it, and I think it is very much needed as they suggest in their memo.

But it requires a methodology to support it and the kinds of checklist measures that have been used to date are simply inadequate to the task for a variety of reasons that we can discuss if you think that's important.

There is a central proposition that I would like to advance. It's on the last page of the memo about the role of adversity. The proposition is that the greater the uncontrollable negative changes in the ongoing situation, be these usual or extreme situations, in terms of the centrality and proportion of usual activities affected following the occurrence of a negative event, the greater the likelihood that disorder will develop.

Ongoing situations become uncontrollable by different routes in which adversity is involved to a greater or lesser extent. The uncontrollable negative changes in the ongoing situation are the final common pathway by which the different environmental and predispositional sources lead to adverse health outcomes.

It is in the different environmental and predispositional sources of uncontrollability in extreme and more usual situations that adversity plays its part. These sources vary with gender, ethnic-racial status, and socioeconomic status or social class in modern urban societies.

That, in general, is where I am in ten minutes at least on adversity, stress, and psychopathology.

**DR. MARLOWE:** Thank you, Bruce.  
Chuck.

**DR. ENGEL:** My name's Chuck Engel. I am sort of a jack of all trades and a master of none in many ways.

I'm a Gulf War veteran and was a division psychiatrist with the First Cavalry Division during the Gulf. I was there for about seven months. So I saw this from sort of an operational perspective, not sort of; I guess a very operational perspective.

Also, my long term interests have been in mind-body medicine even going back to medical school. At the risk of making this a longer story than it has to be, I was originally interested in family practice in medical school. I decided that what I was really interested in was how non-biomedical factors affected people's sense of their health. I felt like I didn't get enough of that in family practice or general internal medicine, and ended up going into psychiatry.

Once I got into psychiatry, I found myself mired on in-patient wards taking care of chronic schizophrenics and realized that my true interest was more in the realm of how psychiatry impacted ambulatory care and how psychosocial factors affected people's health there.

Like I say, that goes clear back to medical school. Subsequent to my Gulf War experience, I trained in epidemiology under Wayne Katon. I'm a psychiatrist by clinical training, and of course, Dr. Katon's interest has been the impact of mental disorders on physical symptom reporting and related areas, and I learned a great deal from working with him there.

I also have had a services interest. My interest is, I'd say, more big picture than at the molecular level. I'm interested in widening our gaze to a certain extent.

Well, to finish the story, what I do now is, in addition to being on Bob Ursano's faculty in the Department of Psychiatry in USUHS, I run a place called the Gulf War Health Center at Walter Reed where we're seeing Gulf War veterans with unexplained physical symptoms. So we're at the point of care with a lot of the folks who are now complaining of symptoms.

I'm interested in the big picture about how information affects people's health, and I'm interested in, a smaller picture, how we as physicians can relate to patients what's happening in their bodies, the clinical perspective, in a fashion that has a positive impact on their health.

I'm interested in services' strategies. I'm currently working with a group, and a few of the members are here, that is looking at a cognitive behavioral exercise strategy for symptomatic Gulf War veterans. I would describe it as a disease generic approach to improving patients' health. I'm interested in how service strategies can change people's health.

I'm also interested in reasoning and critical thought both with regard to how we interpret the research that we do and how we as clinicians think about the information that we have about the individual patient in front of us, and how we relate research findings that deal with groups of people to the clinical setting where we're dealing with individuals. It's often a difficult transition.

So that's the broad picture of my interests.

**DR. KIECOLT-GLASER:** I'm Jan Kiecolt-Glaser from Ohio State. I work with Ron Glaser and have since 1982.

I'm a clinical psychologist by trade. I'm Director of the Division of Health Psychology and Professor in the Department of Psychiatry.

We've been working since '82 on a series of studies looking at stress and immune function. They began by looking at whether a very commonplace stressor, academic examinations, would be associated with immunological changes, and indeed, in a ten-year series of studies with medical students, we found a number of changes.

We next moved to looking at whether people would adapt to a very chronic and long term stress, caregiving for a spouse with Alzheimer's disease or another progressive dementia, and in fact, found that there was not adaptation with a very long term or chronic stress, or at least immunologically.

The most recent work involves wound healing as an outcome. We first compared 13 caregivers and 13 controls in how long it took to heal a small punch biopsy wound and found, in fact, there were large differences, that it took caregivers 24 percent longer or nine days longer to heal the same small wound.

John Sheridan in our group replicated that finding with mice and found that when mice were subjected to restraint stress, it took them 27 percent longer to heal a small standardized punch biopsy wound.

In our most recent study with dental students, we used an oral wound working with Phil Marucha on the hard palate and showed that students who were wounded twice, once after vacation and then once three days before an exam, took 40 percent longer to heal the same small standardized wound during a stressful period.

We're particularly interested in the effects in this arena because they appear very large, much larger than anything else we've seen, and quite reliable. Every student among the 11 dental students took longer to heal a wound during examinations than they had at baseline.

The final major thrust that I'm interested in psychologically has to do with personal relationships. One of the psychological themes for our studies over time has been the extent to which supportive personal relationships are related to immune and endocrine function, and we find in a number of studies that, in fact, supportive personal relationships are associated with better immune function in a variety of ways.

**DR. GLASER:** I'm Ron Glaser, also from Ohio State University Medical Center. I'm a tumor virologist, and I worked with Epstein Barr virus and cancer for many, many years.

But as Jan pointed out, in 1982 we started working together on what was then a relatively new field called psychoneuroimmunology, and basically started to look at very complex interactions in a very multi-disciplinary way between the central nervous system, the endocrine system, and the immune system.

We have a group at Ohio State. There are now 13 faculty in this research group bringing different expertise. So it's very multi-disciplinary. We do functional studies, cell function. We have endocrinologists. We have virologists. We have immunologists. We have behavioral people, and we study different kinds of aspects of stress and immunity and health from multiple directions at the same time.

We do molecular studies and clinical studies and basic immunology studies, and so it's really very interesting from a perspective of a person who really does like to learn other things, about how the body really works as opposed to how it works in tissue culture, and so I found that very fascinating.

Being a herpes virologist, by definition I have to be interested in virus latency, and so what's been very interesting for me is that after reading for many years that stress is one of those factors that's always listed in textbooks on reactivation, for example, of herpes simplex virus, the cold sore virus, to actually -- and nobody understood, for example, how all of this worked -- it was really interesting for me to take virus latency from in vitro studies, which I had been doing for 20 years, and move them into real, live situations in people and looking at, for example, EBV reactivation, latent EBV and other herpes viruses under stress. It's trying to learn real life latency approaches.

So that said, we've also done studies on vaccines. We've shown, for example, that the immune changes that are induced by academic stress that Jan just mentioned in medical students, are biologically large enough to influence both the antibody and virus specific T cell response to Hepatitis B vaccine.

We then did another study with the caregivers, showing that the stress associated with caregiving produced immune changes that are large enough to affect how they respond, both antibody and virus specific T cell response, to flu vaccine compared to those very well matched, non-caregiver controls.

So we're now doing studies on Hepatitis A and *pneumococcus* vaccines in these caregivers to continue that line of research.

You asked us to talk about where we think we'd like to go for the future. I can tell you where we're going for the future because that's what we think is important.

First of all, I think it's really important that we remind ourselves that we really don't know very much about how the body really works, and that we ought to admit that up front. Okay?

When we talk about the interactions between these three body systems, we're talking about complexities that we're just scratching the surface. So, if you don't like the pat answers that we provide, those of us who do this as research, come back 20 years from now and perhaps we'll have better answers as we learn more about what's going on on the interactions between these three systems because we're not only dealing with information that we know about and trying to put that together. What we're really dealing with is information that we don't know about.

There are cytokines that we haven't discovered yet. There are hormones we haven't discovered yet. There are cell populations we haven't discovered yet.

So, we have a lot missing in this puzzle. We have to put that in perspective ain't so smart. That's the first thing. So we have a lot to learn.

And our group, because it's very multi-disciplinary, is trying to start taking that apart from different approaches piece by piece and trying to learn about that.

We believe that both behavioral and pharmacological interventions in a clinical setting are going to be important studies. In fact, we now have a hypnosis intervention study that we're finishing up right now on wound healing, and we have a behavioral intervention study with women with breast cancer ongoing at Ohio State in our group as well.

So we think it's time that this stuff starts being applied in a clinical setting to see whether, in fact, either behavioral, pharmacological, or a combination of both might be appropriate in a clinical setting.

We will continue working on infectious disease issues. Several people in our group are interested in both tuberculosis and, of course, in viral infections.

We're going to be working a lot on wound healing because, as Jan pointed out, these are real observations. I mean the changes that we're seeing in wound healing are significant. The effect sizes are very, very large, and so we have decided to get into mechanism studies on wound healing by looking, for example, directly at a wound site, at the skin very, very early on after wounding

and using a model that will allow us to, for example, look at cytokine production at the local site, migration of cells into the local wound site, and we can relate these activities. We're trying to relate these activities to stress.

Cancer we will continue to work on both in animal models and in human subjects, as well, because obviously that's an important area as well that we think still is under explored in terms of stress.

So those are some of the kinds of things that we're doing at Ohio State and we think are important.

**DR. MARLOWE:** Before we go on, Ron, one thing I'd like you to think about is I think a very important issue that you just brought up, but how do we start going about defining seriously what we don't know, and how do we start going about looking for the processes that we don't understand?

**DR. GLASER:** How do we do that?

**DR. MARLOWE:** Later.

**DR. GLASER:** Oh, okay.

**DR. BAKALAR:** My name is Nancy Bakalar, and I'm a psychiatrist by training, and I may be the only or one of the very few non-researchers in the group here.

I am assigned to the Department of Defense Health Affairs, and I am the Program Director for Mental Health Policy for DOD. I went into that job about two and a half years ago totally blind, not realizing the complexity of what I would face in that job.

As the Program Director for Mental Health Policy in an era of the Persian Gulf War illness, we have many challenges in front of us at DOD, and of course, all of you realize that DOD is on the front lines politically and in the press from other government agencies to address these problems quickly. So I feel like I'm on the interface between the researchers and people who are needing to implement changes fairly quickly to avoid problems in the future, as if that could be done so easily.

Let me just tell you a little bit about what I see DOD doing right now. Of course, from the health affairs perspective, we've taken on the whole gamut from putting prevention into practice, to emphasizing prevention as far as health and psychological measures go.

There's emphasis on physical fitness, smoking cessation, alcohol and drug abuse, addressing those problems and providing treatment; frequent physical exams; immunizations; looking at the whole soldier, the whole service member.

The Department of Defense published in August last year the DOD directive and instruction on joint medical surveillance. This requires the services to do many things to protect the health of the forces, including better medical record keeping, better records of troop movement and exposures, and surveillance for toxic factors. However, I'll share with you that the mind-body split remains a challenge for DOD.

It is very difficult for people who are addressing the potential physical problems, such as chem/bio, to integrate what it means from a psychological perspective to be under those threats. So one of my concerns, of course, is to try to bridge the gap in these groups and try to bring into focus, that there is a connection between the mind-body and stress and physical illnesses.

One of the reasons I asked Ann if I could attend today is that I also think it's very difficult to get the latest research findings and the newest information that you all are discovering and publishing into our policies.

One of the things I would recommend we think about throughout this conference is how does your work get put to good use as soon as possible. I know it's going to take 20 years to find the answers to some of these things, but you all know some things that we don't know and we need to know as we write and develop our policy.

So I would ask you to think about ways in which you can communicate better with us as policy makers on how we might try to take your cutting edge findings and make good, solid use of them on the ground where the troops are.

Finally, I want to introduce another question to the group, and that's how do you as researchers, how do we as people addressing these issues, try to address and change and influence our culture as far as things like the mind-body split and how people think about these illnesses.

And then finally, I would also like to add I think that there are other areas or other specialties we may want to think about bringing into this discussion, and maybe we'll see some of it here today.

Dr. Dohrenwend began to address some of these issues. I'm trained more dynamically than biologically in my clinical work. There are both conscious and unconscious processes that occur in cultures, and it would be helpful, I think, to also look at some of the historical events from unconscious group processes, as well as the conscious, and how those influence what we do as a country both politically and how that translates into war and combat.

And there are certainly analysts who have documented their very lengthy work with patients who have severe physical symptoms and have done analytic work and have improved the physical health of those patients, including very severe cardiac disease and so forth. I think it would be interesting and perhaps helpful addressing illness from that perspective.

How are we changing the biochemical nature of the brain through psychotherapy, through social supports, through group cohesion, through unit morale, through leadership?

Anyway I offer those as questions to the group and suggestions, perhaps.

**DR. ERIKSON:** My name is Kai Erikson. I'm a sociologist, and I teach at Yale University.

I have spent a good part of the past 25 years or so going around to various communities who have either been greatly impacted by some kind of a disaster or thought they were impacted by some kind of a disaster, a distinction that comes up in that heuristic letter and is very important, with the idea in mind of trying to determine the degree to which that among the things that they lost as a consequence of the disaster was a sense of succor, if that's the right word, from the communities that they were a part of in the first place.

The number of places I went to covers an extraordinary range (which proves that I'm not a very highly centered person at all) but it began in Buffalo Creek where Bonnie Green has been, and it went through Three Mile Island where Bruce Dohrenwend has been and Andy Baum, and a large number of other places, which includes an Ojibway Indian band in Northwest Ontario and a group of Haitian migrant workers in South Florida and some of the native villagers that live along the southern coast of Alaska and were impacted by the Exxon Valdez oil spill.

And that has taken me recently -- it seems like a logical sequence to me, but not always to everybody else -- I've spent a fair amount of time in Croatia recently talking to people in western and eastern Slavonia, which are those portions of the country where the combat was most fierce during the war between the Serbs and the Croats in '91 and '92 and again in 1995.

And as a result of all of this, I've come to think -- you know, you were talking about something you'd like to bring into the conversation -- that one thing that I would want to bring into the conversation is it seems to me that one of the things that I've seen in this extremely wide range of different situations is a stressor which isn't talked about a very great deal. What was true of all of these disasters was a feeling on the part of the people who saw themselves as victims of it that the people who had been responsible for bringing the disaster to them lived within the same immediate social world that they did. So that they felt, at the very least, very let down by those other people and, at the worst, very, very deeply betrayed. That is true of the war in Croatia, as well as of these disasters that took place in the United States. And it seems to me if you talk about wounds that take a great deal longer to be cured, that among those wounds is something that we call the traumatic effects. They take a great deal longer to be cured if people come to think that that's the case, at least in part, because it throws into doubt for them as to how much order there really is in the social world and, as an extension of that, how much order there really is in the natural world when the things that they take for granted fall apart.

David was talking last night about various kinds of combat situations. They share in common, for the most part, I think, the feeling that the enemy that you meet in the battlefield comes from across a horizon and it's almost like a natural disaster. Genghis\_Khan comes across the border, you know.

The Genghis Khan in these kinds of situations is very often your immediate next door neighbor, and it becomes a very hard situation to deal with.

**DR. MARLOWE:** It is good to remind us of the line from *Pogo*. "I have met the enemy, and it is us."

**DR. ERIKSON:** Yeah.

**DR. GUZE:** Well, first, I want to indicate that I think that I'm here because of initiatives that were taken by staff leadership in a project that I'm involved in, and I'm very grateful that you were willing to permit an outsider to come in.

I think it might be helpful maybe just a little to tell you something about how I reached the point I'm at. I'm a co-principal investigator of a project that the National Academy of Sciences, the Institute of Medicine contracted to carry out for the Department of Defense. The charge is very broad and somewhat vague, but at least as I interpret it, we are to study the Gulf War Syndrome and review all of the very many previous efforts to understand it and to characterize it and to make suggestions about it. As a result of that kind of review, hopefully we will be able to recommend a change in policy or policies to the Department of Defense so that should something similar occur again, the impact will be less.

Now, I haven't made any secret both within the group that I'm part of and with a few of you yesterday that I don't know whether that's an attainable goal. At least half the time I think it's not.

Now, when I was first asked to take on this responsibility, I asked, "Well, why did you come to me?" And among other reasons, I was told that the decision had been made that one of the co-PIs must be a psychiatrist, which I think reflected a number of assumptions that whoever was key in the Department of Defense for initiating this project was working under.

My first response was to say, well, I was very flattered, but I really didn't think that I would have too much to contribute. Instead I tried to suggest to them that they get somebody else to be a co-PI and perhaps appoint me as a consultant in the area of stress. So I just want to show that there's a kind of connection here.

Now, after they went back and thought about that some more, they came back and finally persuaded me that I should take this on. I'm not unhappy that I've agreed to do it because it's been a very interesting assignment and I've met some fascinating people and learned about wonderfully interesting work. I just don't know whether we're going to be able to come up with something that the Department of Defense is going to think has been worth the time and effort.

Now, I want to just say a word about stress because that's why I'm so pleased about being here. I started out in internal medicine. I was trained, and I'm Board certified in internal medicine, as well as in psychiatry.

During the transition from internal medicine to psychiatry, I became very interested in the work of Harold and Stuart Wolff at Cornell who Dr. Marlowe referred to last evening, and I really became at that point thoroughly familiar with all of their work and the work of people they trained who were carrying on the work all around the country, including in our own medical center.

And I must say that I finally became -- well, I don't know what adjective to use -- severely disillusioned about the whole strategy of their research efforts. I think that the reason I'm interested in this whole business about stress and research about stress is I think we're dealing with one of the most difficult questions that we could possibly come to grips with, and I'm not sure that we've made very much progress.

One thing that I feel is that stress is ubiquitous, whatever definition we use for it. So that it's possible to say that every person's life all the time is lived in the context of varying levels of stress, and stress coming about from a very rich variety of different sorts of experiences.

And if you try to define stress, if you go to a dictionary definition, you really find that most dictionaries say what I've just said because I've copied them from the dictionaries. I think any experience that has a negative impact on people or sometimes even a positive impact, but any experience that has an impact on one's perception, one's feeling, one's ability to function, one's effectiveness can be called a stress.

But we have made zero progress as far as I can see in quantifying stress. We haven't achieved any consensus about whether there's merit or when there might be merit in talking about stress generically so that we talk about stress when somebody's been exposed to, let's say, an infectious agent or somebody's been exposed to a combat situation or somebody's been exposed to severe illness or death in a family or loss of a job or disappointments in marriage or financial reverses. All of these things are stresses, and I think the question arises: does it make sense; is it useful to talk about them all in this generic way?

I could argue both sides of that debate, but I recognize that the fact that we haven't crystallized out a consensus about it is a terrible burden in this field.

Now, the effects of stress are very, very broad, all the way from medical to social, economic, political consequences. I think that's part of the reason that the soldiers and other military personnel have been uncomfortable and a little suspicious about the suggestion that the Gulf War Syndrome may be in some way stress related. I think anyone who has read the newspapers or even more serious publications soon comes to understand that this is a concept that's bandied about very carelessly. There's been very little true quantification. There's been very little effort to see just how consistent the results can be from one laboratory to another if people really make an effort.

So I continue to have a tremendous interest because I think there is such a thing as stress, but until we make better progress in knowing how to characterize it, measure it, distinguish different kinds and have the ability to make some kinds of predictions from a particular event, a particular kind of stress, and a particular population with particular results; until we can do that in some consistent way, nobody is going to take this as a particularly gratifying thing to be told, "Well, your illness probably has something to do with stress."

Now, in my earlier days I did a lot of research myself, and by coincidence, I have a lot of publications dealing with what is today called somatization disorder, and I can tell you that my experience is that this is a very, very complicated and frustrating area to try to study.

Unexplained medical symptoms, including psychological ones, are very widespread. In fact, they're so widespread that I have become kind of a deliberate thorn in the side of many of my colleagues when they report, say, clinical studies or epidemiologic studies and they do not indicate what percentage of their subjects had unexplained clinical manifestations.

In every study that I've ever done, the range of unexplained symptoms would be from 20 to 30 percent, sometimes higher. When I read work from my colleagues and I find they don't even mention this, I wonder what they have done. How have they avoided this? What have they done that I should have done or vice versa?

And so I think we have to understand that unexplained physical and psychological symptoms, jointly, medical symptoms are extremely common worldwide, and so far as I can tell they always have been.

Now, secondly, they are often reported by individuals, quote, patients, who do not consistently identify them as part of any kind of stressful context. Now, if you start pursuing that and making suggestions, a certain percentage of those individuals will say, "Well, maybe there's something to that," but you will always remain, at least I've found, with a significant group of people who insist on these symptoms being present and troublesome, but who do not recognize on their own any kind of stressful context.

So I'm going to be very interested in hearing what some of you, because I understand that many of you are on the front edge of research in this area, are doing, but I really believe that if we're going to make progress, we have got to seriously address in a systematic way the fundamental questions that have to do with how do we define it, how do we measure it, how do we -- for example, is it possible to measure all stresses except in terms of the impact they have on people? Is it possible to measure something we call stressful as a stimulus and just measure its characteristics?

That subject has hardly been addressed in a research mode, and yet it seems to me it's part of the ABCs of research in this area.

Well, thank you very much.

**DR. MARLOWE:** Two points of thought from Dr. Guze's discussion. One which I think we will have to grapple with is how do we create a taxonomy about stressors and stress response. Is there a way to do it? Is there a way to approach mensuration that is not entirely subjective?

And the rule is we have certainly been using various kinds of scales for years. Well, the kinds of things many people will put down as having been extremely stressful are obviously not. The variation is tremendous.

But I think there's another issue that pokes out in this 20 to 30 percent that certainly every worldwide survey puts out of unexplained, unexplainable physical symptoms, and it's one that I think has demonstrated some power with the Vietnam War, probably with the Gulf War. What happens to unexplained constellations of symptoms when there are folk out there who are willing to give you very threatening explanations under which to organize those symptoms and perhaps create feedback loops that may well amplify the effect of the symptoms?

I think some of Barsky's work dealt with this. So let's consider some of these again as kinds of issues.

**DR. FAIRBANK:** Good morning. My name is John Fairbank, and I'm a clinical psychologist by training, and I'm an associate professor of medical psychology in the Department of Psychiatry and Behavioral Sciences at Duke University Medical Center. My secondary appointment is in the Department of Psychology at Duke.

Also, along with Dr. Guze, I'm very pleased to be here as an invited observer from, I guess, serving in my role as a member of Dr. Guze's IOM panel.

My most relevant research, I think, is in the area of post traumatic stress disorder. I guess that's what I've been most focused on over the past 19 to 20 years.

I had the good fortune of starting my research career as a brand new Ph.D. with Terry Keane, who many of you, I'm sure, know through his work, and so, therefore, I got heavily involved in the late 1970s, early 1980s, in a wide range of kind of research endeavors, some early work in developing multi-method, multi-source assessment approaches for identifying cases of PTSD; some clinical studies; basically some efficacy studies looking at cognitive behavior, behavioral and behavior therapy treatments for PTSD in Vietnam combat veterans.

And I guess more recently my work has focused on community samples. I'm one of the co-investigators for the National Vietnam Veterans Readjustment Study, and about ten years ago most of my work focused on nose counting, pretty much identifying how many cases of post traumatic stress disorder were in various at risk and exposed populations.

More recently my research has led toward, kind of the more prevention focus within epidemiology. I'm currently fortunate to be collaborating with Jane Costello, who is a psychiatric epidemiologist at Duke, and Adrian Angold with some of their work. I think the part that really excites me is that we're

doing some longitudinal work with young children and adolescents following up in various communities in North Carolina. It gives us the opportunity hopefully to identify factors that predict exposure in populations, and therefore, that might give us a window to look at ways of perhaps preventing exposure so that we don't have to continually be in the position of trying to develop interventions and tertiary preventions for people once they're exposed.

So in addition to the kind of primary/secondary prevention twist that I've been taking, I'm also quite interested in effectiveness research as well. I think that one of the things that we still lack in this country, and I just came back from a visit to Israel to look at some elements there, a mental health services delivery system. I think they're a little bit ahead of us in terms of thinking programmatically about ways of developing an integrated system of care for people who have been exposed to traumatic events.

And so I'm interested in prevention, but also moving from the efficacy models to treatment effectiveness models as well.

Thank you.

**DR. MARLOWE:** John.

**DR. MASON:** I'm John Mason, and I'm at the National Center for PTSD in New Haven, the West Haven Branch, currently, and I've been working primarily in recent years on hormonal alterations in PTSD.

My work has really been in two phases. The first phase was in essentially basic studies in animals and normal humans in response to stress, often military stress situations.

But I think I'd like to spend most of my time just talking primarily about the conceptual approach that's behind my work, which I think relates to the business at hand here more than any other single thing, and that is hormones. You know, I've been focusing on hormones for so long in relation to stress. What is the strategic reason that I got attracted to hormones in the first place?

And I think really to kind of capture that, at least in my own personal career setting, I think like Dr. Engel I started in a sort of circuitous way. When I left home, I thought I was going to be a surgeon probably just because of family pressures and so on, but after getting deeply involved in physiology as an undergraduate and the work of Cannon, Claude Bernard and others, being interested in the regulatory machinery of the body, the marvelous regulatory machinery that maintains this remarkable state of constancy that Bernard emphasized so much.

As soon as they began to be able to measure chemical changes or physiological functions in the body, what they always found was that there was this vacillation around a mean, that things didn't go too far in one direction before there was a regulatory correction.

And Bernard saw with a sense of marvel the exquisite nature of the regulatory machinery that could do this, and there are so many external conditions and internal conditions to maintain the constancy of these things.

As I started out as a surgeon, New York City at the New York Hospital, Cornell Medical Center, where I was at that time, I was struck by the fact that the first six patients I had with peptic ulcer had what occupation? Would anybody guess in New York City? Taxi drivers.

(Laughter.)

**DR. MASON:** Up to that point I was not particularly psychologically minded, but all of a sudden I said do I want to spend the rest of my life cutting out the stomach in these people or cutting the nerves to the stomach or do I want to find out what it is that gets them from being a taxi driver with the life situations and the Wolff model to the central nervous system response to that, to the somatic illness?

With my interest in Cannon, having implicated psychosocial stress as a cause of adrenal medullary hormonal change and Selye's work was just beginning in which he pointed out that, as he put it, merely nervous stimuli could cause adrenal cortical response, I began to get interested in the psychoendocrine system. What bothered me mostly about the Harold Wolff model or what appealed to me in relating the psychosomatic concept was that you had life situations, which was the social psychiatry part of the disciplinary team that was needed; emotions, which, you know, psychiatry, psychology, clinical psychology; but then he jumped from there to disease.

And as someone who's interested in the organization of the body, how it is organized, what's the regulatory machinery all about, what's its job in an overall way and homeostasis; the thing that was lacking was the mediating mechanisms for me. How do you go from emotions to somatic disease? What's the link between the joint, the wound healing, the immune change and so on, or the cardiovascular system and the brain?

And then when you look at the effector systems that bring whatever is going on outside, whatever is going on inside the brain has to somehow reach the body. How can it do that? And it really seemed only through the three effector systems: the skeletal-muscular system, which has to do with the behavior of speech and so on, adaptation that occurs that way; the autonomic system, which is somewhat limited in its distribution. I used to say just to exocrine glands and smooth muscle and cardiac muscle. I certainly have to add the immune mechanisms and probably others by now, but the link, the mediating mechanism that struck me the most was the neuroendocrine linkage because that provided a link between the brain and intrapsychic processes in every cell in the body no matter what it does.

And, therefore, any disease in the body, any tissue in the body could potentially be affected by psychological processes through the psychoendocrine system.

The other thing that attracted me very much to the psychoendocrine mechanisms and the organization of them was the fact that as I began to get interested in this and work with essentially biologists in terms of my own special abilities and capacities, I needed desperately the collaboration of sensitive clinicians and people who could measure the central nervous system processes that I was interested in hormones reflecting.

So the notion of hormone as a window up into the brain, the idea of hormones as reflecting psychological processes was really extremely important, if not the single most important strategic idea that attracted me to it.

And as I began to pursue this, one of the things I did at the beginning was to measure hormones in myself for several months just in relation to everyday stress and to get some idea of how big the hormonal changes were in a normal person. One of the things I discovered in the course of doing that was that as I tried to predict my own hormone levels after a while, when they were going to go up and when they would go down, I found I was almost totally unable to do that.

My wife on the other hand watching me could tell me --

(Laughter.)

**DR. MASON:** -- with about 90 percent accuracy. So in kind of a funny way I discovered and confirmed the concept of the unconscious.

(Laughter.)

**DR. MASON:** Which led me to Freud's work in a much more sympathetic and eager way.

But it's that sort of thing that has encouraged me to continue to use hormones in relation to stress primarily as adjuncts. I don't think there's anything more difficult in the world than to try to assess and study intrapsychic processes. I hoped the hormonal measurements would aid in that, and at the same time -- in other words, provide support to the people trying to struggle with intrapsychic mechanisms -- but at the same time give some idea of the pathogenic process that was involved.

And just a couple of other guiding principles that I think that came out of that work that have led to what we're doing in PTSD now. It became clear that hormones reflect, as we begin to study the psychological mechanisms and the stimuli that appear to change hormonal levels, not just by emotions in the Wolff model, life situations in the Wolff model, but actually the balance between the opposing intrapsychic forces of arousal mechanisms and anti-arousal mechanisms.

To this day one of my pleas is that we don't forget the anti-arousal mechanisms because in everyday life and people, that probably is the predominant thing to look at in the chronic framework. How do we make the chronic adaptation to a given life situation that persists for a while, and as we found that parents of leukemic children who use denial, for example, suppress hormone levels like cortisol way below the normal level and their own level acutely. When things get worse in the chronic course, instead of going up like people who have high levels chronically, cortisol levels go down still further.

Some of the parents at high levels went higher when things got worse. Some of them though had low levels and went lower when things got worse. So it enlarges the idea of the psychological mechanisms we need to consider in the battery of approaches in this field, I think, with emphasis on the coping and defensive mechanisms as well.

I won't try to develop this more, except to say that in the recent work that we've been doing in PTSD, a lot of these early principles have been extremely useful. We have found a pattern of hormonal disorders.

My other concern was that great focus was placed on stress on the adrenal cortical system and the adrenal medullary system, but the brain is linked with a tremendous number of endocrine systems which often get left out: the sex hormones, growth hormone, prolactin, a whole range of hormones, oxytocin and others and things we don't know about yet, all of which act together in concert to produce the end effect on the organ.

No hormone does anything by itself. Every hormone acts with other hormones antagonistically or synergistically. What you get at any tissue level, any cellular level in the body is the balance of the play between those opposing forces.

So in order to deal with that, we're going to have to do what? We have to measure profiles. We can't just for convenience or expediency of trying to keep things manageable look at just a single thing at a time and expect to explain much.

And so it's a matter of analysis first. Know the individual unit changes in the hormones, but eventually work towards the profile changes.

And so as we see in clinical application, the hormonal alterations in a small profile in PTSD, that profile is much more specific for that disorder than any hormone is for any given psychiatric disorder. We can distinguish PTSD from other psychiatric disorders hopefully much more precisely in detail by using the profile approach, and so that recently we've added things like T3 to the profile that have been left out in the past and may be one of the most useful current biological markers.

But I'll leave those details on the hormonal changes in case there's any interest in pursuing those further later.

**DR. MARLOWE:** Thank you, John.

One thought, in terms of things that have cropped up that I'd like you to file away for this afternoon and tomorrow morning, is we represent here a number of disciplines and a number of scientific domains. One of the questions I want you to ask yourselves in terms of asking others is in terms of your work, what would you like to know? What kind of work would you like to see done in others' domains? What are the sort of things that people in other disciplines could be doing that would illuminate and help understand the work you're doing?

If I have an implicit model in my head for what we're doing, it would probably be in the kinds of things that were published in the proceedings of the Josiah Macy conferences way back when, which really served as the basis for so much of the early attempts to integrate the behavioral in social and neurosciences.

So now we'll go to you, Ben.

**DR. NATELSON:** I'm Benjamin Natelson. I'm a neurologist at the New Jersey Medical School and the VA Medical Center in East Orange.

And I want to thank you, Dave, for inviting me here to tell you about two very different lines of research which have been drawn ineluctably together by dumb luck.

So why a neurologist? Well, the thing that drove my work and drives my work has been an interest in the question of stress and disease. What does stress do other than give us a dry mouth and a tachycardia? How important is that? What does it mean to the organism to be stressed?

And so in my early work, which was driven very much by the thing John has told you about, I looked at stress and the endocrine system to see how well these physiological markers correlated with behavioral activation or emotional arousal.

And then my work perforce moved into habituation and sensitization because I learned that despite the fact that an animal could be extremely aroused, its endocrine response would habituate. In some situations, though, I could stop that habituation and produce a sensitization. That led me and my colleagues into work with rats in which we thought we were able to make a chronic stress model where animals would be subjected to stress, allowed time to recover, and yet the physiological milieu would remain perturbed for days and even weeks.

In the course of doing this research, the sort of bottom line that drove it was to see whether these manipulations would, in fact, produce disease, and so I turned to the gut and most recently to the heart.

So why is a neurologist doing this? Well, back when I was deciding, back in the '60s when everyone specialized in medicine and I had to decide what it was I wanted to specialize in, psychiatry was attractive, but not attractive enough because of the heavy influence of analysis. All of my friends were spending their residencies doing this analysis stuff, which never really made a lot of sense to me in terms of the medicine.

And so I talked to Paul McHugh, who was a neurologist at that time, whom some of you may know, and Paul knew I was leaving where I trained in medicine and I wanted to do a post doc., indeed, was going to do it with him and Gerry Smith. He said, "Well, really you'll have to become a neurologist because as a neurologist you'll grapple with the most difficult organ, which is the organ of behavior, and of course, is the organ that allows environmental factors to get to the body."

So I continued then in these lines of research, and one reason why I like being here so much is that the culmination of that line of research had about five of you and me together less than a month ago at the Academy of Behavioral Medicine Research, where I organized a meeting on "Where's the Beef?" In other words, what really does stress do vis-a-vis organ disease?

And in a nutshell, my take on this, where we had different workshops, is that stress is probably not much of a causative factor, although there are some bits of data to suggest it. But, in an organism that is predisposed to disease, be it an organism with a wound, an organism with an infection a la Sheldon Cohen, an organism with heart disease a la the hamsters I studied with a genetic heart disease, stress is a very, very dangerous condition to occur.

So that line of research trained me over the years as a behavioral neuroscientist, as a physiologist with a knowledge base across a bunch of different organ systems, and as someone interested in disease.

So I was and continue to do that work, and on the side as a medical school faculty member I always had a small private practice, to try and get my kids to summer camp, et cetera. In 1989, that private practice got a sort of baton to the knees, where I was essentially told I couldn't do what I was doing anymore, and I'd better find something else to do. At that time a colleague of mine, who was a pediatric immunologist, had been taking care of patients with an illness called chronic fatigue syndrome. He just couldn't take care of those people anymore because he had discovered that pregnant women could go on and pass the HIV virus on to their children, and he was up to here with pediatric AIDS.

So essentially I met with him at this time where I had to change my practice, and he and I talked, and he said, "Well, okay. Here's my practice," and he gave me this practice of chronic fatigue syndrome, which I started in the fall of '89, some what, nine years ago?

In September I started seeing two new patients with chronic fatigue syndrome, and then I've seen two such patients a week since 1989. So I've seen some thousands of these patients, and by November of 1989, I said, "Hold it. This is a very interesting problem here, these people with unexplained illness, and I've got to start asking some questions about them, doing some little research, trying to find out." They're supposed to have something wrong with their immune system. Maybe I'll do some immune testing. They're supposed to have something wrong with their brains. Maybe I'll do a few MRIs. This was all sort of off-the-cuff, you know.

And so I'm doing this work and trying to get some sense of what it is wrong with these people because obviously these are the kind of patients that I tell my students are patients that fall between the cracks of ordinary medicine. No doctor really wants to take care of them. The specialty thing makes it so that these people are going from one expert to another.

Then there was a call for proposals to set up chronic fatigue syndrome cooperative research centers by NIAID, and I was fortunate enough with all of these pilot data that I'd been accumulating on three-by-five cards to get one of them. That allowed me to start building a team to look at unexplained illness, and then when the Gulf veteran came back and started complaining of things that in the newspaper sounded very much like chronic fatigue syndrome, and when the VA decided to set up a competition for centers to research this illness, I said, "Well, it looks to me like what we are doing in the civilians can be directly related to what's going on in the veterans." We were able to successfully compete to be one of Tim Gerrity's three environmental research hazard centers.

So, I'm doing this animal work on individual differences, things that identify an animal as "stress prone," that is, it doesn't habituate or does habituate, and then I'm doing this work on unexplained illness.

And what we've done in unexplained illness is essentially use stratification strategies to try to identify people who may have some kind of neurologic cause or some neurologic factor in their disease. Our work is now taking us to look also at some individuals that seem to have problems producing an adequate cardiac output.

Again, we're using various ways to try to stratify these individuals so we can see if there are differences. This is in a way saying, there is, indeed, a mind-body difference. but how can I with this background, which essentially is a background in behavioral medicine, take that background and knowledge base and use it to explain or at least try to understand unexplained illness?

And the goals, of course, are what are the risk factors for physiological sensitization? That's a critical question driving us. So whereas there's been a ton of health behavior epidemiology, what kind of research -- if I had a checkbook where I could write the check what would I be doing? Well, I'd probably be doing some physiological epidemiology to try to identify individuals a la the Trier model, where in Trier, Germany they've been able to go out and do some 2,000 repeated stress tests on individuals. They find some individuals whose glucocorticoid response don't habituate, whereas others do. What is the difference between those two groups of people?

My dear friend, Frank Sodetz, who's known to some of you here, likes to talk about these 20 percent or ten percent. It may be what happened in the Gulf or what happens in these calamities is that there's a group of individuals sort of at the tail of the distribution who somehow react to the tragedy or the event or the stressor in a way quite different from everyone else. So he's always encouraging me to study the tail of the distribution. You know, take 100 rats. Phase shift them, and look at the ones that don't recover from jet lag, that sort of question. So physiological epidemiology would be something I'd like to do.

How do we get at this issue of are these individuals indeed different in some physiological way? Yes, they may be amplifying their somatic symptoms, but are they actually feeling inputs differently? Is their reactivity to a fixed stressor the same or different? These sort of physiological questions are driving the work.

What I've laid out for you has been a set of experiments in animals that have looked at stress reactivity, the role of stress in disease, and issues in behavioral medicine which can be carried over to try to understand and try to strategize to understand unexplained illness, again, to identify the risk factors that will produce individuals who have unexplained illness in the next conflict.

**DR. MARLOWE:** A couple of points that I would like people to think about for this afternoon.

One is what Ben has brought up, the entire issue again of vulnerability and predisposition. Within this, how would one do an epidemiological study of physiological vulnerability?

Perhaps of equal importance, one of the things that we really don't have much, if any, data on is the relationship between psychological vulnerability in humans as it appears on standard instruments like the SCL 90 and the BSI and the CPI and all of the rest of these and physiological or possible physiological vulnerability. Are the two correlated? Is there a relationship? In this sense are the body and the brain interacting to produce patterns that may have a relationship?

Now we'll go on to you, Paula.

**DR. SCHNURR:** Well, that's somewhat of a nice segue into some of my work because I have looked at risk factors. I think that's the ticket that got me here in the first place, but looking at psychological vulnerability –

I am from the VA National Center for PTSD, which is a consortium that does and encourages research in education on PTSD. So I think, like Tim, I tend to mostly help other people do research rather than do my own. That's what I get paid for.

My real job, of course, is my research. By training I'm an experimental psychologist, very quantitatively oriented, and I've been always interested in longitudinal problems.

I first started working at graduate school a lot on the subject of PMS. That's how I met Dr. Ader a few years ago at an NIMH conference. But more recently I've been looking at PTSD, which is a fabulous disorder for doing a longitudinal study if you can get the data because it can last a lifetime.

I did a study with Matt Friedman and Stan Rosenberg on a group of Dartmouth graduates who were given the MMPI when they were in college before they went to Vietnam. It was a wonderful opportunity to look at personality as a risk factor for PTSD. In fact, it was.

It looked to me -- this is all kind of interpretive because we didn't have a direct measure of neuroticism -- but it looked like more than anything that neuroticism was a very important predictor, and I should say that there are hardly any studies that have looked at traumatized populations before they were traumatized and tried to understand their pre-traumatic state. There's a lot of data after the fact that, you know, corroborate this, but I was really lucky to do that.

In 1989 when I came to the VA, I was casting about for a research program to start, and I stumbled upon the VA's normative aging study, and since that point in time I've worked with Ron Spiro and Carolyn Aldwin and other people in looking at older veterans.

Now, recently I've gotten less interested in the issue of who develops PTSD and more in the issue of who keeps it. In fact, last week I submitted a grant with John Fairbank and some other people trying to help us understand the development of PTSD.

To some extent, you know, it's understandable that some portion of people- even though most people don't- some portion do develop PTSD, but most people don't keep it. I think we haven't paid any attention to this issue of what predicts remission, this kind of delayed resilience, if you will.

Another thing, I've been lucky in my whole career. I fell into research on studying the physical health consequences of trauma and PTSD. Jessica Wolfe showed me a data set one day in which she was showing that trauma was related to physical health in Vietnam nurses, and I said, "Well, that's great, but what about the PTSD?"

And so lately my real interest has been in PTSD as a major mediator of the relationship between trauma and physical health outcomes, and I'd like to see us really talk about that issue because I think some of us here are PTSD researchers, but PTSD really is a different animal.

John and Rachel Yehuda have shown us that it's biologically different. I'm wondering if the body is set to handle stress reasonably well, but perhaps not traumatic stress, and that's a question I'd like to put on the table for people because PTSD really is different. Most people don't get it. The people who get it, a lot of them don't keep it. So is there something really qualitatively different?

I should say that in my research on PTSD and health, we are finding relationships to self-report and physician diagnosis. I've been interested in behavioral factors as mediators, and I have to say that I'm failing in this regard to find things such as smoking and substance abuse being important mediators, even though they should be because behavioral factors are important in health. I'm not finding a lot of action, especially in terms of smoking.

What else? A lot of people have made the points that I wanted to make. Oh, I think I'd like to encourage us to think in a multivariate sense. I'm very interested in Bruce McEwen's concept of allostasis, and I think it really takes us beyond. Essentially he's saying that the whole is more than the sum of its parts. So all of these subtle things that we might be studying, given our respective interests, when they combine may produce this allostatic load, this great strain on a system that ultimately may be the important breaking point for the organism.

Longitudinal research is really critical, and I like the question about looking at psychological and physiological risk factors. I think the military is the best place to do this, quite honestly. I don't know about the rest of you, but I think I've had great opportunities to work with Nancy Bakalar and Chuck Engel and some other people, and I encourage the military to really think about adding on projects that especially could get at the physiological component.

Let's see. I think I really have made my point. I'll end again with the issue of this stress continuum and the possibility for discontinuity on that continuum with traumatic stress being really, really different. If I could say anything to encourage other people around the table, I'd really like to encourage people in this room who haven't -- like I'm looking at the Glasers. I'm a big fan of your work -- to consider looking at people who have experienced traumatic stress and whether there are very qualitative or quantitative differences in terms of their immune responses.

So I think I'll end at that point and turn things over.

**DR. ADER:** I'm Bob Ader. I'm at the University of Rochester in Rochester, New York. I'm Director of a Center for Psychoneuroimmunology Research.

I've been involved in psychosomatic research in general for some years, and initially I was working as a development psychobiologist. I was working with the effects of early life experiences in influencing normal psychophysiological development and susceptibility to mostly experimentally induced pathophysiological states, and that was one career.

Another career began in the mid-'70s when we demonstrated that one could use Pavlovian conditioning, classical conditioning, to modulate the mean responses, and essentially we had a tiger by the tail and couldn't let go. So our research has since then been confined, if you can call it confined, to studying the nature of the relationships among behavior and neural and endocrine function and immune processes.

The notion, to that date, of course, was that the immune system was autonomous, and myself and some other wise guys, perhaps, were questioning this assumption, and to cut a long story short, I think that war is over. I think that it is no longer possible to study immunoregulatory functions without considering the nature of the neuroendocrine system. We moved from studies of conditioned immunosuppression in which immunosuppressive drugs were compared with neutral stimuli, and the neutral stimuli were subsequently capable of suppressing humoral and cell mediated immune responses.

Since then we've moved to studying immunoenhancement, which is not really the other side of the coin because the mechanisms are totally different for enhancing immune responses rather than suppressing them. A major distinction is that antigen is by definition the most salient stimulus for activating the immune system, and now we were conditioning immune responses per se and not immunopharmacologic responses as we were previously.

In any case, that's a very difficult process, and I don't think we have a particularly powerful paradigm for doing it, but issues that came up obviously in response or as attacks on this entire approach without the effects of conditioning were very small. I don't really know what that means, but it was very small and could not be of any clinical significance.

And so we moved to studying this in animals that spontaneously develop autoimmune disease and found that, indeed, one could use conditioning to promote the survival of these animals using less immunosuppressive drug than what one might normally. This issue of biologic significance is one that I'll return to in a minute, but it essentially underlies much of what the field in general faces. In addition, as our group grew, we got involved in other aspects of this, including the effects of stress, and you know, it's very easy if you're at the beginning of this line to talk about stress. By the time you've gotten halfway around the room, there isn't very much left to say that people haven't already said, and most of which you agree with completely.

I use stress in this context, polite conversation. I hardly ever use it in print because I really don't know what it means. I think the strategy in approaching this -- I mean, I won't get involved in why I don't use it. I think Selye caused as much damage as he did good in terms of directing, providing a focus for research directions, a concentration on the adrenocortical system, a concentration on the adrenocortical system which is displaced.

I think that John Mason's early work, which is a model of looking at endocrine profiles, turns out to be easily extended to the immune system where you have the exact same situation. The complexities are beyond belief, and now we have to put the patterning of immune responses together with the patterning of autonomic and endocrine responses, which, you know, multiplies this factorially, but who said it was simple? I mean, we never do research looking for main effects in a world that's made up of interactions. So we look for the interactions. They're far more interesting. It's a little harder to get research money, grant money for interactions, but that's where the action really is.

Some of our work on stress, for example, involves not physically provoking animals, but doing it psychologically. So we will expose mice not to physical stressors, if you will, but to pheromones elicited by animals that are, quote, stressed, and this is quite sufficient in and of itself to produce major immunologic changes.

It's also sufficient by itself to produce classic stress-induced analgesia, which in this case is opioid-mediated so that it's easy to move off into so-called mechanistic studies involving stress effects.

As an example of our concerns and our research strategies and a certain amount of obstinacy, I suppose, we have in the last several years scientific articles, magazine articles, what have you, declaring that you need not be concerned about the psychosocial influences on the development of ulcers because the cause of ulcers has been identified as *Helicobacter pylori*. We now know the cause of ulcers.

This is utter nonsense in terms of what is necessary and sufficient, and so we've gone back to models that I've used before in which we can induce gastric lesions in animals. We look at this in animals that we've learned how to infect with *H. pylori*, and so far the preliminary data suggest exactly what you'd predict, which is that *H. pylori* by itself is not sufficient to elicit erosions. Physical restraint, if one titrates that, is not sufficient, and the combination produces more than either one of them alone. We will then follow up with studies involving cytokines, other inflammatory agents with respect to the immune involvement in these.

But the bottom line, I think, and what needs to be done -- and I'm not sure it can be done, but I think we understand the strategies -- is to inquire about what is the biologic significance of stress, if you will, or any of these behaviorally induced changes in immune function, which appear to be small. Of course, quite frankly, I don't understand how one might expect any of these changes to be large, whether they're endocrine changes or immune changes, because I can't imagine a defense system like the immune system that could be perturbed to the extent that would produce a response that exceeded homeostatic limits and in and of itself produced disease. That would be not much of a defense system if all it would take would be a little fear and your immune system is thrown completely out of kilter.

However, a perturbation in the immune system in combination with what has been suggested before, a biologic vulnerability or any number of other interacting factors, and that biological vulnerability could be a susceptibility to disease. It could be age. It could be size. It could be any number of things. Those interactions are what I think are worth study, but basically I agree with Ron Glaser's position. I think that the real clinical implications of now understanding immunoregulatory processes as part of an integrated defensive system involving the brain and the endocrine system, we won't really know about this for several years, and the reason we won't is because we don't understand the nature of that relationship to begin with. When we do, I think the clinical implications will go far beyond anything that we have envisioned thus far. I think that it may even go so far, since I'm in friendly company presumably, it may go so far as to redefine certain diseases in the sense that if we have behavioral disorders, we look in the nervous system. Well, you don't know that the proximal cause of that deviation may not have been early infection of the brain.

We thought of diabetes as an endocrine disorder. We now know of it as an autoimmune dysfunction. That changes your approach to treatment, as well as understanding the nature of the pathophysiology to begin with.

So I think the potential of this field is absolutely phenomenal. I think that we're being asked questions which reflect a certain pejorative tone with the expectation coming from the strict biomedical model that if you can't explain it mechanistically, don't tell me about it. I think that's what we all face to a certain extent with respect to any particular aspect of stress phenomenon.

As far as communicating this to agencies that hand out money or communicating it to the public, we have a real problem because communicating this to agencies is to attempt to approach a system that is disease or organ related and not related to the nature of interactions among systems, but it's the interactions among systems that's clearly at least as important, maybe more important, than the interactions within systems.

As far as getting this out to the public, it's already out to the public. Unfortunately, we're not the ones that are getting it there. The people who are getting it there have a different agenda and a different definition, and they're making life more difficult for us, not less difficult for us.

I guess I will stop there.

**DR. MARLOWE:** I think there are a number of important points in Dr. Ader's discourse that we might attend to, one of which is, indeed, the basic question: has the concept of stress as it's been used outlived its utility? Does it have any scientific utility? Are we in need of a real system of redefinition?

The other, I think, comes to part of the thinking that went into the creation of this meeting, and that is the question of the interaction between systems, the, if you will, interfaces involved in the transduction of external events by the brain into internal events, and please let's keep those in mind.

At this point, Fred, I think we'll move on to you.

**DR. HEGGE:** Okay. I'm Fred Hegge, by degree, an experimental psychologist; by training and experience, a physiological behaviorist; by avocation, a scientific tool maker. I've spent most of my career building instruments and methodologies that permit folks to make measurements on freely moving soldiers in hopes of understanding things like sleep in the field, the consequences of stress and fatigue, jet lag, and assorted things over the years.

On 1 October of last year, I woke up to the understanding that for the first time since 1972 I had no administrative responsibilities, having just left the position as the Director of Army Operational Medicine Research in the Medical Research and Materiel Command and returned to WRAIR, which had been the mother ship since 1972 for me. In the last nine months I have been a senior scientist attached to the headquarters rather than to any particular division, and I'll return to that in a minute.

But what I would like to say about the topic of this meeting is that it was on my watch that Gulf War illness became a problem for operational medicine research. It became clear as we watched what was happening that Gulf War illness provided a central organizing principle for operational medicine which for years had been sort of known as RAD, Research Area Directorate, et cetera, in the sense that it involved all the stresses, environmental and situational stressors, that soldiers were exposed to and was a grab bag.

When the Gulf War illness came along, it had several characteristics. One was that the war was short and was not accompanied by high casualty rates, physical casual rates, few KIAs, killed in action, few wounded in action, and perhaps for the first time because of the absence of those who had been maimed and killed, prominence could be given to people who in previous wars were relegated to the back pages of medical journals, the people who are the topic of our concern.

If the mind-body problem provides us with a political and social embarrassment, perhaps what provides us with a professional embarrassment has been the stovepiping of somatic, cognitive, and emotional concerns. Clearly, the topic of this meeting is to break down that stovepipe and begin to put things together in a coherent, to be hoped, and consistent way. Karl will talk this afternoon. He's going to describe what we're doing and should because he is bearing the brunt of that in the command at the moment -- but when we looked at this issue, it became clear that we were going to have to move by indirection, that we could not make a frontal assault on the psychosomatics of the issue, and that's where Dave and Ann came in, and they have behaved admirably in the organization of this conference.

In one sense, this is an end of an attempt to move a program in a direction, but it, I think, in a very real sense is a beginning. It is perhaps the beginning of the solution not only of the Gulf War illness, but, as we've heard around the table, a great many other things as well.

What I'm doing now these days, which may have some relationship to the topic of this meeting, is I have moved full time into the arena of computational intelligence and knowledge engineering, and I've done that as a consequence of my continuing concern for how we capture and utilize our scientific and medical knowledge in ways that take advantage of technological advances and do it smartly so that it becomes more difficult to lose knowledge in the back pages of journals that have to be rediscovered later.

So I am working mainly in the area of breast cancer research, looking at the development of some program evaluation tools that are coming on line, and with a little bit of luck, I will start a knowledge capture in the fall, a knowledge harvest as our current jargon is, in the area of operational medicine, trying to pull together into a knowledge base of reusable knowledge modules, in operational medicine and in stress research.

So that the work that you folks do is going to be grist for that mill, and I may well reach out to you at some point over the next year for help, and I hope you'll give it to me.

**DR. MARLOWE:** Before I go on to Harry, just one point. We have assembled a rather large database covering most of the domains and disciplines here. I would like to say to all of the participants that at some point we will be very pleased -- this has been electronically filed -- to send you each a CD with the database on it.

**DR. HOLLOWAY:** I'm Harry Holloway. I'm a professor of psychiatry at the Uniformed Services University and also a professor of neurosciences there. My long term career has been an interest in extreme environments, and particularly on how groups influence expressions of illness and health behaviors. Most of my career has been devoted to participating in research that has been either epidemiologic or in aiding in the creation of laboratory environments in which research can be pursued. So I've just been a big office boy in science.

I'm going to comment on the other thing I do, by the way. Since I entered medicine- actually as a student of Stuart Wolff and Jolly West and eventually to work with Dave Rioch - fundamentally to pursue that as a research career, it was striking to me that right from the beginning, I loved to take care of patients. So I have a clinic, and I do a fair amount of clinical practice, and I thought I'd start off with that as a perspective, and that is: what are the real consequences of some of the ideas we're hearing about here as they're incorporated?

I'm taking care of a patient right now, and it's a public event because it's a court event, who on the basis of, number one, her firm belief in God, belief in certain religious principles, and with some encouragement from her medical practitioners who had read the information on the impact of stress and stress management, upon expressions of biological processes, elected after consultation with her eight year old son to stop his insulin for his diabetes. He died in two days. She was charged with murder, has been convicted, and I'm part of her sentence.

So if we think these ideas do not have real consequences, let me assure you they do, and that they will be interpreted and utilized in ways that we may not always be able to control or see.

What I am struck by, I guess, very much reflected in Ron's comments earlier, how little we really know in many, many of these areas. I'm also struck by the fact that in the long run we talk about doing science based on what we know now, and as an agnostic I find myself very uncomfortable by that.

I'm not sure whether PTSD is one or many conditions. I know that there are, by my last count, 17 conditions in DSM-IV that are a result of extreme environmental events one way or another. Our current ways of arriving at our classification without clear understandings of causation and fundamental biology, without understanding of the cell or neurobiology, and without understanding about the basic transduction system of environmental signals to them may be nothing more or less than a well intentioned, thoughtful classification system just as that one that we heard about from the Civil War. After all, if we look back then

and we look at people like Jonathan Letterman or Hammond or the other doctors back then, they didn't lack for smarts. What they lacked was fundamental knowledge, and, therefore, the lack of any understanding of infectious disease is, of course, totally absent from their care.

There's no reason, I think, to suggest that we might not have equally large gaps in our knowledge. So to progress beyond phenomenology, it seems to me, we must have better basic science information that allows us to do classification and other disease determinations in this area to answer some of the problems which I think quite cogently have been raised by Dr. Guze.

Beyond that I would suggest that some of the things that were said here are vague wishes. Does DOD support research in this area? And the answer, in my opinion, is absolutely not. If you go to the line and you ask them for time from these troops that are being deployed more, that are being reduced in numbers, the answer is if you're going to take their time to do research, forget it. We are simply in terms of the number of deployments unable to sustain or support that.

Is there an answer to that in terms of prolonged studies? I think that the only answer probably has to do with developing new research techniques that reach out for studies in that area, which may include instrumentation, using nanotechnology and other technologies that are being developed.

I had some responsibilities for developing those programs, while I was the Associate Administrator at NASA, that can monitor physiological changes in the field and under conditions that allow those sorts of studies. I think that it also means that a great deal of the work will have to be carried out at a more fundamental level in the laboratory and in those settings.

The docs in the services may very well support this stuff, but the demands being put upon the line are huge and very demanding, and we simply have to find a new way to do the work if it is to be both prolonged to deal with the chronic models and to develop answers.

Furthermore, our answers -- and this is where I think the past history of stress research does influence us, and I hope we don't get into a discussion of whether there is stress or not stress and the rest of that because I don't think that it's a profitable discussion -- but whether the overall effects of environmental events, including toxicologic events, are important, is a considerable doubt in the mind of the people who support whether or not we'll come up with conceptual models that will lead to any real consequences beyond the conceptual.

Their reason for supporting this, after all, is entirely conceptual. It's partly driven by the overall practical considerations. The overall need to develop better conceptual models that sharpen our capacity to characterize multiple interacting stressors so that we can discuss multi-causality and not be stuck with the kind of univariate analysis which has characterized the past, I think, is another major research area in which we have gaps and tools, and that I hope people at this conference will address.

Having seen your literature I think that the number of people here, I want to express my admiration for you people because I think you have clarified a number of issues and in some ways cleared away some of the ghosts that have haunted us over time in the past. It seems to me that really we have been brought to a threshold, and that recognizing the real size of the challenge is part of recognizing the opportunity.

**DR. MARLOWE:** Bob.

**DR. URSANO:** I'm Bob Ursano, and I'm professor of psychiatry at the Uniformed Services University and also chair of the Department of Psychiatry.

I'll be relatively brief because I am most interested in other people's comments, but it seems to me we've spent a little bit of time talking about, perhaps, philosophic direction and then what we actually do.

Both the direction and the work that I've been involved with now for perhaps 20 years has been looking at individual and community responses to trauma and disaster. As with most of us, I have an aversion to the word "stress." I have grown to appreciate the word "event related changes" in biology and behavior. It seems to me it allows for a broader context to understand both the context in which things occur, as well as to leave open the classification of the type of events.

Along with that, we have often chosen to speak of the work that we have done in what has now become a sizable group, including many of the people here, to look at the social propagation of distress, (perhaps somewhat whimsically SPDs, named similar to STDs), which have a particular meaning in our community.

Trying to understand both how distress gets transmitted between people, as well as how it's translated into biological events really has formed an important part of my character structure. Perhaps the best way to say that, beginning with what, heaven forbid, was psychoanalytic training and remains as a core part of my being, but has been translated into empirical work which allows me to get away from much of the jargon that weighs down that tradition.

My original work was with the prisoners of war in the late 1970s at the School of Aerospace Medicine. I had a career in the Air Force. I can assure you both back then and now, that the idea that mind and body are together is widely attributed to be a delusion of people like us. And that the actual model that is extant in the world, and certainly within DOD and certainly within our medical community itself, is that of what I call the P-3 theory, which is piss poor protoplasm.

(Laughter.)

**DR. URSANO:** In people that actually get ill have had something wrong with them all the time, P-3, and there's no question about that. They're just bad people. Our original work on POWs was really to try and address that piss poor protoplasm perspective and to indicate within our own DOD community, as well as others, that perhaps there are other ways of thinking about it.

One of the outcomes of that POW work was to become involved with Margaret Singer, who became a good friend and colleague now for many years, and she shared with us the term "resiliency," which has become a focus of a lot of our thinking, to think not about who gets ill, but why is it that more people don't get ill. It is the study of resiliency that, perhaps, we forget while we look more at the onset of disease processes.

In the late 1970s, Harry, when he was chair of the department, invited me to come up to the university, and really through Harry and Dave's efforts, we have been able to put together a team looking at traumatic stress now over a long period of time. There's been a substantial focus on the issue particularly of disaster workers in multiple types of events: plane crashes, hurricanes, medical care personnel, certainly combat veterans and those exposed to combat. We conceive of war as a particular type of disaster which has particular types of characteristics and, therefore, a subcategory of our work, as well as more recently looking at motor vehicle accident victims.

I would share with you a couple of perspectives in addition to that of resiliency, which I think fits nicely with the questions of immune function. The questions of anti-arousal that John was speaking of earlier, and perhaps also the most important, I think, often forgotten constructive role of denial and how it has gotten a very bad name.

In addition, one of the drums we have beaten from our own work and, perhaps, to deal with some of the political issues has been to think of PTSD as the common cold rather than as cancer. It may be the most widely spread psychiatric illness that we have all experienced at some time in our lives, and the issue is not whether or not you've had it, but the issue is the few people that don't recover from it.

The incidence of traumatic events is extremely high over a lifetime. Most people will be able to report to you a period of time in which they experienced the symptoms related to PTSD. The issues are how the body metabolizes those symptoms and digests them over time to recovery, and what may interfere with that metabolism for those people where PTSD becomes a cancer rather than the common cold.

Lastly, in this perspective, another piece of our work is that specifically looking at exposure to death and the dead, a perspective that was encouraged by both Harry and Dave. It has turned out to be very important. It relates to many aspects of trauma and disaster, and we've become particularly interested in the cognitive function of identification. Those people who have been working with the death and the dead have thoughts about "it could have been me," and the way by which that cognitive process itself may propagate the distress both biologically as well as socially to those around them.

In my hat as chair of the department, and again with the help of many people around this table, we've brought together a number of perspectives on somatization and somatic symptoms. Chuck and also Deb, as well, in fact, are very much into that perspective.

Certainly the issues of substance abuse. Harry had mentioned that he's working on the history of substance abuse during the Vietnam Era. We've recently set up a laboratory with Bob Post examining issues of kindling and some of the issues of apoptosis, programmed cell death and how it may relate to stressful exposures, and certainly with Etzel the issues of dissociation, which I'm sure he'll refer to, and lastly a large grant in which Ann is very much involved with family violence that's given us an opportunity to take a broad perspective on some of the issues of trauma and disaster in its many forms in our community within DOD as well as in the broader nation.

**DR. BLACK:** My name is Paul Black, and I'm from Boston University School of Medicine in Boston. I have been chairman of the Department of Microbiology and Director of the Cancer Center there for many years.

About a year and a half ago I resigned the chairmanship of the Microbiology Department after 14 and a half years, thank God.

(Laughter.)

**DR. BLACK:** So my responsibilities are a little less consuming now, and I can think more about this field and how it's evolving.

My background is in virology, cell biology, and cancer. When I was Director of the Cancer Center, I came upon -- this was '79 -- I came upon Bob Davis' book which was first published in '80, and I got very interested in this field of psychoneuroimmunology.

I was Chairman of a conference in 1981 and invited Bob Ader to spend a day with us, and he was very humble then, and he wondered how understanding everybody would be --

(Laughter.)

**DR. BLACK:** -- and would they be tolerant of this new discipline. He's not that humble now.

(Laughter.)

**DR. BLACK:** The field has developed so, but anyway, he was very humble then, and we had a wonderful day, and I thought it was nice to bring to the traditional medical establishment this cognizance of this new field, psychoneuroimmunology.

Because I was Chairman of Microbiology and Immunology, the immunology was just booming. These were the great years of immunology, and I thought the immunology would tighten up a lot of the psychiatric research and one would have better indices to measure stress -- pardon the expression -- and other things --

(Laughter.)

**DR. BLACK:** -- that occurred.

So we started to work on psychoneuroimmunology, and I've always been interested in the brain and the immune system, how they interact. As an intern at the Massachusetts General Hospital, I saw a patient who had bilateral rheumatoid arthritis and had a stroke, and the rheumatoid arthritis on the side of the stroke remitted. The joints were not inflamed.

Another instance, if you give somebody or if one develops rheumatoid arthritis and one has a stroke on one side, you don't get the arthritis on that side. So you actually need the nerve to get the arthritis.

Later it's been shown that if you give adjuvant arthritis to mice in two paws and you cut the nerve to one paw, there's no arthritis that develops in that limb. There is in the other limb. So you actually need the nerve to develop the inflammation in rheumatoid arthritis. Those things fascinated me. Also, if you've had polio and a limb is paralyzed and you get rheumatoid arthritis, you don't get it in the paralyzed limb.

So we started studying this with a mouse stress model. I don't want to get into a lot of detail. We put the mice in cold water. It was a cold water swim stress. We didn't let them swim too much because that would add another dimension, exercise, to the already psychic phenomenon, and the cold which appeared as pain to the mice. But we investigated this model, and we were particularly interested in macrophages since they're a key immune regulator in the immune system. We put thioglycollate to elicit macrophages on the peritoneal cavity. In the stressed mice after four days of cold water stress, we examined these macrophages, and to make an awfully long story short, they were activated, and they put out cytokines IL1, TNF, and IL6 - the pro inflammatory cytokines that are necessary for infection - and these cytokines could be secreted normally, but one could induce them many, many fold higher with endotoxin. So we found that the macrophages were activated, that they threw out cytokines that could be induced to make more cytokines. Cytokines are important in the immune system, and they're necessary for inflammation.

We wondered why they were activated, and to make a long story short, we were very interested in the role of substance P. Substance P is an 11 amino acid peptide. It's present in sensory afferent nerves. It's fascinating that this same molecule mediates neuroinflammation and pain. We found that substance P was elaborated into the peritoneal cavity, and again, to make a long story short, we thought the macrophages were primed with substance P so that when you later gave them a secondary or triggering dose, they put out large

amounts of cytokines. And we went on with that research. We proved it was substance P because if we gave antagonists, we wouldn't get the elaboration of cytokines, and if we capsaicinized the animals, which means you destroy the sensory nerve endings, you wouldn't get the elaboration of cytokines.

So that was the basis of our work, but since then many people have found that stress induces cytokines. Parachute jumpers have high cytokine levels. Certain bereaved people have high cytokine levels. People who are stressed, and animals, let's take animals with restraint stress, have high cytokine levels. It doesn't matter whether the stress is physical or mental, emotional, psychological, they have high cytokines.

So I think we can say with a certain degree of certainty that stress can induce cytokines on a systemic level, and cytokines are important mediators of information, as I said, and I think they're very important in the inflammatory response.

The other thing cytokines do is they go to the liver, and they induce the acute phase reactants in the liver. These are a series of substances like fibrinogen, C reactor protein, serum amyloid A, and they're induced in the liver and spill over in the blood stream with stress. There are many animal experiments that show that stress induces the acute phase reactions. It's almost certain that if these experiments had measured cytokines they would have found that cytokines are induced, and these induce the acute phase reactant.

Two things that are important. One is the very inflammatory mediators of stress, adrenalin, epinephrine, norepinephrine, and corticosteroids. They aid and abet this process of cytokine development and acute phase reaction development. In other words, epinephrine augments cytokine production from macrophages, and the corticosteroids, which are, quote, anti-inflammatory, augment the production of acute phase reactants from the liver. So corticosteroids are not universally immunosuppressant. This is sort of a misconception. It's a very complicated subject. They certainly aid and abet certain immune reactions.

So with these two things in mind, that stress can induce cytokines which induce acute phase reactants, one can say that stress may be an important factor in inflammation and inflammatory reaction, and we're in the process of studying this.

We're very interested in the reports where these cytokines and acute phase reactants are appearing now in men that are prospectively being studied for coronary artery disease and myocardial infarction. In certain studies in the early phases of these studies, 20 years and ten years before these men have their heart attacks, they're finding certain cytokines in their blood. More important, they're finding the acute phase reactants from the liver, the C reactive protein, serum amyloid A, and these are agents that will try to help clot, both clot and anti-clot. They help the body to fight infection. And now there are several studies showing fibrinogen is increased and is a risk factor for cardiac disease.

So, in short, inflammatory mediators are appearing in people that may go on to get certain diseases. It may very well be that these may be a product of chronic stress over the years which activates these things, which are going on to produce atherosclerosis and hypertension.

That's all I really want to say now, and just to say that far from being discouraged, I'm very optimistic about this field. No more can we say "How does stress make for these diseases?" We now have certain cytokines that we know can make disease because we know what they do normally. Cytokines IL1, TNF, and IL6 make for sickness behavior. These make for fever. They go to the hypothalamus, and they induce prostaglandins, which make for sickness behavior to rest the host as the host fights infection.

So we know that. We know about psychogenic fever or something that I read that David Marlowe sent me. Osler had noticed that there could be a psychic fever, and he called it hysterical fever. Again, this same thing, and fever is induced by cytokines.

So it's a very fascinating field, and the thing now we have to do is work out the relationships with hormones. The other thing fascinating about stress is we induce both kinds of hormones: hormones that immunosuppress, like corticosteroids and certain catecholamines, and other hormones that immunoenhance, like prolactin and growth hormone. All are products of the pituitary, all are under hypothalamic control, and whether the prolactin and growth hormone enhances or tries to raise up the immunosuppression of the immunosuppressive hormones, we don't know, but there's plenty to study.

And far from being dejected about definitions of stress or that we don't know enough or this or that, I'm very optimistic about the future. I think we now have in our hands certain molecules induced by stress that make people sick or feel sick.

**DR. MARLOWE:** Thank you.

I think that's very challenging, and again, let's consider some of the implications for this afternoon.

Bonnie.

**DR. GREEN:** I'm Bonnie Green. I'm professor of psychiatry at Georgetown University.

I've been studying disasters and trauma since 1974, I guess, and then a lot of my work kind of naturally moved in the direction of looking at post traumatic stress disorder associated with a lot of different kinds of events. I've been really interested in clinical psychosocial outcomes associated with extreme exposure to trauma and have studied disaster survivors and Vietnam veterans and even some work with people who are exposed to radioactive contamination where the stressor there is pretty much information or a kind of psychological stressor. I've also worked on evaluating treatment outcomes associated with a number of these different types of events.

I started out at the University of Cincinnati, and that's where I did a lot of my initial disaster work and long term follow-up of survivors. Since I've moved to Georgetown, I've focused more on individual rather than community oriented events.

The first study we did after I got to Georgetown was looking at women with breast cancer. At that point there were discussions in the DSM-4 about whether a life threatening illness would produce PTSD, and so we were interested. I've always really been interested in the nature of the stressor and how that might be related to people's responses. I've actually spent a fair amount of time trying to sort out objective from subjective stressors. I think quite a few studies in the disaster area, in particular, have been fairly successful in sorting out what's objective, external types of events or whatever, and then the subjective reactions to those, and both of them do seem to be important.

We actually found low rates of PTSD in cancer survivors, and it's interesting. A lot of people are getting interested in that area of life threatening illness. We've wondered whether it wasn't different in the sense of it being, again, kind of an information stressor because when most women find out they have breast cancer, they're not really ill. So they're dealing more with a kind of cognitive stressor.

Another thing that I've been interested in and that we've been working on since I got to Georgetown is trying to sort out some of the more individual links between types of traumas and types of outcomes. Every group that's been studied has had very multiple kinds of -- and, again, I've really stayed in the clinical psychosocial realm in my own work -- but a huge range of types of outcomes probably because so many people have multiple histories of trauma.

A lot of the research in trauma to date has taken target groups of people who have had a particular type of exposure and compared them to people who haven't had that exposure without investigating the history of exposure among both groups and trying to sort that out, if you will.

So we've just been doing a study where we've been screening large groups of people and finding subgroups that have had only singular types of exposure and finding differences, for example, between people who have only had in their histories non-interpersonal trauma events and more interpersonal events and then multiple kinds of exposure and finding differences among those groups, and that's just our screening data. So we're looking forward to the interview data that really have a breadth of psychological and physical kinds of health outcomes.

My most recent work is with colleagues in the area of mental health services research going, I guess, as far as you can from the laboratory into primary care settings and screening people for psychiatric symptoms and needs for treatment. We focused our work on poor women.

In particular, our department just received an infrastructure support program grant from NIMH to develop our department in the area of mental health needs and services for women in public medical care. We already had a study going of which Jeanne Miranda is the principal investigator, where we're screening women in federally funded family planning clinics in Prince George's County for depression, PTSD, trauma history, and a range of problems. We are actually finding very high rates of trauma exposure, high rates of current depression, high rates of current PTSD, and of course those overlap to some extent. We then offer cognitive behavioral treatments and medication treatments in the primary care setting.

These are women who have very little access to any medical care. They're going there for birth control pills, but about 30 percent of them meet criteria for current major depression. So obviously there's a need there. No one is being seen in a mental health setting.

Some of the services research now is moving in the direction of looking at trauma history as a predictor of service utilization, and it will be interesting to take some of this thinking into a setting where people don't have access to health care. So their health care utilization is not going to be able to be a good measure of their physical symptom complaints and concerns because they don't have access to medical care. Only a small portion of these women have Medicaid, and a small proportion have private insurance. But most of the women are not quite poor enough to get Medicaid, and don't have enough money to afford insurance or to get it through their job.

So, basically, they go for birth control pills and kind of manage from there. It's been a really interesting group to work with. It also feels like a good application. It does seem important to me as the services research is getting more interested in trauma history, is what might be the link between a history of trauma or, multiple histories of exposure to not just traumatic life events, but also adversity - general adversity. Exposure to things that we might not conceptualize as traumatic, but things that add to the overall burden of things that people have to deal with and work through and respond to and so forth. What's the link between the exposure and the physical health complaints and the service utilization on the other end?

People here have been talking about what those links are, and I'm trying to learn more about that so I can make some kind of a contribution.

Looking at the group, one of the things that's been interesting is that the people that have come together to do this research are coming out of the areas of depression -- that's Jeanne's area -- and PTSD -- that's Jan Krupnick and my area -- and we are screening people for a depression treatment and for PTSD treatment, and of course those are co-morbid a lot. So they're some of the same people.

One of the things that's been interesting to me is that mental health has been in the last decade or so partly, I think, based on the organization of the National Institute of Mental Health by disorder, has been very much focused on particular problems. I'm guessing in our sample, and I'm looking forward to getting the figures from Ron Kessler, but probably about a third of people who are depressed also have post traumatic stress disorder and a history of trauma.

If we're thinking about treating depression in primary care settings, then we need to be aware that, some people may have PTSD as well, and that may actually change the prognosis for their treatment. It may change the way we want to go about doing that.

So our group is really trying to look more broadly across a number of disorders that are co-morbid at the same time and to incorporate into our treatments a somewhat broader perspective of disorder. Then at the other end, we also look at adversity, as Bruce was talking about, and at the whole pattern of exposure that people have had to traumatic events and that they currently have in terms of the stressors in their life (that have a lot to do in this particular population with being poor), and what are some of the environmental correlates of being poor that place additional burdens on people in terms of what they need to work through.

I'm becoming more interested in the interaction between psychological and medical physical illness complaints and how that translates into seeking services and so forth.

So this is a really great opportunity to hear all of the people here talking about the interactions among these things.

**DR. MARLOWE:** Thank you.

**DR. CARDEÑA:** Hi. I'm Etzel Cardeña. I am a psychologist in the Department of Psychiatry here at USUHS.

The areas that I have concentrated in the last few years are dissociation and hypnosis, and I will try to emphasize how I think these areas have to do with the focus of this conference.

With regard to dissociation, along with particularly Dave Spiegel, I have been working on what has become known as Acute Stress Disorder. That is a disorder that happened in the first month after a traumatic event, and that is defined by the PTSD symptoms, but also by dissociation.

Really the history behind it, is that, when we started looking at collected data, we found out that a substantial percentage of people around the time of a traumatic event, a disaster like a firestorm, a flood, war, et cetera, engage in dissociative experiences or do have dissociative experiences.

I would like to make a tie now to what Dr. Mason said in that I think that one way of looking at dissociation experiences is to think about hypoarousal or some form of a graded experiential event. That is, people feel distant from themselves. They feel distant from the environment. So that was one point that we were able to find. We also know by now that even though

perhaps the majority of people when exposed to a very serious traumatic event will stop dissociating after a brief amount of time, there is a smaller percentage of people who continue dissociating. By now I think there is research that has come from the department here at USUHS and from other places that has shown that dissociation, dissociative experiences seem to be a very sensitive and, in some studies, even a very specific predictor of who's going to have PTSD type symptoms. So not only do we know that people dissociate, but we seem to know now that or we seem to have found that those people who seem to dissociate a lot also seem to have PTSD.

Those are, if you will, two axes of a triangle. Let me talk about the third one, which is somatization. There is now, I think, growing research showing that as much as there is a relationship between traumatic events and dissociation, there is also another axis or another point which is somatization. That is, people who have had serious traumatic events tend to present also with a number of somatic symptoms, and people who dissociate a lot also tend to present with somatic symptoms.

Let me unveil that a bit more. Thanks to things that probably have more to do with classification and politics, I think, than anything else, we know that conversion disorders, somatization disorders were separated from dissociative disorders in the DSM taxonomy. However, if you start looking at these two populations, people with somatization disorder and people with dissociative disorders, you will find that there is a very large overlap. That is, people who have dissociative disorders tend to report a lot of somatization, unexplainable medical symptoms, et cetera, or medically unexplainable symptoms, but it also goes the other way around. People who have been diagnosed with conversion and somatization also tend to report that they have dissociative experiences, like depersonalization, amnesia, things of that sort.

So it seems that even though right now they may be separate, according to the DSM, there is some interesting relationship between having some type of perhaps hyperarousal or degraded form of experience or something along those lines that make some people more likely to have somatic problems or somatic complaints.

I think that is one area that requires a lot more study. To tie with Dr. Schnurr, what we have started with a number of people at this table is a study that is longitudinal, prospective, that involves questionnaires about psychological and somatic symptoms, along with neuroendocrine measures with police cadets to see how they are before they have gone out and see if we can follow them through a long enough time to see what will happen to these individuals. Then try to tie new endocrine measures with other types of complaints because we assume that there is going to be a more interesting series of interactions that will help us understand a bit more.

So that is it, with regard to dissociation and Acute Stress Disorder. The other big area that I have been interested in that I think has a link with the conference is hypnosis, along with Dr. Kirmayer, who is also an expert in that area. I think hypnosis has two interesting issues to add to this type of topic.

The first one is that recent studies, particularly a model by Dr. Vicram Masakera, have proposed that people who are very highly hypnotizable and very low hypnotizable, both people on the extremes, tend to also be prone to a number of diseases. The highly hypnotizables differ in the kind of illnesses that they are prone to than the low hypnotizables, and they're at a higher risk than people who are in medium hypnotizability.

So we can think perhaps that hypnotic ability and, again, to give a very small definition of it, the ability to have a continuous focus of attention on one's experience, that hypnotic ability can actually be a risk factor particularly when it is mediated by distress, depression, things of that sort.

In the model of Dr. Vicram Masakera people who are very highly hypnotizable end up having problems when they also have distress. So they end up focusing their attention on any kinds of issues, complaints that perhaps many of us would not attend to nearly as much.

So I would also propose that hypnotic ability or attention or cognitive processing as a possible mediating or moderating variable should be thrown into how people respond to traumatic events, along with interpretations and other social and cultural aspects.

And finally, two other issues of hypnosis that bear mentioning is that there is by now a fairly long literature of hypnosis that has shown an extraordinary amount of somatic plasticity; that when people are given suggestions for something, at least a certain amount of people will go along with the suggestion. If you give them a suggestion that they will feel less pain, they will tell you that they have less pain when exposed, let's say, to electric shock. If you tell them to actually enhance the experience, they will feel more pain. We have also done studies, and most of this actually comes from Stanford from Dave Spiegel, which has shown that cortical response goes along with people's reports. When they tell you, "I feel more pain," you look at the event related potentials, and indeed, they have enhanced. When they tell you, "I don't feel very much," their response decreases.

So I think in hypnosis there is a vast amount of literature that talks about the importance of communication, of culture, and so on, in the possible inception of many of the symptoms and complaints that are the interest of many of us.

**DR. MARLOWE:** All right. Thank you.

I think Etzel's concern with hypnosis opens the wider issue of the role of suggestibility. Suggestibility going back to Charcot, Bedinsky, Hurst, Symes, everyone concerned with the concept of hysteria, was always considered a major player in the generation of symptoms.

I will ask those remaining to keep within five minutes so that we can push ahead.

**DR. GUZE:** Could I just make one comment? I think if you haven't looked at it, you might find considerable literature that I played a role in generating dealing with what we then called Burcasian zone, and it showed clearly that dissociation and conversion and somatization occurred in the same individuals to a very, very high degree.

One of the other things that we showed was that those people came from families with a lot of antisocial personalities, and you might want to look at those things and maybe add a dimension to your studies. Not only did they come from families, but especially the women with these conditions tended to marry men who were antisocial.

**DR. MARLOWE:**

Jim.

**DR. MEYERHOFF:** Hi. I'm Jim Meyerhoff. I'm Chief of Neuroendocrinology and Neurochemistry at Walter Reed Army Institute of Research and adjunct faculty in the Departments of Psychiatry and Neurology at Uniformed Services University.

I'm very pleased to be here. I thank the organizers for inviting me, many of whom have been mentors to me. I'm especially pleased to see Dr. Mason, who was one of my mentors at Walter Reed when I first came there from Johns Hopkins, and again, thank you.

I'm essentially pursuing a vertically integrated program in the area of, loosely speaking, again, with apologies, the issue of stress or, if you will, the adaptation or lack thereof to exposure to novel or challenging environments.

The basic issues that I think are important and I'm trying to pursue in my models are whether the response to a stressor is adaptive or not adaptive, whether the response habituates or sensitizes, and trying to develop measures of predictability of response.

There are two phases, the basic research phase, the animal phase. We're using the model of social defeat in hamsters and mice. We're finding a prolonged change in behavior, prolonged avoidance of nonaggressive conspecifics, and by the way, in terms of our subject mice, this is not a measure of aggressiveness, but a measure of normal territoriality, which is different than the way we loosely characterize aggression over I would say a select subset of aggression. This behavior disappears. Territoriality from a single day of defeat is missing, is lost for a period of up to four weeks. This is a model where we find strain differences. We hope to be able to study gender differences, and again, predictability. We're using neuroendocrine as well as neurochemical measures as markers in this particular model.

We also hope to look at pharmacological interventions. One of the things that we've found is that diazepam is not particularly effective in reducing the avoidance behavior. It improves some behaviors, but other behaviors are exacerbated. There's anecdotal data from Arik Shalev that benzodiazepines are not helpful in preventing PTSD after trauma.

In terms of human subjects work, we have, I guess, a semi-naturalistic model, kind of rite of passage similar to Part 2 of psychiatry boards or your defense of your thesis if you're a Ph.D. It's a well characterized model where we find our soldiers in this model have blood pressure in the first five months that go up to 170 over 100 and marked changes in every hormone that we've chosen to measure, although the profile, John, is a different time phase. For example, the growth hormone response is delayed, but the big response is in the HPA axis, as well as prolactin and the immune enhancing hormones.

We're using this model to characterize or try to characterize measures that can be implemented in the field that are noninvasive. For example, we've been looking at so-called voice stress analysis techniques to see if they really measure stress or not, which is something that I think has never really been adequately determined. I have a neutral stance with respect to whether or not I'm an advocate of voice stress analysis, but we do have the model that will determine whether it measures stress or does not.

We also want to use this model to study the effect of repeated exposure to stress to determine if it's a good training model, whether individuals do habituate over time, and hopefully to begin to look at the outliers and the people who sensitize, or fail to adapt.

We can use this model for long term follow-up to the extent that we can follow these individuals throughout their military career. At least we have that option in terms of their informed consent participation.

Finally, we're interested in prospective studies of PTSD, and we've been collaborating with Dr. Cardeña because while very important potentially, we don't know whether the changes in the HPA axis reported in PTSD, antedated the trauma. We don't know whether they have prognostic value. We don't know if they have value for indicating what sort of therapy might be useful.

It seems to me that a prospective study would be very important to do in that regard, but it's been difficult to get funding to do prospective studies on the kind of large scale that is needed because of the investment strategy.

Thank you.

**DR. FRIEDL:** I'm Karl Friedl. I'm the staff officer for Army Operational Medicine Research at the Medical Research and Materiel Command. I used to work for Dr. Hegge, and then all of these positions were abolished. I'm sort of the last guy standing there at the moment, but we've got a new general in charge who is supportive of exactly this kind of effort and keeps reemphasizing interdisciplinary research and multi-disciplinary research. He's not parochial, and he makes sure that I talk about Navy and Air Force and Marines when I talk about our programs.

And in that context, I'm also the Chair right now for the Joint Technical Coordinating Group between the services to report on military operational medicine. So you're going to hear more from me right after lunch. I'm supposed to be inspiring post prandial --

(Laughter.)

**DR. FRIEDL:** And I'll talk just very briefly about sort of what we've been talking about between the services in terms of where we're going with the research and why this kind of meeting is so important to help us plot out what those future directions are. We need to come to expert groups like this to discuss this. This isn't a simple thing, and this area most of all, I think, is very difficult. It's been hard for me to put together, but one of the most intriguing areas is physiologic. I'm a physiologist. I would call myself an endocrine physiologist, and I come at this from that direction, which I think is a little different from a lot of people in the room.

I came originally out of a group in Santa Barbara that were primarily avian endocrinologists, and there it's very simple to talk about a hormone influencing behavior, and usually it went in that direction. You know, as far as I know, our mallards weren't religious and they weren't worried about societal context too much, although there are interactions between them. We would look at things like environmental pollutants, oil spills in Santa Barbara and the effects on adrenal lesions and the effect on prolactin, and then suddenly these nesting behaviors go away, and they don't become broody and do what they're supposed to do, and it was a very simple relationship.

I broke the mold of that group a little bit because I had a room full of squirrel monkeys, and I was working at the next higher level there, but I did set up a breeding colony of tree shrews, and wanted to pursue for my Ph.D. work this intraspecific stress model. I had read Dr. Mason's work, and I told my advisor, "I'm even going to join the Army when I get done with this because that's where the action is, where we can really pursue this interesting stress physiology." You may or may not know about tree shrews. You put these guys together and develop a defeat model a little bit along the lines of what Jim Meyerhoff has spent a lot of time studying, where after one interaction you end up with a victor and a subordinate tree shrew. You separate them where they can see each other, and the subordinate animal dies from renal failure within about two weeks, and there are dramatic endocrine changes, a fall in thyroid, testosterone, and so on. And you can tell that they're in trouble by the percentage of time that their tails are fluffed. So we have an indicator of sympathetic stress.

I've been looking for the tail fluff indicator in soldiers ever since.

(Laughter.)

**DR. FRIEDL:** And we know it's not going to be anything nearly that simple, but I think that's one context of looking for stress indicators. Who is going to be at risk, in trouble?

Once I got out of the Institute of Environmental Stress in Santa Barbara, I did really, two bodies of work that I've published in. One involved in giving high dose anabolic steroids to soldiers. There again from a physiological point of view, we ran into the inadequacy of any of the tools that we had to talk about behavior and describe the behaviors that were clearly present in some of these individuals. We couldn't find any kind of psychological scale or battery that would predict some of the behavioral changes that we saw grossly in a few of these soldiers.

We had one perfectly normal legal clerk, as far as we could tell, that after about the sixth week of steroid treatment had a whole afternoon of uncontrollable crying. We had several others who did behaviors that were very uncharacteristic of them. One young sergeant took his first sergeant, threw him up against the wall and started choking him, and a young lieutenant who went up against his battalion commander in front of everybody else in a meeting like this and sort of told off his senior officer. These weren't characteristic of those individuals, but we didn't have any way to kind of describe what was going on. As far as I know in that literature, it still hasn't been worked out. This is a scenario that we're really behind in, I think.

The other piece of work that I did after that was to go to ranger school and study people going through a very severe set of multiple stressors, and in fact, that was the other part of joining the Army. I had to sign up in ROTC so they would let me go to ranger school so we could see what the stress was all about first hand. But years later we got to go in and define the natural history of ranger training and what stood out there was that we had some dramatic endocrine changes falling testosterone, for example, to castrate levels, eventually a rise in cortisol levels, thyroid falling because of the energy deprivation and so on, but nothing that distinguished -- this, I guess, was disappointing originally, but finally turned into a challenge to us -- nothing that distinguished who was going to be successful.

There were some clear-cut behavioral differences, again, that we just couldn't get a handle on in terms of describing in quantitative measures.

So that's my personal background in this area. After lunch I'll talk about where we're trying to go with the program help them to meet better.

**DR. MARLOWE:** Dr. Kirmayer.

**DR. KIRMAYER:** Thank you. I'm Lawrence Kirmayer. I'm Professor and Director of the Division of Social and Transcultural Psychiatry at McGill University.

I should say that I'd like to apologize to everyone here again for being late and missing some of the presentations. I think it's a typical situation of being hassled trying to get an uplift from Montreal to here.

I also wanted to refer to another most distal stress experience that came to mind when Dr. Erikson was talking about the situations he's studied. I'm a survivor of the Montreal ice storm of January, which involved over \$1 billion in damage; 11 people died, and we were 125,000 people without electricity for two to three weeks during the coldest time of the year. This was hardly stressful at all for most people because of a tremendous feeling of social solidarity and people being kind to each other. It was almost like suddenly being in the countryside in the middle of the city with fallen tree branches in the middle of the road and neighbors meeting each other, neighbors who usually hibernate for the whole winter meeting each other.

So it drives home very much what is a major preoccupation for me, which is the social and cultural level of experience and the constitution of the meaning of events and their physiological impacts through those processes. I've been involved in a program of research for about 15 years or so looking at somatization, at medically unexplained symptoms, and so on, predominantly from cognitive and social perspectives. It comes out of my work partly in consultation liaison psychiatry and more recently in cross-cultural psychiatry, and a close research collaboration with the medical sociologist, Jim Robbins, who is now at University of Arkansas.

In that work, we attempted to take some of the assumptions occurring in consultation liaison psychiatry about the specific pathology of people who were somatizers and reconcile them with the cross-cultural work and my own clinical experience with the ubiquity of medically unexplained symptoms.

The dilemma of most people who work in primary care settings and consultation liaison work, is that a very substantial proportion of anywhere from 25 percent in some series up to 60 percent of patients coming for medical care have medically unexplained symptoms. This poses a problem for any kind of theory of specific psychopathology in those people in the sense that there must be some fairly general processes cutting across different people that are giving rise to these symptoms.

The basic clinical dilemma, of course, is validating the reality of those symptoms for people. People are caught on the horns of the dilemma of the mind-body problem which persists and which I and many of my colleagues have written about from a medical anthropological point of view as being fairly fundamental to the North American, we could say Euro-American, concept of the person. Whenever a psychosomaticist has a very integrated theory as a clinician, or as a theoretician that they want to present to patients, they're left with the patient presenting the question back to them saying, "Well, do you mean to say, Doctor, that this problem is all in my head?" And that's a fundamental and inescapable problem up to the present in our society, notwithstanding the fact that as Dr. Ader alluded to, there are plenty of people now offering various holistic viewpoints and offering treatments, often somatic treatments under the banner of holism.

And so I've been very interested in looking at that from a medical and anthropological point of view as a kind of cultural system that shapes our bodily experience. I've done a series of clinical and community epidemiological studies looking at somatization. In the mid-1980s, we did a study in primary care in Montreal, again showing the high prevalence of somatization on various definitions as medically unexplained symptoms as hypochondriacal worry, and as predominantly somatic presentations of depression and anxiety, cutting across different ethnic groups, different socioeconomic levels and so on, and looking at the way in which that influences the doctor's ability to recognize problems, to manage them, and patients' long term illness behavior.

We've also looked at functional somatic syndromes in specialty medicine, fibromyalgia, chronic fatigue, irritable bowel, and comparing them to better explained or legitimated disorders like multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease, to focus in on the issue, again, of the dilemma of delegitimation for patients and the ways in which that may contribute to the disability that the people experience.

And basically what we found in those studies, is that psychosocial factors in the kind of cross-sectional clinical epidemiology that we're doing don't account very well for levels of symptoms, but they do account a great deal for levels of disability that people are experiencing. That fits with some of the community epidemiology in these areas, which suggest that medically unexplained syndromes and functional somatic syndromes, and I think the distinction is quite moot between the two --it has to do with current diagnostic fashions and so on, are very prevalent in the community.

Most people cope well with these things and get by with them, and some people have terrible problems partly because of co-morbidity, partly because of social difficulties, and what we're seeing in the clinical setting then is the interaction of those. I think that's something very important for us to look at.

I think the distinction between medically unexplained syndromes and functional syndromes is moot because I think most people with unexplained syndromes ultimately have some explanation for their symptoms, that they have physiological perturbations that are giving them distress. They are also amplifying those in some cases, although most of the research up till now looking at hypochondriacal processes and amplification with kind of signal detection models suggest that people who are hypochondriacal, in fact, are not amplifying symptoms, that is, that they're not more accurately aware of distress and amplifying it. They are generating distress out of cognitive schemas rather than, say, reading their body. So I think that that cognitive process is extremely important.

We've been very interested in attributional processes, with the idea that how people explain things has a great influence on how they respond, and we developed a kind of a measure of attributional style. At least in one study in England this was found to be a predictor among people with acute viral illness who actually go on to have chronic fatigue; that the tendency to attribute common somatic symptoms to somatic illness is a predictor of the tendency to develop chronic fatigue, as is the intensity with which clinicians investigate people with fatigue symptoms.

So there's an iatrogenic process in which the more MRIs we do and so on, the more people don't accept our reassurances at the end of that process because they've had perhaps a more powerful communication along the way that there is, indeed, something serious and worrisome about their problem.

So I'm very interested in that kind of interactional process, that kind of social process, and that fits with ongoing work that we're doing with different ethnocultural communities. In Montreal we have a very ethnically diverse population. We completed a study quite recently of 2,500 people in the community from different ethnocultural backgrounds, Vietnamese, Filipino, Caribbean, looking at somatization in these groups, and looking at the ways in which people express and understand bodily distress using not only epidemiological methods, but ethnographic methods.

I work very closely with medical anthropologists who spend a great deal of time sitting down with people (hours and days), understanding their illness narratives from the inside. One of the things that's striking in those cases is how complete a story people can give you of very difficult social circumstances that seemingly would explain a great deal of what they're going through. But the reluctance people often have is in making a direct link between that predicament and their bodily distress. And, again, I think that has to be understood in social and cultural terms. So there's a great deal at stake for people in giving a particular kind of account of their problem.

Now, this is important, I think, because it becomes a huge methodological issue for stress researchers, people trying to find a causal relationship between past events and present. At a conference on somatoform disorders in Japan a few months ago, one of the things that came out was the very, very low rate of reliability of the composite international diagnostic interview for somatization disorder, which is a lifetime diagnosis. People's recollection of how many medically unexplained symptoms they had in their lifetime at one point in time accords very poorly with their recollection one year later.

And so memory for symptoms has a great deal to do with current social context and the way people think about things. I would suggest that rather than treating that as simply a nuisance problem, but as a measurement problem for epidemiology, that that becomes a substantive problem of understanding how people think about their bodies, understand their bodily experience, and what the social and cultural determinants are of that. Thinking again from a clinical point of view, that points to powerful things that we try to do as clinicians in terms of reshaping people's bodily experience to help them to cope with that.

So just very briefly in terms of where this research is going, we have a research team on culture in mental health and within that one working group with anthropologists the theme now is body, memory, and identity. We are looking at ways in which bodily experience becomes part of people's individual and social identity and the way in which memory, something that is highly plastic and socially determined, mediates between bodily experience and individual identity, and we're doing that with refugee populations.

I'm working in Japan with colleagues on looking at problems of somatization. We have a variety of other things that I can talk about that are probably too much to summarize in any reasonable time span right now.

**DR. ENGEL:** All right.

As I mentioned before, I'm the Chief of the Gulf War Health Center at Walter Reed, and in my capacity there, I see a lot of Gulf War veterans. I've had a lot of opportunities to get close to the comprehensive clinical evaluation program data, the data that's been collected from Gulf War veterans. I'd like to present some of that and some other things.

I love what was said earlier. "Stress, excuse the expression."

(Laughter.)

**DR. ENGEL:** I'm going to talk to you about stress -- excuse the expression -- physical symptoms and symptom based syndromes. I think everyone here knows that there's a burgeoning literature on the health of Gulf War veterans. This is from a database that we have that's available on the Web that has all of the articles in the peer reviewed scientific literature, as well as some media stuff, on the Gulf War health issue.

Obviously a big question that's been a question on everyone's mind for a long time is: is there a discrete Gulf War syndrome? And there's been some gallant efforts to try and discern whether there is one.

The most remarkable thing about Haley's work was, in my estimation, how he managed to get an uncontrolled study into JAMA.

(Laughter.)

**DR. ENGEL:** But, in effect, he studied Navy Seabees and identified symptom syndromes. It's somewhat analogous to taking a large group of elderly people who participated in World War II, identifying the syndrome of wrinkled skin, and attributing it to their World War II exposure.

Next slide.

And I particularly liked Alvin Feinstein's comment about the factor analytic approach that was taken in discussing this last week at the Gulf War veterans' research conference. "If you don't know what you're doing, then factor analysis is a great way to do it."

But, on the other hand, all of that being said sort of tongue-in-cheek, I think that Haley has to be credited with making a forthright effort to try and discern some meaningful syndromes in this group of veterans.

Go ahead.

The number of proposed etiologies of this gets longer as the list of publications gets longer about Gulf War veterans' illnesses. Most of them are represented here, and then there's different permutations within each of those categories.

Next slide.

And, again, as I don't need to really share with this particular group, it's been an issue of high public visibility and political importance for both Department of Defense and the Veterans' Health Administration and, I think, also Health and Human Services.

As a consequence, there's been this group, the Persian Gulf Veterans Coordinating Board, that evolved that has a research and clinical working group as well as a benefits working group to determine policy and communication strategies around this issue.

Is it a new illness or is it a very old illness in some fashion? This was a quote that I lifted out of a book. I collect old books on psychiatry. This is written by a British psychiatrist named Marr in 1919 in describing combat veterans that he had seen with shell shock.

He says, "There's a general diminution of intellectual activities. The attention is weakened. An effort to concentrate the mind for any length of time on any occupation, and if an attempt is made to arouse effort, dizziness usually results. Memory is not markedly affected, but there's a tendency to forgetfulness, to neglect, for instance, messages and engagements, especially if the neurasthenic symptoms have arisen suddenly. So-called fugues are not uncommon. Memory may be entirely absent for relatively short periods. Lethargy, slight confusions of thought, excessive introspection, fears of ill defined foreboding, vague terrors, anxiety about one's bodily health, and a tendency towards irritability, suspicion, and the feeling of being slighted," which very much describes a lot of the folks that we're seeing at the Gulf War Health Center. Even now, seven years after the fact.

Next slide.

What we do know from published research about the Gulf War health issue is that whatever it is that's happening, that it doesn't seem to be catastrophic. We know or we have a fairly good idea that mortality is not significantly increased, that is, disease related mortality. Accident related mortality is elevated, but disease related mortality isn't up through 1996 in Gulf War veterans compared with era veterans who were not deployed to the Gulf. There is no consistently increased incidence of DOD hospitalizations, although our confidence in that finding is less high because of dropout due to DOD hospitalizations. As we get further out in time, more and more people leave the military and are not eligible for care in that setting.

Next slide.

At the same time, there's been a series of studies which consistently show that Gulf War veterans compared to era veterans endorse more symptoms and more symptom based syndromes. The Iowa study, which was a very nice population based that achieved an acceptable response rate, found that self-reported health related quality of life was also diminished as measured by the SF-36 generally in Gulf War veterans versus era veterans from the State of Iowa.

Next slide.

These are some of the, quote, conditions that were measured within the Iowa study. They were measured telephonically. So, in essence, these are self-reported conditions, and you can see what's in the right column is the prevalence difference. It's an adjusted prevalence difference between Gulf War veterans and era veterans who did not deploy.

So the cognitive dysfunction, fibromyalgia, (diffuse aches and pains in more than one part of the body), some respiratory issues, fatigue, and so on seem to be some of the more significant differences between the two groups.

I think of this in more of a -- well, Kurt Kroenke has referred to it when I've talked with him as the unified symptom theory. In medicine we're taught that we make differentiations in health status and disease status based on the symptom reports that we get from our patients. In some fashion Kurt would see it, and I agree, that symptoms are generic, that they are highly correlated with one another. So you can come up with this thing called a symptom based syndrome, which is essentially some cluster of persistent or bothersome physical symptoms that remain medically unexplained after appropriate and complete medical evaluation, and the diagnosis is based almost exclusively on symptoms.

There are a lot of these diagnoses (next slide). A lot of these diagnoses actually, when you look at research diagnostic criteria, there may be some objective data that are used to formulate them, but in routine clinical practice for most of them, no objective data are usually obtained by clinicians in making the diagnosis. It's really a diagnosis based on clinical history.

And this is a list that I could assemble of some of those that we commonly see and label in clinical practice.

Next.

Craig Hyams and his group commented (in an article that I'm sure most of you are aware of), that poorly understood war syndromes have been associated with armed conflict for a long time, as was noted in the syndrome that the neurasthenic had. These war syndromes have involved fundamental unanswered questions about the importance of chronic somatic symptoms.

The Presidential Advisory Committee took the step of suggesting that stress was an important contributing factor. The Institute of Medicine Committee, in their final report, made a very important distinction, and that is, that the issue is not whether Gulf War veterans are sick so much, but as to what degree are we able to attribute to the cause of illness in the Gulf War.

That's a very important distinction that, I would argue, from the level of the clinician is almost impossible to make.

Next slide.

These are data that are provided by Zahava Solomon's group in Israel where they looked at four groups of veterans of the '82 Lebanon conflict: those that had neither a combat stress reaction in theater or subsequent PTSD; a second group that had combat stress reactions, but did not go on to develop PTSD; a third group that had no combat stress reaction, but then subsequently developed PTSD; and then a fourth group that developed both, had a combat stress reaction in theater and then subsequently went on to develop PTSD. And the main point of this slide really is, if you think of this as a continuum of severity from the neither to the both, that what you see is a dose response relationship across multiple health/behavior domains, and those risk factors.

This is one year out from the war. Things such as medication use, lost work, drinking, smoking, and other problems seem to be strongly related to the level of initial and subsequent distress that these veterans have.

Another thing that's important to appreciate is that beliefs can have a very strong impact on health, somewhat akin to what Dr. Kirmayer was emphasizing.

This is a study of a small town in England where they had a water contamination episode in '94. The contaminant got into a creek about two or three miles up river from the town, and was felt to be distributed evenly in the water. Ultimately, there wasn't any geographic distribution of people who felt that they smelled and tasted it in the water.

In retrospect some time later it became apparent that the concentration in the water that was measured was considerably lower than the level that would be reasonably toxic. What they found was that in those folks who reported that they tasted or smelled the contaminant in the water (in effect, those folks who believed that they had been contaminated) experienced a dose response relationship between the amount of water drunk and subsequent experience of symptoms. Whereas, those who reported that they did not taste or smell, did not experience symptoms in as much of a dose response fashion.

These are data from the PRIME MD 1000 study that Spitzer and Kroenke and others participated in. This sort of relationship can also be found in the Epidemiologic Catchment Area data, which was a five geographic area epidemiologic study of mental illness in the United States in the early to mid-'80s. So it's found both in communities and in health care settings, the relationship between common and treatable mental disorders and physical symptoms.

This slide, the upper half of it where it says "physical," these are people who have symptoms that the clinician was able to say had a physical etiology. The bottom part where it says "somatoform," these are symptoms where the clinician assessed that he could find no discernable medical etiology. If you look to the far right column, that's the column that's easiest to appreciate. As you go up in symptom count – the symptom counts are represented on the far left column – as you got up in symptom count, on the far right column you can see that the percent of those with any mental disorder goes up in a fairly nice, step-wise fashion. So physical symptoms are related to common mental disorders.

The second point is to notice that that relationship is pretty much the same without respects to whether the clinician was able to say that the symptom had an etiology or not. It suggests that this is not an important differentiation. It's not an important mediating factor in this relationship between distress and physical symptoms.

Post traumatic stress disorder and physical symptoms, another issue that we were discussing in the hallway out here, is the notion that stress is a dimension that in many ways it's generic. We like to differentiate it into PTSD, depression, and anxiety. Certainly there are differentiations to be drawn, but on some level it's a unified dimension, just as I speak of physical symptoms as a single dimension. And, in fact, you find that, like other distress syndromes and maybe even more so, there is an important relationship between PTSD and physical symptoms. One region, the North Carolina region of the Epidemiologic Catchment Area studies, Davidson, Glaser and some others looked at somatization disorder in that community. The numbers were relatively small because the prevalence of somatization disorder, as the bottom bullet shows you, is 0.1 to 0.2. I don't recall exactly, but there were about 3,000 people total in the sample. But what they found was that there was a 90-fold increase in somatization disorder in those folks with PTSD. This was, again, a community based study.

Some less rigorous studies have shown 13 to 15 percent prevalence of somatization disorder in those with combat related PTSD due to exposure in the Vietnam War.

It's important to appreciate that like PTSD, which I conceptualize personally as a tip of the iceberg distress phenomenon, somatization disorder is similarly a tip of the iceberg somatic symptom phenomenon. You know, that by looking at the relationship between these two, you've picked two groups of people who are at the ends of two continua, and there's a lot of people that don't meet either criteria for PTSD or somatization disorder where this relationship is also known to follow.

Next slide.

We looked at PTSD and physical symptoms in the Comprehensive Clinical Evaluation Program data set, and this is using a symptom checklist. I think somebody said that a symptom checklist is inadequate. I agree it's certainly the methodology used for most of these studies, and it's time to go beyond it. That was something we talked about in last week's meeting as well.

But in the CCEP everyone filled out a 16-item symptom checklist. These are the symptoms on the far left column. There was an "other" symptom category.

The groups that are differentiated in the table by the four right-hand columns are those people with PTSD, which constituted about five percent of the overall sample. Those people with any psychological condition as the provider diagnosed it using the ICD nomenclature, and then in the medical column are those people who had a medical condition according to ICD codes. Any condition other than physiological or other than a V code or E code, and then there's a V code for healthy, 65.5, and about ten percent of folks were diagnosed by the clinician as healthy. That's the column in the far right.

These are not mutually exclusive columns. The bottom is getting cut off, but the total sample size is about 21,000. There is overlap between these groups.

What you see for each symptom, it's counterintuitive to what we learn in medical school. The prevalence of symptoms is systematically higher, in the tip of the iceberg distress group, still elevated in the sort of nonspecific distress group, less elevated in the nonspecific medical group, and least elevated in the healthy group, but as was mentioned before, symptoms are ubiquitous. In even this healthy group we see higher base rates of symptoms that what people might expect if they're not familiar with looking at this kind of thing.

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We then did a multivariate analysis using ordinary least squares regression and making symptom count as the dependent variable, and so what you're looking at here, in the column that says "Model A," is the effect of having PTSD. That's the coefficient within the regression model. The relative effects of PTSD, after adjusting for other psychological syndromes that were diagnosed by the provider and the exposure count. The CCEP asked folks to rate 20 different environmental exposures from the war as to whether they had experienced them, and then the last variable there is whether or not they had a medical condition.

PTSD's impact on symptoms is greater (as the previous table suggests), on symptom count than medical condition, and for other psychological conditions it's about the same.

The other thing to note is that overall there is a lot that determines symptom count that we're not able to measure as revealed by the R squares, which are low.

Next slide.

There is circularity in reasoning in that many of the symptoms on the checklist you actually might rate as emotional symptoms. So we excluded those, and we reran the analysis to see what would happen to this relationship, and in fact, if anything, it gets stronger.

When you exclude, say, sleep, depression, and those kinds of items, we excluded five of the 16. So this is a count out of 11. You find that medical conditions, the coefficient drops down to .55. That is, those people with a diagnosed medical condition had half a symptom more on average than those without, adjusting for these other variables. Those with PTSD still had almost twofold physical symptoms more than those without.

**DR. DOHRENWEND:** Would you just define the exposure count there?

**DR. ENGEL:** Each person in the program was given an exposure checklist, and it pulled from 20 different environmental exposures that Gulf War veterans frequently described on their return, like sand, chemical, paints, anthrax vaccination, not actual exposures, right.

Next slide.

To which one could easily argue, that's probably also a fairly good proxy measure for distress.

**DR. DOHRENWEND:** You would have thought it would be a much better predictor. Of course, you have the other distress variables in the equations.

**DR. ENGEL:** Yes, and the other thing to keep in mind is that response can vary from zero to 20 on the score. So if they score 20, then the impact of environmental exposures could be very large, relatively large on physical symptoms. So you can't really compare it because it's on a different scale.

So this goes back to the point that I made earlier. We frequently ask patients about physical symptoms with this idea that we're differentiating disease from stress, when, in fact, especially in a working population like we have in the military where the healthy worker effect is operating, to a certain extent. That is, those people with serious physical disease are usually not in the military. The base rates of those diseases are low; in fact, for people with physical symptoms more often not a marker for distress.

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I would underline, and I typically do, some things that were said here. I think in the room we have scientists primarily, and it's not hard to say there's a lot we don't know, but for the clinician on the street, it's very hard for a lot of them to say they don't know. I don't know what that's all about, and certainly in the context of the Gulf War issue, there was a lot of pressure on clinicians to know what these things were, but I think even the common clinician out there experiences that same push.

If you look at 100 charts, I would bet you there's 100 labels, but there's a lot of scientific and clinical uncertainty. In the scientific arena, various groups have reviewed this Gulf War business. They've applied a pretty high test of the relationship of various exposures to subsequent illness, the idea that we don't find convincing evidence of a causal link.

Well, think about it. There's enough uncertainty around determining that that cigarette companies are still able to stand before Congress and cross their heart, hope to die that cigarettes don't cause cancer. We all know that that's a lot of nonsense. So it's a very high-test determination. When you get down to the plausible cause, it's almost equally not useful, because just about anything out there can constitute a plausible cause. That fact is sometimes used by Gulf War quacks, if you want to call them that, people who would like to scare us with hypotheses about what might be going on.

So, in between, there's this large area of uncertainty for epidemiologic research. There's issues, which have been mentioned around the table, that we have difficulty measuring the syndromes, measuring the symptoms, and difficulties deciding if symptoms are justified by underlying medical illness. Then there is the issue of synchronous change, which an epidemiologist would like to look at the event sequence in deciding whether distress causes symptoms or symptoms cause distress. One thing that is very difficult in this arena is that they seem to happen pretty soon after one another, so fast that you can't really sort out the sequence.

And then there's the problem of reverse causality, which is the model that most patients tell us about this. We, as physicians, often have a hard time accepting it, and that is, that these symptoms are causing their distress. It certainly has been empirically shown in longitudinal studies that both are true, that distress leads to subsequent physical symptoms and likewise that physical symptoms lead to subsequent distress.

And then there is the problem of control groups when sorting out the impact of distress or stress. When you're dealing with human beings, it's very hard to do randomized trials in most of these areas. So we're dealing with uncertain evidence. We're comparing Gulf War veterans to Gulf War era veterans. We're not sure whether or not we're comparing apples and oranges.

In the clinical arena, I think somatization is a problematic diagnosis in a number of respects. From a logical perspective, one is that the absence of evidence is not necessarily evidence of absence, and that's where the clinician is a lot of times. They do their work-up, and they can't find anything. So therefore, it's sort of stress as the residual explanation. I mean, frequently, when we can't find anything else, say it's stress, and even on a research level, we have a hard time defining what is stress other than a residual explanation.

So in conclusion, I think that essentially this is a vexing clinical and scientific problem. What we're here to do is to focus on it and try to come to some better understanding of it.

I think it's going to require that we go beyond fairly traditional methodologies. It's going to require that we go beyond -- I'm an epidemiologist -- that we go beyond traditional epidemiologic frameworks for viewing things, this exposure outcome approach. And I think, from a big picture perspective, we also have to get close to the street in this issue. We have to get close to the clinician and learn more about what happens in the doctor-patient relationship, what doctors can and shouldn't say to patients in terms of arousing distress, and then on a societal level, how can we better disseminate information.

I think someone else here also brought up the role of information in stress generation. But certainly, we have to come up with better ways on a societal level and on an organizational level to communicate with large groups of people about problems like this, and we have to get better on a one-on-one basis in the clinical setting.

Thank you.

(Applause.)

**DR. MARLOWE:** We're going to begin now, and as I said just before the lunch break we'll begin with both Ann and I telling you a little bit about ourselves and what we've been doing and what have you so that you won't feel we're trying to evade that responsibility.

Ann.

**DR. NORWOOD:** By way of my introduction, I've been fortunate to know many of the folks from Uniformed Services University since I was a medical student there many years ago -- well, not so many years ago.

I'm back on the trauma team working with Bob and Harry and the others. So I won't go over what they do one more time.

In terms of Gulf War, I was a member of the epidemiological consultation team that went out to Indiana to evaluate the 123rd ARCOM when this first started to develop. Later, through Dave, I had the opportunity to visit the 14th Quartermaster Group, which was hit by the Scud missile in Dhahran. I also served on the Dr. Lederberg's Defense Science Board. So I've had an interest in this area for some time.

I won't again rehash many of the things that have been brought up here. I guess a couple of questions I have in terms of beliefs and attributions, is given the ambiguous stimuli or stimuli, why do some people, seem to look for a very sinister explanation rather than more benign ones?

And the other thing that I've been more aware of, having heard Joe LeDoux speak up at APA recently, is when we talk about a categorization or taxonomy of stressors; I wonder just how much there is out there in terms of external events that we process outside of our awareness, that we don't even know about cognitively and what the impact of those are?

Thank you.

**DR. MARLOWE:** Ann, by the way, is a psychiatrist. She forgot to tell you that.

I'm David Marlowe. I am professionally a social anthropologist. I have, however, spent, I guess, my entire professional career mostly in research and military psychiatry. I did anthropological field research on intergroup violence in Somalia in the late '50s and on medical anthropological issues in North Thailand in the '60s for almost four years.

Beyond that, most of what I have done has been looking at the effects of the kinds of extreme environments we put soldiers into, as well as the effects of their social environment, their unit, on the ability of them to maintain themselves and to maintain some semblance of mental health given the things we do to them.

Rather than review what was a long career, I was Chief of the Department of Military Psychiatry at the Walter Reed Army Institute of Research; retired from there in 1996. At present I am a Senior Scientist with the Henry M. Jackson Foundation and a Senior Lecturer in the Department of Psychiatry at USUHS.

My concerns to a degree have been lifelong professionally in terms of the effects of war and what we might call highly stressful situations on human beings. If anyone is interested in the draft of the report to Rand that I did last year -- it still is not in its final phase -- there are a bunch of copies here that are available. It's rather long.

At any rate, focusing exactly on what we're doing here, I was given the responsibility when the Gulf War deployment began of assessing stress and adaptation among troops in the Gulf, and I took teams over twice during Operation Desert Shield before the actual shooting war began. I had a team over during the shooting war. I had people over afterwards, and we collected a great deal of data on soldiers who remained on active duty after return.

Among the most important data sets, and unfortunately not yet published except as reports, was one of 2,500 soldiers on which we had gathered data in Saudi Arabia, a combination of interview and questionnaire data, before the shooting war began. Of these we were able to gather data on about 1,500 who were their own controls after the shooting war.

There were, in terms of why we're here, some very striking things about this panel, and that brought me to a new appreciation of the issue of vulnerability and possible predisposition. Here we had people who were up against the sub-acute, chronic stresses of the deployment. They had not yet been exposed to the traumatic stresses of combat. The instrument we used was a fairly standard one, the brief symptom inventory. It's a subset of the Hopkins Symptom Checklist 90-R, a standard instrument.

Overwhelmingly the folk who scored extremely high on it prior to initiation of the war were the ones who scored extremely high on it after the war was over and they returned. We had set up an algorithm out of it and a number of other instruments that we used of potential risk for post traumatic stress disorder, and this cohort also produced the overwhelming majority of people who met the criteria of that algorithm. So this is, in fact, probably since the best data in the American soldier disappeared, one of the few prospective studies that was done.

We then did studies with approximately 30,000 soldiers following return using a battery of instruments.

A couple of things in addition to the issue of predisposition, which is why I want to de-focus just for a moment from the issue of PTSD. We must never forget that what we call stress comes in a broad spectrum of environmental impacts, be they social, physical, or what have you on people.

The people who claim to have been most stressed by combat events were the people who were most stressed by the events of the deployment itself. In another study that we did, folk who had deployed, reservists and active duty from Pennsylvania and Hawaii for DOD, we got under a 40 percent return. Interestingly enough, the major difference between people who deployed to Saudi Arabia and people who did not, as contrasted in yet another study with people who deployed to Germany as part of the call-up, et cetera, was that they all reported at this point, double-to-three times the number of physical symptoms as people who didn't deploy to Saudi Arabia.

Now, in all of these groups there's another interesting finding. This is, that people who are most highly symptomatic, and who also reported the highest levels of intercurrent stress in their lives at the time also tended to be the people who attributed their problems to the deployment to Saudi Arabia. Not necessarily to what happened there, but in many cases to other things that were going on in their lives, their marriages, et cetera.

And I think it leads directly to some of the issues here: (a) the increase in reporting of somatic symptoms; (b) the issue of attribution; (c) the issue of what I've come to call subacute chronic stress.

And then as time went on, the increasing stress as people retrospectively in terms of what they were learning attributed more and more of what may have happened to Saudi Arabia. In fact, one of the observations we made in Saudi Arabia was that the later people came in as we interviewed them as opposed to people we saw in September and October. People we saw in December, who were just coming in from the U.S., were far more anxious, far more disturbed, far more concerned about the environment they were in, and far more negative about their ability to cope in that environment because of the saturation they had received from the American media about: (a) the nature of the enemy; (b) his weaponry, and the fact that their stuff was no damned good.

So all of these things come together. My own view is that we were dealing with something like a Matrushka doll, each thing nested within the other, and we're starting out with these global cultural constructs which ultimately have impact on the cell.

I would like to say one other thing, I don't think prospective studies are that hard to do, and I disagree with my dear friend Harry Holloway about time. Most soldiers have a hell of a lot of time. The issue is a cultural phenomenon about lack of time on the part of their commanders because if they say, "I have time for you to access my soldiers," they think it looks bad, and there are a whole bunch of structured points at which one could go in.

Now, the flaw in the studies we did, is the first time we gathered data on these soldiers, was when they were already deployed and in a stressful situation. What we need is data when they are, quote, "*at rest.*" There are situations in which they're at rest. Unfortunately when you work for a service, you go to the Chief of Staff for the Army, who was the person who told us to do these things. He has no authority. All he can do is suggest.

In order to do these things and get access to have folks in the Army, or the Marine Corps, or the Navy agree to do it, it has to come from the Secretary of Defense's Office through the Chairman of the Joint Chiefs. He is the only one who can give these people orders and say: "Let these people in and let them do their thing through the various commanders and chiefs, the various areas."

So with that I'm going to stop, and we're going to kick it over to Karl Friedl.

**DR. HOLLOWAY:** Well, before you go since you disagreed with me --

(Laughter.)

**DR. HOLLOWAY:** -- I want to be clear about the point. My point was that DOD didn't have time, not that soldiers don't have time, and that's a distinction.

The second distinction is I think it ought to be said about the Gulf that a proposed surveillance study was proposed for the Gulf, funding and all of the rest of that, and was directly turned down by the command.

Furthermore, with regard to the Gulf, you've got to recognize that for the first time we sent a major deployment of soldiers in harm's way without a general medical officer in the theater because that was refused. So that the overall tendency in DOD at a command level, not at a soldier level, is to support less and less of this kind of activity at that level.

That's what David ought to be disagreeing with if he's disagreeing with me.

**DR. MARLOWE:** Well, I can both agree and disagree. The problem was that no one at DOD would order the theater commander to do certain things, and that was a problem involving the Chairman of the Joint Chiefs.

The only reason I got in with my team were direct threats made by the Chief of Staff of the Army to the four-star over whose career he still had some determining power, he felt, who was the commander in the theater who tried to keep everybody out, and it was not alone medical assets. Center for Army Lessons Learned, everyone was kept out for various reasons that had to do with the personality of the gentleman involved.

We won't go off on that side.

(Laughter.)

**DR. NORWOOD:** Is this an example of something that might be edited in the final transcript?

(Laughter.)

**DR. HOLLOWAY:** Not by me. I won't edit it.

**DR. MARLOWE:** I said it to the presidential committee in great detail.

**DR. FRIEDL:** Am I going to be in the way for anybody? And can everybody see? I'm sorry I didn't have slides. I hate the viewgraphs, but it's the Army way.

Can you hear me? Do I have to push this down?

**DR. NORWOOD:** No.

**DR. FRIEDL:** Can you hear me just talking?

You've already heard my background and my own personal bias, which I'll just reiterate because it creeps into everything I do. That's this intense interest and, I guess, passion for mechanisms of adaptation to extreme environments and stressors. And in the operational medicine research program, I guess that's what we're about. I've been in this area for about five years now in the program office, and I was an understudy to Dr. Hegge. The first thing we had to do, is define what we were about, and everything else that the Medical Research and Materiel Command does. This is true for the other services, I think, is pretty well defined in terms of there's a group that does military infectious disease, and they develop vaccines for things like malaria and shigella. There's a chem/bio group and they're interested on the biomedical side in better defenses, atropine injectors and that sort of thing to protect against chem/bio threats. They don't do the actual suits.

There's another group on the materiel side that does that, but I was talking in biomedical terms of "skin in" solutions. So that's what we specialize in, and there's usually an area that deals with something like combat casualty care.

Once we've failed in operational medicine and they become a casualty, then we need to take care of them, and that's combat casualty care. That's stuff that might be a little different than what's being done "in the universities." It's maybe not even "the golden hour." Taking care of people in the brass 15-minutes is the way one of our folks has put it and developing materiel that might be somewhat specialized to military uses.

So in the past it was sort of everything else that was left over filled operational medicine. That's not the way we like to look at it, and it's really not the way we've dealt with what we do.

I think this is a better way to put it together, and I'm going to spend a little bit of time on this slide. I want to make sure you can see it.

What we deal with, are all of these operational stressors that degrade. First of all, soldier performance that might lead to them getting injured or killed, but it's the stuff that gets in the way of soldiers or sailors or airmen doing the best job they can do and having that combat edge. So they're a collection of stressors that maybe militarily unique or at least that we'll see in operational deployments and sometimes in training environments as well.

I've grouped them roughly in these four circles, and there's a reason for this. This is the way we've done research for many years. We've been sort of Balkanized. In fact, I could point to each of these circles and name one of our research institutes that has specialized in that area, and there's no cross-talk between them or there hasn't been enough in the past.

We have Department of Neuropsychiatry that deals with psychiatric type stressors, some of the psychological stressors at least. They also deal with sleep and some other areas. They don't talk a lot from Walter Reed with our group up near Natick that's supposed to be doing all of the environmental stressor work, and that's been a special challenge. So that's something that Dr. Hegge faced when he first got in there, and we're trying to figure out how we push these circles together.

These are overlapping circles. They should all be pushed together into one big center. We don't have to be geographically collocated. We're located in a way, that maybe, we're close to where the test subjects are going to be or some unique capability. USARIEM where we do our environmental work is near climatic chambers. WRAIR has been our center of excellence for many years. They were close to NIH, NIMH, where there was a big exchange for a long time, and so there are some other things that naturally developed there.

One of our challenges has been to push these together and also do this between services. So now we talk about Naval Health Research Center out in San Diego as being part of our family, and they have expertise most of all in the epidemiology area.

How much are we doing in terms of the epidemiology of neuropsychiatry, though? Chuck was talking about this last night, and we don't have anybody in DOD who's really, really grappling with that. And so there are still some deficiencies in this area.

What are the things that we're most concerned about then? The reason we exist and are separate from, say, clinical investigations or the work that goes on in universities, is that, we're supposed to come up with interventions. At least algorithms and rules and specifications for the things that are going to make a difference for optimal performance in the field. That's why the commanders would value us, and hopefully we've delivered something to them that they recognize as value added.

I refer to it as putting steel on target, and that's a quote from General Krulak, who said that he just didn't think women could hump a load for 20 miles and then put steel on target. So we did the study with Special Forces men and found out that they had that problem, too.

(Laughter.)

**DR. FRIEDL:** And we're going from there.

So there are a lot of these stressors that are important that we're studying to try to optimize performance, and that's our first and foremost purpose.

Then in helping people to be able to think straight in the face of these degrading stressors, we also prevent injury, and maybe we prevent illness. When we deal with the stress problems, as we saw certainly in our ranger training, that's one of the most extreme forms of training and one of the most extreme models that we've found on the Army side so far. We found suppressed immune function, and this was very interesting to us. We, in fact, were allowed to come in and study these guys because there was a whole class that was wiped out by pneumonia, and they said, "This isn't appropriate. This isn't normal. Come on in and tell us how we'll know when the stress is too much to have safe training because we don't really want to hurt anybody."

And the Marines have come to us more recently and asked the same question. "Come study us in basic training and insure that we're not going to have somebody die from heat or cold or something else." They always get it a little bit wrong though when they try to design the studies for us. They say, "Well, we think this three-day really intensive course is very demanding and requires a lot of energy. Maybe we can solve the problem by just giving them a little more food." In fact, you can live on your fat reserves for an extended period of time, as we discovered even with lean rangers, and the immediate threats are things like thermal strain and some of these other problems. We almost never give any credence to the psychological aspects that overlay all of this.

After all of that and most recently, we've finally gotten some credibility -- I'm talking research -- into concerns about later health, and in the past that just wasn't acceptable at all. I think we're very fortunate, in a way, that the Gulf War illness issue raised its head. It's given us the clout and the impetus to finally take some pieces out of the "too hard" box that we'd sort of been dabbling in for many years and try to move forward with those, and that's what this meeting is all about.

It's the stress piece and somatic consequences of stress and longer term effects that we've never been really given the opportunity to study before. It would be the bottom priority in the past for anything we wanted to do. Now we can say, "Well, and this will also help to prevent future Gulf War illness type conditions," and suddenly it's okay to study. So that's been good for us, and we need to make sure that's charted into all of our research planning. So I think I've said enough about the way we consider what we do, what operational medicine is and why we're doing it, what the concerns are.

I want to just tell you a little bit about what Army after next might entail and some of the concerns. Now, this is a little parochial, but there's also a Navy after next, and the Marines have a concept for operational maneuver from the sea. Everybody is moving in the same direction though. So I've labeled it, "Army after Next," but this is true of all the services.

The next battlefield in Army after that would be the year 2015 timeframe or even beyond that. It will be an even faster moving battle. It's going to be greater dispersion of the forces. We're talking about platoons being replaced by maybe three person teams with very wide dispersions, and these are going to be better-trained people. They're going to have the best training, best equipment we can give them because when you've only got three people out there, every one of them is going to count absolutely. There's increased lethality. One mistake and that might be it. They are dusts. And even today we're being asked to do more with fewer soldiers and deploy anywhere any time, and that's going to increase over time.

Now, the Navy has the same issues. They're downsizing their ships. They're reducing ship crews from whatever they are today to maybe a third that size. They're looking for -- they've got a program called 'Reduced Virtual Presence', ship presence, where they want to instrument their folks. They're a little ahead of our game, which Dr. Hegge had tried to get in place, with some kind of physiological monitoring as well as location monitoring so that on board ship we know where the people are at any time. Especially, if they're part of a ship damage control crew or something. Possibly, they'll be instrumented to tell us something about how they're doing.

Body temperature, heart rate, and basic physiological output is nice, but even a medic doesn't want all of these raw heart rates. Once we do a little sensor fusion, and figure out how to take the essence of a set of these signals and give them a red light, yellow light, green light, that's the information that would come back so that we know where people are and how they're doing. Are they still standing up? They're going to need that on board ship. I think they're ahead in terms of the development of the engineering.

In all of these things and plotting for future challenges here, it seems like the engineering and the technology that we thought, "God, some day we're going to have that stuff," is already there or it's in the foreseeable future. It's turning out, that may be the easy part, and it's understanding what this means and predicting how somebody is really doing, that's going to be tough.

We see all of these proposals that come in from engineering firms, and they say, "We're going to build this temperature sensor." The temperature pill was good, and we had four rangers die from hypothermia, and so a couple of companies came in and said, "Well, we've got a temperature pill. You can instrument these guys, and they'll know exactly what their core temperature is at any time." And the last paragraph in this one proposal said, "And the medical weenies will tell us what the threshold is to plug in for the alarms." Well, we've done the studies now where we went out and actually measured this in the field, and it is possible to do these field studies, but it helps to have noninvasive techniques to do it so that we have a minimal footprint.

We found some surprising things about the physiology, and that's what's so fun about physiology, especially when we get into these sort of extreme circumstances. We keep discovering brand new stuff that everyone goes, "Well, surely you knew that."

At three in the morning in ranger students with temperature pills, we'd be sending in the helicopters, maybe two nights in a row. Then they'd throw the things out because they go down to 35 degrees C. when they're sitting out there in the swamps, and these were in warm conditions. It's just a normal circadian pattern that actually drops a little bit lower in people who are hyperthyroid, have no body fat at that point in the course, and they're sitting out in the environment, and it's a normal phenomenon. A lot of these guys were down to 35, 35 and a half C degrees, which might be used as a diagnostic criteria for somebody coming into the emergency room.

So we've got to do these field studies. We've got to have the techniques to go out and noninvasively collect data, physiological data, and the toughest of all, some handle on psychological data, on how they're doing, before we can start to figure out how we're going to turn that around and provide some kind of command consultation.

So even aboard ships, what are we going to tell the Navy that they should be monitoring to know how somebody's doing? Raw heart rate certainly isn't going to do it, and even temperatures aren't going to be helpful.

**DR. ENGEL:** Can we get them like electronic mood rings or something?

**DR. FRIEDL:** Electronic what?

**DR. ENGEL:** Mood rings.

(Laughter.)

**DR. FRIEDL:** Yeah, there we go. We actually have -- MIT is working on a mood ring for us. It's actually an oxygen sensor, but it's in a ring.

You know, there is a part of this, and I need to show you that because I've made this point now. This is key to everything we do, and here I've labeled it "physiological telemetry," but how do we get insight into what's happening in their heads and performance here?

This is a Norwegian ranger student, a cadet. They have a five-day course that their cadets both from the Naval Academy and their equivalent of West Point have to go through as part of their training. They all pass it so there's no problem with setting up control groups and really fooling around with these guys.

There's a very interesting body of literature in this area from Per Christian Upstad about all of the endocrine changes. He's trying to get into more of the so what happens neuroendocrine in these students when they go through five days of no organized sleep and no food. And so we've had the opportunity to do some studies with them. We've used our temperature pills. This is an example from that ranger study that I told you about where temperature falls at three in the morning.

We've also used the actigraphs developed at Walter Reed. Dr. Hegge was part of the development, and we keep improving our actigraphs.

This is from another study at Fort Benning where you can actually get some semi-quantitative measures of energy expenditure. This guy is wearing one of the actigraphs.

We have got a foot strike monitor that tells us something about locomotory activity, but one of the more interesting things that's being developed now is at the Naval Health Research Center. There's Scott McCaig, who has spent a lot of time analyzing EEG signals, and he's trying to do this in conjunction with a vigilance monitor. We've got all of these people who sit at control panels, and they just have to watch for that once-in-a-while incoming signal that may not happen at all in their whole career. Whether they're on board ship or in a Patriot missile battery, that's kind of boring work, and it's real easy to get these lapses in vigilance. In fact, it was sort of an incidental finding to another study they were doing, where they found out that when they were monitoring EEG, they actually could pick up some distinctive patterns of signals using some kind of neural net processing that predicted lapses in advance of the true lapses. So now we're working on the dry electrode technology so that we could do this with just, say,

two electrodes built into a baseball cap that these Navy guys will wear. They'll be sitting there and will actually get some kind of warning signal, and then we could have something that'll wake them up at the right time.

And it would be interesting to do all kinds of things. You know, we could have a little voice in the back of their head. All of the psychiatrists in the group might wonder about that approach.

(Laughter.)

**DR. FRIEDL:** Or maybe some special aroma that they respond to. You know, the Air Force is talking about a little voice in the cockpit like your child's son saying, "Wake up daddy, you're about to crash!" to bring them back.

So there are some approaches that are being tried in this area. We need more of these research tools, this research tool kit to be able to go out and do those physiological studies, psychological studies fairly unobtrusively.

And I think that was Dr. Holloway's point, that we really do need more of that because it is hard to get in and commanders just don't want to give you their time, and I don't think it's a DOD position. DOD is who? It's us, people that help to decide what some of these studies are going to be and how we're going to fund them. It's sort of a collection of decisions, but for the most part people say, "Yeah, this is worthwhile," especially once we explain it to them. Our generals are pretty smart guys, and they're in favor of trying to come up with the right solutions.

But it is pretty obtrusive, and if they're in Bosnia and it's an actual operational mission, it's a low priority even in the Gulf War. Besides personality problems, their first and foremost mission was to get out there and win the war, and they sure didn't want nutrition teams. We were sort of thrown out of there, or any of these other teams coming in and adding to the burden.

In the future, they're talking about a reduced medical footprint as well. They want more, easy-to-use stuff without even the medic being attached to it or maybe a telemedicine presence or something so that they don't have to have those add-on folks out there. They want just the war-fighters out on the front lines.

So we're thinking about where we're going off into the distant future here. I think what we're trying to get in operational medicine is a set of integrated human performance models most of all.

But I'm reminded by something that my boss told me on Thursday. He said when he was a Division Surgeon, his commander called him in and said, "I want an equation. I want you as the Surgeon to develop an equation for when our soldiers should have their ear flaps down, and their ear muffs." And the guy was serious apparently. You know, it's the very simple -- at what temperature do we say, "Okay?" Everyone, "ear flaps down," or "ear flaps up," and is there something else you have to compute in there?

And so, this got silly. He gave him an answer that was not acceptable, and then had to explain to him at length about why this just wasn't practical and feasible and individual differences and metabolic differences and so on, and I guess he finally had his way.

But that's to illustrate the point that we don't want to end up with high tech solutions to low tech problems. There are all of these fascinating technologies that we're tempted by. We've got to be sure that there's value added when we're going to apply some of this. So we're keenly aware of that, and we have to always be thinking about that.

Now, I just want to tell you quickly about what we think and, where we're going with some of the research that we're doing.

I've broken this into three charts like this, as examples of one part of the program. Our program could be split into protection and enhancement issues.

Now, when we talk about enhancement, we're not creating super soldiers in the sense of something that's better than baseline. We're enhancing performance in the face of operational stressors and trying to bring them back to baseline or something close to it. If we think about enhancement, there are all sorts of things we could talk about in terms of tissue remodeling. How do we prepare soldiers to go out for a new mission where it might require greater strength? And there's going to be bone remodeling and muscle remodeling in effect in the physical training that you go through. We have this problem, for example, in basic training where we have a lot of stress fractures, especially in women, and we have a lot of overuse injuries, and there's a lot of discussion about training in general.

So there are a series of studies that are going on now to develop injury markers, noninvasive injury markers. Right now they're sort of biochemical, urinary markers. They'd be less invasive if we could have some salivary markers. We're trying to understand the relationship between thyroid hormone and then some of the levels of stress that we place on them, the physical stress and biomechanical stress. We're also looking at tissue substrates and regulators and nutritional interventions that might enhance some of the performance and development.

This is the general road map for the next ten years that our labs are already lined up on. That's Navy and Army and a little bit of Air Force. We're trying to think about where we're going for the long range. If we don't think of a point out there, even if it's not where we're really going to end up, and we have some mid-course corrections, and if we don't have something that they target, we have this common problem, at least within our labs, of confusing motion with progress. And people say, "Well, I'm spending my budget. I'm doing a lot of interesting research, and I published in Science," but we want to be sure of where we're going.

So in this case, maybe we're talking about genetically activated enhancement compounds, and I don't think that's out of the question. We're already talking about different sorts of bionic approaches that would enhance soldier physical performance. I think physical performance is one of the least of our concerns in the future though. It's most of all going to be the cognitive and stress load. If you think about that slide I showed for Army after next, there's the technological complexity. There's the isolation stress. You've got three person units that are spread out all over the place.

We had one exercise to try to think about this and to try to develop these requirements in a more systematic way. We did it jointly with the Navy at the Naval War College, and they called it Vanguard '97. We all went away for a week, and we worked through two exercises for the years 2015 and 2020.

One was a volcano/tsunami problem in Indonesia, and the other one was sort of a next version Gulf War. We went through the actual exercise of planning. We had operational commanders from the Navy and Army in the room and thought through, how we would do this, and what are the limitations. What are the problems?

Now, where do we need medical research? I was in one of the operational medicine groups, One of the things that kept coming up was the isolation stress they thought was going to be incredibly important, and the concept for a mental mom, or some kind of synthetic community, and how are we going to structure that. Will it be that little voice in the back of the person's head that makes them feel connected to everybody else?

They came up with a wish list. I think anyone of us could have sat down and said, "Yeah, those are the sorts of ideas we would think about. Something out of science fiction," but it's the kind of approach that we have to keep trying and thinking outside the box and thinking where we're going to go with this. We don't have any good, structured way to develop requirements and think about where we're going in the future, other than pulling together groups like this, subject matter experts that are going to say, "Well, here's what you need to be working on."

And we need that more than we need line commanders sitting in the room coming up with stuff that they've seen on "Star Trek." I could do that. I did do that. My first week in this job, four years ago, in the very first week they said, "You've got to write all of the follow-on work packages to reserve the money for the year '04 for operational medicine." And I said, "How do I do that?" And they said, "Well, you know, you can do as well as anyone. Just think of where we're going to go. What's the follow-on to enhancing visual performance?" I went home, watched "Star Trek," and came back and said, "Okay. I've got it."

(Laughter.)

**DR. FRIEDL:** "We're going to have direct brain, electro-optical interfaces, you know. We're going to have boards."

Dr. Marlowe doesn't know it, but the follow-on to your work package at the time was, "We're going to start trying to screen and develop empaths that'll sense when a unit is in trouble." Those words have been changed since then. I've had the opportunity to revise it.

(Laughter.)

**DR. FRIEDL:** But you were going to develop empaths. You know, how are we really going to do this? It's not going to be line folks sitting around the table that are going to help us think about where we're going. We really do need some help in these areas. Otherwise we don't spend our budgets in a sensible way with clear direction for where it's going. This is another area. This would be in some of the metabolic pieces, and it's almost not fair to draw these straight line arrows. My graphic artist didn't want to do all of the connecting arrows that would have made it look like one of those metabolic charts. In fact, all of these should be interrelated and on one chart, and then you wouldn't be able to read it at all.

When I mentioned hibernation inducer, we're not really going to put soldiers in hibernation, but there are things we can learn from hibernating bears. They come out of their winter sleep, and they've recycled all of their amino acids. They lose no urea nitrogen, no-lean muscle-mass-bone minerals. They can recycle water through the bladder, and it's triggered by some biochemical trigger. If we understood that better, we might be able to do that in soldiers while they're performing and eventually end up with something like a still suit that recirculates water.

The biggest problem in the desert was carrying all of that extra water they need. If there's a way to conserve water better, I could see this.

You know, today if we had something, we could do this with complete water recycling, microclimate cooling built in. What else would we want? And the chemical protective suit so that there would be this suit that would look kind of like those fake sumo wrestler suits that you can get.

(Laughter.)

**DR. FRIEDL:** It would be about that big, I think.

But in the future this could be, some thin skin layer that's going to go over the skin. The MIT media labs are already working on these electronically activated fibers that do all sorts of stuff, even change color to match your background. Technologically that's possible.

Physiologically we need to understand a lot more about what the actual requirements are for physiology in different environments to be able to make it work and to regulate it.

In my second to last slide, we come to the most important one. For lack of a better description, I call it, "stress and performance neuromodulation". Again, my graphic artist always tries to improve on these things and wanted these to be a certain font size. So cognitive memory has been pushed together (whatever cognitive memory is), cognitive and memory enhancers, and this was behavioral strategies to control neurochemistry. I think that the direction we need to be going in, is not giving the drugs to change the neurochemistry, but to understand how neurochemistry is influenced and performance is influenced by behavior, and try to do the smart behavioral things.

It might be nothing more than – or not necessarily soldiers all practicing Yoga. It might be just having the right markers so that we know when a unit is starting to get in trouble, and they just need to be given some rest time. Then a commander would know when to rest them.

Again, we've got to be careful that we're not putting high tech solutions to low tech problems. Dr. Hegge has given me the example of, I think, Moshe Dayan during one of the Egyptian-Israeli wars where he was credited with this great victory and his strategy. They were going to attack at night, and he's briefing all of his commanders, and he looked around, and he thought, "Well, maybe they need some sleep," and so he slept them, and they attacked in the morning, and they had this great victory. When they asked him about it afterwards, he said, "Well, what really happened was I looked around the room, and they were all asleep already. So I said, 'To hell with it. Let's sleep and we'll go when we're rested.'"

(Laughter.)

**DR. FRIEDL:** You know, it doesn't take a special sensor or an actigraph or something for commanders to know when their soldiers are fatigued and when to rest them. We don't need a noninvasive glucose monitor on the back of a wrist watch to say, "They're a little low. Maybe they need to stop and eat."

A hydration monitor might be useful today. You can get performance degradations associated with this sort of involuntary dehydration, but we don't know what's really going to make a difference until we get out there and do those studies.

Along the lines of this area here, there's a lot that's being done with sleep. Right now, we're working on melatonin and whole strategies that involve more than just giving a drug or a hormone to help people resynchronize in rapid deployments.

In cognitive performance, we're looking at a caffeine bar. We've got something called a HUA or HUAH bar.

(Laughter.)

**DR. FRIEDL:** It's just a glucose bar right now, but we found out that it will hold nine grams of tyrosine. Tyrosine really seems to make a difference in some high stress conditions to enhance performance.

There was a nice study done by the Navy folks with Marine sharpshooters in Alaska. Their sharpshooters were cold and fatigued, and never supposed to miss. Yet, their performance degraded down to about 90 percent hits, and that was really unacceptable. In a placebo controlled trial with tyrosine, they were restored to 100 percent hit. We think it's working as a neurotransmitter precursor, and there's some depletion that they benefit from getting the tyrosine on board. It doesn't have any side effects like caffeine. They don't get fidgety or anything, any of those sorts of problems that we know of. So we're doing some more studies with tyrosine. There may be other amino acids that can influence behavior in certain ways, and we can do this in sort of an almost natural way with simple dietary supplements.

The caffeine piece, we're talking about the possibility of maybe using as much as 600 milligrams of caffeine in a HUAH bar with a couple of exclamation marks, I guess.

(Laughter.)

**DR. FRIEDL:** And warnings about when and how to use it. It's being compared now. There's a study about to get rolling at WRAIR where they're going to compare to modafinil compare caffeine and modafinil and sleep deprivation.

**PARTICIPANT:** What's modafinil?

**DR. FRIEDL:** Modafinil is this amphetamine-like drug that the French developed for narcolepsy, but it's not an amphetamine. It's just been licensed by the FDA for use in this country, and so it's pretty exciting because it doesn't seem to have the down side of dextroamphetamine that we've used in a lot of our aviator studies.

**PARTICIPANT:** Is it available?

**DR. FRIEDL:** Cephalon is the company that's marketing it, and I think they've gotten approval or they're very close. The Canadians and the French have already done some studies with Canadian forces and modafinil.

And then there is this area of impending psychiatric casualty predictors. I'd like to say we've got a whole bunch of stuff going in that area. This is, in part, my wish list, and we hold the money out there and say, "Wouldn't you like to work on this?"

We're looking for predictors. I think the best effort we have going right now is one with the SEAR course's, "Survival Evasion Resistance and Escape," at Fort Bragg. Andy Morgan works with Dr. Mason, in collaboration with some of our folks at Fort Bragg, and also at USARIEM to look at predictors like acoustic startle, and hormone levels, on who's going to run into trouble later.

What would be very nice with this Fort Bragg population is to get good baseline measurements before there's any deployment, because this is the center for a lot of our rapid deployment units. We want to get solid baselines on these folks; then find out what happens in these deployments that are likely in the near future, and have something to compare against. We don't have a big database of good baseline. It's not a baseline once they're alerted and told they're going to deploy either, and so that's our hope, that we're going to make some inroads in this area.

The next piece is already being partly done with some of the Gulf War money by primarily extramural performers. We're also looking at immune function consequences as one piece to stress consequences, and I think that effort is going to move forward a little more.

As I mentioned, that started with our ranger studies. We took a field immunologist from USDA along with us to study the rangers. We found out things like T cell induced blastogenesis was markedly suppressed, and approximately 50 percent normal. Now, I guess that's still not anything dramatic if you deal with hospitalized patients who may have really fundamental drops, but it looked like they really were immune suppressed.

When we looked at this in other studies, and in other groups that we thought were pretty stressed in terms of high physical demands, maybe even not getting quite enough food to eat, and a high anxiety component, we don't see an effect that dramatic. We also don't see big problems with illnesses. It was only in the rangers where they're really dramatically food deprived that we saw that kind of suppression, and we see this increase in cellulitis and other infectious disease outcomes.

So I'm not convinced that we have a problem in any of our military training settings anyway. So, before we talk about interventions to boost immune function, which some of our labs want to do, we need to be clear on defining when and where we actually have a problem. So that's got to be the emphasis of that work right now.

I think I've said enough about that. These are the directions we're trying to push in. Again, we have to have something out here that we're throwing up on the wall as a target, but it's going to take a lot more careful thought, and each one of these little areas is really a major research program, I think.

I want to end with one of my favorite slides, and it didn't copy on my scanner very well last night. As you know from my perspective, and trying to understand what would happen to the hormones in some of these guys, this is the team led by Scott that went to Antarctica. This is the picture they took shortly after they got to the South Pole. They thought they were going to be the first there.

They found this tent that Amundsen had left set up. He had been there just about 20 days before, and left a little note for them saying, "We've been and we're gone already." They must have been absolutely dejected. Now, there were consequences to this, I think. This whole team died. This is film that was taken off their bodies later. They died, I guess, of malnutrition and scurvy, but they did all sorts of irrational things even on their way back.

I would say, first of all, that their testosterone levels must have been just dropping, plummeting at this moment when they got there and they found that somebody had beaten them. One of the things they did on their way back, they were found man-hauling and pulling several hundred pounds of rocks on their sleds. They thought it wasn't humane to have dogs do it, and they died pulling those rocks. They said, "Well, we're going to collect geological specimens along the way, because we weren't here for some kind of contest. This was a scientific expedition, and we're bringing back these great samples."

They did a lot of wild things, and I think it was a consequence of whatever happened at the moment, that they were just so fundamentally surprised and depressed by this finding.

It would be wonderful to have some kind of noninvasive sensors hooked up to a team like this to try and understand what happens to the physiology in these settings, and that's the kind of stuff that we're doing with what we call expedition research.

We need more of the right kinds of tools to make those assessments, at least salivary, testosterone, and cortisol. If we can get some better handle on something that really reflects the neurochemistry, we could start to get an understanding on how it correlates with some of the physiological behaviors that we see.

You contrast that with this other team that they're waving to the guy in the rowboat. This was from Shackelton's group that had preceded the Scott team. They never made it to the South Pole. Their boat, the *Endurance*, was crushed in the ice floes, and they were left at the South Pole without a boat, and they had these rowboats. They carried the rowboats, and then they rowed from island to island and finally got to the tip of South America, but they never lost hope. They had a leader who said, "Follow me." They had confidence in their leader, and he came through for them.

Now, you contrast the neurochemistry for this group with the Scott group, and I think we'd see some pretty dramatic differences that correlates the kind of behavior and motivation that follows.

So I'll leave it there and answer any questions.

**DR. MARLOWE:** I just want to underline something. Shackelton's boat in their last long haul rowed 126 hours without stopping, and perhaps sleeping while rowing; but they continued to row until they made a landfall where there was food and shelter.

**DR. FRIEDL:** They believed in their commander. He said, "I'm going to bring you to safety," and every single man survived. It's an incredible story.

What we do need to do most of all is bring together these pieces. This is a book from a meeting I was at about a year and a half ago. I thought it was a fantastic meeting, because for the first time in my experience, we brought together people that were experts in thermal regulation, people from the Karolinska Institute who were studying metabolism. There were sleep people there, and we tried to put it all together to think about stress consequences at the organism level. What we didn't have were any psychiatry and neuropsychiatry people. That part of the discussion was left out of this altogether. So we're getting closer, but we're not there yet.

**DR. MARLOWE:** What's the title?

**DR. FRIEDL:** This is "Physiology, Stress, and Malnutrition, Functional Correlates and Nutritional Interventions."

**DR. MARLOWE:** Dr. Guze.

**DR. GUZE:** May I ask one question? I was very interested in something you said at the beginning of your talk about, and I'm not sure I understood it clearly, so you can confirm that I did if I'm correct -- that the Army is thinking about just a three-man unit?

**DR. FRIEDL:** Yes.

**DR. GUZE:** Okay. Well, now, I'm curious. If you do your studies with three men units in different terrains and you conclude that this has a very negative emotional impact on the men and interferes to some extent with their performance, are you in a position to challenge the decision to move to a three-man unit from a platoon?

**DR. FRIEDL:** No. We get to make recommendations. We certainly don't make policy. But if we did a study like that and there was this important finding, you can bet we would take that up the chain of command.

**DR. MARLOWE:** May I make an observation?

**DR. FRIEDL:** And Dr. Marlowe has done that kind of thing in the past.

**DR. MARLOWE:** Yeah. I think we face a basic problem. The accuracy and lethality of weaponry is such that the Army and Marine Corps are both moving to what has been termed a granular structure, very small units with extraordinarily high lethal capability, but very widely distributed at the battle site.

The alternative is getting people killed. Now, we're already there in terms of three-man units, and it creates a long-term view in terms of stress effect and the possibility of alteration of behavior, a brittleness that wasn't there in mass forces.

The Army's multiple launch rocket system (MLRS), consists of a vehicle manned by a three-man team: a driver, gunner, and commander, (two NCOs, and usually a Spec. 4). However, this is opposed to World War II, Korea, or even Vietnam, which required at least an armored battalion and supporting arms to destroy an enemy armored battalion under those circumstances.

One three-man MLRS team and its truck can destroy an enemy armored battalion in about three minutes, given the smart weaponry that it utilizes and fires. You can't put them together with other people because that makes a target. SLA Marshall, many years ago in World War II, defined the battlefield as the loneliest place on the face of the earth, and that was when we had 240-men companies and divisional frontages of a mile and a-half. Now a battalion frontage is umpt miles, and we have people distributed where they cannot see each other in most of the combat scenarios we would talk about. So the psychological problems, and the problems of stress derived from the lack of that kind of concrete support become greater and greater because the affiliation is now almost entirely symbolic.

Also, if you lose one man in a team, you can't do your job. If the M-1 Abrams tank requires four men to repair the track if it throws the track, if one of the four-man crew is not functional, the tank is not functional because they can't get the track back on. Throwing tracks is a moderately common thing with tanks.

This is a 'New World' of mass armies. The world of perceived direct support from others is vanishing very quickly. In any combat that takes place with a moderately technologically sophisticated opponent, just as the navy is preparing modularized combat-vessels with a power far beyond that of any battleship or Aegis cruiser, it will have crews of 38 or 39 rather than 400 or 500. It is a difficult world to come to grips with, particularly from the point of view of stress, its emotional content, and symbolic value.

**DR. FRIEDL:** There isn't even a front anymore either. In the next battlefield, it will be more like a swarm, and they can descend anywhere. They can either be behind you or elsewhere.

**DR. MARLOWE:** It's usually defined as a cube, umpt miles in every direction.

Fred.

**DR. HEGGE:** The corpsman has always been a very important figure in combat units in terms of support. Three-man teams, three-person teams isolated, what happens to the brass 15-minutes? There is no brass 15-minutes. What happens to combat casualty care in those settings? I think it virtually disappears, and we haven't come to grips with that yet.

**DR. NATELSON:** Although, that scenario is probably for very little combat casualty in this day and age, and if one of those three people is in harm's way literally, I assume there'll be little left to patch up.

**DR. HEGGE:** Right. It might just be dust.

**DR. NATELSON:** Yeah, right.

**DR. GERRITY:** Karl, going back to your next to last slide of the Scott team, there's also an additional tale to be told. That perhaps another attributable reason for their failure also, was their decision to use what was perceived by some at the time, high-tech approaches to reach the South Pole, as opposed to the traditional arctic approaches used by Amundsen.

**DR. FRIEDL:** Amundsen actually went and spent time with the Eskimos and said, "Let's do natural furs." They spent their whole time going down preparing their sledges in the traditional way. They planned how they would kill their dogs systematically as they lightened their load and eat the dog meat, or at least feed that to the other dogs to prevent scurvy.

The British group was performing light opera on the cruise den for each other. Then they set up their committees to start planning when they landed, which is a different problem, and brought along their high tech piece. They had come up with the latest in Parka designs, and they said, "Well, we're going to use ponies instead of dogs," but the ponies felled through the ice. They also had mechanical vehicles that went through the ice, and the high tech really failed big time.

You're exactly right. I think the attempt to use the advanced technology was part of what did them in.

**DR. HOLLOWAY:** I want to make one point because Ben brought it up that we talk about the lethality of weapons, which we ought to still recall that the principal thing that's going to happen to somebody in a battle area is disease or accidental injury. Those are the two things. Non-combat injury will still be the major thing, and those are treatable conditions. The overall idea that there is no comparable thinking within the medical department for an organization that corresponds to this kind of combat organization is, I think, a major critical area at the present time.

Just consider the fact that the last war from which we have adequate medical records is the Korean War. We threw away the medical records coming out of the Gulf. We never kept them during Vietnam because our data processing couldn't come up to snuff to do that and for other reasons, none of them particularly sinister for those of you who like plots, but having lots to do with stupidity and ignorance.

So, the overall capacity to now move into a new age with a medical capacity that is extremely heavy, extremely large, and not articulated to these kinds of combat formations is part of the challenge of dealing with the stressors that we're talking about here. I'm using that word in quotes, dealing with the environmental events, which you may feel severe deprivation, not be taken care of, and they may ask, "What kind of decisions is General Scott making for us?" to go to the point of your last slide.

**DR. HOLLOWAY:** General Scott, by the way, in terms of predisposition, we might just add that one of the things you might not want to do when you go to the South Pole the first time, is pick a person who has just wrecked a battle cruiser.

(Laughter.)

**DR. MARLOWE:** Fred, and then I want to.

**DR. HEGGE:** Ben's comment about people, about lethality. Those soldiers out there in those small teams will be equipped with the most effective body armor. New generations of body armor are coming on board that will fundamentally leave only certain parts of their bodies really vulnerable to a lot of injury, and legs.

And the suggestion is that there are going to be a lot of wounded out there with serious peripheral trauma and not a hell of a lot of help.

**DR. SCHNURR:** This discussion is very interesting to me. I've learned a lot, but my concern really, was trying to clarify the role of your unit. I think you were saying that if you worried about something like this, that the channels are open for you to call it to the attention of the proper people and make your arguments and so forth.

**DR. FRIEDL:** Yes. That is our mission. We're winning wars for 20 years now and today, hopefully with doing the right research. It's too late to start the research once the battlefield commander identifies the problem to us. That's why it's so important for the scientists to come together. This is the group that knows what's possible. Where we are with the science today, and what sorts of interventions or suggestions we might be able to put forward, at least for the research directions we need to be moving in, or solutions that might be applied today, and make those recommendations up our chain of command.

That's the only reason we exist and have any value added, and if we don't provide something useful there, we should be going out of business.

**DR. MARLOWE:** At this point, I would like to make one observation. Those of you, a few of you I suppose, who went through the New York City public schools in my generation, when Scott was presented to us as the beau ideal of what we should grow up to be, there's a certain value added to dying poorly but heroically.

(Laughter.)

**DR. MARLOWE:** And now we come to the hard part, which is to open the floor to the commencement of dialogue about what it is you would like to know from each other, where we ought to go, why we ought to go there, what the central problems are that we should be devoting our time to.

**DR. ENGEL:** I'd like to make one more comment that actually pertains to Karl's brief, if I could. A couple of thoughts.

One is, that it seems to me that there's a focus on an eye blink in time in the history of the military, which is the point of battle, and I suppose it shouldn't surprise any of us that's what the people who are managing are most interested in.

The second related-point is that it seems to me, there is such a focus on the high-tech. I don't know if we were talking around this point? But it seems to me that maybe the message in the vignette is that as it pertains to the military, the military is about people. It's not about hormone levels. It's not about, you know, HPA axes. I don't want to step on anybody's toes here, but I think it's utter fantasy of a "Star Trek" proportion to think that some of these things are likely to come true in the next three decades.

I mean I'm sure there could be frank disagreement about that statement around the room. From veterans, what I hear often is that they feel like discarded trash. Although soldiers, they feel like ash in the trash and leftovers. They're people in the military. And there will never come a day when military isn't about people. Probably, there will never come a day when that point in the battle isn't but an eye-blink in time in the military. And it just seems to me that the other effect of high-tech is that it's dehumanizing. It takes us away; it helps us to forget what we're talking about are three real people in a very real situation where they may be completely annihilated, and I find that disturbing.

In fact, I find that more disturbing than the fact that they might be annihilated. That we're losing sight of the people involved. I know that you're not the determiner of all of these things, but I think that it's very important that we take a focus on people as part of the research agenda. That doesn't mean we can't look at hormones and things like that, but I think we have to be realistic about it. We owe it to the people who are managing the organization to tell them what's realistic with regard to human factors and hormone levels and so on.

And I think we also have to convey the message that how people perform in battle will have everything to do with how we do with them outside that eye blink in time. So enough said about that, I guess.

**DR. MARLOWE:** Chuck, I guess some of us take that for granted. I think what we should consider primarily and what I take implicitly out of what Karl did is really the issue that Ron Glaser began with. All that we do not know and the value of the high-tech would be in elucidating those processes that make us the kinds of humans that we are rather than providing magical solutions.

And I don't think anyone here is looking at a magical or bionic solution. The history of those has been a history of fairly colossal failure.

We're not there. We are at the point where I think many of these devices and innovations might be helpful in trying to understand better how the human, as a combination of brain, CNS, the rest of the physiological system, processing and operating in the universe works. What are the vulnerabilities, and what can we do about them.

And with that, who'd like to begin? Ben.

**DR. NATELSON:** Yeah. I think we need what Tim said, which is sort of a Framingham approach to understanding the risks and vulnerabilities for this sort of RAD 3 mission. We need to be able to figure out if Frank Sodetz is right that the tails of the distribution of these 700,000 people -- the ones who were at risk, and so it all has to be done in advance of the deployment, I guess. When they're deployed, it's too late. And some of us, like Etzel in our group, are trying to figure out ways to do it, but our plan is to do it in a teeny way. You know, take 50 Newark police recruits, and try and get another 50.

I think that what has to happen, and we've learned so much from that sort of epidemiological approach in terms of pathophysiological risk factors and disease, is to use the same approach and add on physiological and behavioral risk factors, and then do the dog work of the longitudinal study.

**DR. MARLOWE:** Well, let me just say I think we have a problem. The problem in the military is the turnover rate. Unless you start out with a very big cohort to begin with, three years later you've got very few people left in that cohort. Unless you can do things -- and it's one of the things I'd like people to consider -- where you're updating the database every year, and it's not just the military.

There was a large epidemiological study, psychiatric, that was started in Chicago. At the end of five-years, 70 percent of the people whom they had begun with were gone. They'd moved.

What is the base you need? And particularly in terms of having enough people, if folks are deployed into high stress situations, and I guess what we need to do is think of two things: (a) What kind of prospective epidemiology, both psychosocial, physiological, and in a funny sense I'm going to use the term "contextual" in terms of what it is people are seeing and believing at the various phases of this should be done? and (b) What kind of laboratory work is being done, or should be done using either animal models, humans where feasible, et cetera, to try to get a handle on some of these kinds of problems?

**DR. ADER:** Just as another procedural point, I think that if you went around the room and said, "Give me one scientific question," you wouldn't have any trouble getting the questions. I think we all start off acknowledging Ron's point that there's an awful lot we don't know.

But I think the reason I found Karl's presentation so great, so important for my understanding of what's going on here is because it said something else, which is, "We don't even know what the questions are?" That is, this group doesn't know what the questions are. His group knows what the questions are. They may not be able to answer them, but we will sit here, and design studies that will take five, ten years to do. What do we care? We're operating in a different world that doesn't have the same end product in mind.

Now, we can be humanistic as hell about what's going on with a given group of three soldiers, but that doesn't help Karl's problem any.

**DR. MARLOWE:** Yes, it does.

**DR. ADER:** Well, I think if I wanted to impose a conditioning paradigm in the pharmacotherapy of a particular disease, I'd try to tell the clinician absolutely nothing about what I do. What I try to find out is, "*What does he need to know,*" because I can modify my paradigm based on his needs.

What I'm finding out is that I don't really understand a lot about what the military needs are. So I'm just wondering whether or not what's needed here in the long term is a new kind of teaching, a new kind of training program that combines some of these things, and perhaps it already exists. I know nothing about military psychology or what kind of training goes into organizational work, and maybe that's more applicable than some basic scientists just sitting in a lab trying to answer some esoteric questions.

**DR. MARLOWE:** I'll let Karl speak in a moment, but I would not be here if our focus was on immediate answers alone. Many years ago in Thailand we were in a meeting with people from the Advanced Research Projects Agency and several other agencies. Because the Vietnam War was going on across the way and they were all concerned about it, my then boss, the late David Rioch, asked, "What are you doing that will give us something now?" "What is it you want?"

David leaned back, and he said, "I'll tell you. In the business we're in, what I want from my people is that 20-years from now someone will look at something they did and say, 'Hey, that was a good idea. Let's follow up on it.'" The Chief of Staff of the Army is theoretically paid to consider what the Army is going to be like 30 to 40 years from now, not today. That's the job of the Vice Chief of Staff who runs the Army day-by-day. If we do not think 30 years in the future, and what is the basic research that should be done, then I think we are making an error that is grievous and that falls into the same trap as those few people who will say, "Well, I want something now." Are there things we can give people now? Perhaps! Are there any indicators? Are there ways of viewing things? Are there ways of considering that we might be able to intervene? But until we understand the processes and dynamics, and what the unasked questions are in order to ask them, we're not going to get there. I think it's very important that in envisioning this, we envision what the big questions are that might lead us into the future, as well as the questions where we might spend sometime wrestling with what can be done proximately.

Is that an answer?

**DR. ADER:** It's partly an answer, yeah. It's an answer I happen to agree with in general. I'm just wondering whether or not Karl finds that a satisfactory answer.

**DR. FRIEDL:** Obviously, I confused you more than I clarified. I think what's really brought this group together, the fundamental piece behind all of this, was the problem of Gulf War illness and the stress piece, whatever we want to call it, somatic consequences of stress, that we just haven't even begun to grapple with.

It seems like from a military standpoint, we should be driving some kind of research program in this area, and right now we don't have a viable program in this area. It makes a big difference for Army and DOD, in general and VA as well, because VA may have to pick up the pieces from this.

Some of the discussions at lunch, and even before that was, "Should we be thinking about programs?" Of course, we should be thinking about programs, not study-by-study, but programs and maybe longitudinal programs that we should be trying to put in place, more like center grants to move this off the dime in some particular direction. We need to plan that out quite a bit and have a lot of discussion before we get there.

**DR. MARLOWE:** Tim.

**DR. GERRITY:** I alluded this morning to a strategic plan for future deployment health that we expect will be released out of the Executive Office of the President in the next couple of weeks. This was a very large effort that was done collaboratively between DOD, HHS, and VA as components of deployment health recordkeeping, research, and risk communication.

Probably, one of the biggest aspects of this plan is, there is going to be a major, or at least, spiritual commitment. We'll see whether or not this gets carried out in actuality and only time will tell. The underlying organizational concept is that we are going to provide care. And there will be continuity of care as well as records from induction to the grave.

In other words, one of the large aspects of this is health evaluation at various periods during the life of a service member beyond their discharge and up to their death. If it actually happens, this will create a framework within longitudinal studies that extend beyond the brief period of time that many service members are in the service. It will also allow us to really look at more long term consequences of deployments.

So I think there's a lot of opportunity that is being presented by this. It was something that was recommended by the Presidential Advisory Committee that should be done. Under a presidential review directive it is done. Now I think it's up to many of us to make sure that it's carried out.

**DR. MARLOWE:** Let me go back to Ron Glaser.

Ron, how do we start about from where we are now discerning what the unknown questions are?

(Laughter.)

**DR. GLASER:** I'm sitting here listening and learning a lot. I purposely intended to come to both learn and listen a lot. I didn't know whether I could make any contributions or not. I don't really have any pat answers, but I've been sort of thinking about some things. I'm not going to be able to answer your questions obviously, because I don't know.

**DR. MARLOWE:** I didn't expect you to.

**DR. GLASER:** I jotted down some notes as I started thinking about the points that you were raising, and the points that you are raising, which I think are logical points to raise in the context of reality as opposed to, "It would be nice to know about this," but the reality is we're dealing with people. What can we learn so far about how we might apply some of the new information that's been generated, say, by mind-body interactions to a military situation?

I had three things that I wrote down. I told you there's new evidence from our lab and others that psychological stress can affect how we respond to a vaccine. There have been a couple of points raised at this meeting already, which I agreed with, and that is one of the major problems historically with wars in terms of health is morbidity and mortality associated with infectious disease. That's not going to go away. So anything that we can do when we give our military 12 vaccines at one shot and ship them off to the Gulf to protect them better against infectious disease would be something that would be good.

Some studies might be done. There's some evidence, for example, with what we know today as opposed to what we might learn about ten years from now. Getting back to my previous point is that we still have a lot more to learn. We do know, for example, that if you inoculate an animal with a vaccine or an antigen and add growth hormone at the same time, you enhance the immune response.

So, it would be interesting to do a study where you used things like that along with the vaccines to see if you can get a more vigorous response to a particular pathogen. That might add a little bit better protection for certain pathogens that they might be exposed to in the field. So that would be one area that could be thought about. Also, some immune enhancing drug or using a hormone concomitant with a vaccine injection and then you can do the antibody T cell studies and see whether, in fact, you get a more vigorous response. That might be something that might be interesting to think about.

Jim Meyerhoff contacted me several years ago. I don't remember if it was by telephone or by letter and over time, but Jim and I have been talking to each other on the telephone at least every once in a while or twice a year. A couple of years ago when I was down for a meeting at the NIH, we had lunch one day. Several years ago when we were first getting our first results on stress and wound healing, I called Jim, and I said, "Jim, we've got a paper that's coming out in *Lancet*. It's really interesting that stress affects wound healing." I said, "The Army has got to be interested in this stuff. I mean, they're interested in wounds." I said, "Who should I call to talk about maybe coming to the Army to get grant support so we can really explore this because we think the Army is going to be interested?"

Well, he was polite.

(Laughter.)

**DR. GLASER:** I didn't get a whole lot of jumping up and down, but you know, "yeah, it's interesting," and I sent to him, I think, a preprint of the paper or something. He said, "Call this person up at Frederick and talk to them and see whether or not there might be some funding."

So I did. I called this guy up at Frederick who was also very polite on the telephone and listened to what I had to say before he responded. He sent me some information, which I put on the corner of my desk because it fit under one of the programs. There are multiple programs that the Army supported, and if you stretched one of them, behavior linked with wound healing might fit under that program if you tried real hard to make it fit. Well, I think after sitting on my desk for about two years, we went to the NIH. We're trying to get a grant now from the NIH on wound healing and stress, but it seemed to me that this has got to be something that the Army has got to be interested in.

People get wounded. Even 30-years in the future they're going to be wounded. Okay? So that's another area that I think could be exploited. There may be some things that might be provided either through hormonal or drug modulation that might reduce the time that wounds healed because of something you could focus on that would be important, like cytokines, for example, for wound healing. Or, you might think about things, recovery in the hospital environment that might be useful in reducing the recovery time of people who were wounded.

And in fact, Jan and just got, (she really wrote much of this review) that I did with her is under review right now on surgery stress and wound healing. Jan can talk about this. There's a whole surgical literature out there on the effects of different kinds of behavioral implications on wound healing and on surgeries -- everything from how much pain a patient will experience to how much anesthesia a person is going to have to use. Anesthesia has effects on immune response, and yet, there's a whole lot of literature out there on that. And that's something that I'm thinking about now as I sit here listening to this.

And the third point that I wrote down was something that might be relevant to the Gulf War Syndrome. I mean I don't know anything about Gulf War Syndrome, any more than what everybody else reads in the newspapers. However, when a lot politics was hitting the fan out there, I got phone calls from all kinds of veterans groups wanting my views about Gulf War Syndrome because they know I worked on stress and immunity.

And my responses were, "I haven't the faintest idea how stress could." I really didn't have any comment at all. I mean, I said all I know about this syndrome is what I've been reading in the paper like everybody else, and quite frankly, that's probably half-wrong and half-missing what we ought to be having to read about. The press is not always accurate.

But as I've thought about this, I tried to come up with an explanation, as I've thought about this meeting. Since I figured I probably wouldn't have much to contribute to the meeting, as I told you when I saw you guys in Cape Cod, (you and Harry, a couple of weeks ago). What if our folks are exposed to an immunotoxicant at low levels.

Now, we don't know a whole lot about what immunotoxicants do. The people who do immunotoxicology also don't know a whole lot about what they do. Historically, I think, immunologists think about major changes in the immune response and that's what you have to worry about.

I think some comments this morning already talked minimal changes in the immune response. I think it was Paul who said, "What are the implications of small changes." Also, Bob when he talked about his autoimmune stuff or his autoimmune mice. These small changes in immune response may be biologically significant. That falls into the area of what I talked about that we don't know a whole lot about. We know something about a normal immune response, and we know something about a severely depressed immune response. We don't know a whole lot about in between.

But, what if there are interactions that take place between immunotoxicants that are inducing small changes in immune response and stress? Without the stress there might be one clinical outcome, which might be nothing or it might be just feeling bad for the day.

**DR. GLASER:** I have a headache or something like that. But together the stress associated changes in neuroendocrines and cytokines that we know induce immunopathology, could induce immunopathology -- that makes us feel sick when we get sick. That interaction with an immunotoxicant that our soldiers, our military are being exposed to in a field environment could trigger something different than what we're used to seeing and catching us by surprise.

And when we're not thinking like that, when we know very little about those kinds of interactions (and the immunotoxicology people don't know very much about them either), presents us with clinical symptoms which we in the medical community have difficulty identifying and diagnosing. So, we look for tags because we're not comfortable saying, as somebody pointed out, "we don't know" -- "I guess it was you" -- "we don't admit" -- "the clinicians aren't ready to admit they don't know what's going on out there."

Well, I mean, there are a lot of things we don't know about. What we're doing is we're adding tags to something just to put a tag on it so we can try to handle it and deal with it when, in fact, maybe we don't know.

But those three kinds of things came to my mind just sitting here this afternoon that I thought maybe might be worth thinking about.

**DR. MARLOWE:** Let me put two things together for half a second. Fred Hegge talked about body armor. One of the findings of the Israelis from the Lebanon War in 1982, was that because of the use of body armor, there had been a radical shift in the pattern of wounding from most wounds in the core to 80-percent of wounds in the arms and legs.

Now we get to the question of stress and healing, and we also get to some evocative and at this point not very good stuff that says that psychotherapy used in the right way seems to lower levels of stress as measured physiologically.

And so now we get to a complex of things in terms of are there paradigms that might be tested in terms of lowering stress, one or other kinds of interventions, and seeing whether or not this leads to more rapid healing, particularly in wounds of the periphery.

Given the data you've already produced on the relationship of stress and time to healing, are there things we can do to shorten that kind of temporal span?

It has potentiality, I think, to be a challenging issue and perhaps a challenging issue in the entire realm of liaison psychiatry.

**DR. HEGGE:** David, I'd like to go back a little bit to when we were talking about the future -- the future warfare.

And, Karl, would you put up your first viewgraphs again? I don't think people understood what we were looking at over there in the lower left-hand corner.

That soldier is wearing land warrior gear. That is the future of the combat soldier, but it is also now of the combat soldier. That equipment is being distributed to the first combat units now going out, and they are starting to learn to use it. The first major technology upgrade of that system will be in two years.

That's the warrior of the future. Let me tell you a little bit about him. See that unit on his gun there? That's a night vision scope. It is an aiming system. It is a battlefield television camera that allows him to transmit images of what he can see and what his sights can see back to his commanders. That eyepiece is a heads-up display, which is powered by a Pentium computer onboard. He's wearing it. He's got it all the time, and it contains a full operating system. It downloads maps, locates him and his colleagues, his companions on those maps. He's got two movement sensors on board, dead reckoning systems, so that when he's out of range of GPS which locates him on the face of the earth, dead reckoning system takes over to plot where he is at any given time. He has two radios onboard. He's got a squad radio, and he has a tactical radio as well.

All soldiers, combat soldiers, will be equipped that way. I suggest to you there is a behavior stream coming off that soldier now in terms of where he is against time. You know about rate of movement. You know where he's moving. You have a voice record. You asked, "How are we going to get stress measurements?" You now have a complete voice record of his communications.

You have latencies between when he was communicated and when he responded. You have content, right? There are also other streams of behavior coming on board.

Now, we're going to be training with this, and we're going to deploy with it. If there ever was a naturalistic opportunity to observe behavior, and ultimately two years from now, physiology coming off that soldier with actual time in operational settings, there it is. It's not 30 years in the future -- it's right now.

And I would suggest to you that we don't know how to exploit that.

**DR. GUZE:** Do other countries?

**DR. HEGGE:** The Australians are working in the same direction. Yes, the NATO countries are working in the same direction.

**DR. MASON:** So is it a mission then for us to try?

**DR. HEGGE:** I don't know. We were talking about the future as though it was somewhere far away, and the answer is, "The future is right now!" No one ever waited until the soldier was ready to change the conditions he faced in battle. I give you World War I for example, in using machine guns and gas. We always threw the soldier into those things and expected him to learn how to adapt to that on the battlefield.

I'm just wondering whether or not we can do a little better this time around? In fact, we are exploiting a new field laboratory that is being created as a course matter. Not for us, but can we use it?

**DR. MEYERHOFF:** Since the camera is recording the target, will they do a good job of recording friendly fire in this training scenario? And I ask that question for two reasons: (1) Dr. Erikson talked about harm inflicted by one's own, if you will, tribe, family. (2) Well, my own translation was of betrayal. But the fact is, as I understand it, friendly fire accounted for, in past conflicts somewhere between 11 and 14 percent.

**DR. MARLOWE:** Twenty percent.

**DR. MEYERHOFF:** As high as 20 percent, Dr. Marlowe says were killed and wounded. And in the Gulf, of course, 55 percent. A lot of vehicles that were destroyed were destroyed by friendly fire. Now, I recognize in terms of Gulf War illness, people who weren't deployed or who weren't in combat developed Gulf War illness, but I'm broadening the discussion, I guess, to include the possible future conflicts.

And the question is, "What is the possibility of interaction with friendly fire?" The two studies I read from Leavenworth were from line officers, Steinway and Schrader, that studied friendly fire. Both concluded that friendly fire incidents are due to stress. Event though the terrain and visibility are important, they conclude that stress was the important or most important variable.

So we have stress on the inside or on the front side going in as a predisposition, arguably, to friendly fire. In this case, I would worry about information overload with two radios going at the same time, plus trying to watch a computer. And on the other end of that -- and this is really a question I have for people who have specialized in PTSD -- what's the impact in terms of PTSD rates in the people who commit or are on the receiving end of friendly fire?

**DR. MARLOWE:** Allow me to point out a couple of things. David Saddah did a study of autopsy materials from all wars we were in this century. On an average, 20 percent of American casualties have our own metal in them. On an average, indirect fire weapons cause also most friendly fire incidents, artillery and bombs from aircraft, et cetera. This can have an impact. If not known, it doesn't.

I do want to get us back on track, however. We are not here to focus on the proximate problems of the military. We are here to focus on an aspect of the human condition, the production of somatic symptoms as a result of exposure to stress.

The military presents us with a laboratory, which under certain circumstances, we expose large numbers of people to both subacute chronic stressors, acute traumatic stressors, and other acute stressors. But the issue is: "What are the processes involved in leading human beings to produce one set of symptoms as opposed to purely psychological symptoms or what have you?"

I don't want us to get lost in issues involving purely military conceptions. I think it is important to note that the Gulf War led to this because it has been one of the first. If you will, mass recognition of something that's been bubbling out there under a variety of names ranging from: multiple chemical sensitivity, chronic fatigue syndrome, neurasthenia, you name it, through the past centuries, is what I'd like us to get back into focusing on those set of issues.

**DR. ENGEL:** Thank you.

I mean, I think when I said an eye blink in time, what I really think that I meant is certainly as it relates to the Gulf War, is that "What did we figure?" One hundred and forty-nine people died in the Gulf War. Now, depending on whom you listen to, we've got 100,000 people standing in line for health care. How do you equate 150 deaths with that? Nobody wants to put them on a balance, but I think the problem arguably doesn't lie at the point of conflict.

**DR. MARLOWE:** Yes, and just let me underline that. In combat terms, the Gulf War was probably, including the Spanish-American War and the Mexican war, the least stressful war Americans have ever been engaged in.

**DR. HOLLOWAY:** For Americans.

**DR. MARLOWE:** For Americans. That's the population we're talking about.

**DR. DOHRENWEND:** I had a question. Really it's one of clarification. And it's possible that you've just given it, but we started this morning with a focus on factors and unexplained somatic symptoms in the military in general and the Gulf War in particular. Then we had this enormously stimulating talk from Dr. Friedl, which challenged us to look at factors in stress and in relation to performance in a barely imaginable war 30 years from now, which is a much broader agenda. And I had some trouble making the connection. Now, maybe we don't have to, but I can see one way to try to make it. I wonder if we know anything about the relationship of the casualties from unexplained somatic symptoms and performance, military performance in the Gulf War.

Is there some reason to believe that there is a connection here? If so, that would knit the two themes, or what I detect as the two themes, together. It's also, I think, an interesting question so far as the role of stress and unexplained somatic symptoms are concerned. I haven't heard of any information on this issue.

**DR. MARLOWE:** There is none. In fact, one of the things I think we can say about the Gulf War is that we do not know whether those presenting significant numbers of psychological symptoms before the shooting war began, were in any way demonstrating performance decrement during the course of the war. This kind of data just hasn't been gathered. We simply do not know.

**DR. DOHRENWEND:** Well, I could think a lot better about these problems if I knew the answer to that question. If that isn't known, I think it should be found out.

**DR. MARLOWE:** I fully agree. Let me say also, you are not being given another agenda by Karl. You were being given background in terms of where the sponsor of this conference is going, but not where the conference is supposed to go.

**DR. DOHRENWEND:** Could you repeat that, please?

**DR. GUZE:** Yes, I'm glad that Bruce raised this question about what topic are we talking about, and I think you did clarify it very well for us.

In the capacity as the co-PI in this IOM National Academy study that I cited earlier this morning, we had the privilege of hearing from people from all the branches of the Armed Services, and the VA about the progress that was being made in developing a cradle to grave, computer-based health record. Now, I know that some of the progress that we were told about, unless it's just extremely exaggerated, looks quite encouraging, but I would like to put on the table a very strong, skeptical comment.

Where does it come from? It comes from my experience as a staff member of a big, very research oriented, academic medical center in St. Louis. I've been complaining for years that I hate to get a request to see a patient in psychiatric consultation, because at least half the time, I can't read my colleague's handwriting. So, I spend an enormous amount of time trying to struggle and get some sense of just why a psychiatric consultation is requested.

Now, let me add one other thing that may seem different. Many of you may not know this, but HCFA, the federal government agency that is responsible for managing Medicare, issued a series of proposed rules about six months ago having to do with the kinds of documentation of doctor-patient interaction if the interaction was to qualify for Medicare reimbursement. And what's more, they even warned doctors that if these rules were not followed very

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carefully, they might be subject to threat of being charged with fraud and desire to defraud the government.

As a result of the outcry among physicians and especially the American Medical Association, HCFA has agreed to postpone the implementation of at least some of these draconian measures, and now there's a lot of discussion about what's to be done.

Now, in that context, I proposed to colleagues in my own department that maybe the only way we could protect ourselves from the draconian HCFA rules would be to stop dictating or writing any kind of individual note, but let's just fill out checklist forms about everything. And now I think it's almost certain, in my opinion, that whatever compromises are worked out between HCFA and the AMA, that physicians and hospitals are increasingly going to move to a checklist approach.

My own experience with checklists is, that I'm satisfied with the ones I fill out, but I am always skeptical about the ones that other people fill out. I think that the military and the VA have got to be certain, not to be bewitched by the high technology of the computerized record. They need to give a lot more thought to how to be sure that the substance of what's going to go into that computerized record is going to be useful -- whether it's to head off another repeat of the Gulf War Syndrome fiasco or something else.

I just wanted to make that point because the computer technology seems to me, moving ahead at a very rapid pace, but what they're going to do with it is still on hold in my mind.

**DR. MARLOWE:** Dr. Kirmayer was next.

**DR. GERRITY:** Well, I just wanted to respond because I think he was directing that to my previous comment.

**DR. GUZE:** Right.

**DR. GERRITY:** And I'll be quick.

You know, first of all, there are two aspects of record keeping here. One is the actual medical record, and the other is periodic health assessment for surveillance purposes. Really in both cases, though what I would say is in the research part of this plan, is that we imbedded in that the necessity. That at the same time that one is considering the medical record, that one also be sure that the data and how the data are recorded, is recorded in such a way, that it would be useful for doing retrospective look-backs, et cetera.

**DR. GUZE:** Now, whether we do it or not is another matter. It's not an easy thing to do.

**DR. KIRMAYER:** I just wanted to make a comment that, in fact, links the two presentation or the original agenda that we had in terms of understanding medically unexplained symptoms and the presentation we had that you're saying represents the sponsor's interests and views of the situation. I think that the portion that we had from Dr. Friedl of the predicament of the soldier has a tremendous influence on how we think about stress problems, and this perhaps also seconds what Chuck Engel was saying.

The portrait is of an isolated individual wrapped in technology whose main interest and the parameters that we're measuring are his efficiency to carry out various strategic tasks. What really counts is that moment of the vulnerable situation he's in and things he has to carry out and things he experiences. That supports a kind of paradigm of stress research and so on that looks at very discrete events, immediate impact on the person, and ignores a whole lot of other psychological and social processes that are part of real life events for people.

I think one of the important things is to see a stressful event or traumatic event as not simply a discrete event, but as something that unfolds as a trajectory over time, over an extended period of time. Most human beings including soldiers it involves a social world around them. And so one of the questions I'm very interested in, and the point made repeatedly, if not most people recover from even very traumatic events, involves the role of human relationships, their interaction, communication, social bonds, the opportunity to narrate and re-narrate the events of one's lives, and the role of recovery.

So the image that we have, looking at the physiological parameters with recording devices and so on in that discrete moment, tends to isolate the person from that social world. Reconstructing that and maybe some of the same technology can do it, particularly if the camera lens isn't only pointing in one direction.

Actually Jamie Pennebaker is doing work right now having people carry around tape recorders and recording the ambient conversations in their social world and looking at the fact that people who are high disclosers about traumatic events tend to congregate with other people who are high disclosers. So that rather than just viewing this as an individual personality trait, you may understand this as part of the social world that a person has that either helps them to deal with things in a certain way or not.

In any event, coming from that kind of a more social/contextual perspective, I would think that we need to rethink the larger context in which the response to stressful events is going to occur and how that unfolds over time.

The most striking observation cross-culturally in this domain is how idiosyncratic North American health psychology is in terms of the things that people ought to do when they're exposed to terrible events, namely, talk about it incessantly to anybody who will listen with as much emotion and affect as possible. As you know, in many other cultures and societies in the world, there's much greater emphasis put on containment and the ability to maintain equanimity and so on in situations and long term.

Now, it may well be different for people in the military where perhaps there's a different ideal of management of emotion and of stress. I think it is important to understand the health implications of that and the tradeoffs that may occur between what works in the moment perhaps physiologically, perhaps psychosocially for people and what the consequences are over time. To make it a more clear, what I'm referring to is the notion that it may well be true regardless of people's social and cultural background and mental history that there is some value to being able to talk about things that are distressing to you. But in many parts of the world and in many contexts, there are tremendous social costs associated with that. So then it's a kind of tradeoff for people. I think that that kind of problem is something that needs to be looked at. There are very distinctive ways in which the social context of the military situation configures people's social work. I would not want to see that excluded because of the image that we have here of this functioning unit, as it was, in this domain.

**DR. MARLOWE:** Let me make one observation in respect to that. The one guiding principle in terms of mediation of stress in military units, has been the preventive level of cohesion and bonding in the primary groups that make up the unit.

If there's a prospective problem, it is the issue of greater anomie on the battlefield in terms of the use of the requirement that the other be symbolic rather than present.

Probably, the most interesting recent finding is one of Arik Shalev's in Israel, looking at debriefing, our most popular indoor sport. Arik has been debriefing units that took casualties in the ongoing conflict in Lebanon. He has come to the conclusion that it really has no direct preventive function, but what debriefing does do that is positive is to create greater cohesion and greater bonds among the members of the group that's being debriefed. However, he can find no way in which it mitigates the possibility of future symptoms arising other than the re-intensification of bonds.

**DR. GREEN:** I wanted to pick up on a couple of things that people were talking about earlier, and they're actually in some funny way kind of conflicting thoughts about this.

One is that a number of people have been talking about baseline data here, and one of the comments that I wanted to make is that when we conceptualize baseline, we need to remember that it's only baseline because it's the first measurement that we've done. It's not necessarily "pre-" any kind of stress or trauma.

And actually there's some data developing that indicates that maybe people who choose to go into the service are people with higher rates of historical developmental trauma than people who don't choose such. You would expect then, that they would have even higher rates of PTSD than the general population, which is about five or six percent of men and ten to 12 percent of women.

So one of the things that maybe we should be thinking about when we think about measuring is that some of the people who we're measuring at baseline may already have PTSD and other trauma related disorders, and we would expect them to be at even higher risk.

But I think that when we conceptualize baseline, we need to not think of that as an unstressed condition and to conceptualize vulnerability in a way that includes prior trauma and possibly also prior PTSD. These are people that we would expect to be very sensitive to the environment.

The flip side of that is if we're going to ask people about that, I think there's some reason to be concerned about how comfortable they would be reporting that information. As I understand it, in DOD studies one can't guarantee confidentiality even of research data. So while I think it might be a good idea at some level to understand trauma history and symptoms of PTSD before people are deployed, they actually may have a strong motivation not to report that information.

And while, in general, in the culture we are relative to other countries, we are perhaps more open to the notion of disclosure. I think if you take people who are already in the military and deployed, there may be a whole other set of cultural restrictions on what people are willing to disclose.

So I don't know how those two things go together. I think that at baseline we have some people who have been through previous experiences and may even already have PTSD, (or certainly have some of the markers of vulnerability from those earlier experiences). And there are people who might be reluctant to report this.

I think that's an inherent problem, and so when we think about looking at markers, maybe that's a really great reason to think about doing biological research where people probably aren't going to be able to influence what their immune systems show.

**DR. MARLOWE:** If I can just respond before we move on Bonnie. I've been in research in the Army, for God knows, almost 35 years. Two things: A lot of what we've done, and particularly a lot of what we did in the ten-year period going up to the Gulf War in a number of things, and found people did not seem to have much of a dilemma telling about problems in their past, or present, what have you, since we offered them medical confidentiality. Another thing, because this included work we did on illicit drug use in the past, at no point in all that time, did anyone attempt to penetrate or ask for the data sets. The response from senior Army officers was always, "Well, of course it has to be confidential, otherwise no one will tell you the truth."

**DR. HOLLOWAY:** Just to add to that, the statements you cannot have confidentiality in DOD is incorrect technically. All you have to do is go through the court-martial chain to decide whether if that information can be kept confidential for that reason.

Is that almost impossible? Is it hard? The answer is, yes, it is hard. Have we done it? We have done it.

**DR. MARLOWE:** Well, we've done it with drug work. You get a certificate of confidentiality from National Institute of Drug Administration (NIDA).

**DR. HOLLOWAY:** That's a consent form you're looking at, not something you've devised for special studies. It can be done.

**DR. ENGEL:** The issue, I think, is one of perception on the part of the soldier more than reality. I think we'll always have a hard time convincing the soldier that there isn't some possibility that things could ultimately be opened up for others to review.

I mean we ought to do the best we can if that's the truth, but I think there will always be some underreporting. I don't know how much of that you can expect with drug abuse.

**DR. MARLOWE:** Well, if you take highly delicate areas, the most delicate is the assessment of one's leaders, company commanders, et cetera. Soldiers have no problem being extraordinarily harsh in non-anonymous questionnaires as well as extraordinarily complimentary, and the patterning of unit says that people seem to be telling the truth. If you're not in the soldier's chain of command, if you're coming in from the outside, they tend to give you their trust.

I think the one important thing in terms of anything that's designed for use in the services that a lot of people who haven't worked with the services don't know is, that everything we do is absolutely voluntary. We can do nothing to order a soldier, sailor or Marine. He or she must sign an informed consent form and voluntarily agree, "I want to fill out this questionnaire or a consent form to provide a drug specimen."

In that sense, we do not have a captive audience. Though in many things, when you do it in physical presence, you get 90 or 95 percent response from the members of the organization.

**DR. BLACK:** David, you keep coming back to our central theme, which is can stress as we know it in soldiers contribute to their symptomatology that has been reported that has been called the Gulf War Syndrome, and can stress, in general, produce the somatization and physical symptoms that we see?

It seems to me to try and reduce this to its simplistic question, well, what do we know about the Gulf war?

From reading your Rand report, David, which I thought was excellent, you make a very good case that this was one of the most, quote, stressful wars we've ever had. Soldiers experienced more prolonged and pronounced stress than in many other wars. Let's not be absolute. Number one.

Number two, there's more post traumatic stress syndrome from the Gulf War even though it's not related to combat and number deal.

**DR. MARLOWE:** No, there's not more post traumatic stress syndrome.

**DR. BLACK:** Okay. Is it less then?

**DR. MARLOWE:** Oh, yes.

**DR. BLACK:** It is less. Okay. So that maybe that kind of stress, combat stress, may predispose more to post traumatic stress syndrome.

So the only way that I feel that you can relate this so-called stress that they experienced to their physical symptomatology is to study this prospectively.

We know that stress produces certain molecules of response. We know the body responds with corticosteroids from the HPA axis. We know it responds with catecholamines possibly opiates as well.

We also know that cytokines are produced by stress. We know that acute phase reactants are produced by stress.

So we do have markers to watch, and it seems to me that if one wants to show the relationship between these markers that echo stress and disease, one would have to study prospectively. I mean I couldn't do that research because it's not very exciting to me, but look what the Framingham heart study has produced, an amazing amount of data, and it's one of the most frequently studied in the world.

Now, I know your problem of keeping soldiers. How long can you follow them up? I can't answer any of that, but I think in some way this has to be addressed, and otherwise you're saying this will be a chronic conundrum. Retrospectively it's very difficult.

**DR. MARLOWE:** I fully agree, and I think one of the things we would like to get on the table before we finish tomorrow is what a reasonably integrated prospective study might look like.

I'd like to try something a little different for the rest of the afternoon, and that is we really have two groups of people here, one who have been working essentially at the biological, neurophysiological central level, the other who have worked at the social and cultural and psychological level. In going back to the heuristic. I think one of the things I would like to see you ask each other of the folks working inside the body, to consider what it is they would like to know from the folks working at the social, cultural, psychological level, and vice versa. What are the things you think might be most important to turn to your colleagues, like Bruce or Kai or Bonnie, and say, "Hey, this is what I really want to know that might be more illuminating to the work that I am doing?"

And would someone like to kick that off? John.

**DR. MASON:** I'm going to give it a try. This is a good example in a way of how the psychoendocrine approach has worked for me. It's been by doing just that, seeking, first of all, interested collaborators who sense a need for collaboration the way I do because they're interested in a larger, integrated view of things, and classically I'll go to them. We're studying a group of subjects under stress. I'll get a distribution curve, and I notice their extremes, some very highs and some very lows, all in the same situation, all in the same environment in the sense of the stressors to which they're exposed, as for example the parents of leukemia children. And I'll be struck physiologically by how low some of the values are. They're really quite low, down in the range almost of endocrine pathology.

And I go to the psychiatrist and say, "Here's Ms. So-and-so," the names of the three patients that are lowest. "What's unusual about them clinically? Is there anything that stands out clinically about these people in the three top people?"

And that has been the single most useful source of leads I've ever found. That's happened in different ways. That's happened with Rorschach psychologists like Margaret Singer, who does more of a global assessment than just, you know, projective testing.

But to get clues, and then at that point many of these people who are so sensitive as observers are reluctant actually to get very involved in research because they could have been shamed because what they're doing is so soft. All they have are global clinical impressions. They can't give you a number. They can't give you a paper and pencil test. So they're a little reluctant about getting terribly involved.

But in the parents study, one of the things it showed was that you can get around such things. If once they think they're onto the relevant -- what they told me was, these three lowest numbers were among those who flagrantly used the psychological defense of denial to such an extent that almost any observer could agree on it. The mother of a six-year old leukemia child was talking about what college she was going to send the child to. We had that level of inability to accept the painful reality.

And so you then can develop a semi-structured interview and go into a predictive study where you do some equilibration between two or three observers. They just handed me a piece of paper after going through about ten patients retrospectively to get a feel for what high, middle, and low cortisol people were. They then began to hand me predictions of the cortisol levels on the basis of their assessment of the effectiveness of defense, not just for then but all defenses, and did a predictive study.

I don't know how much more harder you can get in a predictive study. The next steps that happened, is when we published that, a number of people over the years said, "Well, that's too impressionistic. We need to sharpen up the methodology," and they made up psychometric instruments that were more exacting and reproducible. With each method that they developed, the correlation with cortisol got lower and lower.

(Laughter.)

**DR. MASON:** They were missing something that goes on in the mind of a sensitive clinical observer who reads patients, and tunes into them. I hate to talk about it because it immediately evokes all kinds of rivalry in, the people you're talking about because it means -- everybody is not an equal observer in my personal experience as a biologist who goes to people and says, "Can you explain my data?"

I know some people have and done it very, very, you know, powerfully, and others just don't seem to have whatever it is, intuitive add-on to put together the pieces the way these people do.

But I just have a longing to see more. One of my disappointments is whenever I start talking, here I'm a physiologist, and all I do is plead for more psychodynamic participation.

(Laughter.)

**DR. MASON:** -- in this field of PTSD because I get my greatest comfort and enjoyment out of reading psychotherapy journals. They're a million miles away, and they're never quoted in the PTSD research literature that I can see, except in their own therapy journals, but they explain these patients in a way that makes sense with my hormonal data the way nothing else does.

So I'm very excited about the future prospect of somewhere finding those sensitive instruments, and those people who can do that, and use them at least to get a start.

I have no objection to psychometric systems. We need to bring those in, too. But once you get them in the picture to begin to narrow down to what the relevant variables are, then I think you can bring in the big guns much more effectively and zero in with the psychometric and other instruments to make it more rigorous.

But just to add one other thought along this line -- this is happening to me right now as I've just been doing studies with a large data set of about 100 PTSD patients, Vietnam era. For the first time in my life, I've got the full hormonal profile of 12 hormones, quite a battery in the profile, but also 20 psychometric instruments that go the whole range from acute core symptoms, general psychopathology, characterological, and working through this data set on my own. And as I look at the correlations with cortisol in this large net, screening, fishing expedition -- you can all it anything you want. I don't care because it's a rich, rich way to get leads -- and what's come out of this is that one of the highest correlations with cortisol is an inverse correlation with a symptom of PTSD that's not even in the diagnostic criteria for the disorder.

Does anyone want to guess what that might be? It's a great possibility it's a sleeper in the PTSD picture the way that Helen Brock-Lewis said that it was a sleeper in general for a lot of psychopathology. Forty years in psychotherapy, this was the greatest thing that she overlooked, and she finally came to realize it was this one dimension.

**PARTICIPANT:** Guilt.

**DR. MASON:** Guilt, shame. I think more shame than guilt. Technically people define guilt as having to do with "I wish I hadn't done this particular action or that particular action. I'm a good person, but I just made some mistakes. I flubbed here. I flubbed there, and I'm guilty," as opposed to a kind of more massive denunciation of the self. "I wish I weren't this kind of person. I keep doing this kind of thing."



So in the PTSD patients, it appears or develops more after the return home than it did during the combat experience where they may have had such experiences where they felt guilt and shame as a result of military experience. However, coming back with the startle, the violence, the social dysfunction, the inability to deal with their family in any kind of, reasonable way leads to this increasing, compounding sense of shame and guilt, and each time it happens the cycle repeats. They decompensate and blow everything. It gets worse and worse and worse.

And then it's like a packaged deal with the guilt that appears from the cortisol data, that there's a triad. I don't know. You talked about factor analysis, but to get a single, principal component analysis factor for what looks clinically to be three clear subgroups: guilt/shame, the self-critical depression -- it's not major depressive disorder or depression that you pick up on a Hamilton or the Beck. It's the one that you pick up with the content scale of the MMPI, which if we read those items, it's almost a pure shame/depression scale.

You know, "my sins will never be forgiven." "I wish I weren't such a bad person." "That there is self-condemnation on the kind of global scale."

And the third thing which fits beautifully in a dynamic sense with it, I believe, is numbing, the emotional numbing, withdrawal, and avoidance. These are the very things in a sense that Horowitz talked about. He's one of the few people I saw who talked about the shame not just over, the things we would obviously be ashamed about, but shame at the level of "this bad thing should never have happened. I should have been able to prevent this. I should have been able to have done something or thought of something to prevent the trouble in the first place, the adversity in the first place."

But there's a level of shame that develops just from that Horowitz picked up for denial. He called it massive emotional numbing. It appears to be the only kind of thing in the repertoire of many normal people that appears to be up to the task of trying to deal with the overwhelming sense of shame and guilt and inability to get out of the hole that themselves dug.

**DR. HOLLOWAY:** John, how does the correlation work?

**DR. MASON:** It's inverse for all of them. That is, they're higher --

**DR. HOLLOWAY:** The more shame, the lower the cortisol?

**DR. MASON:** Yes, but I think the way to look at it is the more emotional numbing, the lower the cortisol, and I think that the numbing is proportional to the shame and the depressive response to the guilt and shame.

In fact, Kolb picked that up very early on, Larry Kolb, in describing this primary and secondary phases of the symptomatology or the course of PTSD. First you have the fear and sort of deal with that, and he picked up the guilt and shame part of that, too. Then he said secondarily there is the development of he saw it as an adaptive response, the numbing, as the only way they have to go.

Psychotherapy doesn't have much to offer in terms of dealing with guilt and shame.

**DR. GREEN:** I think it's important to point out or just to highlight that that symptom or that complex is around the interpersonal aspects of the trauma.

**DR. BLACK:** Can I just ask, did they dissect where in the HPA axis makes for the low corticoid? At the adrenal level or the hypothalamus or the ACTH or hippocampus? Do you know? I'm asking, why is there a low cortisol?

**DR. MASON:** Well, that's a very important question. I think the work that Rachel is doing helps in a way. The original pilot study that I did showing the very low cortisol was in a group of patients who were somewhat unique. They were not recruited. This was in the early '80s. They were picked up because the flashbacks appeared as thought disorder symptoms on the BPRS.

We were looking at stages of illness in psychotic disorders, and they came in the emergency evaluation ward, admission evaluation ward. They were picked up as possibly psychotic patients because of that.

And Earl Giller, my collaborator, was on the ball and picked up the PTSD at that stage, even though the diagnosis was rarely made in those days. They were essentially left alone. We didn't know anything about treatment programs or attempts for PTSD at that time. So they were allowed essentially to use their preferred coping, adaptive mechanisms so they could withdraw, avoid, and not say a word, whatever. The whole idea was just to get them out of the hospital and work to get the support they needed and so on to get them out.

But in that group we had -- and they were generally pretty sick, sicker than most. In retrospect, the ward chief says they could not have participated in the recent National Center programs that we had that required submitting to re-experiencing sessions and exposure session to try to reactivate the feelings and so on.

And so Rachel and the rest of us who have worked with The National Center samples have found generally higher cortisol in that original pilot group. She's talked about hypersensitization or sensitization of the HPA axis. I think the degree of reactivity in PTSD patients (originally if we caught them early on), was probably very great just like the men down in SEAR's training are showing these 30-fold increase to military stress down there. Tremendously large cortisol increases, dangerous physiologically possibly to the organism that

hormone changes can be that way. So that adaptive mechanisms have to come into play to prevent that in the future. It may well be that you get to deal with such hyperreactivity that you have to have hypersuppressive mechanisms, drastic, relatively drastic mechanisms come into play, maybe over compensatory in the opposite direction.

So when you see a patient with PTSD, the diagnosis isn't going to be by itself to predict the cortisol level. You're going to have to know the stage of illness they're in. Are they in a decompensated stage, an overextended survival stage, or are they in an adaptive stage where they're able to use their defenses?

In that case they would be low cortisol, lower than most patients and normal people because there's over-compensatory use where they can bring all of their defenses to bear on the thing and get the support that helps them.

Whereas at the other end, if you pushed them like we did in therapy, they can double their cortisol levels. They can come out of that and double if you begin to undermine the defense system. So it's this balance of forces. I think once you know that, then you have a much better chance of talking about markers.

And you can define the various subgroups using this idea. You can begin to talk about characterological features that appear to tie in with the ones that have the most flagrant over-reactivity and think then about using those for predictors or risk factors that could be picked up prior to the combat exposure.

I'm sorry to talk so long. I passionately get carried away with this, because it's the kind of thing I've been trying to do for 40 years, and it's the first time I've really had a large enough body of data to review.

**DR. SCHNURR:** I'd like to ask the biological people what they think about the health implications of this alteration of the HPA axis because I think those of you who are stress researchers have probably been targeting depression as the disorder that you think about, But PTSD really is different; at least long term, chronic PTSD is different, and I'm looking to some of the guys around here and over there, what you think might be different about PTSD.

Should it be protective? Should it be worse? What?

**DR. NATELSON:** Well, I think some of the answer to that depends on a little bit of ignorance about where we are in this. Listening to John, obviously we're hearing that the body of knowledge about what happens in terms of endocrine activation is changing. It seemed simpler in the early '80s, and now it's more complicated.

So we need to know where in the individual's life he is and what that's done with his endocrine milieu.

Now, we know for a fact that if you can up-or-down regulate HPA activity, there are long term consequences at least in terms of an animal's behavior and an animal's ability to grow old. We know that.

We know that if an animal is handled such that its glucocorticoid system is rearranged throughout its life; it shows memory problems earlier, and actually looks like they're hippocampal problems in terms of frank pathology. Some of that may be pharmacological, and that's one of the objects that I have tried to target in this ABMR conference in Cape Cod.

So certainly by manipulating endocrine systems over an animal's or an organism's life span, I think we can say with some assurity that there will be brain and behavioral effects.

But having said that, our knowledge base is very thin. I couldn't say anything else except about these long-term modulations. Some of them pharmacological for HPA axis, but then when you look at the other 12 hormones in John's profile and how they play a role, well, we know nothing in terms of the ultimate consequences to the brain and to aging and to the course of disease.

**DR. GUZE:** I thought that what we heard about this apparently very significant correlation between a certain emotional set of guilt and cortisol levels, though I gather from what you said later that this may vary with where the individual is in the course of the illness; if it's true, it'll be so far as I know the first time there's really been a consistent correlation between an endocrine or other physiological measures and a very specific characterization of the emotional state. That has been almost always unable to prove. So this either is some flaw in the study that I can't suggest what it might be, or this is really unique.

Now, I must say, I started out a little skeptical because I don't know of another time when anything like this has been possible. One of the big difficulties in doing this kind of a search, having toyed with it a little bit myself earlier in the career, is that it is so hard when you're doing psychotherapy with your patient. At the same time, not to be suggesting all kinds of attitudes that the patient will give you back when you ask the right questions.

So I think it will be remarkable if it really holds up and in other laboratories and in a very consistent way, but I think we all have to be cautious.

**DR. SCHNURR:** I could be wrong, but I think it already has been replicated. I know if Rachel were here, she would educate you quite properly in her own work. Those of you who know her know exactly what I mean.

But I think she has shown this not just in Vietnam veterans, but also in Holocaust survivors and is starting to show it in older veterans.

She also showed, I think, that low cortisol in the emergency room in rape victims predicted them developing PTSD. She's shown that people who have PTSD are super suppressors on the DST.

**DR. GUZE:** The correlation I'm talking about is a certain mental state.

**DR. SCHNURR:** Okay.

**DR. GUZE:** And low cortisol. So let's not change the paradigm of the study.

**DR. MASON:** See, I think we should keep in mind that the quest is for taking hormones and making them into something that will serve our own purposes, like a diagnostic criterion. Hormones may or may not be suitable for doing that.

The quest is finding out what the hormones tell us. What do they reflect? What is it in the intrapsychic processes that the hormones are reflecting? So that's the quest.

And I think in the case of cortisol, probably the best I can do at the present time is to indicate the very first experiment I ever did clinically with Margaret Thaler Singer back in '56 or seven, whenever it was.

She detected a dimension that she called engagement or involvement, picking it up from the Rorschach data. She said it was an undifferentiated kind of arousal data. It didn't matter so much what the specific affect was. Whether it was anxiety, fear or anything, but some very undifferentiated kind of arousal that she saw as engagement, where the individual is beginning to have emotional participation with the environment or with the situation or even with some intrapsychic notion. That the fundamental dimension may interact with a lot of things dynamically so that it will be associated with a variety of symptoms in different patients with different disorders.

You'd better be careful about not thinking a particular symptom is going to correlate, but to remember that it's this engagement issue.

So that's why I think Harry had the notion of the numbing and avoidance, which is, you see, a major disengagement mechanism, would make sense as the thing that probably is directly in view here. The other dynamic things that may be linked that have brought the numbing and avoidance into play correlate closely, but are, not directly reflected in the hormones, but reflected in the adaptive response of the avoidance.

**DR. HOLLOWAY:** So it's the numbing and the avoidance that you think was primary?

**DR. MASON:** That's my guess about it, yes.

**DR. MARLOWE:** Can I just make the observation that Margaret is an extraordinarily sensitive observer, and her ability to see the behavior of a patient as well as what's going on in the Rorschach is really exceptionally remarkable.

**DR. MASON:** Well, that's what I mean. She would sit with a patient for 15 minutes and do the TAT and the Rorschach and so forth. Then she would come back and talk to me sometimes a half hour, sometimes 45 minutes, and the topic was, "John, this is the kind of person," and then she would go on and give me a topology and a character description of this person that was phenomenal in its accuracy in terms of predictive power.

**DR. GUZE:** The TAT and the Rorschach have been tested systematically over and over again, and they don't do that kind of thing. So I think it makes me very skeptical to find that some individual has got some kind of fantastic, uniquely gifted insight that nobody else can do.

**DR. MARLOWE:** I think it comes to another issue, and one that I hope we will bring up, and this is the issue of the observation of behavior and from the point-of-view of instrumentation, instruments that look at behavior rather than at attitude, or rather than at secondary impressions.

May I take half a minute? Many years ago, we were doing a study of the ecology of drug use on an Army base. A young man working for me, a psychologist, who didn't do much arm twisting, set up a behavioral inventory, and it had by far the highest correlation with both illicit drug use and the risk for it. He flatly refused to publish because it was his. It had never appeared in the *Mental Measurements Yearbook*. His graduate department at the university he'd gone to, et cetera hadn't sanctioned it. He much preferred to publish the much lower correlation of standardized instruments.

And I think some ways, we may be on the wrong track. I was very interested in our Gulf work. At one point we tried two instruments. We were routinely using the BSI, but for some years in other work, we'd used a DePuy's General Well-Being scale, and we put it, as well as the BSI, into about 1,000 questionnaires in one of our follow-ups.

They both correlated equally with various outcome phenomena. They correlated very poorly with each other. Whatever they were measuring in terms of psychological status, it was global and not the same thing in terms of the actual components of the two questionnaires.

It's a persistent problem.

**DR. MEYERHOFF:** Just two points. (1) Following up on Dr. Schnurr's question, and (2) on the issue on cortisol and specifics on behavior. My recollection is that in one of the papers that was a sequel of Dr. Yehuda's work on cortisol, a paper was by Frank Goenjian, and Dr. Yehuda on victims of the Armenian earthquake. Salivary cortisol levels were inversely correlated with intrusion on the impact of events scale, and that I think it may have been in the *American Journal of Psychiatry* recently.

Another question of memory came up, I think, and McEwen showed this in studies of rats that 21 days of immobilization stress, produced deficits in a memory in two separate mazes. One of them was Y maze test. I think, Conrad was the author of that paper.

This was reversible. This was a transient loss of memory that was reversed within days-to-weeks or so, and the dendritic atrophy, atrophy of the hippocampal CA3 pyramidal dendrites that he found after 21 days of immobilization, was reversible within a week or so. His feeling is that this may be actually an adaptive response.

Dr. Schnurr, this is in response to your question. McEwen thinks that in his rats, the hippocampal or dendritic atrophy may be adaptive because there is a glutaminergic pathway there. I'm speaking for McEwen just from his publications. He's argued that possibly the hippocampal dendritic atrophy may be somewhat protective against the potentially neurotoxic effects of the combination of glucocorticoids and glutamate where glucocorticoids can act by inhibiting the re-uptake inactivation of glutamate at the synapse. And glucocorticoids can also inhibit the uptake of calcium from within the neuron or the egress of calcium.

So the net effect of the glucocorticoids plus glutaminergic firing would be to increase the synaptic levels of glutamate, which in turn, of course, increases intraneuronal calcium, and the glucocorticoids again would exacerbate the increase in calcium.

**DR. MARLOWE:** Ben.

**DR. NATELSON:** I guess I'd like to take a different try to answer your question than John took, I mean, and it's not a question. It's what would I as a physiologist want you social and population and ethological psychologists or epidemiologists to help me with.

Well, I guess I need a more – rather than getting down to a sort of specific emotion, which would be spectacular, but I sort of agree with Dr. Guze's analysis of the literature. What would be helpful would be measures of arousal, perceived stressor intensity that people have doped out in the field that seem to hold up in terms perhaps of probability of PTSD or acute combat syndrome, arousal, engagement, perceived stressor intensity, these sorts of vehicles then that would allow us to say or at least to test the hypothesis that this measure puts this potential soldier, recruit, policeman, whatever, at risk for symptoms or disease later down.

So that would help me certainly.

**DR. MARLOWE:** Kai.

**DR. ERIKSON:** This is partly a response to the question you just asked, but also a response to a number of things that have happened.

I wanted to begin by talking about an observation that has been made in a number of different places where I have visited as an interviewer. Most particularly on Buffalo Creek, where teams of people on both sides of the legal action evaluated the clinical conditions of the people who were victims of the disaster without really knowing a great deal about the individuals themselves. There were a fair number of people qualified as being quite badly disturbed who weren't there at the time of the disaster at all, and the best explanation for which being that they had not seen the water. They had not heard the commotion. You know, they weren't really directly responding to the smoke and the flood.

But they did suffer what everybody else did who was a member of or who lived on Buffalo Creek, which was a major loss in a sense of communality, and a major sense of the social surround.

As a counter-question, I'd be really curious to know whether or not the people who responded in that way measured physiologically the same as the people who were physically there and actually do have traumatic memories as a matter of first hand experience?

And then I would observe that if, indeed, the physiological response was the same, then we're talking about a much more complicated kind of problem than appears in the way we mostly talk about this.

Many people here have talked about the need to distinguish the difference between mind and body. I would think somebody who sits as far out to the outer edge of the social sciences as I do, think there also is a need to kind of lessen the distinction between the individual and the group. Not in the sense that the two are – obviously, they're quite different. But, I would propose that there are stressors that occur not just to the individual, but to the group. You had mentioned that incidentally, when you were talking about the guilt. You used the word "interpersonal," but I'll call it group or call it social or something like that.

But to understand the response of the individual you have to know the individual positioned within the group almost as if the group was the agent that received the stressor. The stress experienced by the person is something, a product of the way they relate to the group as distinct from the way they relate to the stressor itself.

Now, how that becomes a question for the more physiologically minded folks, I'm not altogether sure, but I think it would be really major. It also fits a little bit to your heuristic question about the differences between those people, who are actually impacted by a disaster, or those who think they are.

What kind of difference does that make on the actual measurement of the stress involved?

**DR. MARLOWE:** Yes. Something I'm extraordinarily curious about, I could almost get passionate about it scientifically, but is the pathway the same if we were to do PET scans, for example? Do the same pieces of the brain light up? Do the same physiological changes take place, the same peptides get excreted?

I've often wondered if anyone has ever looked, for example, at conversion-reaction versus -- people whose ailment is not functional, phantom limb pain versus real pain, real pain because there's a limb there. There are both "real pain," but are we operating the same circuits in the brain? Are the same hormones being released? Is it all moving toward a single set of common pathways, or are there multiple pathways that are cognitively differentially organized?

And I think from the point-of-view of looking at the socially determined stressor as opposed to the one that's immediate and life threatening, those were all very conscious in terms of, quote, "the reality for most people." But the stressor whose primary value is its symbolic resonance with cultural values that drives in on you, is this creating the same kind of physiological experience?

**DR. GUZE:** I have a very limited observation to report to you that deals with this. There are a few studies using the PET system, positron emission tomography, that shows, for example, that if an individual is given a task to learn something, to memorize something, a particular part of the brain lights up whenever the individual makes the effort.

After the individual has succeeded in learning it, a different area lights up. So I don't know that that's necessarily, therefore, a paradigmatic observation that would fit for everything, but at least sometimes the evidence suggests that after you've learned something up to a certain point a different part of the brain kicks in.

**DR. MARLOWE:** Janice.

**DR. KIECOLT-GLASER:** A sideways answer to your question in terms of how you'd measure and what to measure related to the physiological question, we had a couple of studies we started some years ago. The first one dealt with newly wed couples, and we selected these couples by screening half the known universe to get couples who were absolutely pristine in terms of mental and physical health insofar as we could tell. The couples we eventually selected and admitted to the CRC for 24 hours represented, I think, eight percent of the couples we originally screened.

We had a catheter in their arm so we could draw repeated blood samples over time. We then had the couples interact for half-an-hour around a problem solving task, which is a common task in the marital literature. We videotaped their interaction. The tapes were scored for behavior by Bob Weiss at Oregon using the Marital Interaction Coding System -- the most common coding system used in marital research.

What we found in those studies was that negative or hostile behavior, which was on the part of both members of the couple, was the variable most strongly associated with both immune and endocrine change over that time. The relationships were, in general, much stronger for women than for men.

We went back and did a small study then with couples who were between the ages of 55 and 75 because we thought that perhaps this might be a reflection of the fact that this was such an unusual and idiosyncratic sample and again found very similar results.

The point of this, I guess, is none of the self-report data that we collected from our couples related to the physiology nearly so well as the behavior. There's something, I think, really important about behavioral samples that may well be captured by the interviews we're talking about that's really strong that you don't necessarily get by people's self-report because of all the defenses that you get in terms of reporting. I don't know what behaviors or particular aspects of behavior are most important for the kinds of things you're talking about here, but if there are ways to sample behavior, it becomes a particularly important thing.

The other thing that was most interesting to me was that the data were much stronger for women than for men. Women's endocrine and immune responses were much more strongly tied to what was happening in the interaction than those of men.

Well, if you look at the marital literature, that actually makes a lot of sense. There are studies from other labs where they look at who remembers marital arguments more and in greater detail -- women much more than men. Women remember positive things in the relationship much more.

Well, if someone remembers events much more and in much greater detail, who's going to have stronger physiological responses to those events? Well, it should be women, and in fact, it is.

So that if I had to choose in some way, I'd be very interested in what kinds of behaviors are most salient to the kinds of symptoms that you're interested in, if there's any way to measure that behaviorally.

**DR. HOLLOWAY:** Allow me to follow up with that question for speculation. There's work by Gold that's been reported in several places that suggests that the overall mobilization of glucose or a glucose bolus immediately changes quality of recall. It is published in lots of places, including the *Journal of the American Psychological Association*.

Is the kind of hypothesis you're making that if we were making those sorts of measurements in that circumstance, we might see -- and I'm going to push it a little as a hypothesis -- a mobilization of liver glycogen as glucose secondary to an adrenal response that would cause a bolus at that time, and that would occur more frequently in women than men? Because that at least would be a clear hypothesis that might be tested in that kind of interaction.

Is that the sort of thing you're talking about?

**DR. KIECOLT-GLASER:** You're getting well beyond the physiology that I speak.

(Laughter.)

**DR. HOLLOWAY:** Well, some other people here know that literature.

**DR. GLASER:** Yes, it would be an interesting hypothesis to test. You're taking it one step further after the introduction.

**DR. HOLLOWAY:** Yes, and where do we go with that kind of research.

**DR. GLASER:** The metabolic change associated with that hormonal introduction.

**DR. HOLLOWAY:** Right.

**DR. GLASER:** Yeah.

**DR. MARLOWE:** Bob.

**DR. ADER:** I'm not going to avoid Jan's comments, but I wanted to get back to your question because I think conceptually it's a very important one that dictates the strategy of research, which had to do with whether or not physical stimuli and symbolic stimuli that may be associated with it induce the same physiologic responses or do any two stressors induce the same physiologic responses.

Students come into my lab using language like "cold stress" and "restraint stress" and "heat stress." And it may take four years, but by the time they leave, they're referring to "cold" and "restraint" and "heat" and what have you because this superfluous label "stress," which I alluded to before. One of the problems that Selye introduced, was a concentration on the common events that occur in response to different stressors.

John's data, Ben's data suggest the answer to your question is they produce different physiologic responses, and even the dimensions of a single response have a latency of magnitude and a duration, and who's to say which of those is the most important parameter of the response, of the reaction?

So if I use two different stressors or if I use the same stressor but find that it increases susceptibility to A and decreases susceptibility to B, then I have to assume that even though both may elevate steroid levels, the mediating mechanism is not the steroid level. It has to be some uncommon factor, not the common factor.

So I think the literature are very, very clear that the same stressor has different effects on different outcome measures, and different stressors can have or the same stressor can have different effects and vice versa.

And I think one of the problems with Selye's analysis essentially, is the concentration on the single one. There's no question in my mind. The data -- it's not a matter of belief -- the data clearly indicate that different stimuli induce different responses, and that's what accounts for the difference, and that's over and above the individual's idiosyncratic perception of these events and the meaning and all the other variables we recognize.

**DR. GLASER:** I agree with what Bob just said, and give you an example of a story that's about to be published that I did in collaboration with John Sheridan in our group.

In our group, we tried to model with animals a lot of the human studies that we do so that we can do mechanism studies, and we've been interested in influenza and stress and herpes simplex virus and stress. We've been modeling these with John Sheridan to be able to do mechanism studies.

Within the group who do animal studies, the use of restraint as the model was the adopted model that all of us have used in a lot of studies, and when you restraint mice, cortisol goes up. You can show the impact of restraint stress on both the virus specific antibody and T cell responses to herpes simplex virus and influenza virus, both memory and primary responses. I mean all of that stuff has been published, and it's a very good stressor to use.

I've been trying to establish a herpes simplex virus latency model in mice for years without success. In fact, there really wasn't one that existed in the literature. People have been trying for many years. But, anyway, a few years ago a group down in St. Louis actually, a guy named Pepos in the Ophthalmology Department, established an eye model, an eye latency model for herpes simplex virus, Type 1, that worked. That is to say you sclerify the eyeball with a needle. You drop the virus on the eye. The virus goes through primary replication, and then goes up the trigeminal nerve like it does in the human being, and it sits there in a latent state. If you then irradiate the eyeball with ultraviolet light, in some percentages of those mice just like in people, the virus is reactivated and you can actually isolate infectious virus by swabbing the eyeball.

Well, when that model came out, we decided that we would take restraint and restrain these animals and try to get a nice stress model that we could do some interesting studies with. We tried for about three years every which way but south to get the virus out with a restraint stress. Even though cortisol was going up we couldn't. Once in a while we could get it out, but not enough to do statistics on or write a paper on or anything.

And so when some of the people in our group started using a different stressor called social reorganizational stress, we decided to try that as well. Let me explain what this is. If you get these mice for instance using males, and you put five mice in a cage after they come in -- you come back a week later and you have five cages. You open up the top of that cage and you look at the mice, there's one mouse in that cage who has very few wounds or no wounds at all. That's the alpha mouse, the boss of that cage. Okay. They've set up a pecking order. They've set up a social network that they've established that this person is the head mouse.

So what you do now is you take that head mouse from each of those five cages and you rotate that mouse every day for four days, and now when you take these mice that have been lately infected with herpes simplex virus, Type 1, using the eye model, you reactivate the virus in a significant number of those mice.

And what's interesting about that study is that the cortisol levels induced by both restraint and social reorganization are about the same. So there's something else, as Bob pointed out, there's something else going on.

Those two stressors are both physiologically stressful at least in term of cortisol and by the way, the restraint paradigm is amazing. It's 12 hours a day for ten days. You would think that that would have -- and it does in all our other studies. It does. It does a good job on those mice -- but whatever it is, it's not enough to reactivate latent HSV-1.

Simply reorganizing those mice -- and, by the way, the alpha male always reactivates so far. We have this preliminary. Beta males, some yes, some don't, but alpha males so far in this first study that we have coming out in this paper always reactivate. So that guy is paying a price for being the alpha male.

But that four days just simply rotating that male mouse is enough to reactivate the virus. So it's a model that we can start taking apart to look at these other things that might be going on, and to me that sends a message that different kinds of stressors are having different physiological outcomes which have different health implications.

**DR. KIRMAYER:** That really just makes the point that I wanted to make from a slightly different point of view, which is that I think that there's plenty of evidence from this type of research that among the most salient and most powerful stressors, if you will, for animals and for human beings are social stressors, and we're fundamentally social beings. So the dichotomy between the symbolic and the environmental stressor is a bit artificial in a sense since what we're usually calling symbolic in many ways is a social stressor. Exactly how that's configured may be shaped by symbolic means, but the making and breaking of affectional bonds and interpersonal conflict and so on, I think, pretty much can be counted upon to be a very significant stressor in most situations.

To me that also points to a role, again, for social science input in the type of study you're talking about to try to characterize at a social level and interpersonal level what some of the salient parameters are of the stressful situation that people are being exposed to. There can be a kind of back and forth dialogue; a dialectic between biological parameters marking some kind of change and social analysis indicating that this type of situation ought to be particularly difficult for people, and ideally then to confirm each other in a way in an ongoing --

**DR. GLASER:** How is that going to play with the lone ranger out there in the field by himself without the social support of being within that platoon?

**PARTICIPANT:** He's in radio contact.

**DR. FRIEDL:** Yeah, they're connected somehow, but it would be a different kind of connection.

**DR. ADER:** I think we have to be careful here. I agree very much with the power of the social factor as being very important, but if we acknowledge that different stressors have different patterns of response, it may not be the magnitude of the effect, but where it's acting and how it's acting. It may not have to produce a cortisol response that is higher than some other; only in combination with other agents.

And I've mentioned this to John, by the way. I think those data are great in terms of reactivation, but don't jump too quickly at the cost of being the alpha because depending upon the species, when that dominant mouse is put into the cage, that's an intruder, and he may lose every battle thereafter.

**DR. DOHRENWEND:** That's what I -- I'd like to know what happened to that. It doesn't sound like--

**DR. GLASER:** We don't know that. It's the first study that we've done, okay? And it opens up a lot of interesting questions, doesn't it?

**DR. ADER:** But what's more is --

**DR. GLASER:** No, no, no. They all get moved. They all rotate.

**DR. DOHRENWEND:** I think I might rather be strapped on a table than forcibly put into a cage where I'm a minority of one and there's possible enemies.

**DR. ADER:** But what's interesting is what if you put all of the alpha mice together in one cage, all five of those. What happens then?

**DR. DOHRENWEND:** The manure hits the fan.

**DR. HOLLOWAY:** I would like to go back to that image of that single person on the screen, which I think could be way too dominant as an image. One of the things that cantankerous humanity has been successful at doing as various kinds of social organizations have arisen is to put together relationships that we don't expect, both informal and formal, to counteract, if you will, the forces of anomie that are introduced by other kinds of organizations. I mean it has been repeatedly predicted that the next kind of social organization with which humans are not familiar will result in the next collapse of society, youth, what have you. You can almost take your pick going back to as long as human beings have been writing it down.

But it may very well be that one of the problems with regard to a person wearing that technology is how that person with that technology develops a new kind of set of social relationships, and that, in itself, may be a question that is important to consider.

**DR. URSANO:** It is also just one stage. I mean, just to emphasize this issue again of the time course that's going on in this, the person may well be in the field in a three unit operation, but that night he may go back to a unit that's much larger. Certainly once he comes out of the field and returns home, he goes back to a unit that's much larger.

**DR. MARLOWE:** Let me make an observation from some of our last wars, and this is where symbolic ties come of tremendous importance.

Individuals are alone on the battlefield. Small groups are alone on the battlefield. What sustains them is what happened before in training, and the bonding of the group and, above all, in the trust that other folk are out there. Where they're supposed to be and what they're supposed to do is providing mutual support. It's when that breaks down that you find groups disintegrating. You find, in military terms, psychiatric casualties hemorrhaging, when the troops have that perception that the ties between people no longer exist.

There is, however, a problem. Usually in the past people have been able to see each other. They may not be able to communicate, but they've been able to see that others are out there. It becomes very problematic at night. There are a lot of observations from World War II about this, when people lost touch with each other, and again, I think the point that's been made by both Ron and Larry Kirmayer we are social animals. Rats and mice are social animals, and we forget our sociality, and it's consequence is our peril. I think it's important that we not forget it and not forget that we are imbedded in systems of relationships at all times.

**DR. HEGGE:** We have a model of combat forces who fight alone or in very small groups and have had for a long time, since at least the First World War, and those are pilots, fighter pilots.

So the land warrior and Army are not something new on the face of the earth, but I will point out that historically with fighter pilots, the number of missions, the number of exposures to that situation is a critical variable in the maintainability and status of the pilot.

**DR. MARLOWE:** Let me underline the symbolic valence before I got to Karl. My late wife's stepbrother was America's premier single handed sailor. His name is Francis Stokes. Francis raced around the world alone twice. He sailed single handed from England to Newport any number of times.

A few years ago we had dinner with him, and he was wondering about going into the next British "Around the World Race," and I said, "Why will it be so important to you, Fran?"

And he said, "Well, gee, you know, if I don't participate in the race, I really can't sit with the guys afterwards and have a drink and talk about it and really be a part of the group."

Now, here is someone doing the loneliest, most isolating thing a human being can do, literally sailing around the world alone in a 41-foot sailboat, and the primary motivator is being eminent.

**PARTICIPANT:** Fear of death.

(Laughter.)

**DR. MARLOWE:** -- in the room with those who sail around the world alone.

**DR. FRIEDL:** I think there's another model of this kind of social isolation stress, and it's when we've had a minority trying to break into something for the first time. You know, if you read the accounts of the first black person who tried to get into West Point or the Academy, especially the more recent account from the first woman, when they're by themselves, they tend to fail. They've succeeded when there were two or three or four of them to sort of bond with, and that's isolation within the group.

**DR. MARLOWE:** Well, Manny Rosenberg's initial work in self-esteem before it got captured and perverted was in schools in Baltimore that were being integrated. What Manny discovered was that there was a very big difference in self-image in view of confidence on the part of black kids until their proportion of the population reached 15 percent. Then it was an almost a digital flip in terms of the alteration in the way they viewed themselves and the way in which they coped with the world.

So I think these are very important phenomena.  
John?

**DR. MASON:** May I just ask another question about somatization? Maybe some of the clinicians here might have an interest in this area.

In psychosomatic theory, it's long been observed on and off in patients in whom you have a symptom and you relieve them of the symptom somehow, (sometimes by surgery or sometimes by whatever), that before long another symptom appears. It gives the impression that a symptom serves some kind of important adaptive purpose.

I just wonder if in the area of somatization does this notion have any application? I wonder, for example, if in relation to shame -- if I'm not functioning well, and doing poorly in my social and work environment, if being physically ill could serve a very important ego supporting function. I just wondered if that's a point.

**DR. KIRMAYER:** Yes, I can answer that, I think, fairly well since I know the literature well. The majority of 'IF' conversion symptoms, which we could take as one example, are isolated and don't recur, the vast majority of them. The problem is how you define somatization.

If you define somatization the way that Dr. Guze and his group has, as people with a lifetime history of many somatic symptoms, then you can fairly well predict that people are going to go on having multiple somatic symptoms.

So you have to distinguish between people who have a few sporadic ones in whom this kind of symptom replacement, I think, is the exception rather than the rule. If people can be helped with their problem, their problem goes away, and I think that idea that there's always symptom replacement is a bit of an old clinical saw that doesn't hold up that well.

**DR. ENGEL:** It may also be related in part to the epidemiology of chronic symptoms in that they're intermittent and relapsing. That seems to be true without respect to which symptom you're referring to. And in these folks who have multiple symptoms they may be running in different time sequences. So one may go away and the other may appear, but --

**DR. MASON:** What kind of intervals? I'm concerned there with the -- such as is it months?

**DR. ENGEL:** I think there's enough variation across different patients that it's hard to make general statements about that.

**DR. MASON:** I was just wondering how soon it would be. Could it be within years apart or months apart?

**DR. ENGEL:** Based on my experience, I'd say more in the months range. It could be years or months, but typically in patients with multiple somatic complaints that are persistent, you're talking about weeks to months.

**DR. MASON:** So there's a phasic pattern, and it's not a matter of overall symptoms cropping up, but it's particular symptoms developing when others were gone in the same time?

**DR. ENGEL:** You know, when you have someone with lots of symptoms, you get all sorts of different patterns. You get some that are running together and some that are running in different time intervals. I'm only guessing that this old clinical lore, which is what I would describe it as, is the idea "get rid of one and another replaces it," may well be a sort of random observation that's related to the fact that these symptoms are recurrent and relapsing in their nature. They tend to run together, at least in a subset of folks.

**DR. GUZE:** I think it's very important to at least be aware -- I don't know that everybody agrees -- but that if you look at patients with what I've defined as somatization disorder and studied with follow-up and family studies, and so forth, there is no evidence (that I'm aware of), of any kind of consistent alteration in bodily function, physiology, or chemistry that correlates with stresses in interpersonal relationships or anything like that.

On the other hand, if you look at the kinds of conditions that the Wolffs were particularly interested in, they characteristically and typically picked things to study where there was a pretty good idea or a very good idea as to what physiological system was involved, and that's what they studied.

Now, many people have urged that the term "psychosomatic illness" be reserved for that latter group and not for the somatization disorders. I think it's possible that the somatization disorder patients don't have any objective physiology. It may all be some kind of cognitive representational notion in the brain, and there is no physiology in the periphery where they have a lot of their symptoms.

**DR. MARLOWE:** I think we forget at our peril that being ill as opposed to being sick, there's a very big technical difference between the two – it does redefine roles and enable you to redefine both social relationship and the ways in which you interact. I will go back to Parsons' observation many, many years ago about the sick role. The American culture of the '50s, was the passport period you had out of complete responsibility for your own life and that of your family. Being sick was legitimate for a whole bunch of other things that otherwise might have been construed as incompetency on your part.

And I think we must remember the social dimensions of being ill in terms of trying to understand the behavior that we see. I think there is a real question, and I have no answer to it, as to whether something like somatization disorder, as Dr. Guze hypothesizes, may be purely cognitive. I find at this stage of my life, it very difficult to pull off the cognitive from the physiological. I've been too influenced by the concept of the transducing brain, and that one is just as powerful as the other.

Fred.

**DR. HEGGE:** Yes. When we first started worrying and thinking about Gulf War illness, I tried to think of not an illness, but a normal process where you would have this kind of really sharp confluence of somatic, emotional, and cognitive components. The model that came to mind was based on some work I had seen at WRAIR earlier and my personal experience, and it's fundamentally bait shyness.

In the human case, it's going to a restaurant, eating a meal, and shortly thereafter coming down with acute gastric distress. This is not an uncommon experience, especially if you spend any time in Mexico and other parts of the world, and now increasingly in the United States I should say.

But as I remember those incidents, it didn't take more than a whiff of the food, the odor of the food, a mention of the event, a recall of the event, or any other of those concatenated stimuli presenting themselves to me, and I would get a queasy stomach. I would feel distress. I would be unhappy.

It struck me being sort of taken with evolutionary thinking of one kind or another that it was a really neat design. Really neat because, the environment had arranged a lesson for me, and the lesson was, 'if you think about,' 'if you smell it,' 'if you taste it,' 'don't do it,' and 'I'm going to remind you,' right,' about what that consequence was.

Now, is that a sensible process that could underlie the development, the course of development of what, because it goes awry in various ways, we now see as disorder and interprets as disorder? Especially since perhaps the precipitating incident may be long gone and fundamentally unrecognizable because what in the hell is an adequate stimulus, may be very difficult beyond the recall of the individual, and so on.

And I just wonder whether that makes any sense to anybody and what's wrong with it because then I'll stop thinking that way.

**DR. HOLLOWAY:** What's the "this"? What's the predicate of your sentence? I'm confused about your predicate. Is your predicate Gulf War Syndrome, somatization disorder, psychosomatic disorder? What's the --

**DR. HEGGE:** Specifically the concatenation that we've been discussing. The concatenation of cognitive, emotional, somatic events where they appear blended together as symptoms, distress, where a causal set of stimuli appears to be absent.

I mean if you could point to the event that was causing it, we wouldn't be discussing it. We would have the explanation. I'm just wondering is this an illness, a disorder, or is it a fairly normal process that is probably well wired into the brains of most organisms that can avoid dangerous things that has gone awry?

**DR. MARLOWE:** Who would like the last word?

**DR. HEGGE:** Yeah.

**PARTICIPANT:** The VA always gets the last word.

**DR. GERRITY:** Really. I did pay for that, didn't I?

There was a very good presentation at our meeting last week on Gulf War veterans' illness by Buchwald, who, looked at the commonalities and overlapping characteristics of chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity, and I would just posit that the extent of that commonality would suggest that there is something to be gained by understanding what are the differences.

In other words, why is it that what triggers the same symptoms -- that there are different things that trigger the same symptoms, and I think that's very, very important. I don't know what the answer is, but I think that there is, you know, a lot of commonality there. I think there's much to be learned about why in some people chemicals, why in some people it's the result of, let's say, an acute infection, et cetera.

The other thing I would just like to say, going back to the social aspect is Dan Clauw, at the same meeting spoke to some evidence. I cannot give you the citation of it or whether it's merely his observation -- that all three of these, if you will, call them disease entities are associated with support groups. You know, all of them have one. Chronic fatigue syndrome, they have support groups. Fibromyalgia has support groups; multi-chemical sensitivity.

And what he noted was that, they have newsletters and things like that; that the chronic fatigue syndrome support groups and the multiple chemical sensitivity support groups are heavily focused on: What caused this? Who is to blame? What is to blame? Whereas the fibromyalgio support groups focus on what can we do to make ourselves better. The actual prognostic outcome is better for the fibromyalgic group than for the chronic fatigue and the multiple chemical sensitivity groups.

**DR. NATELSON:** As someone who worries about those three diagnoses in my work day, let me say that I think we need to view these symptoms, indeed, in a syndromic sense and try to figure out. If they are all the same or are they different?

So I'm starting to look for things that we'll say, "Well, these folks are going here, and these folks are going here." Is there, indeed, a shock organ?

One thing that's intriguing when you look at the literature is that abuse, be it sexual or physical, seems to code for irritable bowel syndrome and fibromyalgio, and chronic pelvic pain. But, darn, we can't find any of that in careful sexual histories, the same risks or the same possibly poor data collection, but doing the same techniques, we can't find any increased prevalence of that in chronic fatigue syndrome. Okay?

So what I'm wondering, are there predictors of some amplification or some organ systems being altered by stress or an individual's perception of how he or she feels after that stress? What we as scientists have to do is work this syndrome all the same. Is it an homogeneous thing, or are there specific risk factors that lead to this presentation rather than that presentation? A little bit like Bob was saying, that perhaps stress may turn on System A and turn down System B in the endocrine system.

And these are things that rather than discuss, we can empirically look at. I feel it's one of the challenges to me researching these unexplained illnesses, to try to figure out these predicates, to see if we can understand. Again, a need for longitudinal studies, so that we can understand who gets what and what is the consequence to him or her.

**DR. MARLOWE:** And that --

**DR. SCHNURR:** Can I answer that just because I've done a literature review on this subject? And I think you're right. I think it should be this way. We should better characterize the outcomes as well as the potential causes, but right now in terms of the role of trauma, it looks like a shotgun, and I came to this meeting partly because it does look so much like a shotgun. I'm kind of confused about that.

I'd love to come away with better hypotheses about targeted systems that should be affected, but right now abuse seems to be related to almost everything except chronic fatigue.

**DR. NATELSON:** But we can't find it, yet.

**DR. MARLOWE:** Okay. Let me give you the charge for tomorrow morning. It's five o'clock. It's been a long day.

I'd like people to think about the following kinds of issues.

What are the sort of prospective studies that should be done, not just through the military, but any environment that you think effective prospective studies can be done?

What from each of your perspectives would be significant cross-disciplinary studies that should be done, you know, whether or not money is available and, again, not just in the military, but in your laboratories, in your clinics, et cetera?

How do we approach the question of vulnerability and predisposition? How do we approach it rigorously so that we can get away from the issue Paula just raised, the shotgun, "Hey, abuse"? Everybody's been abused and by the time we're finished, everybody has been abused, therefore no one has been abused.

And finally, where do we go in terms of intervention and prevention? What are the things that we might consider both to do and to develop research programs and research proposals about in terms of considering how do we convene and prevent some of the processes that we've been talking about take place?

And with that let me thank you all very, very much, and we'll see you all tomorrow morning.



**SUNDAY, 28 JUNE 98**

**DR. MARLOWE:** Before we begin going to the questions I left you with, there is one area I would like to go back to. And I'm afraid I let us get off on a sidetrack yesterday after Karl Friedl's presentation and Fred Hegge's remarks because what we wanted to do was consider out of the sum of the technologies for looking at dry physiology heart rate, activity, et cetera, that had been developed, like the temperature pill, the actigraph, et cetera, and really consider what kinds of phenomena the dry physiology that we are presently able to collect and some of the stuff we may be able to collect in the future, how helpful this might be.

And I think it opened for me another issue and one that, frankly, I don't know much about, but what dry physiological non-invasive measures might be good indicators of some of the less physiological issues, particularly neurophysiological issues, that have been a central concern to a number of folk here and what kind of work has been done and what kind of work might be doable, particularly with animal models, in order to try to find the kind of relationship between the two that might be helpful in doing field epidemiological studies, both in the military and in the civil society?

And I use the term "indicators" very deliberately. I also think of the sort of gross indicator that's been very helpful when you're doing things like research on the epidemiology of drug use, where equations that are really quite adequate, if not accurate, but adequate for description of a situation have been developed with the indicator being people coming into ERs with overdoses and the general distribution of use of a drug in a population.

So I just wonder if there are any thoughts on this area, what kinds of representations we might know about where the sorts of dry physiological indicators using the individual as his or her own control and using a reasonable population in some of the kinds of things Karl was talking about yesterday might also give us insight and pathways into other processes that may be going on in the body.

Any thoughts?

**DR. GUZE:** I don't have a direct answer to your immediate question, but I did feel yesterday that I was surprised that the genetic model has played such a minimal role, if any, in studying stress and its impact on people.

And I would just like to suggest that those who are actively involved in such research give more consideration to it because it is a way of opening up new possibilities.

**DR. MARLOWE:** No. I fully agree. I think one of the issues that continues coming up and blinking around the edges is the issue of predisposition and the issue of probable differences as we look at the bell curve of human physiology and neurophysiology.

And I think, you know, one of the windows we have talked about a little is the question -- and we'll get to vulnerability and predisposition -- but is the question of: Are there cogent relationships between neurophysiological vulnerability or lability, if you will, and psychological vulnerability or lability?

**DR. HOLLOWAY:** But, Dave, I want us not to -- the word "genetic" has now been brought up. In your history, the most prominent model for studying stress prior to 1945 was genetic. It said: All blacks can't fight, could not be mobilized into combativeness because of genetic predisposition.

So when the word "genetic" model is used, I hope that the discussants will define it more precisely than it has been defined sometimes in the past.

**DR. MARLOWE:** Harry, I, of course, would call that a pseudo-genetic model of American racism. Unfortunately, it was a model that was implicit in the military and in many other places.

**DR. HOLLOWAY:** But certainly the people who favored it were the American Society of Epidemiology, --

**DR. MARLOWE:** Absolutely.

**DR. HOLLOWAY:** -- all of the formal organizations, et cetera, et cetera.

**DR. MARLOWE:** But I don't think that's --

**DR. GUZE:** I would agree with what you said, but it seems to me that it has shown itself to be a very useful approach in so much of the rest of medicine. And, you know, for example, one of the things that we have circled around, not come to grips with is the whole issue of various kinds of clinical manifestations that are subsumed under stress disorders.

A strategy for trying to clarify this further is to study the familiarity of different syndromes, different clinical pictures, different courses, responses to treatment. That's a way to begin opening up possibilities for a fresh look at what belongs together, what doesn't.

**DR. MARLOWE:** Yes. I don't disagree at all.  
Paula?

**DR. SCHNURR:** I just wanted to mention that there is genetic work underway. Bonnie, maybe you know more about this than I do, but there's a Vietnam era twin registry. And with respect to the question of PTSD, I think it's been shown with kind of a so-so measure of PTSD that, you know, doing a twin-type model, that there is an inherited vulnerability to the development of PTSD.

But it also appears that there are some genetic factors in exposure itself, which I think the authors of this work tend to believe is mediated through personality, that, you know, combat exposure is not a random event. There appears to be a heritable component in terms of who gets themselves into a combat situation.

Roger Pittman now is also trying to look at biological predisposing factors to PTSD as well. So I think this is a good point, but I'm not sure that you have access to a twin registry for Gulf War veterans. And this is a different phenomenon. What we're talking about with Gulf War veterans is substantially not PTSD.

**DR. MARLOWE:** Yes. I think we all agree with that. I would point out that self-selection, who gets yourself into combat exposure, is comparatively new.

In World War II, that decision was made by General Hershey in the selective service system and what the needs were at the moment. And that was equally true for most of the Korean War, and it didn't begin ending until the very latter parts of the Vietnam War.

I think there was a bias. And the bias came out of World War I, following which all combatants attempted to, quote, "save" their best genetic material. Even the Germans until 1944 exempted almost all university students from military service.

We created the ASTP and V12 programs so that, quote, "our best and brightest people" would be conserved from combat. There, the bias that we did have was to put the less educated and the lower IQs into infantry units.

But this was really culturally driven by the extraordinary response to the percept that an entire generation had been lost in Britain, France, Germany, and even the United States, which proportionately, by the way, suffered as many casualties in its short period in World War I as the British or French or Germans had, given the nature of that war and the whole construct that we had lost a generation of our best.

I think the whole issue of familial patterns, certainly it has been demonstrated that depression and other things is an important one.

Bonnie?

**DR. GREEN:** Yes. The family research on PTSD thus far has been really minimal and I think not exactly -- it's been mixed. The findings on it have been mixed. In at least one study, it was major depression that predicted offspring with PTSD.

And I was going to say: If people are talking about genetic studies, are we talking about looking for a gene? Are we talking about demonstrating that there's some heritability or family component of PTSD?

**DR. MARLOWE:** I think we must be talking about behavioral genetics.

**DR. GREEN:** And if so, I would like to hear more about why that would be useful at this point because I'm not sure that I agree.

**DR. GUZE:** Well, my initial interest in genetics came about from my interest in psychiatric diagnostic systems and nosology. And if you find that a condition does run in families in a consistent way or if you find that two conditions that resemble one another run in different kinds of families, that's a very powerful kind of evidence to encourage you to go further.

Now, the idea of identifying a gene, that's a very tough goal to reach, but there's a lot of value from research under this genetic model for everything clinical, epidemiological, therapeutic, even if we can't identify a specific gene. And it's highly likely that very few of these conditions will be simply the result of one gene.

**DR. MARLOWE:** Fred?

**DR. HEGGE:** Yeah. Dave, you've several times tried to get the group to address the issue of propensity. How would I know propensity if I thought I had stumbled on it? Are we talking about PPP here or --

**DR. MARLOWE:** No. We're --

**DR. HEGGE:** -- pretty fine protoplasm, too sensitive, or what are we talking about here?

**DR. MARLOWE:** We'll come to that under vulnerability and predisposition when we start with the questions. Certainly there is a lot of data that indicates that segments of any population are more vulnerable to broader or deeper stress effects than others. That's what I'm talking about when I talk about propensity. I'm talking about vulnerability.

Chuck?

**DR. ENGEL:** One thought that I would have is that I'm no expert on ergonomics, but it seems to me that it might be useful to think about the challenge within sort of an ergonomic framework, which is that it's a mismatch, rather than a vulnerability, that there are job-related factors and there are person-related factors. And when the two don't fit, then problems result and –

**DR. MARLOWE:** Yes. But I think it's equally fair because all human beings live in context. To define people as vulnerable in certain contexts, obviously folk who break down from combat stress would never break down from combat stress if we never put people into combat.

And I suppose, you know, my own perspective before we move on is, always has been, and will remain multifactorial and we have to consider the interplay between the environmental factors, social, cultural, physical, the individual psychological history, the individual's genetic makeup, which to a degree defines its physiology and its neurophysiology, which also probably gets defined as the brain does in its interaction with the environment.

My implicit model in my head of all of this is considering a pool ball going across a table being hit by a myriad of other balls, which ultimately define the vector that we're coming to. That's my model.

Bob?

**DR. URSANO:** Before we leave the gene question too far because I think it is important, I think Sam highlights a couple of issues for us. One is I think we can hear around the table that those may be particularly difficult studies to do within DOD because they carry all types of political loading.

The importance of that means that it may need to be done in other places. It can be very difficult to get Congress to agree to certain studies within the federal system.

Secondly, I think it highlights that we don't have many molecular biology studies of PTSD of any type. It's in the area in which we're dealing with startle, which is very important but far distant from the phenomena at the cell level.

And then, lastly, there are some good studies on genes and anxiety. I believe it was Dennis Murphy's lab in *Science* a couple of years ago. But it's just a marvelous study, and it takes large populations. It needs a collaborative study done across many sites and that it yields a small amount of variance but very important to our understanding.

The last point I wanted to make in that is that one of the dilemmas I think within DOD we have is that often it becomes: How do we move from that to an intervention in a large population? And it takes time to think through how to get from gene to large population intervention other than selection, which raises all kinds of other issues for us I think as well.

So to the extent that we're driven by practical solutions, it isn't always the most practical area for us to look at, but it is critical to our understanding of the disorder. And we just need more molecular biological studies.

**DR. HOLLOWAY:** And I wouldn't want to leave Paula's remark about the possibility of this leading to people putting themselves in harm's way more frequently as free of any consideration.

There is a literature in the studies on violence in America, those studies that were done along with the Kerner Commission report in the early '70s. Of those, one is a publication called *The Strain of Violence* that, at least as of that date, establishes that well over 80 percent of all congressional award-winners in American history come from the same geographic areas and from the same ethnic stock; that is, Scotch-Irish, living in northern Alabama, Tennessee, West Virginia, Arkansas, eastern part of Oklahoma, et cetera, et cetera. There's a segment of this study which then looked at violence, both civil violence and military violence, as being selective.

The idea that this has been randomized is a hypothesis, but I think when we look at people who actually served, there's a fair amount of evidence that the people who actually serve are not randomized, even in the days of the draft.

And so it seems to me that once we raise the question genetically, it is a question both of exposure and of response to exposure and then of different outcomes; that is, Gulf War somatization, et cetera. These kinds of studies have not been undertaken, to my knowledge.

**DR. URSANO:** DOD does now collect DNA samples as an issue of identification afterwards. The ability to use those samples is highly concerning and very complicated.

**DR. MARLOWE:** Yes. But may I also point out there's been a lot of work done on the culture of violence, particularly with the Scotch-Irish population in the American South and the border states.

And to jump to a genetic decision, it would be like looking at Scandinavians pre-Christianization and post-Christianization, where the most violent group in Europe became the most pacific group in Europe with a massive culture change.

I think we have to be very, very careful about such –

**DR. URSANO:** Let me suggest there are models where this is being looked at, such as David Reese's work trying to understand the contribution of environment as well as the contribution of gene, to which there certainly are intellectual ways to approach the problem. But it is complicated.

**DR. HOLLOWAY:** David, recognizing your argument and so the controversy will not be absent from this meeting, are you saying that, therefore, it should not be studied?

**DR. MARLOWE:** No, I'm not saying that.

**DR. HOLLOWAY:** All right.

**DR. MARLOWE:** But I'm also saying that we should not jump to conclusions.

**DR. NORWOOD:** I'm going to interrupt, and I'm going to ask that we can be like Willie Sutton and go where the gold is in terms of future research. I'm feeling time pressure and wondering if we could start maybe pointing to your questions from yesterday.

**DR. MARLOWE:** We don't want you to suffer PTSD.

**DR. NATELSON:** You asked the question about dry measures that might be used. And we sort of are talking about a very dry measure, which is possible. I don't have the answer to that. I was going to ask Karl and Fred.

Certainly Fred could be able to tell us: What present or emerging technologies do you see that are available or will be available in the next 18 months that could be used in population studies? Anything new in salivary hormone measures that are coming up?

**DR. HEGGE:** That's not my domain, but the one that I find most interesting, perhaps for having both laboratory, ambulatory, and field, truly field, components, is voice, which has, as everyone I think recognizes, waxed and waned over the years.

But in the military, the target system choice right now, as I said yesterday, will be Land Warrior or a similar situation which would have a human in a machine interface. And Land Warrior in its first upgrade go-around will go to voice activation of all its functions.

Now the person wears a little mouse kind of button on their chest, which they move their cursor around and make their selections, but it's the little voice that says they will have on board computer voice analysis capability.

And the question I raise with myself is this -- and maybe Jim might have something to say about that since he's been playing in that arena. Is this an opportunity for us to get the kinds of information that might inform deliberations?

**DR. MARLOWE:** You mean the micro tremor kinds of things?

**DR. HEGGE:** Timing, timing. Historically it runs all the way from changes in spectral content, which a fellow in Texas whose name escapes me believed had personality correlates to the issue of lie detection, which was a micro tremor detection, vocal chord tremor, to the kind of German work Hans Peter Krueger has been doing in terms of timing of voice signals of both inter-phonation intervals, inter-word intervals, and so on, in which he has demonstrated that as a rather sensitive psychophysiological measure.

**DR. FRIEDL:** And up to content.

**DR. HEGGE:** And up to content, yes.

**DR. FRIEDL:** Content analysis. And that's what we're missing most of all, the social interaction piece, which we don't have any handle on. With the newer, high-powered systems that we're developing, it's conceivable that in the future, we would use something like the SPIRE analysis system or later versions of it that are these sort of artificial intelligence analysis systems. It's I guess a refinement of kind of a cluster analysis.

We would look for certain patterns more than just certain words, but phrases would start being used that have some particular meaning for a change in the pitch.

Yesterday we talked about we've got this behavioral measure but we miss out on attitude. How do you pick up attitude in this piece with hard measures?

**DR. NATELSON:** I've got another thought.

**DR. FRIEDL:** Maybe we could start doing it with that kind of analysis.

**DR. NATELSON:** You know, I spend a considerable amount of time trying to look within the body for hormonal measures that correlated with stress. And so basically in the series of experiments, I manipulated animal behavior, arousal, or excitement in a monotonic way and then looked at candidate hormonal systems. And they're relatively insensitive.

The catecholamines were the best of all the systems I looked at. Glucocorticoids were really very insensitive. And then as I'm sort of in this quest for this inside measure, -- Dave and I were talking about this yesterday -- in the animals, overt behavior was quite easy to measure in these steps.

You know, I could tell when the animal was slightly aroused, moderately. And I really didn't turn to what seemed to me to be the appropriate area if we were to move this again.

I was doing animal work. If we were to try to move this into humans, then one would think of the work of Eckman, where he's categorized all the movements of the face and can with a monitor sort of tell you which of the 76 facial muscles is activated and what it means.

Now, obviously I'm talking about an entire line of research, but that would be a line of research where one would see emotion and one would see arousal. And the point David and I sort of came to in our little coffee chat yesterday is: Why are we hunting for within when it's staring us in the face sort of thing, so to speak?

So, again, it's sort of I'm giving you this as sort of the result of my frustrations in this quest, but I do believe that the answer may be more proximal than we had thought and measurable.

**DR. MARLOWE:** From the point of view I think we've got to hunt within importantly, but what I'd like to do now before I get beaten is move to the questions we left you with.

**DR. MEYERHOFF:** Do you want a response to voice stress or salivary or –

**DR. MARLOWE:** Yes.

**DR. MEYERHOFF:** In terms of voice stress, there are several commercial systems for evaluating voice stress. Many of them are targeted at detection of deception. It seems to me that that's a hard question to address. And I don't personally choose to address that issue.

I think first the first requirement is to ask the question: Do these systems reliably measure stress or not? Since our particular human subject stress model is very robust, with blood pressures going up to 170/100 in the first 5 minutes, I thought that would be a good model.

We have evaluated one system, again, having done the digital recordings. And, again, I'll point out there are multiple systems for doing the analytical work.

The first system we analyzed was the CVSA method. And there will be an abstract presented at the American Psychophysiological meetings in which we show that, despite replication of the robust hormonal and heart rate and blood pressure responses in this system, we couldn't find any change in voice stress. Part of that was because we could not establish inter-rater reliability with this technology.

Now, there's too much of a training or subjective element involved in this so-called technology, and I say "so-called" because I don't think it's been sufficiently studied to determine whether it's a technology.

The other question was about salivary measures. As you probably know, of course, you know the cortisol work. Chatterton's published on the use of amylase in saliva as a measure.

The enzyme amylase correlates with plasma norepinephrine, the salivary levels to back up. Although salivary levels of cortisol correlate with plasma levels and changes therein in the case of salivary catecholamines, it's been reported that they don't correlate well with plasma changes. But amylase does, especially in long distance runners and in one or two experiments involving psychological stress where the stressor was mild. However, there were some significant correlations.

And Yang and Yehuda have published that MHPG in saliva correlates with increases in catecholamines. And in our lab, we're trying to compare the two methods head to head to see which is the more robust and convenient measures.

**DR. BLACK:** I just have to ask one last question.

**DR. MARLOWE:** Please.

**DR. BLACK:** Most of these dry measures that we do, physiological and even hormonal, and even voice tremor. And the big question is: So what if it's high? If a tense, anxious, hyper-vigilant person more liable to crash into stress than another?

**DR. FRIEDL:** That's exactly the problem. I mean, we've got to remember dry mouth would also be a reflection of –

**DR. BLACK:** Yes. I mean, I'm not even sure. What's your feeling about that, David?

**DR. MARLOWE:** The problem is we really have no idea because the studies haven't been done.

**DR. BLACK:** Right.

**DR. MARLOWE:** And the studies as to whether or not there are folk who are tense and anxious and who also become highly symptomatic before, during, after, whether or not they're the ones who crack, we don't know.

**DR. BLACK:** Right.

**DR. MARLOWE:** And that's the essential, central problem.

**DR. BLACK:** And that should be something that we should study in our prospective studies.

**DR. MARLOWE:** And that's what I'd like to open it up to now.

**DR. BLACK:** Yes.

**DR. GREEN:** And Persian Gulf illness isn't cracking in combat either. So if we're talking about who is going to develop somatic illnesses when they get home, that's an entirely different question. And it's not even –

**DR. MARLOWE:** That may be an entirely different problem. The only thing that says it may not be if you go back to the -- there's the Zahava Solomon's work and some Arik Shalev's that people who crack in combat are far more prone to develop post-combat syndromes. But the answer is we really don't know that.

**DR. GREEN:** I don't think we have much reason to believe that there's a lot of PTSD in the Persian Gulf. And so part of the question I think is: To what extent can we sort out what the consequences are that are related to the Persian Gulf? The PTSD is a very small piece of that.

**DR. MARLOWE:** Yes, but let's remember that our charge isn't the Persian Gulf and PTSD.

**DR. GREEN:** Right. I thought it was somatic consequences.

**DR. MARLOWE:** It's somatic consequences.

**DR. GREEN:** Right.

**DR. MARLOWE:** And we do not know whether folk who are highly anxious et cetera, et cetera -- you know, again, we simply don't know. And let's begin. What are the prospective studies we should do?

**DR. MEYERHOFF:** You asked about dry physiology. Before you leave that, I have just one question that I want to ask. I understand that in the Gulf War, there's a subset with fibromyalgia-like symptoms.

**DR. MARLOWE:** Correct.

**DR. MEYERHOFF:** There have been a number of studies of pain sensitivity, which is a form of dry physiological measurement, in fibromyalgia. I don't know whether that has been done sufficiently, and I would like to know whether people think that there is room for pain threshold sensitivity measures in folks with stress-related somatoform and other illnesses.

**DR. NATELSON:** Well, I have two bits of data if they're helpful. One, I can tell you is DIS diagnosis of veterans of this conflict who have chronic fatigue syndrome. In a nutshell, there are about 40 percent who have no concurrent axis 1, maybe 35 percent, -- the number has actually been going down in recent months -- who have no DIS diagnosable axis 1 comorbidity. And of the remaining whatever, 60 percent, about two-thirds of them have PTSD by DIS and have also a high Mississippi but PTSD by DIS. So we do find in this group a relatively large group of percent who have PTSD.

Now, the other thing we are doing in these veterans with chronic fatigue syndrome -- and, actually, we've opened that up, not just chronic fatigue syndrome but less specific complaints. When I say "chronic fatigue syndrome," I mean that these people have case-defined chronic fatigue syndrome.

But we have done a touch and pain perception and post-stress analgesia. And the only data that I really have clear in my head are the Von Freiherr data, which are normal, and the pain threshold data, which are elevated.

But there may be -- I'm just not 100 percent sure that we have completed controlled for taking nonsteroidals, which could perhaps affect that. And I don't recollect the stress-induced analgesia data, but we have that -- that experiment we're doing, which are thresholds before and after stress.

**DR. MARLOWE:** Okay. This issue is closed. We will now move to prospective studies. Jan?

**DR. KIECOLT-GLASER:** One of the obvious ones that could be done in terms of the military is the fact that we vaccinate large numbers of people. Leventhal has a nice study with older adults where what he has done is look at symptom perception following vaccination.

And what I don't see crossing literature is that we have the whole psychiatric literature on somatization disorder. And we have a large psychological literature on symptom perception. They're not literatures I speak well, but I don't think they speak well to each other.

And it would be a nice opportunity to see what happened if you could cross those literatures to look at how people respond to a vaccine both in terms of symptom perception as well as antigen processing and look at characteristics of the people who are going to report the greatest number of symptoms related to it.

Related to that in our wound studies, in our first dermal wound study with care-givers, we created identical wounds in care-givers and controls. Care-givers in terms of pain ratings rate the wound as significantly more painful than controls. It's true across the pain literature that greater pain sensitivity is associated with greater distress in general.

And so one of those things that simply may be happening is that people are more distressed and more attentive, but it's a way to sort out what kind of physiology may also be underlying the changes that are being seen.

**DR. MARLOWE:** Let me ask a question. And I think Janice has proposed a very interesting model. But if we were to consider those as an experiment venue starting at the sociocultural level and coming down, how would people approach it as a model? Any thoughts?

What would you want to know beforehand about the folk who were being vaccinated, both physiologically, psychologically, in terms of medical belief, all of the other things we've talked about? Etzel?

**DR. CARDEÑA:** A couple of things. The first one, expectations. There is a rich literature in hypnosis that shows that a number of effects that have been attributed to hypnosis are actually a matter of what people are expecting. So I would want to find out what people are expecting is going to happen beforehand.

And the other one would be what kind of communication they are receiving. That's a study that we are doing in a pilot on the contagion of pseudoseizures. And that is typically done in other cultures, but I think that we should also have some kind of sociogram type of research of what are the sources of information, what is being told, how it is distributed so that people, in part, get different expectations about what is going to happen, different attributions, and so on.

**DR. FRIEDL:** We've got a pilot study that's just being finished now with ranger students, where we gave hepatitis A vaccine. And one of the problems was getting suitable controls. So we used some of the cadre and the investigators that went alongside. So, again, it's pilot data. It suggests that the level of stress that ranger students go through does suppress the response to the antigen.

So we've got some very intriguing data there, but that only begins to scratch the surface of this much bigger picture. It would be interesting to look at something like, especially in terms of expectations, the anthrax vaccine that we're giving people now.

**DR. MARLOWE:** Well, I think this is an interesting and challenging model because we began with a set of cultural expectations, then whatever is going on in the group and the community's transactions.

Kai, do you have any thoughts about this?

**DR. ERIKSON:** I will in a minute.

**DR. MARLOWE:** You still have a 286 chip.

(Laughter.)

**DR. MARLOWE:** John?

**DR. FAIRBANK:** One of the thoughts that I have is that I'm not really sure at this point that I really understand if we have agreed on what the outcome measures are. And I don't know if we have really agreed on what the exposure variables are.

I would submit that we certainly need to be thinking in terms of monitoring studies, which would suggest certain types of designs. I think we do need to think in terms of prospective studies, but I have been really kind of influenced by this -- I think one of the most intriguing things I heard yesterday was: Think in terms of 30 years.

And if we're still struggling with the variables 30 years from now, no matter how many mediators we come up with and potential risk factors, I'm afraid we will not have advanced as far as we would have liked.

And so I would submit that as a part of the program of research, that, really, there needs to be a very concerted effort, which would probably require considerable investment of resources for maybe a five-year plan, where we really do try and understand: What are the outcome variables that we're interested in here, and how can we measure them according to all the classic psychometrics or whatever the variables are in terms of reliability and validity?

And I come to this from thinking about recently responding to one of the Gulf War initiatives and just really struggling after reading the literature with what measures to use to capture these ill-defined diagnoses and/or disorders or symptoms.

**DR. MARLOWE:** If I may, the outcome measures that we would be concerned about initially -- and I don't think we can be that sophisticated -- an aspect that appeals to me about the study Jan just outlined is the perception and expression of somatic symptoms.

And here I think we have encapsulated something that crosscuts both the psychosocial and the biological in terms of what's measurable plus what is produced afterwards in terms of the individual's presentation and, if you will, whether or not, in Kleinman's terms, the individual now presents an illness narrative with a bunch of symptoms that are attributed to having to the vaccination.

**DR. HOLLOWAY:** I'm having a problem listening because I'm not sure what Janice's question was. And so I would want to know. I understood what the set of studies you wanted to do was, but I'm not sure what the question was that was being addressed by those studies.

I hear David's assumptions about what they were, but I want to hear what your thoughts are about them, what the question was or --

**DR. KIECOLT-GLASER:** Well, there actually are a series. The questions could be both symptom perception issues because if you vaccinate people, you're providing a uniform antigen in theory. People respond really differently in terms of what they report as symptoms.

So you're in some ways giving people the same kind of challenge and asking: How are you going to interpret it? With our care-givers, for example, on flu vaccine, some people refuse flu vaccine because they've gotten so sick from it.

Well, you know, people really don't get sick from flu vaccine. It's possible if you had a concurrent illness, but it's also possible that some just simply interpret things in that way. So I'm curious about it in that way. But that's one issue.

The second issue is: Does stress interfere in some ways? Does the style or distress interfere with response? But I was intrigued by the design more than the questions, actually.

**DR. HOLLOWAY:** The reason I was raising the question is that I'm wondering whether there are questions imbedded in that in terms of the previous vaccination history of all subjects that would biologically present problems.

**DR. KIECOLT-GLASER:** Sure.

**DR. HOLLOWAY:** They've already got an antigen history.

**DR. KIECOLT-GLASER:** Yes. You give a novel antigen under those circumstances for exactly that reason.

**DR. HOLLOWAY:** So you only give a novel antigen?

**DR. KIECOLT-GLASER:** Yes.

**DR. HOLLOWAY:** Okay.

**DR. KIECOLT-GLASER:** They have no exposure. Hepatitis A or hepatitis B for those reasons.

**DR. KIRMAYER:** I just want to say that this experimental paradigm in a sense is a refinement of an observational epidemiological paradigm that's already been used to look at symptom perception and illness behavior. I referred to this briefly yesterday, I guess.

In England, Anthony David, Helen Cope, and so on looked at a cohort of people coming to a primary care setting with an acute onset of viral illness and then followed them up six months later to see who had developed persistent fatigue. And they were able to look at certain predictors of that, which included psychological factors.

Now, what's missing from that is a physiological evaluation of those people. And so it doesn't really address the perennial problem of sort of reverse causality in this because it could be that the psychological things that are seen are, in fact, valid manifestations of physiological things.

So in a sense, taking that kind of longitudinal situation, which did show effects, as I mentioned yesterday, of people's attributional style and of the intensity with which they were investigated by the physician, both sort of cognitive and social factors leading to chronicity and disability, which are, after all, the kinds of outcomes that are of greatest importance, so to take that to create a situation, then, or take advantage of an existing situation where you now have an experimental design and to couple that with physiological measures would be a great advance.

Just to say that from that kind of literature -- and that's not the only study of this type. Howard Leventhal's work as well. There is a battery of kinds of things that can be used to look at people's symptom perception and cognitive mediators of that and social influences. So bringing together those two paradigms shouldn't be so difficult.

**DR. ADER:** I'm not sure. Let's put it this way. I think it may be easier to talk about prospective studies if we talked about prospective studies at the same time that we're talking about vulnerability studies.

**DR. GUZE:** What kind of studies?

**DR. ADER:** Vulnerability for measures, outcome measures, what have you. It sounds like it might be more difficult, but, actually, it answers some of the questions because if one takes a population and waits for the self-report of symptoms, which are going to be about as heterogeneous as -- there will be as many as there are subjects.

I'm not sure what you can do with that information when you got all through, as opposed to picking a homogenous population, which is by definition at risk for something or other.

And I think you want a model in which you can vary both the characteristics of the population, on the one hand, and the nature of the challenge on the other hand.

I'm sure that Ron has been asked and Jan has been asked and Paul has been asked and I have been asked by people who have been addressing such measures: What should I measure? And my answer is: What do you want to know? And what you want to know depends upon the nature of the challenge. We work backwards.

So Jan suggests we produce a novel vaccine. Well, that is from my point of view clearly the method of choice. And, to go one step further, as a behaviorist looking at immunology, I would characterize most vaccinations as involving suprathreshold stimulation, levels of potential pathogen stimulation that the person never sees in the real world. So why do we study it this way? Because that doesn't make any sense. Immunizations have a different function.

So if you can titrate the amount of a novel antigen, you're in a position to come closer to the model that exists in the real world; i.e., a stimulus which by itself may be necessary but not sufficient to induce any changes whatsoever.

Now, if I'm working with ulcers, which I've worked with, why would I look at blood sugar level as a physiologic measure? I know how to measure blood sugar level, but its relevance to ulcers escapes me. Conversely, if I'm measuring or working with diabetes, why would I measure pepsinogen levels? I know how to do it, but its relevance escapes me.

So if one starts off with a population that harbors herpes, that's a vulnerable population in that regard. If one starts off with a population that's harboring *H. pylori*, that's a vulnerable population.

What would I measure in those people? I would measure whether or not there's going to be any gastritis or lesions or what have you. If I'm interested in ulcers, then I would look to see whether or not they're harboring *H. pylori* and so on down the line.

I would welcome under those circumstances the psychometrician or what have you, the sociologist who would ask questions about: Within that population, what's the level of social support and all of the other variables we can identify or that have been identified as being relevant to the outcome?

But a priori there is no group of measures which one should take, period, and there are no outcome measures that one should take a priori. It seems to me the question is: What's the nature of that population?

At one level, people who have been diagnosed with PTSD are a vulnerable population. Now, one can wait around in a natural situation to see what develops or one can experimentally manipulate it. And the fact is one can I think safely introduce novel antigens and exert precise control over what it is that you're introducing and dictate what it is you want to measure.

I'm just suggesting that we discuss all of these at the same time, rather than –

**DR. MARLOWE:** Well, I fully agree. And I think one of the issues here is in the characterization of the population for vaccination. And what are the instruments and methodologies and things we have to know to determine whether or not there are segregatable, if you will, patterns of vulnerability?

Fred?

**DR. HEGGE:** Yesterday, the term "ROC" was used, I think from Beth's side of the table, in describing some of the search that had been done, a receive operating characteristic analysis that will allow you potentially to separate sensitivity from biasing factors. And that's almost where we are this morning with your question, the question of symptom perception.

Are we dealing with a scaling question? Are we dealing with a threshold issue? Are we dealing with an output biasing issue? How can we separate that? And it seems to me that there's a psychophysics issue that is sort of central to this question that we have been dancing around and coming very close to at this point. And I just throw that out.

**DR. MARLOWE:** John?

**DR. MASON:** I'd like to come back to John's point and try to follow up in some way. I think I feel a need for a sort of step-by-step logic here in terms of what you need to know first and then what you need to know second and so on.

If you'll pardon that, I feel that I agree with him that if you're going to look at risk factors, you've really got to understand the character of the outcome population and the population that you're interested in, whether it's Gulf War or PTSD or just in a broader way trauma-related or combat-related illnesses.

Somatization may or may not be a part of the next one. We don't know. But it's certainly an important area, and it's a part of PTSD, too. It may be subdivided in some ways to get part of a profile and not other parts and depending on the specific characteristics of the specific conflict and the follow-up after the conflict and so on.

But the idea of needing to first begin with characterizing the population, in this case the Gulf War population, up to this point, to my knowledge, has been very limited, studies in my area, in terms of hormonal profile in terms of a close look at the clinical correlates of biologic measures in this population and so on.

But the idea of the interdisciplinary approaches that you mentioned we should be studying, what things have not yet been brought to bear on the Gulf War Syndrome population that could be brought in and using the knowledge we have from PTSD to guide us? Because if you're not looking at the relevant variables, you can go on forever and never find any.

And if you're ignoring certain variables because they're not easily measured or because they're hard to get, some of the things I brought up yesterday, like the guilt, shame, they're hard to measure. They're hard to deal with.

I know psychiatry is hard. My young colleagues at Yale keeping telling me "Forget psychology, John." They want to move the psyche out of biologicals. It's too hard, they say. But that's no way to solve problems. Take the easy route. It could be deadly.

I'm saying that there's a full way in which we need to develop mental kind of mentality here. First, you can't just use standard instruments. You can't just take a workhorse instrument because it's been used so much. It may not work in Gulf War or PTSD patients as well as it does in college students that it's calibrated in. And you have to use some common sense and modify it, modify the scoring.

You need a lot of creative thinking about characterizing this population. We can't afford to eliminate any instrument, any methodological approach that could pay off, including dynamic psychiatry, in characterizing it.

And then once you have that, it leads you -- you know, core symptoms have to be assessed. Overall psychopathology in a general way needs to be assessed. And also character structure. And there will be a lot of that characterization, and you'll get the lead about what things need to be brought to the prospective study.

If you just get one crack at a soldier before he goes overseas to the next conflict, what are the most important and relevant things that you can do? What can we narrow down from our current population studies?

**DR. MARLOWE:** Well, that's where we hope to get. In order, it will be Paul, Kai, and Bruce.

**DR. BLACK:** Okay. Well, John has brought up a point about variables. And this other person brought up some question about psychophysics. And just the idea of learning something from a person's perception of symptoms after vaccination and the background that the person brings to this, this data has to rest on your findings and your results. And the Glasers have shown that stress influences the response of a vaccine.

Now, most soldiers get vaccinated when they come together and during training or whatever. And it's been shown that people get immunosuppressed in these studies we have been doing at Camp Lejeune, where they get a lot of respiratory disease. And it's the herding and the coming together, the pooling, and the anticipation of the newness it brings for stress. And so stress will influence your results.

The other thing is the Army gives 12 antigens at one time. I don't know of any studies that show that is functionable, that that is operable, that that brings good results. When you go to a traveler's clinic, you need six. They'll say, "Well, we'll give you two today and three the next time" and they titer this.

When we give children vaccine, we give them two or three antigens at once, four tops. There's no basic data that I know of -- I may be wrong -- that shows that the response to 12 antigens is efficacious. And the Army should do that sometime.

We should put that in our prospective study. But I think it's crazy to give -- I don't know whether the response to 12 at once is better than 6, the response to 6 given twice or 4 given 3 times or whatever.

And so your basic science upon which all of your superstructure rests is bad, and your results are not going to be fallacious, I doubt, are not going to be -- go ahead.

**DR. MARLOWE:** To go back to Jan's proposal, it was one vaccine, one novel vaccine.

**DR. BLACK:** And I just want to bring up the 12 because of yesterday. Are you going to give that one with the others or when?

**DR. MARLOWE:** I'll give Harry Holloway a chance to respond to that after we finish with the people who -- Kai?

**DR. ERIKSON:** Actually, I'm going to shift gears a bit. So if those who want to respond --

**DR. HOLLOWAY:** I'll just give a quick response. There were several studies done on antibody response to the vaccination system. And the way those studies are done is whether you can get an adequate response, adequate response being whatever the titer is that they predicted. It's a percentage.

In terms of disease control, there is a fair amount of evidence that there is protection from the military vaccination system. But that's a restudied issue.

In fact, I have another question that's a part of that, which is: Who says the antigen is operating and not the adjuvant? Because these are not a situation in which you're getting pure antigen, but you're getting antigen plus adjuvant to stimulate response as a part of this over-stimulation issue that Bob was raising before.

So I think it's a fairly complex set of questions, but there is, in fact, a quality control operation that goes on routinely to the vaccination. And it's a trade-off, quite frankly.

**DR. MARLOWE:** Kai?

**DR. ERIKSON:** Yes. There is a risk in this kind of conversation that the impetus for me to make the comment that I'm about to make is actually about six or seven minutes old. So I'm moving into an old conversation, moving into a new territory. But I don't think there's any way to avoid it in a meeting like this.

You had asked me earlier about what somebody interested in community might say about vulnerability studies. And I would like to begin my thinking about that by asking you a question, which is: When you talk about a particular population being exposed to a particular kind of problem -- let's say the troops that were in the Gulf War -- and the Army looks for information about who these people were and where they came from, what do we learn about the social background from the people who described themselves as having had some, one or another, kind of symptom?

**DR. MARLOWE:** And obviously before I kick this over to Chuck, who has been doing the studies with the people who have come in symptomatically, the Army maintains a bare database.

There's a lot of information it doesn't include. It includes, however, education, length of time in the Service, how rapidly you have been promoted, the equivalent of an IQ score, race, marital status, home of record, where you came from.

There are a whole bunch of fields in it. There's a tremendous amount of data in it, much of which would not be utile. And there are some very critical things that are not there.

I don't know what you're collecting, Chuck. What do you collect?

**DR. ENGEL:** You mean at the Gulf War Health Center?

**DR. MARLOWE:** Yes.

**DR. ENGEL:** We have actually just recently sort of re-looked at what we are collecting. And so we are about to make some evolution to that. But some of the basic things that we're collecting are: health beliefs, what sorts of things help for folks with symptoms and what sorts of things harm, are the source of their particular harm. These are symptomatic folks already, keep in mind.

We're asking them about their functional state using the SF-36, which is sort of a standard. We're asking them -- we're getting a Prime M.D. at baseline, which is a brief, structured psychiatric interview.

We're getting an abbreviated form of BSI. We're actually just asking three subscales or four subscales: the somatization, anxiety, depression, and the excessive worry. We're asking a series of sort of standard demographic kinds of questions: income, age, so on.

**DR. MARLOWE:** What we collected in the Gulf during the deployment were the BSI, the brief symptom inventory, which is part of, direct from the SL-90. Their perceptions of the stressors that they were exposed to, the anticipatory stressors if they went into combat, basic demographic data, marital data, and some data about home, their perceptions of whether or not they felt their families were being taken care of because of the extraordinarily high number of people who were married, communication, home, et cetera.

**DR. ERIKSON:** See, I would –

**DR. ENGEL:** We're actually also asking sort of a generic social support question, questionnaire.

**DR. ERIKSON:** If I were invited to participate in the kind of question that you do from kind of a far-out sociological perspective, I'm not even sure that I could promise you that these questions would be worth the asking from the point of view of what it costs to really find those things out.

But in my sense of what vulnerability means from that point of view, the kinds of questions that it would seem to me important to know would be birth order.

It would be important to know, if there was any way to measure it, how well the family the people came from functioned. It would be well to know something about their school history, not just their grades and so on like that but how they saw themselves as fitting into kind of the early social structures of which they were a part.

And I think it would be really important to know, if you could find this out, how often, if any, they had been exposed to traumatic events earlier in their own childhood. And this would be partly to find out how they were put together, what kind of protoplasm they had as youngsters but also how they related to the social world, which is part of the furnishings they carried with them.

You bring a personality. You bring a background. You bring a history, but you bring a social experience with you into a situation like that. And it would be very important to know.

I know I'm just amplifying the question, rather than answering it. It's really important to know, to get some kind of a profile of what that background was like.

**DR. MARLOWE:** Bruce?

**DR. DOHRENWEND:** Fortunately, I think this fits quite nicely with what Kai has just said and some of the questions that Dr. Mason raised.

When I thought about what to say about prospective studies, I went back over the information that I thought we had from the reprints. And it's come up here. And it seems to me that we simply lack important information, we lack facts that would enable us to sensibly plan a prospective strategy focused on unexplained somatic symptoms.

So my suggestion would be there have been some epidemiologic studies, but, as far as I know, I didn't see it. There hasn't been a retrospective case control study, which I think, if I'm correct in that -- and if there was one, where was it in the literature? -- a retrospective case control study, in which a good sample of known cases of unknown somatic disorder, a representative sample in sufficient size was compared with a representative sample of Gulf War veterans who had no such somatic outcomes on a series of risk factors that various of us and outside the literature think would be important.

I think Kai mentioned some of them. I think family history would certainly be important here. I think that I would strongly second the history of prior traumatic events and the extent to which they were fateful or non-fateful in the terms that I mentioned earlier.

Some of the variables in the records are extremely important so far as risk factors or vulnerability factors for PTSD are concerned. And if we think that some of these are also important for somatic disorders, they could be added.

In other words, a host of social, psychological, and biological, and insofar as family history may be a genetic indicator, behavior genetic factors could be studied in a retrospective design.

This would give a factual and knowledge base for planning prospective studies I think in a reasonably sensible way. To plan a prospective study, you need some facts to go on. You need some questions about what it is you want to try to account for.

So my recommendation is a retrospective case control study as a first step.

**DR. MARLOWE:** Nancy, Tim, then Paula.

**DR. BAKALAR:** I just want to say that we have already started some of this work in part of our surveillance screening. We still have to get the metal on the target.

But Craig Hyams is working on the recruit assessment profile. And Chuck and I have worked on questions for that. And so has Paula contributed a lot on that.

Where we're asking about parental loss through death or divorce, parental separation, all sorts of abuse that you can imagine, social support, other victimization.

So this would be all the childhood data. And Chuck may want to say a little bit more about how far along we are in that process as far as actually getting the RAP, the Recruit Assessment Profile, instituted.

And then on the HEAR, the Health Evaluations Assessment Review, we're also addressing those questions relevant to adulthood. We're just beginning our work.

The HEAR 1.0 is out. Our efforts probably won't be seen until the HEAR 3.0 hits the streets. But we'll be asking about intercurrent stressors, traumatic, medical, surgical, social, that sort of thing.

In the case of the active duty, we'll be asking about operational assignments, operational combat stress, look for duration and intensity, look for what happened in the operation or on the battlefield.

**DR. DOHRENWEND:** Yes. Could I ask: I think that shouldn't be left out of this case control study, comparison of the actual assignments of the soldiers.

**DR. BAKALAR:** I think we're a little more fortunate in this in that we just put out the questionnaire and gather the data and it's not called a research project, although I'm sure in the future, it will be well-researched. So I'm looking for any input as we're developing these questions.

Any of you can come to me and give me your ideas. That is why I am here, because this is going to be in development over the next three or four months.

**DR. MARLOWE:** May I make one observation before I go to Tim? We gathered data on 20-some odd thousand soldiers after the Gulf War.

It wasn't until a couple of years later in the final data gathering that we put in a physical symptom checklist. It was simply not something that we were moving in the direction of. And the only physical symptoms we were collecting were ones that were extant and things like the BSI and the general well-being scale, et cetera.

Unfortunately, not having the gift of prophecy, none of us had any idea of a thing called Gulf War illness was going to become the major, if you will, medical outcome of the war.

**DR. GERRITY:** I just want to point out there are several research activities going on right now with Gulf War veterans that hopefully will bear some fruit.

One, in particular, is a case control study looking at symptomatic, defining a case, in essence, if you will, as symptomatic with no medical explanation for those symptoms that generally fall in the category of fatigue, et cetera, and controls who do not and looking at a number of risk factors, including psychological, various things, also like job classification, what they did, where were they, and so on and so forth.

**DR. DOHRENWEND:** I think it's extremely important looking at where they were comparing your cases and controls because it is conceivable that some subset was exposed.

**DR. GERRITY:** Right.

**DR. MARLOWE:** Paula?

**DR. SCHNURR:** I just want to put something on the tape that I think is implicit in this room. And this is this group recommends that the military do a better job assessing people as they come in the door.

You know, Bonnie has pointed out that that's not a baseline, but at least it's what they come in the door with. And to the extent that you need that ammunition, I realize all your hearts are in the right place.

But if you want to understand this, the military has to do a better job of measuring people and continuing to measure them through time in terms of what you put in that battery.

I think all of us want to suggest our particular interests. I certainly wanted to measure personality because I think a lot of these other factors play out through personality, but you could do a lot by looking backward if you really commission some very well-done literature reviews, preferably meta analyses, to help you decide what to bring into the battery.

It's kind of like what I call a packing for Europe problem, where you can't take much and what you take has really got to go to a lot of different places.

**DR. MARLOWE:** Yes. May I just say that this is a frivolous battle that some of us fought for 30 years in terms of getting better or more comprehensive kinds of assessment and data gathering into the initial induction of battery that's done? It is one that I certainly got nowhere with for years and years and years.

**DR. SCHNURR:** Okay. Well, it's here. I think we're all saying this. We're all recommending that this be a part of things. And I know Nancy is trying now and Tim has been trying and hopefully we will make some headway.

But if you really want to know the answers to these questions, that's what has to be. You can't wait until after the fact in order to understand it. You want to be able to predict it and hopefully correct it.

There's another point I wanted to make about case control studies, though. And you may want to consider cases control studies because I still think, even though Dr. Haley's attempt to do that was somewhat inadequate, it was the right idea in that there may be multiple entities out there. I've recently been making myself learn about polydimous logistic regression.

So I'm thinking now all the time, instead of case control cases, cases control sorts of designs. But I think in terms of looking backward to look forward, that a better characterization, a multivariate characterization of what you're looking at will help you a lot.

**DR. KIRMAYER:** Just one very brief comment and a caution about case control studies if you do any retrospective data collection in this area. There are repeated studies showing high correlations between somatic syndromes and recollections of stresses. And those recollections go up and down with somatic syndromes.

So, really, this question is not going to be resolved with that kind of data, but we have to have a prospective design. And it's another reason to reinforce that if collecting baseline or early information that is not contaminated by people's process of recollection.

**DR. MARLOWE:** Sam, John, Harry.

**DR. GUZE:** Is it true that there really have been no well-thought-out case control studies?

**DR. FRIEDL:** There are.

**DR. MARLOWE:** There are case control studies.

**DR. GERRITY:** With respect to both?

**DR. MARLOWE:** Yes.

**DR. HOLLOWAY:** That's what I was going to say. The CDC has published at least one that's methodologically quite sophisticated. There is the –

**DR. GUZE:** Well, out of those, well, if there are some good ones, do they suggest variables that ought to be studied in a prospective study? Because I think the idea of, no matter how imaginative we are, when we are starting to collect a database at any time without knowing what we're going to measure that database against, we're wasting an enormous amount of time and effort and money.

So I don't expect a lot from that. I think you have to be very, very careful that you don't build up a huge database that never amounts to anything. And the history of all parts of medicine show that over and over again.

So I think the emphasis on the case control business is very important. But what are the variables in the cases?

**DR. MARLOWE:** Can I make an observation? May I make an observation? The CDC study of the effects of Agent Orange I think is almost one of the best that's ever been done. And what it – and it's very much in the mainstream of the issue we are dealing with here.

And the conclusion that they came to is a very interesting one that the only thing they could point to in terms of the symptom differentiation between the folk who came in -- and they literally did full physical exams of them, and it's in your packets -- and the control group was belief and attribution about the nature and threat value of the symptoms, ex-post facto.

I think one of the problems is this is an extraordinarily thorny arena in which many factors, both before; during; and, above all, after, which we tend to neglect, come into play.

And now Harry, John, and then Nancy, then John Fairbank, and then Tim.

**DR. MASON:** I just have a quick question. What about the feasibility of a pre-deployment assessment? If you can't arrange it as part of induction --

**DR. MARLOWE:** You know, one's hope -- and Nancy can speak to that -- is that it will be done. There are points in the cycle of every Service member's life. You don't want to do it when you know they're going overseas.

But there is a point that's called in the Army P-O-M, POM, preparation for overseas movement. Every soldier does it every year. It takes three or four days. You get your shots updated. You check your will, your power of attorney, a whole bunch of other things.

We have thought and recommended for years now that this would be the ideal time with which to add in because all they do is stand around moving from one thing to another and doing nothing else on those three or four days to view psychometric instruments, to take saliva samples, to do whatever else needs to be done to establish baselines or, if it were feasible, to aliquot bloods, but --

**DR. MASON:** So, in answer to Paula's question, that would be the most feasible things?

**DR. MARLOWE:** That would be the most feasible window when people are not already in a state of alert and apprehension because they know they're going overseas.

**DR. MASON:** Even that could be organized in a way that you could manage that to do the assessment before as part of a routine assessment.

**DR. MARLOWE:** If people would say "Do it," it could be done. And it's probably the most reasonable window that exists because it's when they're doing these other things.

John Fairbank; then you, Nancy.

**DR. FAIRBANK:** I think I've got to think concretely about this. And I'm not optimistic that we'll ever be able -- I mean, I agree with your points, David, that I don't think we're ever going to be able to hang all of the measures on the routine surveillance that the military does. I think it can be improved.

But we need to think about two separate but interrelated tracks. One is the health surveillance, the monitoring, where we want to find out how many cases are out there and get some sense of: What are the exposures that lead to cases of illness?

And that has to be maximally efficient. You know, the measures need to have incredible sensitivity and specificity. But we're not going to be able to hang all of the different kinds of measures, personality variables, all of the different neurobiologic measures, on that track.

But, very importantly, I think that the military needs to think in the long run in terms of a major epidemiologic research program where we do focus on a very comprehensive system of data collection that moves way beyond the descriptives and actually allows us to get into explanatory types of analyses, causal modeling, from taking into account neurobiologic, psychologic, emotional, social factors.

And these really I think do have to be viewed as separate. I think if we try and say, "Oh, gee, we now have the in-the-field ability to take these dry measures" and think of that in terms of that's going to explain, you know, that's going to provide us with a window of opportunity to explain these illnesses, I don't think we'll ever get there.

And that's why I think that there really has to be a major commitment to explanatory epidemiologic research.

**DR. MARLOWE:** That I think is what lay behind the question, prospective studies, because I think the -- I agree with you, by the way, that the answer is we have to target a comprehensible group, a handleable group, to gather this kind of data and in a prospective fashion.

"What is the data we should gather?" and "Why?" are very major questions. I think there's another very major question, which is cost. And we live, those of us who work for the military, much to the surprise of other people, live in a world of very tight monetary constraint. And one of the issues has always been: What can we do with the little we have? And what is the way to maximize this kind of thing?

Now, we'll go to Nancy and then Chuck.

**DR. BAKALAR:** This will probably be somewhat of a repeat of what I said yesterday, but it seems to me that the group has not heard it. So I want to repeat it.

Because of the Persian Gulf War, the DOD published the DOD directive for joint medical surveillance and the instruction. Those came out almost a year ago. Those require that we do surveillance. This is in regulation.

The organizational structure is there. Out of that has been developed the health evaluation assessment tool review. It's -- I don't know -- what, 200 questions maybe.

We get all the demographic data, nutritional data, exercise data, alcohol, smoking, and detail, a lot of questions on: Are you going to work? How many days are you sick? How many days have you been sick over the last month? How many days have you not gone to work over the last month?; aches and pains types of questions, a lot of questions along the line of: Over the last year, has your doctor told you have X, hypertension, hypercholesterol, and on and on? It has a mental health section that we're working on that we can add some of these questions I mentioned just a few minutes ago.

So those of you who have worked for 30 years to try to get this data, now the tracks are organizationally laid down. The money is there. The HEAR is being implemented in all of the 12 regions. Only it started in Region 1 and 2 over the last month or so. Every region now is disseminating this HEAR exam. It's being required by a policy memorandum every year: active duty and beneficiaries.

So the organizational structure is there. We need to know the questions to put in it.

**DR. MARLOWE:** Yes. I think we have two things, Nancy. One is the questions, but the other is: How do we gather data that may indicate physiological vulnerability?

**DR. BAKALAR:** Thank you for reminding me about that. The HEAR is given annually. And that is being considered the pre and post-deployment screen. I envision in the future when men and women come back from a deployment they will be asked to take the HEAR as a post-deployment screener.

But the DOD and the Joint Staff have developed what has come to -- well, they have called it variously. I'm trying to encourage them to call it a checklist, a pre-deployment and a post-deployment checklist.

The pre-deployment will be given within 30 days of deployment. And it might be when they step on the plane or within two or three days of that. It's about eight or ten questions, only one mental health question and very general questions, you know: Are you taking any medications? Do you have enough for the next three months? Do you have any concerns about your physical health? Do you have any concerns about your mental health or your family?; those kinds of questions.

It's just enough to trip the wire to get them seen if they need to be seen. And the post-deployment questionnaire is similar. So we agree with you that we don't want to test people right after they have been notified of a deployment to see how they're doing.

**DR. MARLOWE:** Can I just make one observation out of our Gulf data that the highest single correlation with the BSI was a 10-point self-assessment scale of how stressed you are at this moment?

And that really had the highest single correlation with the entire BSI as an instrument, which tends to be entrained. And if one is up, they're all up. It's very seldom that you get one up and the other is down.

Chuck?

**DR. ENGEL:** Yes. I wanted to highlight what Dr. Fairbank has said, which really I think -- you know, I'm very closely involved with the effort that Nancy is speaking about with regard to health surveillance and developing mental health questions to fit in that. But, at the same time, I think that we shouldn't have misplaced expectations about what that's going to achieve.

Two hundred questions sounds like a lot, but 200 questions really is not that much. And only a subset of those are related to mental health. And I think that sort of surveillance and monitoring population indices, that's an important organizational activity that we need to do.

It will be a hypothesis generator for what I would see as a very important parallel activity, which would be -- and I think it needs to be a mental health epidemiology program within the military, not just one prospective study, because there's lots of questions to be asked. I mean, part of the difficulty is there are many, many questions around the table that people are interested in. And I think that there needs to be a program.

In terms of a starting point, the point has been made that we don't know what the measures are, we don't know in many ways what the questions are. I think in order to start a -- you know, the first step in starting a prospective study is to develop a cross-sectional baseline.

To my knowledge, there has never been any formidable population base study in the military of mental illness. There have been several efforts in the U.S. and the U.K. and elsewhere doing population-based studies using state-of-the-art techniques for measuring mental illness, including unexplained physical symptoms.

I think that there needs to be a large sort of probability sample generated and that a cross-sectional study of mental illness needs to be done within the military.

And a subset of those folks can be prospectively followed. But that needs to be designed as maybe an initial step in what would be a larger, ultimately larger epidemiologic program.

**DR. MARLOWE:** Let me make an observation in respect to that. In the course of the '80s and then in the post-Gulf period, with active-duty samples, using in each case what are fairly standard instruments today in the Gulf sample, primarily the BSI, prior to that, Dupuy's General Well-Being scale, which was standardized on the national ambulatory health surveys in the '70s, we got data all told, let's say, on about 60,000 people. We were able to do a little bit of prospective work.

There are some very real problems. Scores with the military population are much different and much lower, lower in the direction of towards what would be considered far greater pathology than the civil population. Some of this is inherent in the number of questions that are answered negatively in a military population about control of your own life, which are built into both of these.

The higher folk go or certain kinds of jobs that provide greater autonomy provide much higher scores. You've got to re-norm everything. It's not that we are without it. What we are without in this sense is a serious prospective study.

And I think I have to go back in terms of what we're doing to the question: Why a prospective study? And the question really derives from the following. Ben keeps bringing up the ten percent at each tail.

Are we really concerned about a targetable, vulnerable population that we must look at before the fact if we put people into high-stress situations, into harm's way, into erosive situations, whatever they may be, that is going to produce the bulk of folk who are going to produce in this case somatic symptoms and perhaps psychological symptoms very often as well or is it a different kind of process, one that the instruments that we have classically used to say people are psychologically vulnerable really don't predict these kinds of outcomes? And we're dealing with something else.

What is their a vulnerability? Is this vulnerability psychological, psychophysiological, psychosocial? What are we dealing with? My own feeling is that, crude as some of our tools may be -- and I hope there are people here who have greater sophistication and expertise in the arraying of tools. This is the only way we will get a first whack at the question of: What are we dealing with? Are we dealing with the pure power of the external event or, as I think, the external event interacting with individuals who may be more vulnerable to it?

Five years ago most people working in PTSD were researching, many people, that all human beings exposed to traumatic events would suffer PTSD. Today a significant number of people working with PTSD are saying: Wait a minute. This is a narrow, special population that gets it and keeps it. And they seem to be different from other folk.

That's a band of people who seem to have a special vulnerability, whether it's in their genes, their individual psychological histories, or what have you we still in a sense haven't parceled out.

My question in terms of the issue of folk who generate significant numbers of somatic symptoms, the folk who come in, what, before, during, and after leads people to either produce these kinds of symptoms as a result of interaction with certain kinds of life experiences or doesn't.

I think another paradigmatic issue -- and we have a number of people here who have worked with it -- would be Three Mile Island, where from a purely medical exposure point of view in terms of hard exposure to a pathogen, almost nobody got exposed. This was not Chernobyl.

And, yet, we had significant rises in symptomatology, in many cases prolonged. And we have a bunch of people here who have done work on it. And I'm sorry Andy Baum couldn't come. He was another.

And I thought that might be another piece to look at in terms of the power of perception of an event to produce some of the kinds of symptoms and increased medical usage that we have seen with folk coming out of the Gulf War, with Agent Orange, et cetera.

Ben?

**DR. NATELSON:** Well, there is indeed a small literature that one can consult as to risk factors for unexplained illness. And, again, they're not the kind of prospective things that we need to do, but what they are are evaluation at Point A.

Laurence was talking about the person who comes in with the acute febrile illness that Simon and his group in England have done. There was a paper in the *Lancet* within the past 18 months on an acute viral gastroenteritis triggering irritable bowel syndrome; the old work, of course, in Navy recruits in mono, which was a recruit sort of thing that I envisage as something valuable to do.

Buchwald has done some of this work on the acute onset of mono. So there is a literature that we can turn to pick out areas that would be important to target.

While I have the microphone, the only other thing I would like to ask is if we are able to use the military, Nancy, that would obviously be tops, but if not, the sort of thing that you're doing with the police recruits. But then in my thinking about your work, I'm saying: Well, how often does a policeman really get in harm's way? How often does he have to take his gun out?

So one thing that we might want to do briefly here is think about other populations. And one that came to mind is these EMS people. All of them are in -- they're not in harm's way themselves, but they are in gory accidents and, of course, from the work in the military on death care and providing for corpses as something that can trigger perhaps these symptoms.

We need to think about groups that we can get our hands on if there will -- it sounds like there won't be as many problems as was thought. But that might be another avenue to pursue.

**DR. MARLOWE:** I fully agree.  
Tim, you have been trying. Then we'll take a break.

**DR. GERRITY:** It's tough with a gregarious bunch of people. I wanted to first come back on what you said about the perception because one of the things that distinguishes Gulf War illnesses, it appears, from chronic fatigue syndrome, from multiple chemical sensitivity and fibromyalgia is the chronicity of it in a sense of onset because it appears -- you know, Ben, you're squinching your face at me because if you look at the temporal nature of accession into the registries, I think up until recently, it's been a fairly monotonic increase, in other words, and that with the exception of the event being the Gulf War itself, nobody is able to identify a specific event that says, "I was good this day, and I was bad the next day."

And some of this, the degree to which perception has played a role and the media plays a role, there is some data that is coming out from some of the centers and from the Naval Health Research Center that shows blips in accession into the registries immediately following some newsworthy event; Kamisea, for example. You know, the people started reporting to the registries very soon afterwards. So I think that really is very important here.

Then just a couple of informational things. Sam, you asked about who is going to care in terms of collecting all of these studies together and really looking at -- well, what I mean is that there is lots of research being done. And what will be done with that research? Let me just --

**DR. GUZE:** Well, what I've tried to state, let me state clearly. I just feel any kind of epidemiologic research is very expensive in time and money.

And the natural tendency all of us have to wrestle within ourselves and in our colleagues is the suggestion: Well, let's measure this, too -- that's an interesting question -- or let's measure that. It's easy to measure.

And pretty soon you've got an enormous range of variables that were not necessarily picked on the basis of some clear rationale in terms of the outcome variable that you're interested in.

Now, I'm not saying that sometimes this kind of strategy doesn't end up with very, very exciting results. I can't think of one at the moment, but I'm not prepared to be categorically negative about it.

I do think that exhortations about how we ought to do research has to be very, very circumspect and very specific. Otherwise I don't think they're particularly helpful to serious investigators.

Now, on the other hand, I think if a handful of people who are studying the same problem get together and talk about what they have done or what worked for them or what didn't, that could be valuable to that group in a very immense way.

So I just wanted to be sure that my point was -- I am not trying to be categorically pessimistic. I just think that the chances of it coming out with a useful result seem to me to be small.

**DR. GERRITY:** Okay. I misunderstood, you know, what you had said. I think you are absolutely correct. I think that, in addition, if one thinks of some large prospective studies, one also has to keep in mind the value of smaller, highly focused studies, really directed towards some specific hypotheses that are being tested.

I would just like to volunteer or offer to whatever mechanisms to get out to members here the annual report to Congress on Gulf War veterans' illnesses research so that you can actually look and see what is being done right now and might help in your thought processes as well as what we might want to do next.

**DR. MARLOWE:** Before I go to Paula, let me just reinforce this. I think one of the things to think about in terms of a prospective study is something that does not involve hundreds of thousands of people.

I know of no one who is prepared to pay for what I think are the two best epidemiological studies done, New Castle upon Tyne and Framingham. And Framingham you remember was terminated because of its cost.

Paula?

**DR. SCHNURR:** Well, that's actually a segue into what I wanted to say and emphasize, the cost-effectiveness of what John's proposing. The surveillance is good because it tells you about an individual before he or she has whatever stressful experiences.

It doesn't really help advance science very much, but it helps with individual case diagnosis. What John's suggesting is like a two-stage design in an epidemiological study, where you put a lot more money and focus onto a smaller sample that has some of the same measures as the larger sample. And I think that actually is a cost-saving kind of thing.

Again, what you add to that focused work could be based very much not on us sitting around the table and saying "Measure personality. Measure the anxiety sensitivity index" or whatever but by careful study groups that would help you decide what belongs in that kind of battery.

I think you ultimately will save money. And you could have different programs focused on performance in the field versus getting symptoms later on versus alcoholism or whatever kind of outcome you wanted to look at. It really would be cost-effective.

**DR. MARLOWE:** Bob?

**DR. URSANO:** I just wanted to broaden the angle of the lens for the moment on something that I think will sound like apple pie, motherhood, and the flag. But in some ways, I'd hate to have this conference not state it.

Number one, given the discussion going on, to not lose track of how difficult it is to hold such a conference like this, which is really a compliment to Dave and Ann and the others involved with this, to try and work across disciplines. I think we could reach consensus on the idea.

And I want to underline this is non-trivial in the present climate, that further understanding of the somatic (health consequences) of stress are critical to the Department of Defense.

We need to be sure we say that clearly because in the present world, which is organ-based, disease-based, technology-based, or technique-bound, meaning molecular biology, the dilemmas of providing funding and ongoing support for those activities by an office, as Karl and Fred have pointed out, which is shrinking to minimal, and of which this is a very small piece of that office, -- I mean, don't lose track of it: This is not their office; this is one sliver of their office -- becomes a critical issue.

Secondly, I wanted to emphasize that if we agree on that, that we might also want to at least reach minimal consensus that there needs to be present within DOD the organizational structure and funding to support research across levels from molecular to organ to interpersonal to group. Studies should be done inside and outside the military. If we agree that there needs to be both the structure and the funding to accomplish it, we might then also want to agree that there need to be something like collaborative studies. The word "centers" was used before. That has pluses and minuses, but collaborative studies to address this.

Thinking of Sam's comment that we aren't going to dictate research to investigators, what we want to do is create structures that allow for this process to continue across investigator lines and to be sure that those needs aren't forgotten because in our system, as you know, Dave, it's real easy, as is happening everywhere in the world, for that to get swept away, particularly in the present climate.

**DR. MARLOWE:** Well, I can't select anyway and when you leave an institution, you're socially dead 18 months later.

**DR. URSANO:** But it may be very important -- and I'm glad to get to say this before the coffee break -- that we get some consensus about that so Karl and Fred and others can at least fly that flag when they go back, which really may carry more weight than any other prospective comments would.

**DR. MARLOWE:** No. I absolutely agree. And one of my hopes would be that some of the folk here might in the future consider both collaborating with each other and with some of our folk.

**DR. URSANO:** And that Karl and Fred may have the opportunity to propose some specific structures around this issue.

**DR. FRIEDL:** And Tim.

**DR. URSANO:** Yes.

**DR. GERRITY:** Well, thank you, Karl, because this has nothing to do with anything personal. It has to do with something very practical. And that is I think for something like this to be successful, it has to span both DOD and –

**DR. URSANO:** I agree completely. I was being DOD-bound.

**DR. MARLOWE:** One of the things I'd like to start with and a couple of people have said: A) How do we articulate neurophysiological, psychophysiological kinds of studies with the sociocultural dimensions that are so obviously both implicit and explicit in the issues we have been talking about?

You may remember I gave you the issue of cross-disciplinary studies. I'd like to throw this open as an issue when you talk more about psychological and psychodynamic aspects, but I'd really like to throw this open as an issue.

Again, one of the issues remains the issue of a perception and a meaning of symptoms, a perception of the kinds of things that may or may not have happened to you, the pattern of organizing response to them, the social appropriateness or inappropriateness of the behavior you should exhibit, the storm of cultural presuppositions and information that we live in.

And I guess if I can go on for a minute, I'm trying to keep the focus not on Gulf War, but one of the things that has intrigued me about the Gulf War symptom etiological business is its extreme cultural sensitivity.

When it began, people were all talking about exposure to oil fires. And then at the NIH workshop, one datum ended that for a while. And that was the position to the folk who put out the oil fires. And, much to my surprise, they did not use respirators because they used nothing that would cut down on peripheral vision. And none of them were sick.

We then moved to nebulized uranium for a possibility of exposure to residual sarin, anthrax vaccinations, et cetera, et cetera, et cetera. We moved etiologically through time to the crystallization in both the media and among groups of people and on the internet and referentially to people moving from an impossible etiological agent responsible for a set of symptoms often very different through time, et cetera, demonstrating cultural sensitivity to whatever it was being

presented to the kinds of things that were in the environment as well as a major factor in my point of view which was the crystallized conspiratorial view of government, distrust of governmental institutions, government medicine, and, in fact, with most of medicine institutionally.

I would suggest that all of these things come to bear in terms of what we see as people's references. But I'd like to go to: Where do we go if we're going to set up studies? How do we integrate the cultural, social, and sociological, the social, psychological with the other kinds of factors that have been mostly talked about?

And who would like to take it up? Laurence?

**DR. KIRMAYER:** Well, I think you've touched on a number of important themes. And I don't think there's any substitute for careful ethnographic work to look at what the experiences of people who took part in that war who are symptomatic and what their experience is subsequently.

It puts me in mind of a project one of my graduate students is doing right now in Halifax, Nova Scotia, where there is an epidemic of environmental sensitivity syndrome, large numbers of people who are convinced that they have been affected by various toxins in the air and so on.

And in very widespread belief in Nova Scotia, that's due to the effects of cities like Washington and New York and Boston that are all producing horrible toxins as the kind of effluvia of megalopolis that then is carried on the Gulf Stream in prevailing winds up to Nova Scotia. And so talk about paranoid views. I mean, this is widely held. I mean, I don't know. It may be true, too, of course, like all of these paranoid ideas.

I mean, it's a movie with Mel Gibson, "Conspiracy Theory." You know, it turns out to be a real program that existed at McGill, of course. M. K. Ultra that he refers to is the former head of the department that McGill was involved with.

Anyway, so people are convinced of that, on the one hand. So that's one part that may, in fact, parallel what you may find among some people afflicted by the Gulf War situation.

The other part that may be parallel again is that people in Nova Scotia in terms of collective identity and ethnic identity in the larger context of Canada see themselves as extremely marginalized, as on the edge of things.

And so that feeling of being on the edge of things, perhaps ready to fall off and into the ocean or float away from the rest of Canada combined with that sense of being exposed to the toxic results of the excess of other parts of the world that are much more successful than they are (because since the last couple of generations, it has been an economically depressed area as well) I think are all ingredients, then, going into explaining the popularity of a particular set of ideas that are available.

I mean, these ideas are available to everyone. And so the issue is not where the ideas themselves come from but what the anthropologist Dan Sperber has called the epidemiology of representations. Why is it certain models and certain ideas take hold among people, become widespread, and then have a terminating effect on their illness behavior, illness experience?

So, to understand that, as I say, means to begin to see the world from the point of view of the afflicted people, not from someone on the outside deciding what are the important parameters but spending enough time with them to see what is impinging on them and how the world is constructed from their point of view.

I think that kind of ethnographic work can lead aside from providing information, in and of itself, to ideas about what are the pertinent questions to ask people, both specifically in this particular historical situation and perhaps more generically in some ways.

I mean, if you think of ideas of marginality, you think of ideas of vulnerability more generically, there may be ways to frame those questions to anticipate some future situations. But certainly the whole thrust of ethnography always is to deal with the specificity and with the local knowledge, rather than the more generalizable notion.

But, as I say, I think this example from Halifax is a very different situation where, nevertheless, you deal with a lot of people who are afflicted, who have lots of symptoms, who are consuming a lot of health care, who have the different levels of disability is an example of a social process that we can maybe draw elements from. So that's one thing I would say.

The other part since I have a background in experimental psychology; in fact, in physiological psychology, the other part that interests me is the way in which those larger social processes shape the processes of memory and of bodily experience very powerfully. And so I think that there's a role when we talk about sort of interdisciplinary connections.

This kind of work has not been done much, but my fantasy is that we need a psychophysiology of metaphor, a psychophysiology of narrative in which we look at what actually happens in situations where people are recollecting, recounting, telling stories in different ways.

And the closest work to this work that I'm familiar with in recent times is Jamie Pennebaker's work looking at disclosure. But I think that kind of work can be expanded to take into account other kinds of social factors that have been sort of factored out a little bit in his work, where he finds that narrating a traumatic experience has certain psychophysiological consequences.

And I think to put back in the social element is to begin to ask for narrating, to who, under what circumstances, what kind of narrative, and what are the psychophysiological consequences of that. I think that's a kind of research program, if you will, that could be conducted in concert between social scientists and psychophysicologists that so far has not really occurred.

So those are two domains perhaps. I think one stands on its own and perhaps has the greatest heuristic value and hypothesis-generating value in terms of the ethnography and the other represents a truly interdisciplinary kind of program of social psychophysiology. And there are a few people, like Ron Cacioppa and other people, working in that area.

That's all.

**DR. MARLOWE:** I would just like to make a couple of observations. First, is there anything published on what I will now call sick province syndrome, as opposed to sick –

(Laughter.)

**DR. KIRMAYER:** No, no. It will be another year or so before –

**DR. MARLOWE:** Another point I would make is, addition to a psychophysiology of metaphor, I've become quite passionate about our need to create a psychophysiology of belief.

**DR. KIRMAYER:** Of what?

**DR. MARLOWE:** Belief. What is it going on in the brain and the body when someone believes? And what are the external structures?

Just as an aside, I think we all know how much the movie industry has created the image of a conspiring, evil government. I happen to have a son who is a very successful film writer. And he was doing a screenplay for Warner Brothers in which, as usual, the villains were a bunch of government scientists creating a potentially evil monster.

And I said: Hey, look, Andrew. Leaving aside your Quaker College professor mother, you grew up in a house whose father was a government scientist. All my friends and colleagues, we never do things like that.

And he said: I know.

And I said: Well, tell me why. Is it political?

He said: No. The lawyers are very explicit. The government never sues.

(Laughter.)

**DR. MARLOWE:** He said: If I were to make it a scientific lab that belonged to an unnamed cigarette company or a cigarette company with a name that never existed, Philip Morris' lawyers would have Warner Brothers in court in 24 hours.

So if you really want to know why. And one of the things I think we tend to forget is the degree to which most people create belief – and, after all, if it is printed in the newspaper or in the movies, it must be the way things really are.

I think Laurence has opened up a very major set of areas in terms of trying to start to put things together across what some of us believe to be the biological spectrum extending from culture to the cell.

Who else has some thoughts about that?

**DR. GUZE:** Could we just ask Laurence one follow-up question? What's the clinical picture like of the people in Nova Scotia?

**DR. KIRMAYER:** It's very similar to people with multiple -- well, in fact, it is also called multiple chemical sensitivity, people. In DSM, they would be the undifferentiated somatoform disorder. Most of them don't have enough symptoms to reach the older somatization disorder thing, although in DSM-IV, maybe they do.

They have respiratory symptoms, fatigue, trouble concentrating. When I say "respiratory symptoms," feelings of tightness and discomfort in the chest, dyspnea, a lot of nonspecific symptoms, and so things that can be seen in the anxiety domain in the end, things that can be seen in sort of low-grade depression, dysphoria but really across the whole range of physiological systems.

And, again, the big issue is not what are the symptoms, there's nothing distinctive. And you can go looking for syndromes. There's nothing distinctive in this kind of syndrome. What's distinctive is the attribution. The attribution is, I have been exposed to some bad chemical somewhere.

I should say I can't resist keeping on this theme of paranoia because from a Canadian point of view, American culture -- and from the American point of view, American political scientists have written about this -- is a very paranoid culture. I mean, there's a very strong tendency to attribute anything bad that has happened in the United States to the malevolent agency of another human being.

We don't have that accounted to the same extent. We have a very benign view of authority.

**DR. MARLOWE:** We attribute it to us.  
(Laughter.)

**DR. KIRMAYER:** That's right. We get it all off our chest. That's the old psychodynamic process there.

**DR. MARLOWE:** That's right. It was our pollution over across the border.

**DR. KIRMAYER:** Exactly, exactly. But I think it is sort of gradually creeping up on us. And it's another way. Ben and I were just talking about this issue, that this kind of cross-national comparisons of these social processes become extremely interesting because, although they're not experiments and can't ever be because there are too many things that can't be controlled, they can still be extremely illuminating because of the very powerful effects of the social differences.

**DR. BLACK:** I'm still not clear. Is there objective evidence of pollution of sulphur dioxide or acid rain or anything objective?

**DR. KIRMAYER:** Well, I'm sure there's objective evidence of pollution, but in general I think people who go from Montreal to Halifax think the air is wonderfully fresh and clear sea air. So I would say compared to Montreal –

**DR. BLACK:** Obviously a psyche-type phenomenon?

**DR. KIRMAYER:** Yes, yes. To a very large degree, this is in the realm of illness behavior. I mean, I would never say it's just psychological in the sense that I think that there's white noise going on in our bodies all the time. They're mild physiological dysregulation that's the norm, if you will.

And so the issue is: How does one live with that? And under certain circumstances, one lives very poorly with it. And it becomes extremely distressing.

So I think there's something for people to hang their attributions on. But it's the attributions themselves that are becoming part of the kind of cognitive amplification and a lot of health-seeking and other kinds of problems I think.

The people themselves, of course, are vociferously against this and reject any kind of psychological -- and this is also pertinent to the Gulf War situation, obviously -- reject any psychological attribution because there's a lot at stake for them in terms of both a social stigma associated with that and what kinds of resources they can claim in terms of the legitimacy of their disability and their trouble and so on.

**DR. MARLOWE:** I just want to make one quip. Many people have said that if Canada breaks up, the Maritime provinces will come and try to join the United States. I expect this is the first psychosocial evolution towards American behavior.

Tim?

**DR. GERRITY:** I know, David, that you're trying to get to specific research ideas, but I want to emphasize what you had said by personal anecdotal experience.

I have been involved with Gulf War issues since the Gulf War. I was part of a team that was deployed, an interagency team that was deployed, in March of 1991 to investigate the potential health consequences of the oil well fires.

And I have a very clear memory in my mind of being at Camp Freedom in Kuwait City a couple of miles from the Al Ahmadi oil field. And I was standing out at sunset. The fires were beautiful, quite awesome.

And I was talking to a soldier. He said, "You know what this is over there? That's Agent Oil." And so, speaking of metaphor, the metaphor was created on the spot, quickly.

The other thing which I thought was interesting as well was before he said that, he asked me: "Do you work for the CIA?" because I was in civilian clothing.

Our measurements of the air pollution indicated that with the exception of particulate matter, that all other air pollutants were at the level of Houston, Texas. You wouldn't want to live a lifetime in it. Let's put it that way. And we wrote a report in April that stated that. We were the first ones in there to actually make atmospheric measurements.

There was an editorial in the next month's issue of *Scientific American* that said that clearly we were the agents of the government to minimize the potential impacts.

And Tom Wicker wrote an editorial in the *New York Times* stating much the same.

**DR. HOLLOWAY:** I want to add one thing to that in terms of developing the belief that Dave was talking about. You already referred to the Agent Orange, which had an excellent CDC study, which demonstrated fundamentally that you could not attribute to Agent Orange the outcomes that were found.

And, yet, I have a tape at home that was made very recently, sent to me by the VA, that has the President of the United States communicating to all people from Vietnam that Agent Orange clearly causes your disease.

So if one wants to understand belief and belief system, we also ought to be talking about the agencies of belief.

**DR. KIRMAYER:** Just something very, very briefly about the notion of belief within current anthropology and to some extent within cognitive science, I would say. There's been a strong critique of the idea of belief as though there's certain -- because it implies a kind of folk psychological idea that there's certain kinds of ideas that people hold overly intensely that are patently wrong and that beliefs are somehow different from knowledge, which we all have, which is, you know, a correct way of thinking about things and that is dispassionate and that is easily modified by fact.

Basically the position has been that belief is just knowledge. The issue is that knowledge is embodied and carried in action. And if you want to understand beliefs, rather than simply asking people for what they believe, you have to look at their actions and at the social networks that they're imbedded in.

So this comes back to this idea about: Who are the agents involved, what kind of discourse, what kind of transactions are going on with certain kinds of ideas?

And this gets us close, then, to those ways of looking at things that people are deeply invested in, which they can't always tell us or won't always tell us. It's not simply a matter of recording "Do you believe this or that?" but actually looking at ways in which certain kinds of knowledge, certain kinds of attributions are deployed and are used in everyday life for people.

So identifying what those crucial contexts are in which a person, in effect, enacts what their real beliefs are, enacts the kind of knowledge that they're most invested in is likely to be most predictive of subsequent behavior.

**DR. MARLOWE:** I would qualify. I think there is a realm of belief which armors the individual against all data that might dispute or be disagreeable to that belief. And I think there's a lot of historical evidence for this.

Jim?

**DR. URSANO:** A question for Dr. Kirmayer. It's been reported in the past that economic dislocation can affect the expression of subcultural belief systems.

And I recall that some years ago, maybe in early '90s, the Government of Canada had to stop offshore fishing by Canadian fishermen. Of course, that's a major industry in Halifax, in Nova Scotia.

Is there any correlation between that and the time frame of the cultural change or belief system change you're talking about?

**DR. KIRMAYER:** Absolutely. I think another determining factor in this is what I refer to as marginalization, primarily economic marginalization. And I think that that's a huge factor. Interestingly, though, it's not simply a factor. It's not a strong factor at the individual level.

In other words, if you look at socioeconomic level, you find a weak correlation with medically unexplained symptoms. And it cuts across socioeconomic levels. So it is the problem that is affecting the whole community that then affects many individuals at different levels, even though they're better off than others. So that's a stronger effect perhaps than the effect on the individual within -- I'm speaking now within developed countries and situations with people.

**DR. MEYERHOFF:** That leads me to another question. If reservists were disproportionately affected in the Gulf War, which I've heard, -- I don't know if it's true -- to what extent is it addressable, the issue of economic dislocation if they had to give up lucrative jobs; in addition, had to be separated from their families? So it was kind of a double hit in some cases, involuntary separation from both family and presumably lucrative employment. Even though they were employed, in some cases it wasn't the employment of choice to be in an inhospitable environment.

Can that be modeled in terms of: Can you study other groups, like civilian groups, who were economically not by choice dislocated from family and from their preferred job to another job that's less preferred?

And Bob Ursano had a suggestion of a possible model in that regard.

**DR. KIRMAYER:** Just to say one thing about that that's interesting. There was a large Quebec study, I guess a review and study, of disability following low back pain, low back injury.

And the strongest predictor of outcome is work satisfaction, pre-injury work satisfaction. So that's much more important than any biological factor or anything measurable at the level of people's injury.

**DR. MARLOWE:** Okay. First Etzel and Paul, then Sam, then Chuck.

**DR. CARDEÑA:** I would like to address the question you posed in a somewhat different fashion and along the spirit of what the Center had said. I think there would be a possible model to use in even what Larry had said.

We could have a person who would do ethnography. We could have a psychologist who would go and do different cognitive tests. We could have physicians, et cetera.

But I think what would make it fly is whether there would be some funding waste that would allow for actual, real multidisciplinary research to occur. I don't know that there is such a thing, and I don't know if it can happen.

Unless it happens, I think that we can all talk until we are blue that we would like to integrate into a multidisciplinary event. But if there aren't grants that might allow for different simultaneous level types of research where a center might be organized along the lines of a problem, rather than an institution, I don't foresee it happening.

**DR. MARLOWE:** Let me make an observation in respect to that. It's been done in the past in the Army. I've done it. The question is that you have to have a manageable, targetable group. You cannot go beyond a few hundred people because of both the time intensity and needs in terms of doing ethnography and doing all of the other things.

When you go to this kind of multidisciplinary study, it is a very temporally and people-expensive business in terms of doing it. One can view it as a parallel issue to a wider prospective study, but it's targeting a specific group that can be studied intensely in this fashion with the data gathered.

Paul?

**DR. BLACK:** Just talking about belief for the moment and cross-cultural, cross-disciplinary activities, I think one of the problems we continually encounter is the veterans' attitude towards stress. And it's amazing the tenacity with which they reject this concept.

To be stressed and have the manifestations of stress is bad. To be physically ill is okay, to have pneumonia. But to be stressed and have your disease psychologically based is very bad.

How do we combat that? I think we almost need the help of the social scientists. But it's impeding a lot of -- I mean, the presidential review board, the conclusion was there's no physical agent that we can put our hands on that causes this syndrome.

NOVA just put out a big special that came to that same conclusion. And the veterans just won't believe it.

**DR. MARLOWE:** I think in terms of some institutions like the military, -- I was thinking about this after Karl's presentation yesterday -- there is an entry point. And that entry point is the effects of stress of cognitive behaviors allied to performance. People accept that stress will degrade high-level cognitive behaviors. I think that perhaps is in some senses from a public relations point of view the entry point to get people to start understanding, once you lay out stress effects on the performances they're interested in, what the other effects are in the body.

What I did for a while with every senior military person I met was give them a copy of De Masio's book "Descartes' Error" because I think what we are up against is the classical Cartesian mind-body dichotomy as people play it out in their own heads and refer to it in respect to themselves.

Chuck, Sam.

**DR. KIRMAYER:** I just wanted to respond to that very briefly because I and my colleague Alan Young and so on have written quite a bit about the metaphor of stress and the way in which that has shifted.

And I think very ironically what has happened is a consequence of the VA's pushing forward the idea of PTSD. I think not very long ago and still in many clinical settings people are very happy to use the attribution of stress because it is not a psychological attribution for them. Stress is in the air. If you define stress, it was not my fault. I was under terrible stress.

Because of the existence of PTSD, what has happened is stress has been psychologized. And now for many people, especially in the VA system, "stress" is a code word for a psychological disorder, which people continue to push away because it implies a kind of level of personal culpability and blame that is very painful for people and very de-legitimizing.

So I think that to me, it's striking that most of the patients I have seen in the medical setting are very happy when we talk about stress because that's not psychological for them in the same way as having depression is psychological or having some other problem is a blot on their personhood. But stress, "well, you know, I'm in a tough situation". So that's an acknowledgement of that.

So I think, unfortunately -- and there are probably other factors as well, but one identifiable one is the meaning of PTSD, which has shifted from being started very much as the kind of attribution that, "Look, we have been under terrible circumstances. Anybody in these circumstances would get sick. It says nothing about me as a person".

But, as research has shown and so on, it now is colored by exactly the same kind of connotations that other psychological conditions are because of fundamental dualism in our whole culture, which is the things I'm responsible for and things that just happen to me.

Psychological problems are the former. They're the things that I'm responsible for, even if in a larger sense they're not. But that's how they're colored morally.

**DR. GERRITY:** Just real quick as this is important. A co-phenomenon, if you will, was that, at least at a national level, VA was not saying that it was PTSD. VA suggested that it was stress. What happened was that the media and the veterans translated stress into PTSD I think because of the contextual nature of it.

**DR. MARLOWE:** Next will be Sam. I just want to make one observation. It, nevertheless, remains a fact that in our popular literature, our magazines, things like Parade, newspapers, stress is still the most respectable reason for any problem that you have.

Sam?

**DR. GUZE:** Well, I really wanted to speak to the sort of sociological point of view that we began with. But I would like to say I can understand why it's hard to convince the veterans that stress caused their illness. I'm not convinced. I have read the literature. I have talked to people. And why am I not convinced? Because the concepts we use are so vague, so slippery, so useless, so contradictory that there isn't any firm basis.

So it seems to me I would -- I don't know if it's true, but I would wonder whether the better educated veteran would be the most skeptical. If he or she knows something about the nature of evidence, how science establishes the validity of some hypothesis, they would say, "Well, that's a lot of bunk."

I want to come back to this business about the Nova Scotian epidemic. I personally find what you articulated as appealing, and I just implicitly accept there's a lot of validity to it. So, therefore, I put that up first because I'm going to really ask a kind of skeptical question.

What's the value of that kind of research from a practical point of view? In other words, will it come out that we'll be able to take that and prevent the Gulf War syndrome or prevent the Nova Scotian syndrome? And if so, how would we do that?

You see, I think that there's a lot of research that's very interesting. And those of us who enjoy research and are interested in these puzzling correlations and so on and testing hypotheses get really focused. But I wonder if you have considered how could that information be used to turn the people in Nova Scotia around. What would it take?

**DR. KIRMAYER:** I don't want to monopolize. I mean, it's a great story. I'll answer that with another story, which is the story of Repetitive Strain Injury (RSI) in Australia.

About 10 years ago or so, 15 years ago, when people started using computer keyboards in Australia, they started getting sore wrists. And the rheumatologists and orthopedic surgeons in Australia decided this was something called RSI and it was compensatable, that you could get Workmen's Compensation for this. Over a period of three or four years they had exponential growth in cases of RSI, in which people were claiming disability.

When the insurance companies recognized that this was going to be a financial catastrophe for them, they asked for a bunch of studies. And social scientists were involved and so on. And people decided that this was essentially an illness of attribution, that there were some small number of people who had carpal tunnel syndrome and other people who had mild forms of wrist strain, but this was not a serious condition and there was no demonstrable pathology in the vast majority of people.

That was then widely publicized. And insurance companies decided not to compensate. The prevalence of this disorder disappeared. So that's an example, if you will, of how social information and interpretation had a dramatic effect on the prevalence and the disappearance of an illness.

Now, I would take it one step further, which is to say a little more sympathetically -- and there's now a social science literature critiquing the role of social scientists in this whole process because there are still issues about these people's actual plight and whether they're better served now than they were when they were being compensated and so on. So the only way we're going to answer that is by going back and spending time with people and really looking at what's going on in their lives.

So that's the ultimate plea for doing the kind of research that I'm talking about.

**DR. URSANO:** Let me underline just one word that Larry said that I don't want to lose track of, which is imbedded in this issue, the question of epidemics. There are other social epidemics that occurred that have major medical consequences, such as epidemics of suicide that we see in our populations. So that being able to study the way in which suicide propagates through populations at risk can be a critical issue for the medical care of those groups.

**DR. MARLOWE:** There are some that are even more major, like koro. And I almost put an article on koro in the packet. It's a wonderful psychiatric disorder and one that comes epidemically in China, India, and other places.

**DR. GREEN:** I am actually picking up on something that Harry said and then that Sam said. And it's related to the whole issue of attribution. I think most people assume that much of the illness is an attributional problem, that people may have problems that are more common that they attribute to their exposure in the war or whatever.

One of the things when we were studying the people who were exposed to radioactive contamination that was clear was that part of the distrust came from the way that the information about it was released; that is, that the company that was releasing the radioactive waste into the water lied about it for ten years. And then when somebody exposed it, they said, "Well, there was a little bit of radioactivity released, but it wasn't very much."

When that was shown not to be true, they said, "Well, actually, it was a little bit more, but it's not dangerous". At this point, why would anyone ever believe anything that they said again?

So I think that one of the things that might be useful is to spend some energy -- and maybe there's a whole literature on this that somebody should just review -- on the communication of information because I think that those decisions about how information gets communicated -- and sometimes the information is, "We don't have a clue" -- is very, very idiosyncratic, very politically determined.

And I don't think we're going to eliminate everybody's physical complaints, but it does seem that some focus on how information about unknown kinds of things are communicated is useful because there have been incidents where it's clear that there hasn't been complete honesty about some of this stuff. And so it feeds into people's skepticism in feeling like: Well, if they're lying about that, there's probably something else. And that's kind of human nature.

So maybe some work on communication of information in the military and other settings would be useful.

**DR. MARLOWE:** Bonnie, in a sense, showing my age, aren't you saying that we really need to revivify the kinds of things that we talked about in social and preventive psychiatry in the '50s and '60s in terms of looking at the impact of the systems?

**DR. GUZE:** She wasn't even alive then. You want her to --  
(Laughter.)

**DR. MARLOWE:** That the individuals were imbedded again. They're not very good. Laboratory stuff never --

**DR. GREEN:** Understanding that, some --

**DR. MARLOWE:** It may be a very wise thing to do, by the way.

**DR. GREEN:** It doesn't even have to be research. It could be more thought about quality.

**DR. GERRITY:** DOD and VA recognized that it had done an extremely poor job -- and I don't think that's an exaggeration -- on communicating with veterans. That's why for the future deployment issue we have an emphasis on risk communication.

ATSDR, the Agency for Toxic Substances and Disease Registry, which deals with Superfund sites, is a very enlightened agency in this regard and probably has some of the best knowledge about that. But you're absolutely correct. Kamisea with respect to the Persian Gulf is a classic example of poor risk communication.

**DR. MARLOWE:** Yes. One of the questions I think we might ask from a research point of view is, "What is the population good communication doesn't work with?"

Paula?

**DR. SCHNURR:** I just wanted to get back to a comment someone made about stress kind of being acceptable. Everybody says they have stress. Well, everybody says that, but nobody wants stress to be the explanation for their physical symptoms.

When you've got symptoms, the public, believes it's a sign of weakness. We're talking about vulnerability and predisposition. It seems so real. How could it possibly be that way, the clinical wisdom?

I used to work with a lot of PMS patients doing research. And it was just rejected uniformly as an explanation. People wanted a biological explanation. There's comfort in that.

And so, even though everyone will easily say, "I have a lot of stress in my life. And stress is causing this, and stress is causing that," once they feel sick, that explanation is going to be rejected in favor of something that is biological.

**DR. ENGEL:** My comments have to do with stuff we have passed by. There was brief mention by Dr. Kirmayer with regard to the Quebec study, the follow-up study of predictors of back pain. He mentioned that work dissatisfaction was a predictor of subsequent back pain onset. And Stan Bigos has found a similar finding in Boeing workers, a five-year prospective study of back pain. So that has been replicated.

The other thought that I wanted to mention related to what Dr. Guze said around the value of ethnographic research, and it also ties right in with the information discussion. And that is that yesterday Dr. Kirmayer mentioned the idea of research around the predicament of the soldier.

And I think that to the extent that we are able to understand and climb into the soldier's world and understand what the pushes and pulls are from the soldier's perspective, then that puts us in a position to then move to what's the best way to communicate the dangerous world that we're going to put the soldier into, what's the best way to communicate to them the risks versus the potential benefits of the anthrax vaccination and so on, and to study strategies, even in randomized trial fashion, different strategies of informing them about the risks of preventive health mechanisms.

I don't mean to bring up something that might already be a sore point, but I think yesterday, Karl, when you were giving your brief, I was having a very visceral response to the way that we were talking about real people. I heard that there was a similar sort of visceral response at a meeting the week before to a similar sort of briefing.

I think sometimes in the military we get so used to talking to our colleagues that we forget how people receive our message in other settings and we frame our message to a different group. And then they hear it in a very different way.

We have to understand the world of our audience in order to best tailor information for them that can maximize our credibility and get us off of this track of faux pas after faux pas in communicating.

**DR. MARLOWE:** Harry?

**DR. HOLLOWAY:** I kind of feel like the person who offers marriage counseling and is dealing with the situation in one spouse says, "We have a communications problem," the other one says, "No we don't."  
(Laughter.)

**DR. HOLLOWAY:** Having read the literature of all the commissions that have acted on the Gulf War, I've got to say that I totally agree with Sam that the concept of stress does not further, as far as I can tell, an operational language for understanding the causation of a given patient's illness. For instance, I don't know how much just in terms of combat toxicology is contributing to the symptom pattern that has come out. I don't know how much comes from the overall problems of unemployment.

Remember that the division that's leading the -- the point of the spear that's cutting the Iraqi army in two immediately upon success is demobilized and discharged. That's the regulars. That's just on one side of it.

So we have a downsizing army, people who are losing their jobs in terms of marginalization. We have multiple sources of contamination. We have various problems in terms of exposures to bacteriological environment in that same setting.

So the idea of stress when we then communicate that to the soldier and what I hear as a soldier (because I've worn lots of green in my life) when you say that to me is that you're planning not to study those other factors. That's immediately what I hear. I hear a straightforward statement about what it is you ain't going to do.

By the way, that's based on about 30 years experience watching exactly what I did and others did in that circumstance. So I don't think it's without a database. So I think there's a real problem if we think we're going to use stress as a major concept for communication.

**DR. MARLOWE:** Let me make the observation, however, that all of these commissions have talked about stress as a cofactor, not as a cause, that we discussed the other day and I think we are probably all in agreement that we're dealing with a fuzzy, I at times might say empty, at times so universal it's meaningless catch-all that we call stress.

**DR. HOLLOWAY:** Dave, what those commissions, in fact, said was, "We don't know the cause, but stress is an important factor".

**DR. MARLOWE:** But stress --

**DR. HOLLOWAY:** If you remove all other factors and you leave stress in, the message I've got to tell you is –

**DR. MARLOWE:** You know, what we're doing is talking in shorthand about the percept of the consequences of these things. Certainly when I interviewed and surveyed people in the Gulf before the war, among regulars, the biggest concern at that point wasn't the war. It was that they were going to get pink slips when they got off the airplane when they came back. This was true particularly among noncommissioned officers.

**DR. GUZE:** You know this business of stress, if I can just add one short addendum or a footnote? If you take care of somebody with a duodenal ulcer and you say, "Well, there's no question. We've gotten this upper GI tract. You've got the ulcer and comet helicobacter and comet," so, you know, one of the things that we have learned over the years in taking care of patients with duodenal ulcers is that when people get upset and they're tense and they're angry, that very often intensifies the pain and discomfort and indigestion.

I've never had a patient who has taken umbrage at talking about that. It's when you bring it up when you don't know what corresponds to that ulcer in the duodenum because then you slip in all of the things that Harry was mentioning.

I don't know that it's possible. I don't even know that we can change our mind-sets so we don't use the concept of stress any more until we define it more precisely.

**DR. MARLOWE:** It's a comparatively new concept, and maybe we should use the consequences, what have been loosely called the stress responses, the physiological and other ones, as the parameters for explanation.

Certainly I'll go back to the remark I made yesterday in terms of initial treatment of folk in Italy during World War II, when I was quoting Ed Weinstein: If I told them that the symptoms were perfectly reasonable ones because they're the ones you feel when there are folk out there who are trying to kill you, the symptom is moderated: "I wasn't crazy. I wasn't weak. I'm in a real situation".

I fully agree. And, you know, I think one of the quests that we have is an operational language. The folk who are working with physiology and neurophysiology have, at least at one level, an operational language, which is the alterations in hormones and neurotransmitters, et cetera, in heart rate.

I think we have the problem of: How do we communicate? Stress has become our commonest metaphor for communication. And it's one I think we would all agree is comparatively meaningless. It's sort of an empty category that we apply to all kinds of things.

It's like the use of certain hallowed four-letter words in the military which have no sexual connotations whatsoever. They're empty adjectival intensifiers. And people think they have other connotations, but they don't.

John?

**DR. MASON:** With regard to the prospective study idea, I think it's clear that you could individually ask each of the disciplines that are up here and represented here.

If you ask me, I could give you the five hormones I would recommend that be measured if there's any possibility of measuring hormones.

**DR. MARLOWE:** Well, as a matter of fact, that's what I'm going to do next. I'm going to ask each of you: What are the primary things you would want –

**DR. MASON:** That's straightforward. There's no problem. Each of us has our own cherished approach. A much tougher question is the team organizer. There are not as many of those around.

I know I see one in the room here, Karl, who has already demonstrated an ability of putting it all of it together and carrying you off. Rachel Yehuda is another of them, maybe others I don't know of.

That's another question that is of crucial importance because you get all of the ideas and all of the methods. And then the actual project itself can falter terribly.

But if I could just make one last attempt –

**DR. MARLOWE:** Yes.

**DR. MASON:** -- to focus on the idea of some kind of unsuspected or overlooked sleeper factor that would be common to the problems, to the Gulf War problems, the Vietnam problems, some kind of difficult to perceive issue?

As I listen and hear Harry Holloway, what's really going on with the Gulf War people -- and he gave me the impression that one of the most universal things that happened was a sense that they win the war.

The next thing you know is they're out, they're gone. They've been wronged somehow. There's a way of perceiving that they have been wronged. And we can use a lot of words to try to convey what's going on, but when you're wronged, you're angry. You sense rejection. You feel inferior. You feel shamed. You feel like you don't have control. There's no control over the very important things in your life, the adversities in your life and so on.

And this seems to be a bit of what you were saying, I think, and Jim brought up about the attitude of the province people that there's a fundamental pride/shame axis reaction there that maybe takes the variations on the theme the way that plays out.

**DR. MARLOWE:** I beg to differ with that interpretation. The overwhelming majority of Gulf War veterans certainly two years after the war viewed it as a positive experience and that they had done a very positive thing.

**DR. MASON:** The ones with the syndrome?

**DR. MARLOWE:** Not the ones. I said "the overwhelming majority."

**DR. MASON:** That's what I'm talking –

**DR. MARLOWE:** One of the questions would be: --

**DR. MASON:** -- about: the ones with the syndrome.

**DR. MARLOWE:** -- What would the difference be between them and the ones who have come in with Gulf War illnesses? We make the same characterization of Vietnam vets. And, again, overwhelmingly they viewed their experience in a positive light, --

**DR. MASON:** But we're focusing on the ones that --

**DR. MARLOWE:** -- et cetera.

**DR. MASON:** -- developed the syndrome.

**DR. MARLOWE:** But I think what we may have to focus on there is what is the difference because when you look at the folk, one of the questions is: Why did people with the same set of experiences not come back with this sense, you know, remembering one other thing --

**DR. HOLLOWAY:** But I do want to challenge your view, David, in the following way. I actually am talking about those who are symptomatic; when I was talking to John, not all or even the majority. But I do want to challenge the view in the following way.

It's inevitable, I think, for a serving soldier to talk about a universal response in situations to move from a job where they are central to the concern of an entire nation, where what they are doing is important, to a time of peace, when what they are doing, particularly within the U.S. society, is rejected by the larger community.

By the way, David, I think this is quite separate from how they view the work they did when they were doing this. I'm talking now about that general question and perceiving oneself as marginal, as opposed to non-marginal. And I would propose only as a hypothesis that proceeding from centrality to marginality may be an issue with regard to deployed troops that deserve some examination as affecting other psychological processes.

**DR. MARLOWE:** Yes. I would not dispute that. In fact, I would go on to say that for many regulars returning from the Gulf, one of the things that has been least attended to is that they were marginalized when they came back by their own organizations. They had just successfully won a war. The same thing happened after Panama. They were immediately put into square one training cycles with almost no leave. There was the parade. They got ten days off, much different than the British forces and French forces, by the way. And then they were put back for the most basic stuff.

Now, there may be reasons for this. I don't think it's an issue we have time to pursue. I would like now to go to the issue of asking each of you: -- and I'll begin with you, John -- If we were to be able to set up a study, despite all of the pitfalls Bob Ader and others have talked about, what does each of you think in your own domains and looking at other domains? We'll start out with you and the five T hormones and we'll go around the table.

**DR. MASON:** Well, certainly I would begin with the thyroid profile. The most striking combat-related PTSD findings, hormones, for me personally so far have been T3, free and total T3.

And I would follow that with norepinephrine, epinephrine also, though that's not as consistent as norepinephrine, and then cortisol, which is a little more complicated to interpret, I think terribly important, but I couldn't give up any of those three. I would like to add testosterone also.

Now, that would mean ideally that you'd have to have at least one 24-hour urine sample and one 9:00 a.m. blood to 9:00 a.m. blood sample. Ideally I'd rather have 2 24-hour samples in a row in a 48-hour period with a blood sample in the middle, but it's that simple.

With that, I think we have a powerful profile that can do a pretty good job as far as norepinephrine approaches are concerned, telling you whether the syndrome we're looking at is anything like the World War II, which we are doing getting data or not for the Vietnam era-related syndrome.

**DR. MARLOWE:** Ben?

**DR. NATELSON:** I think if I were doing this, there would be two things I would want to know about. First, I'd want some measure of emotional burden, whether it was life stress, trying to look at the things that a social psychologist can tell us would be distressing, so that we could come up with some sum for stressor intensity because I think that's going to be critical, although hard to grab.

Then in terms of trying to come up with physiological predictors, I really don't know how good basal hormones would be. I sort of think that they may not be as helpful. And so we'd need to have a challenge system.

And, again, I started thinking about this sort of Treier stress reaction, trying to identify people who physiologically are different from the great bulk of people.

So perhaps two sessions. The more times you have to interface with your subject, the harder it is, but two to three interfacing sessions where you could measure blood pressure, where you could measure -- I won't talk about the variables.

Cardiovascular and endocrine response to a standardized stressor would be I think incredibly helpful to provide at least some sense of -- John would have the baseline data. And here I'm saying that we would have post-challenge data.

**DR. SCHNURR:** David, I need to ask a point of clarification because I'm not used to saying what I want to do until I know why I'm doing it. Who would we be studying? And what would we be trying to know in such a study?

I'm sorry to be flip about it, but --

**DR. MARLOWE:** Let's say we're studying a battalion of American military soldiers and Marines and that our concern is: Who are the people? We're putting them into a hostile, stressful situation with various kinds of exposures, not necessarily combat. And the question is the one we began with here: Who are the people most likely to develop physical and somatic symptoms?

**DR. SCHNURR:** Well, then I think, actually, the reactivity paradigm that Ben is talking about is really crucial. I think you get a lot of mileage from kind of a proximal construct, like personality and coping. And those are also things that I don't really know what they mean. But somehow they're reasonably predictive because an individual's background and experience may funnel through those kinds of variables. You get a lot of mileage out of it.

In terms of characterizing stress, I also would want to echo something I said yesterday. I think there may be some explanatory power in summing small, incremental stressors and the concept of allostatic load. I go back and forth. Is this just extra baggage to think about not interactive models now but tiny additive models, just little grains of sand that add up, by themselves having no meaning but all of a sudden being a dune?

And I think that if I were doing a study -- and I think I may want to try to do this in my own work -- to think small and additively because I'm usually going for the interaction or the big, main effect.

I like big number kind of things, but there's no cause of Gulf War illness. First of all, there's no Gulf War illness. There's a bunch of things that masquerade as such, but there are multiple causes with multiple mediators. And I think that a methodological approach that would combine many small things might get you a lot more explanation.

**DR. MARLOWE:** Chuck?

**DR. ENGEL:** I'm going to take an approach that I have learned from talking with congressmen and reporters at the Gulf War Health Center. When you're faced with a question that you aren't sure exactly what to do, you just make up your own question and answer.

I think I would take sort of a threefold emphasis. One is a programmatic, rather than a single prospective study. And that is: What is the epidemiology and natural history of somatic symptoms in the military? I don't think that we know that.

And the second issue is: How does information that we might disseminate and, as was stated earlier, impact on the predicament of the soldier in such a way that creates outcomes that deal with health, that exacerbate those symptoms or lessen those symptoms?

And then the third area, which is one that comes just from interfacing a lot with these folks. I agree with the notion that they feel marginalized, not so much because of their experience during the war but because of their experience subsequent to it. We need reach-out and care strategies for them.

And I think we should be looking at system of care strategies that aren't necessarily hospital-based or even health care-based but ways that we can help them to feel embraced and that improve their health status over time.

**DR. MARLOWE:** Fred?

**DR. HEGGE:** Yes. What all of you've got is a hammer. Everything looks like a nail. I have found myself profoundly unsettled by what I've heard in the last day and a half.

I find myself unable to give a cogent description of independent variables, dependent variables, declarative knowledge in this arena. In a sense, I'm echoing what Sam said.

When we started out that first day and we said what we were interested in, I said that I was in the knowledge harvest business these days. And I said the first thing I wanted to do in this hall was, in fact, to do a knowledge harvest in operational medicine.

I think maybe I've changed my plans a little bit. And what I really want to do is do a knowledge harvest in the domain we've been talking about.

I'd like to find out what this domain is, "What is to be measured? How do we measure it? What are the variable structures?" and to do it systematically.

And I'll be talking to Karl about that at some point.

**DR. MARLOWE:** Harry?

**DR. HOLLOWAY:** Presented with a battalion with which I can do a prospective study, I would save my money until I had a good question, clear definition of the variables, a true program that could be supported, knowledge that I was going to receive or have a program that's going to address the questions that come up here and not a single-shot affair.

I'd try to find folks like my colleagues and their suggestions to have an input into that, but I think the really critical thing is to be very clear about our questions and be very clear about the independent and dependent variables. To further the overall discussion across disciplines of ways in which we can communicate with each other using an operational language within the language that comes out of the press.

And the last part of it is I would spend some money on how to retranslate that operational language so that it could be communicated to the population that is distressed and that is exposed.

**DR. MARLOWE:** So you believe there's nothing that can be done now?

**DR. HOLLOWAY:** Well, I think there are lots of things that can be done now, but I'm really doing exactly what I heard Chuck say. I'm making up my own question.

(Laughter.)

**DR. HOLLOWAY:** And my question is: How do I further the game, as opposed to: What do I do in the next five minutes? And so my question is aimed at: How do I further the game?

And I think to further the game, one of the things I do is I've got to have a systematic approach that allows me to address the sort of things that we have heard from Nova Scotia and Halifax at the same time I'm addressing the sorts of things I hear from what's happening to the immune system at another level and at a microbiologic level. And that is not a single follow-up study.

**DR. MARLOWE:** No one was talking about a single follow-up study.

**DR. HOLLOWAY:** Well, I'm saying you've got an opportunity to do a study. And you've got a bunch of people, and you've got them standing there. Part of the money I will take is I will send it to a laboratory and let Bob do some experiments.

(Laughter.)

**DR. MARLOWE:** Bob?

**DR. URSANO:** Let me take my five seconds to articulate priorities of moving forward along the line of what you've said. And to reiterate, number one would be a programmatic approach that assures structures and funding for a cross-disciplinary approach from laboratory to field, from molecular to group, including DOD, VA, and civilian, to study military and nonmilitary populations, to examine event-related changes in health, behavior, and performance. The necessary piece of that is a programmatic approach over time that includes the necessary structures and functions.

Secondly, I would reiterate what Bob said way back in the beginning about the importance of any programmatic or longitudinal study making sure to consider time in its study design. Pre-event risk, onset, development, and sustaining functions are very different questions than the ability to examine them. And how to examine them may be quite different.

In terms of the own areas that I think may be forgotten and need to be remembered in our present context in which we live, firstly, we should remember to not only look at the combat risk environment as being the spot where we spend most of our time or money. Perhaps more important than that in terms of potential interventions that may come of such efforts is to study the recovery environments in which soldiers operate. These include the interpersonal interactions when they occur in units, outside of the combat field, as well as at home and at time of homecoming.

And, lastly, I think one of the areas that holds potential for interventions and articulating what has been said before by many others and my own particular interest is the contribution of perception, which I think can be looked at across molecular animal and human studies from the issues of cueing and understanding cueing in conditioning studies to the levels of belief, to the levels of knowledge, to the levels of fear attribution, and to the level of meaning in the complex social groups in which we live. All of those fit from my view into the level of understanding perception and how it influences outcome of health, behavior, and performance.

**DR. BLACK:** I agree with much of what's said. And I think what I can offer is some type of analysis of the immune function, the field in which I work. And I think there it would be important to determine cytokines; interleukin-1; interleukin-6; and TNF, tumor necrosis factor. It would be nice to look at those before and after a provocative session such as we've just heard. And it would be good to have those as a baseline for future studies.

I also think it would be nice to measure acute phase reactants, like fibrinogen and C reactor protein, since these occur 20 years before people have their heart attacks. And I think they're due to stress. And these would be the acute phase reactants from the liver, and it would be nice to have a baseline of that to refer future analyses against.

All things being equal, if one could before and after a provocative stress session, it would be nice to measure immune activity; that is, lymphocyte and macrophage function.

And there are tests for that to see how this person responded to a stress and to see if he or she became immunosuppressed and then have that as a reference point for data collected later after some type of combat or serving in the military or some deployment activity.

**DR. MARLOWE:** Bonnie?

**DR. GREEN:** Well, I was thinking of this in some ways as maybe the variables that we might want to put into an RFP if we were asking for proposals as things that we would be interested in. So, what's an inclusive cross-sectional list of areas that might be important to look at and then maybe, as Tim was saying earlier, put out RFPs and get competing proposals and to study some of these things: developmental history, including family history of illness, trauma history, some history of psychiatric disorder, but particularly screening for PTSD symptoms before people go over; and also some information about expectations for types of activities and exposures during the Service; and also the possibility of testing some, again, in the overall idea of looking at communications kind of educational models, how do we go about educating soldiers in terms of what they might expect and what we expect from them and some testing of that communication.

**DR. MARLOWE:** Etzel?

**DR. CARDEÑA:** Thanks.

Well, I would like to endorse the framework proposed by Bob Ursano that is a multidisciplinary programmatic endeavor. And, not to overlap with what other people have said, the ones that I would add would be disassociation as in dissociative traits and dissociative reactions to perhaps a challenge task, not because I believe dissociation is going to account for all of the people who are presenting these conditions, but I think they may account for a subgroup.

So that would be one, and the other one would be some measure of suggestibility. I know it may be programmatically difficult, but it could be a hypnotizability test. But it could also be just a number of questions that have to deal with suggestibility to emotional contagion or just outright suggestions without any induction. And we know that people do respond very differentially to outright suggestions. So those are the two that I would add to the menu.

**DR. MEYERHOFF:** Well, when you're talking physiological measure, you're talking specifics. I think that in terms of investment strategy, I wouldn't invest in one where there was no evidence that was involved, which limits us to: What do we know so far about the Gulf War illness, as one example, or PTSD, as another example?

I think that if pain thresholds were abnormal in Gulf War illness, that pain thresholds could be measured in a prospective study but not if we don't have a some kind of evidence that it might be involved.

I think we already have evidence that dexamethasone suppression is abnormal to a degree in Yehuda's data in a PTSD population, also basal cortisol low, adrenergic indices high, although Scott Orr and Pittman have shown that in home visits, they're not elevated. But, nonetheless, I would probably want to add similar neuroendocrine measures to what John Mason has proposed because, so far as I know, in terms of their findings of abnormality in PTSD, they have only been studied after the trauma. And it's only by doing a prospective study that we know how to really interpret the data we already have.

**DR. MARLOWE:** Karl?

**DR. FRIEDL:** Just from an endocrine perspective, I would say what we have always observed. And I think the classical approach is to do some kind of challenge test, to tweak the system, find out what you get. But the one thing we know about those tests is they're enormously variable in terms of biological variability and day to day. And so there are always problems in interpreting that, as opposed to getting a good, stable baseline as well. I've always thought of that as the way we would really understand how an individual is filtering and perceiving whatever the stress is. And that's our endpoint and the reason to do it.

But, of course, there are so many other variables and pieces that enter into this as well as some organic dysfunction that doesn't allow them to respond that way. And so the measure in that case wouldn't be particularly useful.

So whatever we end up doing, I think we need redundant measures. We need some checks on the systems so that we can say that we've at least got some confirmation of what we believe to be happening there.

**DR. MARLOWE:** Larry?

**DR. KIRMAYER:** I guess there are three areas that I would want to look at. The first is social, what we could call social position. We came up here talking about marginalization to look at people's employment situation, pre and post, their exposure, to look at their family system and social network in some way.

The second thing would be to look at the illness meanings and symptom meanings that people have, which include attributions but which go beyond that to include experiences people have of prototypical cases of things. They can't give you a clear account of their attributions but can tell you of somebody just like them who had something and that exerts a very powerful effect on their illness behavior and experience.

And the third thing would be to look at their relationship to the health care system; that is to say, what actual contacts have they had, do they have, what sort of loops are they imbedded in with care providers of various types that may be part and parcel of their problems. So those are the dimensions that I would want to look at.

I guess one last thing related to what Chuck said is I think that it's possible to conceive of a study that's a little bit different. We talked about this, in fact, intervention study. I mean, the main thing that's happened in the area of somatization therapeutically is people looking at the role of reattribution. And I think trying to do reattribution work with people also becomes a very sensitive way of understanding what's at stake for them and adopting a different way of looking at their problem.

I wouldn't be too quick to assume that people can't change their opinion. Oftentimes, nobody has tried. They're just sort of bouncing off a variety of hard positions that they're facing. And nobody is really engaging them to renegotiate the meaning of their symptoms.

**DR. MARLOWE:** Grant?

**DR. MARSHALL:** Well, I think you have said some really interesting things. And I don't disagree with anyone. I particularly like Chuck's idea of learning more about the prevalence of somatic symptoms of ill-defined origin in the military because there are no data right now to allow us to make any comments about that.

My own predilections go in the direction of preexisting personality and psychiatric history, the kinds of things that Bonnie and Paula talked about. But I will say that if you put a bunch of personality psychologists in a room, there would be a great deal of contention about what the basic domains of personality really are. I don't know that that's true on the harder side of the scientists here, but I would guess that it is just from the discussion that we have been having.

The other focus I would like to see us have is on resilience factors as well as predisposing vulnerability factors. The factors that may initiate a problem are not necessarily those that maintain it over time. And I think that those shouldn't be neglected. They're not opposite sides of the same sort of psychological coin.

**DR. MARLOWE:** Tim?

**DR. GERRITY:** For a second, I'll put on my research manager's hat. There is a bill before Congress which I think has a very good chance of being passed coming out of the House Veterans Affairs Committee, H.R. 3980, which contains in it a mandate, if you will, that a center for the study of post-war illnesses be established. Coming out of HVAC, its intent is to establish it much along the same lines as the PTSD Center in White River Junction. That is, it would involve both research, education, and clinical care.

There is also, though, a mandate in this that this be done in cooperation, collaboration with the Department of Defense. And so I think we have potentially an opportunity to create the kind of structure that's being talked about in which an integrated approach to this problem can be carried out.

And, as I said, I think that has a good chance of passing. I think it will provide a lot of opportunities if we can actually utilize this opportunity appropriately.

I just want to add from a scientific perspective that in the realm of exposures, that, again, one not think just of the exposures, if you want to talk about, again, -- pardon the expression -- stress exposures of combat, et cetera, those things are directly military-related but exposures that are -- for example, in the Gulf War, people were exposed to CNN, for example. People were much more exposed to events at home and then coming back, exposure to all of the post-war instant analyses of what happened and what didn't happen and what went wrong, et cetera, et cetera.

**DR. MARLOWE:** Bruce?

**DR. DOHRENWEND:** If the outcome that we're mainly interested in is the occurrence of unexplained somatic symptoms and disorders, then I find myself in agreement with Dr. Holloway.

I would want to see the results of those case control studies that I understand are underway and in various stages of analyses, those retrospective case control studies where the cases are personnel with these somatic problems who have to be -- I'd like to be assured that they were very carefully and intelligently designed. I mean, case control studies are simple in overall conception. They're not simple with regard to how they're designed, how the cases are constituted, how the controls are constructed, and so on. So I would certainly want that.

If the outcome is broader and has to do with short and long-term adaptation and its psychological and physical correlates, then I find that the arrays of suggestions have been very impressive. I don't find much to disagree with. Among them, I single out those that are most appealing to me and that I know most about and that I would like to learn most about. And they would be, of course, a history of major negative and positive events over the life course that have been mentioned by Dr. Natelson and others. I would like to look at that especially and be educated myself about allostatic load, as described by McEwen in relation to my notion of uncontrollable negative changes following exposure to a stressor. I found that intriguing, but it's intriguing to someone who is very ignorant about this area of what would be involved. But I understand that for me, it seemed to provide a framework congruent with my notions about changes in outcomes that embraces a number of the interests of the more biologically oriented people here.

But I don't know what they think about it because there's been no real discussion of it. But I would love to learn. At 12:00 o'clock, that's not a very good time to make a plea for education.

Now, there were a few variables that I think given this broader interest in terms of short and long-term adaptation of the people in this battalion, that we would want to measure prior to whatever their fate is, immediate fate, assignment fate is.

I think that the literature on combat, Vietnam veterans and so on, would nominate age at entry into the military, certainly. It would nominate education, which I guess you get routinely. And whatever stage they've reached, they actually completed it. I think it certainly would nominate IQ or the surrogates, which I guess you collect routinely. I think it should include past experience with prejudice and discrimination where your troops are ethnic or racial minorities. If women are involved, I think you could ask the same question. If you have a mixed-gender battalion, I would certainly want to know more about social position, a great deal more than has been mentioned, and the experiences related to their past social positions, gender, SES, and ethnic/racial status.

That's the kind of thing that I would add, I think, given this more general interest in adaptation. But I think it's nice for you to hear that and nice to hear these things from everybody else. But what I really would like if it's the narrower focus on unexplained somatic symptoms is the results of these case control studies and if they're not adequate, doing an adequate one.

**DR. MARLOWE:** Bob?

**DR. ADER:** I'm going to wait until Harry gets his battalion and gives me a call.

(Laughter.)

**DR. ADER:** I think that if you were to actually implement all of the suggestions that have come around the table, you're going to need more than a battalion anyway.

In terms of the incidence of somatic symptoms and the number of measures, I think we're a little bit out of balance. If one is going to take hormonal measures, then I think John is right. You need a constellation of hormonal measures. If you're going to measure these or autonomic responses, I think Ben is right. You need a reactivity score. It's not enough just to take these measures.

Basically, the question of who is likely to develop somatic symptoms, if that's the question and what would you measure, that contains within it the assumption that what you measure would be common to all the somatic symptoms that would develop.

And that's what we discussed yesterday or the point I tried to make, which is that there is no common denominator to all of this or at least no important one. So what you measure is dictated by what the question is, what the outcome is likely to be.

Now, you can do this clinically and wait around for this to happen or you can do it experimentally, in which case you look to induce the problem. Now, a lot of this obviously can't be done with humans, which is why I work with animals, where I can induce it. But, on the other hand, there are things you can do. And, in addition to their psychologic vulnerability, there are biologic vulnerabilities.

For whatever reason, some of these people in a given population may be immunocompromised. Well, the fortuitous occurrence of an infectious agent in an immunocompromised host is different than it is in a normal host. And does the combat situation influence immunocompetence?

Yes, we could measure cytokines and all these other kinds of things except that some of them are biologically relevant to some disease processes and some of them are not. So until you've decided what it is you're going to measure or induce, I don't think you can answer the question.

I think that, given a large enough population, however, not only can you induce it, but you can titrate it. And, again, I would go back to something else I mentioned, which is that the biomedical model induces -- and I'm not saying anything new. Rene Dubos wrote a very small or a very large essay titled "The Mirage of Health," which I would recommend. He's a microbiologist and recognized that the way disease is studied in the laboratory is very artificial. It's induced in ways that are calculated to unconditionally elicit that disease, but that's never the way people are exposed. And I think we've got to study this in a way that people are actually exposed, which is to say that yes, of course, germs are important. They may be necessary, but they are not by themselves sufficient or we'd all be sick most of the time.

And the issue is not what I think we should measure. The issue is a conceptual one, which is how you would strategize the research in the first place.

**DR. MARLOWE:** Nancy?

**DR. BAKALAR:** Well, there are several problems that I would be interested in. One would be to understand more about the role of leadership and illness. And I think it would be interesting to study leaders' styles and their communications, both with words and with behaviors towards their troops, and see how healthy those troops are. And if we had a small population we were looking at, we could look at all the biological, the physiologic, psychosocial, psychological factors as a function of climate within a unit.

Going back to the Nova Scotia question, you had a question about: What would you do with the ethnological data? I wonder what would happen to that population if the government became truly interested in the economic state of those people and made some interventions for improving economic conditions. So in the military, I would like to do a few studies of small groups and get some ethnological data and find out really what's on people's minds and then address those questions, those problems, those issues, and see if there is a difference in their health or levels of different hormones or whatever.

Finally, I want to make a pitch for synthesizing research findings on a regular basis and communicating that to people who have to put metal on target as far as policy goes. I think there is an abyss that we need to bridge in your group communicating with people who write policy and try to implement changes in how we take care of our folks. And we need to find more interfaces and opportunity to do that.

**DR. MARLOWE:** Kai?

**DR. ERIKSON:** I'm at a slight disadvantage on two counts. One of them is I'm the 19th or 20th speaker, which is kind of cruel. But the other is even worse, that I was out of the room when Bob was talking. And I know from things that other people said, that you talked a little bit about the nature of multidisciplinary work. So I hope I'm not repeating anything that you say.

It's very hard to add particular items at this point, but obviously as a sociologist, there are many people who would like to get information that would add to the physiological profile of the people before they come into the point of being studied.

A lot of people want to talk about the psychiatric profile. Clearly there are two or three of us very interested in the social profile, some of the things that Laurence said and that Bruce said. And so obviously the social profile would be things that I would be interested in, "social position" being a good word for a lot of them. But I would list them.

I'd like to make a different kind of comment, which is just something about what multidisciplinary means, to say that it's very hard for me to think of a particular study which is multidisciplinary. It seems to me almost contradictory in terms because the very nature of multidisciplinary work is that people focus on one set of factors and almost put blinders out, rule out of their line of vision different kinds, and that what I would imagine, if I headed an institute looking for research in all of the things that we're talking about, what I would try to imagine is since we're talking about a family of perspectives, we probably ought to be talking about a family of researches, too, and we ask: What of the kinds of questions that were raised today are best answered by, let's say, finely grained ethnographic research of the kind that Laurence brought up? What of the kinds of questions that we asked are best answered by retrospective research or less expensively answered by retrospective research? And what kind of questions, then, have to be asked only by prospective research? And what brings where the multidisciplinary comes in is that people actually listen to, actually pay attention to, and actually respect the findings that come out of these several different approaches?

**DR. MARLOWE:** Sam?

**DR. GUZE:** Well, I'll try to be very brief. First, I would endorse almost everything that Bruce Dohrenwend said about what to look at. And I think to just underline the point that he made two or three times in his remarks, I think we have to have a precise set of goals for the research. Otherwise, I think we're going to end up wasting a lot of time and money and effort.

If the goal is to try to learn something about prediction of adjustment in the military and in the immediate post-military life, then I think I would support Bruce's list except that I think he implied it, but I would certainly be looking for a lot more detail about the family history, about schooling history, about relations with friends, about work history, about sexual history and marriage if there is such. I think that those things are likely to contribute maximally to guessing how well people are going to do as active-duty soldiers under different kinds of circumstances and how they will do after they're discharged.

I think if we want to have a broader set of goals, then I think we do need a huge enterprise with a lot of money and a lot of different kinds of investigators. And that would be wonderful. All of those who are given to the academic life can always support that, but I don't know whether that's realistic.

**DR. MARLOWE:** Well, it would be wonderful.

I want to thank each of you for your thought; your contributions; and I think, above all, for setting out in many ways the limitations to what we know and to how we might go about it or whether we should go about it. Also for setting out the need for clear definition of where we're going and perhaps the underlying thought that something as specific as looking at somatic outcomes may be preliminary. We may have to look at the gross issue of vulnerability and adjustment.

I would like to thank you also for having put up with me for almost two days as your chairman. It has been a privilege, and I highly appreciated all of you and everything each of you has had to say. And I think we can all say that. Thank you very much.

(Applause.)