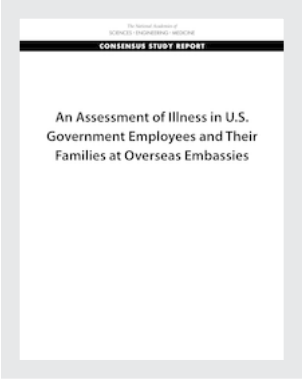

An Assessment of Illness in U.S. Government Employees and Their Families at Overseas Embassies (2020)

DETAILS

76 pages | 8.5 x 11 | PAPERBACK
ISBN 978-0-309-68137-7 | DOI 10.17226/25889

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SUGGESTED CITATION

National Academies of Sciences, Engineering, and Medicine 2020. *An Assessment of Illness in U.S. Government Employees and Their Families at Overseas Embassies*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25889.

An Assessment of Illness in U.S. Government Employees and Their Families at Overseas Embassies

Standing Committee to Advise the Department of State
on Unexplained Health Effects on U.S. Government
Employees and Their Families at Overseas Embassies

David A. Relman and Julie A. Pavlin, *Editors*

Health and Medicine Division

Division on Engineering and Physical Sciences

A Consensus Study Report of

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

THE NATIONAL ACADEMIES PRESS
Washington, DC
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, NW Washington, DC 20001

This activity was supported by Contract 19AQMM19C0090 between the National Academy of Sciences and the Department of State. Any opinions, findings, conclusions, or recommendations expressed in this publication do not necessarily reflect the views of any organization or agency that provided support for the project.

International Standard Book Number-13: 978-0-309-68137-7
International Standard Book Number-10: 0-309-68137-5
Digital Object Identifier: https://doi.org/10.17226/25889

Additional copies of this publication are available from the National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 334-3313; http://www.nap.edu.

Printed in the United States of America

Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2020. *An assessment of illness in U.S. government employees and their families at overseas embassies.* Washington, DC: The National Academies Press. https://doi.org/10.17226/25889

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STANDING COMMITTEE TO ADVISE THE DEPARTMENT OF STATE ON UNEXPLAINED HEALTH EFFECTS ON U.S. GOVERNMENT EMPLOYEES AND THEIR FAMILIES AT OVERSEAS EMBASSIES

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This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We thank the following individuals for their review of this report:

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report nor did they see the final draft before its release. The review of this report was overseen by **Linda A. McCauley**, Emory University, and **Robert F. Sproull**, University of Massachusetts at Amherst. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

Contents

Acronyms and Abbreviations

3-PBA	3-Phenoxybenzoic acid
3T	3 Tesla
ABIT	Acquired Brain Injury Tool
AChE	acetylcholinesterase
CDC	Centers for Disease Control and Prevention
DoD	Department of Defense
DOS	Department of State
DR2	Disaster Research Response
FDA	Food and Drug Administration
FSO	Foreign Service Officer
GAO	Government Accountability Office
GuLF STUDY	Gulf Long-term Follow-up Study
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
IEEE	Institute of Electrical and Electronics Engineers
IPM	Integrated Pest Management
IRB	Institutional Review Board
MED HART	Department of State, Bureau of Medical Services Health Alert Response Team
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MR	magnetic resonance
MRI	magnetic resonance imaging
mTBI	mild traumatic brain injury
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
NTP	National Toxicology Program
OCD	obsessive compulsive disorder
OGA	Office of Global Affairs
OP/Ops	organophosphate/organophosphates
PPPD	persistent postural-perceptual dizziness
RF	radio frequency
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TMS	transcranial magnetic stimulation
U.S.S.R.	Union of Soviet Socialist Republics

Preface

An individual assigned to the U.S. Embassy in Cuba was awakened one night at home in Havana in 2016 by severe pain and a sensation of intense pressure in the face, a loud piercing sound in one ear with directional features, and acute disequilibrium and nausea. Symptoms of vestibular and cognitive dysfunction ensued. A handful of other cases involving colleagues with similar features began that year, and others in the next. Few people were aware of these cases until spring 2017. In addition, the mechanisms and origins were mysterious, and for these and other reasons, there was a delay in recognizing an important cluster of unexplained illnesses, and an early failure to investigate them in a concerted, coordinated, rigorous, and interdisciplinary manner.

In some ways, the problem presented here is an age-old one; that is, how to detect and recognize important anomalies or signals, in a complicated, "noisy" background. Public health systems have grappled with this problem for centuries. In the 1990s, the Centers for Disease Control and Prevention (CDC) conducted population-based surveillance for "unexplained death and critical illness" in persons less than 50 years of age, with features suggestive of infectious cause, at four sites in the United States, and found a surprisingly high incidence of 0.5 cases per 100,000 per year (Hajjeh et al., 2002). The most common clinical presentation was neurologic; a known infectious cause was discovered for only a minority of them; and no obvious relationships among cases were uncovered (Nikkari et al., 2002). But the landscape that countries face today in which the cases in question arise, is an even more complicated one. Not only must governments consider a wide variety of evolving natural causes in a rapidly changing world, but also an increasing threat of disease of deliberate human origin, both accidental and purposeful.

The cases of the Department of State (DOS) employees in Cuba and China have attracted much attention. Among the reasons and ramifications, the clinical features were unusual; the circumstances have led to rampant speculation about the cause(s); and numerous studies, along with the charged political setting, have had consequences for international relations.

The committee was asked by DOS to review the cases, their clinical features and management, epidemiologic investigations, and scientific evidence in support of possible causes, and advise on approaches for the investigation of potential future cases. The committee faced a variety of challenges in responding to these requests (see Section 2). In particular, much of the detail and many of the investigations performed by others were not available to it, either because they are classified for reasons of national security or restricted for other reasons (e.g., internal department deliberations, protected health information, etc.). Thus, the committee had only limited amounts and kinds of information. Despite these challenges, the committee arrived at a number of observations and recommendations, after carefully reviewing the information that was available.

First, the committee found a constellation of acute clinical signs and symptoms with directional and location-specific features that was distinctive; to its knowledge, this constellation of clinical features is unlike any disorder in the neurological or general medical literature. From a neurologic standpoint, this combination of distinctive, acute, audio-vestibular symptoms and signs suggests localization of a disturbance to the labyrinth or the vestibulocochlear nerve or its brainstem connections. Yet, not all DOS cases shared these distinctive and acute signs and symptoms. In fact, the cases are highly heterogeneous. Some patients described only a set of nonspecific, chronic signs and symptoms indicative of disruption of vestibular processing and/or cognition and diffuse involvement of forebrain structures and function, raising the possibility of multiple causes or mechanisms among different patients, as well as for the same patient.

Second, after considering the information available to it and a set of possible mechanisms, the committee felt that many of the distinctive and acute signs, symptoms, and observations reported by DOS employees are consistent with the effects of directed, pulsed radio frequency (RF) energy. Studies published in the open literature more than a half century ago and over the subsequent decades by Western and Soviet sources provide circumstantial support for this possible mechanism. Other mechanisms may play reinforcing or additive effects, producing some of the nonspecific, chronic signs and symptoms, such as persistent postural-perceptual dizziness, a functional vestibular disorder, and psychological conditions.

The committee is left with a number of concerns. First, even though it was not in a position to assess or comment on how these DOS cases arose, such as a possible source of directed, pulsed RF energy and the exact circumstances of the putative exposures, the mere consideration of such a scenario raises grave concerns about a world with disinhibited malevolent actors and new tools for causing harm to others, as if the U.S. government does not have its hands full already with naturally occurring threats. Because the committee was not able to assess specific scenarios involving malevolent actors, one strong suggestion is that follow-up studies on this topic be undertaken by subject-matter experts with proper clearance, including those who work outside the U.S. government, with full access to all relevant information. Second, the committee was concerned about the possibility of future new cases among DOS or other U.S. government employees working overseas, either similar or dissimilar to these, and the ability of the U.S. government to recognize and respond to these cases in a coordinated and effective manner. The next event may be even more dispersed in time and place, and even more difficult to recognize quickly. Toward this end, the committee offers a number of observations, best practices, and recommendations for clinical management, surveillance, and a systematic response in anticipation of future health events. These observations and recommendations should be reviewed and acted on now. It is imperative that the United States recognize and quickly respond to future cases with a well-coordinated, multi-disciplinary, science-based investigation and effective interventions. Finally, the committee is concerned about how best to manage the continuing care of those already affected, and how to strengthen the nation's commitment to the health and well-being of those who serve the country overseas. Both of these priorities need and deserve additional attention and resources.

On a personal note, it was an honor and privilege to work with a wonderful committee and staff at the National Academies of Sciences, Engineering, and Medicine. Every person contributed unique and important insights and ideas. Finally, it was humbling to learn of the commitment and sacrifices made by those who work for DOS and the rest of the U.S. government in difficult and challenging circumstances overseas. It would behoove us all to consider how we can provide greater support.

David A. Relman, *Chair*
Standing Committee to Advise the Department of State on Unexplained Health Effects on U.S. Government Employees and Their Families at Overseas Embassies

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Summary

In late 2016, U.S. Embassy personnel in Havana, Cuba, began to report the development of an unusual set of symptoms and clinical signs. For some of these patients, their case began with the sudden onset of a loud noise, perceived to have directional features, and accompanied by pain in one or both ears or across a broad region of the head, and in some cases, a sensation of head pressure or vibration, dizziness, followed in some cases by tinnitus, visual problems, vertigo, and cognitive difficulties. Other personnel attached to the U.S. Consulate in Guangzhou, China, reported similar symptoms and signs to varying degrees, beginning in the following year. As of June 2020, many of these personnel continue to suffer from these and/or other health problems. Multiple hypotheses and mechanisms have been proposed to explain these clinical cases, but evidence has been lacking, no hypothesis has been proven, and the circumstances remain unclear. The Department of State (DOS), as part of its effort to inform government employees more effectively about health risks at posts abroad, ascertain potential causes of the illnesses, and determine best medical practices for screening, prevention, and treatment for both short and long-term health problems, asked the National Academies of Sciences, Engineering, and Medicine (the National Academies) to provide independent, expert guidance.

The Standing Committee to Advise the Department of States on Unexplained Health Effects on U.S. Government Employees and Their Families at Overseas Embassies faced several challenges in assessing these clinical cases, including lack of access to individual-level health and other information, evolving and changing clinical features over time, and a highly heterogeneous population in terms of the timing and type of clinical symptoms and signs, to include those whose symptoms were only acute, only chronic or both. However, the committee was able to identify distinctive clinical features, consider possible causes, evaluate plausible mechanisms and rehabilitation efforts, and offer recommendations for future planning and responses.

CLINICAL FEATURES

A distinct set of unusual clinical manifestations occurred abruptly in some individuals at the onset of their illness, and the illness became chronic and debilitating for some, but not for all. The most distinctive clinical aspects of the illnesses were the nature of the onset and the initial features: the sudden onset of a perceived loud sound, a sensation of intense pressure or vibration in the head, and pain in the ear or more diffusely in the head. Most individuals reported that the sound or these other sensations seemed to originate from a particular direction and were perceived only when the individual was in a specific physical location. Some also reported sudden onset of tinnitus, hearing loss, dizziness, unsteady gait, and visual disturbances. From a neurologic standpoint, this combination of distinctive, acute, auditory-vestibular symptoms suggests an effect localized to the labyrinth or VIII cranial nerve or its brainstem connections.

Chronic symptoms suffered by many of those affected suggested problems with vestibular processing and cognition, as well as insomnia and headache; these manifestations are more consistent with diffuse involvement of forebrain structures and function, such as cerebral cortex or limbic structures. However, no consistent picture of brain injury emerged from laboratory-based tests of vestibular function. It is possible that these subsequent, more persistent symptoms were caused by sequelae of the same initial insult or that they occurred secondarily as an accommodative response. For those without reports of an acute initial phase, the symptoms

could be from a separate cause or a similar exposure that resulted more exclusively in forebrain dysfunction.

PLAUSIBLE MECHANISMS

The committee found the unusual presentation of acute, directional or location-specific early phase signs, symptoms and observations reported by DOS employees to be consistent with the effects of directed, pulsed radio frequency (RF) energy. Many of the chronic, nonspecific symptoms are also consistent with known RF effects, such as dizziness, headache, fatigue, nausea, anxiety, cognitive deficits, and memory loss. Patient clinical heterogeneity could be due to variability of exposure dosage conditions, differences in interpretation of non-physiological vestibular stimuli, and anatomical differences that could influence individual exposure and/or response.

The committee also considered chemical exposures, infectious diseases and psychological issues as potential causes or aggravating factors. Although some reports suggested that exposure to organophosphates (OP) and/or pyrethroids from insecticide spraying in Havana could be a cause or contributing factor, the committee concluded that this mechanism was not likely because there was no convincing evidence of acute high-level exposures and the clinical histories of affected U.S. Embassy personnel were not consistent with acute OP poisoning. However, as insecticides can increase the risk or severity of adverse outcomes after exposure to a wide variety of physical or psychosocial stressors, the committee cannot rule out subacute or chronic OP and/or pyrethroid exposures as a possible contributing factor to nonspecific chronic symptoms.

Infectious agents known to be prevalent in Cuba at the time of the U.S. Embassy cases and capable of causing neurological manifestations most prominently include Zika, which was epidemic in Cuba in 2016-2017. However, after reviewing the medical and public health literature, the committee found it highly unlikely that Zika was the cause of the constellation of signs and symptoms reported among DOS personnel.

The acute initial, sudden-onset, distinctive, and unusual symptoms and signs are difficult to ascribe to psychological and social factors. However, the significant variability and clinical heterogeneity of the illnesses affecting DOS personnel leave open the possibility of multiple causal factors including psychological and social factors. These factors could exacerbate other causes of illness and cannot be ruled out as contributing to some of the cases, especially some of the chronic symptoms or later in the course of illness in some cases. Finally, the committee concurred with the diagnosis of persistent postural-perceptual dizziness (PPPD), a functional (not psychiatric) vestibular disorder that may be triggered by vestibular, neurologic, other medical and psychological conditions and may explain some chronic signs and symptoms in some patients.

Overall, directed pulsed RF energy, especially in those with the distinct early manifestations, appears to be the most plausible mechanism in explaining these cases among those that the committee considered, along with PPPD as a secondary reinforcing mechanism, as well as the possible additive effects of psychological conditions. The committee cannot rule out other possible mechanisms and considers it likely that a multiplicity of factors explains some cases and the differences between others. In particular, the committee could not be certain that the individuals with only the chronic set of signs and symptoms suffered from the same cause(s) and etiologic mechanisms as those who reported the initial, sudden onset set of signs and symptoms.

REHABILITATION

The committee recommends early evaluation and treatment, a supportive environment, and an interdisciplinary approach for rehabilitation of chronic neurological conditions. Without information on patient-specific treatment approaches and responses, it was difficult for the committee to develop recommendations on specific neurologic rehabilitation alternatives. For those with chronic vestibular symptoms, a diagnosis of PPPD offers a potential avenue for rehabilitative interventions.

FUTURE PREPAREDNESS

Part of the committee's task was to provide advice in anticipation of future threats to DOS personnel and their families' well-being. To that end, the committee proposes a number of recommendations in order to enhance future responses.

Recommendation 1. The Department of State should expand its collection of baseline and longitudinal data and biological specimens from all personnel prior to and during overseas assignments.

The committee believes that there should be routine data collection for all DOS employees on foreign assignments, including collection of whole blood, plasma, and urine, as well as general medical and neurological examinations, and local environmental assessments. The Acquired Brain Injury Tool (ABIT) is a clinical assessment tool currently used pre- and post-deployment to inventory the same neurological, vestibular and auditory symptoms that were identified in DOS personnel in Cuba. However, given that the nature of future events is unknown, it would be wise to revise it and include symptoms beyond those encountered in Cuba and China.

Recommendation 2. The Department of State, with support from the U.S. government, should establish plans and protocols now to enable comprehensive, expeditious public health and research investigations in the future, should a cluster of new cases warrant investigation.

The committee recommends that a response capability be prepared and authorized in advance of the next potential set of cases, so that the necessary collection of information for a proper public health investigation of U.S. embassy employees can be undertaken in a timely fashion and made available immediately.

Recommendation 3. Following the identification of a possible new case cluster, the Department of State should ensure the collection of data critical for an effective investigation.

The committee suggests that DOS utilize an expert panel described in Section 6 to provide advice on the collection of routine medical data. In addition to the collection of data pertaining to individual diplomats, it is critical that additional public health and epidemiological surveillance data be obtained to provide the temporal and geographic context for the health presentation of individuals.

Recommendation 3-A. If research or assessments support the possibility of radio frequency (RF) energy as a cause of illness experienced by some of its employees, the Department of State should train and equip employees with the capability to measure and characterize their exposure to RF energy in real time should the need arise in the future.

Recommendation 3-B. The Department of State should develop a systematic approach for toxicological diagnoses, and a protocol that supports this approach.

Recommendation 4. The Department of State, with support from the U.S. government, should provide for appropriate personnel to identify public health emergencies and activate the necessary response.

DOS should consider a change in policy so that it enables structured medical investigations of affected individuals in a manner that does not preclude, but is separate from private medical care. The National Institutes of Health Disaster Research Response (DR2) Program may serve as a valuable model for a coordinated system-wide research response to public health emergencies. In addition, to facilitate early identification of health threats to Embassy personnel, the committee suggests an expanded role for health attachés**.**

Section 1

Introduction and Charge to the Committee

In late 2016, U.S. Embassy personnel in Havana, Cuba, began to report the development of an unusual set of symptoms and clinical signs. For some of these patients, their case began with the sudden onset of a loud noise, perceived to have directional features, and accompanied by pain in one or both ears or across a broad region of the head, and in some cases, a sensation of head pressure or vibration, dizziness, followed in some cases by tinnitus, visual problems, vertigo, and cognitive difficulties. Other personnel attached to the U.S. Consulate in Guangzhou, China, reported similar symptoms and signs to varying degrees, beginning in the following year. As of June 2020, many of these personnel continue to suffer from these and/or other health problems. Multiple hypotheses and mechanisms have been proposed to explain these clinical cases, but evidence has been lacking, no hypothesis has been proven, and the circumstances remain unclear.

The Department of State (DOS), as part of its effort to inform government employees more effectively about health risks at posts abroad, ascertain potential causes of the illnesses, and determine best medical practices for screening, prevention, and treatment for both short and long-term health problems, asked the National Academies of Sciences, Engineering, and Medicine (the National Academies) to provide independent, expert guidance.

The task of the Standing Committee to Advise the Department of State on Unexplained Health Effects on U.S. Government Employees and Their Families at Overseas Embassies, detailed in Box 1, included provision of advice to DOS on best practices in their approach to current patients and prevention or mitigation of potential future incidents. The committee's task was not to "solve" the mystery surrounding what caused the symptoms experienced by personnel in Cuba and China, but it did include the evaluation of proposed plausible mechanisms. Given the limited time available to the committee and the unavailability of relevant, detailed information about individual patients, the committee was not able to accomplish everything in the broad Statement of Task; however, it was able to address a number of critical issues.

The committee faced several challenges in assessing these clinical cases. Many of these challenges relate to the extreme variability in the cases. First, because of federal rules for protection of health and other information, the committee was not privy to health or other personal information about individuals, other than that which was voluntarily provided to the committee directly by a small number of affected DOS employees. Therefore, the committee could not link anonymized data about specific individuals from different clinical providers or clinical investigators. The Centers for Disease Control and Prevention (CDC) is the only U.S. federal agency with the authority to link health data from different sources about individual patients, and CDC did in fact undertake an investigation of these cases with the goal of establishing a case definition; however, CDC did not become involved until one year after the earliest events and only reviewed records rather than interviewing all of the affected individuals. The committee was not afforded access to CDC's final report of this investigation until near the end of the committee's term. Thus, the committee was blind to the different clinical tools and assessments used by different clinical providers or clinical investigators on the same patient.

A second challenge was that cases evolved over time and patients were evaluated by different clinicians and investigators after widely varying amounts of time following the onset of

their symptoms and signs, including up to several years later. Thus, the evolving and changing clinical features of these cases and the non-uniform timing of the clinical investigations created a second source of variability. Third, the patient population was highly heterogeneous in the timing and location of their overseas assignments; their roles and assignments while overseas; their ages, past medical and career histories and other demographic features; and in their clinical symptoms and signs. In general, the committee did not have access to individual-level information except for several instances where affected DOS employees agreed to tell their story before the committee. Furthermore, when viewed on their own, a number of these clinical signs and symptoms are nonspecific, i.e., they might be experienced by persons suffering from a variety of conditions. Despite these challenges, the committee did its best to collect, extract, and evaluate some shared or distinctive clinical features of these cases, evaluate some plausible mechanisms and efforts to treat some of the patients, and then offer recommendations for future management of these and potential new cases.

This report is organized into five subsequent sections:

- Section 2: Methods and Data
- Section 3: Clinical Features
- Section 4: Plausible Mechanisms
    - Directed Radio Frequency Energy
    - Chemicals
    - Infectious Agents
    - Psychological and Social Factors
- Section 5: Acute Treatment and Rehabilitation
- Section 6: Looking to the Future/Recommendations

Sections 3-5 are each organized according to Sources of Information; Assessment and Findings; Summary; and References.

BOX 1
Statement of Task

To facilitate the Department of State (DOS) in implementing one of its responsibilities to protect U.S. government employees and their family members overseas, the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine will form a Standing Committee to Advise the Department of State on Unexplained Health Effects on U.S. Government Employees and Their Families at Overseas Embassies. This committee will collaborate with the DOS Bureau of Medical Services on best practices including but not limited to health monitoring, medical interventions, risk assessment, and exposure mitigation for overseas locations that may present a higher risk of adverse health effects. The standing committee will evaluate current DOS practices for pre- and post-assignment health screening, provide expertise on potential epidemiologic studies, help with characterizing and understanding the current cases of potential acoustic trauma, and develop a better understanding of possible causes of these cases and approaches for future incidents whether of an apparent acoustic nature or a different environmental or clinical presentation. The standing committee will also keep DOS abreast of any emerging concerns, interventions, and protective measures as these come available. The committee will organize ongoing

discussions, take on specific tasks and possibly issue classified and unclassified reports and recommendations on a variety of topics of importance to DOS in regards to health effects from potential exposures overseas.

The standing committee will provide a forum for discussion of scientific, technical, and social issues relevant to effective health management and protection of staff and family members assigned to overseas locations. The committee will consider relevant scientific, technical, and policy issues including but not limited to:

- Review of the current situation, to include discussions of epidemiologic investigations, case definitions, study methods, controls, and alternative hypotheses;
- Review the active research agenda, including defining what types of information ought to be collected and archived against possible future needs, and any potential additional studies needed;
- Assist in the optimization and deployment of screening protocols and assessment of treatment options, to include a review of currently available screening devices and technologies, appropriate level of baseline testing for a large number of personnel and policy needs;
- Review data, findings and conclusions generated by and for the U.S. government;
- Review scientific evidence of possible causes and approaches to addressing potential future incidents of unexplained clusters of medical symptoms;
- Determine the need for collection of relevant environmental data (e.g., biologic, acoustic, radiologic, chemical, toxicological) that might be useful in current and future situations; and
- Provide guidance on determining a clinical case definition.

Section 2

Methods and Data

The National Academies of Sciences, Engineering, and Medicine assembled a 19-member committee with expertise in clinical medicine to include neurology, neuro-ophthalmology, audiologic, and vestibular medicine, psychiatry, infectious diseases, and rehabilitative medicine, along with experts in epidemiology, environmental science and engineering, toxicology, neurobiology, neuroradiology, health effects of electromagnetic radiation and microwaves, exposure and risk assessment, and health monitoring. The committee members' biographical sketches are included in Appendix A.

The committee held two in-person meetings (December 18-19, 2019; February 24-25, 2020) and one virtual meeting (May 11-13, 2020); each of them included public sessions with external experts (see Appendix B). The committee reviewed the clinical data about the U.S. Embassy personnel published by clinical teams from the University of Miami (referred to here as "Miami") (Hoffer et al., 2019) and the University of Pennsylvania (referred to here as "Penn") (Swanson et al., 2018), as well as information about the U.S. Embassy personnel presented by Miami and Penn, as well as a clinical team from the National Institutes of Health (NIH) during the committee's meetings. During the February 2020 meeting, the committee heard from experts on the health effects of exposures to chemicals and to directed radio frequency (RF) energy. During the May 2020 meeting, the committee heard from three experts in the fields of mild traumatic brain injury (mTBI), and vestibular and cognitive rehabilitation.

During a closed session at each of the two in-person meetings, the committee met with former U.S. Embassy personnel from Cuba and China, who suffered from some of the clinical manifestations that are the subject of this report, and who volunteered to speak with the committee about their own cases. In order to protect their privacy and their personal health information, the committee omitted details from this report that might enable identification of these individuals.

The committee also reviewed studies of patients associated with the Canadian Embassy in Havana, published and presented by investigators from Dalhousie University in Halifax, Nova Scotia (referred to here as "Dalhousie") (Friedman et al., 2019).

The committee acquired access to the final report of the CUBA Unexplained Events Investigation conducted by the Centers for Disease Control and Prevention (CDC) on the U.S. Embassy Havana patients near the end of this study.[2] It is referred to here as "the CDC Report."

Throughout the course of this study, the committee received information from DOS that was germane to its tasks, and had multiple opportunities to speak directly with current DOS employees within the Bureau of Medical Services. For this, the committee is appreciative.
The committee approached its reporting task by determining the topics and issues on which it felt sufficiently informed to be able to offer findings and conclusions, given the information provided to it. The committee then considered recommendations, supported by these findings, which might assist DOS in understanding and managing these cases, as well as in managing potential future health events. The committee also reviewed the information through the lens of

[2] Centers for Disease Control and Prevention. 2019. Cuba unexplained events investigation - final report. Received by the committee on April 28, 2020.

established procedures for investigating clusters of unknown health events (see Box 2). These procedures, among other things, emphasize the importance of standardized data collection.

It is the committee's view that the information made available to the committee on DOS patients from China is too sparse and fragmentary to be able to draw any substantive conclusions about these cases and their relationship to the cases from U.S. Embassy Havana. The committee's report therefore focuses on the personnel associated with the U.S. Embassy in Havana.

Of note, from a systems perspective, each agency and organization that has reviewed these cases during the past several years has had available to them different sets of data. There are myriad reasons, including different institutional responsibilities, approaches, investigative tools, timing of investigation, and access to classified information. Although the committee did not have the benefit of data and investigative tools that were available to others, the study may have benefitted from information that either was not obtained by others or was not available at the time that other investigations took place. As a result, experienced investigators from different organizations logically may reach different conclusions based on their own data sources and limitations.

BOX 2
Steps for Investigating Clusters of Health Events (CDC, 1990)

Stage 1 – Initial contact and response—collect information from the person or groups first reporting the issue

Stage 2 – Assessment—determine the likelihood that cases of illness or injury are above expected numbers or rates; verify the diagnosis or determine biologic plausibility; define the characteristics

Stage 3 – Feasibility study—examine the potential for an epidemiologic study to link the health event and a putative exposure

Stage 4 – Etiologic investigation—determine the potential disease or injury exposure relationship

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Section 3

Clinical Features

SOURCES OF INFORMATION

The clinical investigators presented data to the committee as aggregated summaries of patients' histories, physical examination findings, and results of laboratory testing and neuroimaging. These data were obtained from well-established methods of clinical assessment (Friedman et al., 2019; Hoffer et al., 2019; Swanson et al., 2018), as well as procedures that were investigative (i.e., experimental) in nature (Balaban et al., 2016; Verma et al., 2019). Experimental procedures included novel interpretations of results derived from well-established procedures (Friedman et al., 2019; Hoffer et al., 2019) and results obtained from newly developed, but not yet standardized, technologies (Balaban et al., 2016; Friedman et al., 2019; Verma et al., 2019). Individual patient-level data were not provided to the committee. DOS and the four clinical teams (Miami, Penn, National Institutes of Health [NIH], and Dalhousie) appropriately cited patient privacy and diplomatic and other security concerns in limiting data shared with the committee to the aggregate summaries only. The NIH team provided detailed multi-disciplinary clinical diagnoses of all patients that they evaluated, though this information, too, was provided to the committee in summary format. This made it impossible to link specific symptom constellations, physical examination results, and laboratory or imaging test findings within and between affected individuals for diagnostic purposes.

The committee was afforded an opportunity to speak directly with eight patients associated with U.S. Embassy Havana or with the U.S. Embassy or Consulates in China.

The CDC Report indicated substantial overlap in the populations of Havana patients included in the Miami, Penn, and NIH summative data. In fact, it was difficult for the committee to determine to what extent some individual patients may have been reported two or more times and whether the patients interviewed were among those included in the summative data from these three clinical sites. Importantly, the evaluations included in the summative data were generally separated from the original case events and from each other by considerable periods of time. Therefore, it was difficult to know whether differences in the reported signs and symptoms were due to changes from time of onset to the time of various evaluations, or because of the different evaluation procedures employed at the different sites, or because different subsets of patients were included in the different summaries.

ASSESSMENT AND FINDINGS

Clinical Features of Personnel Who Spent Time in Havana

The committee compiled signs and symptoms reported by DOS employees that spent time in Havana, based on information provided by the four clinical evaluation sites (Miami, Penn, NIH, Dalhousie) in presentations to the committee or in publications, as well as the signs and symptoms of affected employees interviewed by the committee in person. The committee included the sparse and fragmentary information on the China and Canadian patients here for the sake of a few comments.

The committee finds that the most distinctive and specific clinical features of these individuals occurred acutely at, or soon after the time of onset of their illness. In contrast, the chronic features that persisted for weeks, months, or years after the initial onset (in those individuals who reported an acute distinctive phase) were less specific to these DOS personnel and more common among general populations of patients with a variety of neurological or systemic conditions. The committee reasoned that the acute, more distinctive clinical features would be more informative about the possible cause(s) of the overall illnesses, rather than the chronic, less specific features.

The most common and distinctive features of the initial onset and acute phase of the illness in Havana personnel were the sudden onset of a perceived loud sound, sometimes described as screeching, chirping, clicking, or piercing, a sensation of intense pressure or vibration in the head, and pain in the ear or more diffusely in the head. Most individuals reported that the sound or these other sensations seemed to originate from a particular direction or that they perceived them only in certain physical locations. Individuals interviewed by the committee described alleviation of the symptoms by moving from their initial location to a different one, e.g., into a different room of the building in which they were located. According to data from Miami, 25 of 25 individuals perceived a loud sound, and according to data from Penn, 28 of 35 individuals from Havana, and 12 of 12 from China perceived a loud sound. Of the 35 Havana individuals assessed at Penn, 16 reported a sensation of pressure or vibration in the head and18 described the sound or pressure as directional or as restricted spatially in their immediate environment. Variable numbers of individuals reported the accompanying sudden onset of tinnitus (8 of 25 reported this at Miami and 6 of 21 at Penn), ear pain (7 of 25 at Miami and 7 of 21 at Penn), hearing loss (8 of 25 at Miami and 9 of 21 at Penn), dizziness, unsteady gait (4 of 21 at Penn), and visual disturbances (14 of 21 at Penn).[3] Importantly, the committee finds this constellation of acute symptoms with directional and location-specific features to be very unusual, and to the best of its knowledge, unlike any disorder reported in the neurological or general medical literature.

Some of the acute signs and symptoms persisted or recurred and became chronic in some individuals, including dizziness (23 of 25 at the time they were examined at Miami and 13 of 21 at Penn), fatigue (10 of 21 at Penn), impaired balance (numbers not available), headache (6 of 25 at Miami and 16 of 21 at Penn), impaired concentration (5 of 8 at Miami and 8 of 21 at Penn) and memory (5 of 8 at Miami and 11 of 21 at Penn), depression (numbers not available), and insomnia (18 of 21 at Penn). These latter symptoms alone do not inform a specific etiologic diagnosis and can be due to a wide variety of common disorders (including viral and other inflammatory conditions, persistent postural-perceptual dizziness, chronic fatigue syndrome, traumatic brain injury, posttraumatic stress disorder, depression, and others). Most of the eight individuals that the committee interviewed described both early, acute onset and chronic clinical features, and continued to be debilitated.

The summary descriptions available to the committee of cases involving Canadian Embassy personnel from Havana failed to mention the perception of a loud sound, sensation of intense pressure or vibration, or ear pain, but did include impaired balance, headache, vertigo, tinnitus, and some of the same chronic clinical features as the U.S. Embassy personnel. The committee did not have sufficient information about U.S. Embassy personnel from China to be able to assess overall similarities or dissimilarities with cases from Havana.

[3] These numbers were extracted by the committee from publications and presentations by the clinical investigators, and not from the patient clinical records or from direct examination of the patients by the committee.

One problem with all of the data presented was that it lacked an appropriate control group (i.e., individuals who were present in the same environment as the U.S. Embassy employees who reported the acute phase of the illness, but were not exposed to whatever caused those distinctive signs and symptoms). It is noteworthy that the Canadian Embassy employees shared much of the environment of the U.S. Embassy employees, but generally lacked the acute signs and symptoms. Hence, it is possible that other exposures (viral illness, toxic chemicals, etc.) may have caused the chronic signs and symptoms shared by both the U.S. and Canadian personnel, while the acute signs and symptoms limited to the U.S. Embassy employees may have had a different cause.

The committee notes that the CDC Report also identified a biphasic onset of symptoms, with a set of early, sudden-onset symptoms and a set of later, more chronic, and less specific symptoms. The CDC Report defined a "presumptive" case as having components of each set.[4] Out of 95 records that CDC reviewed, they found 15 who met their case definition, along with 31 other "possible" cases. Out of the 15, over 2 years after the initial symptoms, six were still undergoing therapy with four unable to work and two needing modifications to work. Unlike CDC, the committee did not have the ability to link disparate findings from different clinical sites and times to the same individual. However, it is the committee's impression that only a subset of individuals who suffered from the early set of signs and symptoms, also suffered from the later set of signs and symptoms. Conversely, only a subset of individuals who reported suffering from the late set of generally more common signs and symptoms, also described the more distinctive early set and in particular, the sudden onset of a directional or location-specific loud noise, pressure or pain. Because of these various aspects of case heterogeneity, the committee found it difficult to know with certainty that all cases were due to the same cause(s), and in particular, whether the individuals with only the chronic set of signs and symptoms suffered from the same cause(s) and etiologic mechanisms as those who reported the initial, sudden onset set of signs and symptoms.

Laboratory Test Results and Physical Examination Findings Reported for Embassy Personnel

DOS personnel underwent physical examinations and different tests at different study sites, at different times during the course of their illness. The committee did not have access to primary reports or complete data. Nonetheless, it sought to identify and summarize pertinent test results and exam findings for which available data were adequate.

Vestibular and Balance Assessments

Patient questionnaires, physical examinations, office-based tests of balance performance, and vestibular and oculomotor laboratory tests were used to evaluate patients. The clinical teams from Miami and Penn selected tests based on each patient's symptoms. Thus, patients did not undergo a consistent set of diagnostic evaluations at either site. Clinicians at NIH appeared to use a more consistent approach and set of test procedures.

Self-report questionnaires (e.g., Dizziness Handicap Inventory) and tests of balance performance (e.g., dynamic posturography) showed high rates of impairment and poor performance. The clinicians involved in these assessments interpreted these data as evidence of inner ear or brain injury (Swanson et al., 2018). However, self-report questionnaires and tests of

[4] The CDC case definition for a **presumptive case** required at least one of following in the initial phase (head pressure, disorientation, nausea, headache, vestibular disturbances, auditory symptoms, vision changes) and at least one of the following in a separate secondary phase (vestibular disturbances, cognitive deficits).

balance performance cannot be used properly to make specific diagnoses, as abnormal results may arise from structural, functional, or psychiatric disorders alone or in combination. Thus, these data indicate a high level of impairment in many patients at the time of testing, but do not provide any information about potential causative agents or specific mechanisms of injury.

Vestibular laboratory tests such as the video head impulse test, caloric test, vestibular evoked myogenic potentials, rotary chair test, and oculomotor examinations can provide information on the structural integrity of peripheral (inner ear) and central (brain) vestibular and oculomotor pathways. Test procedures vary across laboratories and several tests require cooperation and volitional effort on the part of patients to yield meaningful and consistent results. Consequently, findings from one center may not be directly comparable to findings from another center in the absence of descriptions of test procedures employed and thresholds for reporting normal versus abnormal results. Data published (Balaban et al., 2020; Hoffer et al., 2019) and presented by the clinical team at Miami were derived from a small number of established laboratory tests plus a battery of new assessment tools (i.e., experimental tests) developed by that group (Balaban et al., 2016). Data published (Swanson et al., 2018) and presented by the clinical team at Penn were derived predominantly from office-based tests. Only a portion of patients were evaluated with standard vestibular laboratory tests and only a portion of those results were published or presented. The Dalhousie team also used a small number of established vestibular tests (Friedman et al., 2019) but only examined Canadian patients. The NIH team employed an extensive battery of established tests, though their assessments were generally conducted later, from months to over a year, in the course of patients' illnesses and thus were less informative about potential early deficits. Some results were inconsistent across centers, although perhaps in part because they studied different individuals. For example, the Miami group reported high rates of absent or reduced-amplitude vestibular evoked myogenic potentials (Hoffer et al., 2019), whereas the Dalhousie group reported higher than normal mean amplitudes on those tests (Friedman et al., 2019).

The committee concluded that the aggregate data derived from the subset of well-established clinical laboratory diagnostic tests presented by the four clinical groups performed weeks, months, or years after the initial onset did not identify a common pattern of structural injuries to the labyrinths or brains of patients that could explain the reported vestibular symptoms. In the absence of patient-level data, the committee could not determine with certainty if any reported abnormalities coincided with key aspects of clinical histories for individual patients.

Neuropsychological and Psychological Assessments

Patients underwent neuropsychological testing at Penn and NIH in various cases, weeks, months, or years after symptom onset. The Penn team presented aggregate results in a non-standard manner (i.e., the total number of patients with abnormal scores on each subtest of the test battery that they administered). The NIH team presented results in a more standardized clinical fashion, though still in aggregate. Neurobehavioral and cognitive evaluations in these situations are quite challenging. Standard assumptions and fact-finding methods used in normal clinical settings may be misleading, raising validity concerns (Lees-Haley, 1995). The committee concluded that no distinct pattern of clinically diagnosable cognitive deficits could be discerned from these data. A more comprehensive and uniform assessment approach to the entire group of patients earlier in the course of illness may have provided a better opportunity with regard to diagnosis and treatment issues.

The NIH team also presented aggregate data from psychological testing. The results showed psychological distress in some patients in a pattern that may be seen in those suffering from a variety of chronic medical conditions or somatic symptom disorders. These results indicated an increased burden of illness in patients with chronic symptoms but offered no insights into an initial cause.

Imaging Studies

The committee reviewed the radiological studies from Penn and Dalhousie. The Penn group found essentially normal conventional structural magnetic resonance imaging (MRI) results months to years after initial symptoms. They subsequently reported that among 40 Havana patients compared to 48 healthy controls, there were small group differences in the average brain volumes in specific lobes, a decrease in mean diffusivity in the midline inferior cerebellum, and differences in functional connectivity in auditory and visuospatial networks (Verma et al., 2019). Difficulties in replicating results are common in studies of small patient groups using MR measures with low signal to noise ratios, and which involve a number of computational steps and algorithms that are known to perform imperfectly (based on frequent failures to replicate) (De Santis et al., 2014; Jonathan et al., 2007; Landman et al., 2007). Generally, studies of this type require a replication cohort (which was not available) to determine if the findings are reliable. The committee was not provided the results of efforts to correlate imaging findings to clinical findings, and most subjects examined did not show the pattern of imaging findings reported in the average, which further diminish the clinical value of the reported findings. Investigators at the NIH performed imaging on a small number of the Havana cohort at even later dates (i.e. years in some cases and did not find any differences from normal subjects, but their studies are ongoing).

The Dalhousie group also reported normal structural MRI findings, and reported changes in diffusion tensor imaging of the white matter tracts in the posterior part of the corpus callosum and the adjacent part of the fornix (Friedman et al., 2019). These types of changes are subject to the same caveats as the Penn findings (and a lack of congruity between the two studies is noted). However, the Dalhousie patients may not have had the same clinical disorder as DOS employees, as noted above.

In summary, the committee felt that none of the imaging studies performed so far were sufficient to serve as a basis for a case definition or for management of individual subjects.

General Comments About the Patient Evaluations

The committee finds that as a routine, general approach to cases with neurological manifestations, patient evaluations should be performed as soon as possible after onset and should include a complete neurological examination, followed by a standard whole brain MR scan, with and without contrast, preferably performed at 3T, with diffusion weighted imaging and a T2* sensitive sequence (susceptibility weighted imaging is preferred) to detect microbleeds. If the case involves auditory or vestibular symptoms, fine cuts might be added through the inner ear; for visual symptoms, fine cuts through the orbit; and for cases with somatosensory or motor phenomena, fine cuts through the cervical and thoracic spinal cord. Functional MRI is not well-suited to single subject studies. Similarly, diffusion tensor imaging for tractography is not reliable as an indicator of abnormalities in individuals.

In neuro-otology, there is no consensus about a standard test battery for auditory or vestibular symptoms. Evoked potentials are fairly simple, objective measures of slowing of

conduction in these sensory systems, due to a variety of causes, but are not uniformly accepted as a standard for evaluation.

Additional testing should be undertaken as clinically indicated. Blood should be collected as soon as possible after the onset of symptoms, and both plasma and whole blood frozen and stored for future toxicological, infectious, and other appropriate evaluations. All of these evaluations are routinely available in any modern large hospital, but may require plans in advance for referring Embassy personnel to such a facility as soon as possible after onset.

SUMMARY

The most distinctive clinical aspects of the illnesses described in DOS Havana personnel are the nature of the onset and the initial features: the sudden onset of a perceived loud sound, a sensation of intense pressure or vibration in the head, and pain in the ear or more diffusely in the head. Most individuals reported that the sound or these other sensations seemed to originate from a particular direction and that they were perceived only when the individual was in a specific physical location. Different numbers of individuals also reported sudden onset of tinnitus, hearing loss, dizziness, unsteady gait and visual disturbances.

From a neurologic standpoint, this combination of distinctive, acute auditory-vestibular symptoms suggests an effect localized to the labyrinth or VIII cranial nerve or its brainstem connections. The committee found this constellation of acute symptoms with directional and location-specific features to be very unusual and, to the best of the committee's knowledge, unlike those associated with any disorder reported in the neurological or general medical literature. The sudden onset and immediate amelioration with change in location makes an infectious or toxic cause less likely, while the repeated testimony that the symptoms were experienced only in specific physical locations near windows or as originating or emanating from a particular direction raised the possibility that they were due to some physical force that could penetrate windows but not walls. As such, we considered in detail the possibility that these acute symptoms may have been caused by directed RF energy, as well as toxic, infectious, and psychological processes.

The more chronic (later phase) problems suffered by Havana personnel included mainly vestibular processing and cognitive problems as well as insomnia and headache. From a neurologic standpoint, these cognitive symptoms and insomnia are more consistent with diffuse involvement of forebrain structures and function, such as cerebral cortex or limbic structures. While these chronic symptoms are common complaints, it is quite possible that in those personnel with the dramatic initial phase auditory and vestibular symptoms, these subsequent, more persistent symptoms were caused by sequelae of the same initial insult or that they occurred secondarily as an accommodative response. In those personnel without reports of an acute initial phase, these chronic symptoms could suggest an exposure or cause distinct from those with an initial phase, or a similar exposure that resulted more exclusively in forebrain dysfunction.

A key problem in the committee's assessment was the lack of information collected in a systematic fashion from every affected individual from the initial onset of the first case, as well as from control individuals. By relying on routine clinical evaluation and management of these individuals within the U.S. commercial health care system, significant information was lost due to delays, differences in insurance coverage and consequent differences in clinical work-up of each case, and lack of a standardized approach. The information was also firewalled in distinct silos by Health Insurance Portability and Accountability (HIPAA) regulations, making it almost

impossible to put together a coherent picture. CDC is currently the only organization that has the ability to penetrate these firewalls, but they were not involved until many months after the primary investigations by Miami, Penn, and NIH. A plan that solves this issue would be of great benefit to DOS and its employees. Baseline visual, auditory, and vestibular data from each individual would have helped as well, given that deficits in these systems can often occur with aging.

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Section 4

Plausible Mechanisms

Multiple kinds of mechanisms might contribute to the observed phenomena in the Department of State (DOS) personnel. The committee narrowed the investigation to four, based on their previous appearance in analogous outbreaks of paroxysmal symptoms, their presence in similar localized settings, information available from other investigators, and most notably the known constellation of medical effects (centering on neurologic findings of acute onset). As discussed in Section 3, the acute symptoms with directional dependence are highly unusual, and unlike any disorder reported in the neurological or general medical literature including those with known infectious, inflammatory, or toxic mechanism. The committee felt that these acute symptoms were more consistent with a directed radio frequency (RF) energy attack, and explored possible related mechanisms. At the same time, the chronic symptoms that were reported are often seen in patients after head trauma, as a result of chemical exposure, infectious diseases, or stress in a hostile environment. There did not appear to be any evidence for usual forms of traumatic injury, but the committee did evaluate possible chemical and infectious causes as well as psychosocial causes, for the chronic symptoms.

DIRECTED RADIO FREQUENCY ENERGY

Sources of Information

The committee relied on open source data from published literature as well as firsthand reports from clinicians, researchers, and affected DOS personnel shared in person at its December and February meetings, to evaluate the plausibility of directed RF energy exposure as a cause of both the acute and chronic clinical signs and symptoms discussed in Section 3 (Clinical Findings). While the committee did review the significant body of scientific literature on the potential therapeutic and palliative applications of electromagnetic energy (e.g., medical radiotherapies) (Citrin, 2017; Mohan et al., 2019; Saitz et al., 2019; Suh et al., 2020; Tsao et al., 2018) and the health risks of microwave radiation (e.g., cell phone emissions) (FDA, 2020; NTP, 2018a,b), this subsection primarily restricts its focus to RF biological effects that are consistent with the clinical and personal (by DOS patients) observations.

Observations from clinicians (including published summaries of symptoms and experiences) and DOS personnel were considered with respect to known biological effects of a wide variety of RF exposures (defined as 30KHz-300GHz, including microwave radiation as 300MHz-300GHz). The committee used these personal and clinician observations to identify known RF biological effects that should be either included or excluded from consideration in explaining the signs and symptoms in DOS personnel.

Assessment and Findings

Low-level RF exposures typically deposit energy below the threshold for significant heating (often called “nonthermal” effects), while high-level RF exposures can provide enough energy for significant heating (“thermal” effects) or even burns, and for stimulation of nervous and muscle tissues (“shock” effects) (IEEE, 2019). While much of the general public discussion

on RF biological effects has focused on cancer, there is a growing amount of data demonstrating a variety of non-cancer effects as well, in addition to those associated with thermal heating.

Based on a review of these information sources, the committee finds that many of the acute, early phase symptoms and observations reported by DOS employees are consistent with RF effects, including a perceived clicking sound within the head even when the ears were covered, a perceived force/pressure sensation within the head and on the face, perceived spatial localization and directionality of these perceived phenomena and other loud sounds, hearing loss, tinnitus, impaired gait and loss of balance, as well as the absence of heating sensation and absence of observed disruption of electronic devices in the immediate environment. In addition, many of the chronic, nonspecific symptoms are also consistent with known RF effects, such as dizziness, headache, fatigue, nausea, anxiety, cognitive deficits, and memory loss.

The absence of certain observed phenomena can also help to constrain potential RF source characteristics. For example, the absence of reporting of a heating sensation or internal thermal damage may exclude certain types of high-level RF energy.

There are multiple possible mechanisms for non-thermal RF biological effects, including apoptosis and cell oxidative stress (Barnes and Greenebaum, 2018; Ilhan et al., 2004; Salford et al., 2003; Steiner and Ulrich, 1989; Zhao et al., 2007). RF-induced, non-thermal cell membrane dysfunction (Ramundo-Orlando, 2010) can occur from coherent excitation (Fröhlich, 1988) above 1 GHz due to a variety of effects including electroporation, metabolic changes, pressure fluctuations, and voltage gated calcium channel disruption (Pall, 2013, 2016). However, many of the cognitive, vestibular, and auditory effects observed in DOS personnel are most consistent with modulated, or pulsed, RF biological effects.

There was significant research in Russia/USSR into the effects of pulsed, rather than continuous wave (CW) RF exposures because the reactions to pulsed and CW RF energy at equal time-averaged intensities yielded substantially different results (Pakhomov and Murphy, 2000). According to Pakhomov and Murphy, the Russian-language studies "indicated that pulsing may be an important (or even the most important) factor that determines the biological effects of low-intensity RF emissions" (Pakhomov and Murphy, 2000, p. 2). Military personnel (in Eurasian communist countries) exposed to non-thermal microwave radiation were said to have experienced headache, fatigue, dizziness, irritability, sleeplessness, depression, anxiety, forgetfulness, and lack of concentration, as well as internal sound perception for frequencies between 2.05-2.50 GHz (Adams and Williams, 1976). The review by Pakhomov and Murphy noted that many of the studies from the former Soviet Union were flawed in one or more ways, but that some were well done, replicated, and credible.

Pulsed RF effects on the nervous system can include changes to cognitive (D'Andrea, 1999; Lai, 1994; Tan et al., 2017), behavioral (D'Andrea and Cobb, 1987), vestibular (Lebovitz, 1973), EEG during sleep (Lustenberger et al., 2013), and auditory (Elder and Chou, 2003) function in animals and humans, though many RF exposure characteristics (carrier frequency, pulse repetition frequency, orientation, power densities, duration of exposure) complicate direct comparisons of different experiments (D'Andrea et al., 2003). Some animal studies have shown conflicting results, however, even when using the same exposure system. For example, researchers using the Transformer Energized Megavolt Pulsed Output (TEMPO) microwave pulse apparatus with high peak power RF energy but low specific absorption rate (SAR) values observed a negative effect on cognitive function in rats (time perception and discrimination tasks) (Raslear et al., 1993), but other researchers found no observable behavioral changes in rhesus monkeys (D'Andrea et al., 1989; Ziriax et al., 1999). It should be noted that the low SAR

values for both animal models were lower than whole-body SAR thresholds known to disrupt behavioral performance (D'Andrea, 1991; D'Andrea and de Lorge, 1990; de Lorge, 1984).

In 1961, Alan Frey identified a new, RF-induced auditory phenomenon in both normal and deaf humans that became known as the "Frey effect" (Frey, 1961) (see Appendix C). The areas near the ear were most sensitive to these RF exposures; modulating the RF energy could produce a variety of effects including the perception of "buffeting of the head" or pressure on the face/head without dizziness or nausea, a "pins and needles sensation," and a sound described as a "buzz, clicking, hiss, or knocking" within the head for RF frequencies between 0.4-3 GHz, depending on pulse width, pulse-repetition frequency (PRF), and peak power density (Frey, 1962). These reported symptoms are consistent with some of the first-person accounts provided to the committee. Frey reported these symptoms with an RF source transmitting at 1.3 GHz (which provides the greatest absorption depth into cortical tissue) with a PRF of 244 Hz, 6 μs pulse width, peak power density of 267 mW/cm^2, and average power density of 0.4 mW/cm^2 (Frey, 1962). Others have demonstrated that GHz range, pulsed RF energy (~14μs pulse width) interacting with common materials can produce external sounds that are audible to nearby humans (Sharp et al., 1974). This is also consistent with potential smartphone microphone excitation from RF energy that would lead to an external, audible clicking sound from the phone. The ability for a pulsed RF source to create internal and external auditory stimuli simultaneously agrees with published and personal reports. Importantly, the Frey effect may be induced without causing identifiable structural injury to neural or labyrinthine tissues.

The potential for RF sources to stimulate the vestibular end organs via thermoelastic pressure waves (see Appendix C) or to excite central nervous system pathways via transduction akin to the Frey effect is not known. However, if these effects exist, this unusual form of vestibular stimulation could lead to very confusing perceptions, as central vestibular pathways do their best to resolve the non-physiological pattern of end organ stimulation resulting in perceptions of physically impossible motions, unexpected reflexive postural responses to them, and faulty inferences about external forces causing them. Affected individuals could report different sensations in response to the same external stimulus; thus, it is consistent with this scenario that the early phase reports of the perceptions of affected individuals varied from one individual to another, and may have been difficult for the individuals to describe. With regard to vestibular and balance systems, the functional vestibular disorder of persistent postural-perceptual dizziness (PPPD) may be triggered by any condition that causes symptoms of vertigo, unsteadiness, or dizziness, or disrupts balance function, even if transiently and without causing structural injury (Staab et al. 2017). The NIH team diagnosed PPPD in one-quarter of patients that they evaluated. Patients with PPPD commonly report problems with cognition and fatigue in addition to core symptoms of unsteadiness, dizziness and susceptibility to motion stimuli (Stone, 2016).

If a Frey-like effect can be induced on central nervous system tissue responsible for space and motion information processing, it likely would induce similarly idiosyncratic responses. More general neuropsychiatric effects from electromagnetic stimuli are well-known and are being used increasingly to treat psychiatric and neurologic disorders. In 2008, the Food and Drug Administration (FDA) approved transcranial magnetic stimulation (TMS) to treat major depression in adults who do not respond to antidepressant medications (Cook, 2018). Ten years later, the FDA approved office-based TMS as a treatment for obsessive compulsive disorder (OCD) (FDA, 2018) and portable TMS to treat migraine (Jeffrey, 2013).

The benefits derived from purposeful short-term exposures to therapeutic neuromodulation contrast with the adverse neurologic and neuropsychiatric symptoms described

by individuals exposed to electromagnetic fields (e.g., high tension electrical transmission cables) over longer periods of time (Pall, 2016) as summarized by Stein and Udasin (2020).

Summary

The committee finds that many of the acute, sudden-onset, early phase signs, symptoms and observations reported by DOS employees are consistent with RF effects. In addition, many of the chronic, nonspecific symptoms are also consistent with known RF effects, such as dizziness, headache, fatigue, nausea, anxiety, cognitive deficits, and memory loss. It is not necessary for RF energy sources to produce gross structural damage to cause symptoms. Rather, as with the Frey effect or potential thermoelastic pressure waves, RF sources may trigger symptoms by transiently inducing alterations in brain functioning.

There are several types of data that would be helpful and could improve both the findings and their level of certainty. While there are several studies on the health effects of continuous wave and pulsed RF sources, there are insufficient data in the open literature on potential RF exposure/dosage characteristics and biological effects possible for DOS scenarios. Specific experiments would be needed with RF exposure and dosage characteristics (frequency, pulse repetition frequency, pulse width, incident angle between potential source and subject, duration of exposure, number of repeated exposures, etc.) to quantify the biological effects, but would be ethically difficult to justify. In the absence of such data, it is difficult to align specific biophysical effects within the potential RF exposure regime that could explain specific medical symptoms reported by DOS personnel and the variability in specific experiences and timelines of individuals. Patient clinical heterogeneity could be due to variability of exposure dosage conditions, differences in interpretation of non-physiological vestibular stimuli, and anatomical differences that could influence individual exposure and/or response.

CHEMICALS

Sources of Information

DOS asked the committee to consider the plausibility of organophosphate (OP) or pyrethroid insecticide exposure as a cause of the clinical signs/symptoms observed in U.S. Embassy personnel in Havana. This possible cause was raised by Canadian investigators who reported decreased cholinesterase activity, temephos (an OP), and pyrethroid metabolites in blood samples collected from some Canadian Embassy personnel and Canadian tourists who were in Havana during the same period as the affected U.S. Embassy personnel. Additionally, the timing of some cases in U.S. Embassy personnel coincided with widespread spraying of OP and pyrethroid insecticides in Cuba in 2016 to mitigate spread of Zika virus by mosquitos.

To address the plausibility of the OP/pyrethroid insecticide hypothesis, the committee examined five sources of information: (1) the Research Report, “Havana Syndrome: Neuroanatomical and Neurofunctional Assessment in Acquired Brain Injury Due to Unknown Etiology” (Friedman et al., 2019); (2) formal presentations to the committee by Claire Huson (DOS Office of Safety, Health, and Environmental Management), Cynthia Calkin and Alon Friedman (Dalhousie University Faculty of Medicine), Marion Ehrich (Virginia-Maryland College of Veterinary Medicine), and Nick Buckley (University of Sydney); (3) feedback provided during a question and answer session with DOS Bureau of Medical Services staff; (4) the National Toxicology Program publication, “Systematic review of long-term neurological effects following acute exposure to the organophosphorus nerve agent sarin,” (NTP, 2019); and (5) peer-reviewed scientific literature.

The committee considered three general issues: (1) What is the strength of the evidence that affected individuals were exposed to OP or pyrethroid insecticides?; (2) Were exposures at levels that might be expected to cause toxic effects?; and (3) How similar are the signs and symptoms of acute, subacute, or chronic exposures to OP or pyrethroid insecticides to the distinctive acute signs and symptoms and the less specific chronic signs and symptoms associated with cases from Havana?

Assessment and Findings

With respect to the question of exposure, information presented by Claire Huson regarding the DOS Integrated Pest Management (IPM) program indicated that pyrethroids (lambda cyhalothrin, cyfluthrin, permethrin, and cypermethrin) were used in U.S. Embassy offices and residences in Havana; thus, the potential for exposure of U.S. Embassy personnel to these insecticides was quite high. OPs were not included in the IPM program and it is DOS IPM policy not to allow outside contractors to apply pesticides in U.S. Embassy offices or residences. Consistent with this information, the committee heard in a question and answer session with DOS medical staff that OPs were not detected in environmental samples collected from the residences of U.S. Embassy personnel some months after the incidence of unexplained illnesses. However, this information does not rule out the possibility that U.S. Embassy personnel were exposed to OPs in their residences proximal to the onset of symptoms because OPs are relatively short-lived in the environment (half-life of several days in the outdoor environment and weeks to months in the indoor environment depending on dust levels, light, and humidity). Moreover, information provided by presenters from Dalhousie University indicated widespread heavy spraying of OPs (including the OP chlorpyrifos) and pyrethroids throughout Cuba to prevent the spread of Zika virus by mosquitos. If the images of pesticide spraying shown in the formal presentations to the committee were reflective of actual conditions in Havana, it is highly likely that U.S. Embassy personnel were exposed to OPs either when they were in public spaces or via overspray that drifted from public spaces into U.S. Embassy offices and residences. As an aside, targeted exposures of individuals to OPs are also possible, as illustrated by the assassination of Kim Jong-nam, half-brother of North Korean leader Kim Jong-un, who died after two women allegedly applied OP nerve agent to his skin in the Kuala Lumpur airport on February 13, 2017, and by the attempted assassination of a former Russian spy and his daughter in Great Britain in 2018. However, these individuals showed acute symptoms of cholinergic poisoning associated with their exposure to OPs.

OP exposure is also monitored by measuring AChE activity in blood samples because OP insecticides inhibit AChE. AChE activity was not measured in blood from U.S. Embassy personnel. The Dalhousie University research team presented data they believed demonstrated significantly decreased AChE activity in at least a subset of Canadian Embassy personnel and Canadian tourists who were in Havana during the same time as affected U.S. Embassy personnel. Based on these data and targeted analysis of OPs and pyrethroid metabolites in serum samples that identified the OP temephos and the pyrethroid metabolite 3-PBA in blood from a subset of individuals (although the overlap between individuals with AChE inhibition and detectable OPs/pyrethroids is not clear), the Dalhousie University group developed a working hypothesis that neurological effects were due to chronic low level cholinesterase inhibitor toxicity. These data cannot, however, be considered supportive of this hypothesis. One reason, based on information presented to the committee, is that the Dalhousie group measured AChE activity in serum/plasma samples. However, AChE is a membrane-bound molecule found in blood only on erythrocytes; thus, whole blood samples, not serum or plasma, are required for accurate

determination of AChE activity in blood. Another concern with the Dalhousie measurements is that AChE levels should always be compared to the established reference values of the clinical laboratory in which the measurements are performed, rather than to the values of a specific and limited set of experimental controls, because laboratory reference values are generally based on many more samples and reflect a more realistic range of normal activities. The Dalhousie study relied instead on experimental controls. A second reason is that the number of Canadian personnel with detectable levels of temephos or 3-PBA was much smaller than the number of individuals with symptoms. A third reason is that Canadian personnel were not sampled at the time of initial signs and symptoms.

Absent data regarding the concentration of OPs or pyrethroids in relevant environmental samples collected proximal to the onset of symptoms or in samples from affected U.S. Embassy personnel at the time of initial signs and symptoms, it is not possible to determine whether exposures were at levels that might reasonably cause toxic effects, particularly in vulnerable individuals. This issue is complicated by the fact that there is growing evidence that at least some of the neurotoxic effects of OPs are mediated by mechanism(s) other than or in addition to AChE inhibition (Anger et al., 2020; Costa, 2006; Naughton and Terry, 2018; Pope, 1999).

With regards to the overlap of symptoms between chemical exposures and the Havana cases, epidemiologic and clinical studies have linked occupational or environmental chemical (including OP and pyrethroid insecticide) exposures to a subset of the distinctive early phase symptoms and many of the nonspecific chronic problems suffered by some of the U.S. Embassy Havana cases (see Appendix D).

Acute OP poisoning manifests as a clinical toxic syndrome known as cholinergic crisis, which includes parasympathomimetic symptoms (sweating, tears, rhinorrhea, salivation, urination, diarrhea, increased bronchial secretions and bronchoconstriction, and bradycardia), muscle fasciculation followed by flaccid paralysis, loss of consciousness and seizures (Eddleston et al., 2008; Hulse et al., 2014). Subacute and chronic OP exposures involving doses that do not cause significant AChE inhibition, do not cause cholinergic signs but can be associated with neurotoxic effects not only in individuals with occupational exposures, but also in the general public. OP-associated neurotoxic effects, which may or may not be associated with AChE inhibition in affected individuals, include hearing loss, tinnitus, dizziness, headache, fatigue, motor incoordination, nausea, insomnia, anxiety, memory deficits and inability to concentrate (Anger et al., 2020; Ashok Murthy and Visweswara Reddy, 2014; Choochouy et al., 2019; Crawford et al., 2008; Dassanayake et al., 2007, 2008, 2009; Dundar et al., 2016; Edwards and Tchounwou, 2005; London et al., 1998; Richter et al., 1992; Roldan-Tapia et al., 2006; Ross et al., 2013; Teixeira et al., 2002). Some of these effects were reported among affected DOS employees stationed in Havana.

There are significantly less epidemiologic and clinical data available regarding the neurotoxic effects of pyrethroids than there are for OPs, but published studies report associations between acute, subacute, and chronic pyrethroid exposures and hearing loss, visual disturbance, tinnitus, dizziness, headache, nausea, fatigue, and deficits in memory and concentration in occupational cohorts and in the general public (Campos et al., 2016; Chen et al., 1991; Lessenger, 1992; Müller-Mohnssen, 1999; Richardson et al., 2019; Teixeira et al., 2002; Xu et al., 2020; Zeigelboim et al., 2019). High dose acute pyrethroid exposures are also associated with tremors and seizures (Bal-Price et al., 2015).

Summary

In summary, the committee concludes that it is not likely that acute high-level exposure to OPs and/or pyrethroids contributed to the unexplained illnesses observed in the Havana cases because there is no convincing evidence of acute high-level exposures and the clinical history of affected U.S. Embassy personnel is not consistent with acute OP poisoning. It is also unlikely that subacute or chronic OP or pyrethroid exposures precipitated the onset of the distinctive acute symptoms associated with the Havana cases. However, given experimental data indicating that interactions between pesticides (particularly OPs) and psychosocial or physical stressors, the latter including noise and non-ionizing radiation, can increase risk and/or severity of adverse outcomes, the committee could not rule out the possibility, although slight, that exposure to insecticides, particularly OPs, increased susceptibility to the triggering factor(s) that caused the Embassy personnel cases. Alternatively, differential exposure to insecticides amongst affected individuals may have contributed to the clinical heterogeneity of the acute symptoms noted in Havana cases, since OP and pyrethroid exposures are associated with a subset of these acute symptoms (see Appendix D). The committee also finds it plausible that subacute or chronic OP and/or pyrethroid exposures contributed to the nonspecific chronic symptoms observed in affected U.S. Embassy personnel.

INFECTIOUS AGENTS

Sources of Information

The committee reviewed published medical and public health literature, including results of searches of PubMed for infectious diseases, Cuba, and neurological features.

Assessment and Findings

The committee considered endemic and epidemic infectious diseases known to have been present in Cuba during 2016-2018 and focused on those with known neurological manifestations. Some of these diseases could be excluded based on their dissimilar clinical features relative to the signs and symptoms reported by U.S. Embassy personnel in Havana, such as rabies or Guillain-Barré syndrome as a post-infectious complication of campylobacteriosis. Several mosquito-borne infections received further attention because of their prevalence and association with relevant, albeit rare, clinical features. These included dengue, chikungunya, and Zika virus infections. All three have been associated with encephalitis, Guillain-Barré syndrome, transverse myelitis, and neuro-ocular disease (Mehta et al., 2018). All of these complications are rare. For example, it has been estimated that approximately 0.1 percent of all chikungunya infections develop neurological disease (Economopoulou et al., 2009). Risk factors include underlying co-morbidities, and the extremes of age. However, nearly all of these chikungunya cases with neurological complications also presented with typical acute systemic manifestations (i.e., fever, rash, arthralgia, and conjunctivitis). Although dengue has been the most commonly reported arboviral infection in Cuba (Guanche Garcell et al., 2020), the epidemiology and incidence of Zika in Cuba is particularly relevant to the timing of the DOS personnel health events.

Travel surveillance and genomic epidemiology revealed a large, unreported, and delayed Zika outbreak in Cuba that followed Zika outbreaks elsewhere in the Caribbean by about one year (Grubaugh et al., 2019). Zika disease began in Cuba in the latter half of 2016 and peaked in fall 2017. Genomic surveillance confirmed dengue disease in Cuba in 2014 and 2015 and a chikungunya outbreak in 2014, but little or none of these two diseases in 2016 and 2017. It is believed that implementation of an intensive mosquito control program based on insecticide use

beginning in February 2016 may have delayed the establishment of Zika virus and subsequent disease in Cuba until 2016-2017. (The committee considered the possible role of organophosphate and pyrethroid insecticide exposure in the DOS personnel illnesses—see Section 4, Chemicals.) Thus, the timing and relative prevalence of Zika in Cuba justify further comment on this infection as a possible cause of the DOS personnel cases.

A population-based observational study of Zika infection in the French West Indies in 2016 provides a valuable description of the neurologic complications of this disease (Lannuzel et al., 2019), and a reference against which the clinical features reported in DOS personnel (see Section 3) can be compared. In 2016, 66,600 persons in Guadeloupe and Martinique sought medical attention with manifestations of Zika infection. Of these, 87 presented to the major referral centers on the two islands with neurologic manifestations. Of the 87, 54 (62 percent) had peripheral nervous system (PNS) involvement, and of those 54, 40 were diagnosed with Guillain-Barré syndrome. Among the other 14 with PNS disease, 8 had cranial nerve palsies; in all 8, the facial nerve was involved, and in 4 of them, there was involvement of the vestibulocochlear nerve. Of the 87, 19 had central nervous system (CNS) involvement, with encephalitis the most common diagnosis. Of the 87, 14 had both PNS and CNS disease. Of 76 patients available for follow-up, 19 had residual disease at a median of 14 months after presentation.

Thus, the overall rate of Zika neurological complications seen in the main clinical referral centers during this epidemic year in the French West Indies was approximately 0.1-0.2 percent of those with known Zika infection (Lannuzel et al., 2019). This is similar to the rate for chikungunya on Reunion Island in 2005-2006. Approximately 5 percent of this small subpopulation with Zika neurologic complications shared a feature with the illnesses reported in the DOS Cuba patient cohort (i.e., vestibular disease, manifest as dizziness, nystagmus, and/or vertigo). A smaller number had hearing loss, memory difficulties, and visual loss. Thus, Zika virus can cause a few of the acute and chronic clinical features reported in the DOS Cuba patient cohort, but these features are quite rare with Zika and would not be expected to occur at all in a population of less than 1,000 people with Zika. None of the patients in the DOS Cuba cohort are said to have suffered from the much more common manifestations of Zika: rash, fever, arthralgia, myalgia, and conjunctivitis.

Summary

In summary, the committee considered possible infectious etiologies that might explain the clinical features reported in DOS employees and focused on those infectious agents known to be prevalent in Cuba and capable of causing neurological manifestations. Among those agents, Zika infection received attention from the committee because it was epidemic in Cuba in 2016-2017 and is known to be able to produce relevant neurological findings. However, after reviewing the medical and public health literature, the committee found it highly unlikely that Zika was the cause of the constellation of signs and symptoms reported among DOS personnel, especially the acute, sudden onset, initial phase clinical features, for two major reasons. First, Zika is not known to cause an abrupt onset illness nor an illness with the collection of findings reported in the initial phase of the DOS employee illnesses—especially in the absence of rash, fever, arthralgia, myalgia and conjunctivitis. Second, the relevant neurological features of Zika are exceedingly rare and statistically would not be expected to occur in any DOS employee in Havana, and certainly not more than one.

The committee could not rule out the possibility that some employees were infected by Zika, and that it contributed in some fashion together with other causative factors to the chronic

clinical findings, especially during 2017. The committee is not aware of serological testing for Zika or any other infectious agents among DOS Embassy Havana affected personnel.

PSYCHOLOGICAL AND SOCIAL FACTORS

Sources of Information

As noted in Section 3, clinical investigators presented data to the committee as aggregated summaries of patients' histories, physical examination findings, and results of laboratory testing including neuropsychological assessments. Individual patient-level data were not provided to the committee, other than what the committee learned from direct interviews with a small number of affected DOS personnel.

Assessment and Findings

Acute Symptoms

The committee carefully considered three possible roles for psychological and social factors in the morbidity experienced by DOS employees: (1) psychiatric disorders as primary causes of symptoms; (2) psychiatric disorders as secondary sequelae of other causes of illness; and (3) psychological and social factors co-existing with other causes of illness. As with all other potential causes and mechanisms reviewed by the committee, evidence was sought for and against specific associations between psychological and social factors and patients' symptoms. The committee did not regard psychological and social factors to be default explanations for enigmatic symptoms but endeavored to make a positive identification of their potential contributions to morbidity. These efforts were constrained by the limits of data collected and presented by the clinical teams from Miami, Penn, Dalhousie, and NIH, which offered an incomplete picture of the range of acute and chronic symptoms over space and time, and in particular about the course of illness of individual patients. Nevertheless, it appeared that a biphasic distribution of acute and chronic symptoms (see Section 2) offered coherence to the patterns of neuropsychiatric symptoms reported by the clinical teams and patients themselves.

In general, psychological factors may cause or contribute to emotional symptoms (sadness, frustration, irritability, anxiety, and anhedonia), vegetative symptoms (sleep, energy, and appetite changes), and cognitive symptoms (attention, concentration, and memory problems), as well as enigmatic somatic symptoms. At the milder end of the spectrum, these may fall short of fully diagnosable psychiatric disorders (i.e., transient and self-limited responses to life circumstances) or may represent adjustment disorders (i.e., periods of poor adjustment to stressors, including other illnesses). More severe or persistent symptoms may constitute major depressive or anxiety disorders, either as primary, secondary, or co-existing illnesses. In cases where individuals are exposed to potential threats to life or limb, acute and posttraumatic stress disorders may develop, manifesting with symptoms of re-experiencing, avoidance, hyperarousal, and negative mood and cognitions regarding the triggering event. The development of acute and posttraumatic stress disorders rests on the perception of threat by affected individuals. As such, reactions may vary considerably among exposed persons.

Potential threats attributed to human causes are more likely to trigger traumatic stress symptoms than threats attributed to natural causes, especially when the threat is thought to arise from the concerted efforts of an adversarial group (e.g., warfare) rather than isolated actions of individuals (e.g., unprovoked assaults) (Bromet et al., 2017; Staab et al., 1999). Environments that include incomplete, inconsistent, or erroneous information about potential threats may

exacerbate and perpetuate symptoms. After reviewing the nature of these disorders, the committee concluded that such reactions could not cause the initial sudden-onset distinct and unusual audio-vestibular symptoms and signs described in Section 3 or by CDC, but that psychological or psychiatric disorders could conceivably contribute to some of the other acute and chronic symptoms in some patients.

The committee then considered the possibility that acute auditory and vestibular symptoms described by DOS patients were hallucinations or delusions. Psychotic disorders may cause hallucinations involving any sensory modality. Auditory hallucinations are common, whereas vestibular and balance hallucinations are uncommon. However, auditory hallucinations caused by primary psychotic disorders usually take the form of human voices or other human sounds, less often other natural or mechanical sounds. Importantly, the committee received no evidence that any patients had psychiatric symptoms indicative of primary, secondary, or co-existing schizophrenic spectrum disorders, brief reactive psychoses, mood disorders with psychosis, psychoses related to substances of abuse, or psychoses associated with major cognitive disorders. Therefore, the committee found it very unlikely that any of the acute or chronic symptoms experienced by patients were caused by these conditions.

Patients with delusional disorders may describe a variety of sensory experiences that they relate to plausible (i.e., non-bizarre) but not factual causes. The most common delusions are paranoid in nature. Affected individuals are otherwise normal from a psychiatric perspective. Delusional disorders do not cause other emotional, vegetative, or cognitive symptoms. Infrequently, delusions may be shared by a few individuals close to the index case. The committee did not receive information about the psychiatric or psychological status of individual patients; therefore, it could not make a determination about the presence or absence of delusional disorder as a cause for the distinct acute symptoms in any affected persons. However, the committee did conclude that delusional disorders could not explain the full range of symptoms reported by the entire group of patients.

Reports in the medical literature (Bartholomew and Baloh, 2020) and mass media (Borger and Jaekl, 2017; Hurley, 2019) have opined that mass psychogenic illness (also known as mass hysteria or epidemic hysteria) was the cause of patients' symptoms. These reports cited the challenging political and security circumstances surrounding the diplomatic missions in Cuba and China, the frequent harassment experienced by DOS employees in their homes, the lack of evidence for a clear external cause for patients' symptoms, and the absence of a definitive pattern of structural deficits on medical examinations in support of this conclusion. The committee considered this possibility, while keeping in mind that the likelihood of mass psychogenic illness as an explanation for patients' symptoms had to be established from sufficient evidence. It could not be inferred merely by the absence of other causal mechanisms or the lack of definitive structural injuries.

Studies of mass psychogenic illnesses have found that social and environmental variables are important in triggering these events. Thereafter, social connections or exposure to developing cases either in person or vicariously through word of mouth or media, including social media, are necessary to sustain them (Bartholomew et al., 2012; Boss, 1997; Cole et al., 1990; Knight et al., 1965). However, adverse social circumstances are not required preconditions. Well-documented cases of mass psychogenic illnesses have occurred in groups that were under no identifiable external stress or internal strain at the onset of events (Bartholomew et al., 2012). Most individuals affected by mass psychogenic illnesses do not have pre-existing psychiatric disorders. Rather, in most events, index cases developed their initial symptoms in response to idiosyncratic interpersonal circumstances or after exposures to perceived or actual but benign

environmental stimuli (Bartholomew et al., 2012; Boss, 1997; Cole et al., 1990; Knight et al., 1965). However, it is important to recognize that mass psychogenic illness may follow index cases afflicted with serious medical conditions or exposed to harmful environmental agents, especially when potential causes of illnesses affecting index cases are unclear or misattributed to agents, actual or perceived, that may affect the larger group (Bartholomew et al., 2012). The term "mass" may be mistaken to imply that large numbers of individuals must be involved over a short period of time in these events. However, the medical literature shows that one-third of incidents since the 1970s involved fewer than 30 individuals and approximately 20 percent of events lasted longer than 30 days (Cole et al., 1990). For communities under chronic stress, resolution may take months (Bartholomew et al., 2012). Nonspecific dizziness, lightheadedness, and fatigue have been described commonly in mass psychogenic illnesses, but complaints similar to the directional audio-vestibular symptoms reported by affected individuals from Cuba have not (Bartholomew et al., 2012; Cole et al., 1990). Events of mass psychogenic illness end when the potential for social contagion is reduced (not necessarily eliminated) by separation of unaffected individuals from sources of contagion and when the majority of unaffected or previously affected individuals reach the conclusion that the inciting event was physically benign or no longer poses a risk (Bartholomew et al., 2012).

These key characteristics of mass psychogenic illness have strong parallels with outbreaks of infectious diseases and have been investigated successfully using similar rigorous epidemiologic methods since the 1960s (Knight et al., 1965), including detailed examinations of index cases and subsequently affected individuals, contact tracing, and careful investigation of the environments in which the events occurred (Bartholomew et al., 2012; Boss, 1997; Cole et al., 1990; Knight et al., 1965). As described in Section 3, the committee noted two constellations of signs and symptoms, one of them acute, occurring at the onset of some cases with more distinct and unusual features, and the other chronic, occurring later in the course of these cases or with subacute onset in other cases. However, in the absence of patient-level data, the committee could not identify index versus subsequent cases. Furthermore, the committee received no epidemiological evidence about patterns of social contacts that would permit a determination about possible social contagion. Without access to these data, a retrospective diagnosis of mass psychogenic illness is considered to be speculative at best and subject to necessary criticism (Jacobsen and Ebbehøj, 2016, 2017; Jansen et al., 2016). Thus, the committee was not able to reach a conclusion about mass psychogenic illness as a possible cause of the events in Cuba or elsewhere.

Chronic Symptoms

Despite extensive clinical evaluations, definitive causes of chronic symptoms have not been identified in most DOS personnel with ongoing morbidity. However, approximately one quarter of patients examined by the clinical team at NIH were diagnosed with persistent postural-perceptual dizziness (PPPD) and at least one patient received that diagnosis after a series of clinical examinations conducted elsewhere. PPPD is a functional (not psychiatric) vestibular disorder that may be triggered by vestibular, neurologic, other medical, and psychological conditions (Staab et al., 2017). Thus, its presence provides no information regarding the initial causality of patients' symptoms. On the other hand, its presence may inform treatment as there are data from uncontrolled and small controlled investigations to support the use of vestibular (including visual) habituation exercises, cognitive behavioral therapy, and serotonergic antidepressants (selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors) for treating this condition (Popkirov et al., 2018; Staab, 2020). When symptoms of

PPPD occur in the setting of additional morbidity such as cognitive symptoms and psychological distress, expert opinion and clinical experience suggest that a broader array of treatments, including cognitive rehabilitation and third-wave psychotherapies (e.g., Mindfulness, Acceptance and Commitment Therapy) may be helpful.

Summary

As stated previously, the committee sought positive evidence that psychological and social factors may have caused or contributed to symptoms reported by DOS personnel. The acute initial, sudden-onset, distinct and unusual symptoms and signs described in some affected DOS personnel (see Section 3 and CDC Report) cannot be ascribed to psychological and social factors in the absence of patient-level data. The significant variability and clinical heterogeneity of the illnesses affecting DOS personnel leave open the possibility of multiple causal factors over time and place, both for individual cases and for the population. Like other mechanisms reviewed by the committee, psychological and social factors could exacerbate other forms of pathology and have to be considered as contributors to morbidity in some of the cases, especially for individuals with chronic symptoms.

The chronic vestibular symptoms experienced by some DOS personnel are consistent with persistent postural-perceptual dizziness. This functional vestibular disorder may be triggered by vestibular, neurologic, other medical, and psychological conditions, and offers a potential avenue for rehabilitative interventions.

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Section 5

Acute Treatment and Rehabilitation

SOURCES OF INFORMATION

The committee's Statement of Task requested an "assessment of treatment options." However, as discussed above, individual-specific data on treatment and clinical outcomes were not readily available to the committee. It was privy to anecdotal information about the treatment of some individuals, but this information was not standardized or systematic. The approach to initial treatment and rehabilitation was also complicated by a number of factors including remote locations and difficult access to specialized care, diverse clinical presentations by affected personnel, and a variety of reporting schemes at different times. It is beyond the scope of this report to assess the efficacy of specific treatments of individuals. It is important to note that in most injuries to the brain or vestibular system, poorly understood recovery or compensatory mechanisms lead to functional improvement over time. Non-pharmacologic therapies targeted at the person's deficit enhance or quicken the process of functional improvement.

Acute Treatment

The information available to the committee about the acute treatment of Department of State (DOS) personnel derived from direct testimony to it by affected personnel, summative reports in the literature, or information provided to it by the clinical investigators. In general, the personnel were treated acutely with rest and instructions to avoid the circumstances associated with the initial signs and symptoms. In the absence of recovery and out of an abundance of concern, some personnel were transferred to Miami where further evaluation was performed. Very limited information on treatment that occurred at that time was available to the committee.

Chronic Treatment

The data available to the committee on chronic treatment derived from direct testimony to it by several affected personnel, reports in the literature, and a presentation by Penn clinicians involved in the care of the affected DOS employees and their families. In general, the data were presented in summary form without specific details. For example, the granularity of the detail was at the level of general cognitive, neuro-optometric, vestibular and vocational rehabilitation interventions. Some more specific information is found on page 1130 of the publication by Swanson et al. (2018). The committee lacked specific information on patient-specific treatment approaches and responses, which would have helped in generating recommendations on potential alternatives. However, information made available to the committee suggested that affected individuals did improve after referral to vestibular or cognitive therapy.

Given these limitations, the committee focused its efforts instead on a review of the current state-of-the art in neurological, vestibular, and neuropsychological rehabilitation, with the goal of offering general guidance (this section) and recommendations (see Section 6) for treatment of patients with unexplained neurological or other medical manifestations like these in the future.

ASSESSMENT AND FINDINGS

The committee distinguishes observations related to care of the acute syndrome from those for longer-term care of the chronic syndrome associated with the Embassy employees in Havana.

Acute Treatment

In the case of acute symptoms that are thought to be caused by injury to the central nervous system, it is important that expert clinicians perform an evaluation as early as possible after the onset of the illness. This can include immediate care by on-site medical personnel, but it is unlikely that such personnel will be expert in the assessment of neurological injuries. In addition, although some level of care can and should be provided by telemedicine, it is very likely that parts of the neurological examination and much of the required early testing will not be feasible on-site. Hence, both to avoid further injury and to insure the most rapid access to expert care, there should be plans in place, as needed, for each embassy to remove the affected individuals to a protected site where this evaluation can be done. The actual indicated treatment will be specific to the type of injury that has been sustained. If removing personnel is required for evaluation, this evaluation should be completed as soon as possible and then personnel should be returned to whatever is the most supportive environment. Rehabilitation will also be guided by evidence of damage to specific parts of the nervous system.

Chronic Treatment

The absence of a known cause of the symptoms and signs in the affected DOS employees complicates initial treatment and early rehabilitation to some degree. However, it is not unusual for patients to develop chronic nonspecific symptoms (e.g., fatigue, dizziness) following acute medical events such as mild traumatic brain injuries, acute peripheral vestibulopathies, cardiovascular or cerebrovascular events, cancer treatments, and complex surgical procedures, which may differ among individuals (Donnell et al., 2012; Gunstad and Suhr, 2001; Julien et al., 2017; Pavawalla et al., 2013; Polusny et al., 2011; Voormolen et al., 2019) despite the same exposure and mechanism of injury (Collins et al., 2016; Gardner et al., 2019; Nelson et al., 2019; Si et al., 2018). Thus, even in the setting of an identified precipitant, it is not always clear that the acute event and the chronic symptoms are directly related. Nevertheless, the absence of a known cause or mechanism does not diminish the value or relevance of management guidelines. Accordingly, the committee offers general guidance below on the future management of patients with clinical presentations similar to those of DOS Embassy employees; for example, as commonly seen in individuals suffering from mild traumatic brain injury (Bomyea et al., 2019; Chen et al., 2019; Iverson et al., 2015; Kontos et al., 2018, 2019, 2020; Sweeney et al., 2020; Yue et al., 2019).

1. **Early evaluation and treatment are essential.** A significant body of literature demonstrates that the earlier an evaluation is undertaken and treatment initiated, the better the outcome (Belanger et al., 2015; Lacour and Bernard-Demanze, 2014; Lacour et al., 1976, 2020; Mittenberg et al., 1996; Ponsford et al., 2002). In general, early treatment can prevent development of chronic neurological conditions (Gil-Jardine et al., 2018; Mittenberg et al., 1996; Ponsford et al., 2002; Seabury et al., 2018; Snell et al., 2009; Twamley et al., 2015; Wade et al., 1998), which are much more difficult to treat (Hiploylee et al., 2017; Perry et al., 2016; Snell et al., 2009, 2019).

2. **Avoid removing personnel from supportive environments.** A supportive environment contributes to treatment success in rehabilitation of chronic symptoms that develop after brain injury or other acute medical events such as those listed above (Polich et al., 2020; Vanderploeg et al., 2018). Relocation of affected personnel to a site for chronic rehabilitation without providing for social supports, such as family or close colleagues, can result in social isolation and exacerbate anxiety. The committee heard accounts of such.
3. **Initial treatment should emphasize early assessment, education, and return to activity.** Proactive therapeutic interventions, sleep hygiene and exercise are simple but helpful measures.
4. **Chronic neurological syndromes require a multi-disciplinary approach.** Treatment of chronic syndromes may require more intensive treatment. The length of time to recovery may be months, and some residual symptoms may persist. Experience with persistent postural-perceptual dizziness (PPPD) provides useful lessons.

The diagnosis of PPPD in some Havana cases informs prognosis (Popkirov et al., 2018; Staab, 2020). With a well-integrated, multi-disciplinary treatment plan of physical and psychological therapies and medication provided over a course of 3-6 months, most patients with PPPD are able to achieve a reduction in symptoms to a level at which they are not impaired in their performance of routine daily activities inside or outside the home. Despite improvement, they may remain vulnerable to temporary (hours to days) exacerbations of symptoms on exposure to provocative stimuli such as extensive physical activity or motion-rich environments. Approximately 10-20 percent of patients in the general population who have had PPPD for more than 4 years remain work-disabled by their symptoms even after achieving their maximal response to currently available treatments (Schaaf and Hesse, 2015; Trinidade and Goebel, 2018).

As described previously, psychological disorders may develop as secondary complications of acute illnesses, regardless of cause. Data provided by the National Institutes of Health (NIH) team suggested that a considerable number of patients with ongoing physical symptoms may be experiencing clinically significant psychological distress. The most likely causes of these symptoms are secondary depressive, anxiety, traumatic stress, or somatic symptom disorders. The committee had no individual patient-level data with which to reach any conclusions about the presence of these conditions among patients with persistent symptoms. However, all of these are treatable conditions, which means that proper diagnosis and application of scientifically validated therapies could lead to a reduction in morbidity and improvements in functioning among affected individuals, regardless of the nature or cause of the initial illness or the presence of co-existing chronic conditions.

5. **Understand the phenotype.** Personal characteristics and situational and biological differences may all impact approach and response to treatment. In general, phenotypes that predict a more successful response to neurological rehabilitation include higher level of education, resilience in other settings, and job satisfaction. Negative prognostic features include stressful job and life situation, previous history of depression, and anxiety. Significant efforts are under way to identify genetic and other factors that may affect responsiveness to neurological rehabilitation. Further efforts to link mechanism of injury with clinical manifestations (phenotype), and

selection of and response to different treatment modalities will be important. The committee anticipates that a telemedicine team (see Section 6) assembled to help locally available clinicians in situations like those faced by the affected DOS employees would understand this evolving literature and adapt their approaches to the latest interventions available.

6. **Testing and therapies without established validation should be for research purposes only.** The committee was asked to comment on the use of diffusion tensor imaging to establish brain injury and on visual rehabilitation for vestibular symptoms after brain injury in DOS personnel. As noted in Section 3, the findings with diffusion tensor imaging did not convince the committee of the validity of this approach as a diagnostic method, although it may have value as a research method in future events. Visual training therapy is widely practiced for patients with vestibular symptoms, but the evidence base for this type of treatment remains controversial (Barton and Ranalli, 2020). Hence, while there is not adequate evidence to recommend such therapies for routine treatment of patients suffering from traumatic brain injury (TBI) or symptoms similar to TBI, the committee concluded that if clinicians based on their judgment wanted to offer them to individual patients, that the patients should be informed that the therapy was not supported by adequate evidence, but that there were reports of it being helpful in some patients.
7. **Interdisciplinary consultation.** The committee observed that a potential shortcoming of the medical evaluations and treatment received by DOS patients was that they were provided by teams focused on one area of clinical medicine (e.g., otology in Miami, brain injury at Penn). When symptoms are as enigmatic as those experienced by DOS patients, early involvement of a broader group of clinical specialists, paired with experts in epidemiology and environmental exposures (e.g., toxicologists, radio frequency engineers, and others as determined by the situation) would reduce the chances that early clues about causality would be missed or that premature conclusions would be drawn about potential diagnoses. These additional experts could contribute in person or virtually.

SUMMARY

The committee lacked information on patient-specific treatment approaches and responses, which would have helped in generating recommendations on potential alternatives. In reviewing best practices in neurological rehabilitation, the committee finds that early evaluation and treatment are essential for optimal outcomes, a supportive environment is important, and an interdisciplinary approach for rehabilitation of chronic neurological conditions is best, as are appropriate and early education and realistic expectation-setting.

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Section 6

Looking to the Future and Recommendations

The committee recognizes that Department of State (DOS) employees serve a vital role to the country and are vulnerable to a wide range of potential threats. Their health and well-being is a national imperative. The committee believes that DOS has a tripartite ethical obligation to safeguard the well-being of deployed personnel. This entails the prompt identification of threats, expeditious diagnosis and treatment, and the provision of rehabilitation and long-term care for service-related injuries. The committee believes that this is an enduring fiduciary responsibility of DOS much like that afforded to military service members and others who have sustained injuries or disabilities in the performance of their government duties.

Clarity about the nature of the illnesses that first began to affect DOS employees in Cuba in 2016 and subsequently in China, and the causative mechanism(s), remains elusive. What is clear is that a distinct set of unusual clinical manifestations occurred abruptly in some individuals at the onset of their illness, and that the illness became chronic and debilitating for some, but not for all individuals. It is also clear that there is significant heterogeneity among a larger population of affected employees; some did not experience the distinct set of manifestations at onset, and some have had only nonspecific common manifestations. This heterogeneity may reflect evolution of the illness over time, multiple mechanisms at play within and between individuals, and the varying methods used to investigate these individuals at different clinical study sites.

Among the plausible mechanisms that the committee considered, directed radio frequency (RF) energy, especially in those with the distinct early manifestations, appears most germane, along with persistent postural perceptual dizziness (PPPD) as a secondary reinforcing mechanism, as well as the additive effects of psychological conditions. The committee cannot rule out other possible mechanisms (see Section 4), and again, considers it likely that a multiplicity of factors explains some cases and the differences between others. Commencement of appropriate neurological rehabilitation methods early in these illnesses, even without a diagnosis, would have been helpful.

The committee recognizes the impossibility of going back in time to examine the affected individuals early in their illness, gather evidence for or against any of the possible mechanisms, and begin treatment. The committee and others are limited today in what can be pieced together about these cases. However, the committee believes that it would be useful, and even imperative, for actions to be taken now in anticipation of future cases. Although these future cases may resemble in some fashion those that began in Cuba and China in 2016-2018, they need not be similar. Early in a future "event," cases may not be identifiable as such, and the existence of an event worthy of attention may not be initially obvious. Planning should accommodate all of these possibilities.

The committee's purpose is both to respond to the needs of U.S. government employees in the wake of the experience in Cuba and China as well as to anticipate future threats to their well-being. While the committee clearly needs to understand these events in order to be able to respond to a recurrence, the larger issue is preparedness for new and unknown threats that might compromise the health and safety of U.S. diplomats serving abroad. It is not enough to design a plan that prepares DOS for the past. The emergence of the novel pathogen SARS-CoV-2 is a

stark reminder that DOS must be thoughtful and creative in its anticipation of future threats, both natural and human-made, and agile in its response. To that end, the committee proposes a number of recommendations in order to enhance future responses.

Recommendation 1. The Department of State should expand its collection of baseline and longitudinal data and biological specimens from all personnel prior to and during overseas assignments.

A major limitation to establishing associative or causal health effects among DOS personnel assigned to Cuba or China was the lack of pre-exposure or baseline health status. It is critical to identify changes in the health of embassy personnel from their baseline if a threat occurs. To make these determinations, medical staff who collect necessary information at the time of the incident must have access to baseline information on the affected individuals. Therefore, for surveillance, the committee believes that there should be routine data collection for all DOS employees on foreign assignments, including collection of whole blood, plasma, and urine, as well as general medical and neurological examinations. Given the nature of the symptoms of the Havana personnel, baseline visual and auditory examinations would be useful, at least for personnel assigned to locations where similar kinds of events might take place. Baselines should be updated regularly, and whenever a significant medical or environmental event occurs. For the affected cohort of DOS employees, DOS should establish ongoing registries to identify any late-onset symptomatology or illness attributable to exposures at post.

The Acquired Brain Injury Tool (ABIT) is a clinical assessment tool that is currently used by DOS pre- and post-deployment to inventory the same neurological, vestibular, and auditory symptoms that were identified in DOS personnel in Cuba and China. However, given that the committee does not know the nature of future events, it would be wise to revise it and include symptoms beyond those encountered in Cuba and China. Establishing a pre-deployment baseline is key.

In addition, to be of maximal value, the committee suggests that the ABIT—and other assessment tools—be modified to obtain relevant epidemiological data such as physical location and local environmental parameters at the time of symptom onset to identify potential sources of threat. In order to ensure the sensitivity and specificity of the evaluation of personnel overseas, the committee recommends that the ABIT be reviewed on a periodic basis by an expert panel of physicians and scientists who can keep the assessment tool forward-facing with respect to present and future threats. The committee suggests that this panel include specialists in general internal medicine, neurology, infectious disease, physiatry, tropical medicine, pharmacology, toxicology, biostatistics, epidemiology, environmental health, bioterrorism, and psychiatry, so as to gather information on natural and human-made threats that might affect embassy personnel. The committee recommends that revisions be based on evolving epidemiological patterns or knowledge of potential malign threats. In addition to the data currently collected, the committee strongly recommends collecting data on prior brain injury and additional assessment of prior and ongoing psychiatric symptoms that might be primary or secondary sequelae from a novel threat.

Recommendation 2. The Department of State, with support from the U.S. government, should establish plans and protocols now to enable

comprehensive, expeditious public health and research investigations in the future, should a cluster of new cases warrant investigation.

In considering needs for a response to future DOS cases, it is important to differentiate between personal medical care (which must remain private), research (which must remain voluntary), and the public health necessity for evaluating information on individuals in a way that may impinge on their privacy in order to protect the health of other embassy personnel or their future well-being should there be a public health threat. It appears that the Centers for Disease Control and Prevention (CDC) assumed this public health role with respect to the cases from Havana, but only did so beginning 1 year after discovery of the first case, when there was much less to be gained from their actions. The committee recommends that a similar response be prepared and authorized in advance of the next potential set of cases, so that the necessary collection of information for a proper public health investigation of U.S. Embassy employees can be undertaken in a timely fashion and made available immediately. It is critical that these protocols be developed in an open and transparent manner with the Foreign Service Officer (FSO) community in order to build and maintain trust. To assist with the aforementioned surveillance, DOS should receive increased resources for MED HART (DOS Bureau of Medical Services Health Alert Response Threat) in order to allow for more timely and agile responses to unexpected and novel threats to personnel. The committee notes that while MED HART was intended to provide operational medical support, it was not necessarily designed to perform epidemiological surveillance and analysis in an effort to identify new case clusters in real-time. An occupational health surveillance system that allows DOS to identify high-risk populations and worksites, emerging work-associated problems, hazardous conditions and exposures, and that can target and evaluate interventions, as outlined in the 2018 National Academies report on occupational safety and health, would benefit overseas DOS locations (NASEM, 2018). DOS should also be provided resources to create such an occupational health surveillance system that could provide ready access to information should an investigation need to be launched. The committee suggests that DOS utilize an expert panel to provide advice on the collection of routine medical data.

In addition to the information that may be necessary to counter a public health emergency involving Embassy personnel, a research investigation may be needed. Participation by Embassy personnel in this type of investigation should be subject to the same human subjects protection rules that apply to all human subjects research. In considering the lessons learned regarding the ethical conduct of environmental research following the *Deepwater Horizon* oil spill by the Gulf Long-term Follow-up Study (GuLF STUDY) (Resnik et al., 2015), the committee urges DOS to prepare in advance for the conduct of human subjects research that might pertain to an unexpected health hazard. The GuLF STUDY investigators recommended that investigators identify an Institutional Review Board (IRB) and be ready to engage in research when and if it became necessary. To that end, the expert panel described here could also inform the training of research teams that could be deployed and it could facilitate the engagement of the broader DOS community, whose trust will be necessary for the conduct of research. Protocols and consent forms could be developed in advance, and revised and modified to account for the specific populations, threats, and urgencies involved in a particular emergency. Such an approach would facilitate a rapid response in an emergency and the collection of data that might be unavailable if usual research approvals had to be initiated coincident with the emergence of a threat. Protocols should stipulate a longitudinal design so that subjects can be followed over time and clinical outcomes captured. The GuLF STUDY investigators strongly recommended this proactive

approach to "ensure adequate review by IRBs and other groups of complex ethical issues without jeopardizing rapid response to a public health emergency" (Resnik et al., 2015, p. A230). The committee believes such attention to anticipatory governance will enable the expeditious and systematic collection of data necessary to elucidate novel threats while ensuring human subjects protections.

Recommendation 3. Following the identification of a possible new case cluster, the Department of State should ensure collection of data critical for an effective investigation.

In addition to the collection of data pertaining to individual diplomats, it is critical that additional public health and epidemiological surveillance data be obtained to provide the temporal and geographic context for the health presentation of individuals. In this manner, patterns may emerge that will lead to the identification of clusters of individuals who have become ill, and inform possible causes. This will facilitate the early identification of threats, and also give credence to individuals who present with curious symptoms. When several patients present concurrently and these associations can be made quickly, it lends credibility to each patient's presentation whereas previously they might have been met with skepticism. This is a critical aspect of early threat identification and recognition of disease clusters. DOS might consider a mechanism for real-time, self-reporting by employees of concerning signs and symptoms. Continuous monitoring of these reports by a multi-disciplinary panel of medical and scientific experts might complement other approaches for health information gathering.

Medical surveillance provides a strategy for illuminating one (i.e., the medical) dimension of a potential health threat. The other critical and complementary strategies include surveillance of potential environmental factors. Routine environmental surveillance comes with the added potential advantage of detecting a threat early and before adverse effects have occurred. Tremendous advances are being made in sensor technology that provide the means for stationary, personal, or wearable devices that capture signal or material or both for evaluating the presence of chemical, biological, or physical agents. Such sensors could be randomly and routinely deployed or be available for response under circumstances when there is concern. One way that medical and environmental surveillance can be effectively integrated is with the collection and archiving of baseline biological and environmental specimens that are available for comparison to samples collected after event onset. It may be that the etiologic agent (metabolite or marker of its biological effect) is present within one or more biological materials (blood, serum, urine, hair, nails) or environmental samples. For example, in addressing the hypothesis put forth by the Canadians about possible etiologic agents in Havana, organophosphate insecticides or their clear biological effect (cholinesterase inhibition) would be apparent in appropriate biospecimens collected within a suitable timeframe of symptom onset and/or suspected exposure. Using appropriate chain-of-custody procedures, levels could be compared to those in baseline samples (preferable) and/or to normative population distribution values such as are available from CDC's National Health and Nutrition Examination Survey (NHANES).

Recommendation 3-A. If research or assessments support the possibility of radio frequency (RF) energy as a cause of illness experienced by some of its employees, the Department of State should train and equip employees with

the capability to measure and characterize their exposure to RF energy in real time should the need arise in the future.

Capturing a suspected exposure event in real time is critical to establishing cause and effect given the transient nature of the suspected exposure mechanism. It is within the state of the art of RF electronics engineering to measure incident RF energy power levels, frequency bands, pulse width, pulse repetition rate, and angle of arrival. A system could also record secondary effects on other electronics in the vicinity of the employees as well as their own notes on their actions to characterize the situation. Modern electronic measurement devices that are compact and user-friendly require only modest investment for development and deployment. Operationally, a systematic series of RF energy characterization measurements could be made by an embassy employee to map out the spatial energy incident at a particular location. The set of measurements would indicate the direction of incident RF energy, as well as the impact of physical barriers (e.g., walls, doors, etc.) on the transmission of the RF energy and the correlation with the perceived effect by the employee.

In addition to potential trigger and/or monitoring sensors that characterize the exposure characteristics, further experiments are required to demonstrate causal links between an RF exposure regime and biological dysfunction observed or experienced by DOS employees. This would enable an RF exposure diagnostic kit for simultaneously measuring exposure characteristics and estimating potential dosage levels for individuals. Capturing both sets of data (exposure characteristics and biological damage) would allow direct cause and effect to be established and help researchers develop mitigation techniques to counter future exposure events and provide immediate, appropriate medical care based on the exposure.

Recommendation 3-B. The Department of State should develop a systematic approach for toxicological diagnoses, and a protocol that supports this approach.

The absence of such an approach hampered the committee's assessment of toxicants as possible contributors to the illnesses in DOS employees from Havana. With respect to missing data for these employees, such a protocol might include more detailed records of pesticide and other potential chemical use (e.g., more extensive environmental sampling for OPs and pyrethroids, particularly proximal in time and space to the occurrence of symptoms in affected individuals), and the archiving of biological samples collected from affected individuals at the time of initial symptoms for subsequent targeted testing of environmental chemicals suspected of contributing to these illnesses. A valuable model for a coordinated system-wide research response to public health emergencies is provided by the National Institutes of Health (NIH) Disaster Research Response (DR2) Program.[5] This program was motivated by many of the same goals and has successfully addressed many of the same needs as the system the committee envisions for DOS in the future.

Recommendation 4. The Department of State, with support from the U.S. government, should provide for appropriate personnel to identify public health emergencies and activate the necessary response.

[5] See http://dr2.nlm.nih.gov (accessed July 24, 2020).

To facilitate early identification of health threats to Embassy personnel, the committee suggests an expanded role for health attachés. Health attachés are diplomats with specialized knowledge in health-related issues who engage in global health diplomacy to promote U.S. national interests, serve as liaisons with in-country counterparts, and provide technical assistance to Embassy personnel and local stakeholders. Health attachés are cross-trained in foreign affairs, international law, and other domains, as well as the public health disciplines. They are not present in every Embassy and in fact are posted sparingly around the globe. Most are on loan from the Department of Health and Human Services, CDC, the Food and Drug Administration, NIH, or from the Office of Global Affairs (OGA) in the Office of the Secretary of Health and Human Services. Others have hailed from the Department of Defense and the U.S. Agency for International Development. As of 2014, their work was coordinated with DOS's Office of Global Health Diplomacy (Brown et al., 2014). The committee believes that health attachés can serve as a critical nexus of timely information from in-country and cross-agency sources. As such, they would be well positioned to identify and respond to threats quickly, provide advice, and collect relevant data needed for informed responses. The committee urges increased budgetary support for health attachés posted in U.S. embassies. It suggests prioritization for their deployment based on perceived need and/or threat in order to utilize their interdisciplinary skills in an optimal fashion.

To remain responsive to the threat environment, DOS should engage in regular action reviews, or root cause analysis of sentinel events, to borrow a process from the Joint Commission on Accreditation of Healthcare Organizations (Joint Commission on Accreditation of Healthcare Organizations, 1998), in order to minimize delays in the identification of novel threats or in their communication from posts to Washington, DC. DOS should establish a system such that the intensity of an investigation into a new health threat rapidly escalates in real time, as needed. An established team with institutional knowledge that can quickly incorporate specific medical and environmental specialty expertise depending on the nature of the condition is best suited for such investigations. An associated advisory board might add expertise on relevant political, environmental, and other matters, in order to provide context for interpretation of unusual medical findings. As the committee already noted, DOS should consider a change in policy that enables structured medical investigations of affected individuals in a manner that does not preclude, but is separate from private medical care. Such medical investigations may be reserved for pre-specified circumstances in which there is concern that multiple DOS employees are the subject of a health attack. The committee urges additional specificity of response to the findings of the July 2018 Government Accountability Office Report in order to ensure that the proper information flow occurs between posts and Washington (GAO, 2018).

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A

Committee Biographies

David A. Relman, M.D. (*Chair*), is the Thomas C. and Joan M. Merigan Professor in Medicine, and Microbiology & Immunology at Stanford University and chief of infectious diseases at the Veterans Affairs Palo Alto Health Care System. He is also senior fellow at the Freeman Spogli Institute for International Studies (FSI), and served as science co-director at the Center for International Security and Cooperation (2013-2017) at Stanford University. He is currently director of a new Biosecurity Initiative at FSI. Dr. Relman trained at the Massachusetts Institute of Technology and then Harvard Medical School, followed by clinical training in internal medicine and infectious diseases at the Massachusetts General Hospital in Boston, and then a postdoctoral fellowship in microbiology at Stanford. Dr. Relman was an early pioneer in the modern study of the human microbiome. His recent work focuses on the features of human microbial community assembly and the basis for community stability and resilience. His previous work has included the development of methods for pathogen discovery and the identification of several historically important and novel microbial disease agents, as well as the use of genomic technologies for understanding human–microbe interactions. In the 1990s, he worked with the Centers for Disease Control and Prevention on its Unexplained Deaths and Critical Illnesses Project. Among policy-relevant activities in health and biological security, Dr. Relman served as vice-chair of the National Research Council committee that reviewed the science performed for the Federal Bureau of Investigation 2001 anthrax letters investigation, chair of the National Academies of Sciences, Engineering, and Medicine's Forum on Microbial Threats (2007-2017), and is currently a member of the Intelligence Community Studies Board (2016-present). He is an advisor to the Nuclear Threat Initiative and the Center for Strategic and International Studies. Dr. Relman was a founding member of the National Science Advisory Board on Biosecurity (2005-2014), a member of the Working Group on Biodefense for the President's Council of Advisors on Science and Technology (The White House) (2016), and served as president of the Infectious Diseases Society of America (2012-2013). He was a recipient of the National Institutes of Health Pioneer and Transformative Research Award and was elected to the National Academy of Medicine in 2011.

Doris-Eva Bamiou, M.D., M.Sc., Ph.D., is professor of neuroaudiology at the University College of London (UCL) Ear Institute. She is also an honorary consultant in audiological medicine at the UCL Hospitals and Great Ormond Street Hospital. She has been director and organizer of the current trends in auditory processing disorders instructional courses (since 2001) and UCL master class in auditory processing disorders (since 2008) and program director of audio-vestibular medicine at UCL since 2010. She has served as secretary elect of the British Society of Audiology; chair of the Auditory Processing Disorders Specialist Interest Group (BSA); and editor of the Neuro-otology Module of the eBrain e-learning module (RCP and EFNS). She is also secretary of the International Association of Physicians in Audiology. Dr. Bamiou earned a Ph.D. in neurology from UCL.

Linda Birnbaum, M.S., Ph.D., is the retired director of the National Institute of Environmental

Health Sciences of the National Institutes of Health. She is also director of the National Toxicology Program. In these roles, Dr. Birnbaum oversees federal funding for biomedical research to discover how the environment influences human health and disease. Her research focuses on the pharmacokinetic behavior of environmental chemicals, the mechanisms of action of toxicants—including endocrine disruptors and the linking of real-world exposures to health effects. Dr. Birnbaum earned a B.S. in biology from the University of Rochester and an M.S. and a Ph.D. in microbiology from the University of Illinois at Urbana-Champaign. She is a member of the National Academy of Medicine.

Michael Boninger, M.D., is professor and endowed vice chair for research in the Department of Physical Medicine and Rehabilitation at the University of Pittsburgh School of Medicine. He has joint appointments in the Departments of Bioengineering, Rehabilitation Science and Technology, and the McGowan Institute of Regenerative Medicine. He is also physician researcher for the Department of Veterans Affairs and senior medical director for Post-Acute Care for the Health Services Division of the University of Pittsburgh Medical Center. Dr. Boninger has an extensive publication record of more than 250 peer-reviewed papers. His central research focus is on enabling increased function and participation for individuals with disabilities through development and application of assistive, rehabilitative, and regenerative technologies. Dr. Boninger also has extensive experience and publications related to training researchers and served as associate dean for medical student research in the University of Pittsburgh School of Medicine for a number of years. Dr. Boninger earned a B.S. in mechanical engineering and M.D. at The Ohio State University. He completed his residency in physical medicine and rehabilitation in Ann Arbor at the University of Michigan Medical Center. He is a member of the National Academy of Medicine.

Ronald Brookmeyer, M.S., Ph.D., is professor in the Department of Biostatistics and interim dean of the Fielding School of Public Health at the University of California, Los Angeles. His research is at the interface of biostatistics, epidemiology, and public health. He uses the tools of the statistical and informational sciences to address global public health problems. A main theme concerns statistical and quantitative approaches for measuring and forecasting the health of populations. Dr. Brookmeyer has worked on the development of methods for tracking the course of the global HIV/AIDS epidemic and has also worked extensively on issues of biosecurity, such as anthrax. Dr. Brookmeyer has ongoing projects concerning the health problems of aging populations such as Alzheimer's disease. His research interests in biostatistical methodology include survival analysis, epidemic models, epidemiological methods, and clinical trials. Dr. Brookmeyer earned a B.S. in mathematics from Cooper Union for the Advancement of Science and Art and an M.S. and a Ph.D. in statistics from the University of Wisconsin. He is a member of the National Academy of Medicine.

Caroline Buckee, D.Phil., is associate professor of epidemiology in the Harvard T.H. Chan School of Public Health. Dr. Buckee was also named associate director of the Center for Communicable Disease Dynamics. Her laboratory (the Buckee lab) uses mathematical models and data science to understand the mechanisms driving the spread of infectious diseases, particularly pathogens like malaria that effect vulnerable populations in low-income countries. Her focus is on the use of new technologies, including mobile phone data and pathogen genomics, to understand and control disease threats, and to prepare for, and forecast, epidemics. Her work led to an Omidyar Fellowship at the Santa Fe Institute, where she developed theoretical approaches to understanding malaria parasite evolution and ecology. After receiving a D.Phil. from the University of Oxford, Dr.

Buckee worked at the Kenya Medical Research Institute to analyze clinical and epidemiological aspects of malaria as a Sir Henry Wellcome Postdoctoral Fellow.

Timothy J. Buckley, Ph.D., is director of the Exposure Methods and Measurements Division within the Environmental Protection Agency's National Exposure Research Laboratory. He previously spent 16 years within academia at the Johns Hopkins Bloomberg School of Public Health and The Ohio State University School of Public Health. His work is broad ranging and includes the development and application of exposure methods; measurements; and models to chemical, physical, and biological stressors within community and occupational settings. Exposure is treated comprehensively considering all relevant routes and pathways and typically includes biomonitoring to further inform this research. These studies have been applied in the context of health studies to evaluate environmental determinants of effects that are both salutogenic and adverse (e.g., cancer, neurotoxic, and respiratory). His work is strongly tied to the environmental interests and concerns of communities and has helped to identify and inform issues of environmental justice. His research has led to numerous funded grants and the publication of more than 75 peer-reviewed journal articles. Dr. Buckley has a Ph.D. in environmental science and exposure science.

Joseph J. Fins, M.D., is the E. William Davis, Jr., M.D. Professor of Medical Ethics, professor of medicine, professor of medical ethics in neurology, professor of medical ethics in rehabilitation medicine, professor of medicine in psychiatry, professor of health care policy and research, and chief of the Division of Medical Ethics at Weill Cornell Medical College. His interests include ethical and policy issues related to the diagnosis and treatment of severe brain injury and disorders of consciousness. A member of the adjunct faculty at The Rockefeller University, he is also affiliated with the Yale Law School, where he is exploring the legal and ethical issues surrounding severe brain injury from a civil and disability rights perspective. He is also conducting research on ethical implications, including the diagnostic role of functional neuroimaging, neuroprosthetic devices used to promote functional communication (such as deep brain stimulation), the experiences of patients and surrogates touched by brain injury, and public policy for this population (civilian and military). As a board-certified internist physician and medical ethicist, his other interests include palliative care, research ethics in neurology and psychiatry, medical education, and methods of ethics case consultation—drawing on the American Pragmatic tradition. He earned an M.D. from Weill Cornell Medical College and is a graduate of Wesleyan University. He is a member of the National Academy of Medicine.

John C. Gore, Ph.D., is director of the Institute of Imaging Science and the Hertha Ramsey Cress University Professor of radiology and radiological sciences, biomedical engineering, physics and astronomy, and molecular physiology and biophysics at Vanderbilt University. He has served formerly as a member of the National Advisory Council for Biomedical Imaging and Bioengineering at the National Institutes of Health. His research interests include the development and application of imaging methods for understanding tissue physiology and structure, molecular imaging, and functional brain imaging. He has published more than 700 original papers and contributions within the medical imaging field. He is fellow of the American Association for the Advancement of Science, the American Institute of Medical and Biological Engineering, the International Society for Magnetic Resonance in Medicine, the American Physical Society, and the Institute of Physics (United Kingdom). Dr. Gore obtained his Ph.D. in physics at the University of London in the United Kingdom and has been an active leader in imaging research and applications

for 40 years. He also holds a degree in law. Dr. Gore is a member of the National Academy of Engineering.

Walter J. Koroshetz, M.D., is director at the National Institute of Neurological Disorders and Stroke (NINDS) within the National Institutes of Health (NIH). Previously, he served as deputy director of NINDS under Dr. Story Landis. Together, they directed program planning and budgeting and oversaw the scientific and administrative functions of NINDS. The mission of NINDS is to advance the fundamental knowledge about the brain and the nervous system and to use that knowledge to reduce the burden of neurological disorders. He has held leadership roles in a number of NIH and NINDS programs, including NIH's Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative; NIH Helping to End Addiction Longterm (HEAL) Initiative, the Traumatic Brain Injury Center collaborative effort between the NIH intramural program and the Uniformed Services University of the Health Sciences; and the establishment of the NIH Office of Emergency Care Research. Dr. Koroshetz earned a B.A. from Georgetown University and an M.D. from the University of Chicago Pritzker School of Medicine and completed residency training in internal medicine and neurology. Prior to coming to NIH, he was professor of neurology at Harvard Medical School, vice chair of neurology, and director of stroke and neurointensive care services at Massachusetts General Hospital. Dr. Koroshetz is a member of the National Academy of Medicine.

Pamela Lein, M.S., Ph.D., is professor of neurotoxicology and chair of the Department of Molecular Biosciences in the School of Veterinary Medicine at the University of California, Davis. She is also a faculty member of the MIND Institute at the University of California, Davis. Research goals in her laboratory include identifying novel therapeutic approaches for preventing brain damage following exposure to chemicals that cause seizures; understanding the cellular and molecular mechanisms by which environmental factors interact with genetic factors to increase risk for neurodevelopmental disorders, such as autism spectrum disorders, and neurodegenerative diseases, such as Alzheimer's disease; and determining how pesticides alter communication between nerves and immune cells in the lung to cause airway hyperreactivity, a major symptom of asthma. This research leverages diverse model systems ranging from primary neuronal cell culture to zebrafish to rodent models and multiple techniques ranging from cellular and molecular techniques to in vivo imaging to behavioral studies. Professional societies of which she is a member include the Society of Toxicology, the Society for Neuroscience, the International Neurotoxicology Association, and the American Society for Pharmacology and Experimental Therapeutics. She earned a B.S. in biology from Cornell University, an M.S. in environmental health from East Tennessee State University, and a Ph.D. in pharmacology and toxicology from the University at Buffalo.

Saafan Malik, M.D., M.B.A., is a physician-neuroscientist with more than 15 years of experience in the field of traumatic brain injury and neurological disorders. He served as director of the Research Branch at Defense and Veterans Brain Injury Center (DVBIC) at the Department of Defense from 2014-2019 and acting deputy division chief of DVBIC from 2019-2020. During his tenure at DVBIC, he directed an active research portfolio of 72 clinical research protocols at DVBIC headquarters and across 22 clinical/research network sites within the military health system (MHS). Currently he is acting deputy director of Research & Development Directorate/J9, Defense Health Agency (DHA). In his current role, he provides leadership, oversight, and management of all divisions within the R&D Directorate/J9, DHA. He serves on numerous

government scientific steering committees. Prior to DVBIC, he served as senior research investigator in the Department of Neurosurgery at the University of Pennsylvania Perelman School of Medicine and then at the Texas Tech University Health Sciences Center. He has authored several peer-reviewed publications and book chapters and given national and international presentations. His M.D. is from King Edward Medical University and neurosurgery training at the Cleveland Clinic Foundation. He held postdoctoral fellowships at the University of Pennsylvania and at the Carolinas Healthcare System. Dr. Malik also holds an M.B.A. in health care management from Western Governors University.

Jeffrey S. Palmer, M.S., Ph.D., is group leader of the Human Health and Performance Systems Group at the Massachusetts Institute of Technology Lincoln Laboratory (MIT LL). He has expertise within the threat-relevant, biomedical disciplines associated with bioeffects and neurological damage mechanisms related to acoustic or directed energy exposures. He has worked in research laboratories in academia, industry (International Business Machines Corporation [IBM] and General Electric [GE]), and federally funded laboratories (Physical Sciences Laboratory, MIT LL). At MIT LL, he is the leader of the Human Health and Performance Systems Group, which focuses on objective, technology-based, human-centered solutions to measure, model, and modify cognitive and physiological function for enhancement, sustainment, or recovery. Dr. Palmer has been with MIT LL for 22 years, and some of his earlier work included directed energy research on modeling and testing of materials interaction effects. He currently oversees research in health monitoring, as well as the applied neurological, cognitive, and psychological technologies portfolio that includes neurocomputational damage modeling along with acoustic and auditory health research projects. These projects include measurement and modeling of the health effects of high power lasers and high power microwaves on biological tissue and phantoms. To support these and other activities, he initiated the creation of a new interdisciplinary laboratory to measure the interaction of biological materials with photonic, electromagnetic, acoustic, and mechanical sources. He has authored book chapters, technical articles, and given invited talks international conferences on DNA biometrics and forensics, biomechanics, cell biology, materials science, soldier nanotechnology, bio-chemical defense, polymer science, high-energy lasers, microelectronics packaging, wearable biomedical sensing, and neurocognitive technologies. He has served on editorial boards for journals in biomechanics, molecular science, biomedical informatics, and biosensors. He has chaired technical conferences for the National Science Foundation (NSF), the Department of Homeland Security, and the Institute of Electrical and Electronics Engineers (IEEE). Currently, he is vice chair and chair-elect of the IEEE Engineering in Medicine and Biology Society's (EMBS's) Technical Committee on Wearable Biomedical Sensors and Systems and the EMBS conference editorial board for tissue engineering and biomaterials. In addition, he has served as an advisor on senior military studies of enhancing health and performance; a North American Treaty Organization (NATO) human factors and medicine research technical group; and an NSF Nanosystems Center on Advanced Self-Powered Systems of Integrated Sensors and Technologies (ASSIST). Dr. Palmer received mechanical engineering degrees from New Mexico State University (B.S. with math minor), Rensselaer Polytechnic Institute (M.S.), and MIT (Ph.D. with bioengineering focus). His doctoral work focused on measuring and modeling biomechanical function and damage of protein networks from the molecular through tissue scales.

Gregory B. Saathoff, M.D., is a board-certified psychiatrist who holds joint appointments as professor in the Departments of Emergency Medicine and Public Health Sciences at the University of Virginia (UVA) School of Medicine. He also serves as executive director of UVA's Critical

Incident Analysis Group (CIAG) and since 1996 has served as the Federal Bureau of Investigation's (FBI's) conflict resolution specialist. He continues to serve in this capacity as chief psychiatric consultant for the FBI's Behavioral Analysis Units and Crisis Negotiation Unit. Since 1992, he has taught medical students, residents, and fellows correctional psychiatry on-site at a men's maximum security prison. In his faculty role, he served as elected chair of UVA's General Faculty Council. From 1985 to 1994, Dr. Saathoff served as a major in the U.S. Army Reserves Psychiatry Medical Corps. He was called from Reserve Duty during Operation Desert Storm and deployed as a medical corps psychiatrist, earning the Army Commendation Medal in 1991. As a member of UVA's Kuwait Project, he studied societal trauma in Kuwait subsequent to the Iraqi occupation and has served on the faculty of the Saudi-U.S. Universities Project located at the King Faisal Specialist Hospital in Riyadh, Saudi Arabia. In addition to the Middle East, Dr. Saathoff's work has taken him to projects in the former Soviet Union, Western Europe, and Australia. In 2006, Dr. Saathoff was appointed to the Research Advisory Board of the FBI's National Center for the Analysis of Violent Crime. He has served as principal investigator on federal grants relating to public response to weapons of mass destruction and Internet radicalization. After receiving his undergraduate degree from the University of Notre Dame and his M.D. at the University of Missouri School of Medicine, Dr. Saathoff completed residency training in psychiatry at the UVA School of Medicine.

Clifford B. Saper, M.S., M.D., Ph.D., is the James Jackson Putnam Professor of Neurology and Neuroscience and chair of the Beth Israel Deaconess Department of Neurology at Harvard Medical School. Dr. Saper earned a B.A. in biochemistry and M.S. in neurobiology from the University of Illinois, then his M.D. and Ph.D. in neuroscience from Washington University in St. Louis. After a residency in neurology at New York Hospital-Cornell University Medical Center, he then was on the faculty at Washington University and the University of Chicago, where he was the William D. Mabie Professor of Neurology and Neuroscience and chair of the Committee on Neurobiology, before taking his current position. The focus of Dr. Saper's research is on brain circuitry that controls basic functions like wake-sleep, circadian rhythms, body temperature regulation, and eating and drinking. He is a member of the National Academy of Medicine.

Mark J. Shelhamer, M.S., Sc.D., is professor of otolaryngology at Johns Hopkins University. He was previously at the Massachusetts Institute of Technology (MIT) where he worked on sensorimotor physiology and modeling, including the study of astronaut adaptation to space flight. He then came to Johns Hopkins where he continued the study of sensorimotor adaptation with an emphasis on the vestibular and oculomotor systems. He has applied nonlinear dynamical analysis to the control of eye movements, including investigations of the functional implications of fractal activity in physiological behavior. In parallel with these activities, he has had support from the National Aeronautics and Space Administration (NASA) to study sensorimotor adaptation to space flight, amassing a fair amount of parabolic flight ("weightless") experience in the process. He also serves as advisor to the commercial spaceflight industry on the research potential of suborbital space flight. From 2013-2016 he was on leave from his academic position to serve as NASA's chief scientist for human research at the Johnson Space Center. He has a B.S. and M.S. in electrical engineering from Drexel University and a Ph.D. in biomedical engineering from MIT.

Jeffrey P. Staab, M.D., M.S., is professor of psychiatry and director of the Fellowship in Consultation-Liaison Psychiatry in the Department of Psychiatry and Psychology at the Mayo Clinic College of Medicine and Science. He is also consultant in the Departments of Psychiatry and

Psychology and Otorhinolaryngology—Head and Neck Surgery at the Mayo Clinic. His research, which is funded by the National Institutes of Health, Department of Defense, and Mayo Clinic, covers a range of problems at the interface of psychiatry and medicine, including functional otologic and neurologic disorders and illness anxiety. He is best known for investigations of the differential diagnosis and treatment of chronic dizziness. He is author or co-author of more than 130 scientific articles, reviews, chapters, and abstracts. He serves on the editorial boards of six scientific journals in the fields of psychosomatic medicine and otorhinolaryngology. Dr. Staab received a B.S. in chemical engineering from Northwestern University, an M.S. in bioengineering from Carnegie Mellon University, and an M.D. from the University of Pittsburgh.

Jonathan D. Trobe, M.D., is professor, ophthalmology and visual sciences; professor, Department of Neurology; and co-director, Kellogg Eye Center for International Ophthalmology at the University of Michigan. Dr. Trobe's research has covered a wide spectrum of neuro-ophthalmic entities, as well as studies of utilization of health care personnel and application of clinical trial data to medical practice. His research interests include neural visual pathway disorders, double vision, pupillary abnormalities, eyelid disorders, higher order disorders of visual integration, traumatic brain injury, and disorders of high and low intracranial pressure. In 2001, he was appointed editor of the *Journal of Neuro-Ophthalmology*, serving until 2009. He has written and taught widely around the world and authored nearly 200 peer-reviewed scholarly articles. For the American Academy of Ophthalmology, he authored *The Physician's Guide to Eye Care*, a widely used textbook. He has also authored The Eyes Have It, a web-based and mobile application designed to teach non-ophthalmologist providers and assess their ophthalmic knowledge. Dr. Trobe received his medical degree from Harvard University and completed residencies in ophthalmology at Wills Eye Hospital and neurology at the University of Miami. He completed a fellowship in neuro-opthalmology at the Bascom Palmer Eye Institute.

David Whelan, M.S., Ph.D., is professor of the practice in electrical and computer engineering at the University of California, San Diego. Dr. Whelan's expertise is in electromagnetic systems engineering for sensing, imaging, and communications, as well as in the management of science, technology, and innovation. He designs and engineers aircraft, RADAR and Light Detection and Ranging (LIDAR) systems, space-based communications and navigation systems, and diagnostic sensors for high-energy density physics experiments. His work has been used in space mission systems, airborne navigation, and surveillance systems. Dr. Whelan's 34-year career in the aerospace industry included science and engineering research positions and eventually executive research and development management as vice president and chief scientist of the Boeing Defense and Space Systems. He also served as office director for two of the Defense Advanced Research Projects Agency (DARPA) systems offices. While at DARPA, Dr. Whelan created many legacy joint programs with the Air Force, Navy, and Army, most notably, the Discoverer II Space Radar Program, the Army's Future Combat System, and the Unmanned Combat Air Vehicle for Navy and Air Force. He previously worked at the Hughes Aircraft Company as program manager and chief scientist for the B-2 Bomber Air-to-Air Radar Imaging Program. He also worked as a physicist for the Department of Energy's Lawrence Livermore National Laboratory on X-ray lasers and the Advanced Nuclear Weapons program. He started his career at Northrop where he was one of the key designers of the B-2 Stealth Bomber and contributed to the YF-23 Advanced Tactical Fighter. He has numerous publications on electromagnetic radiation, laser plasma phenomena, and defense systems. He holds more than 50 patents on navigation systems, radar systems, antenna, and low-observable technology. He is a fellow of the American Physical Society, the Institute of Electrical

and Electronics Engineers, and the American Institute of Aeronautics and Astronautics. He earned a B.A. in physics from the University of California, San Diego, and an M.S. and a Ph.D. in physics from the University of California, Los Angeles, where he studied Type III Radio Solar Bursts and Nonlinear Energy Flow. Dr. Whelan is a member of the National Academy of Engineering.

B

Meeting Agendas

First Meeting of the Standing Committee to Advise the Department of State on Unexplained Health Effects on U.S. Government Employees and Their Families at Overseas Embassies

December 18, 2019

National Academy of Sciences Building
2101 Constitution Avenue, NW
Washington, DC 20418
Lecture Room

Wednesday, December 18, 2019

DATA-GATHERING SESSION

10:30 a.m. – 10:45 a.m. **Greetings from Sponsor and Charge to Committee**
Mark Cohen, Medical Director, Department of State

10:45 a.m. – 12:45 p.m. **Presentations on Medical Investigations**

Moderator – **David Relman,** Professor of Medicine and Microbiology and Immunology, Stanford University

Acute Presentation of an Acquired Neurosensory Syndrome
Michael Hoffer, Professor, Department of Otolaryngology, University of Miami
Carey Balaban, Professor of Otolaryngology, Neurobiology, Communication Sciences and Disorders, and Bioengineering, University of Pittsburgh School of Medicine

What Underlies Havana Syndrome
Douglas Smith, Robert A. Groff Endowed Professor and Vice Chairman of Neurosurgery, University of Pennsylvania, and Director of University of Pennsylvania's Center for Brain Injury and Repair

Multimodel Neuroimaging Reveals Neurotoxins as a Likely Underlying Cause of Illness Among Canadian Diplomats
Alon Friedman, Professor of Neuroscience and Dennis Chair in Epilepsy Research, Dalhousie University

12:45 p.m. **ADJOURN**

Second Meeting of the Standing Committee to Advise the Department of State on Unexplained Health Effects on U.S. Government Employees and Their Families at Overseas Embassies

February 24-25, 2020

National Academy of Sciences Building
2101 Constitution Avenue, NW
Washington, DC 20418
Lecture Room

Monday, February 24, 2020

DATA-GATHERING SESSION – OPEN TO THE PUBLIC

Session III—Epidemiologic Investigations

2:45 p.m. – 3:45 p.m. *Recommended Epidemiologic Investigations for Future Incidents*
Caroline Buckee, Associate Professor of Epidemiology, Associate Director of the Center for Communicable Disease Dynamics, Harvard T.H. Chan School of Public Health

Session IV—Possible Mechanisms of Injury—Radio Frequency Energy

3:45 p.m. – 5:30 p.m. *Moderators*
Jeffrey Palmer, Group Leader, Human Health and Performance Systems Group, Massachusetts Institute of Technology Lincoln Laboratory
David Whelan, Professor of Practice, Jacobs School of Engineering, University of California, San Diego

Neurologic Illness and Pulsed Radio Frequency/Microwave Radiation
Beatrice Golomb, Professor in Residence, Medicine, University of California, San Diego *[via Zoom conference call]*

5:30 p.m. – 6:00 p.m. **Committee Q&A**

6:00 p.m. **ADJOURN**

Tuesday, February 25, 2020

DATA-GATHERING SESSION – OPEN TO THE PUBLIC

Session IV Continued—Possible Mechanisms of Injury—Radio Frequency Energy

8:45 a.m. – 12:00 p.m. *Moderators*
Jeffrey Palmer, Group Leader, Human Health and Performance Systems Group, Massachusetts Institute of Technology Lincoln Laboratory
David Whelan, Professor of Practice, Jacobs School of Engineering, University of California, San Diego

Correlation of Mild Traumatic Brain Injury and Biological Effects of Weak Electromagnetic Fields
Frank Barnes, Distinguished Professor (Emeritus), Optics, Nanostructures and Bioengineering, University of Colorado

Multi-disciplinary Analysis of Microwave Induced Sound and Pressure in Human Heads
James Lin, Professor (Emeritus), Head of the Bioengineering Department, Director of the Robotics and Automation Laboratory, and Director of Special Projects in the College of Engineering, University of Illinois at Chicago

Potential Adverse Effects Following Directed Energy Exposure
Stephanie Miller, Bennett Ibey, and Jason Payne, Air Force Research Laboratory

12:00 p.m. – 1:00 p.m. **Working Lunch**

Session V—Possible Mechanisms of Injury—Chemicals and Toxicants

Moderator
Linda Birnbaum, Former Director, National Institute for Environmental Health Sciences

1:00 p.m. – 1:30 p.m. *Department of State's Overseas Integrated Pest Management Program*
Claire Huson, Director, Policy, and Special Studies, Department of State's Office of Safety, Health, and Environmental Management

1:30 p.m. – 2:00 p.m. *Neurotoxic Agents and Routes of Exposure*
Pamela Lein, Professor, Department of Molecular Biosciences, School of Veterinary Medicine, University of California, Davis

2:00 p.m. – 2:45 p.m. *How to Make a Toxicological Diagnosis*
Marion Ehrich, Professor, Virginia-Maryland College of Veterinary Medicine

2:45 p.m. – 3:00 p.m. **Break**

3:00 p.m. – 3:45 p.m. *Organophosphate Intoxication*
Nick Buckley, Professor of Clinical Pharmacology, Sydney Medical School, Australia *[via Zoom conference call]*

3:45 p.m. – 4:15 p.m. **Committee Q&A**

4:15 p.m. **ADJOURN**

Third Meeting of the Standing Committee to Advise the Department of State on Unexplained Health Effects on U.S. Government Employees and Their Families at Overseas Embassies

May 12, 2020

VIRTUAL MEETING (ZOOM)

DATA-GATHERING SESSION – OPEN TO THE PUBLIC

2:45 p.m. – 3:30 p.m.	**Preparation for Medical Emergencies** **Aubrey Miller**, National Institute of Environmental Health Sciences' Chief Medical Officer and the Head of the National Institutes of Health Disaster Research Response Effort
	Rehabilitation Approach Should Similar Unexplained Health Effects Occur
3:30 p.m. – 3:35 p.m.	*Introduction* **Michael Boninger,** Professor and Endowed Vice Chair for Research, Department of Physical Medicine and Rehabilitation, University of Pittsburgh Medical Center
3:35 p.m. – 4:00 p.m.	*Brain Injury Rehabilitation* **Ross Zafonte,** Earle P. and Ida S. Charlton Professor and Chair, Department of Physical Medicine and Rehabilitation, Harvard Medical School
4:00 p.m. – 4:25 p.m.	*Vestibular Rehabilitation* **Susan Whitney,** Professor, Physical Therapy, University of Pittsburgh
4:25 p.m. – 4:50 p.m.	*Cognitive Rehabilitation and Cognitive Behavioral Therapies* **Douglas B. Cooper,** Adjunct Associate Professor, Department of Psychiatry, UT Health–San Antonio
4:50 p.m. – 5:30 p.m.	**Discussion with Committee**
5:30 p.m.	**ADJOURN**

C

Additional Comments on Directed Radio Frequency Energy

In order to create the Frey effect of hearing and sensation of pressure within the head, there are four distinct steps involving the energy conversion from radio frequency (RF) to acoustic modalities. First, the RF energy penetrates the skull and couples to the neural tissue as a function of impedance matching and absorption in the tissue, with penetrations of 2-4 cm for frequencies of 915 MHz to 2.45 GHz (Brace, 2010). This coupling, in turn, creates a rapid oscillation of temperature changes that leads to a rapid, volumetric thermal expansion and contraction of local tissues (i.e., the increase in thermal energy causes an increase in kinetic energy of atoms, pushing against neighboring atoms to create an expansion or swelling in all directions). The oscillating tissue expansion and contraction launches a thermoelastic pressure wave (Lin and Wang, 2007; Yitzhak et al., 2009). If operated at the right pulse repetition frequency, the thermoelastic pressure wave can propagate to and excite the cochlea and vestibular organs at the resonance frequency of the cranium (Lenhardt, 2003; Yitzhak et al., 2014). Intracranial focusing is possible depending on the incident angle of the incoming RF radiation. Localization and intensity effects within a room can be achieved through nonlinear beat wave effects with careful design of the RF source and antenna. The absence, however, of electromagnetic disruption of other electronics within the immediate home/office environment suggests an upper bound to the RF energy, with implications for a potential RF system design. The average power densities associated with some of these effects (e.g., Frey effect hearing) are so low that they would not disrupt nearby electronics in a fashion similar to high-power microwaves (HPM) (Hoad, 2007; Jinshi et al., 2008). The lack of perceptual heating would also rule out other non-lethal HPM systems that have been developed for crowd control (e.g., Department of Defense's 95GHz Active Denial System that only penetrates the skin to 1/64 an inch but heats the skin to uncomfortable levels within seconds) (D'Andrea et al., 2008; DoD, 2020; Nelson et al., 2000).

It is well-known that the vestibular end organs and regions of the brain involved in processing of space and motion information may be excited by energy sources other than rotational or linear accelerations. External sonic, galvanic, and magnetic stimuli are used for diagnostic, experimental, and therapeutic purposes in neuro-otology and vestibular research such as generating vestibular evoked myogenic potentials (sonic), investigating vestibular response thresholds (galvanic), and as emerging therapies for chronic dizziness (transcranial magnetic and electrical stimulation) (Cha et al., 2013). Clinical observations also suggest that certain patients with vestibular disorders (e.g., Ménière's disease) may be susceptible to exacerbations of their symptoms in response to rapid changes in atmospheric pressure as occur with quickly moving weather fronts or changes in elevation during air or land travel (Gürkov et al., 2016). However, the potential for RF sources to stimulate the vestibular end organs via thermoelastic pressure waves or to excite central nervous system pathways via transduction akin to the Frey effect are not known. If these effects exist, then a few observations may be made about their potential manifestations. A thermoelastic pressure wave would be omnidirectional thereby stimulating the vestibular end organs in a non-physiological manner. This unusual form of vestibular stimulation could lead to very confusing percepts as central vestibular pathways do their best to resolve the non-physiological pattern of end organ stimulation resulting in sensations of physically impossible motions, unexpected reflexive postural responses to them, and faulty inferences about external

forces causing them. Affected individuals could report different sensations in response to the same external stimulus; thus, immediate reports of affected individuals may not be veridical and sensations may vary from one individual to another. If a Frey-like effect can be induced on central nervous system tissue responsible for space and motion information processing, it likely would induce similarly idiosyncratic responses.

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D

Environmental Chemicals

Environmental chemicals reported to be associated with signs and symptoms similar to the chronic signs and symptoms observed in Havana patients (pesticides are in italics).

Symptoms	Chemicals Associated with Symptom
Ototoxicity, vestibulotoxicity, tinnitus, vertigo	• Organic solvents (benzene-based and aliphatic hydrocarbons, 1,2-dinitrobenzene, toluene, trichloroethylene, xylene) • Nitriles, carbon disulfide, asphyxiants (CO), metals • *Organophosphorus pesticides (OPs)* and other phosphate-based chemicals (acute and chronic exposures) • *Acute pyrethroid exposure* • Quinine (chronic exposure)
Sensorimotor function	• Bismuth • Brevetoxins • *Pyrethroids* • *Organophosphorus pesticides (OPs)* • Metals (Pb, Cd, thallium)
Vision	• *Acute OP exposures* • Chlordecone (kepone) • Carbon tetrachloride, carbon disulfide, 2,5-hexanedione, methanol (formate) • Quinine
Motor dysfunction (incoordination, muscle weakness)	• *Acute and chronic OP exposures* • B-N-methylamino-L-alanine (BMAA), domoic acid, tetanus toxin • MPTP, ethanol, 3-nitropropionic acid • Carbon monoxide, carbon disulfide, toluene • Metals (Pb, Mn, Hg, As)
Concentration/memory deficits	• *Acute and chronic OP exposures* • *Many pesticides that target neuronal signaling molecules* • Metals (Pb, Mn, Hg) • Solvents
Headaches, fatigue, insomnia	• *OPs and pyrethroids*

SOURCES: Alcaras et al., 2013; Anger et al., 2020; Ashok Murthy and Visweswara Reddy, 2014; Campo et al., 2007; Chen et al., 1991; Choochouy et al., 2019; Crawford et al., 2008; Dassanayake et al., 2007, 2008, 2009; Dundar et al., 2016; Edwards and Tchounwou, 2005; Fuente and McPherson, 2012; London et al., 1998; Mont'Alverne et al., 2016; Müller-Mohnssen,

1999; Pham et al., 2016; Richter et al., 1992; Rohlman et al., 2011; Roldan-Tapia et al., 2006; Ross et al., 2013; Spencer et al., 2000; Teixeira et al., 2002; Zeigelboim et al., 2019.

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