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Chronic Traumatic Encephalopathy in the Brains of Military Personnel

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ABSTRACT

BACKGROUND

Persistent neuropsychiatric sequelae may develop in military personnel who are exposed to combat; such sequelae have been attributed in some cases to chronic traumatic encephalopathy (CTE). Only limited data regarding CTE in the brains of military service members are available.

METHODS

We performed neuropathological examinations for the presence of CTE in 225 consecutive brains from a brain bank dedicated to the study of deceased service members. In addition, we reviewed information obtained retrospectively regarding the decedents' histories of blast exposure, contact sports, other types of traumatic brain injury (TBI), and neuropsychiatric disorders.

RESULTS

Neuropathological findings of CTE were present in 10 of the 225 brains (4.4%) we examined; half the CTE cases had only a single pathognomonic lesion. Of the 45 brains from decedents who had a history of blast exposure, 3 had CTE, as compared with 7 of 180 brains from those without a history of blast exposure (relative risk, 1.71; 95% confidence interval [CI], 0.46 to 6.37); 3 of 21 brains from decedents with TBI from an injury during military service caused by the head striking a physical object without associated blast exposure (military impact TBI) had CTE, as compared with 7 of 204 without this exposure (relative risk, 4.16; 95% CI, 1.16 to 14.91). All brains with CTE were from decedents who had participated in contact sports; 10 of 60 contact-sports participants had CTE, as compared with 0 of 165 who had not participated in contact sports (point estimate of relative risk not computable; 95% CI, 6.16 to infinity). CTE was present in 8 of 44 brains from decedents with non–sports-related TBI in civilian life, as compared with 2 of 181 brains from those without such exposure in civilian life (relative risk, 16.45; 95% CI, 3.62 to 74.79).

CONCLUSIONS

Evidence of CTE was infrequently found in a series of brains from military personnel and was usually reflected by minimal neuropathologic changes. Risk ratios for CTE were numerically higher among decedents who had contact-sports exposure and other exposures to TBI in civilian life than among those who had blast exposure or other military TBI, but the small number of CTE cases and wide confidence intervals preclude causal conclusions. (Funded by the Department of Defense–Uniformed Services University Brain Tissue Repository and Neuropathology Program and the Henry M. Jackson Foundation for the Advancement of Military Medicine.)

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Since 2001, more than 2.7 million U.S. military personnel have been deployed overseas, often encountering attacks with high explosives such as improvised explosive devices and suicide bombs.[1,2] Owing to advances in protective equipment and military medicine, service members commonly survive these attacks, often without apparent physical wounds. However, survivors frequently report neuropsychiatric symptoms, including chronic headaches, nausea, sleep disorders, concentration and memory problems, mood and behavioral disturbances, substance abuse, and suicidality, which are often diagnosed as postconcussive syndrome or post-traumatic stress disorder (PTSD).[3-7]

Chronic traumatic encephalopathy (CTE) is a disorder with specific neuropathological characteristics that are seen in autopsied brains of decedents with histories of repetitive traumatic brain injury (TBI), particularly impact TBI (defined as injury caused by the head striking a physical object, often from blunt force). CTE has most often been reported after longstanding participation in contact sports, including American football, combat sports (e.g., boxing and wrestling), rugby, hockey, soccer, and even baseball.[8-11] CTE has also been identified in other circumstances of repetitive impact TBI, including domestic abuse, epileptic seizures, and head-banging behavior in persons with autism.[12-14] However, CTE-related lesions have also been reported to be associated with single, moderate-to-severe TBI events.[15,16]

Much of the persistent symptomatology among service members who have been exposed to combat — and specifically those with blast exposure — overlaps with clinical presentations that are attributed to CTE, including cognitive dysfunction, behavioral changes, mood disorders and disturbances, substance abuse, and suicidality.[17] There have been anecdotal reports of pathologic features of CTE in the brains of military veterans, and these reports have led to the suggestion that military service, and blast exposure specifically, is associated with CTE, and that pathological features of CTE may underlie neuropsychiatric outcomes that service members have had after exposure to combat.[18-21] Military service, including that involving blast exposure, has also been incorporated into the National Institute of Neurological Disorders and Stroke diagnostic criteria for traumatic encephalopathy syndrome, which is the proposed clinical diagnosis that corresponds to CTE.[22]

We performed neuropathological examinations of a consecutive series of brains from the collection of the Department of Defense–Uniformed Services University Brain Tissue Repository (www.researchbraininjury.org), a bank dedicated to the study of donated brains from deceased service members.[23] We assessed the incidence of TBI in civilian and military life (including blast exposure), psychiatric disease, alcohol and substance abuse, and suicidality in service members with or without CTE.

Material and Methods

Brain Donation and Decedent History

The Department of Defense–Uniformed Services University Brain Tissue Repository, located in Bethesda, Maryland, receives offers of brain donations for neuropathological examination and research from the next of kin or legal representatives of deceased military personnel. The brain bank is not allowed to solicit brain donations from families of the deceased but instead uses an outreach campaign that includes brochures, media coverage, public service announcements, social media, and word-of-mouth recommendations from other donor families. The current study was conducted according to a protocol approved by the Uniformed Services University institutional review board.

Inclusion of a brain into the brain bank, with a few exceptions, is based simply on the donor's service in the military, whether the person was on active duty or retired from the military at the time of death, and is irrespective of the person's TBI history, neuropsychiatric disease, or other factors. Decedents' histories are gathered retrospectively from semistructured interviews with family or next of kin, from other medical or legal representatives, and from available medical records, including postdeployment questionnaires, clinical records, autopsy reports, and death certificates.

Neuropathological and Immunohistochemical Examinations

Each brain in our study was fixed in 10% buffered formalin for 2 to 5 weeks and, according to our routine neuropathological diagnostic procedures, was examined for gross pathological

findings by one or more neuropathologists. Tissue samples were obtained from regions of the brain chosen at the discretion of the neuropathologist at the time of the initial assessment. An average of 13 (range, 5 to 23) tissue block samples were obtained from different regions containing cerebral cortex from one or both cerebral hemispheres of each brain, including from some or all these locations: the frontal, temporal, parietal, and occipital neocortex; the entorhinal and parahippocampal cortex; the cingulate cortex; and the insular cortex.

Immunohistochemical analysis for phosphorylated tau, which is the essential diagnostic test for CTE, was performed as part of the assessment of each case. Staining for beta-amyloid, amyloid precursor protein, ionized calcium-binding adapter molecule 1 (IBA-1, for microglia), and glial fibrillary acidic protein was performed in each case, and staining for other proteins, such as α-synuclein, ubiquitin, and TDP-43, was performed, as indicated, in some cases; these stains were not considered to be directly informative in the assessment for CTE and thus were not examined systematically for this study and are not reported here. Tissue processing and sectioning, histologic preparation, and immunohistochemical protocols were performed on all samples by means of identical procedures. Samples were prepared with the use of an automated tissue processor (ASP6025, Leica Biosystems). Each tissue block was paraffin-embedded and cut into 5-μm–thick sections for staining and evaluation according to immunohistochemical protocols, including assessment for phosphorylated tau with the use of antibody AT8 (mouse antihuman monoclonal antibody; dilution, 1:2000; epitope retrieval time, 10 minutes) (MN1020, Thermo Fisher Scientific), with the Leica Bond III automated immunostainer with a diaminobenzidine chromogen detection system (DS9800, Leica Biosystems). All slides were digitally scanned with the use of the Aperio AT2 whole-slide scanner (Leica Biosystems) and were stored on a Biolucida (MBF Bioscience) Web-based server. Slides were reviewed either digitally (with the use of Aperio ImageScope [Leica Biosystems]) or with the use of bright-field microscopy (or both).

Assessment for CTE neuropathologic changes was performed by the first and last authors, who were unaware of decedent case histories and interpretations from previous neuropathological assessments, which were made before the publication of the most recent diagnostic criteria for CTE. We assessed brains for CTE by examination of immunohistochemical staining for phosphorylated tau according to published consensus criteria, requiring phosphorylated tau aggregates in neurons, with or without glial tau in thorn-shaped astrocytes, at the depth of a cortical sulcus around a small blood vessel, in deeper cortical layers not restricted to subpial and superficial regions of the sulcus.[24] For the purpose of this study, the presence of a single pathognomonic lesion was sufficient for a diagnosis of CTE.

ASSESSMENT OF TBI EXPOSURES AND CLINICAL CHARACTERISTICS OF THE DECEDENTS

A history of TBI was classified as TBI that had occurred during the decedent's military or civilian life. A military TBI was defined as a TBI that had occurred during activity related to military service and was further classified as either impact TBI or blast exposure. A military impact TBI was defined as a reported TBI from impact head trauma during military service without associated blast exposure. The history was considered positive for blast exposure if it included at least one specific report of blast exposure or if blast exposure was inferred by the nature of the person's military career, such as service in the Special Forces or in explosive ordnance disposal. Civilian TBI was classified either as related to contact-sports participation or as non–sports-related (e.g., motor vehicle accidents or assaults). A contact-sports history was defined as participation in recognized or organized athletic activities that have the potential for TBI resulting from repeated impact with other participants, playing equipment or surfaces, or both.[25]

STATISTICAL ANALYSIS

This study had no prespecified statistical analysis plan. Demographic characteristics, psychiatric diagnoses, alcohol or substance abuse (excluding tobacco), and manner of death are presented descriptively. Relative risks were calculated as the ratio of the percentage of decedents with CTE who had a given type of TBI exposure to the percentage of those with CTE who did not have the exposure. We calculated confidence intervals for relative risks using the Taylor series estimate of the variance, except for

one ratio with a denominator of zero (contact-sports exposure), for which we calculated an exact confidence interval using the IRI command in Stata software, version 15.0 (StataCorp). The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used to infer causal effects.

RESULTS

CHARACTERISTICS OF DECEDENTS AND BRAIN SAMPLES

The brains were obtained from 2013 through 2021 and were consecutive except for brains that were excluded owing to incomplete sampling or staining at the time of review (9 brains), nonmilitary status (5 brains), absence of decedent information (1 brain), or poor specimen condition (1 brain). The neuropathological study included brains from 217 men and 8 women, with an average age of 48.2 years (median, 49; range, 18 to 87) for men and 47.8 years (median, 52.5; range, 20 to 63) for women. The decedents comprised both retired and active-duty members of all military branches; 20 served in the Special Forces, most commonly as Navy SEALs (13 decedents). Race or ethnic group was reported in 199 of the 225 cases; 171 decedents were White, 15 were Black, 8 were Hispanic or Latino, 3 were Asian or Pacific Islander, 1 was Native American, and 1 was biracial (not otherwise specified).

Lesions diagnostic of CTE were found in 10 of 225 cases (4.4%); half the CTE cases had only one pathognomonic lesion, 2 had four lesions, and 1 had five lesions. Two of the brains with CTE (from decedents who were 72 and 87 years of age) had severe neuropathologic changes characteristic of Alzheimer's disease, including widespread neurofibrillary tangles and senile plaques throughout the cerebral cortex, that precluded accurate assessment of the number of CTE-related lesions. The degree of neuropathologic changes characteristic of Alzheimer's disease in these two cases suggested a high likelihood of cognitive impairment or dementia.[26,27]

Demographic and clinical characteristics of the 10 cases of CTE are shown in Table 1. The psychiatric diagnoses in the CTE and non-CTE groups are shown in Table 2. The distribution of CTE cases according to age and photomicrographs of selected CTE cases are shown in Figures S1 and S2 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

MILITARY AND CIVILIAN TBI

A total of 60 decedents (26.7%) had a history of participation in one or more contact sports, most commonly American football (in 27) and combat sports (in 15). Other sports included rugby, hockey, soccer, lacrosse, baseball or softball, basketball, and flag football. One person each was a skateboarder, a competitive skier, a mountain biker, and a bull rider; all of them had associated head injuries.

A total of 44 decedents (19.6%) had one or more civilian non–sports-related impact TBIs from motor vehicle accidents, falls, assaults, and other causes. As a result of civilian non–sports-related impact TBI, 29 decedents (including 7 of the 10 with CTE) had had one or more episodes of loss of consciousness or coma (in 14 decedents), skull injury (in 8), concussion (in 5), post-traumatic mental or cognitive changes or deficits (in 4), post-traumatic seizure disorder (in 3), or intracranial bleeding (in 1) in association with the TBI. One decedent in the CTE group had hereditary hemorrhagic telangiectasia (the Osler–Weber–Rendu syndrome); in the brain of that decedent, the only pathognomonic CTE lesion that was identified was adjacent to the site of a previous resection of a vascular malformation.

Of the 45 decedents with a history of blast exposure, 3 had CTE, as compared with 7 of the 180 decedents without blast exposure (relative risk, 1.71; 95% confidence interval [CI], 0.46 to 6.37) (Table 3). Of the 21 decedents who had a history of military impact TBI, 3 had CTE, as compared with 7 of the 204 decedents without military impact TBI (relative risk, 4.16; 95% CI, 1.16 to 14.91). Among the 44 brains from decedents who had a history of civilian non–sports-related TBI, 8 had CTE, as compared with 2 of 181 brains from decedents without a history of civilian non–sports-related TBI (relative risk, 16.45; 95% CI, 3.62 to 74.79). In all 10 cases of CTE, the decedents had a history of playing contact sports. Of the 60 decedents who had a history that included contact sports, 10 had CTE, as compared with none of the 165 decedents who did not have a history of playing contact sports (point estimate of relative risk not computable; 95% CI, 6.16 to infinity). In the CTE group, the

Table 1. Clinical Characteristics and Exposures in Military Decedents with Chronic Traumatic Encephalopathy (CTE).*

Case No.	Age	Military Branch (Special Forces)	Psychiatric Disorder	Alcohol or Substance Abuse	Traumatic Brain Injury			Contact Sports	Manner of Death	Lesions Related to CTE
					Military Blast	Military Impact	Civilian Non–Sports-Related Impact			
										no. (no. of cortical slides)
1	31 yr	Marines (NR)	Depression	Alcohol abuse	NR	NR	MVA with LOC	American football (high school, multiple concussions), martial arts	Natural	1 (14)
2†	41 yr	Navy (NR)	NR	NR	NR	NR	MVA with LOC	Soccer	Natural	1 (19)
3	44 yr	Navy (SEAL)	PTSD, depression, anxiety	NR	Yes	Yes	Two MVAs, one with LOC	Wrestling, boxing	Suicide	4 (15)
4	46 yr	Navy (SEAL)	NR	Alcohol abuse	Yes	Yes	Assault with LOC, MVA, skydiving accident	American football (high school, college, arena), martial arts	Suicide	5 (13)
5‡	54 yr	Army (NR)	PTSD, depression	Alcohol abuse	NR	NR	Assault with LOC	American football	Suicide	5 (9)
6	57 yr	Navy (NR)	NR	Polysubstance abuse	NR	NR	MVA without LOC	Skateboarding, with associated head injury	Natural	1 (14)
7	57 yr	Marines (NR)	PTSD	Alcohol abuse	NR	NR	NR	American football, basketball, baseball	Natural	1 (14)
8§	59 yr	Air Force (NR)	PTSD, delusional disorder	Alcohol abuse	Yes	Yes	MVA	Competitive skiing, wrestling	Suicide	1 (18)
9¶	72 yr	Navy (NR)	NR	NR	NR	NR	MVA	Boxing with history of knockout	Natural	NA (17)
10‖	87 yr	Navy (NR)	NR	NR	NR	NR	NR	American football (junior high school through military league)	Natural	NA (11)

* All cases involved brains of male service members. LOC denotes loss of consciousness, MVA motor vehicle accident, NA not assessed, NR not reported, and PTSD post-traumatic stress disorder.
† The history included hereditary hemorrhagic telangiectasia (the Osler–Weber–Rendu syndrome), with brain vascular malformation and previous resection. A CTE-related lesion was noted only adjacent to the resection site of a previous vascular malformation.
‡ The assault was associated with chronic post-assault mental changes.
§ The MVA was associated with severe traumatic brain injury (closed head injury and intracranial bleeding). Skiing was associated with multiple head injuries.
¶ The MVA was associated with coma that lasted for 19 hours, temporary anterograde amnesia that lasted for 18 days, and the development of post-traumatic seizure disorder and mild cognitive impairment. The history also included dementia (diagnosed 13 years before death) with progressive cognitive decline. CTE-related lesions could not be quantified owing to severe background neuropathologic change characteristic of Alzheimer's disease.
‖ The history included dementia. CTE-related lesions could not be quantified owing to severe background neuropathologic change characteristic of Alzheimer's disease.

Table 2. Clinical Features in CTE and Non-CTE Groups.*

Variable	CTE (N=10)	Non-CTE (N=215)	Total (N=225)
Age at death — yr	54.8±16.0	47.9±13.9	
Psychiatric disorder — no. (%)	6 (60)	82 (38)	88 (39)
PTSD — no. (%)	5 (50)	47 (22)	52 (23)
Alcohol or substance abuse — no. (%)	6 (60)	91 (42)	97 (43)
Suicide — no./total no. (%)	4/10 (40)	45/206 (22)†	49/216 (23)

* Plus–minus values are means ±SD. CTE was identified in 10 of 225 brains that underwent autopsy (4.4%; 95% confidence interval, 2.2 to 8.0).
† Data on cause and manner of death were available in 206 of 215 non-CTE cases.

most common contact sports were American football (in 5 cases, including 3 in combination with other contact sports) and combat sports (in 5 cases, including 3 in combination with other contact sports).

PSYCHIATRIC DISORDERS, ALCOHOL AND SUBSTANCE ABUSE, AND SUICIDALITY

A total of 88 decedents (39.1%) had a reported history of at least one psychiatric disorder, most commonly PTSD (in 52 decedents), depression (in 44), or anxiety (in 25) (Table 2). Of the decedents with CTE, 6 (60%) had received at least one diagnosis of a psychiatric disorder, as compared with 82 (38%) of the decedents without CTE; PTSD was the most common diagnosis in both groups. A total of 6 decedents with CTE (60%) had a reported history of alcohol or substance abuse (or both), as compared with 91 of those without CTE (42%).

Data regarding a definitive cause and manner of death were available in 216 cases. Most deaths (124) were from natural causes. There were 49 suicides (22.7%), and 40 deaths (18.5%) were categorized as accidental (including 12 deaths due to drug overdose). The average age at death was 55.4 years in cases of death from natural causes, 37.8 years in the cases of suicide, and 38.5 years in the cases of accidental death. The remaining deaths were by homicide (1 death) or occurred in manners that remained undetermined (2 deaths) after investigation by medical examiners. Suicide was the manner of death in 4 of the CTE cases (40%) and in 45 of the 206 non-CTE cases (22%) in which there was a confirmed cause and manner of death.

DISCUSSION

In our assessment for the presence of CTE in the brains of 225 deceased active-duty and retired military personnel, there was a broad age range among the decedents and various exposures to head injuries sustained in military and civilian settings. We found CTE in 4.4% of the brains, half of which had only one CTE-related lesion, and it is unclear whether those minimal histopathological findings were of clinical significance. Two CTE cases involved the brains of elderly decedents that also had severe neuropathologic changes consistent with Alzheimer's disease, which made interpretation of the extent of CTE pathologic changes and clinical features difficult.

The small number of CTE cases makes the study underpowered to conclude that blast exposure was or was not associated with CTE. However, all decedents who had military-related blast or impact exposures and had CTE also had participated in contact sports that had the potential for head injuries, and in addition often had a history of non–sports-related civilian TBI. The estimates of the relative risk of these two types of civilian exposures with respect to CTE have wide confidence intervals and are unadjusted for multiple comparisons, so no causal conclusions can be drawn; however, the relative risks were numerically higher with civilian exposures than with military exposures.

Few community-based studies have been performed to assess CTE, and most have used brains from banks that focus on aging or neurodegenerative disease, with average ages at death of over 70 years.[25,28,29] In those studies in which a history of contact-sports participation was available, findings of CTE were uncommon in decedents with no history of contact-sports participation. One study reported CTE in 21 of 66 (31.8%) deceased elderly former contact-sports athletes and in none of 198 age-matched controls without contact-sports history.[25] In that study, 35 of the 66 former athletes had served in the military, and there was no significant difference in CTE frequency in the brains of military athletes as compared with nonmilitary athletes. In a convenience sample of 202 brains of former American football players from a brain bank focused on contact sports, CTE was found in

Table 3. CTE and Exposure to Traumatic Brain Injury (TBI) among the 225 Military Decedents.*

Exposure Variable	Total Decedents with Exposure (N=225)	Cases of CTE		Relative Risk (95% CI)
		With TBI Exposure	Without TBI Exposure	
	no. (%)	*no./total no. (%)*		
Military blast	45 (20.0)	3/45 (6.7)	7/180 (3.9)	1.71 (0.46 to 6.37)
Military impact TBI	21 (9.3)	3/21 (14.3)	7/204 (3.4)	4.16 (1.16 to 14.91)
History of contact sports	60 (26.7)	10/60 (16.7)	0/165	Not computable (6.16 to infinity)
Civilian non–sports-related impact TBI	44 (19.6)	8/44 (18.2)	2/181 (1.1)	16.45 (3.62 to 74.79)

* Confidence intervals for risk ratios were calculated with the use of the Taylor series estimate of the variance, except for one ratio (history of contact sports) with a numerator of zero, for which a confidence interval was calculated using the IRI command in STATA statistical software, version 15.0 (StataCorp). The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used to infer effects.

87% of the brains.[30] This included 21% of brains from decedents who only played high school football, 91% from those who played football through college, and 99% of those who played in the National Football League. Although there may be unique circumstances in the military that confer a predisposition to repetitive or severe impact TBI that could lead to CTE, we found only 10 cases of CTE lesions in 225 brains of military personnel. The difference in CTE frequency among football players as compared with the military series reported here may provide information regarding the extent of the problem that CTE represents in the two populations. We did not have data to explore the duration or number of trauma exposures, which makes a comparison of our results with other series of CTE difficult.

High rates of psychiatric disorders, alcohol and substance abuse, and suicide have been found among active-duty and retired military personnel, and these complex problems were represented in our series in proportions that are similar to those in the general military population.[31-35] Because of the small number of cases of CTE in our series, our study was underpowered to explore relationships between CTE and these factors. Moreover, we also could not establish the temporal relationship between these factors and CTE. For example, we cannot confirm or refute whether psychiatric disease developed before or after CTE. Nevertheless, pathologic features of CTE were not found in most of the cases of suicide, alcohol or substance abuse, or psychiatric disease in our series.

This study has limitations. First, gathering accurate TBI history represents a challenge. Some aspects of TBI history in our study, including blast exposure, other military TBI, and both sports and non–sports-related civilian TBI, were obtained retrospectively from next of kin as a primary means of information in many cases and were dependent on the knowledge and recall of those sources. Obtaining accurate military TBI history is also limited by the fact that blast exposure and impact TBI often occur simultaneously from blast winds propelling objects and debris or from the person being thrown by a blast onto a stationary object.[36] Furthermore, certain training exercises are associated with repeated, subconcussive blast exposures (e.g., firing shoulder-mounted rocket ordnances and participating in breaching exercises).[37,38] We attempted to identify blast exposure in our series by using a combination of brains from decedents with positive reported history along with those who we inferred had had blast exposure from the nature of the their military activity (e.g., Special Forces operators and explosive ordnance disposal personnel, who have a high incidence of these exposures). These limitations are potential sources of measurement error.

Our series represents a convenience sample of brains donated by families. There may be acquisition bias that favors TBI history and decedents with psychiatric or behavioral symptoms that may not be representative of the general military community. The brains in this study were also not sampled in a completely uniform way; however, they were sampled extensively, with an average of 13 cortical samples per case, a process consistent with the protocols in other similar CTE studies.[25,28,29] Consensus guidance for CTE diagnosis recommends sampling five sites containing — or often containing — cerebral cortex,[24] which we exceeded. Several donated brains were not analyzed owing to poor preservation or other impediments.

Among 225 brains of deceased military personnel donated to a military brain bank, we found 10 cases of CTE, half of which were characterized by minimal neuropathologic changes. All the decedents with CTE had a history of participation in contact sports, with or without additional civilian impact TBI unrelated to sports. The small number of CTE cases and the wide confidence intervals for relative risk prevent definitive conclusions with regard to associations or causality of blast exposure and CTE.

The views expressed in this article are those of the authors and do not necessarily reflect the views or policies of the Uniformed Services University, the Department of Defense, the U.S. government, or the Henry M. Jackson Foundation for the Advancement of Military Medicine.

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