Research Recommendations
WTC Scientific/Technical Advisory Committee
Draft for discussion 1/22/2012

RESPIRATORY DISEASES:

The committee recommends additional research on the effect of WTC exposures on the development of chronic respiratory diseases. Specific topics include:

- Continue to do follow-up studies on all WTC-exposed groups (firefighters, rescue and recovery workers, residents, children, police and emergency service workers, etc.) for whom persistent WTC-related respiratory symptoms and effects (asthma, rhinitis, sinusitis, etc.) have been documented and/or demonstrated.
- Determine whether existing persistent health effects among various exposed groups follow an exposure-effect gradient (as demonstrated with firefighters)
- Explore genetic, environmental and other clinical co-factors associated with improving versus worsening pulmonary function and COPD.
- Investigate the best diagnostic approaches to patients with respiratory symptoms but normal pulmonary function testing; develop clinical guidelines.
- Investigate the role of inflammation in the persistent drop in pulmonary function among WTC first responders, including correlate lung function changes with inflammatory biomarkers in blood, blood, sputum, or nasal/bronchial brushes.
- Is inflammation a possible mechanism only in highly exposed or is it also possible at lower exposures?
- Are there potential randomized clinical trials for treatment strategies to reduce the likelihood of COPD developing?

SARCOIDOSIS:
The committee recommends additional research on sarcoidosis which seems to be in excess in all of the major post-WTC cohorts. The WTC HP should encourage the four major cohorts to conduct cooperative studies to investigate genetic, demographic, occupational and clinical risk factors for sarcoidosis associated with 9/11 exposures.

CANCER:
The committee recommends continued follow-up all WTC-exposed cohorts currently under study for cancer incidence and mortality. The committee also recommends that studies should be done to detect pre-malignant changes using biomarkers in blood or sputum as well as use of other clinically appropriate techniques to detect evidence of pre-cancerous lesions or mucosal changes. Toxicological and mechanistic research should be done to better understand potential carcinogenicity of WTC dust and components.

MEDICAL SURVEILLANCE:
Research should be conducted on optimal methods of medical surveillance and screening for WTC dust-exposed. Should WTC dust exposed be screened for auto immune diseases or other diseases not yet identified as WTC-related? Should enhanced screening for lung or other cancers be considered in light of both risks and benefits associated with screening tests?

HEALTH EFFECTS AMONG CHILDREN:
The committee recommends that research on pediatric environmental health effects of 9/11, including respiratory, developmental and endocrine impacts should be an immediate priority. We know very little about the health effects of the WTC disaster on the more than 30,000 children living or attending school or daycare in the area. Given children's increased susceptibility to harm, especially in critical periods of development, it is imperative that NIOSH move quickly to support in depth studies of respiratory impacts, developmental effects and endocrine disruption for this rapidly dispersing cohort.

MENTAL HEALTH INTERVENTION STUDIES:
The committee recommends that the WTC HP should solicit proposals for mental health intervention studies. While studies show substantially increased rates of PTSD and other psychiatric diseases in WTC populations, studies to define the best treatments would be valuable; clinical trials at one or more of the centers would be a logical next step.

BIOSPECIMEN REPOSITORY:
The WTC HP should solicit proposals to develop a biospecimen repository of blood and other biological samples collected with informed consent for research from individuals seen at the WTC funded health clinics. Such samples would be an important resource for future studies to investigate associations between WTC exposures and health effects.

CROSS CUTTING ISSUES:

- Are there medical conditions in WTC-exposed patients that cause, are caused by, or are otherwise related to another condition in the same patient (rather than existing simultaneously but independent in the same patient). For example, do heart conditions (not covered) develop after treatment for a respiratory condition (covered)?
- What is happening in females vs. males in the health program? Research that may be based only on male participants does not consider important sex differences in the incidence of certain diseases, response to treatment, and long-term outcomes.
- Consider the applicability of participatory action approaches to the WTC HP.
- Recognize that WTC research is 'disaster science.'

Comments from individual WTC STAC Members

Virginia Weaver

It was a pleasure meeting you and working with you on the STAC over the last few days. Here are my three recommendations:

1. Mental health interventions study – my rationale for this is that, while there are studies showing substantially increased rates of PTSD and other psychiatric diseases in WTC populations, studies to define the best treatments would be valuable to this population as well as others impacted by both man-made and natural disasters. The team at NYU seems to be thinking along these lines based on the systematic review data presented to us but a clinical trial at one or more of the centers would be the logical next step.
2. Research to determine the best diagnostic approach to patients with respiratory symptoms but normal pulmonary function testing. Again, some work in this regard has been done in terms of oscillometry and end expiratory CT scans and so I will defer to my pulmonary colleagues on the committee as to whether this goal has been achieved. However, my rationale is that, as with recommendation #1, the value is clear for WTC populations but would also extend to many other patients with toxic inhalation and symptoms but normal initial testing. Once the approach is clear, guidelines issued through the American Thoracic Society would be valuable
3. The last one is a no-brainer – continued funding of cancer research.

William Rom

Research topics need to emphasize respiratory disease since that is by far what the respondents suffer from.

1. First, what are the biomarkers that may predict COPD especially emphysema?
2. Are lung function changes correlated with blood inflammatory markers?
3. Will asthma or airway changes e.g. Constrictive bronchiolitis predict emphysema?
4. What are the characteristics of small airway disease in WTC dust-exposed?
   Can sputum or airway/nasal brushes predict asthma or airway diseases?
5. Are there any proteomic or genomic or metabolomic predictors of COPD in WTC dust-exposed?
6. Longitudinal studies would be much more helpful than cross-sectional since there are large cohorts already in screening and treatment clinics.
   Are there potential randomized clinical trials for treatment strategies to reduce the likelihood of COPD developing?
7. Are there blood banks and gene repositories that can be used currently and going forward that can predict COPD/emphysema?
8. How often and how should WTC dust-exposed be screened?
9. Can inflammatory markers in blood, sputum, nasal/bronchial brushes be used to correlate with COPD/emphysema?
10. Do WTC dust exposed or those with PTSD have increased sleep apnea? Does sleep apnea correlate with small airway disease markers?
11. Do WTC dust exposed have increased cancer biomarkers in blood (proteomics, genomics) or sputum, and should they be undergoing CT screening for lung cancer?

12. What cell line systems or transgenic mice can be used to model WTC dust exposure?

John Dement

Thanks for the reminder. The following are my three research recommendation:

1) Further research in the role of inflammation in the persistent drop in pulmonary function among WTC first responders. This cohort is unique with regard to exposure characteristics and offers the opportunity to investigate the natural history of many respiratory diseases, including COPD and RADS. Some consideration should be given to developing a serum bank for WTC responders to be used for future studies.
2) Combined analyses of sarcoidosis cases, pooling cases from the various WTC cohorts. This could be a descriptive study, perhaps followed by a case-control analysis if the number of cases is sufficient.
3) Expanded study of respiratory effects among WTC exposed children. Several schools were in the dust path and further follow-up of those exposed is needed. For these analyses, an appropriate control population is needed.

Thomas Aldrich, MD

Attached are three proposed research priorities for the WTC HP, one fairly well-developed and the other two just outlines.

I'm a little concerned about COI, and each proposal is followed by a brief note about COI.

1. GENETIC, DEMOGRAPHIC, OCCUPATIONAL, AND CLINICAL CHARACTERISTICS OF PATIENTS WITH WTC-ASSOCIATED SARCOIDOSIS.

Sarcoidosis probably represents a genetically-primed excessive and abnormal immune response to any of a number of antigens. The frequent involvement of lung, skin and eyes has suggested an airborne route of antigen exposure. In addition to the well-known association of beryllium exposure to the development of a granulomatous disorder indistinguishable from sarcoidosis, environmental factors such as wood smoke, tree (especially pine) pollen, insecticides, mold, flight deck work on aircraft carriers, metalworking, construction work, and firefighting have been associated with increased risk of sarcoidosis.

Unusually high annual incidence and point prevalence of sarcoidosis has been demonstrated in all of the major post-WTC cohorts, with 26 new cases found in FDNY (Izbicki Chest 2007), 38 at Mt Sinai (Crowley AJIndMed 2011), 23 at NYU (Parsia AJRCCM abstract 2010), and 43 in the registry (Jordan JOEM 2011). (At least some of the registry cases overlap with those reported in other cohorts, but it is clear that there are at least 100 new post-WTC cases). Each of the cohorts may have identified additional cases since their publications. Stored blood is available for at least the FDNY patients, and fresh blood

samples can be obtained from most patients. In addition, FDNY has reported 25 firefighting-associated sarcoidosis case pre-9/11 (Prezant Chest 1999). These >100 cases represent a unique cohort of sarcoidosis cases, the majority of whom had defined temporal onset and a relatively well-established environmental trigger.

The WTC HP should require the four major cohorts to conduct a cooperative study of genetic and clinical characteristics of the identified post-9/11 sarcoidosis cases. The study should include at the least two controls groups: non-WTC-associated sarcoidosis cases matched for gender, age, race/ethnicity, occupation, and smoking history; and non-sarcoidosis WTC-exposed persons, similarly matched. The PI could be from any of the cohorts, but a representative of each should be included and should guarantee access to records and patients.

Note regarding COI: I was one of several authors (not first, second, or senior author) of the FDNY sarcoidosis paper in 2007. If I were not a member of the WTCHP STAC, I might well propose a study of this sort in any future RFP from the WTCHP, but, as a member of the STAC, I will undertake not to do so and not to accept any salary or other support from any contract or grant from the WTC HP on this topic.

2. EARLY DETECTION OF LUNG (AND PERHAPS HEAD & NECK, ESOPHAGEAL, GASTRIC, COLONIC) CANCER AND BIOMARKERS FOR PRECANCEROUS LESIONS.

The WTC terrorist attack led to exposure of large numbers of persons to multiple potential carcinogens. Because of the largely inhalational route of exposure, lung cancers (and also perhaps head and neck, esophageal, gastric and colon cancers) might be expected to be the most likely cancers to emerge at higher-than expected rates in the future. It is still too early to expect sufficient clinical manifestation of any WTC-associated solid tumors to be reliably detected. However, it may be possible to demonstrate evidence of pre-cancerous lesions or mucosal changes in exposed persons.

The WTC HP should solicit proposals to evaluate the presence of known biomarkers for existing cancers or "precancerous" conditions in persons with high and low exposure to WTC and in matched, non-WTC controls. Studies could be of blood biomarkers, exhaled air or BAL DNA adducts or other biomarkers.

Bronchoscopic photodynamic evaluation could also be considered to be responsive to this priority.

Perhaps there are Head and neck, esophageal, gastric, colon, or other types of photodynamic evaluations that also could be considered.

I have no COI related to this proposal.

(Third proposal redacted for potential COI)

Guille Mejia

I strongly recommend research that focuses on:

1. Co-morbidity: We need a close look at medical condition(s) in a patient that causes, is caused by, or is otherwise related to another condition in the same patient rather than looking at a medical condition existing simultaneously but independent in the same patient. For example developing a heart condition (not covered) after treatment from a covered condition (respiratory).

2. The health status of female WTC HP participants. What is happening and what is being seen in females vs. males in the health program? Relying on results of research that may be based only on male participants does not take into consideration important differences between men and women (and minorities) related to the incidence of certain diseases, how they respond to treatment, and the long term outcomes.

Findings from these types of studies may (or may not) identify other conditions for coverage, have implications for treatment, diagnostic testing and medications, or raise more questions, etc.

Susan Sidel

Attached is a short memo with my research choices.

Can we leverage top talent in specialties outside the WTCHP?

After reviewing the 2011 Research Grants, it occurred to me that we have a self-perpetuating system: Staffed only with specialties appropriate to diagnose and treat The List; we don't have specialists with interest and expertise in researching conditions other than those they were initially hired to treat. Maybe that's part of the disconnect, why The List and available research does not reflect what is actually happening to people.

1. Review the Methods & Protocols used to Collect & Collate Disease Data of Responders & Survivors in the WTCHP's. Implement Elements of Participatory Action Research (PAR) in this Study.

   - Past and present research and data methods do not provide a comprehensive overview of diseases caused by WTC toxins. Necessity mandates continual focus on renewing and re-validating illnesses previously negotiated for monitoring and treatment.
   - This is why we do not have accurate cancer numbers; the data was not collected or collected but not collated.
   - The List contains health effects treatable within the purview of the medical specialties of WTCPH staff or specialists easily accessible at a Center of Excellence (Occupational Medicine, Pulmonologists, Psychiatrists, Gastroenterologists). Other likely WTC disease consequences requiring different specialists for diagnosis and treatment are not included.
   - It is unclear if Monitoring and Treatment patients diagnosed elsewhere with a WTC-related condition, not on The List, has that diagnosis reflected in any WTCHP data.
   - Responders complain that symptoms and ailments, "likely" WTC related conditions were/are ignored by WTCHP doctors, as they are not on The List. Their medical records reflect only List ailments and symptoms ignoring all other possible WTC related health issues particularly if undiagnosed.

- Impoverished by ill health, specialized diagnosis is difficult for many Responders and Survivors to access. Many specialists in NYC do not accept any health insurance, let alone NYS Workers Compensation, GHI, and Blue Cross (held by many city employees) or Medicare/Medicaid.
- It becomes circular: There is a lack of diagnosis and therefore data; downplaying the need to expand The List particularly as non-List WTC conditions must be diagnosed outside the WTCHP.
- "Essentially Participatory Action Research (PAR) is research which involves all relevant parties in actively examining together current action (which they experience as problematic) in order to change and improve it. They do this by critically reflecting on the historical, political, cultural, economic, geographic and other context which make sense of it. ... it aims to be active co-research, by and for those to be helped. Nor can it be used by one group of people to get another group of people to do what is thought best for them - whether that is to implement a central policy or an organizational or service change. Instead it tries to be a genuinely democratic or non-coercive process whereby those to be helped, determine the purposes and outcomes of their own inquiry." - Wadsworth, Y. (1998)

2. Study Autoimmune Disease(s) as a Consequence of Exposure to Toxins Present at the WTC.

    - The WTCHP have been quite insular. This would be a terrific opportunity to expand our pool of specialists and leverage the expertise of top medical centers in NYC.

    - Hospital for Special Surgery (HSS) of NYC, is the #2 Rheumatology Center, nationally, and a teaching hospital for Cornell Medical School.

3. Effect of WTC Toxins on Women's Health Issues.

Julia Quint

1. Effect of WTC exposures on the development of chronic respiratory disease (COPD, sarcoidosis, lung cancer, etc.)
   Conduct research and continue to do follow-up studies on all WTC-exposed groups (firefighters, rescue and recovery workers, residents, children, police and emergency service workers, etc.) for whom persistent WTC-related respiratory symptoms and effects (asthma, rhinitis, sinusitis, etc.) have been documented and/or demonstrated.

   Examples of questions/issues that could be addressed in the research/follow-up studies:

   - ◆ Whether existing persistent health effects among various exposed groups follow an exposure-effect gradient (as demonstrated with firefighters)

   - ◆ Whether there are differences or similarities in the persistent health effects of the various WTC-exposed groups that may predict a risk of chronic respiratory disease

   - ◆ Whether inflammation is the mechanism by which the adverse respiratory health effects were induced in the various exposed groups. Is inflammation a possible mechanism only in highly exposed as indicated by the in vivo toxicological study by Gavett et al. and the in

vitro study by Payne et al., or is also possible at lower exposures as indicated by the in vitro study by Wang et al.?

- ◆ Are there biomarkers (effects or exposures) that would help to predict the risk of developing chronic respiratory disease?

2. Effect of WTC exposures on the risk of developing cancer
Conduct toxicological and epidemiological research and continue to follow up all WTC-exposed groups currently under study to identify excess cancers.

Examples of questions/issues that could be addressed in the research/follow-up studies:

- ◆ Did WTC exposure increase the presence of PAH- or benzo(a)pyrene –DNA adducts in non-smokers in the various exposed groups? If so, do the concentrations of PAH-DNA adducts correlate with level or time of WTC exposure?

- ◆ Did WTC exposure increase the risk or reduce the latency of testicular cancer, prostate cancer, and Non-Hodgkin lymphoma among firefighters who are already at risk for these cancers based on their occupation? IARC classifies firefighting as an occupation as 2B, Possibly Carcinogenic in Humans. A meta-analysis by the IARC Working Group found that these cancers were statistically significantly increased among firefighters.

- ◆ Possibility of short, high exposures to WTC dust inducing cancer via an inflammation mechanism

- ◆ What is the theoretical lifetime cancer risk (using the default assumption that the risks are additive) associated with exposure to the 72 carcinogens (most of which are genotoxic and 15 of which are human carcinogens) identified in the WTC dust?

- ◆ Would WTC dust be carcinogenic if it were tested in an NTP animal bioassay?

3. Will WTC exposures have long-term effects on the health of children?
Continue to conduct follow-up studies of exposed children and children born to exposed women and men to determine if they develop long-term health effects.

Examples of questions/issues that could be addressed in the research/follow-up studies:

- ◆ Are the children of pregnant women who were exposed to high levels of PAHs at increased risk for developing cancer because of in utero exposure (indicated in the studies by Perera et al.)?

- ◆ Are children with persistent symptoms at increased risk of chronic respiratory disease compared to adults with similar symptoms and levels/types of exposures?

- ◆ Whether stress-induced low birth weight caused adverse effects on the academic achievement of children born of WTC-exposed pregnant women

- ◆ Long-term effects on the academic achievement of children enrolled in schools in areas directly affected by the WTC disaster
- ◆ Are children at increased to develop cancer compared to similarly WTC-exposed adults?

Kimberly Flynn

As a STAC member, I appreciate the opportunity to provide input on the important question of WTC research priorities.

First, I wish to raise a number of ideas that should inform NIOSH's approach to research solicitation, review and funding, then I list three research priorities

Approach to WTC Research:

NIOSH should solicit a diversity of proposals at different levels of funding, including pilot studies, clinical trials, mechanistic studies, epidemiologic studies and basic science research. Especially important would be work that creates resources that can be used by multiple investigators.

NIOSH should solicit proposals that address health effects to populations throughout the geographic zones of impact defined by the Zadroga Act.

NIOSH should recognize that WTC research is 'disaster science.' The understanding that 9/11-related health impacts were the result of a disaster, with all the complexity and uncertainty disaster ushers in, should inform RFPs and the proposal review process. Post-9/11, researchers and doctors affiliated with the clinical centers and data centers have worked to address the challenges of a context that differs in key ways from standard scientific research. Especially with respect to the survivor populations, reviewers must take into account that a standardized body of pre-existing medical data for study subject does not exist. In addition, the absence of reliable and comprehensive environmental measurements makes quantifying exposures impossible. It is critical that these and other limitation in available data deriving from the unique nature of the WTC disaster or the negligence of the Environmental Protection Agency not become an insurmountable barrier to conducting the research required to meet the 9/11-related health needs of survivors.

WTC Research Priorities

1) Research on pediatric environmental health effects of 9/11, including respiratory, developmental and endocrine impacts, should be an immediate priority. We know very little about the physical health effects of the WTC disaster on the more than 30,000 children living or attending school or daycare in the area. The only data that currently exist are WTC Health Registry surveys completed by parents of some 3000 children, and a handful of molecular epidemiology studies correlating various developmental and mutagenic effects with the presence of pollutants in cord blood – the so-called WTC pregnancy studies.

The WTC Health Registry's initial questionnaire survey found that two to three years after 9/11, parents of children who were less than 5 years old on 9/11 and enrolled in the health registry reported twice as much newly diagnosed asthma than average levels for the northeastern United States for that age group.

Nonetheless, there have been no lung function studies following up on what appears to be a widespread respiratory impact. In addition, there have been no studies of non-respiratory health impacts, except for a handful of studies by Dr. Frederica Perrera's team at the Mailman School of Public Health, some of which show neurodevelopmental and mutagenic effects of in utero exposures to WTC-derived PAHs. Given children's increased susceptibility to harm, especially in critical periods of development, it is imperative that NIOSH move quickly to support in depth studies of respiratory impacts, developmental effects and endocrine disruption for this rapidly dispersing cohort.

2) The President's Cancer Panel has called the capacity to collect and preserve biologic samples essential. Blood banking from which DNA, RNA and proteins can be recovered should be done for both survivors and responders, and should include freezing live cells. This would be especially important for the pediatric population, which should be followed longitudinally. In the past decade, researchers have detected DNA adducts in the cord blood of WTC-exposed pregnant women, as well as PBDE concentrations that were found to be correlated with neurodevelopmental impairment revealed when their children were given standardized tests during the first six years of life.

Individual toxins such as PBDE should be assayed in blood samples. In addition, more powerful techniques are available for assessing genetic damage and disruption of cell physiology, such as genomic DNA sequencing and expression profiling. As technology evolves, along with an understanding of the interplay of genetic variance interacting with external environmental factors, especially environmentally induced epigenetic changes, the blood bank would prove to be an invaluable resource for numerous researchers. Failing to blood bank now for the WTC pediatric population means foreclosing a key opportunity to investigate the biological basis of disorders caused by exposure to WTC toxins during intense phases of growth.

Finally, understanding the biological effects of complex mixtures can open the way to more accurate assessment of the WTC-exposed. In addition, this would expand a knowledge base for future disasters and as such, would be an enduring benefit that can still be draw from what was otherwise an unmitigated tragedy.

3) Since the underlying disease process of WTC illnesses is poorly understood, mechanistic studies of WTC-related asthma, sarcoidosis, interstitial lung disease, as well as thyroid cancer should be initiated now. Such studies will address 'diagnostic uncertainty' and 'treatment uncertainty,' in the language of the Zadroga Act. The translational benefits of these studies may be substantial, as they may provide insights into more effective intervention. Such studies may also contribute to an understanding of the carcinogenic potential of WTC exposures.