Standardized Postmortem Examination Guidelines for Individuals Dying After Environmental Exposures Related to the Collapse of the World Trade Center on September 11, 2001

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Introduction

Destruction of the World Trade Center (WTC) on September 11, 2001 caused the largest acute environmental disaster in the history of New York City (Claudio 2001; Landrigan 2001; Landrigan et al. 2004; Nordgren et al. 2002).

The National Resources Defense Council and others determined in 2002 that a comprehensive health registry of individuals exposed to air contaminants in the aftermath of the destruction of the WTC on September 11 was needed to assess the potential health impacts and consequences over time of the high intensity environmental pollution that resulted. Several such programs are currently in place, including the Mount Sinai World Trade Center Medical Monitoring Program (Herbert et al. 2006), the Fire Department of New York (FDNY) WTC Medical Monitoring and Treatment Program, and the collaborative World Trade Center Health Registry hosted by the New York City Department of Health and Mental Hygiene (NYC DOHMH) and supported by ATSDR/CDC (Brackbill et al. 2006; link to registry found at: www.wtcregistry.org). These programs have provided important data that has informed development of clinical guidelines to identify, evaluate, treat, and refer patients with conditions that could be related to the WTC disaster (Friedman et al. 2006; accessible at http://www.nyc.gov/html/doh/downloads/pdf/chi/chi25-7.pdf).

Although much has been learned about the health problems experienced by exposed individuals in the five years since the WTC collapse, many questions remain about both current health problems and health effects that exposed people may yet develop over the long term. In particular, there has been great public concern that deaths of exposed individuals caused by conditions such as cancer may have been related to

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their exposures. Unequivocal documentation of associations between such conditions and the WTC collapse will require epidemiological evaluations of populations, and it will be years before definitive studies can be performed. In the meantime, there is a current and pressing need for guidance in the approach to individual cases that may be related to exposures associated with the WTC collapse. The need is further exacerbated by the planned implementation of a new WTC fatality investigations program that may evaluate many such cases.

These guidelines have been developed in response to the need for a standardized approach to postmortem examination of individuals exposed to the WTC disaster. Because individuals who were exposed to the WTC disaster can be found across the country, consistent standards are a need not only for New York, but for the entire nation. These guidelines are intended not only to potentially benefit families of individual decedents, but also to provide pathological data that will help clinicians to better understand and treat the conditions affecting survivors of the WTC collapse. Recommendations such as those for collection and retention of tissues may also facilitate scientific research to better understand exposures and health effects caused by the WTC collapse.

Exposures after the WTC Attacks

The combustion of jet fuel at temperatures above 1000°C resulted in a dense and toxic atmospheric plume containing a complex mixture of materials including soot, metals, volatile organic compounds, and acid gases. The eventual collapse of the World Trade Center towers pulverized concrete, glass, and other building contents, generating tons of particulate matter composed of concrete dust, fiberglass, asbestos, lead,

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polychlorinated biphenyls, organochlorine pesticides, and polychlorinated furans and dioxins, which dispersed over lower Manhattan and beyond. Exposures continued long after September 11th due to disturbance of settled dust and persisting fires at the WTC site (Landrigan et al. 2004; McGee et al. 2003; Nordgren et al. 2002; Lioy et al. 2002).

Overview of medical conditions associated with the WTC collapse

In the five years since the WTC attacks, a number of health effects related to WTC exposures have been documented. From early after the collapse, clinical and epidemiological assessments have documented a high prevalence of respiratory symptoms in exposed individuals (CDC 2002; Landrigan et al. 2004; Brackbill et al. 2006; Herbert et al. 2006). Persistent cough, reactive airways dysfunction syndrome, asthma, and chronic obstructive pulmonary disease have been reported in some workers involved in the aftermath of the WTC collapse (Prezant et al. 2002; Skloot et al., 2004). Symptoms of gastroesophageal reflux have been an unexpected but common problem in exposed people (Prezant et al. 2002). Rare reports have included granulomatous pneumonitis related to foreign body deposition (Safirstein et al. 2003) and eosinophilic pneumonitis (Rom et al. 2002).

It is unclear what long-latency conditions will develop over time. Given the range of environmental hazards produced by the WTC collapse, the range of individual exposures, and the varied susceptibilities of exposed individuals, a broad range of illnesses and pathologies may occur among exposed individuals over time. Concerns have already been expressed that conditions such as cancer and sarcoidosis may have resulted from WTC exposures. Clearly, there is a need for organized follow-up of deaths of people exposed to the WTC collapse.

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Autopsy protocol

This protocol describes the recommended techniques for postmortem examination of an individual who is suspected to have died at least in part due to exposure to the collapse of the WTC. It is not intended to replace standard autopsy technique but, rather, provide additional guidance for hospital pathologists, forensic pathologists, and others involved in postmortem examination of such individuals described herein. In light of the potential for inhalational-type injury, careful attention to examination of the upper and lower respiratory tracts and upper gastrointestinal tract is warranted. As it has done in the past with other diseases, the autopsy may make significant contributions to our understanding of diseases related to exposures associated with the WTC collapse by elucidating specific pathologic entities or identifying potential markers of exposure. The actual performance of the autopsy dissection should be considered only a part of the postmortem examination as a whole, which also relies heavily on vigorous clinical review and correlation with pathologic findings. Such clinical reviews will, likely, require communication with programs currently in place to track exposed individuals and document their exposures, including the Mount Sinai World Trade Center Medical Monitoring Program, the FDNY WTC Medical Monitoring and Treatment Program, and the World Trade Center Health Registry.

Clinical Information

Both clinical and pathological information must be considered in evaluating a decedent's cause of death and contributing conditions. For diffuse lung diseases, especially the interstitial lung diseases, a multi-disciplinary approach using clinical, radiological, and pathological information is often required for optimal interpretation and

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meaningful diagnosis. Appropriate medical record reviews and witness interviews should be performed. Clinical guidelines have been developed to aid in obtaining appropriate exposure and symptom histories, which are very important to consider in assessment of causation (Friedman et al. 2006; accessible at http://www.nyc.gov/html/doh/downloads/pdf/chi/chi25-7.pdf). History should include inquiries about the following:

- Direct exposure to the cloud of debris and dust released by the collapse of the towers;
- Duration, type, and intensity of exposure to dust, smoke, and fumes in the days and months after the disaster; and
- Whether onset of symptoms occurred after, but within plausible proximity to, WTC exposure.

In addition to history of WTC-related exposures, other relevant occupational and environmental history should be obtained. Smoking status, recreational activities, and social history are also important. Documentation should also be sought about how long medical conditions of concern have been present.

General Approach

A complete postmortem examination should take place as soon as possible after death, using any of a number of standard general and specific autopsy techniques. A narrative description of such standard autopsy techniques is beyond the scope of these guidelines and the reader is referred to standard references of autopsy technique (Ludwig 2002; Hutchins et al. 1994). Although complete postmortem examination is preferred, limited autopsy (especially in hospital-based cases) may be preferred by some next-of-

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kin. In such instances, the importance of examination of the upper and lower respiratory tracts and upper gastrointestinal tract, in addition to clinically suggested areas, should be stressed to next-of-kin granting permission.

Tissue Sampling and Histological Examination

In light of the high potential for respiratory-based illness, particular attention should be focused on evaluation of the upper and lower respiratory tracts.

Formalin perfusion fixation, using methods previously described (Ludwig 2002) is the preferred method for fixation and evaluation of the lungs. For all cases, a minimum of two sections per lobe from both lungs, sections of upper and lower airways, and sections of visceral and parietal pleura should be submitted for histologic examination using standard hematoxylin and eosin (H&E) staining techniques. In cases of known or suspected fibrosing lung disease, special care should be made **not** to focus tissue sampling solely on fibrotic areas of the affected lung(s) but to adequately sample "normal' areas or "less affected" areas adjacent to fibrotic areas of the lung. Similarly, if lung cancer is present, both the tumor and uninvolved areas of lung should be sampled. If lung cancer or mesothelioma is present, a minimum of two tissue blocks should be taken from involved areas.

While light microscopic evaluation of standard H&E-stained sections of lung using polarizing lenses and/or special histochemical stains (i.e., iron stains for ferruginous bodies) can provide useful semi-quantitative information about particulate matter in the lungs, the circumstances of the WTC collapse require a more quantitative mineralogical assessment of tissues. Methods, such as atomic absorption spectrometry (AAS) and energy-dispersive X-ray spectroscopy (EDS), can help further elucidate the

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type of particulate matter to which an individual may have been exposed. Testing should be performed by an experienced laboratory with appropriate quality assurance controls. Over time, clearance mechanisms will likely result in reduced measured tissue burdens, which should not be misinterpreted as indicating a level of exposure lower than the individual's actual exposure at the time of the WTC disaster.

Tissue samples from each lung should also be fixed in glutaraldehyde for further studies via electron microscopy (see below under special studies for further instructions).

A minimum of 50 g of lung tissue from each lung should be fixed in 10% formalin and another 50 g snap-frozen in liquid nitrogen and then maintained frozen at -80 °C (or, if snap-freezing is not possible, simply frozen at –80 °C) and kept for additional studies as outlined below. Such tissues will be maintained for further studies if needed.

If mineral fiber analysis is contemplated, European guidelines recommend pooling 3 lung pieces of 1-2 cm^3, one from the apex of the upper lobe, one from the apex of the lower lobe, and one from the base of the lower lobe. Tumor tissue should be avoided, because it contains few particles and can result in a false-negative fiber count. Paraffin wax can be contaminated by asbestos fibers, so paraffin embedding should be avoided (De Vuyst et al. 1998). Sample drying and traumatic manipulations should be avoided, because they can cause fiber breakage and affect determination of fiber length (Dodson 2006).

Additional tissues that should be evaluated by standard H&E-stained sections include:

- Brain

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- Upper, middle, and lower esophagus (GE junction)
- Heart (sections of ventricular myocardium and coronary vessels)
- Lymph nodes (preferably thoracic/ mediastinal and abdominal/ mesenteric)
- Liver
- Pancreas
- Spleen
- Stomach
- Small and large intestine
- Kidney
- Adrenal
- Vertebral bone marrow
- Other organs as guided by macroscopic findings and/or clinical records

Toxicology

Ideally, certain body fluids and tissue samples should be retained for possible toxicological studies:

- Blood: Antemortem blood should be spun down and the supernatant saved (frozen) for potential future studies. If antemortem blood is not available, postmortem blood from "central" acquisition (i.e., heart) or "peripheral" acquisition (i.e., femoral puncture) can be saved in a similar fashion.
- Urine: Urines samples should be saved (frozen) for potential future evaluation for toxins of concern.
- Solid organs: Liver is the solid organ or choice if liquid specimens (i.e., blood) are not available. If blood is not available, a fresh sample of 50-100 g of

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liver tissue from the right lobe can be frozen for potential future toxicological studies.

Special studies

Electron Microscopy (EM): Specimens can be sent to and evaluated by a designated facility utilizing EM to assess the presence of particulate metals, minerals (including asbestos fibers and other silicates [i.e., quartz]), and fibrous glass.

Specimens should be fixed in an appropriate aldehyde (3% glutaraldehyde) solution. Ideally, the specimen should be cut into cubes of less than 3 mm square and placed in fixative as quickly as possible. Tissues to be evaluated by EM should not remain in fixative for more than 4 days. Specimens should be referred for evaluation before then or, if longer term storage is anticipated before referral, the tissue should be embedded in plastic according to standard preparation of samples for EM study.

Alternatively, formalin-fixed and paraffin-embedded tissues or formalin-fixed tissues alone may be submitted for evaluation by EM (although contamination of paraffin by asbestos fibers is a potential concern for mineral fiber analyses).

Mineralogical evaluation: Specimens can be further evaluated at a designated facility by additional studies (i.e., EDS and AAS) designed to identify and quantify elemental composition of particles in tissues. Glutaraldehyde-fixed tissues are preferable for evaluation by EDS, though formalin-fixed tissues may be used.

Controls for EM and Mineralogical Analyses: Because mineral particles and fibers can be detected in the lungs of anyone if highly sensitive methods are used, interpreting measured lung burden of particles and fibers requires a control population and reference values for the methods used. Variables such as age, sex, smoking,

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occupational exposures, and rural vs. urban residence should all be considered in defining control populations to establish reference values (De Vuyst et al. 1998).

Access to Stored Tissues and Body Fluids: Formalin-fixed and/or frozen tissues or body fluids preserved according to these guidelines should be stored in a fashion that facilitates access for future study, such as at a designated facility. Appropriate local oversight and procedures will need to be developed to track inventory and manage access to stored samples in the event of specific findings that warrant further study or the development of novel approaches for evaluation of stored samples.

Assessment of Information and Categorization of Relation to WTC Exposures

The basic approach to evaluation of autopsy information in the setting of WTC exposures is much the same as in other autopsy settings. Gross and histological findings of disease, mineral and mineral fiber analyses, and clinical information should be correlated, leading to determination of the disease causing death and concurrent pathologic processes. In addition to describing and diagnosing disease manifestations, correlation of pathological and clinical information also underlies determination of extent and severity of disease, an important issue in compensation settings.

A unique feature of determining cause of death in those with histories of environmental exposures related to the WTC collapse is the desire on the part of decedents' families and loved ones to know if WTC exposures caused the diseases leading to death. As already noted, at this point in time, in many (perhaps most) cases there will likely be insufficient data to definitively address this question due to the lack of sufficient case reports and epidemiological data documenting associations between exposures and mortality.

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The issue of how causality between WTC-related exposures and adverse health effects will be established and categorized over time is an important one. An Institute of Medicine report issued in 1994 provides relevant guidance on assessing causal links between exposures and adverse health effects (IOM 1994). The report also provides a system for categorizing the level of certainty that an implicated exposure is causal. Although that report focused on adverse reactions to pediatric immunizations, the approach it took to assessing causality is very relevant to the issue of determining causation of adverse health effects by WTC-related exposures. In the current setting of scientific uncertainty, use of the following categories and descriptions adapted from the IOM report is recommended to classify the relationship between death and WTC exposure [italicized text excerpted directly from the Institute of Medicine report (IOM 1994)]:

Level 1: *The evidence establishes a causal relation: Epidemiologic studies and/or case reports provide unequivocal evidence for a causal relation, and biologic plausibility has been demonstrated.*

Level 2: *The evidence favors acceptance of a causal relation: The balance of evidence from one or more case reports or epidemiologic studies provides evidence for a causal relation that outweighs the evidence against such a relation. Demonstrated biologic plausibility*…is… *supportive of a decision to accept a causal relation but insufficient on its own….*

Level 3: *The evidence favors rejection of a causal relation: Only evidence from epidemiologic studies*…should be…*a basis for possible rejection of a causal relation. Such evidence*…should be…*judged as favoring rejection only when a rigorously*

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performed epidemiologic study (or a meta-analysis of several such studies) of adequate size (i.e., statistical power)…does…*not detect a significant association between*…WTC exposure…*and the adverse event. The absence of demonstrated biologic plausibility*…should be…*considered supportive of a decision to reject a causal relation but insufficient on its own to shift the balance of evidence from other sources.*

Level 4: *The evidence is inadequate to accept or reject a causal relation: One or more… case reports or epidemiologic studies*…are available…*but the evidence for a causal relation neither*...outweighs…*nor*…is…*outweighed by the evidence against a causal relation. The presence or absence of demonstrated biologic plausibility*…should be… *considered insufficient to shift this balance in either direction.*

Level 5: *No evidence bearing on a causal relation: Putative associations between*…WTC exposures…*and adverse events*…that are not addressed by…*any case reports or epidemiologic studies*…should be…*placed in this category. Demonstrated biologic plausibility alone*…should be…*considered insufficient to remove a given*…WTC…*-adverse event association from this category.*

As epidemiological information and relevant case reports accumulate, the evidence for or against association of WTC exposures with medical conditions will change, thus possibly changing which of the 5 levels is used to categorize causation of particular adverse health outcomes. It will therefore be of great importance to follow new information and apply it as it becomes available.

Challenges and Recommendations for Application of the Guidelines

There are many challenges to the application of these guidelines. Perhaps the most important challenges are knowledge gaps that cause great uncertainty about

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evaluation of data and assessment of causation. There is little information from relevant control groups that can be used to generate clear and non-controversial reference values for assessments of mineral particle and mineral fiber levels in the lungs of WTC-exposed individuals. It is unknown at what rate clearance of these materials from the lungs of exposed individuals will occur, further complicating the use of these measurements in assessing exposures.

An especially difficult problem is that adequate epidemiological data does not yet exist to quantify relationships between WTC exposures and diseases causing death. This is an important issue for assessment of causation of diseases that occur with appreciable background rates in unexposed people. Examples of WTC-related conditions that are common in both exposed and unexposed populations include upper airway cough syndrome, asthma, and gastrointestinal reflux disease (Brackbill et al. 2006; CDC 2002; Landrigan et al. 2004; Prezant et al. 2002; Skloot et al. 2004). In the absence of uniquely WTC-related pathology, assessing causation by WTC exposures of individual deaths from common conditions will likely continue to be an area of controversy so long as definitive epidemiological findings are unavailable. Should clusters of rare conditions be detected in exposed populations, attributing individual deaths from such conditions to WTC exposures may be less controversial.

Another challenge to the use of autopsies in understanding pathologies affecting the exposed population as a whole is that, in general, autopsy rates are very low. Thus, autopsy data will be affected by whatever selection bias is introduced by only evaluating information for those decedents for which there was motivation to obtain autopsies. Autopsy information on a broader group might be obtained if follow-up programs like the

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Mount Sinai World Trade Center Medical Monitoring Program, the FDNY WTC Medical Monitoring and Treatment Program, and the World Trade Center Health Registry were engaged to explain the scientific and personal value of postmortem examination to their populations in advance of death.

The pressures induced by implications of autopsy findings for compensation, litigation, and media scrutiny represent additional challenges to those engaged in post-mortem evaluation of individuals who were exposed to the WTC collapse.

The following measures are recommended to address these challenges:

1) Research: Research is especially needed to document epidemiologic associations between WTC exposures and disease; and to develop, standardize, and generate guidelines for interpretation of lung mineral particle and mineral fiber burdens.

2) Promote autopsies: Measures are needed to promote autopsies for decedents with a history of exposure to the WTC collapse.

3) Create a system for storage, inventory tracking, and provision of access to retained tissues and body fluids: An organized approach to sample storage, inventory tracking, and access would facilitate re-evaluation of old samples with new tests; and would be useful for future research investigations. Ideally, this "tissue banking" system would also be able to accommodate biopsy specimens taken as part of diagnostic work-ups on patients, since such specimens could be as, or even more, informative than autopsy specimens.

4) Establish an expert panel for initial implementation of the guidelines: This expert panel would be multidisciplinary in membership, including expertise in pathology, clinical evaluation and care of the medical problems of WTC-exposed people, and

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epidemiology. Clinical expertise represented might include both generalists and specialists in areas such as occupational and environmental medicine, pulmonary medicine, and other specialties as dictated by patterns of disease in WTC-exposed people. Likewise, pathology expertise represented might include both generalists and specialists in pulmonary pathology, toxicology, and other areas relevant to diseases experienced by WTC-exposed people. Although many details would need to be resolved about the nature of the expert panel and its specific policies and procedures, its general missions would include the following:

(A) Disseminate and promote use of protocols for a standardized approach to postmortem examination to those in the community engaged in the evaluation of individuals who die, potentially, from exposure to the WTC collapse. The protocols will provide guidance on the use of pathological and other information (such as antemortem clinical data and exposure information) to ascertain, to the extent possible, causation of pathology and death by WTC-related exposures. The expert panel will also review and update protocols at appropriate intervals.

(B) Periodically review the scientific literature for epidemiological studies, case reports, and studies demonstrating biological plausibility relevant to assessing causation by WTC-related exposures of diseases causing death. For specific causes of death, the expert panel will designate (and update prior designations, as warranted) levels of evidence indicating potential causation by WTC-related exposures. The expert panel will disseminate their designations to stakeholders and will use them to assign level of causation in individual cases reviewed by the panel (see below).

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(C) Upon request, review autopsy materials from individual cases referred by stakeholders, including families, physicians, or public health officials. Such reviews would apply standard protocols and designated levels of evidence for causation of various diseases developed by the expert panel (see above) to achieve uniform characterization of pathological abnormalities. Although the expert panel will develop the precise procedures to be followed, it is anticipated that case evaluations will involve review of histology by several pathologists and discussion of pathological, clinical, and mineralogical information by the group. The results of individual autopsy reviews conducted by the expert panel will be reported to requestors, as appropriate, but individually identifiable information will otherwise be kept confidential in compliance with applicable rules and regulations.

(D) Coordinate and oversee creation of a secure electronic database of individual cases referred to the expert panel for review of autopsy materials. Information stored in the database will be used to evaluate for patterns in deaths potentially due to WTC exposures. The expert panel will report on its assessments and findings in evaluation of cases to the medical and scientific communities and public at regular intervals. In general, such data will be reported in aggregate form to protect individual confidentiality.

(E) Identify research needs. While the expert panel will not have a primary role to conduct research, it will be have a unique ability to identify particular causes of death that should be studied to document epidemiologic associations with WTC exposures. It may also be in a position to facilitate collaborations among researchers and clinicians and suggest research materials.

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Conclusion

These guidelines have been developed in response to the need for a standardized approach to postmortem examination of individuals exposed to the WTC disaster. This is a need for the entire nation. Postmortem examination in the setting of death after WTC exposure involves integration of pathological, clinical, and exposure information. At the current time, there will often be insufficient epidemiological data or case reports to help definitively determine whether exposures related to the WTC collapse caused death. As additional information becomes available, the nature of these relationships will become more apparent. The autopsy has a key role to play in this process. These guidelines are intended not only to help the families of decedents, but also to provide pathological data to help clinicians better understand and treat conditions affecting survivors of the WTC collapse.

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Dear Dr. Weisseman,

I have read with considerable interest the manuscript entitled "standardized postmortem examination guidelines for individuals dying after environmental exposures related to the collapse of the World Trade Center on September 11, 2001" by Lento et al.

I have a number of questions and comments for you to consider as you move forward with this document. The manuscript is well-written but has some significant flaws. Here are some of my concerns:

1. I am unclear as to who will be using this document. If intended for general pathologists in community practice (and we have to presume that not all exposed individuals, or even a majority, will die in university settings), many of the suggested collection and storage strategies will not happen. Also, as emphasized throughout the document, clinical history correlation is essential. How will consistency of information be handled? Who will provide this essential information to the prosecutor? In a perfect world all individuals with documented exposure to the WTC collapse would be registered in one database constituting a centralized repository of the key information required for correlation with autopsy findings.

2. It would seem to me that victims' family members need to buy into the importance of obtaining autopsies. Without this, given the current autopsy rates at non-university hospitals around the US, I doubt that more than 25% of exposed individuals who die will undergo autopsy. What about forensic deaths, will they be included? Furthermore, if legal liability issues are tied to the process (which I suspect they must), this may influence whether pathologists at a given hospital feel competent to perform the autopsy. Fiber analysis, for example, is not a standard part of the autopsy and is expensive. Most community hospitals will not readily assume these expenses.

3. I think the idea of this document is reasonable but is perhaps a bit ahead of the process. For this to be a useful set of guidelines, there will need to be a central authority to handle the information and material gained from the autopsy. That central clearing house could then correlate the information gained with the appropriate exposure information and clinical disease manifestations, if any. Is there funding for such an authority? Wouldn't it be reasonable to have your clinical experts review the exposure data for all registered individuals in advance, to insure that this would be available at the time of autopsy?

4. My recommendations would be to:

1) First establish the common centralized registry that will document exposure.

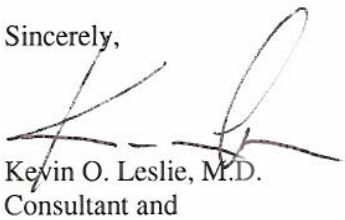
2) Establish an expert clinical review panel for evaluating both the exposure histories and the early follow-up information regarding clinical manifestations during some agreed-upon period following exposure.

3) Create a "minimal essential" autopsy protocol with collection vials/containers, special solutions, and mailers as a "kit", to be forwarded to the hospital were the registered individual dies. The protocol itself should explain both the importance of the gathered information and explicit detail in terms of what is expected from the pathologist. General statements such as "...particular attention should be focused on a valuation of the upper and lower respiratory tracts" on page 7 line 6, are too vague to be useful. In the kit, a form could include details about specific gross information deemed to be essential, and furthermore would specify where and how to take sections from larynx, trachea, and lung. Because some of the resultant diseases may be "interstitial diseases", make sure that the protocol sections are taken to always include peripheral and central parenchyma, along with cross-sections of the major airways. There may be sensitivities on the part of community pathologists to participate; nevertheless the document should not hesitate to be explicit regarding what is desired and how to collect it.

5. Finally, as a means of making all this happen, I would suggest that a symposium be convened, sponsored by the three main agencies currently registering potential victims. At the symposium many of the "nuts and bolts" could be worked out regarding the central repository of information, the creation of the clinical, pathology, epidemiology, and toxicology expert group, a consensus achieved regarding the composition of the "WTC autopsy kit", and importantly, funding. By the end of the symposium, it will be clear what elements have been overlooked and how best to approach them.

Thank you for allowing me to review this document and participate in this important work.

Sincerely,



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November 1, 2006

David N. Weissman, MD
Director, Division of Respiratory Disease Studies
National Institute for Occupational Safety and Health

Re: WTC Postmortem Examination Project

Dear Dr. Weissman:

Thank you for inviting me to formally review for NIOSH the "Standardized Postmortem Examination Guidelines for Individuals Dying After Environmental Exposures Related to the Collapse of the World Trade Center on September 11, 2001."

I wish to begin by stating that I have great respect for the difficulties involved in such an undertaking and for the authors of this proposed project. Despite this respect, I have serious concerns about the ability of this project to accomplish its aim. Part of this concern is that the aim is unstated and/or easily misinterpreted. This project was proposed to answer legitimate public concern about WTC-related disease. While the authors and this reviewer share such concern, it would be helpful if the authors were to admit, rather than perpetuate the myth, that the understanding of disease and its causality is far more complicated than the public would presume. In a perfect world, causality is based entirely on science and many might believe that pathologic findings (autopsy or biopsy) provide the ultimate perfect scientific evidence. However, typically causality is based on epidemiologic study and biologic plausibility. Pathology might confirm but rarely provides primary evidence. Throughout this document, there is confusion about this concept and therefore the role of the pathologist in this process. This proposal is not an epidemiologic study but a pathologic study. The authors of this document should know better than most that we cannot expect the science of pathology to answer the question of causality unless there is a "signature" that is (1) identifiable (2) unique, (3) permanent and (4) is present within the tissue of concern.

Let us examine this last statement in greater detail because within it lays multiple assumptions that have not been proven to exist for disease of any type after World Trade Center (WTC) exposure. Analysis of WTC Dust by Meeker et al from the US Geologic Survey attempted to define a WTC Dust "signature". Preliminary work was useful in identifying a predominance of slag wool in original and remaining dust (circa 2004-5) obtained from commercial and private buildings. This work was preliminary and based on a small number of samples. Nor, did they study tissue samples. This work concentrated only on the dust and ignored chemical analysis because it was doubtful

that polyaromatic hydrocarbons would have remained in residential dust years later. This same problem holds true for biologic specimens. In fact, the NYC Fire Department in collaboration with the CDC, performed extensive bio-monitoring analysis of minerals and chemicals in over 300 highly exposed firefighters on specimens (serum and urine) obtained only 4 wks after 9/11/01. When compared to non-exposed firefighters, antimony and two dioxin congeners were the only analytes elevated at statistically significant levels. As these analytes were present at far below clinically significant levels, this "signature", even if found in other lesser exposed populations, would be of doubtful utility. Second, there is no evidence that even if identifiable, the "signature" is unique. This especially holds true for mineral and chemical analysis. Third, there is no data that a "signature" of any type (chemical, mineral, fiber, etc.) present in the dust would have the bio-durability to survive for human tissue analysis years later. In fact, the pathogenic culprit may be non-specific chronic inflammation initiated by any of multiple possible "signatures" which have long since vanished. In theory, biodegradation successfully eliminates the "signature" but the enzymatic inflammatory process left unchecked causes the disease. Finally, all "signatures" would be expected to lie in portals of entry (upper and lower airway, upper GI tract) but non-pulmonary diseases (ex. cancers and autoimmune diseases) of current and future concern to WTC exposed patients may involve distant organs where no "signature" would likely be present. End-organ or systemic diseases may be the result of chronic inflammatory processes or other even less well understood mechanisms. Therefore, given the absence of any scientific evidence that there is a unique, identifiable, and permanent WTC tissue "signature", this project cannot assess causality.

Given the present level of pathologic science, only epidemiologic studies can assess causality. Short-term studies already completed by the NYC Fire Department, the Mt. Sinai Consortium and the NYC DOH WTC Registry have provided reasonable certainty that the "WTC Cough" aerodigestive syndrome and several mental health problems (most notably PTSD) are related to WTC exposure. Such evidence is provided by a dramatic increased incidence in exposed populations; an exposure intensity dose dependency to these diseases (based on arrival time) and biologic plausibility in both animal and human studies. Long-term studies will be required for identification of late emerging diseases such as cancers, autoimmune diseases and others. Such studies will be complicated by our inability to define cumulative exposure, the need for long-term studies with huge numbers when studying common diseases (ex. colon cancer) and the impact of longitudinal dropout especially on the study of rare diseases (ex. mesothelioma, polymyositis). Clusters of uncommon disease, while providing clues, may only complicate matters. It is unfortunate that the autopsy on NYC Police Detective Zadroga was highlighted by the media as evidence for WTC related disease. There was little if any in the pathologist's report that proved WTC related disease. Rather, that conclusion was reasonable based on the patient's prior excellent health, his exposure, the temporal relationship of the disease and the rarity of the pathologic findings in this type of patient.

What this proposed postmortem pathology study can do is collect data for analysis, generate hypothesis and possibly in conjunction with epidemiologic studies provide answers to these hypotheses. Once one accepts that this is scientific study rather than a causality study, several additional issues become problematic. First, there is no control population for pathologic comparison. Second, the methods for storage and analysis of the specimens must be clearly stated. Since these analytic methods are quite complicated, all specimens should be sent to one or several pre-designated

pathologic centers with expertise in this type of mineral, chemical and fiber analysis. None of this is planned for in this document.

Consistent with all federal research guidelines and ethical considerations, all parties including patients (for biopsy specimens), surviving family members (for autopsy specimens), physicians, government and others must be made aware that this is a scientific study and that it is not designed to attribute causality. That will create yet another problem. In my opinion, the current primary motivation for this study is causality. Causality is important and all parties (patients, scientists, government, lawyers, judges etc.) are equally interested in it. However, the politics of causality cannot be ignored and all parties, arguably with those in science as an exception, have an undeniable self-interest in its determination. Unfortunately, this means that this study has many insurmountable barriers to overcome. If it was a causality study, as many incorrectly presumed, patients or their survivors would not participate unless it is clear that the decision process is flawless and transparent. As it is not a causality study, few will have the motivation to participate and those who do will still be concerned about whether findings can be used to incorrectly attribute causality.

I wish I could provide a solution rather than merely insights into the process. I believe that anyone administrating this project in its current form will have difficulty achieving its unstated aim (to provide a better scientific understanding of disease) or its implied aim (to provide a better understanding of WTC-related disease). I suggest the authors begin their revision by first demanding a better understanding of what is being asked by all parties involved and then by providing to those interested parties a better understanding of what can be realistically attained.

Sincerely
David J. Prezant, MD
Professor of Medicine, Albert Einstein College of Medicine
Chief Medical Officer, Office of Medical Affairs, FDNY
Co-Director FDNY WTC Medical Monitoring & Treatment Program

Standardised postmortem examination guidelines for individuals dying after environmental exposures related to the collapse of the World Trade Center on September 11th 2001

Comments by Prof Anthony Seaton
Institute of Occupational Medicine
Edinburgh
Scotland

1. The initial impact and fire would, because of the temperature involved, have moved toxic fumes and gases upwards and would only have affected those above at the time. The temperature is likely to have carried these toxics a considerable distance from the site and it may never have reached ground level in significant concentrations. There should be data on this. It might be thought misleading to imply that such toxics would have impacted on those in the vicinity. The dust cloud from the collapse is likely to have been the principal cause of any respiratory or other adverse effects. Such a dust cloud would be expected to have comprised overwhelmingly non-respirable particles when measured by mass and to have caused irritant effects on exposed mucus membranes and, in extreme cases, suffocation. The dust to which individuals were exposed is unlikely to have been fundamentally different to that to which building and demolition workers are exposed on a daily basis; the differences are that the duration was relatively brief but that in many individuals the concentration was extremely high.

2. The lung only responds in a limited number of ways, as outlined below. I know of no reason to suppose that the dust from WTC is likely to have been uniquely toxic or to have beeen able to cause new, unrecognised lung diseases. On the contrary, the effects are predictable and unsurprising, and would not differ from those of any high level relatively brief exposures to irritant dusts.

3. I am not clear as to how much asbestos was incorporated in the WTC or what concentrations were found in the dust cloud or in ambient air subsequently. However, it seems highly unlikely that sufficient concentrations would have been inhaled by individuals in the vicinity to cause asbestos-related diseases, with the exception of demolition/rescue workers employed on the site (and others working alongside them) for some weeks without appropriate respiratory protection.

4. Such dust clouds would be expected to provoke the symptoms of cough, wheeze and breathlessness acutely, together with irritation of eyes and nose. Excessive coughing might plausibly be expected to raise intra-abdominal pressure sufficiently for those with gastro-esophageal reflux to experience exacerbation. All such symptoms would be expected in the large majority of cases to be temporary. Brief exposure of a few days or weeks would not of course be expected to cause cancer.

5. In any population there would be expected to be a subgroup of individuals who are relatively susceptible to airway irritants. These would include asthmatics. Such individuals would experience more prolonged symptoms, often requiring an increase in their therapy. In addition, it is likely that among those heavily exposed there would be a proportion in whom asthma developed for the first time – the so-called reactive airways dysfunction syndrome. Such individuals would have required treatment for asthma and in general most would be expected to have recovered over a few weeks. Finally, a very small proportion of those most heavily exposed might be at risk of two other pulmonary responses – bronchiolitis obliterans and pulmonary fibrosis. The former would be expected to have come to light within a few weeks at most of exposure as severe irreversible airflow obstruction. It would be a most unlikely consequence of exposure to dust, but might have been anticipated among any exposed to high concentrations of gases or fumes. The latter, pulmonary fibrosis, is in my opinion an unlikely consequence of the sorts of exposures that occurred, but would be a relatively late consequence occurring after months or years.

6. The lung and its airways are generally remarkably well protected against inhaled irritants, but their defenses can be overwhelmed by high dust concentrations. Most of the dust inhaled at the time by those exposed will have been coughed up or swallowed. That retained, some of the repirable component, will have been cleared over a relatively short time period by the normal defenses including the lymphatic system of the lung. In most individuals, the best sites for detecting dust inhaled in life are the hilar and mediastinal lymph nodes. The lung parenchyma itself is likely to retain smaller amounts. Any post-mortem examination looking for such residues should include mineral analysis of these nodes.

7. A post-mortem examination is a means of establishing the immediate cause of death. It is not generally useful in determining the fundamental causes of that disease. It is of course important that it is done competently and I believe that the recommendations made would help towards this end. However, for use in establishing association of immediate cause with episodes such as the WTC collapse, it is necessary for the protocol to be linked to an epidemiological database. It should be borne in mind that any such post-mortem protocol will of necessity introduce a bias since it requires particular efforts to be made and draws attention to the possibility of a link. For example, in an individual who has smoked, was exposed to the collapse and who dies of chronic obstructive lung disease, a pathologist or lawyer might be tempted to ascribe the death to the collapse. This of course cannot be done logically without consideration of relative dose and toxicity of the inhaled substances. Similarly, any post-mortem study using controls should ensure that the control lungs are treated in exactly the same way as the “case” lungs, since otherwise there will be a tendency to over-emphasise positive findings in the cases.

8. Post-mortems may be linked to epidemiological data, and I have experience of this in the coal industry. Ideally, a protocol such as this should be used. The objective would not be to determine individual proximate cause of death, but to determine the association of causes of death with the WTC collapse. Such a

study could be designed and would, in the absence of controls, need to use an index of exposure determined in life or measured in lymph nodes to link to particular hypothetical disease states found at post-mortem. In my view this would be a very inefficient and costly method of determining association and in view of the likely rarity of chronic lung consequences of the collapse that might be demonstrable pathologically (as opposed to the frequency of death from cancer and chronic obstructive lung disease in the population at large) I would not recommend it. An appropriately designed mortality study or longitudinal morbidity study is a much more efficient means of establishing relationships to environmental factors.

9. It is important to be clear in this document that the sole purpose is to determine the disease causing death in individuals and that the post-mortem is not likely to be capable of determining the cause of that disease. It is also important to clarify the purpose of the expensive and detailed mineral analyses. I see no purpose in these unless they are to be used for epidemiological reasons, in which case a study protocol should be agreed beforehand and this should include appropriate controls.

10. Pathologists should be aware that any study focussing attention on lung disease in those exposed to the collapse will bring to light rarer lung disease – sarcoidosis, pulmonary eosinophilia, various fibroses and arteritides and so on. Post-mortem cannot determine the cause of these; only epidemiology can establish whether they have an exposure-related link to the collapse. I would suggest further careful consideration and clarification of the objectives of this exercise before committing to its funding. What precisely are the objectives? How likely are they to be achieved by the proposed methodology? Do the ends justify the means?