LETTER TO THE EDITOR

By Lemuel C Bray

Validity and Peer Review Complaint

I would like to register a complaint about the validity of the conclusions and the peer review of: *PSYCHOLOGICAL TESTING OF CEREBRAL MALARIA PATIENTS*, "The Journal of Nervous and Mental Disease," vol. 147, #6, 1968 by Kastl, A.J.; Daroff, R.B.; and Blocker, W.W.

http://journals.lww.com/jonmd/Abstract/1968/12000/Psychological_Testing_of_Cerebral_Malaria_Patients.4.aspx

Why worry about the validity of this study?

Because the focus of the treatment of the victims of cerebral malaria has long been "behavioral" instead of "organic" in the United States and, because, the Department of Veterans Affairs relies on this study to deny compensation to the victims of cerebral malaria. I would therefore, like the Journal of Nervous and Mental Disease to make a full retraction of its validation of the Kastl, et al. study.

The problems:

No valid control group for the conclusions:

"Upon recovery no measurable organic residual was found." (pp 553) "Certainly the directions of the obtained results suggest common impairment for cerebral malaria patients, and the fact that there are no significant differences when both groups have recovered suggests there is no organic residual." (pp 557) And "In addition, we feel the present results provide substantial evidence of the absences of residual organicity in cerebral malaria. On every test and measure but two, the performance of the cerebral malaria patients when recovered is either indistinguishable from, or superior to, a group of matched malaria patients without cerebral involvement."

Both groups had the disease so it cannot be concluded by comparing them that the disease does not cause residual impairments.

The first key that there was a problem with this study was the following statement on pp 554: "The fact that the M group reported significantly more disturbance during youth (e.g. having been in many fights, having had trouble in school) can probably be understood as an attempt to exaggerate pathology, in order to increase the likelihood of being medically evacuated to the United States. (The patients with cerebral malaria were aware that their more serious condition would necessitate evacuation.)" This statement goes against reason. If the patients wanted to be evacuated they would exaggerate their premorbid wellness and denigrate their post-morbid condition not the reverse.

A study of Table 1, pp 554 shows there is a deficit in "Years of schooling" for the M group. Do the math and you find these results:

Malaria Group (M)	Cerebral Malaria Group (CM)
2 x 12 = 24	6 x 12 = 72
3 x 11 = 33	3 x 11 = 33
4 x 10 = 40 . .	
TOTAL 97	105
97 / 9 = 10.78	105 / 9 = 11.66

Essentially, after casting out the equals, **this study compares four tenth grade drop outs in the M group with four high school graduates in the CM group and then concludes; because the cerebrally involved high school graduates had IQs only slightly lower than the non-cerebrally involved tenth grade drop outs, the high school graduates displayed no lowering in IQ????**

And as for the disturbances in youth, isn't it expected that 10th grade drop outs will have more difficulties in youth than high school graduates? **Why wasn't the military induction battery of tests used to determine the pre-disease IQ levels for matching these subjects?** Percentile rankings could have been used to match both the diseased groups M and CM with a legitimate control group which did not have the disease p. falciparum malaria which is synonymous with "cerebral malaria" according to the pathology texts cited below.

Blocker, Webster W., MD et al.'s report on the same 1200 p. falciparum patients noted a patient who developed a "paranoid schizophrenic reaction" "one week after becoming afebrile." This patient's symptoms continued and were conveniently discounted as a "functional psychosis," not related to his malaria diagnosis. (*THE PSYCHIATRIC MANIFESTATIONS OF CEREBRAL MALARIA*, The American Journal of Psychiatry, vol. 125, pp 192-196, 1968) This report leads one to question if the U S Army had a pre-determined desired outcome of the Kastl, et al. study. The reason the Army might do this rests in the inability of the cerebral malaria victims in first getting beyond the denial of any deficit (thus not knowing they had been damaged) thereby allowing the Military the opportunity to avoid the compensation of the victims.

Why aren't the cerebral malaria victims aware of contracted mental deficits?

Think of ETOH intoxication. It presents a global brain deficit which is not recognized by the intoxicated. (As in the trouble of getting the car keys away from an intoxicated individual) Cerebral malaria also presents a global deficit but from occlusions of the brains capillaries with the casts of red blood cells emptied by the parasite. (See the pathology texts cited below.) The difference is that ETOH intoxication is usually a passing chemical or drug effect. The occlusions from cerebral malaria infection block oxygenation of the affected brain cells and thus some permanent damage probably occurs.

AN ADEQUATE PREMORBID POSTMORBID comparison has not yet been done. The global nature of the damage would make adequate assessment by post morbid testing difficult. (Otherwise why use a comparison group at all?)

And finally, I question the reliance on pre-motem examinations to override post mortem findings for making a diagnosis of "cerebral malaria."

Post mortem examinations record p. falciparum infection as synonymous with cerebral malaria. Please note that considering the pathology of the disease the most reliable indication of cerebral involvement would probably be a body temperature over 104, severe cramps and headache. The occlusions that occur in the brain also occur in the muscle tissue at the same time causing the cramps. There may be no other discernible cerebral signs because of these symptoms except a post morbid indication of amnesia which could easily be missed unless the examiners are specifically looking for it. Amnesia appears to be a function of the reality check area which also seems to be responsible for recording long term memory.

Discussion of problems created by the Kastl, et al. suspect study:

John Booss, MD, Department of Veterans Affairs National Director of Neurology at the VA Connecticut Healthcare System in West Haven, CT, in his testimony before the Subcommittee on Benefits, House Committee on Veterans Affairs , on July 16, 1998 stated:

"Malaria is caused by infection in the human with a parasite of the genus Plasmodium. The diagnosis of malaria is made by examination of blood smears for the parasite. Humans are infected with Plasmodium through inoculation by the Anopheles mosquito carrying the organism, which it received by biting an infected human. There are several species of Plasmodium, one of which is Plasmodium falciparum. Infection with Plasmodium falciparum leads to falciparum malaria and is the cause of "cerebral malaria".

Nils R. Varney, Ph.D., Director of Training at the Iowa City VA Medical Center, in his testimony before the Subcommittee on Benefits, House Committee, on July 16, 1998, stated:

"The results of the study suggest that cerebral malaria may have multiple neuropsychiatric symptoms which could be problematic years after the acute illness had been "cured." As compared with wounded veterans who did not have cerebral malaria, the 40 Vietnam veterans who participated in my study who contracted malaria manifested substantial problems with depressive mood, "personality change," feelings of subjective distress, memory problems, emotional labiality, and neuropsychiatric symptoms very similar to small seizures, such as memory gaps and staring spells.

Although these findings are statistically and psychometrically more sophisticated and reliable than the clinical observations reported over the previous 2500 years, our study is only the most recent to suggest that cerebral malaria[1] is a cause of long-standing neuropsychiatric symptomatology in adults who survive the illness."
"The message to be drawn from this research is that there may be some Vietnam veterans at risk for suffering from a persistent neuropsychiatric syndrome which can produce a wealth of psychiatric psychological, neuropsychological, neuro-psychiatric and neurological symptoms."

Rezek et al. *Autopsy Pathology's* definition of Cerebral Malaria: "Cerebral malaria is synonymous with P. falciparum infection but not all cases show gross evidence of the disease. What may be found are petechial hemorrhages on the surface and in the white matter, and a diffuse grey or leaden hue to the whole brain, especially the cortex.
Dr. Varney used "cerebral malaria" in REZEK's more glogal sense which is supported by SPENCER et al.'s Tropical Pathology.
The narrower meaning, used almost exclusively by the U.S. Military and the DVA, that the patient showed very definite neurological symptoms (delirium, etc.) during the acute phase of the illness, was used by Dr. Booss in his citation of the Kastl, et al. study to denigrate Dr. Varney's testimony.
A study of Herbert Spencer et al.'s *Tropical Pathology*, pages 329 to 439 on the "Pathology of Acute P. falciparum Infection" reveals that the parasite invades cellular tissue early on in the acute phase of the falciparum infection.
"P. falciparum infection in the non-imune commonly has a short course if untreated and death may result before any immunity can be established. The picture seen at autopsy thus depends on the duration of infection, whether the patient has had a single or repeated infection, and the prevailing pathogenic developments such as shock or hemolysis. Following treatment the parasites may be removed from the blood though the other basic pathological processes are unchanged"
Central Nervous System
"Lesions in the brain in malaria have been described in detail only in acute P. falciparum infection and black water fever." (Black water fever results from p. falciparum infection when the casts of the red blood cells excreted in the urine turn it black in color[2].)
"Macroscopic; the leptomeninges may be intensely hyperaemie and the combination of congestion of malarial pigment gives a characteristic colour which is

almost diagnostic of malaria. Small petechial haemorrhages may be present on the surface of the cerebrum and cerebellum. The brain is often oedematous, increased in weight and has some broadening and flattening of the gyri. The cut surface is slate-grey, the deeper shades being found in the grey matter of the cortex and the basal ganglia. Scattered through the white matter of the brain, sometimes extending down into the cord, there may be small petechial hemorrhages and very rarely a larger localized haemorrhage. The later ventricle may be dilated and the choroid plexus is congested.
1
2 (Lemuel C Bray's note)
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Irregular areas of softening have been reported by are rare and thrombosis has not been observed in the larger vessels.
"These changes are usually most evident in patients who have died of 'cerebral malaria' with clinical evidence of involvement of the central nervous system. Pigmentation of the brain may however , be seen in individuals who have malaria without signs of 'cerebral' involvement. The poor correlation between clinical and pathological findings has been frequently noted by pathologists (MAEGRAITH, 1948), THOMAS (1971) suggests that the present of petechial hemmorhages correlates best with clinical evidence of central nervous system involvement."
The above post mortem pathology and "*text book statement*" supports Dr. Varney's hypothesis and not that of Dr. Booss's denigration of the Varney hypothesis.

STUDIES NEEDED

1. Brain damage assessment.
Obtain the inpatient records and DD214s for the subjects of the KASTL, Albert J. et al.'s study; "PSYCHOLOGICAL TESTING OF CEREBRAL MALARIA PATIENTS"; THE JOURNAL OF NERVOUS AND MENTAL DISEASE; Vol. 147, No. 6 pp 553-561 in 1968. Compare the IQs found by the study, which should be entered in the inpatient charts, with correlated IQs obtained from the pre morbid induction test scores found on the DD214s, as KASTL, et al. should have done. This study should be corrected and circulated widely because of the damage caused by the misinformation in the original KASTL report. See VARNEY, Nils R., et al.'s, "NEUROPSYCHIATRIC SEQUELAE OF CEREBRAL MALARIA IN VIETNAM BETERANS," THE JOURNAL OF NERVOUS AND MENTAL DISEASE, Vol. 185, No. 11; pp 695-703.
2. Economic damage assessment to the individual.
Compare the "earned income" of 5,000 vets who had p. falciparum infection with 5,000 vets who had equivalent induction test scores, served in the same units in Vietnam but do not have any history of concussion or other possible sources of organic brain damage no matter how subtle.
Other groups to compare with the control group:
Multiple traumas
Right side concussions
Left side concussions
Those whose service involved close work with outgoing large gun fire.
3. Suicide rate study. (preliminary)
Obtain the names and social security numbers of 5,000 p. falciparum malaria victims who recorded a body temperature of 104.5+ with a severe headache and/or cramps for a study group from the Army Surgeon General. The study group should be balanced for an average of 40 to 45 years from the date of

infection. Obtain the cause of death from the Social Security Administration for all of the deceased in the study group. Compare the suicidal death rate and the accidental death rate with the national average for men of the same age group. If the suicidal deaths total less than 25 there is no problem. (Suicidal deaths should total approximately 24 for the national average of 12 per 100,000 per year for 40 years.) Probably 50 suicides among the group would not cause significant concern. But what if there are 100 or more?

SELF REALITY CHECK SYNDROME POSTULATE

If brain damage shows as a precursor of suicide, it is probably due to a decreased in stress tolerance.

Self reality check syndrome is seen as a condition caused by subtle injuries to the brain which include injury to the "reality check center usually located in the mid parietal region of the right hemisphere of the brain. "Self reality check syndrome" is a nomenclature I came up with for the symptoms that I have after I read the May 1995 issue of DISCOVER MAGAZINE, THE BRAIN THAT MISPLACED ITS BODY.

http://discovermagazine.com/1995/may/thebrainthatmisp502

I suffer from subtle manifestations of traumatic brain disease since a 1969 accident. My condition was finally diagnosed as organic in origin following years of "behavioral and PTSD" treatment by the Department of Veterans Affairs in 1985.

The delay was at least partly because of my continuous denial of "any problems related to the accident." The only objective residuals were: (1) subtle loss of feeling on the back of the left forearm, hand and left side of the face; (2) reoccurring transient ischemic attacks which included: (a) "pins and needle" sensation on the left side of the face near the ear and around the lips lasting several minutes; (b) reoccurring burning sensation similar to an acid burn on the inner region of the front of the left upper leg, (originally I thought this was related to an agent orange exposure in the same area while handling 2-4D barrels on the Dong Ha river during one of the "Prairie" operations: (c) a sharp pain in the left shoulder lasting only a few seconds and occurring primarily when running down steps: (d) absences or staring spells lasting up to 45 minutes, of which I had no conscious awareness, but, which my wife had noted but since she hadn't known me before the 1969

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accident thought it was just my nature. After a later accident in 1990, I became aware of the absences and noticed they occurred when I craned my head to the right as in looking for on coming traffic at a stop light. This was after many minor fender benders that I always blamed the other driver for because I was sure he must have been speeding to come into my path so

quickly after I assured myself there was no on coming traffic.
In 1985 I was finally faced with the fact that my work performance had become inferior because I got a job doing the same thing several other employees were doing and it was so obvious I could no longer deny it. I could no longer blame the bosses for my short term employments or circumstances for my poor performance. It felt like there was a demon within that was sabotaging my work.
In similar situations before the accident I had always been a top performer. I was the first to finish exams in school and often the only one with a perfect score. As I recall, my junior high school IQ test score was 146 and my military induction scores were at a similar percentile ranking. (In 1985 I was tested to have a residual of 126 verbal and 98 visual spatial IQ bringing the diagnosis of right side brain injury)
On reading THE BRAIN THAT MISPLACED ITS BODY by James Shreve, (Discover Magazine, May 1995, http://discovermagazine.com/1995/may/thebrainthatmisp502) in 1996, I finally discovered the nature of the demon that had been plaguing me for some 26 years (41 years now). I realized the problem of "getting the car keys from an intoxicated person" was that they were beset with a temporary chemically induced reality check problem. The difference is that they sober up and it goes away until they create the problem again.
My reality check deficit never goes away. I am easily stressed into poor performance as was shown on the 1985 neuropsychological testing by the VA, but usually I am unaware of the poorer performance until the stress is removed and I can look at the results. I've made adjustments in my reactions to the problems it creates but it is always there, worse when I'm stressed. My first psychiatric diagnosis was "adjustment disorder". Well if your reality check is out of order you certainly have an adjustment problem. And it is rather difficult to make behavioral adjustments to organic problems if you are unaware that you have an organic problem. The left brain

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(conscious side) sees everything done to the best past performance. It is the reality check that corrects this impression when something goes wrong.
I hope this postulate helps the Nervous and Mental Disease treatment community in understanding a subtle difficult residual of minor right side TBIs and subtle global brain injury from such conditions as cerebral malaria or oxygen depravation.
In addition I hope the Journal of Nervous and Mental Disease will take responsibility for the miss information presented by the conclusions of the Kastl, et al. report and inform the Department of Veterans Affairs of the invalidity of its reliance on the Kastl, et al. report for treatment and

compensation of victims of p. falciparum malaria.

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Mind & Brain / Senses

http://discovermagazine.com/1995/may/thebrainthatmisp502

The Brain That Misplaced Its Body

Though paralyzed on one side, Mrs. M. claimed she wasn't--at least until she had cold water poured in her ear. Then, for a while, her brain could again perceive her body. And a neuroscientist could glimpse a secret about how we construct reality.

by James Shreeve

From the May 1995 issue; published online May 1, 1995

Mrs. M. is adamant. People are saying her left side is paralyzed, and she knows they are wrong. Several days ago the 76-year-old Californian suffered a stroke. She now sits in a wheelchair while a doctor in a crisp cream-colored suit bends over her, asking questions. She answers them with perfect coherence. Does she know where she is? Yes, she is in a hospital, brought here by her daughter. Does she know what day of the week it is? Of course. It is Tuesday afternoon.

Then the doctor starts in again about her hands. Can she use her right hand? Yes. Her left? Yes, of course. He asks her to use her right hand to point to a student who is taking notes, and she obliges. He asks her to point to the student with her left hand instead. This time she doesn't move.

Mrs. M., why didn't you point? asks the doctor. For the first time, she hesitates.

Because I didn't want to, she answers.

In fact, fibers in the motor cortex on the right side of her brain, which controls movement on her left side, have been irreparably damaged by the stroke, and she will never use her left arm again. But Mrs. M. is not a stubborn old woman refusing to admit a difficult truth. A few minutes later Mrs. M. looks at her left hand, resting inertly in her lap.

Doctor, she asks, whose hand is this?

Whose hand do you think it is?

Well, it certainly isn't mine!
Then whose is it?

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It is my son's hand, Doctor.
Mrs. M.'s claim would be peculiar enough if her son were in the room, but he is miles away, unaware that in his mother's mind his hand has become attached to her arm. Mrs. M. is suffering from a condition called anosognosia, which sometimes appears when a stroke has cut off blood being supplied to the brain through the middle cerebral artery. The stroke damages regions in the brain's right hemisphere that include a territory called the right parietal cortex, a patch of neurons about two-thirds of the way back along the brain. The two parietal cortices (there is one in the left hemisphere also) are known to be involved in directing the brain's attention to movements, objects, and sensations on the opposite side of the body, as well as in the perception of that entire side of the body in space.
While otherwise clearheaded, patients with damage to the right parietal cortex are unable--not just unwilling--to acknowledge the radical change that has overcome the left side of their body. (The term anosognosia derives from nosos and gnosis, the Greek words for disease and knowledge.) One of the best-known victims of the condition was Supreme Court justice William O. Douglas, who suffered a right-hemisphere stroke in 1974 that paralyzed his left side and eventually forced his retirement. He initially dismissed the paralysis as a myth, and weeks later he was still inviting reporters to go on hiking expeditions with him. When one visitor asked about his left leg, he claimed that he had recently been kicking 40- yard field goals with it in the exercise room and soon planned to try out for the Washington Redskins.
Mrs. M.'s form of anosognosia is even more extreme: she not only flatly denies she is paralyzed, she refuses to admit that the limp limb on the left has anything at all to do with her. One such anosognosiac became so incensed that somebody else's leg was cluttering up his hospital bed that he heaved the thing out and was subsequently amazed to find himself on the floor. Another claimed that the arm on the left belonged to his daughter, who was trying to seduce him.
We are used to thinking of our bodies as our selves, says Vilayanur Ramachandran--the inquisitive doctor in the cream-colored suit. Something has gone wrong here that calls that fundamental truth into question.
Anosognosia is a fleeting condition, in most cases fading away within two weeks of the stroke that caused it. In the interim, however, patients like Mrs. M. may provide a window through which we can glimpse how we all perceive reality, how our minds organize and cope with the cognitive blitz of everyday life. While most of us have no trouble fessing up to ownership of our various body parts, we all are sometimes willfully ignorant of signals our bodies send to our brains--there might, for example, be a tiny twinge of ankle pain that we'd rather not notice just before that weekend tennis game. In a new theory, Ramachandran claims that anosognosia can help explain why, how, and even where in the brain such everyday denials take place and how we combine them into a representation of the world around us. If he is right, this theory may also shed light on the function of dreams, and even on the mechanisms of memory itself.

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Looking at patients like Mrs. M. can be spooky at first, says Ramachandran, a neuroscientist and physician at the University of California at San Diego, and the Salk

Institute nearby. But then you realize you're really looking at yourself, in amplified form. Ramachandran has made a career out of using spooky phenomena to reveal the workings of the brain. With optical illusions, he has explored the neural circuitry of vision. More recently he helped track down the neural basis for phantom limb, the sensation that most amputees have that their lost arms or legs are still attached to their bodies. His findings helped illuminate how the brain restructures itself during learning. From patients who feel phantom arms in the empty space beyond their shoulders, it was a logical step to look next at patients who denied arms that were indisputably real.

Ramachandran was unsatisfied by the two conventional explanations for the rending of body image demonstrated by anosognosiacs. The first is Freudian: to protect the ego against the appalling truth that one side of the body has been rendered permanently senseless, the mind simply refuses to admit to the facts at hand. But patients with paralysis caused by stroke in the left parietal cortex rarely deny their condition. Why should only people with right-brain stroke need to protect their egos from the truth?

The second explanation is more neurological and less psychoanalytic: anosognosia is a special case of a more general syndrome that textbooks refer to as unilateral neglect. Some stroke patients with damage to the right parietal cortex fail to recognize anything in the left side of their perceptual domain. If they are asked to follow an examiner's finger as he moves it across their visual field from right to left, their eyes track the finger up to the midpoint, then stop. Patients with unilateral neglect may eat food from only the righthand side of a plate, or shave only the right side of the face. Anosognosiacs like Mrs. M. often exhibit such behavior, too. Perhaps they are simply neglecting their paralysis in the same way they disregard everything else on the left side.

Clearly the two phenomena seem related. Yet Ramachandran thinks this explanation, too, leaves much unaccounted for. Patients with neglect will ignore an object in the left side of the visual sphere, but they will readily acknowledge the object if their attention is drawn to it--if, for example, an examiner wiggles his finger in the neglected side of their visual domain and says, Now do you see it? Anosognosiacs, on the other hand, do not passively ignore their paralysis; they actively deny it, in spite of their complete inability to move. If pressed to account for such a conflicting state of affairs, they remain silent or try to explain it away, often concocting elaborate stories or chillingly surreal rationalizations. Neuroscientist Edoardo Bisiach at the University of Milan in Italy reported one 74-year-old stroke patient who repeatedly claimed that his left hand belonged to the doctor examining him. The doctor finally grasped the paralyzed hand between his own two and held it up to the patient's face.

Whose hands are these? he asked.

Your hands, the patient replied.

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How many of them?

Three.

Ever seen a man with three hands? the doctor asked.

A hand is the extremity of an arm, said the patient. Since you have three arms, it follows that you must have three hands.

There is more going on here than simply an indifference to or neglect of the left side of the body, says Ramachandran. And that's what's crying out for an explanation.

One explanation might be that anosognosiacs only appear to be ignorant of their paralysis while in fact they are fully aware of what has happened but for some reason do not wish to express it. To test this hypothesis, Ramachandran devised a devilish experiment. He presented Mrs. M. and two other elderly stroke victims with a simple choice. They could

win themselves a small box of candy or some other trivial reward by completing a task requiring one hand, such as fastening a large nut onto a bolt mounted on a heavy base or stacking some blocks. Alternatively, they could earn a much larger box of candy by successfully finishing an easy activity requiring two hands, such as tying a bow or cutting a circle out of paper with scissors. All three subjects exhibited neglect and denied the paralysis on their left side, but they were otherwise alert and aware of their physical condition. (One even responded to the choice by chiding, I am diabetic, Doctor. I don't eat candy. You should know that!) For control subjects Ramachandran chose two stroke patients who were also recently paralyzed on the left side by stroke and showed clear signs of neglect but no trace of anosognosia.

As might be expected, the controls unhesitatingly chose to obtain the small box of candy by performing the task requiring only one hand, expressing surprise that anyone would even present them with such a choice since the two-handed tasks were obviously beyond their ability. But in 15 out of 16 trials, the anosognosiacs opted to try to win the large box of candy. After fumbling feebly with the laces or scissors, they would remain silent or offer some excuse for their failure. (I guess my arthritis is acting up. Oh, I've never been very ambidextrous.) Curiously, they never seemed to learn from their previous botched attempts or even remember them from one trial to the next.

It's very strange, says Ramachandran. No matter how often they failed, they never showed any sense of surprise or frustration.

The inextinguishable faith in their two-handed abilities seemed to indicate that if the anosognosiacs knew they were paralyzed, that knowledge lay deep, buried well below the level where it could be freely accessed by their conscious mind. Yet certain things they said hinted at tacit knowledge of their condition, meaning that the information had been recorded in some part of the brain, whether or not it was immediately available. After failing repeatedly at the bimanual task of tying a shoelace, Mrs. R., a former journalist

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who was now in her seventies, later told a student that the nice Indian doctor asked me to tie a lace, and I did it, with both hands.

Normal, unparalyzed people don't feel the need to draw attention to the fact that they can use both hands; they just do it, says Ramachandran. As Shakespeare said, 'The lady doth protest too much.'

To probe the depth of that tacit knowledge, Ramachandran made use of an experiment performed earlier by Bisiach and his colleagues. They had temporarily reduced the symptoms of an anosognosiac by the simple means of pouring a small amount of cold water in her ear. The treatment wasn't as far-fetched as it might sound. In addition to hearing, our ears function as our gyroscopes. They house fluid-filled canals lined with microscopic hairs that sense acceleration; this information is transmitted through nerves known as the vestibular system to different parts of the brain. Some of these parts direct our bodies to make the adjustments needed to maintain our balance. Other parts, like the parietal cortices, are responsible for letting our eyes steadily track moving objects. To do so, they need to have information about how our bodies are moving in space--thus the connection between the vestibular system and the parietal cortices, and the basis for Bisiach's seemingly bizarre treatment.

Bisiach's patient, a right-brain stroke victim in her eighties, claimed that her arm belonged to her mother, who had apparently left it behind in the bed when she was discharged from the hospital. When Bisiach poured cold water in the woman's left ear, her overstimulated vestibular system began to send confused signals to her brain, which concluded that her head was turning, and after a few minutes she involuntarily began

moving her eyes rapidly back and forth to compensate--a process known as nystagmus. The patient was asked again whom the arm belonged to, and this time she admitted that it was her own. Bisiach ran a series of cold-water trials and found that it took anywhere from 15 seconds to two hours for the effect of the cold water to wear off. But once it did, the woman would invariably lapse back into the eerily unconcerned delusion that her arm was her mother's.

Look, it's queer, but that's how it is, she said.

Ramachandran decided to try Bisiach's experiment on Mrs. M. Working with fellow San Diego neuroscientists Leah Levi and Lance Stone, he poured cold water into her left ear and waited until the rapid eye movement of nystagmus appeared. Asked to identify the owner of the arm lying in her lap, she stated that it was hers, of course. She also acknowledged that the arm was paralyzed. When Ramachandran asked her how long she had been in that condition, she accurately replied that she had been unable to move her arm for several days. Remarkably, it seemed that all the time Mrs. M. had been denying her paralysis, the knowledge of it was nevertheless being recorded in her brain. Yet when the effect of the cold water wore off several hours later, she not only reverted to denying the paralysis, she had no recollection of ever having come out of that state of denial. It was as if there were two completely separate Mrs. M.'s: an anosognosiac version who was convinced that she was perfectly able to move her arm, and a cold- water version

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who acknowledged her paralysis but expressed total ignorance that she had ever denied it. The curious effect of the cold water on Mrs. M. fit neatly into a hypothesis brewing in Ramachandran's own mind. At any given moment in our waking lives, our brains are flooded with information pouring in from various senses, all of which has to be fitted coherently into a perspective that's based on what our stored memories already tell us is true about the world. In order to act, the brain must have some way of selecting from this superabundance of detail and ordering it into a consistent belief system, a story that makes sense of the available evidence.

But what happens when the information arriving from some source conflicts with the existing plot? If the conflicting information is only mildly important, one easy response might be to just ignore it. The twinge of pain in the ankle of that weekend tennis player, for instance, does not jibe with the reports received from other joints and muscles, much less with his senses' appreciation of the glorious sunny day and his memory of last week's exciting game. To keep the story consistent and intact, his brain edits out the information coming from pain receptors in the ankle. He might deny to himself that the pain exists, or he could rationalize it to fit with the prevailing belief system, perhaps by telling himself it will go away as soon as he loosens up.

As an analogy, think of a military general in a war room, planning for a battle, says Ramachandran. He would ordinarily collect evidence from a large number of scouts, add it all up, and arrive at a decision on what to do next. Let's say the information from his scouts led him to call for an attack the next morning. But just before the scheduled attack, imagine one more scout arrives and tells him that he has underestimated the enemy's strength by a quarter. Even though that new information contradicts everything else he has been told, the general cannot afford to rethink the whole decision. Instead, he simply ignores the report from the new scout or tells him to get in line with what everybody else is thinking. He may even tell him to lie in order to preserve troop morale.

Ramachandran describes this metaphoric general--who roughly corresponds to Freud's concept of the ego--as a die-hard conservative coping with reality by promoting the status quo and denying or rationalizing away any information that threatens it, in the interest of

preserving stability. Such everyday defense mechanisms are not really maladaptive: they keep the brain from being hounded into directionless indecision by the sheer number of possible stories that might be written from the material available from the senses. Frequently, however, new, conflicting reports arrive that are too critical to ignore. If a scout presents a general with last-minute news that the enemy possesses nuclear weapons, it would be disastrous for the commander to carry on according to the existing plan. Likewise, the weekend tennis player can deny knowledge of his sensitive ankle without penalty, up to a point. If the pain receptors in his ankle are commanding attention whenever he puts weight on the leg, to ignore them would defeat the purpose of having pain receptors in the first place. Instead, the tennis player abandons the prevailing story--Tennis anyone?--and constructs a completely new one in line with the undeniable truth shooting up his leg from his ankle: Better rest up this week.

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To balance the conservative, maintain-the-status-quo strategy of the general, there must therefore be another decision maker, an anomaly detector, as Ramachandran calls it. The anomaly detector's job is to constantly evaluate the general's official story, decide when the conflict between the old belief system and new information passes a certain threshold, and then intervene, destroying the official story and working with the general to write a new one.

Mrs. M.'s anomaly detector has fallen asleep at the post. Her brain endeavors to construct a plausible story about her body image according to the evidence received from various sensory systems, just like a normal brain. But then a radically conflicting report arrives, one that a normal brain would quickly perceive as too anomalous to fit into preexisting beliefs. (I am telling my hand to move, and it is not responding!) Since the anomaly detector is not doing its job, however, the incongruous information is swallowed into the existing story, and Mrs. M.'s brain fails to recognize its incompatibility. The general is free to file away the tragic news of her paralysis, maintaining the status quo with a blanket of denials, rationalizations, and confabulations that can accommodate even the most bizarre conflict because there is nothing holding it up to scrutiny.

Since we know which part of the brain is disabled in anosognosia, the curious delusions of a damaged mind may thus provide the means to anchor the airy abstractions of Freudian psychology in the physical flesh of the brain. In Ramachandran's scenario, the story-building of the conservative general--Freud's ego--largely involves the left side of the brain, where the language centers called Broca's area and Wernicke's area are also located. Challenging the general's story, on the other hand, can take place only in a healthy right hemisphere. So according to his theory, when Ramachandran poured cold water into Mrs. M.'s left ear, and by means of the vestibular system stimulated brain areas in her right hemisphere, he reawakened the anomaly detector, which promptly saw that the general's story had been clearly outrageous for several days. She was then able to grasp the reality of her condition until the cold-water stimulation faded and the anomaly detector went back to sleep.

Does that mean the anomaly detector actually resides in the right parietal cortex--an area known to be damaged in anosognosiacs like Mrs. M.? It would be unreasonable to suggest that such a complex cognitive function exists in some precise location in the brain, Ramachandran says. But given the breakdown in anomaly detection shown in anosognosia, it would seem that the parietal cortex and associated areas damaged by the stroke are somehow involved.

A key question to resolve is whether the extreme denials of anosognosiacs represent a breakdown in anomaly detection in general or are only an isolated aberration specific to

how they perceive their bodies. One circumstantial hint that Ramachandran has tapped into a global process is a certain common pattern in stroke victims. Patients with rightbrain stroke damage, even those who don't exhibit anosognosia, often appear oddly oblivious to illness or other problems, carelessly shrugging off news that they have a malignant tumor or that a loved one has been in a serious accident. Since the right side of the brain is commonly thought of as the emotional hemisphere, such blasé responses have

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previously been considered a result of the stroke's suppression of emotional circuits. Ramachandran's model suggests instead that the affected circuits are involved with anomaly detection: the patients do not react to disturbing information, because their active left-brain circuits have filed it away as too threatening to the status quo, and no complementary critique of that action takes place in the right hemisphere of the brain. Meanwhile, it is common for victims of stroke in the left side of the brain to suffer a contrary fate. Far from denying their illness and problems, they dwell on them, their obsession with all that is wrong spiraling down into deep depression. In the global model Ramachandran envisions, these people have no left-brain general operating to smooth over life's difficulties by repressing information. Instead, they struggle to attend to every unpleasant detail.

Ramachandran plans several lines of research to test his hypothesis experimentally. One is already under way: he is studying the responses of anosognosiacs to a situation in which sensory information about their arm has been intentionally brought into conflict. The experiment makes use of a trick wooden chamber. The subject's hand is placed in the box through a hole in the front, and the subject looks down on it through a hole in the top. Unbeknownst to her, however, the box contains another hole in the rear and a system of mirrors that enables a hidden accomplice of the examiner to extend a hand into the box from behind a partition. The mirrors substitute an image of the accomplice's hand for the subject's. (Both hands are gloved, to mask the deception.) The examiner can then tell the patient to move her hand or keep it still, at the same time giving a surreptitious cue to the accomplice to do just the opposite. The subject's visual system thus receives one message while at the same time her sense of body position and movement is sending a completely conflicting one.

In a recent trial, an anosognosiac's paralyzed left hand was placed in the box, and she was asked to watch her hand and move it to the beats of a metronome. The accomplice was given a cue, and the hand in the box began to move accordingly. On the first trial, the patient's response left everyone utterly perplexed. Not only did she show no surprise at seeing her hand moving up and down, she denied seeing any hand at all. When Ramachandran repeatedly asked her what she saw, she admitted that the box was not empty. But there was definitely no hand inside. There was a wedding cake.

Though it is only guesswork, Ramachandran believes that in response to such a bizarre mix of signals, her brain simply canceled all inputs and substituted a hallucination in their place. In a later trial, a different patient reported that her left hand moved when she was asked to move it, a result that might be expected given her professed denial of her paralysis. But then Ramachandran asked her to place her good right hand in the box instead and move it. Once again she said she could see the hand moving--even though his accomplice was keeping her hand still. Thus the patient was patently denying an obvious truth that had little to do with the left-side paralysis itself--an indication, perhaps, that the functions damaged by the stroke involved more than the specific circuits concerned with the left side of the body.

The minute there was a discrepancy in the existing story, she tried to make it fit, because her anomaly detector wasn't there to catch it, says Ramachandran.
To better test whether the anomaly detector is global or specific to body image--or whether it exists at all--Ramachandran plans a series of experiments using a brain scanning technique called functional magnetic resonance imaging, which can pinpoint areas of the brain activated by stimuli. It would be extremely suggestive, for instance, if part of the right parietal cortex implicated in anosognosia was activated when normal subjects detected the anomaly in an object quickly glimpsed, such as a flashed image of a red ace of spades.
Until Ramachandran has a chance to use this high-priced imaging equipment, though, he is the first to admit that his theory of the nature of mind is highly speculative. But he doesn't mind speculating further. Much of his reasoning hangs on the mysteriously therapeutic effect of cold water poured into an anosognosiac's ear. The most common explanation for this phenomenon follows from the view that anosognosia is a manifestation of unilateral neglect, wherein the stroke-damaged patient ignores all that is happening on the left side of the perceptual domain. It could be that the shock delivered to the vestibular system by the cold water jump-starts the right parietal cortex, enabling the patient to again pay attention to everything on her left side, including her paralysis. Ramachandran finds this answer unsatisfying for the same reason he balks at attributing anosognosia to neglect in the first place: the patient isn't simply ignoring her paralysis, she is adamantly denying it. He believes instead that the cold-water stimulation triggers circuits in the parietal cortex involved in anomaly detection, allowing a patient like Mrs. M. to perceive the glaring discrepancy between her belief that she can move and the sensory evidence that she patently cannot.
While the cold water's effect on the vestibular system is no doubt implicated in Mrs. M.'s recovery of perception, what fascinates Ramachandran is the rapid eye movement that accompanies this sudden release from denial. What if her apprehension of the disturbing truth of paralysis was linked to another context in which rapid eye movement appears just as repressed information is allowed to well up to the surface? There is only one state in normal life where your eyes move back and forth and you pull up unpleasant memories and disturbing beliefs about yourself, he says, and that is the REM, or rapid eye movement, sleep that produces dreams.
According to Ramachandran, while we are awake the left-hemisphere general is working hectically--selecting, ordering, and repressing information to produce a coherent story for subsequent action. Our anomaly detector intervenes only at critical junctures, since the brain's story has to be consolidated under the constant pressure to respond to new stimuli. As a result, some information may end up being repressed that might actually prove useful in the future. In REM sleep, the brain can review these buried perceptions and memories of the past and rehearse them on the risk-free stage of dreams--what Ramachandran calls nature's own virtual reality. If the information still cannot be accommodated under existing beliefs, the material is repressed again, unless the dreamer

happens to be awakened accidentally and temporarily glimpses the script in progress. But we remember very little of our dreaming. Most of it, Ramachandran suggests, is comfortably and invisibly integrated into the belief system supported by the conscious mind, which in the process becomes progressively more liberated from unnecessary defenses.

At the risk of pushing the metaphor too far, Ramachandran says, imagine the general during the day, in the heat of battle. He doesn't have time to review the contrary reports from every scout who comes in, so he shoves them into file drawers marked Top Secret. When he has a chance to relax late at night, he takes some of these files out of the drawer and gives them a second look. The anomaly detector joins the general over drinks, as it were, and shows him where the files dangerously contradict the official story. In my view, this is what is happening each time you dream. You open your top-secret files and psychoanalyze yourself, deciding which memories to repress and which to uncover.

The link between the cold-water confessions of an anosognosiac and the normal function of dreams in REM sleep is still hypothetical. Curiously, however, the currently popular therapy called EMDR (Eye Movement Desensitization and Reprocessing) relies on the purported ability of the therapist to relieve the distress of repressed traumatic memories by focusing the patient's eyes on a finger waved rapidly back and forth. Ramachandran does not actively support or plan to use the therapy on anosognosiacs, but he finds the coincidence with his own hypothesis intriguing. We're not saying that putting cold water in somebody's ear makes them dream, he says. But perhaps the stimulation mimics REM and some of the phenomena that happen during dreaming, one of which is this dredging up of unpleasant memories.

His plan to test this aspect of his theory is simple: he intends to awaken anosognosiacs from REM sleep and ask about their dreams. In contrast to Freud's notion that dreams are wish fulfillments, Ramachandran's idea predicts that anosognosiacs should dream that they are paralyzed, since during REM their anomaly detector should be reawakened. It may even be that dreams cure anosognosia. By reviving the anomaly detector night after night, an anosognosiac integrates the fact of paralysis into his or her belief system over several days.

Ramachandran plans to conduct the same low-tech experiment on victims of anterograde amnesia, in which brain trauma destroys the individual's capacity to form long-term memories after the injury occurred. Anterograde amnesiacs are equally forgetful of emotionally neutral information, such as a list of words, and major circumstances in their lives, such as the identity of people whom they've met since their injury. Even attending physicians have to reintroduce themselves to anterograde amnesiacs every time they enter their presence--as if they had never met before. According to Ramachandran's hypothesis, these amnesiacs may have lost the capacity to consolidate any information into a working story in the left side of their brains. Instead, their generals indiscriminately file all inputs into drawers marked TOP SECRET, where they cannot be accessed by the conscious mind. Since these are the drawers that are opened during REM sleep, an amnesiac awakened while dreaming might be able to recover memory of some recent

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events. In any case, it's worth a try.

My colleagues would give this idea maybe a 10 percent chance of being right, Ramachandran says. I'd give it 30 to 40 percent. But even if I'm wrong about the entire theory, it does suggest some interesting directions, doesn't it? Who would have thought to wake up amnesiacs and ask them about their dreams?

STATEMENT OF
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July 16, 1998
http://www4.va.gov/OCA/testimony/hvac/16JY98JB.asp

Mr. Chairman I appreciate the opportunity to talk about my research on cerebral malaria in Vietnam Veterans.

Malaria may have afflicted as many as 250,000 ground troops in Vietnam, making malaria nearly as common as gunshot wounds. This statistic is relevant to Vietnam veterans today, because while they may have recovered from the malaria illness itself, a number of these veterans developed cerebral malaria and may have been left with neuropsychological and neuropsychiatric symptoms involving problems with mood, temper and memory which could be mistaken for PTSD.

Let me start with a bit of history. A consistent body of clinical literature dating from 500 BC through the early 20th century has reported that individuals who survive cerebral malaria frequently developed depression, memory loss, personality change, and temper problems as long-term secondary effects of the disease. This constellation of neuropsychiatric deficits was observed often enough among survivors of cerebral malaria in turn-of-the-century, Britishoccupied India that the syndrome was christened *Tropical Neurasthenia.* Forrester, a leading expert of his day, reported that cerebral malaria was the single most important cause of mental illness in British-occupied malarial endemic zones. Scores of papers were written about malaria and tropical neurasthenia during the 19th century, and most neurology books of the time contained long sections about cerebral malaria and its neuropsychiatric sequelae. It

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should be noted in addition that clinical observations about cerebral malaria leading to psychiatric-like symptoms were first recorded in the writings of Hypocrites and Galen, which is 2,000 years before the colonial British experience or the war in Vietnam.

Among the acute brain related complications of cerebral malaria are swelling of the brain with flattening of the cerebral gyri, brain injury from high fever, multiple small hemorrhages throughout subcortical white matter, ring hemorrhages around large blood vessels, blockage of capillaries by "log jams" of blood cells (causing hypoxia in watershed zones of cortex), severe hypoglycemia, and permanent discoloration of the brain to a blue-gray .

The key point from this abundant literature is that malaria, in its severest form, may cause brain damage which may persist after the malarial illness itself has been cured.

In our research, the neurobehavioral status of 40 Vietnam veterans who reported being treated for malaria while in Vietnam was compared with that of a group of combat veterans who sustained gunshot/shrapnel wounds in Vietnam, but did not contract malaria. The purpose of requiring veterans in the comparison group to have been wounded was to control for medical treatment of a non-lethal condition and to ensure that both groups had been exposed to similar levels of combat experience.

The results of the study suggest that cerebral malaria survivors may have multiple neuropsychiatric symptoms which could be problematic years after the acute illness had been "cured." As compared with wounded combat veterans who did not have cerebral malaria, the 40 Vietnam veterans who participated in my study who contracted malaria manifested substantial problems with depressive mood, "personality change," feelings of subjective distress, memory problems, emotional lability, and neuropsychiatric symptoms very similar to small seizures, such as memory gaps and staring spells. Although these findings are statistically and psychometrically more sophisticated and reliable than the clinical observations reported over the previous 2,500 years, our study is only the most recent to suggest that cerebral malaria is a cause of long-standing neuropsychiatric symptomatology in adults who survive the illness.

The message to be drawn from this research is that there may be some Vietnam veterans at risk for suffering from a persistent neuropsychiatric syndrome which can produce a wealth of psychiatric, psychological, neuropsychological, neuropsychiatric and neurological symptoms.

In summary, these findings suggest that further investigation and attempted replication by other groups of independent investigators may be appropriate. If additional studies can confirm that Malaria, or more importantly, the post malaria neuropsychiatric syndrome is a cause of mental problems in Vietnam veterans, then improved treatments could be developed.

It is not my intention to complain about the VA, the Army or Vietnam veterans. Our findings may offer good news for an undetermined number of Vietnam veterans in that they may have

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mental symptoms which are the result of a neurological disease. With that change in perspective regarding their symptoms, it would logically follow that there would be changes, improvements we hope, in their treatment. In our experience, many of the malaria veterans can be found in PTSD clinics and their lives are substantially improved with neurological treatment.

This concludes my remarks. I would be happy to answer the Committee's questions.

STATEMENT OF
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HOUSE COMMITTEE ON VETERANS' AFFAIRS
July 16, 1998
http://www4.va.gov/OCA/testimony/hvac/16JY98JB.asp

Thank you Mr. Chairman and members of the Subcommittee on Benefits for this opportunity to discuss the matter of potential long-term neuropsychological outcomes associated with malaria and in particular, cerebral malaria. My name is John Booss and I am the Director of Neurology for the Department of Veterans Affairs based at VA Connecticut Healthcare System in West Haven, Connecticut, and Professor of Neurology and Laboratory Medicine at the Yale University School of Medicine. I am testifying before you today as one of the Department of Veterans Affairs experts on neurological conditions and their potential association with the combat experience. I am one of thousands of clinician/researchers in the VA system who provide clinical care for veterans and who conduct research relevant to some of the unique health problems, combat-related and non-combat-related, posed by participation in military service. The issue that we are discussing today is complex and controversial and is an example of why VA supports clinician/researchers.

VA has long been concerned about infectious diseases and their outcomes among veteran populations. Our research programs in infectious disease range from endemic infectious agents (such as malaria) in areas to which service members have been deployed, to emerging pathogens (such as multiple drug resistant TB) that pose new threats and concerns about the health of the veteran community.

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The Office of Research and Development Medical Research Service reviewed a research proposal from Dr. Nils Varney from the Iowa City VA Medical Center in 1988 to carry out research on the neuropsychiatric consequences of cerebral malaria in Vietnam veterans. Following a competitive merit review process, funds were awarded to Dr. Varney for his proposed research from 1989 - 1992. A paper titled "Neuropsychiatric Sequelae of Cerebral Malaria in Vietnam Veterans" reporting on this research was published in 1997 in the Journal of Nervous and Mental Disease (185:695-703). Much of the controversy surrounding this report involve four issues:

1. There is no medical or laboratory confirmation that the majority of the 40 patients were infected with malaria;
2. There is a lack of documented medical evidence that supports a diagnosis of cerebral malaria;
3. Dr. Varney's interpretation of his data is inconsistent with other interpretations from documented malaria cases;
4. Dr. Varney has made unfortunate and unsupportable extrapolations from a study of 40 veterans to the entire Vietnam experience.

This is not to say, however, that Dr. Varney's hypothesis lacks value. Indeed, further investigation could refine our understanding of the long-term consequences of malaria infection. What we suggest is that an assessment of Dr. Varney's work reveals some methodological and interpretational problems, that should be carefully considered before we make decisions that change health benefits policy. We must look at Dr. Varney's work in the larger context of our scientific knowledge about malaria.

Before I go on to discuss Dr. Varney's work in more detail, I want to consider some background regarding malaria itself. Malaria is caused by infection of the human with a parasite of the genus *Plasmodium.* The diagnosis of malaria is made by examination of blood smears for the parasite. Humans are infected with *Plasmodium* through inoculation by the *Anopheles* mosquito carrying the organism, which it received by biting an infected human. There are several species of *Plasmodium*, one of which is *Plasmodium falciparum.* Infection with *Plasmodium falciparum* leads to falciparum malaria, and is the cause of "cerebral malaria". Of all falciparum malaria cases, many published studies have estimated that approximately 2% are diagnosable as "cerebral malaria" which causes loss of consciousness and other neurological, psychological, and neuropsychological signs and symptoms. One study in particular examined 1,200 cases of falciparum malaria among troops deployed to Vietnam and found 19 who fit criteria for cerebral malaria. The paper reporting these findings was published in the Journal of the American Medical Association in 1967 (JAMA, 202:679-682). With this background, I will now turn to Dr. Varney's work.

An earlier study of malaria from Dr. Varney's group was reported in VA Practitioner in February 1989. In that paper, 30 Vietnam veterans were studied who reported having had

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malaria, accompanied by at least 12 hours of amnesia. Twelve of 17 medical records supported a diagnosis of malaria, but the remainder were reported as lost or destroyed. There was no report of examination of blood smears for the malarial parasite, nor was the diagnosis of "cerebral malaria" reported from the available medical documents. Hence in the 1989 report the diagnoses of cerebral malaria were not established medically. All subjects had co-existing medical conditions that could have contributed to the reported findings. Hence there is ambiguity about the cause of the neuropsychologic findings reported.

Unfortunately, the report of Dr. Varney and his group in the November 1997 issue of The Journal of Nervous and Mental Disease does not resolve the ambiguities. There is again no requirement for laboratory verification of the "malaria group". Of 40 veterans studied, service records were found for 37, of which 14 had a diagnosis of malaria cited. A search for the diagnosis of cerebral malaria was not reported, and no report of blood smears for the parasite was made. This is in contrast to medical reports on malaria at the time of the conflict in Vietnam in which microbiologic confirmation of actual infection was obtained [JAMA, 202:679-682, 1967; Military Medicine, 138:795-802, 1973]. To reiterate, the most recent report from Dr. Varney's study did not require medical diagnosis of malaria in order for a subject to be included in the malaria group, nor did inclusion require a medical record citation of cerebral malaria. This is a significantly lower diagnostic standard than the wartime reports.

Other researchers have examined the long-term effects of malaria infection on brain function. In 1998 Anthony Dugbartey and colleagues reported in the Journal of Nervous and Mental Disease (186:183-186, 1998) on their follow-up study of 142 individuals in Ghana with medically documented uncomplicated falciparum malaria (i.e. not cerebral malaria). They evaluated these individuals' psychiatric and cognitive status using self-report questionnaires and compared their results with a similar group of 30 individuals with no life-history of malaria. These researchers found comparisons between the malaria and control groups showed small differences on scales of anxiety and depression with no observed differences in higher level brain functions such as thinking clearly or remembering. They suggest that falciparim malaria may cause a long-term, subclinical or subtle mixed depression-anxiety syndrome.

Dr. Varney's paper presents certain issues as factual that diminish the validity of his conclusions. First, he states that "it is estimated that about 250,000 Vietnam veterans were hospitalized for falciparum malaria during the course of the war." The basis for that estimate is unclear, as the reference for this figure cited by Dr. Varney (Connor, et.al., 1976) does not contain that figure. A compilation of military cases from another source (Clinical Infectious Diseases, 16:320-329, 1993) is considerably lower. He further states that "those who were hospitalized were at high risk for cerebral malaria." This latter statement is true only if one accepts a rate of 2% among all falciparum malaria cases as constituting a high risk.

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To summarize, whether the 40 veterans studied by Dr. Varney ever had cerebral malaria has not been medically demonstrated and the extrapolation of the number of veterans with

cerebral malaria appears to be in error. Evidence from other researchers indicates that uncomplicated falciparum malaria results in, at worst, mild psychiatric sequelae. What about veterans who actually had cerebral malaria in Vietnam? Could they have neuropsychological effects to this day? I don't think we have a conclusive answer to that question, but given the serious acute nature of cerebral malaria, the possibility certainly exists. Were a veteran with a history of falciparim malaria with or without documented acute cerebral symptoms to complain of symptoms suggesting complex partial seizures, anxiety, and/or depression, careful clinical evaluation of those symptoms and appropriate therapy would be warranted. This would constitute accepted practices and standard of care in any VA hospital.
The Department of Veterans Affairs is particularly mindful of the disease burden, both combat and non-combat, carried by those who have served in deployments around the world. Research such as Dr. Varney's, despite our reservations, reminds us that diseases are complex. For this and other reasons, the Department of Veterans Affairs will continue to fund scientifically sound research that explores disease associations that might affect the health of our veteran patients, either acutely or in the long term.
Thank you Mr. Chairman. I will be happy to take any questions you may have.
The below statement is added because of the reported higher rate of ALS in Veterans. It is postulated that this could be because of the higher incidence of subtle TBIs that occur in a war zone (now documented in the current conflicts)as well as the incidence of p. falciparum malaria. An easy paper study could prove or negate this postulate.,

STATEMENT OF
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GULF WAR EXPOSURES
July 26, 2007

http://www4.va.gov/OCA/testimony/hvac/sh/070726LD.asp

Mr. Chairman and members of the Subcommittee, thank you for providing the Department of Veterans Affairs (VA) this opportunity to discuss VA's response to the health care and other needs of veterans who have served in combat in Southwest Asia. With me today is

☐ Mark Brown, PhD, Director, Environmental Agents Service, Office of Public Health and Environmental Hazards

☐ Timothy O'Leary, Director, Biomedical Laboratory Research and Development Service, Director, Clinical Science Research and Development Service, Office of Research and Development and

☐ Eugene Oddone, MD, MHSc, Director, Center for Health Services Research in Primary Care and Principal Investigator, National Registry of Veterans with ALS

My testimony today will address three major topics: 1) VA's efforts towards improving clinical care and our understanding for the illnesses affecting veterans who served in the 1991 Gulf War, 2) how these efforts have helped us in responding to the health care and other needs of our troops fighting in this same region today; and 3) VA's response to concerns about potential increased risk of Amyotrophic Lateral Sclerosis (ALS, or "Lou Gehrig's Disease) among military service members.

BACKGROUND

The United States deployed nearly 700,000 military personnel to the Kuwaiti Theater of Operations during Operations Desert Shield and Desert Storm (August 2, 1990, through July 31, 1991). Within months of their return, some Gulf War veterans reported various symptoms and illnesses that they believed were related to their service. Veterans, their families, and VA subsequently became concerned about the possible adverse health effects from various environmental exposures during Operations Desert Shield and Desert Storm.
Of particular concern have been the symptoms and illnesses that, to date, have eluded specific

diagnosis. More than 130,000 Gulf War veterans have participated in the two health registries that VA and the Department of Defense (DoD) maintain. In addition, more than 335,000 have been seen at least once as patients by VA. Although the majority of veterans seeking VA health care had readily diagnosable health conditions, we remain very concerned about the veterans whose symptoms could not be diagnosed.

I would like to provide a brief description of some of the programs and initiatives VA developed in response to health concerns of veterans of the 1991 Gulf War. I will also focus on how these new programs have benefited the veterans who are now returning from the current conflicts in Southwest Asia, specifically veterans from Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) and their families.

VA INITIATIVES FOR SOUTHWEST ASIA COMBAT VETERANS

The VA Gulf War Veteran Health Registry. Even before the 1991 Gulf War cease-fire VA had concerns that returning veterans might have certain unique health problems including respiratory effects from exposure to the intense oil fire smoke.

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In response, VA quickly established a clinical registry to screen for this possibility. The new voluntary health registry examination also helped encourage new combat veterans to take advantage of VA health care programs. VA has long maintained health registries on other atrisk populations, including veterans exposed to radiation, and Vietnam veterans exposed to Agent Orange.

Formally established by law in 1992, VA's Gulf War Veterans' Health Examination Registry is still available to all Gulf War veterans, including veterans of the current conflict in Iraq. It offers a comprehensive physical examination, and collects data from participating veterans about their symptoms, diagnoses, and self reported Gulf War hazardous exposures. As of June 2007, this program evaluated over 100,000 Gulf War veterans, or about 1 in 7 veterans. The program has also seen nearly 7,000 veterans who served in the current conflict in Iraq, who as Gulf War veterans themselves, are eligible for this program.

After 15 years, the principal finding from VA's systematic clinical registry examination of about 14 percent of 1991 Gulf War veterans is that they are suffering from a wide variety of common, recognized illnesses. However, no new or unique syndrome has been identified. Registry data has significant limitations. VA recognizes that in the long run, establishing high quality epidemiological research studies is the best approach for evaluating the health impacts of service in the 1991 Gulf War (or in any deployment). VA has adopted that approach.

New Compensation for Undiagnosed Illnesses. Many new Gulf War veterans encountered problems when they tried to prove that their difficult-to-diagnose or undiagnosed illnesses were connected to their military service. This affected their access to disability compensation. In response, VA asked Congress for authority, granted under Public Law 103-446, to provide compensation benefits to Gulf War veterans who are chronically disabled by undiagnosed illnesses when certain conditions are met. This statute as amended authorizes VA to pay compensation for disabilities that cannot be diagnosed as a specific disease or injury, or for certain illnesses with unknown cause including chronic fatigue syndrome, fibromyalgia and irritable bowel syndrome.

Symptoms potentially covered include 1) fatigue; 2) skin signs or symptoms, including hair loss; 3) headache; 4) muscle pain; 5) joint pain; 6) neurologic signs or symptoms; 7) neuropsychological signs and symptoms, including memory loss; 8) signs or symptoms involving the respiratory system ; 9) sleep disturbances; 10) gastrointestinal signs or symptoms; 11) cardiovascular signs and symptoms; 12) abnormal weight loss; and 13) menstrual disorders. This is a unique benefit for Gulf War veterans, and more than 3,300 have received service connection for their undiagnosed or difficult to diagnose illnesses under this authority. Veterans from the current conflict in Iraq are also eligible for this special benefit.

Epidemiological Research on Gulf War Veterans. Despite the value of VA's Gulf War Health Registry program, additional epidemiological research is required to properly characterize any possible long-term health effects of Gulf War 1 service to the average Gulf War veteran. This is because the registry participants are self-selected, and therefore do not represent the average veteran. Registry findings demonstrate that Gulf War veterans are not showing up with any unique health problems; however, these findings do not tell us if veterans are suffering from any diagnoses at rates different from expected. That requires population-based epidemiological and related research studies, which VA has carried out.

VA Gulf War Veteran Mortality Study. VA researchers have been continuously monitoring the cause-specific mortality of all Gulf War veterans in comparison to their non-deployed

peers. In post-war monitoring, Gulf War veteran mortality from most causes is not significantly different in comparison to non-deployed peer as controls. Moreover, the mortality for both groups is less than half that of matched civilian controls. This is almost certainly because people who choose to go into the military are healthier to begin with.

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Initially, Gulf War veterans have shown an increased risk of death from accidents, especially motor vehicle accidents. VA's data shows that this is a temporary effect, and by 6 years postwar this difference has disappeared. This overall pattern is very consistent with earlier mortality data from Vietnam veterans.

New Clinical Guidelines for Combat Veteran Health Care. Early on, VA recognized the need to assure training of our health care providers to allow them to best respond to the specific health care needs of Gulf War veterans with difficult-to-diagnose illnesses. With that in mind, and in collaboration with the Department of Defense (DoD), VA developed two Clinical Practice Guidelines on combat veteran health issues. This included a general guideline on post combat deployment health, and a second dealing with diagnosis of unexplained pain and fatigue. These clinical guidelines give VA health care providers access to the best medical evidence for diagnoses and treatment. Developed in response to veterans of the 1991 Gulf War, today VA highly recommends these for the evaluation and care of all returning combat veterans, including veterans from OEF and OIF. (also available on line at www.va.gov/EnvironAgents)

New VA "War-Related Illness & Injury Study Centers:" Specialized Health Care for Combat Veterans. In 2001, as part of VA's overall health response for veterans returning from the 1991 Gulf War, VA established two War Related Illness and Injury Study Centers (WRIISCs), at the Washington, DC, and East Orange, NJ VA Medical Centers (VAMCs) Today, these two centers are providing specialized health care for combat veterans *from all deployments* who experience difficult to diagnose or undiagnosed but disabling illnesses. VA now anticipates concerns about unexplained illness after virtually all deployments including OEF and OIF, and we are building on our understanding of such illnesses.

Currently, VA is expanding on this program to better meet the health care needs of new combat veterans suffering from mild to moderate traumatic brain injury. To that end, VA is establishing a third WRIISC at the Palo Alto VA Health Care System. This will take advantage of their unique assets including a Polytrauma Unit, interdisciplinary program on blast injuries which integrates the medical, psychological, rehabilitation, prosthetic needs of injured service members, their programs in traumatic brain injury, spinal cord injury, blind rehabilitation post traumatic stress disorder, and research into new and emerging areas of combat injuries and illnesses. This is a critical development because combat injuries we see today among OEF and OIF veterans are much more likely, compared to previous wars, to involve some degree of traumatic brain injury. This has been the result of the types of weapons commonly used to attack our troops, including improvised explosive devices, blasts from landmines, artillery and mortar attacks, and the resulting shrapnel produced from such devices. Many of the long-term chronic health effects from traumatic brain injury appear similar to the difficult-to-diagnose and treat illnesses currently being treated by the WRIISC programs today.

Expanded Education on Combat Health Care for VA Providers. In response to health problems faced by veterans of the 1991 Gulf War, VA developed the Veterans Health Initiative (VHI) Independent Study Guides for health care providers titled, "A Guide to Gulf War Veterans Health." Although originally focusing on health care for combat veterans from the 1991 Gulf War, this study guide remains highly relevant for treating OEF and OIF combat veterans, since many of the hazardous deployment-related exposures are the same for both conflicts.

VA also developed several additional VHI Independent Study Guides and other materials relevant to veterans returning from Iraq and Afghanistan. These include the Under Secretary for Health Information Letter "Preparing for the Return of Women Veterans from Combat Theater," (IL 10-2003-011), which provides guidance on the special care needs for women OEF and OIF combat veterans.

Another VHI independent study guide in this series, "Endemic Infectious Diseases of Southwest Asia," provides guidance to health care providers about the infectious disease risks

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in Southwest Asia, particularly in Afghanistan and Iraq. The emphasis is on diseases not typically seen in North America.
Similarly, "Health Effects from Chemical, Biological and Radiological Weapons" was developed to improve recognition of health issues related to chemical, biological, and radiological weapons and agents.
The guideline, "Military Sexual Trauma," was developed to improve recognition and treatment of health problems related to military sexual trauma, including sexual assault and harassment.
Similarly, "Post-Traumatic Stress Disorder: Implications for Primary Care" is an introduction to PTSD diagnosis, treatment, referrals, support and education, as well as awareness and understanding of veterans who suffer from this illness.
"Traumatic Amputation and Prosthetics" includes information about patients who experience traumatic amputation during military service, their rehabilitation, primary and long-term care, and prosthetic clinical and administrative issues.
Finally, "Traumatic Brain Injury" presents an overview of Traumatic Brain Injury issues that primary care practitioners may encounter when providing care to veterans and active duty military personnel. All are available in print, C.D. R.O.M. and on the web at www.va.gov/VHI.
VA National Training on Health Care for New Combat Veterans. Based on our experience treating veterans from the 1991 Gulf War, VA recognized the need to quickly familiarize all VA health care providers on the unique health concerns of new combat veterans returning from Iraq and Afghanistan. VA has sponsored multiple regional education conferences and a three-day National Conference on "Providing Health Care for a New Generation of Combat Veterans Returning from OEF and OIF," in April 2007.
The conference objective was to sharpen the response of VA providers to new and transitioning combat veterans coming to us today, and to the new physical and behavioral health care challenges that these returning veterans bring with them. The meeting included plenary sessions featuring VA and DoD leadership, and breakout presentations from national and international experts describing their clinical and research experiences with new combat veterans.
Approximately 1,400 people attended this event, from throughout all of VHA. The target audience was VA primary care providers from around the country, including social workers, psychologists and mental health professionals, physicians, physician assistants, nurses, and others who provide direct care to new combat veterans returning from Iraq and Afghanistan. National subject matter experts from VA, DoD, and academia, presented their recent experiences responding to the health care needs of new combat veterans. The goal was to give VA healthcare professionals the tools they will need to respond to the unique and sometimes complex healthcare needs of returning combat veterans, and to develop the necessary competencies to provide optimal care. The deliberately multidisciplinary approach also helped providers to focus on more integrated health care delivery, foster networking. and share best practices, all of which should enable us collectively to improve outcomes for returning wounded service members.
Breakout session topics covered Polytrauma; Pain Management; Behavioral Health; Diversity Issues; Prosthetics; and Special Topics for New Combat Veterans.
Outreach to Combat Veterans and their Families. VA has many programs designed to help returning combat veterans and their families. To help veterans of the 1991 Gulf War and their families be more aware of VA's health care and other benefits that are available for them,

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and of new research results on Gulf War veterans' health, VA initiated the "Gulf War Review" newsletter, which is regularly mailed out to over 400,000 veterans from that conflict.
VA has developed many new outreach and information products for new combat veterans and their families. The Secretary sends a letter to every newly separated OEF and OIF veteran, based on records for these veterans provided to VA by DoD. The letter thanks the veteran for their service, welcomes them home, and provides basic information about health care and other benefits provided by VA.
Similarly, in collaboration with DoD, VA published a new short brochure called "A Summary of VA Benefits for National Guard and Reservists Personnel." To date, over one million copies have been distributed. The new brochure summarizes health care and other benefits available to this special population of combat veterans upon their return to civilian life (also available online at www.va.gov/EnvironAgents). "Health Care and Assistance for U.S. Veterans of Operation Iraqi Freedom" is a new brochure on basic health issues for that deployment (also available online at www.va.gov/EnvironAgents).

Finally, VA started the " OEF and OIF Review," which is mailed to all separated OEF and OIF veterans (over 700,000 individuals as of July 2007) and their families, on VA health care and assistance programs for these newest veterans (also available online at www.va.gov/EnvironAgents).

Combat-Theater Veterans' Enhanced Access to VA Health Care. VA provides combat veterans enhanced enrollment placement and cost-free health care services and nursing home care for conditions possibly related to their service in a theater of combat operations after November 11, 1998 for a 2-year period beginning on the date of their separation from active military service. These veterans are placed into enrollment Priority Group 6 if not otherwise qualified for a higher enrollment Priority Group assignment and have full access to VA's Medical Benefit Package.

Veterans, including activated Reservists and members of the National Guard, are eligible if they served on active duty in a theater of combat operations during a period of war after the Gulf War or; were in combat against a hostile force during a period of "hostilities" after November 11, 1998 and, have been discharged under other than dishonorable conditions. Veterans who enroll with VA under this authority retain enrollment eligibility even after their 2-year post discharge period ends under current enrollment policies. At the end of this 2-year period VA will reassess the combat veteran's information (including all applicable eligibility factors existing at this time) and make, as appropriate, a new Priority Group assignment.

Special Depleted Uranium (DU) Surveillance Program. Special armor piercing munitions and tank armor made from depleted uranium (DU) was used with great effect by US forces during the 1991 Gulf War, as well as more recently during the initial phases of OEF and OIF. However, some veterans returning from these conflicts have had concerns that DU may have affected their health. In response, in 1993, VA established the DU Follow-up Program at the Baltimore VA Medical Center to monitor the health of veterans who had retained DU fragments in wounds - typically from "friendly fire" incidents in 1991 Gulf War. The program provides ongoing and thorough detailed physical examinations for affected veterans, including a broad array of testing of the blood, immune, reproductive, and central nervous systems, and of kidney and liver function.

In 1998, in response to increasing concerns among Gulf War veterans, this program was expanded to offer DU screening for any veteran concerned about possible DU exposure, and not just those with possible retained DU fragments or with other types of high exposure risks. The program is also open for veterans who served in OEF and OIF.

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Researchers with VA's DU Follow-up Program have not identified any clinically significant uranium-related health effects among veterans from exposure from inhalation or from retained DU fragments. There are however some concerns about certain physical changes that have been noted in imbedded DU fragments, and indications for surgical removal of fragments are currently under review by this group.

VA and DoD will continue to monitor health effects in this population, which includes both 1991 Gulf War veterans and veterans from the current conflict in Iraq.

New VA Toxic Embedded Fragments Surveillance Center. In response to health concerns for new OEF and OIF combat veterans suffering from retained embedded fragments composed of a wide range of metals and other materials as a result of blast injuries from improvised explosive devices, VA is establishing the Toxic Embedded Fragments Surveillance Center at the Baltimore VA Medical Center. New studies indicate that some metals, such as certain tungsten alloy fragments, are highly carcinogenic in rats and may pose a health hazard in veterans. Some metals are also known or presumed to be human reproductive hazards, including lead, cadmium, nickel, and copper.

The Baltimore VA DU Surveillance Program has shown us that retained DU fragments and other materials are not necessarily inert in the body, and may change over time to produce potential toxic health effects. Such effects may be minimized and managed through careful ongoing medical surveillance.

New Combat Veteran Health Surveillance. The long-term epidemiological studies supported by VA assessing the health effects of the 1991 Gulf War on veterans who were deployed to Southwest Asia took a considerable amount of time. Today, we appreciate the importance of rapidly monitoring the health status of new combat veterans and have initiated surveillance and studies to more rapidly identify any health effects that may occur from this current conflict. This has been made possible via VA's electronic inpatient and outpatient medical records, which summarizes every single visit by a combat veteran including all

medical diagnoses. For example, according to VA's July 2007 update "Analysis of VA Health Care Utilization among Southwest Asian War Veterans," since fiscal year (FY) 2002 over 700,000 OEF and OIF veterans have left active duty and become eligible for VA health care. About 35 percent of these new veterans (over 250,000) have received VA health care at least once since 2002.

This simple surveillance shows that new OEF and OIF veterans are coming to VA with a wide range of medical and psychological conditions. No special conditions stand out, and therefore these new combat veterans are being assessed individually to identify all their outstanding health problems. VA will continue to monitor the health status of recent OEF and OIF veterans using updated deployment lists provided by DoD to ensure that VA tailors its health care and disability programs to meet the needs of this newest generation of war veterans. Also using this new combat veteran roster, VA has developed a new clinical reminder in the electronic health record to assist VA primary care clinicians in providing timely and appropriate care to new combat veterans.

INDEPENDENT REVIEWS ON GULF WAR VETERANS' HEALTH

VA has sought advice on the health of combat veterans serving in Southwest Asia from a wide range of external advisory groups. For example, VA has long relied upon the independent scientific advice of the National Academy of Sciences (NAS) Institute of Medicine (IOM) to help evaluate potential associations between environmental hazards encountered during various military deployments and specific health effects. This external review process has resulted, for example, in VA recognizing about a dozen diseases as presumed to be connected to exposure to Agent Orange and other herbicides used during the Vietnam War, and to the dioxin impurity some contained.

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The National Academy of Sciences was established in 1863 with the signature of President Abraham Lincoln, to "investigate, examine, experiment, and report upon any subject of science or art" for agencies in the federal government. In 1970, the NAS created the IOM to provide independent, objective, authoritative, credible and timely scientific analyses on medical and health issues.

The US Congress, through US government agencies, regularly seeks the IOM's unique scientific advice on a broad range of health-policy issues. Their studies are conducted by independent committees of volunteer scientists composed of leading nationally and internationally recognized experts, selected by the IOM based on their expertise, good judgment and freedom from conflict of interests. The IOM requires that a committee's formal findings and recommendations are evidence-based whenever possible and noted as only expert opinion when that is not possible. Each IOM report undergoes extensive formal internal and peer review by external experts who are anonymous to the committee, and whose names are revealed only once the study is published.

Congressionally Mandated NAS/ IOM Veterans' Health Reviews. The NAS/ IOM's highly developed formal review process has proven invaluable to VA for establishing fair, scientifically based disability policies for veterans. Their reputation for objectivity, scientific integrity, and independence means that their reports stand as authoritative even when their findings fail to please all stakeholders. Since 1991, IOM has completed nineteen independent reviews of Gulf War health issues (see attachment). For evaluation of Gulf War-related health effects, Congress directed (in Public Laws 105-277 and 105-368) the NAS to "identify the biological, chemical, or other toxic agents, environmental or wartime hazards, or preventive medicines or vaccines to which members of the Armed Forces who served in the Southwest Asia theater of operations during the Persian Gulf War may have been exposed by reason of such service." Public Law 105-277 further required the NAS, for each substance or hazard considered, to determine, to the extent feasible, (1) whether a statistical association exists between exposure to the substance or hazard and the occurrence of illnesses, (2) the increased risk of the illness among exposed human or animal populations, and (3) whether a plausible biological mechanism or other evidence of a causal relationship between the exposure and illness exists.

VA RESPONSE TO PREVIOUS NAS COMMITTEE "GULF WAR & HEALTH" REPORTS

The 2000 Report. The initial 2000 NAS committee report in this series, "Gulf War & Health Volume 1," reviewed health effects from exposure to the four potential hazardous exposures related to the 1991 Gulf War. These included sarin, depleted uranium, vaccinations, and pyridostigmine bromide ("P.B.," a nerve agent protecting drug used by DoD). The report contained 13 findings, of which four indicated a positive association between some health

outcome and the reviewed general risk factors. Many were obvious, such as an association between a large exposure to the military nerve agent sarin and severe health effects including death. Others were related to common side effects of drugs and vaccines seen among civilians or military personnel using these agents to protect their health.

Following review by a VA Task Force, VA determined that establishing new presumptions of service connection for any diseases based on the report findings was not necessary. This was primarily because the types and degree of exposures associated with long-term health effects described in the NAS committee report had either not occurred during the 1991 Gulf War (for example, severe, life-threatening and immediate nerve agent poisoning), or that the related health effects were transitory and short-lived (for example, a normal sore arm following a vaccination). Those findings were published in the Federal Register, as required by the relevant statutes that established this process.

The 2002 NAS Report. The second 2002 NAS committee report, "Gulf War & Health Volume 2," reviewed health effects from exposure to pesticides and solvents used during the 1991 Gulf War. An important issue was that virtually all the pesticides and solvents used during that

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conflict were in common approved use throughout the civilian and military at that time. The report contained 77 findings, of which 21 indicated a positive association between a pesticide or a solvent and some general health outcome. These were primarily for various cancers and serious hematological disorders (e.g., leukemias, non-Hodgkin's lymphoma, multiple myeloma and aplastic anemia), subtle general neurological effects detected via neurobehavioral tests, and other health effects (e.g., reactive airway dysfunction syndrome, and allergic contact dermatitis).

Following review by a VA Task Force, VA determined that it was not necessary to establish new presumptions of service connection for any diseases based on the report findings. This was in part because the NAS committee findings were generally limited to long-term, chronic occupational exposures that do not directly correlate to potential hazards of service or exposure scenarios for the 1991 Gulf War. Furthermore, individuals who were chronically exposed to relatively high levels of these environmental hazards as part of their military occupation, whether or not during service in that war, may qualify under existing VA service connection policies for benefits for diseases resulting from such exposures. It should be pointed out that VA's decision to not establish any new presumptions does not alter existing claim procedures, nor does it prevent any veteran from establishing service connection for any disease that could be related to their service in the 1991 Gulf War. Rather, it merely means that each case must be decided on its facts and merits, as is currently the case for veterans from any era.

The 2004 NAS Sarin Update Report. In 2004, at the request of the Secretary of Veterans Affairs, a new NAS committee completed a special update on long-term health effects from exposure to the nerve agent sarin. The initial 2000 NAS committee report described above had concluded that available scientific evidence could not show an association between trace sarin exposure and subsequent long-term adverse health effects. In response, the Secretary of Veterans Affairs determined that there was not an adequate basis to support establishing presumptive service connection for any long-term health problems resulting from low-level sarin exposure.

After the completion of the 2000 NAS committee report, several new studies on sarin effects in laboratory animals were published that were not available to the NAS committee when they conducted their initial review, and which some saw as requiring a new look by the NAS committee. The new NAS committee reviewed 19 epidemiological studies of sarin health effects published since the earlier 2000 report, including studies of U.S. and U.K. veterans of the 1991 Gulf War potentially exposed at Khamisiyah, Iraq in 1991, of civilians exposed during the Japan sarin terrorist attacks in 1994 and 1995, and all the studies used in the earlier 2000 NAS committee report. They also reviewed over 100 animal studies.

The August 2004 NAS Sarin Update came to the same conclusions as the earlier 2000 report. In other words, and consistent with their earlier findings, the NAS committee was not able to find a scientific basis to associate any disease with exposure to low levels of sarin, based upon their exhaustive review of the relevant scientific literature.

The 2004 NAS Report. The third full NAS committee report, "Gulf War & Health Volume 3: Fuels, Combustion Products, and Propellants," contained nine positive findings on long-term health effects related to exposure to the reviewed agents. These included associations between exposure to combustion products (e.g., smog) and lung cancer, cancers of nasal

cavity and nasopharynx, cancers of the oral cavity and oropharynx, laryngeal cancer, bladder cancer, low birth weight/intrauterine growth retardation and exposure during pregnancy, preterm birth and exposure during pregnancy, and incident asthma. They also reported an association between exposure to hydrazine rocket fuels and lung cancer. As with previous reports, an important point is that most of the agents considered were in common use throughout the civilian and military at the time of the 1991 Gulf War.

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The NAS committee considered over 33,000 potentially relevant references, and focused on about 800 epidemiological studies on persistent health outcomes associated with exposure to oil-fire products, diesel-heater fumes, hydrogen sulfide (a specific combustion product), hydrazines and red fuming nitric acid (as rocket propellants), and gasoline and jet fuel. The committee pointed out that fuels and related combustion products are common pollutants with an abundant scientific health literature available for their review. Combustion products included ambient air pollution "smog," combustion products from motor vehicles, and fumes from stoves and heaters using a wide variety of fuels. Fuels included gasoline, kerosene, diesel and military fuels including JP-4, JP-5 and JP-8. Finally, to ensure a focus on information that would be the most relevant to veterans of the 1991 Gulf War, the committee emphasized studies of long-term rather than short-term health effects. A VA Task Force reviewing the new NAS committee report determined that new presumptive service connections were not warranted because none of the specific hazardous agents reviewed, or the exposure levels experienced by most Gulf War service members, were significantly different compared to U.S. civilians or to troops not deployed to the Gulf War.

The 2006 NAS Report "Volume 4: Health Effects of Serving in the Gulf War." The September 2006 fourth full NAS report reviewed peer-reviewed scientific literature on the health status of veterans of the 1991 Gulf War. The report was intended to inform VA about illnesses and clinical issues including possible relevant treatments, which might have been overlooked among this population, regardless of the specific underlying cause. It documented increased rates of certain illnesses among Gulf War veterans, based on a review of 850 epidemiological and other studies of this group, which they selected from among over 4,000 potentially relevant reports. They concluded that " VA and DoD have expended enormous effort and resources in attempts to address the numerous health issues related to the Gulf War veterans. The information obtained from those efforts, however, has not been sufficient to determine conclusively the origins, extent, and potential long-term implications of health problems potentially associated with veterans' participation in the Gulf War."

The NAS committee identified numerous serious limitations in existing epidemiological studies of Gulf War veterans, in large part due to the lack of veteran exposure data. However, they did "not recommend that more such studies be undertaken for the Gulf War veterans." Rather, the committee recommended "continued surveillance to determine whether there is actually a higher risk in Gulf War veterans" for illnesses that current research has identified as possibly appearing at higher rates among Gulf War veterans, specifically, brain and testicular cancer, ALS, birth defects, and post-deployment psychiatric conditions.

The NAS committee also concluded, "Every study reviewed by this committee found that veterans of the Gulf War report higher rates of nearly all symptoms examined than their nondeployed counterparts." Not surprisingly, they reported that symptom-defined "unexplained illnesses," consistent with Chronic Fatigue Syndrome, Fibromyalgia, Irritable Bowel Syndrome and Multiple Chemical Sensitivity, were the most common health problem reported in studies of Gulf War veterans. However, they concluded that "the results of that research indicate that although deployed veterans report more symptoms and more severe symptoms than their nondeployed counterparts, there is not a unique symptom complex (or syndrome) in deployed Gulf war veterans."

They also found that "Gulf War veterans consistently have been found to suffer from a variety of psychiatric conditions," including PTSD, anxiety, depression and substance abuse. Similarly, they found that available studies have "not demonstrated differences in cognitive and motor measures" in deployed versus non-deployed veterans, and show no apparent increase in risk of peripheral neuropathy, cardiovascular disease or diabetes. Finally, they reported difficulties in interpreting data on birth defects, and found little data supporting objective respiratory illnesses among Gulf War veterans. A VA Task Force reviewing the new NAS committee report determined that new presumptive service connections were not warranted because existing VA policies and procedures for disability compensation effectively cover veterans with these health problems. These include, for example, VA policies recognizing service connection for

PTSD, and for service connection for difficult to diagnose or undiagnosed illnesses.

The 2006 Report "Infectious Diseases." The October 2006 fifth NAS report in this series, "Gulf War and Health Vol. 5: Infectious Diseases," reviewed published, peer-reviewed scientific and medical literature on long-term health effects from infectious diseases associated with Southwest Asia, including those diseases relevant to the 1991 Gulf War and to Operations Iraqi Freedom and Enduring Freedom (OIF/ OEF). They identified over 20,000 potentially relevant scientific reports, and focused on 1,200 that had the necessary scientific quality. They focused on nine infectious diseases that were 1) prevalent in Southwest Asia, 2) diagnosed among U.S. or other troops serving there, and 3) known to cause long-term health problems. They also focused upon those infectious diseases that appeared to be of special concern to veterans who served in Southwest Asia. These were Brucella (causing brucellosis); Campylobacter; Salmonella and Shigella (causing diarrheal disease); Coxiella burnetii (causing Q fever); Leishmania (causing leishmaniasis); Mycobacterium tuberculosis (causing tuberculosis); Plasmodia (spp) (causing malaria) and West Nile Virus (causing West Nile fever). They selected these from among about 100 naturally occurring pathogens that potentially could have infected U.S. troops in the 1991 Gulf War, or in OIF/ OEF. The NAS committee identified 34 different long-term health effects in their report that might appear weeks to years after initial infection, associated with these nine infectious diseases. Most if not all identified long-term health effects are well-known to be associated with the initial acute infection. A VA Task Force is currently reviewing the new NAS committee report to determine if new presumptive service connections are warranted.

OTHER REVIEWS ON GULF WAR VETERANS' HEALTH

The IOM's reputation for scientific rigor, independence from the political process, and freedom from bias has made it an influential source of information on the nature of Gulf War veterans' health. In addition, since the end of the 1991 Gulf War, at least 13 other committees have been established, both in the United States and the United Kingdom, to help evaluate Gulf War veteran health issues. Other committees (and date of publications) include:

☐ Armed Forces Epidemiological Board. U.S. Department of Defense, 1996, 1999, 2000, 2000.

☐ Goss Gilroy Inc. Canadian Epidemiological Study of Gulf War Veterans. 1998.

☐ The Rt Hon The Lord Lloyd of Berwick. Independent Public Inquiry on Gulf War Illnesses. 2004.

☐ U. S. Department of Veterans Affairs, Research Advisory Committee on Gulf War Veterans Illnesses, James Binns, Chair. Scientific Progress in Understanding Gulf War Veterans' Illnesses: Report and Recommendations, 2004.

☐ U.S. Department of Defense Special Oversight Board for Department of Defense Investigations of Gulf War Chemical and Biological Incidents. Final Report, 2000.

☐ U.S. Department of Defense. Report of the Defense Science Board Task Force on Persian Gulf War Health Effects, 1994.

☐ U.S. Department of Health & Human Services, National Institutes of Health Technology Assessment Workshop Panel. The Persian Gulf Experience and Health. 1994

☐ U.S. Government Accountability Office. Gulf War Illnesses: DOD's Conclusions About U.S. Troops' Exposure Cannot Be Adequately Supported. 2004.

☐ U.S. Presidential Advisory Committee on Gulf War Veterans' Illnesses: Interim Report. 1996.

☐ U.S. Presidential Advisory Committee on Gulf War Veterans' Illnesses: Final Report. 1996.

☐ U.S. Presidential Advisory Committee on Gulf War Veterans' Illnesses: Special Report, 1997.

☐ United Kingdom Parliamentary Office of Science and Technology. Gulf war illnesses: Dealing with the Uncertainties. 1997.

☐ United States Senate, Committee on Veterans' Affairs, Report of the Special Investigation Unit on Gulf War illnesses. 1998.

Collaboration with the VA Gulf War Veterans Research Advisory Committee. One of the most recent advisory groups on Gulf War veteran health issues has been the VA Research Advisory Committee (RAC) on Gulf War Veterans Illnesses, chaired by Mr. James Binns. VA has been pleased with recent efforts with the RAC to lay the groundwork for improved research on Gulf War veterans' health. VA and the RAC have agreed to several important steps to improve the quality of VA's Gulf War research portfolio. The RAC has recommended scientific experts to serve as research review panel members of a new scientific merit review board. In addition, VA consults with the RAC regarding the relevancy of proposals that have been identified as being fundable. VA and the RAC will also work together to identify researchers who can partner with VA investigators.

VA RESEARCH ON GULF WAR VETERANS' HEALTH

VA's Office of Research and Development (ORD) early on recognized that while there were few visible casualties associated with the 1991 Gulf War, many individuals returned from this conflict with unexplained medical symptoms and illnesses. To date, VA, DoD and the Department of Health and Human Services (HHS) have funded a total of 330 projects pertaining to the health consequences of military service in the Gulf War, as described in Annual Reports to Congress on Federally Sponsored Research on Gulf War Veterans' Illnesses. Although the causes and successful treatment of GWVI remain illusive VA's ORD has committed to continued funding of relevant research in this area.

In addition, the Institute of Medicine recently announced (in a report described in more detail later) that Gulf War and other combat veterans may be at increased risk for amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease) as a result of their service. Accordingly, VA's ORD is supporting a research portfolio composed of studies dedicated to understanding chronic multi-symptom illnesses, long-term health effects of potentially hazardous substances to which Gulf War veterans may have been exposed to during deployment and conditions and/or symptoms that may be occurring with higher prevalence in Gulf War veterans, such as ALS, multiple sclerosis and brain cancer.

While VA, DoD and HHS funds its Gulf War research independently, each closely coordinates its efforts with the others to avoid duplication of effort and to foster the highest standards of competition and scientific merit review for all research on illnesses in Gulf War veterans. The Research Subcommittee of the Deployment Health Work Group, which is a component of the VA/ DoD Health Executive Council, currently conducts this coordination. HHS participates in both the Deployment Health Work Group and its Research Subcommittee.

ALS RISK AMONG VETERANS

ALS is a rare, progressive and nearly always fatal disease of the nervous system. About 5 to 10 percent of cases appear to be inherited but the cause of the remaining 90 to 95 percent of cases is not known. Although certain environmental exposures have been considered as potential causes of ALS, none have been clearly tied to this disease.

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In December 2001, based on pre-publication announcements from two studies suggesting that Gulf War veterans were at greater risk for ALS, VA announced that it would explore options for compensating veterans who served in the Gulf War and who subsequently develop amyotrophic lateral sclerosis (ALS). VA in 2001 implemented a policy of referring all Gulf War ALS claims to VA's Central Office for special review.

More recent scientific publications suggest that all veterans may be at greater risk of developing ALS. A 2005 study published in the journal Neurology (Weisskopf et al.) evaluated ALS risk among veterans from World War 2, and the Korean and Vietnam Wars, and reported as a group these veterans were at significantly greater risk for ALS compared to civilians. The two studies that supported VA's ALS policy for Gulf War veterans were published in 2003, and also suggested that veterans from the 1991 Gulf War were at similarly greater risk for ALS (Horner et al., Haley).

In response to the suggestion that all veterans might be at an increased risk of ALS, in May 2005, VA contracted with the NAS/IOM to evaluate the scientific basis of all relevant studies. In their November 10, 2006, report the IOM committee concluded that although there are significant limitations to these studies, there is "limited and suggestive evidence of an

association between military service and later development of ALS."

What the IOM Found. Following a thorough review of relevant scientific literature, the IOM committee in their November 2006, report identified one "high-quality cohort study that adequately controlled for confounding factors and reported a relationship between serving in the military and later developments of ALS" (the Weisskopf study). They also found "three related studies [that] supported the association" but which were of variable quality (which included the Gulf War veteran studies).

They concluded, "On the basis of its evaluation of the literature, the committee concludes that there is limited and suggestive evidence of an association between military service and later development of ALS." This is the IOM's weakest positive category of association for a health effect. However, the committee concluded, "[a]lthough the study has some limitations . . . overall it was a well-designed and well conducted study. It adequately controlled for confounding factors (age, cigarette use, alcohol consumption, education, self-reported exposure to pesticides and herbicides, and several main lifetime occupations)."

A VA Task Force consisting of the Under Secretaries for Health and for Benefits, the OGC, and the DAS for Policy and Planning was established to review the new IOM report.

VA Research on ALS. Although presently, there is no effective treatment for ALS, ORD currently supports a broad research portfolio dedicated to understanding the cause(s) and treatment for this devastating disease. Recent advances in neurological research may allow for the development of strategies to promote the restoration of nerve function. The development of novel strategies and technologies for the development and delivery of therapeutics for ALS patients remains an important goal in ALS research. ORD-funded projects are directed towards improving our understanding of the continuum of the development, progression, treatment and prevention of ALS."

Several VA investigators are conducting research on ALS as it relates to military service during the first Gulf War. This work includes identification of biological markers to identify cases of ALS, examination of the effects of pesticides and insecticides used during the Gulf War on the progression of ALS and examination of the prevalence of ALS in Gulf War veterans. One project is examining the overall and cause-specific mortality risk of ALS, multiple sclerosis or brain cancer in a group of more than 620,000 Gulf War veterans and assessing the demographic, military and in-theater exposure characteristics associated with the risk of deaths from these diseases.

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VA researchers are also studying new ways to selectively increase the ability of therapeutic agents to enter the brain and spinal cord without compromising the blood brain barrier. While this barrier protects the central nervous system from harmful agents, it also limits the ability of many therapeutic agents to enter the brain.

VA investigators have ongoing research projects studying the use of stem cell transplants as a means to restore lost function following the loss of neurons associated with ALS, Alzheimer's disease, Parkinson's disease, spinal cord injury and stroke. Stem cells derived from neurons, as well as from hematopoietic (blood) cells, are being studied. It is hoped that these stem cells will mature into adult neurons and replace damaged neurons. In addition, VA investigators are examining gene therapy to deliver growth factors and other small molecules needed for regeneration and/or protection of the brain and spinal cord.

VA investigators are also examining the use of a neuromotor prosthesis to enhance communication and increase independence for veterans suffering from ALS. A neuromotor prosthesis is a brain-computer interface that uses an electrode that picks up brain signals and sends them to a computer for decoding. The brain signals are translated into commands to power electronic or robotic devices, or to communicate via word processing, e-mail or the internet. VA researchers have already demonstrated the potential usefulness of this technology in an ALS patient and are developing multi-site studies designed to improve this technology and improve the lives of individuals suffering from this disease and their families.

ORD also supports a national registry of veterans with ALS to identify, as completely as possible, all veterans with ALS and to collect data for studies examining the causes of ALS. The registry is designed to track the health status, collect DNA samples and clinical information and provide a mechanism for VA to inform veterans with ALS about research studies for which they may be eligible to participate. The registry will provide VA with a valuable mechanism for involving veterans in clinical trials and other studies that may yield improved outcomes for ALS. In addition, data gathered as part of the registry has the potential to benefit not only veterans, but also the larger community of individuals with ALS.

Other exciting ALS projects supported by ORD include a 15-site clinical trial to determine the tolerability and efficacy of sodium phenylbutyrate as a new therapy for ALS, and a study examining a compound that has been shown to delay the onset of ALS symptoms in animal models of the disease. Finally, ORD supports a cooperative effort to collect and store highquality biological specimens donated by veterans diagnosed with ALS for use in biomedical research.

Anthrax Vaccine Research. ORD supports a study utilizing state of the art technology to investigate and characterize the response of human cells to anthrax vaccination and other agents. This study represents a novel approach to identifying underlying mechanisms operating in specific cell populations which are influenced in response to exposure to anthrax vaccination. It is hoped that this study will disclose biological processes that may improve our understanding of the illnesses affecting Gulf War veterans.

LESSONS LEARNED

VA developed a wide range of health care and research programs to benefit veterans of the 1991 Gulf War. Lessons learned from this process have provided significant benefits to new combat veterans returning today from Southwest Asia. Both groups of combat veterans - those who served in the 1991 Gulf War and those who are serving in OEF and OIF, remain a high priority for VA. This issue of a possible increased risk for being diagnosed with ALS for all service members remains a large concern for VA. In response, VA has initiated new research on this possibility, and is considering how to respond to findings of the recent IOM report on this issue.

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THE JOURNAL OF NERVOUS AND MENTAL DISEASE
Vol. 147, No. 6

Printed in U.S.A.

PSYCHOLOGICAL TESTING OF CEREBRAL MALARIA PATIENTS

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The performance of nine patients with cerebral malaria on a battery of psychological tests, administered while they were ill and again when they recovered, was contrasted with the performance (while ill and recovered) of a matched group of nine patients with malaria alone. Results indicated that the cerebral malaria patients while ill suffered characteristic impairments in several aspects of cognition (*e.g.*, in recent memory, visual motor functioning and psychomotor speed) suggestive of organic dysfunctioning, which were not present in patients with malaria alone. Upon recovery, no measurable organic residual was found.

Falciparum malaria is a frequently encountered illness among U. S. troops in South Vietnam. A cerebral syndrome is a well recognized complication of this type of malaria and our experience with the clinical manifestations of cerebral malaria has been previously reported (2, 4). The clinical signs varied but were broadly divided into five groupings: disturbance of consciousness, acute organic mental syndrome, movement disorders, focal neurological signs and acute personality changes. Nineteen cases of cerebral malaria were diagnosed during a 10-month period at the 93rd Evacuation Hospital, Long Binh, South Vietnam, and nine of these served as subjects (*Ss*) in this investigation.

The present study was designed to measure more precisely, by means of a psychological test battery, the effects of cerebral malaria on intellectual functioning. The tests selected were those found sensitive to intellectual change in previous research: the Wechsler Adult Intelligence Scale (WAIS) (15), the Wechsler Memory Scale (WMS) (14), the Bender Motor Gestalt Test (1, 7) and the Rorschach Test (11). Review of the medical and psychological literature revealed that cerebral malaria patients had never before been examined with such instruments. Testing seemed indicated to provide answers to three questions. 1) Despite the different clinical manifestations of the illness listed above, are there common impairments in intellectual functioning? 2) If there are common impairments, are they sufficiently distinct to be of clinical utility in differentiating cerebral from noncerebral malaria in borderline cases? 3) Is there any residual organic brain damage? Generally it has been stated that survivors of cerebral malaria are free of residual disability (6, 12), but actual measurement of intellectual functioning has not been made.

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The authors gratefully acknowledge the assistance of Major John A. Bowman and Specialists Bennie Stover, John Posh and Robert Quick.

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METHOD

SUBJECTS

Eighteen soldiers hospitalized at the 93rd Evacuation Hospital, Long Binh, South Vietnam, served as *Ss*. Nine were independ-

TABLE 1

Mean Values on Seven Matching Variables of Malaria and Cerebral Malaria Groups, with t tests Comparing the Means

Matching Variables	Malaria	Cerebral Malaria	*t*
Age	21.11	22.56	0.66
Military rank	3.56	3.89	0.60
FSIQ upon discharge	104.44	101.67	0.58
Years of schooling[a]	10.78	11.62	1.24
Days afebrile	3.22	3.22	0.00
Days to retest	6.56	8.33	1.37
Number of difficulties reported during youth[a]	7.44	1.75	4.55[b]

[a] Cerebral malaria group $N = 8$.
[b] Significant at $<.001$ level.

ently diagnosed[4] by the hospital neurologist (RBD) as cases of cerebral malaria (CM group), and the other nine comprised a matched group of patients with malaria alone (M group). The basis for the matching was similarity of temperature pattern, though subsequent analysis revealed that *S*s were well matched on several other parameters.

PROCEDURE

All *S*s were first tested approximately 3 days after their fever had remitted, *i.e.*, after 3 consecutive days of fever below 102°F. (They were not tested at the peak of their illness because of gross incapacitation and the possible confounding effects of high temperature on test performance.) At that time one of the psychology technicians administered the WAIS and the Bender Test, and the hospital psychologist (AJK) administered the WMS and the Rorschach. Initially the technicians were naive with respect to the purposes of the study, but about halfway through they inadvertently discovered that they were testing malaria and cerebral malaria patients. However, they did not know the direction of the anticipated results, so that conscious manipulation of data was not possible. The fact that one of the authors administered two of the test instruments while aware of *S*s' classification is clearly a flaw in design. This arrangement was unavoidable because he was the only psychologist in South Vietnam. (The consistent pattern of results from all four tests suggested that this flaw did not significantly alter the findings.)

All *S*s were reexamined with the same four instruments just prior to scheduled discharge from the hospital, approximately 7 days after initial testing. Thus each *S* was tested twice—once while ill and again when recovered. At various times during hospitalization, each *S* also received the Minnesota Multiphasic Personality Inventory (MMPI) and a medical-social questionnaire based on Wells and Ruesch (16).[5] These instruments were included to ascertain if the CM and M groups were matched with regard to several measures of personality and background.

RESULTS AND DISCUSSION

MATCHING PROCEDURE

Table 1 shows that there are no significant differences between the M and CM groups on six of the seven matching variables: age, rank, full scale IQ upon hospital discharge, years of schooling number of consecutive days afebrile (temperature below 102°F) when first examined, and number of days to retest. The fact that the M group reported significantly more disturbance during youth (*e.g.*, having been in many fights, having had trouble in school) can probably be understood as an attempt to exaggerate pathology, in order to increase the likelihood of being medically evacuated to the United States. (The patients with cerebral malaria were aware that their more serious condition would necessitate evacuation.)

This interest was also reflected in the contrasting MMPI scores (Table 2) of eight *S*s

[4] The diagnostic criteria utilized are described elsewhere (4).

[5] A copy of this questionnaire is available from the senior author on request.

TABLE 2

Mean MMPI Scores for Malaria and Cerebral Malaria Groups, with t Tests Comparing the Means

Scale	M	CM	*t*	Scale	M	CM	*t*
L	3.25	5.50	2.18[a]	Pa	10.62	7.62	1.20
F	9.50	2.62	2.89[a]	Pt	28.00	26.00	0.65
K	11.25	18.75	4.52[b]	Sc	28.62	25.88	0.73
Hs	12.62	14.75	1.29	Ma	24.38	18.88	4.70[b]
D	20.50	21.50	0.37	Si	27.75	23.75	0.76
Hy	17.38	21.75	1.95[c]	A	55.12	40.75	3.75[d]
Pd	27.00	23.25	1.34	R	45.62	52.88	2.09[c]
Mf	22.50	17.88	2.01[c]	Es	48.75	58.38	2.63[a]

[a] $p < .05$.
[b] $p < .001$.
[c] $p < .10$.
[d] $p < .01$.

in the CM group and eight *S*s in the M group. (One *S* in each group failed to complete the MMPI.) *S*s with cerebral malaria scored significantly higher on the L, K and Es scales ($p < .05$, $p < .001$ and $p < .05$, respectively), and suggestively higher on the Hy and R scales ($p < .10$). This pattern suggests that the CM group was trying to appear in the most socially acceptable light, to convey normality and freedom from symptoms and to indicate that their ego functioning was intact. The suggestive elevations on Hy and R imply some use of repressive defenses. In contrast, the malaria *S*s scored significantly higher on the F, Ma and A scales ($p < .05$, $p < .001$ and $p < .01$, respectively), and suggestively higher on Mf ($p < .10$). This pattern seems to represent an attempt to exaggerate emotional illness and psychological distress. (Masculine role identification and feelings of euphoria are emphasized, perhaps to deny the physical aspects of their illness.)

Thus, in terms of both the social history and personality inventory, the malaria group seemed to wish to appear impaired psychologically, whereas the CM group sought to affirm complete recovery. The effect of this situational variable on the questionnaire and personality test was interesting in itself, although our primary concern was that such motivations on the part of the M group not affect performance on the four test instruments. Our subjective impression was that the M group did not attempt to perform more poorly on the test battery. This impression was supported by the obtained results—the M group scored higher on almost every performance measure.

The groups did vary in two respects: amount of medication and amount of staff interest and attention. Although the additional medication that the CM group received was not of the type that would affect mental functioning, a more perfectly controlled experiment would require identical medication for both groups. This control was neither possible under field conditions nor in the best medical interest of the patients. The effect of greater staff interest in the cerebral malaria patients is difficult to quantify. It apparently did not enhance performance, since the CM group almost never performed at higher levels than the M group. Generally we feel that excellent matching was obtained, within the limitations of field experimentation.

WECHSLER ADULT INTELLIGENCE SCALE

With the exception of the similarities subtest, there were no significant effects of either condition (malaria *vs.* cerebral malaria) on degree of health (ill *vs.* recovered) on the six verbal subtests of the WAIS. A two-way fixed effects analysis of variance

TABLE 3

Mean Scores on WAIS Variables of Malaria and Cerebral Malaria Groups, while Ill and when Recovered, with F Ratios Comparing Performances

Variable	Group	Ill	Recovered	F_a M *vs.* CM	F_h Ill *vs.* Recovered	F_i
Information	M	9.00	9.56	0.28	0.70	0.01
	CM	9.33	10.00			
Comprehension	M	8.78	10.22	0.06	3.46[a]	0.06
	CM	8.78	9.89			
Arithmetic	M	9.89	11.00	0.54	2.48	0.28
	CM	8.56	10.78			
Similarities	M	8.56	10.44	0.38	5.70[b]	0.05
	CM	9.11	10.89			
Digit span	M	9.22	9.89	1.06	2.20	0.64
	CM	7.44	9.67			
Vocabulary	M	9.67	9.67	0.09	0.09	0.09
	CM	9.33	9.67			
Verbal IQ	M	96.33	101.78	0.17	4.50[b]	0.17
	CM	93.67	101.78			
Digit symbol	M	7.78	9.56	2.72	20.30[c]	0.98
	CM	6.44	9.22			
Picture completion	M	10.11	11.67	1.15	6.04[b]	0.10
	CM	9.11	11.11			
Blocks	M	9.56	10.33	0.36	4.41[b]	1.10
	CM	8.33	10.67			
Picture arrangement	M	10.56	11.44	3.82[a]	1.15	0.00
	CM	8.78	9.78			
Object assembly	M	9.22	13.00	2.96[a]	11.39[c]	1.01
	CM	8.55	10.67			
Performance IQ	M	96.11	107.44	3.14[a]	10.75[c]	0.07
	CM	88.44	101.78			
Full scale IQ	M	95.78	104.44	1.36	8.73[d]	0.10
	CM	90.89	101.67			

[a] $p < .10$.
[b] $p < .05$.
[c] $p < .001$.
[d] $p < .01$.

(5) performed for each of the verbal subtests separately revealed that only for the similarities subtest was there a significant overall finding—a difference in performance while ill as compared with performance when recovered ($F = 5.70$, $p < .05$). As indicated by an insignificant interaction ($F = .05$) and subsequent t tests,[6] this difference occurred in both groups and seems to represent a simple practice effect (Table 3). Overall verbal IQ was also significantly different while ill and when recovered ($F = 4.50$, $p < .05$). The insignificant interaction ($F = .17$) and subsequent significant t tests suggested that both groups improved through simple practice.

Following Wechsler (15, p. 217) some deficit in arithmetic, similarities and digit span was anticipated for the CM group while ill, but was not found. Our findings were more like those of Ladd (10), who noted no significant difference on any verbal subtest, between brain-damaged and neurotic patients. Another explanation for the absence of the anticipated findings was the very small sample size in the present study. As expected, information, comprehension and vocabulary were not affected by condition or degree of health.

In contrast to the verbal subtests, all

[6] Copies of all t test computations are available from the senior author upon request.

TABLE 4

Mean Scores on WMS Variables of Malaria and Cerebral Malaria Groups, while Ill and when Recovered, with F Ratios Comparing Performances

Variable	Group	Ill	Recovered	F_c M *vs.* CM	F_h Ill *vs.* Rec.	F_i
Information	M	5.22	5.44	0.03	0.45	0.03
	CM	5.22	5.33			
Orientation	M	4.33	4.78	2.13	8.51[a]	0.96
	CM	3.78	4.67			
Mental control	M	5.33	7.22	0.44	4.60[b]	0.14
	CM	5.11	6.44			
Logical memory	M	6.94	8.89	3.91[c]	6.53[b]	0.75
	CM	3.67	7.61			
Digits	M	10.44	10.78	0.61	3.14[c]	1.81
	CM	8.78	11.22			
Visual memory	M	6.56	9.67	0.24	8.61[a]	0.06
	CM	6.78	9.00			
Paired associates	M	16.44	19.33	3.80[c]	9.40[a]	0.29
	CM	13.61	17.72			
Memory quotient	M	86.78	104.22	3.33[c]	17.93[d]	0.32
	CM	75.44	98.22			

[a] $p < .01$.
[b] $p < .05$.
[c] $p < .10$.
[d] $p < .001$.

performance subtests individually, as well as overall performance IQ, did show significant effects of condition or degree of health. Of primary interest here were the differences between the M and CM groups, when both were ill. F values were suggestive ($p < .10$) of differences between the groups on picture arrangement, object assembly and performance IQ, and near suggestive on digit symbol. A series of one-tailed t tests showed that the direction of differences was consistently such that the CM group performance was inferior, yet the difference was significant only for the digit symbol subtest ($t = 1.91$, $p < .05$). When the groups recovered, the difference between groups was no longer significant ($t = .47$). (There were no significant differences between the groups when recovered on any subtest.)

The significant impairment of the CM group while ill on digit symbol is certainly consistent with the cognitive impairments of organic patients described by Wechsler (15), and also found by Ladd (10). That the effects are less marked for the other performance subtests in the present study is probably due to the small sample size. Certainly the direction of the obtained results suggests common impairment for cerebral malaria patients, and the fact that there are no significant differences when both groups have recovered suggests that there is no organic residual.

WECHSLER MEMORY SCALE

Table 4 shows that there were suggestive overall differences ($p < .10$) between the two groups on logical memory ($F = 3.91$), paired associates ($F = 3.80$) and overall memory quotient ($F = 3.33$). Subsequent one-tailed t tests showed that the direction of differences was such that the CM group performance was significantly inferior ($p < .025$) when both groups were ill ($t = 2.37$, $t = 2.18$ and $t = 2.25$, respectively). When both groups recovered, no significant differences between their performances emerged, for these or the other five measures.

The significant differences found between the groups while ill was consistent with the expected pattern of cerebral dysfunctioning described by Wechsler (14) and also noted in several more recent studies (3, 8, 9). The

TABLE 5

Mean Scores on Bender Gestalt Test Tachistoscopic and Copy Phases of Malaria and Cerebral Malaria Groups while Ill and when Recovered, when Scoring is Done by Experienced and Inexperienced Scorers Using the Hain Method

Scorer	Administration	Group	Ill	Recovered	F_c M *vs.* CM	F_h Ill *vs.* Recovered	F_i
Experienced	Tachistoscopic	M	10.11	3.78	15.32[a]	36.39[a]	0.61
		CM	15.78	7.56			
	Copy	M	5.56	4.33	0.82	3.70[b]	0.46
		CM	7.11	4.56			
Inexperienced	Tachistoscopic	M	10.33	4.00	4.79[c]	12.94[d]	0.74
		CM	12.22	8.33			
	Copy	M	6.00	5.44	0.38	1.94	0.70
		CM	7.44	5.22			

[a] $p < .001$.
[b] $p < .10$.
[c] $p < .05$.
[d] $p < .01$.

fact that mental control, digits and visual memory were not affected in a systematic way may again be due to the small sample size.

With the exception of the information subtest, all subtests showed a significant or suggestive difference in performance while ill as compared with performance when recovered. Subsequent t tests showed that this improvement was present in both groups and represented a simple practice effect.

The WMS results indicate that there is a common impairment in the memory functioning of the CM group as compared with the M group. Upon recovery there are no significant differences between groups, suggesting that there is no organic residual.

BENDER MOTOR GESTALT TEST

Seventy Bender Motor Gestalt Test protocols were scored blind by an experienced scorer (AJK), and also by an assistant unfamiliar with the test (inexperienced scorer). The method employed was that developed by Hain (7). (There were four protocols for each *S:* one from the 5-inch tachistoscopic presentation phase while ill, one from the copy phase while ill, and one from each phase obtained when *S* recovered. Two protocols were lost, leaving a total of 70 rather than 72.) The results of the scoring are presented in Table 5.

We note that for both experienced and inexperienced scorers, there were significant differences between the CM and M groups for the tachistoscopic presentation phase ($F = 15.32$, $p < .001$ and $F = 4.79$, $p < .05$, respectively). Subsequent one-tailed t tests showed that Bender protocols, when scored by the experienced scorer, revealed marked differences between CM and M groups both while ill ($t = 3.37$, $p < .005$) and when recovered ($t = 2.25$, $p < .025$). For the inexperienced scorer the two groups were statistically distinguishable only when recovered ($t = 1.98$, $p < .05$). (This finding was unexpected and will be discussed below.) Table 5 and subsequent t tests also indicated that both groups showed significant improvement on retesting (for both scorers). For the copy phase, Table 5 and subsequent t tests showed that there were no significant effects on Bender Test performance of either condition or degree of health (for both scorers).

These results suggest that Hain's scoring system is quite effective in discriminating between the CM and M groups and in detecting improvement in both groups, at least for the tachistoscopic presentation.

(As might be expected, the method is more effective with a more experienced scorer.) The significantly higher scores of the CM group suggest that they perform much like the brain-damaged group in Hain's study. (The lack of discrimination for the copy phase may be due to the use of a tachistoscopic phase first; Hain's method was based on the use of a copy phase alone.)

The fact that the two groups were readily distinguished on the tachistoscopic phase *when recovered* suggested that residual organicity was present in the cerebral malaria patients. To investigate this possibility, eight judges made global ratings of the protocols obtained when both groups recovered.[7] (Also protocols obtained when both groups were ill were rated, the order of rating the two sets of protocols being randomized.) For each *S*, judges were given both the tachistoscopic and copy phase protocols. They were asked simply to give a global impression of the probability of organic dysfunctioning, on a four-point scale. Their ratings were then dichotomized into "organicity" (ratings of very probable and probable) and "no organicity" (ratings of possible and no organicity). It was hypothesized that if residual organicity were present, the judges would be able to discriminate successfully between the protocols of the CM and M groups. Tolor and Schulberg in their classical review have indicated that organically impaired groups can be discriminated from comparable nonorganic groups by the method of global ratings (13, p. 136).

The results of these ratings are presented in Table 6. They show that not one of the eight raters can discriminate to a statistically significant extent between the CM and M group protocols obtained when both groups recovered. Only two raters could distinguish

[7] Judges were obtained from the Psychology Service, Letterman General Hospital, San Francisco, and the authors gratefully acknowledge the assistance of the judges, and the Chief Psychologist, LTC Richard Cook.

TABLE 6

Number of Correct Judgements of Organicity from Bender Protocols by Experienced, Semiexperienced and Inexperienced Raters

p values represent the probability that the number of correct judgements is greater than expected by chance alone.

Experience	Rater	Protocol	Group I[a]	Protocol	Group II[b]
E	A	12	$p = .071$	10	$p = .408$
E	B	12	$p = .071$	12	$p = .120$
E	C	11	$p = .165$	11	$p = .241$
S-E	D	12	$p = .071$	08	$p = .408$
S-E	E	12	$p = .071$	07	$p = .241$
I	F	13	$p = .024$	11	$p = .241$
I	G	10	$p = .313$	10	$p = .408$
I	H	07	$p = .313$	12	$p = .120$

[a] $N = 17$; 8 CM patients and 9 M patients, while ill.

[b] $N = 18$; 9 CM patients and 9 M patients, when recovered.

the protocols at a level even approaching suggestive significance ($p = .120$). On the other hand, a majority of the raters were able to distinguish the protocols of the CM and M groups when both were ill. Rater F correctly identified 13 of the 17 protocols ($p = .024$) and raters A, B, D and E, 12 of 17 ($p = .071$). (It is of passing interest that level of experience did not seem to affect ratings strongly. The experienced raters had been using the Bender Test for more than 5 years, the semi-experienced 1 to 5 and the inexperienced had almost no acquaintance with it, yet it was one of the inexperienced raters who discriminated the two groups most accurately when both were ill.)

The fact that the raters cannot distinguish the protocols of the two groups when recovered supports the concept of the absence of residual organicity. The presence of a temporary organic brain syndrome is suggested by the consistent discrimination between the two groups when ill, by these same raters. The fact that the scoring method did distinguish between the performances of the two groups when healthy suggests that this method may tap an extremely subtle form of organic dysfunction-

TABLE 7

Mean Scores on Rorschach Variables of Malaria and Cerebral Malaria Groups, while Ill and when Recovered, with F Ratios Comparing Performances

Variable	Group	Ill	Recovered	F_c M *vs.* CM	F_h Ill *vs.* Recovered	F_i
R	M	9.78	10.00	3.87[a]	0.03	0.00
	CM	7.89	8.00			
W	M	7.78	7.56	8.61[b]	0.11	0.00
	CM	5.78	5.56			
D	M	1.89	2.22	0.01	0.23	0.01
	CM	2.00	2.22			
F	M	3.89	2.89	1.72	0.25	1.72
	CM	3.89	4.33			
ΣC	M	1.39	1.39	3.76[a]	0.07	0.05
	CM	0.83	0.67			
M + 1/R	M	.208	.262	2.24	0.06	0.50
	CM	.342	.314			
T/R	M	20.00	15.04	0.42	1.08	0.07
	CM	16.00	13.60			
TT/C	M	37.84	29.04	5.61[c]	4.72[a]	0.05
	CM	28.32	21.23			

[a] $p < .10$.
[b] $p < .01$.
[c] $p < .05$.

ing, which may not always be clinically significant.

RORSCHACH TEST

A series of eight F tests (Table 7) indicated that there were four significant or suggestive overall differences between the two groups on Rorschach variables presumed to be sensitive to organic dysfunctioning. The variables selected were based on the work of Reitan (11). Subsequent one-tailed t tests showed that the significant difference ($F = 5.61$, $p < .05$) between groups on mean total time per card (TT/C) and the suggestive differences between groups on total number of responses (R) and the weighted sum of the color responses (ΣC) were not related to significant or suggestive differences when both groups were ill or when recovered. Subsequent one-tailed t tests for the significant finding ($F = 8.61$, $p < .01$) regarding the number of whole responses (W) showed that the direction of differences was such that the CM group performance was significantly inferior only when the groups were ill ($t = 2.33$, $p < .05$).

This finding was consistent with one of Reitan's results—he found that W+1 was significantly lower in his brain-injured group, as compared with the controls. The fact that no other significant differences between groups were found in the present study may be due to our very small sample size ($N = 18$) as compared with his ($N = 192$). Another possible factor was the reluctance of all our *S*s to produce many Rorschach responses. This greatly reduced the number of scorable determinants.

Although we have only one significant finding for the Rorschach Test, that finding is consistent with a possible cognitive impairment in the CM group while ill, which is no longer present when they recover.

CONCLUSIONS

Our results showed common impairments in the intellectual functioning of cerebral malaria patients while ill, as compared with the performance of a matched group of malaria patients without cerebral involvement. These impairments were manifested in the areas of recent memory (particularly recall of paragraphs and paired associates), psychomotor speed, visual motor integration and visual organization. Impairments of this type may be conceptualized as re-

flecting cerebral dysfunctioning. The true extent of disability during the height of illness was not measured because extreme restlessness, obtundation or even coma made testing impossible until some recovery had begun.

The small number of *S*s in the present study prevents us from confidently stating cutting scores on various tests to determine definitively cerebral involvement in malaria cases. However, low scores on the following tests and measures, in the context of preservation of functioning on the other tasks of the test battery, is certainly suggestive of cerebral malaria: 1) WMS memory quotient, 2) WMS logical memory, 3) WMS paired associates, 4) WAIS digit symbol, 5) tachistoscopic phase of the Bender Test, scored with the Hain method, 6) clinical impression of impaired Bender Test performance and 7) number of whole responses on the Rorschach Test.

In addition, we feel that the present results provide substantial evidence of the absence of residual organicity in cerebral malaria. On every test and measure but two, the performance of the cerebral malaria patients when recovered is either indistinguishable from, or superior to, a group of matched malaria patients without cerebral involvement.

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