THE NATIONAL ACADEMIES

WORKSHOP ON DIFFERENTIAL SUSCEPTIBILITY OF OLDER PERSONS TO ENVIRONMENTAL HAZARDS

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DR. WEGMAN: I would like to welcome you to the Workshop on Differential Susceptibility of Older Persons to Environmental Hazards.

I am David Wegman, and I have been chairing the Committee on Studying the Health and Safety Needs of Older Workers and we have the pleasure now to work with the EPA on this workshop to develop the best possible understanding of the association of environmental toxic materials with aging factors.

It is a pleasure to be part of this workshop today and to take from it what we can to inform our own deliberations as we finish our report.

I am going to turn the podium over to William Colglazier from the National Academy to start the program going.

DR. COLGLAZIER: Let me, also, welcome you here, especially those who braved the snow to make it this morning but also to the audience that is listening over the web and maybe some of the people who hoped to be here today are

staying at home where it is nice and warm and listening over the Internet.

We are very pleased to cohost this workshop at the National Academies which includes the National Academy of Sciences, the National Academy of Engineering, the Institute of Medicine and the National Research Council, and we are cosponsoring the workshop with the US Environmental Protection Agency, the National Institute on Aging, the National Institute of Occupational Safety and Health and the Archstone(?) Foundation and the agenda for the workshop has been organized by a Steering Committee that is chaired by David Wegman who also chairs our committee that is looking at issues related to older workers.

However, this workshop is really focused on older persons, the differential susceptibility of older persons to environmental hazards.

The US EPA has a special initiative that our keynote speaker I am sure is going to talk about called the aging initiative and there is a brochure which I hope you picked up on the outside that explains in more detail EPA's initiative.

The workshop is intended to bring together experts

who will help us to formulate research in a practice agenda to help guide EPA in their new initiative. The EPA intends that its initiative will be developed through an open participatory process designed to shape the national agenda on environment and aging.

Next spring the EPA will hold public meetings throughout the country based on the findings of this workshop. The EPA is soliciting input from many stakeholders including older Americans to ensure the development of an adequate and comprehensive national agenda on environment and aging.

The National Academies are very pleased to assist the EPA in this initiative and in this workshop and gratified that the EPA called on us to help bring together experts to present and discuss relevant issues leading towards what we hope will be a comprehensive agenda in research and practice dealing with this initiative.

We are, also, relying in part on several past initiatives which I think have been quite useful and relevant to this task. There was a previous report done by the National Academies Institute of Medicine that suggested the need for further examination of the factors that

contribute to differential susceptibility of older persons and after our keynote address our first speaker, Dr. Robert Vestal will summarize the findings and conclusions of that report and several other members of that committee I think are presenters today and our second speaker will be Dr. Philip Landrigan. He will talk about another earlier report which dealt with similar concerns but for a different population, that of children.

The Steering Committee I think has put together a challenging and engaging format that I hope will not only involve the people that are in the audience today but also people over the web and they will be able to ask questions of presenters as well.

Let me just list some of the key issues that we hope the workshop will address during the day, questions that we hope some answers could be provided.

The first is what scientific evidence exists to support the hypotheses that the elderly are differentially susceptible as compared to younger people to environmental threats and for what illnesses and diseases and what specific hazards and does the scientific evidence suggest the extent to which the elderly are differentially

susceptible or differentially exposed to such hazards and what scientific evidence exists to support the choice of effective interventions at the primary or the secondary level taking into account any special challenges of intervening with the elderly?

Let me now turn to our keynote speaker. We are very pleased that she could also brave the snow and get here today. Governor Whitman of course is the Administrator of the US Environmental Protection Agency. She was the Governor of New Jersey. There she developed a very strong environmental record. During her tenure New Jersey's air became significantly cleaner, likewise New Jersey's waterways, coasts and oceans also became much cleaner. She won voter approval for the state's first stable funding source to preserve 1 million more acres in New Jersey of open space and farmland.

She has been a strong proponent of what is called smart growth, trying to encourage development in built areas and also in helping to clean up ground fill sites for new development.

During her tenure of almost 2 years at the EPA I think she has been recognized as a strong environmental

steward.

The National Academies have been pleased during her tenure to collaborate on several projects and we are certainly very pleased to have her here today.

So, we look forward to her remarks.

GOVERNOR WHITMAN: Thank you very much for that kind introduction, and I am delighted to see those intrepid people who were able to make it through the snow, but I am equally pleased with those who are going to be joining us over the web so that we can prove that neither rain nor sleet nor snow shall keep us from our appointed rounds or in this case keep us from a discussion that I feel has enormous import for the future of our country really.

I am very happy to be able to be here to start this discussion about the impact that the environment has on the health of older Americans.

It was 15 years ago that the National Academy of Sciences issued a landmark study that discovered sound biological reasons to support the belief that the effect of the environment on people changes with age as does the ability to respond to environmental exposures.

I commend the Academy on its efforts on this issue

over the years and I want to thank them for hosting this very important workshop to more fully examine these environmental issues and the interrelationship and interestingly enough and I know you will be discussing this, the impact goes both ways and we need to be aware of that as well and we need to have a sensitivity to that.

Our country is undergoing a dramatic change in demographics. By the middle of this century our population over 65 will have doubled from where it is today. There is no doubt that the rapid growth of a senior population coupled with the fact that older Americans are more vulnerable to environmental hazards makes this a population that deserves our special attention.

As a result during my tenure at the Environmental Protection Agency we have made protecting the health of our older Americans a top priority of the agency.

The older we are the more susceptible we become to the threats from the environment which may cause chronic or life threatening conditions. Poor indoor air quality as well as ozone and particulate matter in outdoor air exacerbate respiratory conditions. They can trigger asthma attacks and limit activity levels as we all know from those ozone alert

days when people are urged, anyone with a respiratory condition is urged to stay indoors.

Older immune systems are also less able to fight off some of the water-borne microbes such as Cryptosporidium or E. coli.

In order to study and prioritize environmental health risks such as these, the EPA has launched an aging initiative in October of this year.

The initiative encompasses three areas that I would like to share with you. The first is research and development of preventative actions to address environmental health threats; second, research to address the impact of the rapidly aging society on our environmental and that is the part that is often overlooked. As people rely and take more medications those begin to turn up in our water systems and we need to understand what that impact is and how we can address those potential problems that that poses and we are encouraging older Americans to volunteer in their communities to help reduce environmental hazards and protect the environment for persons of all ages.

One of the first things we did when we began to develop this initiative was to look within our own agency to

determine what research was already under way, and as we did this as is true so often in government we discovered a lot about ourselves, and we in fact discovered that there were 75 different initiatives throughout the agency that focused on the concerns of older Americans, and so one of the main purposes of our new initiative is to consolidate those efforts to develop a more unified approach to our research.

We have, also, developed a strong foundation for encouraging senior volunteers to help with environmental efforts in their communities. Our nation's senior population is one of our most precious natural resources and we will continue to work to find new ways to increase the opportunity for them to help educate others as to the importance of environmental protection in order to protect not just the senior population but all of the country and all our populations.

While this is a good start there is much more that needs to be done and certainly much more that can be done and the aging initiative will help us to focus our efforts, integrate our research throughout the entire agency and partner with other interested groups to determine how best to meet these environmental challenge.

Indeed to be successful our efforts need the help of dedicated partners and that is why I am particularly glad that so many of you are here today and are participating over the Internet in this workshop.

I am pleased to announce that even at this early stage we are already closely collaborating with two institutions within the National Institutes of Health including the National Institute on Aging and the National Institute for Environmental Health Sciences recognizing that we have a number of federal partner. Not only did we discover 75 programs within our own agency, we know that there are many other agencies throughout the Federal Government that are also focused on these issues, and none of us have the disposable resources to duplicate efforts.

We need to focus. We need to be working together if we are truly going to maximize and leverage our capabilities. In addition to further the volunteerism component of our aging initiative we are looking for ways to partner with the Corporation for National Community Services which is administering President Bush's freedom corps.

This is just beginning and we will continue to seek partners within the Federal Government and beyond as we

move forward with our aging initiative within the agency.

During the next year we will be crafting a national agenda on the environment and aging and this workshop is the first step in that process which is why we are very glad that you have agreed to contribute your time to this effort today.

Over the next 2 days we are asking for your suggestions. We are looking for your expertise and any ideas to help us shape this national dialogue that we want to encourage and to help us with the agenda and prepare for the series of public meetings that you heard about a moment ago.

The public meetings are going to be held in Florida, Pennsylvania, California, Iowa, Texas and Washington, DC, and they are designed to ensure that all voices are heard from across a broad spectrum of stakeholders that includes the state and local governments, that include aging and health professionals and older Americans and their families and the sorts of challenges that they find themselves facing.

Only by opening up this process and encouraging this type of active participation can we expect to get a more complete and comprehensive picture of the issues that

we are facing and the needs that we need to address, where to focus our research, where to focus our efforts and the most effective way that we can address these issues in a way that makes sense to the individuals themselves where they live and where they do their business.

Your work here today and tomorrow is going to help us lay the groundwork for those meetings and is really critical to their success.

We are not going to be able to maximize what we are seeking without your help and without the agenda that you are going to help us develop over the next 2 days.

Each of you brings a unique set of experiences and a unique set of ideas to the table, and I know that this workshop is going to be extremely valuable to us for the ideas that we are going to get from it.

The challenge we face to improve our quality of life for all Americans is an overriding one. It is what our agency is all about and I want to thank you for your participation and your willingness to help us meet that challenge particularly for the older population.

Working together we can assure that for older Americans, for all older Americans that the years ahead are

truly golden years, are years that can really be enjoyed and not ones where because of environmental concerns people are forced to curtail their life style and their quality of life.

Again, I want to thank you. I want to thank the National Academy for hosting this. I want to thank you for the partnership that you have provided over the years and I want to thank all of you whether you are here in person or listening in for your willingness to share your expertise and your knowledge.

I am very excited by this initiative. I believe we have at the agency a lot to offer to help improve the quality of life for all Americans and in this instance particularly for our older population.

Thank you all very, very much for being here today.

(Applause.)

DR. WEGMAN: It is a very good start to our session here to hear from Governor Whitman and to understand at some beginning level what the challenge we have to face is to draw together this information.

Those of you who have had a moment to look at the

agenda will see that it is a very, very tight agenda.

There are lots of presentations that are going to occur quickly and the timing for open discussion is quite limited at the end of each of the days at the end of today and then the end at around noon tomorrow.

I hope that you will take some time at the breaks and at lunch to carry on conversations around the issues that are raised and to bring to our attention any issues that you think need to be addressed that aren't addressed or issues that are raised by what is addressed.

We do have a tight time schedule and therefore we will be keeping a time clock on people. There will be a green, red and yellow light here that you will follow and we really do urge you to stay close to the agenda so that we can make our presentations in a timely fashion.

It is exciting that we have so many presentations because it suggests that at least we have the beginning of a lot of knowledge and it will be interesting to find out where we are at the end of the day and one-half.

To begin the process Governor Whitman referred to the report from the National Academy of Sciences in 1987, and Robert Vestal is going to share with us some memory of

that and a sort of an update of where he thinks we have come with that report as a backdrop to this meeting.

DR. VESTAL: First of all I would like to express my appreciation for being invited to participate in this workshop today and tomorrow.

It is really gratifying that after 15 years this whole issue of aging and the environment is being highlighted once again and I am personally very eager to hear some of the newer work that has been done since our committee prepared this report back in 1987.

The background is that in 1985, the Environmental Protection Agency and the National Institute for Environmental Health Sciences requested that the National Academy of Sciences evaluate current information about the effects of environmental chemicals on aging processes and the aging population and to recommend research strategies.

My task will be to try to summarize the conclusions and recommendations of that committee work. The work actually began in 1986, with the formation of the Committee on Chemical Toxicity and Aging.

We held several meetings over a period of I think it was 15 months or more. Ed Masoro this morning thought it

was closer to 2 years. It has been a while back and my memory isn't that good about the precise details.

We heard presentations by committee members and invited experts and then ultimately a report was published in 1987, as you know entitled Aging in Today's Environment, and I must say that as I looked back through that report and reviewed the conclusions and recommendations I think it has much to inform us today about what needs to be done still.

The committee was comprised of 16 members including the cochairs Bob Butler and Emil Fitzer. Five of us participating in this workshop were members of that committee, Drs. Gilchrest, Fred de Serres, Peter Spencer and Ed Masoro and myself.

The committee began its work by recognizing several general considerations, first and foremost the obvious rapid growth of the elderly population and also the increasing complexity of environmental factors such as pollutants, extensive pharmaceutical use among the elderly, nutrition and various life style factors.

It was, also, acknowledged that environmental exposures vary but they might be more problematic for the aged especially those with chronic disease and one indicator

of chronic disease is that over 70 percent of the elderly take at least one pharmaceutical preparation regularly and over 25 percent have heart disease.

The committee also recognized three important questions, first what is the nature of aging itself; what is the nature of the environmental exposure and then what is the physiological or medical condition of the aging or aged subject or population?

Moving to the general conclusions it would be impossible to summarize all the data, and I commend the report to any of you who are interested in looking at it.

There were five major conclusions. The first was that, and I will be interested in Ed's comments about this later on. We were discussing this this morning but at that time the initial conclusion of the committee was that the evidence supports the concept of intrinsic aging and noted that there are a number of theories which provide potential mechanistic insight.

It was, also, noted that although environmental exposures can cause changes that simulate aging and examples would include sun exposure and smoking which can accelerate aging of the skin and UV radiation which promotes cataract

formation and natural or industrial toxicants that can contribute to age-related neurologic diseases, in spite of this no single agent can cause the earlier appearance of all aging processes.

The second conclusion was that humans exhibit varied responses to the environment itself and varied patterns of aging and these can be influenced by a variety of factors including differences in environmental exposure, again, nutrition, pharmaceuticals, life style choices, such as smoking and exercise or sedentary life style and occupation and genetic differences and then interactions between individual genetic constitutions and the environment.

The committee also recognized that there was very little information on the impact of environmental factors on aging processes per se but acknowledged that there are available tools that would be potentially useful for studies including the use of animals undergoing dietary restriction or genetic manipulation in order to extend life spans so that obviously the impact of in an experimental setting the impact of an environmental change could be studied in that setting with those kinds of models.

The fourth conclusion was that although important little is known about the specific effects of environmental exposures on human aging. What is known is that extremes of air pollution or environmental temperature may be more injurious or even fatal to the elderly than to younger adults.

Drugs though beneficial cause adverse effects more frequently in the elderly in part due to disease severity, use of other drugs or misuse of medications and to some extent due to age itself and also there is an increased susceptibility to the effects of environmental toxicants.

Life style and medical care can decrease or delay the onset of heart disease, stroke and even some types of malignancy. It was,also, noted interestingly that there is a positive effect of good interpersonal relationships with the presence of a sense of purpose of goals and of structured daily lives on the physical health indices and on survivorship in the elderly and finally it was concluded that the increased incidence of chronic diseases that are often associated with aging need not be characteristic of aging processes themselves. It was noted that the reduction of disease in old age might be attainable through

modification of environmental exposures and that research would likely enhance our understanding of the interplay between aging processes, the environment and disease, also, that research hopefully will provide information on the prevention of environmentally induced age-associated disease.

There were quite a number of recommendations made by the committee, first a couple of general ones. One was that systematic screening of environmental agents for influence on aging processes would be premature in the absence of more basic information on aging.

It was, also, acknowledged that a better understanding of basic mechanisms of aging, how they could be affected by the environment and how aging itself might affect toxicity is needed.

There was developed a rather extensive research agenda. I counted at least 16 specific recommendations. One was, the first was to identify and elucidate fundamental mechanisms of aging and to continue to search for valid biomarkers of aging.

Another was to study the effects or continue the study of the effects of dietary restriction and nutritional

constituents on life span and specific physiological functions, and we will hear more about that from Dr. Masoro.

Also, it was recommended that we collect toxicity data including toxicokinetics and pharmacodynamics on older organisms as a standard part of normal toxicity testing of various agents.

It was recommended that studies be conducted on the responses of aged laboratory animals to specific toxic agents. However, in general it was recommended that these kinds of studies be restricted to the study of specific experimental issues rather than broadly screening a variety of environmental agents.

It was, also suggested that attempts be made to identify archetypal toxic agents or reference compounds to be studied along with non-toxic agents as negative controls in order to mimic age-associated diseases or biological markers of aging. MPTP was noted as an example.

It was recommended that epidemiological techniques be used to study early environmental exposures that can predispose to neurological disorders later in life and seek causal mechanisms and also to conduct longitudinal epidemiological studies of populations and age-associated

characteristics and diseases on which information about toxic exposure is available, to also study the roles of genomic instability and chemical free radicals, to investigate genetic susceptibility to the effects of drugs and their biotransformation, in addition to the effects of multiple drug therapy and disease severity as potential causes for the increased incidence of adverse drug reactions in the elderly.

It was recommended to evaluate the potential detriment to health created by the exposure to multiple drugs and other chemical substances, such as vitamins and environmental agents.

It was recommended that research be conducted on the effects of advanced age on pharmacokinetics, bio-accumulation and other drug and chemical interactions including hepatic drug metabolizing enzyme inducers and inhibitors, the influence of dietary factors, smoking and other environmental factors, to also study the potential role of age-related differences in the frequency of genetic polymorphisms at relevant loci in relation to the susceptibility to the effect of pharmacological and environmental agents.

Another recommendation was to investigate age-related short and long-term effects of drugs and chemicals, to assess the potentially unique susceptibilities of the elderly population and to increase efforts to develop animal models of aging, whether whole animal organ systems, tissues or cellular systems for studying aging and environmental interactions.

Another important recommendation I think was to encourage the establishment of systematic autopsy studies especially in populations followed for exposure to high concentration of environmental agents.

There were, also, a couple of recommendations actually I think three or four regarding education, one to enhance the general public and health care provider awareness of the nutritional needs of the elderly and of nutritional programs that over one's lifetime could prevent or delay age-associated diseases and also to warn the public and health care professionals against unsubstantiated claims of various dietary regimens that are promoted to extend life or prevent disease in some way.

It was recommended that there be greater dissemination of the evidence and information that links

specific environmental factors with disorders found in the elderly and this would include the impact of smoking, UV radiation, inappropriate nutrition choices and so on and there was as you might expect the general recommendation that the scientific community be encouraged to focus on this field of what at that time we called gerontotoxicology and of course it was felt important to encourage government and private initiatives to promote the training of professionals in the development of academic programs that would require and develop skills for those working to the interface of gerontology and toxicology and finally, of course, there were some recommendations regarding funding and resources. It was felt that in setting funding priorities consideration should be given to the potential advantages of advancing our knowledge of aging and the environment and hopefully we are seeing a recognition of that with this workshop and the EPA initiative, to encourage efforts and fund efforts to develop aged animals in order to assure the availability of adequate numbers for this kind of research, to encourage efforts to develop banked reference collections of cells and tissues and fluids for future research and then finally the overall recommendation was that a high priority be given to research

on aging and the effects of the environment on aging processes particularly in light of the impact of the demographic shift toward an increasingly aging population, and hopefully that provides an overview and I hope a foundation for the work of this workshop and going forward as this EPA initiative takes shape.

Thank you very much.

(Applause.)

DR. WEGMAN: A wonderful starting model for our schedule. Thank you very much and also, exciting to know that that base is available for us.

I understand, unfortunately, the report is no longer in publication, but it is available in copy form and I think it maybe should be reborn in its historical context because it provides very valuable information for us as we go forward from here.

I would like to continue this overview with another member of that committee, Ed Masoro from the University of Texas who is going to discuss aging biology physiology and the effects of diet.

DR. MASORO: I thank everybody for inviting me, again, and it was wonderful to hear Dr. Vestal review many

of the things that I remember and some of the things I no longer agree with, but I certainly agreed with the committee at the time.

This really will be a pretty broad overview of what aging is in terms of the knowledge base that we have gotten, a little bit on the human physiology and then a bit on my pet caloric restriction in rodent models.

I think to start the biology aging you have to define aging and aging is defined in a variety of ways. Maybe the most common way is to say it is what happens with the passage of time, but that is not really the definition most of us are worried about. The one that we are worried about really is the senescence, and I am going to be using aging and senescence as synonyms. So, this is my definition. You should always push anybody lecturing on aging to tell you what he means by aging.

So, what I mean is the degenerative changes that occur during adult life that underlie an increasing vulnerability to challenges and there decreasing the ability of the organism to survive.

Now, we would very much like to measure the rate

of aging in individuals and biomarkers have been sought. Biomarkers of aging have been sought. There is really no general agreement about that and although all of us know when we see an old person about aging in that sense the real problem is that we don't really know how to quantitatively define it and so essentially gerontologists have had to be willing to deal with population aging and usually what they do is they measure the age-specific death rate which is the fraction of the population that dies during a given age interval, for instance between 21 and 22 years of age and they do this plot. The put the age-specific mortality rate; this one is per 1000 individuals, and they plot this on the Y axis and on the X axis is the various age intervals and this gives you a very complicated set of curves. I will take the one for 1970, as an example and what you see is that the newborn is obviously very vulnerable, that by 11 years of age we get to minimum vulnerability and then there is a very marked increase in vulnerability and that would be even more marked if you had only males rather than both males and females and that during the teenage years relates to the desire to be able to get into hazardous circumstances and then you end up with a shoulder there and a fairly linear

thing and you can see this is a log scale on the Y axis and so essentially we are seeing a roughly exponential increase in mortality and this exponential increase is viewed as a measure of the rate of aging and if you will see that in 1910 and 1970, they are pretty similar looking exponential increases. So, it looks like there is no change in the rate of aging with those 60 years but there certainly was a very big change in the hostility of the environment and so basically because of the people in 1910 living in a more hostile environment there was at every age a higher age-specific mortality.

Now, we have plenty of evidence that aging occurs broadly and we can get this kind of data from a variety of mammalian species, invertebrate species and so on. The thing is that it is a puzzle that we get it and it is a puzzle really for two reasons, that senescence is so widespread. In the first place it doesn't look to be thermodynamically essentially to occur. It is not a thermodynamic necessity. If you consider that the organism is able to use the energy of the environment to generate from a fertilized ovum a complicated organism then it is very difficult to explain why the much apparently

simpler task of maintaining this kind of structure is lost.

So, it also is difficult to understand from an evolutionary point of view because something as devastating to fitness, to evolutionary fitness you would expect would have been selected against and would have disappeared from the population.

So, we are caught with the problem of addressing two questions, and these two questions are what the gerontologists, the biological gerontologists at least for the 20th century spent their time on. Why does senescence occur; in other words what is the answer to this puzzle, and second, how does it occur? What are the biological mechanisms that underlie aging and this has really been the story of biological gerontology throughout the 20th century and continues as we go into the 21st century.

Now, I think we have a reasonable idea of why aging occurs and I think we have certainly made greater strides on No. 1 than we have on No. 2.

According to the evolutionary biologists the ultimate cause of aging is the decline in the force of natural selection with age after sexual maturation and the rate of this decline will relate to the extent to which the

environment is hostile when the population evolves or when the species evolves. Species that evolve in a highly vulnerable population, a highly hostile environment will certainly have a very rapid rate of decrease in the force of natural selection while those that evolve in less hazardous circumstances will age more slowly because the force of natural selection will decline less rapidly.

Now, if this is not quite clear to you I think the genetic mechanisms that the evolutionary biologists feel that underlie this will make it clear. First was Medowar(?) of about oh, more than half a century ago where he postulated that the accumulation of mutations with late life deleterious consequences would occur, that if indeed a deleterious mutation only expresses late there is no way the force of natural selection can eliminate it from the population and therefore it will accumulate and so these mutations accumulating in the population Medowar felt was the basic nature, the basic reason for aging, why aging occurred.

Now, Williams a few year later had a different mechanism which goes by the awful name antagonistic pleiotropy, but what he basically said was if you had an

accumulation of mutations or a set of genes that lead to wonderful development, rapid development and the generation of a large number of progeny that these will be selected for even if they are catastrophic at a later stage of life when the force of natural selection is no longer a force and so one that George Martin gives that I think is very interesting he says, "You know, genes that set up a large testosterone level probably lead to increased fitness in the young and to prostate cancer in the old," and I think that is a little bit of an exaggerated kind of thing but it gives you a feeling for what Williams was getting at.

Now, a third mechanism, one that I think probably holds although I think there is evidence that the first two mechanisms certainly do contribute to aging, I think the third one of Kirkwood is probably the major one namely that natural selection favors the genetic make-up which apportions energy between reproduction and organismic maintenance so as to maximize fitness, to maximize the number of progeny generated.

In so doing there is simply not enough energy that is going to be available to ward off aging by making repair. There is inevitable damage occurring to the organism through

the process of living and the organism will not fully repair that because of this apportionment of energy and he views it that an animal that ages, that is in a very hostile environment and therefore has much damage will respond to that environment by generating a genome that leads to very rapid reproduction, a big burst of reproduction early in life and very little into maintenance and they will age quickly and animals that live in a less hostile environment will get most progeny by not having a burst, by putting more energy into maintenance and thereby they will age more slowly and this will given their set of circumstances, environmental circumstances lead to the largest number of progeny.

Now, in terms of, so I think that this pretty well says why aging occurs, at least as we think it does at this time. The question of approximate mechanisms has been much more difficult to deal with and I think Martin, Norstad and Johnson have come up with a very important thing saying that there are private mechanisms, idiosyncratic of a certain species or group of individuals. Indeed you could see that the idea of accumulation of mutations could easily lead to mechanisms that are unique for a given subset of the

biological world and that there are public mechanisms that are aberrational widely, namely the fact that all organisms are going to in the process of intrinsic living, will generate free radicals, will get in environmental circumstances that will damage them and therefore we have then the public mechanisms which is the ability to repair this damage that is inevitable and I think I will leave this first part of the talk by saying that the extent of the imbalance between the damaging actions of stressors or harmful agents, I call them stressors; you probably would want to view them as harmful agents and they can be both intrinsic and extrinsic and the counter damaging actions of protective, that is the mechanisms that protect against damage, that there it is the imbalance between them and the extent of that imbalance that sets the rate of senescence.

So, that views how we look at senescence in terms of the general biological thing. Now, I thought I would go a little bit over human physiology and I would start of course with the fact that really good measurements on quantitative measurements on human physiology of aging weren't done until the 20th century and a very famous slide on this was done by Nathan Shock who did much, his group did

much of the seminal work in this area and what they simply showed was that everything was going down hill physiologically at different rates depending on the various systems that they measured.

Now, I think Shock understood that this is deterioration. He didn't put blood pressure on there because he didn't want to have anything go up but it is really deterioration rather than decline that he was talking about.

Now, this early work of Shock and many others has been criticized of course as people have gotten more sophisticated and they criticize it on several grounds. One, is the inadequate attention to possible confounders and I am going to go through these four sequentially of cross-sectional studies.

Now, you have to realize that with human work most of the data you have relative to human physiology comes from cross sectional because a lifetime longitudinal study is not possible on a human simply because they would outlive the investigator. So, essentially we have to deal with cross sections where we study at one given time of 20 year olds, 30 year olds, 90 year olds and so on.

Now, this is fine except that as a gerontologist

you theoretically are studying it because you want to learn about aging and it is quite important to realize that other things affect people of different ages besides that of aging and one is of course cohort effects and I give you one example. Bob Katzman at the University of California, San Diego points out that it is very hard to say to what extent cognitive function has been deteriorated due to aging from a cross-sectional study because of the fact that for instance in the United States the amount of formal education has increased markedly during the 20th century. So, if you compare a 90 year old with a 20 year old and find a difference in cognitive function and that the 90 year old is down compared to the 20 year old is it because of aging or is it because he is simply less educated?

So, this kind of confounder, this generational confounder is one that has to always be considered. The other one is selective mortality. People die more quickly if they have risk factors for the most prevalent diseases, for instance coronary heart disease. Therefore is you are measuring the HDL level and you are comparing 90 year olds and 20 year olds you have to recognize that those 90 year olds are giving you a biased view in this sense in that most

of the people with low HDL have already died.

So these two things mean that the data that you are getting about physiology always has to be worried about in this regard and I think this is very important for you to realize that as you work in your field that the database that we have about the physiology of aging is to some extent suspect.

Now, you can try to deal with that by longitudinal studies and to a certain extent they will circumvent that. Of course you can do only short periods of an individual's life and they are useful to let you look at this, but there are real problems there, too because you need a stable experimental structure over an extended period of time and you have subject dropout. I know you don't have stable methodology because basically technicians turn over and I can tell you from running a laboratory that is a very big change.

I, also, found in reviewing for the National Institute on Aging going to laboratories that they tend to change their methodology because they find a better method. Well, as soon as you do that it makes it hell to be able to interpret the study and I also found that sometimes the

institution itself buys new instruments and throws the old ones away. So, you have a very difficult time I think in terms of longitudinal studies being a solver for this and also there are similar confounding effects to cross-sectional studies. I was going to go over that, but I think my time is getting too tight for that.

So, I will not go over that of why there are also similar confounders. Now, the next thing is the inadequate assessment of health status of the subjects and I think that is a fair enough criticism.

The old workers did some pretty strange things. They would study young medical students and people in a hospital that the medical students were dealing. So, it is true they didn't pay attention to this and so -- oh, this was just my summary slide. It is that basically there are these problems of cross-sectional studies but you are stuck with them anyway.

So, there were criticisms but I am not convinced that the way the thing has been cleaned up by trying to get people who are free of disease and study them is really very useful and I don't think it is particularly very useful for this group. I think it has a certain kind of value for

gerontology to look at people free of disease as a reductionist but you folks are here asking the question what are old people like, and old people are alike physiologically from the whole series of things that they have and one of the very big things that they have is of course age-associated disease and age-associated disease is a common occurrence and from our evolutionary theory is an integral part of aging and this is where, Dr. Vestal, I disagree with what we came to the conclusion with at our last committee meetings, and these are a list of the diseases that are just many others.

Now, you have the problem that age-associated diseases are so common if you really take it seriously as some of those really vigorous procedures were to exclude you are going to end up with a very small fraction of the population. If you look at 70 year olds and look at these diseases and the several more that they have what fraction are you going to find that are totally free of these diseases? So, I think they are not only an integral part of aging but they also are so universal in the population that the selection to get somebody totally free of age-associated diseases really is an academically interesting thing to do

but really sort of in a sense a foolhardy mission.

Now, I think I won't go over it again. You can see that basically we would expect on the basis of evolutionary theory that there would be age-associated diseases and they would be an integral part of aging.

Now, I would like to go over next the whole issue of the fact that there is tremendous heterogeneity in the aging population and a very good example of it was done at the National Institutes of Health at the Baltimore Longitudinal Study of Aging where they took something in which you have a very marked decline namely glomerular filtration rate and they found that one-third of the population that they looked at didn't have that decline at all.

So, even when you have very robust phenomena like the drop in glomerular filtration rate what you will find is that it does not transcend throughout the population.

So, we do have to worry about individual things and of course Rowe and Kahn in 1987 came up with the concept of usual and successful aging and usual aging was those exhibiting substantial deterioration in physiological functions with increasing age in the absence of discernible

disease and the second was successful aging, those without discernible disease who exhibit minimal change in physiological function with age.

Now, this concept certainly brings you to the fact that there is going to be great heterogeneity and Rowe and Kahn were convinced that this related primarily to their environment and while he didn't think the genetics were a big factor, why they didn't think that I don't know. It seems to me it would be both, but I am very troubled with this whole story of successful and usual aging because I think it is misleading. It is misleading in that it makes individuals who hear it feel that you can age without ever going through marked physiological deterioration and the question, the thing is you can't.

In the first place there is a very small fraction of the population that is going to be free of disease. So, in a sense and I noticed that Rowe and Kahn have backed away from that in their more recent writing; so, they no longer stress being free of disease as they did originally but it is really not valid to say in advancing age that you are going to be free of deterioration and let me give you my big example for it. I guess maybe it is because I come from the

State of South Carolina and I saw Strom Thurmond run for the Senate 6 years ago and I see Strom Thurmond today. Now. Strom Thurmond 6 years ago won the election because it was indeed successful aging. Since them he has had to have tremendous support.

I went over the literature and I find that if you look at the report on centenarians, yes, there is an occasional centenarian who does remarkable things but most centenarians are absolutely disabled. They have all sorts of problems. They have to be supported in a tremendously vigorous way.

So, what I think would be far more valuable than successful aging which implies you can age without this problem is to say that people age at different rates.

Now, the fact that they age slowly doesn't mean that they are not going to show as long a period of deterioration and I will give you my reason that I say that. I have worked for 30 years on calorically restricted rats. They are absolutely healthy long after all the other animals are dead but if you ask the question how many days do they undergo deterioration of a marked nature the answer is I have found that about 115 days occurs for the ad libitum fed

and 115 days for the restricted. They are very old when this occurs but they show the same period of deterioration. So, I think we have to have an open mind to know whether successful aging will lead to less period of deterioration, less deterioration or not.

I don't think that those data are in and I think successful aging is misleading because of that as a concept.

Now, I don't know if I have any time. I don't have any time. So, I won't be able to go over caloric restriction.

DR. WEGMAN; You have 5 minutes.

DR. MASORO: I have 5 minutes. Okay, then I will briefly go to my first love. This is what if you restrict calories that you get.

You see the survival curve for A&R, animals that were ad libitum fed for A and restricted for R and one was ad libitum fed and two was restricted and as you can see they live very much longer. The survival curve is shifted way over to the right by caloric restriction.

If I look at tenth percentile survivors and you look at this experiment where we tried to see what would happen in group four where we actually started our

restriction when they were young adults, 6 months of age. So, they were well past sexual maturity and had full skeletal development what you see is that it is just as effective in a young adult in terms of leading to very long length of life as it is when started soon after weaning.

The animals are more useful in a variety of physiological functions. The particular rats that we used had these major disease problems, each one of these things as you can see, the nephropathy which was a huge problem with the ad libitum-fed animals almost disappeared with caloric restriction. Cardiomyopathy was markedly affected and a variety of other tumors although I must say that what you see for leukemia and lymphoma is true for all tumors. They are very much delayed but eventually those tumors appear in these animals.

Now, from the point of view of this meeting I think what is tremendously interesting is that there is evidence that caloric restriction protects from the harmful effects of acute stressors and it doesn't make any difference how old the animal is. Old and young they are both protected.

Let me give you the next slide?

This is on surgical stress and as you can see certainly the amount of body loss as the animal ages goes up between a fairly young rat and a fairly old rat but in both cases they responded to dietary restriction with much less loss of weight. This is the work of Jim Nelson's group showing the response of the footpad to the injection of an inflammatory agent and as you can see this is a log scale on the X axis you can see that markedly retarded inflammatory.

This is a study that occurred with my colleague Arvin Richardson. By accident.he had a commercial company maintain the quality of his thermal control of his rat colony. I won't mention the name of the company but they screwed up and the thing got out of control, got very hot and what you can see is that although he had these animals in exactly the same facility right next to each other that the survival was much greater for the restricted animals than for the at libitum fed and finally Dr. Duffy and his group at the National Center for Toxicological Research reported that caloric restriction protects rats from the action of a variety of toxic chemicals and this will occur again at all ages, and I think what is tremendously interesting is that caloric restriction retards aging and

genetic manipulations in invertebrate species retard aging and those very ones that retard aging in invertebrate species also protect the invertebrate animal from toxic agents.

So, there is a very close tie between toxic, the ability to resist toxic agents and the ability to retard aging.

Now, it looks like the mechanisms for the retardation of stress or the increased stress resistance really related to cellular events like the fact that these animals are able to more easily increase their heat shock protein response as well as the fact that throughout the life span the calorically restricted animals maintain daily afternoon peak glucocorticoid levels that are substantially higher than those of ad lib fed animals and I think I am probably well over my time.

Yes, it says, "Stop," or something else.

Thank you very much.

(Applause.)

DR. WEGMAN: I am afraid although I warned people about the presence of this clock on the podium I didn't warn you about the actual time that it relates to. The yellow

light comes on when you have 5 minutes left in your time. So, you should just watch it in those terms, and we are okay on timing now.

So, I am very pleased with the attention the speakers are giving to the time.

We are going to turn now to the other end of the age spectrum where we in fact begin our aging process and have Phil Landrigan from the University of Mount Sinai in New York, CUNY, part of CUNY, I can never remember, part of NYU, to come and present the results of another Academy report that was done on pesticides in the diet of infants and children.

DR. LANDRIGAN: While they are loading up my CD let me just begin by thanking David, thanking the Committee for having invited me to be here. I think there are some interesting parallels between the examination of children as an especially vulnerable group within the population and the examination of the elderly.

It is a obvious that a lot of the specifics differ, but still the fundamental logic that the notion that different groups within the population have different exposures, different vulnerabilities, some of which are

externally driven, some of which reflect the playing out of genetic factors there are lots of parallels between the two, and I would argue that the common thread that unites the two is the notion that it is just no longer sufficient. It is just no longer an adequate reflection of reality to do risk assessment in which we pretend that the whole population is comprised of healthy 21-year-old adults.

I mean for a long time risk assessment was done that way. In the old days when our ability to handle data systems was restricted that was probably the best that we could do but with today's computing power and with our expanding knowledge of differences in physiology and in exposure at different stages of life -- that is not me although he is a good friend. That is it. I tried to send this down the other day, but the file was too big. That gives you a warning of how long the talk is going to be.

Okay, here we are. So let me tell you about our 1993, report on pesticides in the diets of infants and children. This is what the report looked like and I thought what I would do is divide the talk into three components, first take a couple of minutes and tell you about the historical context in which the study arose, then say a bit

about the study itself and then finally talk about some of the real world consequences that have taken place in the decade now, the almost decade since this report appeared in the summer of 1993, and I think it is worth talking about that last part of the exercise because I would suspect that if the work that we are addressing here today is successful here at the Academy and if a good report comes out in a few years from your group that it is probably going to have real world consequences different in specificity but not unlike an overall design of what resulted from kids' report. So, it is probably worth reflecting on that experience.

So, this was the situation. It was a committee that was supposed to exist for only 2 years, but in fact it existed for 5 because it took us a great deal longer time to collect the data that we wanted than we had anticipated. The data were fragmented, very dispersed across a number of agencies and just took forever to put together, but the committee was convened in 1988 by the Senate Ag Committee. Senator Leahy of Vermont was the Chair of that Committee at that time and the notion for the committee arose out of conversations between Senator Leahy's staff and the staff here at the Academy.

It is worth noting that a year before in 1987, in addition to the aging report that we just heard about in the last two presentations there was also a report from the Academy which was entitled The Delaney Paradox. I won't go into it in any detail but it pointed out some strange inconsistencies in pesticide regulation in which natural foods and processed foods were dealt with in two different ways and it was obvious that there wasn't a completely systematic way of regulating pesticides in agriculture in this country.

There were, also, things going on externally, the last three things I put up there. It was clear to everyone doing pediatrics and public health that patterns of disease were changing in kids.

There were various clues from around the country, poisoning episodes and such, a big poisoning episode that occurred in Jamaica where all the deaths were in children, but the adults walked away. There was evidence that kids were differentially vulnerable to pesticides and then the inconsistencies in the system which had been highlighted by the Delaney report.

So, let us talk a bit about each of those, first

of all about changing patterns of disease and this will tie in kind of neatly although the perspective is a bit different with what Dr. Masoro just said.

The major causes of disease in American kids today and indeed in kids in any of the developed nations, not the Third World but here and in Japan and Western Europe are chronic diseases, asthma, cancer, developmental disabilities, learning problems. These are the disorders that cause kids to come to hospital. They are the conditions that disable kids and this has been referred to, the switch from the old pattern which was dominated by the infectious diseases to the so-called "new" pediatric morbidity has been referred to as the epidemiologic transition and it is interesting if you get into international health and start looking at different countries that are moving along the spectrum towards industrialization at different rates that the epidemiologic transition, so-called, takes place at different times in different countries. There are some countries in the world today that are well along the transition although not as far along as we are. Mexico would be an example of that and then there are some countries that are still predominantly still in the infectious disease era

where the average life span at birth is something like 35 or 40 years. A number of the Sub-Saharan nations in Africa fall into that category.

So, it is a continuum, not an all or none between the developed and the Third World. This modestly entitled graph, the conquest of pestilence in New York City is something I copped from the wall of the Health Commissioner at 125 Worth(?) Street. The line that runs across the slide is the crude death rate from 1800 to almost the present and there are several nice lessons to take from this. The first is that the average life span in 1800 was only about half as long as it is today and most of those deaths as you will have seen from Dr. Masoro's slide occurred in early life. There were people who lived to a ripe old age. There just weren't so many of them because many more were culled early on and that great loss of future years of life has the aggregate effect of reducing average life span.

Then of course you will see if you have got keen eyes that mortality back then was dominated by the periodic sweep of epidemics through the city, cholera, smallpox, yellow fever, 1918 influenza.

Another interesting thing you will see is that the

great decline in mortality began somewhere around 1880, long before the advent of penicillin or the sulfa drugs or most of what we call modern medicine and of course it had to do with the construction of water systems, decent housing, basically engineering controls. I hate to say this to medical students but engineers have probably saved a lot more lives than doctors.

So, here is what is going on today. We have done a very nice job of AIDS and TB notwithstanding we have done a nice overall job of bringing the infectious diseases under control, but various chronic diseases are creeping up on us. These are the data from CDC on childhood asthma. These are data from NCI on childhood cancer. The good news here is that mortality is going down because treatment has substantially improved but the bad news is that reported incidence of both leukemia and brain cancer, the two most common forms of childhood malignancy are going up. Nobody is quite sure why.

Various birth defects are increasing in incidence. This is hypospadias, a congenital defect of the urethra in baby boys. Its rate has doubled according to these data from CDC and there was a recent report published in pediatrics

just a few months ago from a birth defects referral center in Connecticut showing an increase in the rate of this condition which is approaching ten-fold, not just doubling.

These are data on testicular cancer, a curious black/white discrepancy but among white men in this country there has been something like a 50 to 60 percent increase in the incidence of testicular cancer over the past 30 roughly years and this of course is a disease of young men. So, the seeds are probably laid down in childhood. The precise cause is not really known.

Developmental disabilities are very common. I don't want to say that they are increasing in frequency. Some would. I think the data are too poor to either sustain or refute that statement, but be that as it may these disorders are very common and depending on what definition you use anywhere from 3 to 8 to even 12 percent of babies that are born are afflicted with developmental disabilities from the severe to the mild.

If you do the math here there are about 4 million babies born each year in this country. So, 3 to 8 percent is anywhere from 120,000 to 320,000 kids are born each year with one or another of these and other milder problems.

It is worth pointing out, too, that there is such a thing as subclinical toxicity, that there are kids who are impaired some because of their encounters with toxins such as lead, some because of obstetrical problems, some because of genetic make-up, kids who are functioning with less than a full endowment who have lost some points in IQ who have some alterations in behavior but who haven't actually graduated to the point where they can be pigeonholed and diagnosed as falling into one of these conditions, and a lot of the discussion these days about the low level toxicity of lead, the notion that kids who are exposed to lead and have blood lead levels of 5 or 10 or 15 micrograms involves this kind of thing, subclinical toxicity, subtle reductions in intelligence, alterations in behavior.

Another factor that was going on back in the late 1980's that was involved not directly but certainly parallel to the genesis of the kids report was the publication of this document. It didn't reproduce very well. I am sorry, but this was a report from the NRDC called Intolerable Risk: Pesticides in Children's Food and this was a report in which NRDC and another group called Mothers and Others for a Livable Planet, Meryl Streep you will recall, Wendy Gordon,

Laurie Mott were the principals in that and this was the report that described the alar episode in which the chemical alar, not strictly speaking a pesticide but rather a growth retardant that was sprayed on apples to keep them ripe for a longer period of time on the shelf, this was a chemical that had been allowed to say on the market for roughly 25 years, had been through several toxicologic reviews, strong suspicions had been raised not about the alar itself but about its principal breakdown product, a hydrazine derivative as being a potent carcinogen and the environmental group expressed great frustration with that circumstance and I think that brouhaha in the general press factored into the decision by the Senate Ag Committee to create our committee here at the Academy.

So, here was our committee. It was a great group. We had obstetricians, several pediatricians, food scientists, a gentleman from the food industry, toxicologists, East Coast, West, even a Canadian and it is important to point out that the report was unanimous which of course doesn't always happen with Academy committees and this was the charge that the Senate gave to us. They wanted us to answer three questions. Are kids more heavily exposed

to pesticides than adults? Are they more susceptible and then they wanted us to switch gears and turn to policy and answer the question did the decision practices and the laws that were then enforced do an adequate job of protecting children against pesticides and that latter component devolved into a discussion of risk assessment and then also of risk management slash standard-setting procedures.

So, let me take you through those. Our ultimate conclusion which has been, which we actually didn't invent, this comes from the grand old man whose name I am blocking on who was the pediatrician in chief at the Mass General in the 1960s, the quote that kids are not little adults, John Crawford is his name and we expropriated that because we thought it made so much sense in the context of our committee's work and we looked first at the exposure question, the first bullet there and it didn't take us very long to figure out that kids are proportionately more heavily exposed to pesticides than adults for several reasons. First of all, they drink more water, eat more food, breathe more air pound for pound. So, they take into their bodies more of any pesticide that is in those environmental media. The discrepancy with water is particularly striking.

A baby drinks seven times as much water per day per kilogram of body weight as a 21 year old. It is really quite a striking difference. So, if atrazine or some other pesticide is in a drinking water supply the potential for exposure is quite substantial.

Also, of course, kids have odd behaviors or at least we consider them odd. Kids don't. They live on the floor. They put their hands in their mouths. They are very oral and exploratory and all of those factors increase their exposure.

So, the exposure question was fairly easy to answer. The question of differential susceptibility biologically based susceptibility is more difficult and the specifics differ but it gets into some of the same complicated issues that you will have to grapple with in the case of the aging but one difference is that, one profound difference is of course development is going on. Organ systems are being established. In the brain for example cells are moving about. They are trailing behind them the processes that become axons. They need to establish dendritic connections with millions of other cells. If those connections aren't established at precise moments in time

opportunities are lost because the cell moves on and that is why the resulting damage is permanent. A lot of it is irreversible and there are parallels in the lungs, in the immune system, in the reproductive organs, in the hormonal signaling system.

Then there is the question, I went in reverse order that the second one there is the notion that kids are less well able than adults to deal with certain chemicals. A classic example is the organophosphate pesticides. Kids, newborns just lack some of the enzymes that are required to break down the organophosphates. So, if a little baby picks up a chemical such as chlorparafos(?) or diazenon(?) and gets it into his or her body the stuff will have a half life of something like 36 hours. In your or me if we have all of our enzymes and we don't have some inborn error of metabolism we will get rid of the stuff with a half life of about 4 to 6 hours. So, there is quite a substantial discrepancy.

On the other hand, there are some chemicals that kids actually handle better for the simple reason that they don't have the metabolic capacity to upgrade these chemicals to their toxic active metabolites and so they excrete them

before the damage is done and then lastly there is the actuarial issues which certainly relates ultimately to gerontology.

Kids have a long time to live ahead of them for the most part. So, if damage is laid down in early childhood by some molecular hit kids have six or seven decades to suffer the ultimate consequences.

So, our conclusion then in regard to the first two questions of the congressional charge was yes, children are more heavily exposed. Children by an large with some countervailing examples but not too many are more susceptible.

Now, what about decision practices and risk assessment practices that existed back then? Well, we looked at tolerances. Tolerances are the principle mechanism by which EPA limits exposure. Tolerance is really a standard. It is the upper limit concentration of a pesticide in an apple that is legally permissible. If the concentration rises above that tolerance level the Food and Drug Administration can seize the apple and remove it from the shelves.

So, how are tolerances set? In the old days they

were set through a two-stage process. First a risk assessment was done to ascertain how much disease a particular pesticide was going to cause at a particular dose level and then that health-based risk assessment was weighed against economic and agricultural considerations. It was an art that was not easily described to us by any of the several folks who came before the committee, but it clearly went on in the real world and it was clear that there were trade-offs made between economics and health.

There are a lot of these tolerances by the way. If a pesticide is used on 50 different crops that pesticide will have 50 different tolerances. That is why there are so many. There are roughly 600 pesticides on the market. So, we came to the conclusion after several years of review that there were some fundamental problems with traditional risk assessment as it was then practiced. First is that it focused almost exclusively on young adults and this has obviously got a carryover message for your deliberations here.

Secondly, it looked at only one chemical at a time and I know from my conversations with my geriatric colleagues at Sinai that polypharmacy is a huge problem in

the elderly and yet pharmacologic risk assessment is mostly done one chemical at a time. So, there are some obvious parallels there.

There is the issue that lots and lots of chemicals have never been tested for toxicity and data are particularly lacking on developmental toxicity and so in many cases the risk assessment that goes on is a data-free exercise shall we say. Actually there is more data for pesticides than for so-called "industrial chemicals" but even in the realm of pesticides there are lots of gaps and as I said a few minutes ago tolerances were set through a balancing process. Health considerations were not usually in the driver's seat. They were usually trumped by economic considerations.

So, based on that review this is what our committee concluded. We said that overall kids should be able to eat a diet consisting of nice fruits and vegetables and other healthy foods without having to worry about pesticides in those foods. More specifically we recommended that changes be made in regulatory practice. We said that we opined that tolerances should be based principally on health, that the data, the child-specific data should be

used in undertaking risk assessment as the scientific basis for tolerance setting and we made the usual recommendations about collecting more and better data and the bottom one there was quite controversial but we recommended that when data were lacking, when information for example on developmental toxicity simply was not available that a safety factor be inserted into risk assessment to compensate for that lack of information.

In a miracle of timing we, also, made recommendations about better toxicity testing and one of the things we called for which I think is quite directly relevant to the work of this committee is we recommended the toxicology be done in such a way that chemicals be administered to the animals early in life and then the animals followed for the whole life span, not arbitrarily sacrificed at some particular age.

After all you have seen from the slides of the previous speakers that most natural disease occurs late in life. Most toxicology truncates that experience and so the interplay between early exposures and genetic composition is lost.

So,the report came out in a masterpiece of timing

in June 1993, just a few months before the 104th Congress swept into town, but curiously 3 years later in the summer of 1996, in the closing weeks of the 104th which was the first Congress that Speaker Gingrich led the Food Quality Protection Act came out.

The Food Quality Protection Act was one of those rare pieces of legislation that was passed unanimously by both houses of Congress. There was not a single dissenting vote, and it was signed into law by President Clinton in the summer of 1996, and these were the major provisions, and you will see that there is an amazing congruence between the major provisions of that act and the principal recommendations of our NRC committee.

So, this is what I am talking about when I say that a well-constructed committee report that takes on real problems and makes coherent recommendations can really have profound effects in the real world and I think that the work of our committee did have an enormous effect in shaping this law and then in the last minute or two because I see the hook is approaching I will just mention every so briefly a few other things that have happened as a consequence of the law having been passed.

One thing obviously that has happened is that procedures for pesticide regulation have been tightened up, not as much as I personally would like. I would like to see EPA reacting more aggressively when data are lacking but still a third ten-fold safety factor has been applied to about roughly a third, a third safety factor not always ten-fold has been applied to about a third of the pesticides that the agency has reviewed over the past 7 years and then other things have happened as well.

In September 1996, just a month or so after the act was passed Administrator Browner established the EPA's Office of Children's Health Protection and this office has been reaffirmed by Governor Whitman and in the present administration and it serves as sort of a little, I consider it a little conscience within EPA whose job is to keep the agency thinking about children when standards are being set whether it is air standards, water standards or pesticide standards or procedures for cleaning up landfills. That is what the office has done. It is tiny but the people are dedicated and I think it has been an important force within the agency.

Another thing that happened was our Earth Day of

1997. The President and Vice President signed this Executive Order on children's environmental health which basically commanded all the agencies of the Federal Government to consider the impact on children's health of any major policy changes and that Executive Order established a Presidential task force on environmental threats to children's health which was reaffirmed by President Bush and continues in existence to this day and that task force has had some very important, made some very important decisions.

They decided that developmental disabilities, asthma, cancer and injuries should be the four principal focal points of child environmental health research across the Federal Government and they also made the recommendation that a major prospective longitudinal study, epidemiologic study of many thousands of children be established so that we could look in a longitudinal way at the impact of early exposures in child health and deal with some of the exact epidemiologic issues, issues of selection bias and survivor bias that Dr. Masoro was talking about and that in fact is actively in the planning stage today.

Other things have come out, too, the formation of that Presidential task force, the engagement of the

agencies, particularly the EPA, the NIEHS and to some extent ATSDR and CDC has led to the establishment of the National Network of Research and Prevention Center, a National Network of PEHSU which are clinical units in children's environmental health. EPA has done a nice job with STAR grants and the National Children's Study, and I think that is about it.

Thank you very much.

(Applause.)

DR. WEGMAN: We have finished the overview and just before the morning break we are going to begin a series of presentations on hazards, mechanisms and outcomes and although we would have liked to have organized these in a set of logical groups the organization gives more time to people's lives who are doing the presentations.

So, we will start with a presentation from another member of the committee we heard about earlier, Barbara Gilchrest who is going to speak about environmental effects on the skin.

DR. GILCHREST: Thank you. It is a pleasure to be here. I feel very fortunate to be here. Actually I spent over an hour circling the airport on my way in and I am

very, very pleased to have this opportunity to share our work and the problem of the effect of ultraviolet light on the skin of older persons.

Aging in the skin is a very complex process and ultimately is a process which takes one from this very healthy pristine skin of the child or young adult to a very damaged and disease prone skin of the older adult, and there are really two distinct processes that play a role. One is termed intrinsic aging and this can be understood as the clinical, histologic and physiologic changes that can be observed in sun protected skin of older adults and a second process which is the super position of primarily ultraviolet damage on skin and has come to be termed photo-aging. It can be construed as those clinical histologic and physiologic changes that are observed in habitually sun-exposed skin of older adults and I would like to say that the skin is a particularly instructive organ in which to examine effects of environment because there are these sun-protected areas throughout life which really serve as a control and it is very apparent in examining the skin of an older individual what that environmental impact has been.

I don't know why the slide is not down and while

we are getting the slide just to make the point that the skin is a major environmental barrier between the environment and the internal milieu and my remarks will focus very much on the effect of ultraviolet light on this organ but there are many other impacts, environmental impacts which are reflected in skin.

Should I advance the projector? These slides never fail to go down. Okay, I now have something called main menu up here. So, I need both the menu for changing the slides here and the -- okay, can something be done to get me the mechanism for changing slides? Otherwise I will ask for the next slide?

So, intrinsic aging has a rather minimal impact on the appearance of skin as can be appreciated by examining habitually sun-protected areas but it does include multiple functional deficits whereas photo-aging in contrast has a major impact on the appearance of skin but also exaggerated functional deficits of which probably the best studied is loss of immune function which is exacerbated in chronically sun-exposed skin and for the purpose of the presentation this morning the phenomenon of photocarcinogenesis, UV induced skin cancer is virtually restricted to sun exposed

skin.

This is a slide that I am afraid I wasn't here and I don't know if Dr. Masoro might have shown it. Yes, it is shown at every gerontologic conference and these are data that were collected by Nathan Shock's group to illustrate the progressive decline in optimal function for multiple organ systems within the body over the adult life span and one thing one notices other than that there is a decline that is very reliably present in every organ system, another thing to notice is that no one here studies the skin.

However, since that work was done there has been a great deal of work done by a number of groups around the country to do similar studies, cohort studies across the decades of adult life to examine the impact of aging on the function of human skin and listed here are discrete functions and somewhat overlapping functions in some instances of the skin, all of which have been shown in well-controlled studies to decline with age in apparently healthy individuals and this includes essentially every function of the normal skin.

This is the same slide but I have highlighted in yellow those functions which might conceptually be related

to carcinogenesis which is the environmental vulnerability that I wish to emphasize this morning. There are changes in barrier function which may be relevant to chemical carcinogenesis. There certainly are well-documented differences in clearance of chemicals from the dermis. Vitamin D is produced in the skin, the active form of vitamin D and plays a role in the normal differentiation of the epidermis which is the most, by far the most cancer prone portion of the skin and vitamin D production is clearly compromised with aging.

Immune responsiveness as was already mentioned plays a major role in carcinogenesis and is impacted in skin both by virtue of local immune deficits and systemic compromises in T cell function, for example, and I will come back later in the presentation to the issue of DNA repair capacity which has been rather extensively studied in recent years and is quite surprisingly compromised with age in normal skin.

I wanted first just to review the skin situation with skin cancers in this country, first to deal with non-melanoma skin cancers of which the most common is the basal cell carcinoma, about 80 percent of skin cancers and the

second most common squamous cell carcinoma constituting most of the remaining skin cancers in the United States of which there are more than a million cases a year. Well more than half of all human malignancies are skin cancers and this number has been rising every year perhaps in part because of better reporting but also because of true increases in incidence and a number of authorities have referred to this as an epidemic of skin cancer.

Skin cancer is strongly related to sun exposure epidemiologically and in animal experiments. Non-melanoma skin cancer occurs overwhelmingly on sun-exposed body sites. Those who are fair skinned and particularly those who sunburn easily and freckle easily are by far at highest risk of this malignancy and there is a very strong epidemiologic connection to the degree of past sun exposure.

Skin cancers are also linked epidemiologically to other environmental carcinogens aside from ultraviolet radiation. The classic one, the relationship that was elucidated in the 19th century is with tar, for example, the chimney sweeps' scrotal cancers. Cigarette smoking also increases the risk of skin cancer statistically and that is a very interesting interaction that presumably occurs with

ultraviolet light because these cancers continue to occur in chronically UV exposed areas and another environmental carcinogen which is not as important today as it was a century ago is arsenic which at one point was found for example in well water and the very well-documented relationship of basal cell and squamous cell cancers in Bowen's disease in farmers for example who were exposed to arsenic.

Now, the relationship, like all cancers skin cancer non-melanoma skin cancer increases in incidence with age but there is a very striking also epidemiologic relationship to the intensity of insulation or sun exposure and these are data from the SEERS, showing that with age there is an increase in incidence in both a fairly northern city with quite a low incidence of skin cancer for the United States which is Detroit and also an increase with age among residents of New Mexico which has one of the highest skin cancer incidences in the United States but the point that I wanted to emphasize this morning is that if you subtract the effect of insulation, how much sun people are exposed to in different parts of the country and instead you choose as 100 percent incidence rate the incidence rate

observed in the last decades of life and then plot these data backwards as a percent of that maximum incidence you find that no matter where you are there is an incredibly strong susceptibility that increases with age alone.

So, this is a typical basal cell cancer, typical because of its rodent ulcer appearance, its location in a chronically sun-exposed area and its occurrence on a very fair skinned woman, a woman of Irish ancestry.

Another basal cell carcinoma, this is on the back of the neck of an older man, another chronically sun-exposed site. Please note also the so-called crow's feet here are, not crow's feet but sailor's skin which is characteristic of severely sun damaged skin, chronically exposed skin and such relationships between the occurrence of basal cell cancer and the degree of background skin damage has been mapped out in the HANES study and we see that both in men and in women the prevalence of basal cell cancers goes up strikingly again in areas that appear severely sun damaged, again, emphasizing that relationship between UV exposure and basal cell cancer.

This is a squamous cell carcinoma which occurs characteristically in maximally sun exposed areas here on

the bridge of the nose and again note in this older woman she also has very extensive changes of photo damage surrounding this cancer.

Another squamous cell cancer in a chronically sun-exposed area immediately in front of the ear. This lesion on the lip in a smoker and squamous cell cancer of the lip is, this is quite a prevalent site, again because of its great deal of sun exposure and in individuals who smoke almost certainly a combined exposure to carcinogens in cigarette smoke and the UV and I hope these are projecting well. If not maybe we could lower the lights a little bit.

This is an individual who has very extensive actinic keratoses which are a pre-malignant lesion and can evolve into squamous cell carcinoma. He is undergoing a treatment with 5-fluoro-uracil which accentuates the presence of these actinics but I simply wanted to make the point that they are in an incredibly photo distribution in the maximally sun-exposed areas of his face and that these are incredibly common lesions in the American population. A Caucasian after age 50 almost certainly has at least some actinic keratoses in our country.

Now, I wanted also to comment on melanoma which is much less common than the non-melanoma skin cancers but a huge public health problem. In the year just ended there were 53,600 new melanoma cases and 7400 melanoma deaths. The great majority of these cancers are strongly sun related and are attributed to sun exposure. They occur again in sun-exposed areas in fair-skinned people in highly insulated or highly sunny parts of the country and in animals there are now a number of animal models in which you can establish the causality between UV exposure and subsequent melanoma and like the non-melanoma skin cancers and again almost all cancers there is a definite increase in incidence with age that is independent of other factors and just to emphasize the importance, the epidemiologic importance of this particular malignancy it is one of the most rapidly increasing potentially fatal malignancies in the United States. This bar, this is an old slide, says that the projected lifetime risk for melanoma for individuals born in 2000 was 1 in 75. In fact that number was not only achieved but the lifetime risk this year is going to estimated to be 1 in 71 or 72 and note that since statistics were first kept in the 1930s this incidence, lifetime risk has increased

approximately 20-fold which is just an enormous increase and shown here again a somewhat old slide and these trends have continued melanoma has been increasing at a rate greater than essentially any other malignancy in the United States with the exception of lung cancer in women which is attributed to changes in smoking pattern but melanoma is, again, I am sorry I touched the wrong thing on the screen. If I could have that, I would like the next slide.

Could I have the next slide, please?

Okay, where is all this melanoma risk in our population? It is certainly in older age groups and it is very specifically in older men. Men over the age of 50 account for more than half of all melanoma deaths in the United States and this also is very much connected to ultraviolet exposure.

I wanted to show you this slide. This is actually a postcard from Copenhagen but this has a great deal, many authorities believe to do with this striking increase in melanoma risk that has been observed in our country and in developed countries around the world, and this has to do with changes in we believe almost exclusively in changes in exposure to ultraviolet light that over the past 100 years

people now expose much greater areas of the body surface to UV. They do so recreationally, vocationally and perhaps particularly for melanoma which is strongly epidemiologically associated with intermittent intense sun exposure people now have the ability to get on an airplane in the middle of the winter and go to the Caribbean or the Mediterranean and there are quite extensive epidemiologic data that have identified this type of intermittent intense sun exposure as a major risk factor for melanoma.

So, melanoma, this is a lesion of superficial spreading malignant melanoma in the mid-back with the characteristic features of variation in color, irregular border, an area of regression. This is a lesion on the nostril of an older fair-skinned Caucasian woman. This is actually a nodular melanoma that accounts for only 10 percent of melanoma but it tends to be a very bad actor. This is a lentigo malignant melanoma on the cheek of an older man. These characteristically occur in chronically sun-exposed sites whereas the superficial melanoma and nodular melanoma tend to occur more in areas that are intermittently sun exposed such as mid-back in men or the posterior calf in women and this is an advanced melanoma

that resulted in this woman's death shortly after the photograph.

So, what factors then contribute to skin cancer in the elderly? This is the reverse of the point made by the previous speaker. Certainly there is cumulative exposure to carcinogens over the lifetime and again predominantly UV, increased induction times for mutations that might have occurred early in life, plenty of time for these to evolve and to accumulate additional mutations in the same cells. The issue of decreased DNA repair capacity, I will come to that in just a moment. Decreased immunosurveillance which has been very well documented, a reduction in number of Langerhans' cells which are the bone marrow derived outpost cells of the immune system that are located in the epidermis as well as loss of T cell function systemically and in the skin, a decreased number of melanocytes or pigment cells that constitute the intrinsic barrier to ultraviolet irradiation, a general dysregulation of keratinocyte proliferation. Again, keratinocytes are the cells that go on to become basal and squamous cell cancers and altered dermal matrix has been postulated to also contribute and this has also been shown to be directly related to sun exposure.

These are data from Larry Grossman's group at Johns Hopkins University and this was a study published a few years ago in the PNAS and I think a very important study and they looked at a group of individuals who had developed basal cell carcinoma versus a group of similarly complexioned control subjects who had never had a basal cell carcinoma and they studied in this particular study their lymphocytes and in an assay that looks at the host cell reactivation assay that looks at the ability of the host cell to repair a damaged plasmid, a UV-damaged plasmid and then they reported this out as an activity and there are two very interesting findings here.

One is that individuals who experience basal cell cancers at an early age, in the second, third, fourth decade of life have a substantially and statistically quite significantly reduced ability to repair UV-induced DNA damage. That is one and secondly, that in this control population of presumably normal individuals who have not yet had a basal cell cancer there is a very distinct and highly statistically significant decrease in their ability with age to repair this damaged plasmid.

The same group subsequently published additional

data in which they examined both dermal fibroblasts and circulating lymphocytes and found that this repair did decrease with age, repair capacity shown here and that in a counter parallel fashion the mutation frequency, the frequency of mutations that were introduced into the test plasmid by the host cells also increases linearly with age in an exactly anti-parallel way, certainly suggesting this would predispose to cancer and very, very briefly in the last minutes I want to share with you data from my own group examining similarly the impact of age on DNA repair capacity and in the studies that I will show you we cultured normal dermal fibroblasts from sun-protected areas of newborns, young adults or old adults and then UV irradiated the cells in culture and collected the DNA and looked at the amount of DNA damage in the form of thiamine dimers and six four photo products that had been introduced and I had expected a more intimate group. So, this will not project very well but by slot blot perhaps you can appreciate that with time after irradiation the amount of DNA damage as reflected by the bond antibody decreases with time and if we look as a function of age we find that in the red bars the newborn cells rather rapidly eliminate about half of the DNA damage

whereas the young adult as shown in blue and particularly the old adult as shown in yellow virtually do not remove thiamine dimers within 24 hours and for the six four photo products which are removed more rapidly the young, the newborns remove these essentially completely within 24 hours whereas the adults remove them much less rapidly and this is quite statistically different even in these small groups.

We then looked again at cultured fibroblasts from sun-protected areas of the donors in different age groups and looked at message level and protein level of a number of proteins that are involved in cell cycle regulation and DNA repair and this work was published a couple of years ago now in the FASEB journal and shown on the left is a representative Northern blot analysis. Again, I apologize that it probably doesn't project too well but on the right hand side are the representative old adult donors as opposed to young, newborn or young adult donors and I think you can readily see that the amount of mRNA expressed for these different proteins goes down with age and these are densitometric analyses in which the newborns are shown here in blue, the young adults in red as a function of age and the old adults in green and these are quite statistically

significantly different amounts of message as a function of age and in the Western blot analysis looking at protein levels again these are representative donors to show you the reduction in the old donor as opposed to the young adult donor and these are densitometric analyses comparing a group of young adult donors to old adult donors and again very statistically significantly different levels of these repair proteins even in these small groups.

So, to conclude, skin cancer is overwhelmingly attributable to environmental carcinogens. Of these UV exposure is by far the most common and this has been made even more important by the ozone depletion which has occurred in some parts of the world in recent decades, that skin cancer both in non-melanoma skin cancer and melanoma incidence increases exponentially with age.

Many of the known age-associated skin changes logically contribute to this vulnerability and of these the now quite well documented decrease in DNA repair capacity is likely to be a very major contributor and this cartoon says, "They beach themselves like this every summer and there is no scientific explanation, and so until there is we are going to have to think of something to do about sun

exposure and old skin."

Thank you.

(Applause.)

DR. WEGMAN: We now have time for a short break, a quick splash of coffee and back to resume at 20 after 11. So, I apologize for the tight timing again but it would be great if you came back quickly so we could begin on time.

(Brief recess.)

DR. WALLACE: Good morning. I am Bob Wallace from the University of Iowa College of Public Health, and I am just sitting in for my colleague Dr. Craig Zorling who was also a member of the panel and is pacing up and back in front of Gate 47 at Lambert Field hoping to get here.

So, let us just continue with our theme of the environment and aging. Dr. Floyd Frost is with the Lovelace Respiratory Research Institute and is going to talk about emerging water-borne infections.

DR. FROST: Good morning. I enjoyed some of the earlier discussion about some of the epidemiological study design problems. As a kid it always concerned me having relatively small ears that I noticed that everyone who was old had relatively big ears and that obviously you had to

have big ears if you were going to survive to old age. It was a study design issue that is fairly prevalent I think at least for small kids.

I am going to talk about some of the issues on water-borne disease. We have been dealing now with, I have been dealing with some of the water-borne disease issues for 25 years and some of the things that have occurred to me in terms of where are we heading and what are the future risks of water-borne diseases and how these might affect an aging population.

Over the past 20 years we have had two emerging fairly serious emerging water-borne disease, perhaps you could call them epidemics. My wife says that they are not epidemics unless there is some indication that they are going to go down someday, but there are certainly shifts that have occurred and water-borne giardiasis happened in the 1970s and through early eighties and then water-borne cryptosporidiosis happened in again the 1980s and 1990s. These were relatively new events and they were always a bit surprising to me because the epidemiologists, the older epidemiologists who kept talking about these diseases as being or these organisms as being non-pathogens were really

pretty smart. These guys were very good infectious disease epidemiologists. They knew the diseases pretty well and it was always surprising why these organisms were thought to be non-pathogens for all these years and then all of a sudden they occur as what we all now emerging infectious diseases.

I went to a talk in the 1970s of a man named Rendor who actually did some work in the 1950s using what they called prisoner volunteers and he had these prisoner volunteers actually ingest some Giardia cysts and the idea was to see what the infectious dose was.

He presented this at a meeting and was actually given quite a hard time by a number of young epidemiologists who thought this was fairly immoral, not knowing of course that in Texas college students could be recruited to do the same thing for a probably much smaller price.

There in fact were no serious effects and in fact there were very few even minor effects of this experiment in the 1950s of giving people Giardia cysts.

He made an interesting, it was an interesting discussion because he said, "Well, the purpose of the study was not to study the infectious dose for Giardia because Giardia at the time was a non-pathogen and who cares about a

non-pathogen? We were really interested in studying Endamoeba histolytica(?) which is a pathogen and we wanted to use Giardia, this non-pathogen as a marker or some sort of model for infection with Endamoeba histolytica.

Actually I thought that the students gave him a pretty hard time. He was a smart guy and he was actually doing some pretty good work but I think it brings up an interesting issue this smart guy doing interesting work saw the world very differently in 1950, than we were seeing it in the early 1970s.

Another thing that happened that is kind of an interesting event is that in the mid-1950s there was an outbreak giardiasis outbreak in the city of Portland, Oregon. The people actually did a very good job of investigating this outbreak and submitted the article for publication to several journals and they all rejected it, and again the same thing kept coming up, how could Giardia cause epidemic illness because Giardia is a non-pathogen?

No one would believe that this non-pathogen could cause illness. It was finally published many years later in a report, an EPA report, a meeting report that included the article.

Another chapter in sort of the evolution of my thinking in this occurred in the 1990s. In this case we are looking at cryptosporidiosis. There was a small town in southern, well, Medford, Oregon had an outbreak of giardiasis or cryptosporidiosis that was attributed to its water supply, perhaps incorrectly but nonetheless there was an outbreak of cryptosporidiosis there but the pieces of the puzzle never fit together and the article never got published because it just didn't make sense. You couldn't actually pull together a coherent picture of what was going on here but there was one interesting event. There was a tanker truck driver in the area who realized that there was no one in the city of Talent, this is a small town not too far from Medford and no one in that town was getting sick from cryptosporidiosis, and he thought well, obviously is this is a water-borne organism these people are not getting sick; this water must be safe and so he decided to haul some water from Talent to a nursing home actually a VA facility in Medford and distributed the water to the people in the VA hoping that it would protect them from cryptosporidiosis.

Well, in fact it did just the opposite. That water caused a very major outbreak of cryptosporidiosis in this

nursing home. Clearly there was something about the Talent population that made them immune to the effects of cryptosporidium in their water that when you took that water to another population it was actually quite capable of causing illness.

Now, what was it? Why did that tanker truck driver make such wrong conclusions? In fact, is he making any worse conclusions than the scientific community makes, and I think probably not. It is something he and most of us really didn't understand and still don't completely understand. We conducted serological studies of cryptosporidium looking at antibody response to the antigens and found very high levels in the city of Medford at the time of the outbreak which dropped dramatically.

We found very high levels in the city of Talent that did not drop dramatically over time. When we looked at this town water supply, the town water supply got most of its water from the city of Ashland sewage outfall, and it was treated but sort of marginally treated, and so that water was of fairly low quality which probably explains their high rates of endemic infection with crypto.

Now, several years later I went to another

outbreak, a crypto outbreak in Collingwood, Ontario. In this outbreak the health officer was perplexed about the outbreak because it appeared as though the only cases of Cryptosporidiosis that occurred in that city were visitors to the city. Collingwood is a city on one of the lakes and, one of the Great Lakes and they obtain their water from the lakes. It is filtered but not terribly well and a lot of people come up from Toronto. They have vacation homes on the lake and they would come up on the weekend.

Those were the people who were getting sick from Cryptosporidiosis. It was not the people who resided in Collingwood. In fact, the physicians in the town of Collingwood rejected the concept that there was an outbreak at all, so much so that shortly after this incident the health officer was fired. The lab director in Toronto who helped us with the serological study in the area was, also, fired and all reference to the outbreak disappeared from the Internet connection on the Collingwood newspaper.

Now, we did a serological study in Collingwood, and it turns out because of a public worker's strike that there was leftover sera sitting in the freezers from the time before the outbreak and during the outbreak and we were

able to look at serological responses to Cryptosporidium, and we found again as we kind of suspected at that point high levels of serological response before the outbreak, during the outbreak and after the outbreak in residents of Collingwood.

These are people who were not sick, who were being tested for routine serological tests and again suggesting that endemic exposures were occurring frequently.

Now, I immediately linked this incident to the tanker truck driver in Talent, Oregon doing the same thing and in fact we found the same thing serologically in both sites.

Now, what does this have to do with Dr. Rendorf and his presentation? Why was Giardia a non-pathogen in 1950 but a pathogen in 1970,and why is Cryptosporidium an emerging infectious disease now but it was not an infectious disease of any concern years ago? I think if you looked back at stool surveys that were done in the 1930s and 1940s and we find high levels of carriers for Giardia. They actually didn't look for Cryptosporidium at the time but they found that in two populations, Wythe(?) County, Virginia as well as New Orleans about half of the kids

carried Giardia. A significant fraction of the adults even had Giardia. I think it was right around 15 to 25 percent of the adults even had Giardia.

So, it was a fairly common infection in those days but yet when we did a stool survey in Washington State in the 1970s we found that only 6 percent of the kids were carriers of Giardia and almost no adults would be carriers.

So, what happened? What I think is happening in this case is the endemic carrier state for Giardia and probably for crypto has shifted over time so that these emerging epidemics that we have observed in water-borne diseases are not emerging epidemics of new pathogens but emerging epidemics that result from shifts or changes in our susceptibility to illness from infection.

By removing the pathogen from the ongoing everyday lives of people we actually may be doing some small perhaps even moderate amount of good but during an epidemic or when people are infected they are much more likely to get sick, and in fact when we looked at travelers coming back from Russia we found very high prevalence or occurrence, incidence of giardiasis in the 1970s and early eighties in travelers coming back from Russia.

It is most likely that people in Russia were not suffering from giardiasis. I mean they could not have developed space programs sitting on a toilet all the time. They were becoming immune to these pathogens in their water or actually organisms because are they pathogens? Well, maybe, maybe not depending on who you are and doing quite fine. It was the Americans who came over there who were coming back with giardiasis and other diseases.

So again, the emergence of these infectious disease epidemics, water-borne disease epidemics is really a shift in susceptibility rather than a shift in the organism itself.

Now, what does aging have to do with all this? Well, we are making some major progress in reducing our endemic exposure to a number of these water-borne agents by having better water treatment. We definitely have much more effective water treatment now than we did 20 years ago.

Our exposure to a lot of organisms is going down. I think it is uncertain at this point what will happen as time progresses and we have an aging population because we have two things as potential problems. This aging population may be increasingly susceptible to illness but

much more importantly during an epidemic I mean there are problems that will occur occasionally. Water treatment systems are never perfect and they do fail on a regular basis. When they do fail in the future especially with both an aging and a susceptible, largely susceptible population we are likely to see much larger epidemics.

I had a professor in college who suggested that disasters in Mexico would be much more likely to cause major problems than disasters in the US because of the endemic infection rates of these organisms.

I wanted to show you briefly one problem that we kind of think, well, if something happens we are going to be able to detect it pretty quickly, but this is a Clostridium difficile. It is an organism that infects probably most of us. There are toxin carrying strains of C. difficile and it is a fairly uncommon infection, but over time what has happened is that its prevalence has gone up dramatically. It has gone up to a fairly high level and in fact what we see over a period of 1982 to 1998 is in the older populations we have a 6000 percent increase in the occurrence of Clostridium difficile related deaths and this occurs regardless of whether you look at underlying cause of death

or any cause mentioned on the death certificate, very, very large increases. We published this some years ago and we published it in the Emerging Infectious Disease Journal which is an Internet-related journal and one of the disadvantages of that is that your article comes up every time anyone searches for Clostridium difficile.

So, I have received over 100 e-mails from people whose, usually relatives either have or have died from Clostridium difficile and this is an increasingly serious problem. It is I don't think very well understood. It is thought to be related to antibiotic treatment which disrupts the intestinal system of older Americans but these e-mails don't suggest that to be the case at all. I have reports of people who are winning golf tournaments and then 3 weeks later they were dead from a Clostridium difficile infection. These are not frail elderly and more than a few of these folks, and it seems as though the people who did not have the prior antibiotic treatment were in fact coming in, not being diagnosed and dying or being diagnosed right before death too late to actually do any good in terms of treatment.

This is a, I think a major problem, C. difficile

is and in fact the VA is quite concerned about the occurrence of it, but it also illustrates the issue that here is an epidemic that happens that we picked up quite by accident and nobody is looking at this. It is partly because it did not have its own code. It was other specified bacterial pathogens but it in fact encompasses almost all of the deaths in that category, but also because nobody has really taken a look at time trends in terms of what is going on and I think certainly it is something we need to be doing fairly carefully because I think it is going to be hard to predict what the, as I suggested what is going to happen as the aging of the population continues.

We really don't know how that changing susceptibility of the population is going to play out, what agents are going to affect this population and how severely are they going to be affected. I think we need to have a fairly good and rigorous detection system and I think we need to take seriously the diseases among the elderly.

I think another potential problem here is I don't think people really take this too seriously. They are assuming that these people were frail; they were going to die anyway; so what is the big deal? They died maybe a week

or two earlier. The e-mails I am getting don't suggest that to be the case at all and I think that when we are really assuming that all of these people who are dying from infectious diseases in the elderly are frail and ready to die anyway it may not be entirely true. I am sure some are but there is something we need to immunize ourselves against because there are healthy elderly whose lives are being cut short because of these infectious disease epidemics and in many cases the environmental components to these are really unclear. There is a component for antibiotic treatment. I don't think that entirely explains the epidemic. It may explain as much as half of the epidemic but even if you took half of this away as you see these 6000 percent increases they would still be major epidemics or as my wife would say time shifts in the occurrence of diseases because we have no idea whether these things are ever going to go away, but we need to be taking a look at this and taking action to try to find out what is going on and why it is happening and most importantly what we can do to stop it.

So, thank you.

(Applause.)

DR. WALLACE: Thank you, Dr. Frost. Our next

speaker is Dr.Mary Wolff who is with the Department of Community and Preventive Medicine as well as the Cancer Center at Mount Sinal School of Medicine.

DR. WOLFF: I actually don't have as much information on this topic as I thought I had when I agreed to give this talk which sort of fits some of the information we have heard before. So, using the data that I have, a lot of it from our own work over the past few years I am going to talk a little bit about timing and exposure and then a little bit of what little data that we have on susceptibility factors of absorption and distribution and possibly gene environment effects.

I was very interested this morning in Dr. Vestal's remarks about the fact that more pharmacologic and toxicologic information is needed about older organisms and that includes information on changes in genetic polymorphisms that affect metabolism distribution of such agents over time.

So, with that I will give you a few examples, some of which are very well known but which still serve us with regard to exposures over the life span. So, these are data that Andy Anderson and I collected in Michigan in 1978,

where there had been a point exposure to polybrominated biphenyls. So, in this case actually the younger people had higher levels partly because of their body size and partly because of breast feeding but then for DDT which was the highest kind of exposure on farms in Michigan at that time there was a very clear age-related effect but this sort of platform at older ages which we see a lot for these persistent organic pesticides and then for PCBs which behaves like a pesticide a similar pattern but at lower levels because the intensity of the exposure was less and in fact what we see, and I am going to show you a couple of examples of this but it is not really well established is almost this U-shaped curve of both absorption and response to pesticides that hasn't been very well explored but that clearly is important with respect to aging people.

This is from a recent study that we did at Sinai, a breast cancer study. So here the scale is about one-quarter of the earlier slide but we still see the same pattern with DDE and PCB rising with age and transnonochloride(?) a much lower level but again a persistent pesticide residue.

Data that we have on young women and children show

diminishing levels today. Data from Canada among women of reproductive age have shown a very steady decline in most of these. This is a chlordane residue, dieldrin and DDT and these are cross-sectional data for breast milk but they fit almost perfectly we believe with a half life of about 8 to 12 years in humans for these persistent residues.

On the other hand, PCB residues are fairly constant suggesting that they haven't declined. That is not altogether true in all the western countries but in the US that is what I think is so.

Then these are summary data from the recently published Long Island breast cancer study just to show you the differing orders of magnitude. These PCBs probably represent about three-quarters of the total PCBs. So, this is probably about four, about three and then diminishingly low levels of these persistent pesticides and that again is because of regulation in 1972, so that we have experienced about three half lives which is close to clearance. However, they are still not gone at least in older people and that maybe something we need to look at in the future.

I looked for the purposes of this talk for market basket surveys of PCBs, of pesticides since the 1960s. Those

data exist but they are not online and my filing system is not adequate for me to find them, but this is typical enough and again displays the sort of stuff that Phil was talking about this morning that young kids have higher nanograms per kilogram per day in exposure to pesticides from the market basket. That is because of their body size and because they take in a lot more food and that those intake levels vary over age so that in this case from the market basket perspective there doesn't really seem to be a lot greater susceptibility for older people and then this is the difference between a market basket around 1990 and a market basket around 1985.

So, there has been a big decline since the 1960s but there were still detectable levels of DDT in the market basket and in fact the market basket from the year 2000 I don't have the average data but DDT is still widely, it is the most commonly detected pesticide in the market basket of the FDA. The highest level is in the mid-parts per billion and then these are the next highest pesticides that were detected.

Peronethrin(?) is a pyrethroid(?). It is the new age pesticide that is replacing chlorpyrefos(?) now across

the country and especially in New York and the detectability was low but the highest levels were much higher and again we are still detecting these persistent pesticides in the food chain and where that is from we can speculate separately.

So, CDC's report of the national exposures in the year 2000 had some quite remarkable data on alkylphosphates and phthalates and this represents a shift in more than one way.

First of all what we are exposed to now are more organophosphate kinds of metabolites and the 2002 report which will come out in January will report on pyrethrins and other new age pesticides. So, everyone is eagerly awaiting that and in fact the thing that is detected in highest in a lot of recent surveys including this one but people who are able to use this new age technology to look at these more polar metabolites find the highest levels of compounds of this sort are the phthalates.

So, there has been a shift from these neutral lipid-soluble pesticides like DDT to the ones that we are going to detect in urine because they don't resist. We can't detect them uniformly because they are only around for a matter of days after you are exposed to them and perhaps in

the case of phthalates because they are so ubiquitous there are studies that suggest that there are fairly consistent levels of phthalates in people over time but these are the compounds that we are going to be studying in the next few years. The older population still has a lot of DDT and those kinds of pesticides in them, but everybody is going to be exposed to these pesticides from use indoors and from their existence in the market basket.

So, I do want to talk a little bit about susceptibility in terms of the disposition of pesticides in different compartments in the body and my particular favorite compartment is adipose tissue. It is something that we have been looking at for a number of years and trying to understand in particular because in the breast cancer literature it suddenly emerged that there was a positive correlation between DDT levels and BMI which epidemiologists liked but the pharmacologists thought was counter intuitive and we have gradually come to understand or at least I have in my data, and I am not sure that I have convinced everyone else but these are some recent data. This is my latest schtick and so for DDE and PCBs if you look at current levels and BMI, the yellow bars and orange bars BMI as

reported at age 20 and this is in a breast cancer population. So they were 55-year-old women. Both DDE and PCB show positive association with BMI as reported at age 20 and I think that is because fatter people get rid of it more slowly.

DDE is not associated in the green bars with BMI reported currently, the day the blood was collected and again we think that is because the fatter people have not gotten rid of it whereas PCBs and there is no continuing exposure to DDE; DDE is not in the food chain anymore whereas PCBs are and PCBs with current BMI show an inverse relationship and we have a number of data sets in which we have found exactly the same thing, and in fact if you really splinter the data up in some of these populations you can see that women who were lean at age 20 and lean at age 60 have about the half the levels of women in the total opposite extreme which is fat at age 20 and fat at age 60. So,this represents the potential problem for older people, and it is interesting. It kind of fits with what Dr. Masoro was talking about this morning that caloric restriction may reduce toxicity.

One way that this could be relevant is that

initial exposures, lean people have higher levels but they get rid of it much faster and so the long-term toxicity may be reduced. I am not sure that that is true but it is something that we can look into.

Similarly for the new age pesticides that are excreted in urine it is known and this again is an example of a U-shaped curve, this is the only population I had that was useful for looking at this but if you look at children it is known that the levels go up from birth to adolescence and it is also known and these are not my data; this is in the literature that levels go down with aging and that is above the age of 50.

So, here these are data from an older population of women and again you can see that there is a significant decline in creatinine levels and creatinine reflects urinary clearance.

Now, whether that means that pesticides are also cleared less rapidly I am not certain but it is again something that it would behoove us to look at in the future.

One thing that is not particularly relevant to the kind of aging we are talking about which has really captured my imagination because we are doing a lot of work in

children these days and on effects on birth outcomes of women who are exposed to environmental contaminants and this is something that one of our recent speakers brought to my attention, we know that smoking exerts a very dramatic effect on birth weight and other birth outcomes but birth weight is the one that is most generally looked at and almost all populations see a decrement of about 250 grams in birth weight of women who smoke but what has been seen in several studies I have since discovered in looking up these references is that older mothers have a much greater, experience a much greater effect than younger women.

So, here you can see that women who are older, over 35 years old who smoked, their babies were 300 grams lighter. That is 10 percent lighter, you know, of a 3000 kilogram baby whereas 17-year-old women who smoked there was a 100-gram deficit. Neither is good but the fact that older women have such a dramatically increased risk for low birth-weight babies this suggests that exposure to these kinds of toxins is certainly going to differ as well.

We are collaborating with Rich Siegel in Albany now to look at effects of PCBs in aging workers. We examined a lot of workers at Mount Sinai. We went to GE in the 1970s

and looked at the workers at the General Electric plant there which was the plant that dumped all the PCBs in the Hudson and we are now working to see whether people are exposed and Rich has resurrected the surviving members of this occupational cohort and obtained funding through DOD to look at the effects of PCBs in these aging workers and I include this slide just because I had so little information regarding exposures in older people and because I am interested in the decline in terms of susceptibility again and the decline in one's ability to deal with external toxins and Rich believes that PCBs mirror the effects in aging in terms of depleting certain kinds of enzymes and increasing risk factors such as lipid peroxidation and in particular because he is interested in the brain, in dopamine-mediated factors and therefore that cognitive and motor functions decline with time.

So, just to end up I will talk a little bit about gene expression and gene frequency which reflects inter and intra-individual variability in response to exposures and the example that we are looking at now in pregnant women is the gene PON-1 which results in an enzyme that is responsible for detoxifying the paraoxon intermediate of

organophosphates.

This again seems to represent a U-shaped curve in terms of expression of PONS so that levels at birth are about one-third that of mothers because the gene is not yet fully expressed and then it rises with age, but levels evidently decrease. The populations that we have because they are pregnant mothers are too young. We don't actually see a decrease in age. We see racial ethnic variations, but the literature shows that this gene, the expression of PON decreases with age and that is important, very important for dealing with organophosphate metabolism but also these genes have a lot to do with cardiovascular disease because they detoxify lipid peroxides and that brings us to the sort of selective mortality that was presented by Dr. Masoro this morning.

I have this slide here just as a place keeper because what I really wanted to talk about were the housekeeping genes like the p450 in Phase I, Phase II p450 and Phase II GST and NAT and the change in expression of those genes with age and frankly I just couldn't find any information and our data didn't support it, but it is known that gene frequencies change with age. There is not a lot of

information about it and there was an RFA a couple of years ago from NIEHS to look at it and here I present just a list of three genes for which it is known that the frequency decreases with age because there is such high risk for the MTHFR, the folate gene and the low activity gene presents such great risk that it is just lower in aging populations and the same for APO and BRCA genes.

So, the same may be true for the more common polymorphisms such as the CYP genes and p450 but to my knowledge that hasn't been done and we haven't done it. I am not going to do this slide.

So, in summary we know to look at although I think the information is obviously limited at least in my ability to uncover it and that is that absorption and disposition of pesticides changes with age and you have to recognize the differences between the persistent and the less persistent pesticides.

I second the statement this morning that there is much to be found in the pharmacologic literature about this because there is information about how response to drugs differs with age and I think we need to look into that.

The other thing is that input sources vary over a

person's lifetime. You really can't use cross-sectional data very effectively on an individual basis because whereas we used to think that measuring DDT in adipose tissue was a good measure of a person's lifetime exposure I am not so sure that that is true anymore. DDT levels in the diet change with time and a person's ability to deal with them is dependent on a number of factors and it is not constant and so again I thank the organizers for inviting me and I look forward to the rest of the conference.

Thank you.

(Applause.)

DR. WALLACE: Next, Dr. Bernard Weiss from the Department of Preventive Medicine at University of Rochester will talk about risk augmentation and I asked him about that and I think he means not how can we increase risk but what is the increased risk associated with environmental exposures on top of aging.

DR. WEISS: I suppose to reduce the cost of Social Security we could augment the risks. That is not what I am going to speak about. I am going to speak about the incremental risks. We know that there are risk factors associated with aging but environmental exposures can add an

increment. Sometimes an increment is quite significant.

We think about aging as a time of decline and in this poem by T. S. Eliot, the Love Song of J. Alfred Fruefrock(?) Fruefrock laments aging and he reviews his life and decides was it worth it after all, but there are also philosophers like the great pitcher Satchell Paige from the Negro Leagues who talked about aging in another way as events catching up with you. We know that changes take place with aging. For example in 1956, Seymour Kety plotted changes in oxygen consumption in the brain and what I show here is that a very small increment in the rate of decline of .1 of 1 percent per year produces profound effects over a lifetime. That I think is a kind of risk factor we have to be aware of, these very slowly growing differences between what you might call normal aging and aging that is accelerated by exposure to environmental toxicants.

There are functional changes taking place as we age, changes in flexibility of thinking so to speak, what we call or what the psychometricians call fluid intelligence as opposed to crystallized intelligence which is what those of us who are older can boast of.

I am going to use metals to begin with as examples

of what happens with aging. In the 1950s an epidemic of methylmercury exposure hit the fishing village of Minamota in Japan. The source was fish and shellfish contaminated by the discharge of mercury from a factory and it produced effects all through the nervous system. It produced sensory effects. It produced motor defects and more non-specific symptoms.

This famous photograph by Eugene Smith shows how we began to perceive methylmercury as a developmental neurotoxicant. This is a child of a mother who consumed the tainted fish. The mother did not experience signs of methylmercury toxicity but the child's brain was warped.

Joan Kramer exposed mice prenatally to methylmercury and many of them showed no effects at all until they became old at which point they began to display changes in the structure of the eye, changes in skeletal structure, obesity and even functional changes so that there was a slowly growing decrement in function as a result of the prenatal exposure, something that Phil Landrigan talked about earlier.

We also note from some of these data in both non-human primates and the human primates that the consequences

can be delayed by an extraordinary amount.

Debra Rice who is part of EPA now exposed monkeys to methylmercury for the first 7 years or so of life. Then she stopped. Later when at least male monkeys were ready to be bar mitzvahed they began to show the first evidence of toxicity, changes in motor and sensory function. They slipped from their cages. They couldn't hold on. This is something that the attendants brought to Debbie's attention. Then if you look at the bottom chart you will see that the changes in the human population in Minamata occurred over a long period of time and there are still people now because the government took over the fact for again sustained compensation who come in complaining that they are experiencing the effects of Minamata disease. Some of the Japanese authorities will argue with it, saying it is just a way to get welfare, but others pay serious attention to those claims because we know that central nervous system in many respects declines with age.

Again, with lead we think about it as a developmental neurotoxicant. This is a decline in the levels of blood lead in children thought to be associated with adverse effects. There has been a steep decline since 1970

and the reason for those criteria consist primarily of scores on IQ tests and other indices of neurological development. A very small shift in this distribution has enormous consequences for society, a 3 point shift, much less than the variability from one test to the next over a population means a much higher proportion of individuals assigned to a category of mental retardation and of course a lower incidence of people in the superior category, enormous economic and social and cultural consequences. Think about 10 micrograms per deciliter as the level at which currently now we believe adverse effects begin to appear.

In a study from Pittsburgh of Herb Needleman and Muldoon you can see that in older women even lower levels are associated with changes in neurological performance, for neurobehavioral performance and we also have to remember that bones, the skeleton stores lead and as we age the skeleton demineralizes and lead blood levels can go up.

Think back to IQ again. If IQ has been diminished by early exposure to lead there are other consequences that are correlated with the decrease in IQ. This chart shows that IQ is related to longevity. If we decrease IQ which is a global measure of neurobehavioral function we would also

enhance mortality.

Manganese ia another metal that has lessons to teach us. In the South American mining communities where manganese is mined a syndrome known as luquitamonganica(?) appears in miners exposed to manganese dust, manganese dioxide. It looks a little bit like Parkinson's disease but it also has some neurobehavioral features such as abnormal laughter and crying. This is a clinical syndrome and it arises from manganese being deposited in the brain, notably in the structure known as globus pallidus which is part of this big complex basal ganglia circuit.

Donna Murglar and her associates from the University of Montreal undertook a study of the population examining the relationship between blood manganese which has not a terrific exposure index but serves roughly as one and neurobehavioral effects. This is a chart that shows that in older individuals exposure has serious consequences or significant consequences compared to those who are younger.

Fred Hockberg from Harvard went down to Chile to study miners, miners who had been retired for a number of years. He compared their performance on tests of motor function with controls.

This chart shows that movement amplitudes in a special test he set up and tremor amplitude with a relatively simple device show a much higher proportion of what you might call dysfunctional miners than in controls. These are people who do not show clinical evidence of manganese toxicity. The disability is detected only by the application of neuropsychological measures.

Manganese has been linked to Parkinson's disease although it is not the same but now more and more evidence has begun to emerge that there are environmental risk factors for Parkinson's disease and the clearest indices are those associated with living in rural areas and farming and again it is an incremental risk not one that is the basic process.

McGeer and associates at the University of British Columbia I think in 1988 published data based on analyses of brain tissue showing the decline in the number of cells in the structure known as substantia nigra, the degeneration of those cells, loss of those cells results in eventually the onset of Parkinson's disease.

Over a lifetime we lose cells in that structure. Again, if we accelerate that loss by 1 percent per year you

can see that instead of losing 40 percent of your nerve cells there at about age 73 or 74 you lose that much about 10 years earlier. That has enormous consequences for the prevalence of Parkinson's disease.

I have made three curves here. The right-most one shows the age-related prevalence of Parkinson's disease in an urban population. If you displace that by 5 years, it is now in the middle curve, you can see that you have a much higher prevalence in the population as we get older. Again, such a very small shift produced by exposure to a neurotoxicant has enormous economic consequences. Here I have charted annual medical care costs per 100,000 people, what is it one million? Because it costs society about $12,000 a year to care for a Parkinson's disease patient.

We have other evidence of delayed effects. This is a quotation from a British investigator who examined the relationship between the incidence of polio in certain areas of Britain and the later onset of motor neuron disease or ALS and look what he said. "There is a relationship in those areas between the incidence of polio and the incidence of ALS," and how could this come about? Well, the post-polio syndrome tells us something about it. The syndrome can erupt

many years after the patient has apparently recovered. The source, the death of motor nerve terminals with aging.

As with the post-polio syndrome and with Parkinson's disease here is a schematic of what might be happening in the nervous system. We know that cells can compensate for the loss of other cells and that is why you have to lose a lot of cells in substantia nigra for the clinical syndrome of Parkinson's disease to occur. The surviving cells take over and to a certain extent they can compensate. They start pumping out more dopamine but there is a cost. The cost is that after you get this erosion of cell numbers or their ability to pump out dopamine you are getting increased transmitter production. You are getting increased output. You can accumulate these toxic products. You reach the stage of functional exhaustion and the cell dies.

Well, all is not lost. If you look at the times in master swimming for free style and individual medley swimmers now in their seventies are doing about as well college swimmers were doing 30, 35, 40 years ago and as we age we may lose fluid intelligence, the ability to respond to new things but we have the advantage of experience which

is an important way in which we compensate for this loss and again this famous philosopher tells us how we might deal with this process.

Thanks very much.

(Applause.)

DR. WALLACE: Dr. Kirby Donnelly is a professor at the School of Rural Public Health at Texas A&M and is going to talk about adult onset exposure assessment.

DR. DONNELLY: I guess before I start I should go ahead and give you my disclaimer. The title is wrong. There is no such thing as adult-onset exposure. I think we are exposed in utero and it continues through life.

So the more important question actually is how does our exposure change over time. The second disclaimer is that my experience primarily in exposure assessment is with children.

A lot of the data that I will show you or the little bit of data that I will show you this morning comes from some of the studies that we are doing with children and in addition to that a lot of my research is focused on chemicals.

So, I will to a large extent ignore bacteria and I

guess the last disclaimer is that I will probably ask more questions than I will answer.

So, the first question is define older adults. The regulatory agencies when they worry about exposure at a Superfund site one of the things that they consider is the small child on the left who gets onto a site every day ingests a couple of hundred milligrams of soil and what is his risk associated with that exposure, and I can assure that that small child would probably tell you that not a small child on your right is an older adult and the child on your right would probably tell you that I am an older adult and I will tell you that I don't think you are an older adult until you hit at least 100. So, there is another question for you. How do you define older adult?

The issue,however, becomes what chemicals are we exposed to and what environmental chemicals represent a threat to older adults. There is conclusive evidence in the literature that alligators exposed to DDT or endocrine disruptive chemicals can experience severe reproductive problems. However the evidence is less conclusive with respect to older adults.

We know these chemicals are in the environment. We

know that exposure takes place but we really don't have any significant data to help us understand the importance of this problem.

There are known insignificant differences between children and adults and older adults. There are certainly differences between adults and older adults and children in absorption.

There are demonstrated differences in children and how quickly they can take up certain metals and other chemicals and certainly as we age there become differences in our abilities to absorb certain types of chemicals.

Distribution is very important in terms of what target organ may be affected by exposures and then we have already talked about this morning some of the differences in metabolism between children and adults and older adults.

These are certainly very well documented and these will influence ultimately excretion and how long some of these chemicals might be retained in older adults.

So, this slide gives you an idea of some of the factors or the various factors that can influence the health status of adults and all of this kind of fits together and it is difficult for me to stand here this morning and tell

you that any of these dominates other factors and in fact it really depends on the individual where they are living and a variety of other things.

Certainly occupational factors are very important. What are their occupational exposures; what is the dose and duration of those occupational exposures; how have they changed over the life span of that organism?

Environmental factors become a very significant issue. Is this an individual who lives in a contaminated area such that they may have significant environmental exposures or is this an individual who lives in a rural area that is not close to any agricultural production and is in a setting such that they may have minimal environmental exposure? So this is certainly an important factor.

Life style and nutritional exposure, we have already heard one of the speakers this morning talk about the fact that most older adults take a variety of different medications.

So, we know that in terms of life style exposures they have exposure to certain types of medications. Do they drink alcohol? Do they smoke cigarettes? These are life style factors and certainly there are diet or nutritional

factors that will influence not only their exposure, their uptake, their metabolism, their distribution but certainly also their health status and then what we seem to be developing as one of the major factors that affects the health status of adults and certainly this is true with older adults are the genetic factors. What genetic predisposition exists that may increase or enhance sensitivity towards environmental exposures and towards getting certain types of disease?

As I began to prepare the information to come here and make this presentation I made this list and actually this is something I present to the students in terms of the different target organs that we deal with and what organs may be affected by toxic chemicals and as I was trying to prepare this I was going to underline those target organs that are most important in older adults, and I think this would probably be fairly easy to do in children but with older adults really we can't pick a specific target organ because these are all target organs. There is certainly concern about exposure in the respiratory tract. We know that older adults have a propensity towards cataracts and there are problems with the skin and the eyes.

We have just heard discussions about problems with the central nervous system, some of the chemicals that can affect the central nervous system.

Many of these chemicals get to the liver. The liver becomes a target organ. Many of the metals will precipitate in the kidney and cause problems in the kidney. Certainly there are problems in the hematopoietic system. Reproductive system, maybe this is one that in older adults we can overlook but we do know that for all of us that cancer is a disease of aging and so certainly this is a significant problem and without a doubt there are other effects.

This is the paradigm that the regulatory agencies use to try to establish a link between a chemical exposure and a health effect and basically what it says is a chemical is released in the environment. It is transported to a receptor in sufficient concentrations or at a high enough dose to produce an adverse effect and so what we are trying to do in the event of a chemical that gets into the environment is to determine if there is a linkage between an exposure and an adverse effect.

What we are looking at today or the issue that we

are trying to deal with today is what characteristics of that receptor make them more sensitive or less sensitive than a younger adult.

This is the exposure model that is used to estimate cumulative daily intake and basically what we do is we take the concentration in the media. If it is in parts per billion we have to multiply it times the conversion factor to get to parts per billion. That is multiple times an ingestion rate, an exposure frequency and an exposure duration. It is assumed that the upper 90th percentile level of each and every one of us drinks about 2 liters of water per day and I can tell you having come from Texas that in July and August if you go out and mow the lawn chances are you will drink much more than 2 liters of water per day but the issue in the context of older adults becomes how does that ingestion rate change and not only does the ingestion rate change but it is also likely that the exposure frequency will change and certainly with older adults the exposure duration becomes much longer.

So, what are the differences in exposure? Well, if someone is infirm, if they have some type of a disability or an illness that requires them to stay indoors they will

spend more time indoors. They will receive larger exposure to indoor air pollutants. They will receive larger exposure to other chemicals that might be inside a house or inside a hospital or inside some type of a residence where they are.

Certainly there are likely to be differences in occupational exposure. One of the reasons I thought I got invited here was because I am old and I have been exposed to chemicals most of my life through occupational exposures because that is what I do in the lab, but what I found is that as i get older the graduate students are less likely to let me get into the lab and so my exposures have been reduced but with other types of workers we don't know how those changes take place.

We assume that as workers get older their knowledge of safety procedures, their knowledge of how to use personal protective equipment and work with chemicals improves and so one might assume that their exposure would be reduced and yet there is also that complacency that occurs as we get older that some workers will say, "Ah, you know, I am 45; I am 50 years old. I haven't died yet and I have heard this from people before, and so, therefore, I must not be getting sick from these chemicals."

So, we really need to know whether in an occupational environment the exposure goes up or the exposure is reduced and certainly with older adults there will be differences in intake of air, food and water and this will also have an impact on potential for exposure and certainly the potential to exposure for a variety of chemicals as well as again the nutritional status of that individual.

So, what are the chemicals of concern in the context of older adults and I am going to give you the laundry list that I came up with, and before I show this I want to emphasize this is the list that I came up with. It probably to a large extent is influenced by the fact that a lot of these are chemicals that I work with to some extent or have experience with from the research standpoint and I will also tell you that this list is probably much longer than what I am going to show you.

First on the list are the metals. Aluminum has been associated in a variety of studies with a propensity towards presenile dementia. We certainly know that exposure to arsenic in drinking water is associated with a variety of different cancers and then as we have just seen there is

also concern about exposure to lead and the effects with regard to hypertension or possibly the central nervous system disabilities.

This does not mean that other metals aren't as much of a problem. I think that probably most of the metals that are likely to be retained in the body may be a significant problem in older adults if significant exposure has occurred.

Organochlorines. I put this on the list because these are persistent pesticides that tent to bio-accumulate. Now, to a large extent they haven't been used at least in this country for a little over 30 years and so one might think that these are no longer a problem in this country and that hopefully tissue levels are going down.

Some of the work that we have done in the Lower Rio Grande Valley of Texas shows that although these chemicals are not supposed to be used in the environment we still see relatively high frequencies of organochlorines, more specifically DDT in a fairly broad range of environmental samples.

Next, we have the organophosphates and I added the organophosphates to the list at least in part because these

are one of the classes of pesticides that are most broadly used in this country today.

In addition to that we know that as adults age some of their mental capacity becomes more challenged and these are chemicals that more directly attack the central nervous system and can do damage to that particular organ.

Particulate matter in the context of respiratory disease for someone who has a pre-existing respiratory condition certainly this can be a problem. Polycyclic aromatic hydrocarbons, these are ubiquitous environmental pollutants. Any combustion source, manufactured gas plant residue, cigarette smoke, these are all sources of polycyclic hydrocarbons. So, certainly these are a concern and I put others up there just so that I didn't have a -- this is kind of a never-ending list. If you include the others you have got to include things such as endocrine disrupters, ozone, carbon monoxide, organic solvents, etc. There are a variety of chemicals to which adults and older adults are exposed. Our understanding of which of those are likely to have the most significant impact is somewhat limited.

Now, I would like to very briefly discuss a couple

of the populations that we are actually working with and the first population I am going to show you is a group of refugees who live in Sungait(?) Azerbaijan and actually on the slide in front of you you see three different generations.

The group in the lower left is a group of children and in the upper left you see mom and dad and in behind mom in the upper left hand corner of that picture is grandpa. So, there are three generations of one particular family. Now, you may look at that and say, "What in the world are they doing?" Actually this family informed us that their income level is relatively low. They are refugees from the western part of the country due to a sort of unrest in the western part of the country. They have had to move into the more populated areas of the east and because of their income level they couldn't afford an apartment. So, the only residence that was available was this abandoned petrochemical facility which is where they live, and they just happened to find out that by mining glass from this landfill they can increase their income by over 100 percent. So, this is a significant activity for them. They make a large amount of money out of this and you can see from the

picture on the right side of the slide this is a run-off water pond that is adjacent to their residence, that there are a variety of oils and probably also heavy metals in this area.

So, the question that we hope to get some answers to within the next few years as we monitor this population is what level of exposure do these children have; what level of exposure do their parents have and what level exposure do we see in the grandparents? Are there differences? Are there differences because of behavioral activities? Are there differences because of genetic characteristics? How do the exposures differ and how potentially do the adverse effects of those exposures differ?

Then this is the population that we are studying and this is one of the groups from that population in the Lower Rio Grande Valley of Texas and this is a wonderful lady. I have to tell you how great she is. When we go to visit her house she comes out. She kisses the graduate students. She gives everybody a hug and this is grandma. She is taking care of her young son here and we know from 3 years of monitoring her son that he is exposed to organophosphate insecticides. In fact in this particular

population where we are monitoring 51 different children 100 percent of the children that we have obtained urine samples from have detectable levels of organophosphate insecticides in their urine.

We know that the children are exposed. What we don't know at this point is whether or not the older adults are exposed and if they are exposed what are the potential detrimental effects of those exposures?

If we look at the overall distribution of the exposure and that is not this particular slide but what we know is that the distribution of concentration of organophosphates in the urine varies in this population by over two orders of magnitude.

About 80 percent of the population has less than 10 parts per billion organophosphate in their urine. About 10 percent of the population have concentrations greater than 100 parts per billion and we actually had one child and to put all this in perspective 100 parts per billion is about the level that you would see in an individual who was working as a pesticide applicator and we actually had one child in this population who was 3 years old and she had a level of 500 parts per billion detected in her urine. We

monitored her over a period of time. It did come down but the highest level we saw at one point was 500.

Now, if we look at the distribution of organophosphate metabolites in urine by age what we see is that for the very small child who doesn't get outside who is not crawling around on the floor and probably puts their hand in their mouth less often the concentration is relatively low, less than 10 parts per million. The average for a 1-year-old child is about 50 parts per billion and if we think about it this is the age where children are crawling around on the floor. They are more likely to put their hands in their mouth and we also know that they pick up a lot of pesticides from the floor in the dust and it gets on their hands and they put their hands in their mouth and that becomes a source of exposure.

Now, I think it is safe to say that most older adults probably don't put their hands in their mouth quite as often as a 1-year-old child would but what we don't know is as we look at this slide we can see that as the child gets older there is a reduction in pesticide levels in the urine. We do see an increase in 4 years that we really don't quite understand and unfortunately we don't have data

beyond this. So, we don't know what happens in the older population whether it is the older children or the older adults and certainly this is cause for concern.

So, my conclusion. We know without question that there are significant differences in pharmacokinetics, absorption, distribution, metabolism and excretion as we age and these are likely to influence both the retention of toxic environmental chemicals as well as the potential for these to cause adverse effects.

Certainly older adults for a variety of reasons may be more susceptible to environmental exposures and so this is also cause for concern and perhaps and I emphasize perhaps persistent chemicals may be of greatest concern because these are chemicals that can accumulate in bone, that can accumulate in lipids and they are tissues that as we age we may build up concentrations from.

Before I finish I do have to acknowledge our sponsors. The pesticide study was sponsored by an EPA STAR grant as well as an NIEHS Center for Environmental and Rural Health. The study in Azerbaijan is sponsored by an NIEHS Suprfund basic research grant.

Thank you very much.

(Applause.)

DR. WALLACE: Okay, so, we he have had caloric restriction, market baskets, various exposures and so that all comes down to lunch.

So, for the speakers in the southwest corner of the building is the Members' Room and we will be hosting you. For everyone else there is a very nice refectory in the lower level of the building. For those listening to the webcast you are on your own but for everybody we are going to try to reassemble at one-forty p.m., Eastern.

Thank you.

(Thereupon, at 12:45 p.m., a recess was taken until 1:50 p.m., the same day.)

AFTERNOON SESSION 1:50 PM

DR. LANDSBERGIS: My name is Paul Landsbergis from Mount Sinai School of Medicine in New York City and I would like to start off this afternoon's session.

We have scheduled approximately a 15-minute period of time for questions and comments from the audience for this morning's speakers. There will be a similar time period set aside later in the afternoon for the afternoon speakers. So, I would like to open the floor to the audience and any questions or comments that you may have for the speakers.

DR. GARRETT: Hi, Andrew Garrett from the EPA. I have a couple of questions actually for Dr. Masoro. I was wondering if the caloric restriction reduces the variabilities you see in the expression of age-related changes and if that might be a way of starting to parse out environmental versus genetic effects, particularly since it seems like the genetic homogeneity in that population would be tremendous.

DR. MASORO: I wouldn't say that across the board that it reduces variability. It certainly does in certain things, for instance the non-existence of nephropathy is an example of clearly reduction of variability but across the

board that is not how it works.

DR. GARRETT: And is Mary Wolff around? I was wondering if you have some more information on the changes in PON in peroxidase levels with aging. I think that is one of the real determinants of age-related sensitivity differences in the very young and it would be really interesting to hear about it a little bit more in the aged. I was also wondering if there are differences in the PON polymorphism in the frequency of the allele in the aging population, if you have any information about that.

DR. WOLFF: As I told you I couldn't at least from my data or from the literature find any differences in age-related frequencies of the commonly occurring polymorphisms that is you know the frequency of the at-risk allele for PON is 20 to 60 percent depending on race, ethnicity but the expression of PON is extremely variable so that those levels are said in the literature to decline with time and we know that they are much lower in neonates.

DR. WEGMAN: In terms of the work of our committee for looking at older workers some of the presentations this morning identified the issue of cohort effects and how you struggle with cohort effects in trying to examine problems

that have to do with aging.

I wonder what thoughts you might have in terms of what realistic model study design for longitudinal study might be appropriate that while they can't get around the possibility of a life-long study of a whole population might still gain insights that avoid some of the well-described selection effects of any cross-sectional or short-term prospective study?

DR. WEISS: I put a question something like that to Neil Stockbeck who first raised the question of declining sperm counts in industrialized countries. You saw data earlier about the rise in testicular cancer, for example and hypospadias.

Now, since the, especially the testicular cancer the symptom occurs in young men, it would be possible because of the longevity of these substances like dioxin to take samples from the mothers of these clinical cases and correlate them with the levels prevailing in the victims, and I think maybe a similar question could be asked about breast cancer, say, on Long Island.

For early breast cancer, could you take samples from the living mothers of these patients and correlate them

with levels in the patients or see whether or not they represent a particularly susceptible population?

DR. WOLFF: I think that is a good idea and there are a number of studies going on, say, looking at sisters, and NIEHS has a new study looking at sisters of breast cancer and so on, but I am not sure that that resolves the cross-sectional problems.

Joe has got a bright idea.

(Laughter.)

DR. SCHWARTZ: I just want to comment on the dismissal of cohort studies on the grounds that,you know,no one could do a cohort study for that long. I don't think that that is actually the case. There have been a number of cardiovascular cohort studies that went on for a very long time and the Framingham study, you know, you can outlive the principal investigator. You know, you get new PIs and they go on. The normative aging study started in 1965. The average age of participants today is in the eighties. It is continuing.

Now, it didn't happen to measure back in 1965, all the things that we might have wished it had measured, but it does have frozen blood samples back into the seventies. So,

there are some things that we could go back and take a look at.

The Nurse's Health Study is going strong and started in 1975. So, let us not dismiss the possibility that the solution to a cross-sectional study is a cohort study. That is a possibility, and there are cohort studies that go on for 30 years or longer and which could give us a lot of information about these things and some of them even have frozen blood. So, you don't have to wait 30 years from now to get the answers. You can sort of go back and add in some money to existing cohorts and maybe learn not everything we would like to know but certain things.

DR. SIKES: Cathy Sikes with the EPA. I wondered if each of the panelists could go through what they would see would be the important research priorities for the next 30 years?

(Laughter.)

DR. DONNELLY: I would have to say based on my research area I would certainly think exposure assessment would be the most important thing to look at.

DR. WEISS: Longitudinal studies are frustrating and expensive but I am not sure either in animals or humans

that we can do without them because otherwise there will always be lingering questions about the events that occur early in life that have an impact on function later in life.

DR. WOLFF: I would second the idea that we need more exposure information and I don't know from what sort of populations it might be available but in just trying to think of something that would interest me I would go back to what I suggested about the U-shaped curve and the fact that some of the susceptibility factors in young people in terms of exposure, absorption and excretion are similar to those in old people and that that would be a relatively easy kind of group of studies to do.

DR. FROST: I guess I feel that you have got a variety of things happening throughout life and by the time you have reached old age you have had a number of exposures that really complicate any potential study, and I think we really need to start taking a look at each of these things individually. To some extent you can do cohort studies but cohort studies are really limited to things that occur fairly often unless you have got an enormously large cohort available to you. You really have to maybe start looking at some alternatives looking at markers, biomarkers for effects

and see if there is some better way of getting a more prevalent disease or disease state that you can investigate.

DR. GILCHREST: Knowing that it wouldn't address a lot of concerns of the EPA and of this audience I would just like to touch again on an aspect of the skin which makes it I think uniquely valuable in exploring environmental impacts and that is the existence of control areas so that you can have one, you do have single individuals who throughout their lifetime, you know, they start with the single genetic make-up and part of the skin is environmentally exposed to identifiable carcinogens in the case of UV or an identifiable agent and adjacent areas aren't and you can learn a lot about what is causing aging changes or presumed aging changes and perhaps methodologies of that kind could be adapted to looking at things that we think of for example as normal neural aging, if you could piece out something that was protective and this approach at least in skin is being extended to look at effects, specific genotype effects and an example is the polymorphism in the melanocortin-1(?) gene which regulates pigmentation in skin but is also clearly involved in the immune system and it is possible, and people are now looking at the associations of the

different genotypes with different rates of aging and different rates of carcinogenesis and getting at very specific pathways that are impacted by the environment and again it is not clear to me certainly how to use this approach for many of the environmental agents that are of concern, but it certainly works nicely in skin and it would be very nice if one could device a way to identify a control tissue within individuals.

DR. MASORO: My thoughts are how would one go further in learning about caloric restriction. I have many thoughts that regard but I don't think that it would be terribly relevant to your goal here.

DR. VESTAL: As a non-toxicologist but as a clinical pharmacologist concerned with human drug metabolism and drug response I guess I would wonder about the effects of long-term chronic exposure to medications that might inhibit or induce the biotransformation of important toxic agents and you know for example one might detect higher levels of certain toxicants in the presence of certain kinds of inhibitors of biotransformation. So, I think that might be, that kind of medication-toxicant interaction might be worth looking at.

PARTICIPANT: Phil Landrigan mentioned that there is a large universe of chemicals that has yet to be tested. This echoes a National Academy of Sciences report now some 20 years old and there is great hope that the developing science of toxicogenomics will allow us more rapidly to parse out which chemicals are possible problems in terms of human health effects and which may not be .

This has been a traditional approach of toxicology for 30, 40 years, really a look-see type of approach. Let us take this chemical and see if it has a problem associated with it.

The other way of approaching this is an approach which is more commonly used by physicians where there may be a disease cluster, a high incidence disease which merits attention and that focus is placed on this high-incidence disease cluster because it is a public health problem and that intensive investigation of this reveals possibly an environmental agent which is triggering the disease process.

Toxicologists have shied away from this approach. I am not sure why and if public health is our long-term goal I would ask this committee to consider whether or not a dual(?) approach might be a beneficial approach over the

next 30 years since that question was raised, that is not just looking at chemicals for the sake of determining which may be hazardous and which may not but in fact looking at disease, especially high-incidence disease and finding out what really is causing that disease process.

DR. FROST: I think having investigated a number of disease clusters over time they are very frustrating. One of the things -- shying away from them is not an illogical thing to do. They are very frustrating, very difficult and unfortunately tend to be fairly non-productive unless you are starting with something that is kind of interesting that you have a hypothesis to begin with such as a cluster of diseases in a particular chemical plant or people with a common set of exposures but oftentimes when you start with the clusters of disease in public health it is very hard to make much sense out of them.

So, I think there is some merit in that but we have to be careful in how we approach those so that we can be productive with the time we spend on these investigations.

DR. GILCHREST: I suppose no discussion of the future of the field would be complete without discussing

microarrays and things of this kind but recently there is a whole area of science opening up which would allow one to screen an enormous number of genes, of signal transduction pathways, etc., in exposure to a variety of chemicals and know one at least while I was here this morning touched on that as an approach to try to sort out epidemiologically the relationships to put the agents in proper relationship to the diseases and I suspect that there will be ways to use that kind of extremely powerful screening technology to identify vulnerable pathways to identify agents that might be producing unwanted end points.

PARTICIPANT: I am just reflecting on some of the comments this morning and that is we have really been focusing on the impact of the environment on the aging versus the other challenges, the impact of the aging population on the environment and I would just wonder if any of the panel members have any comments on what are the kinds of things that we maybe need to build into our epidemiologic studies. I am just thinking in terms of the recent outbreaks aboard cruise ships and if you look at people who go on cruise ships as well as you look at our housing for the elderly all of those issues often are driven by

economics more than they are by putting an elderly person into the safest environment as opposed to a close confined area where if you didn't come in with an infectious disease you may well move out. The issue with the medications and waste water treatment now, but I wonder if you have any thoughts of kind of the mega trends that we are seeing as our society accommodates more individuals with disabilities and those are more in the elderly population than the others.

Issues that we may be as we look at individual outcomes we need to begin to look at and include in some of our research issues.

DR. WEISS: Well, it may involve low exposures to pesticides because as people get older they give up their suburban lawns and go elsewhere.

DR. FROST: I think that we can expect to be surprised as we, you know, we have never had a population like this before. I don't think anywhere in the world has had such a large emerging very old population to deal with. So, we really don't know what is going to happen. We can set up models as much as we like but in reality you know was there any way to predict that when those legionnaires went

to their convention that they were going to get sick? We didn't know it until they got sick. So, I think we are going to be surprised and probably surprised fairly commonly about the new challenges and problems that this very large aging population is going to present.

DR. LANDSBERGIS: I would like to thank this morning's speakers for this session. Thank you very much.

(Applause.)

DR. LANDSBERGIS: And I would like to introduce our first speaker for this afternoon, Dr. Joel Schwartz from the Department of Environmental Health, Harvard School of Public Health who will be speaking on effects of air pollution on sensitive subgroups.

DR. SCHWARTZ; Actually the e-mail I got said that I was supposed to talk about cardiovascular effects in the elderly. So, I am going to talk about cardiovascular effects in the elderly, but I would be glad to modify it if you like.

I thought I was supposed to talk about effects of environmental pollutants on cardiovascular system in the elderly. So, let me give it a try. Now, there are lots of environmental pollutants out there and I don't know about

all of them. So, I am going to talk about a limited subset and that doesn't mean that the other things have no impact on the cardiovascular system. It just means I don't know anything about them, and as I get older I know less and less. So, you know it is going to be an increasing problem.

So, the pollutants that I do know something about and so the ones I will talk about are lead, briefly, come back to that and airborne particles.

Now, you feed lead to animals, their blood pressure goes up. So, that is a cardiovascular effect, higher blood pressure is bad for you, I mean unless you are one of those rare people suffering from hypotension and there have been several dozen epidemiology studies and I did a meta analysis of them and you know almost all of them show positive effects. The weighted average is certainly significant. They sort of look like the animal studies. There are modest effects of lead exposure in moderate dose ranges, general population studies on systolic blood pressure and there have also been a couple of prospective studies that have shown that lead is prospectively associated with the development of hypertension subsequently such as one by Howard Hu in the normative aging study.

So, clearly metals can affect the cardiovascular system and I am going to turn away from lead although it is my first love because there isn't so much lead exposure around for adults although as was mentioned you can't actually excrete this stuff. It is socked away in your bones and as you get older it comes out again and so you are going to see that lead a second time as you get older and I would like to go on to talk a little bit about air pollution.

Now, providentially this is a picture of December in 1952, 50 years ago in London, so exactly 50 years ago today the air pollution concentration in London shot up, stayed high for a couple of days and then came down again because there was a low level thermal inversion and the wind velocity was zero and the city filled up with smoke and the mortality shot up and then came down again and what you don't see on this picture is it never quite came back to normal. It stayed elevated for weeks afterwards. Okay, there was a long tail of a little bit higher. So, we know that airborne particles can kill people and in fact many of these deaths were from cardiovascular disease and in fact the largest relative risk for death in London in this week of 1952 was sudden death, people who dropped dead which is

generally cardiovascular although we never know unless we do autopsies.

So, we know that particles can affect the cardiovascular system and at high doses we get high effects.

Now, how could that happen? What are the potential mechanisms whereby breathing in a particle which you might think would predominantly have pulmonary effects affects the cardiovascular system? Well, there are a number of possibilities. We know that these particles produce inflammation in the lung. They might get through into the blood and indeed we now have evidence that combustion particles do penetrate into the blood and even reach the heart and the liver. They may produce inflammation. That inflammation could lead to cytokine cascades. There are also irritant receptors in the lung and you could therefore have autonomic effects. They might affect clotting factors, systemic inflammation or they might have direct effects on the heart and the vascular system and what do we know about this? Well, we are just beginning to develop the evidence and there is some evidence pointing in every direction. So, we don't know which of these things is going to turn out to be the more important mechanism but we certainly are

beginning to see things that suggest that there is probably more than one. For example, chamber studies of human volunteers, i.e., graduate students show that fibrinogen levels increase following exposure to concentrated air particles in double-blinded studies with exposure to no other pollutants and then that has been confirmed by epidemiology studies, one in London and one that I did here in the US.

So, increases in fibrinogen, risk factor for acute ischemic event. Electrocardiogram changes and here we do have some specific information on the elderly. Again at EPA's labs in North Carolina they have exposed people in chambers, healthy elderly volunteers and they have been able to demonstrate decreases in heart rate variability.

Now, in the Framingham heart study and in a number of other prospective cohort studies lower heart rate variability is a risk factor for sudden death.

So, we are starting to see these intermediary biomarkers that may be telling us something about why we are seeing these associations. There are a number of panel studies that have been done in elderly subjects in the US that have also reported decreases in heart rate variability

and Diane Gold will speak to you in more detail about those tomorrow. So, I am going to skip over them.

I will just add that there is newly developing information on ST segment depression in these elderly subjects.

Now, young graduate students put into those chambers did not show decreases in heart rate variability. So, this clearly is a place where we are seeing indications of differential susceptibility with age.

Since the committee that invited us here does focus on occupational effects I should mention that we do have one study in an occupational group, boilermakers where we were able to show that occupation exposure to particles resulted in reduced heart rate variability in middle-aged workers.

So, it is not limited to the elderly but certainly the bulk of the evidence is pointing to greater susceptibility in the elderly.

Well, lower heart rate variability is a risk factor for arrhythmia. So can you actually see arrhythmia? Now, I really like this study because I used to tell my students that you know the problem with mortality is that

you know you only observe it once and we have to do these long studies and wait until people finally die, stuff like that but this is a study we did where we had people die for us repeatedly.

We went to a clinic where they implanted defibrillators into the chests of people who were at high risk of arrhythmia. These defibrillators continuously monitor the electrogram of the patient and if they detect what looks like the onset of ventricular fibrillation they fire just like those paddles only you know the wires go right into the heart. So, you don't need as much power and so what we did is we looked at people who actually had firings and we asked, well are you more likely to die on high air pollution days among these people who died multiple times and the answer was -- this did not come out very well. These are PM 2.5 concentrations in Boston going from 0 to 30. The current standard is 65. It is not on the chart and the odds ratios for a discharge as a function of concentration may go up to 1.8 at you know about 25 micrograms per cubic meter. The association was significant but it was stronger for black carbon and NO2 which are markers of traffic particles. I will come back to that.

This is a study on animal exposure. These are animals that were either exposed to air or to concentrated air particles and you can see changes in the morphology of the lung and of the blood vessels in the lung and when they did a morphometric assessment of these blood vessels they found that the ratio of the lumen of the vessel to the wall thickness had changed. So, if they had normal animals that were exposed to air, a sham exposure in the same chamber this was the ratio. If they were exposed to concentrated air particles there was a substantial reduction in the interior diameter of these vessels.

Now, if you do that to vessels in the lung that can have implications for the heart which is trying to pump blood through those vessels. There have, also, been studies that have shown not merely pulmonary inflammation but systemic inflammation following controlled human exposures. Controlled exposures of volunteers to diesel particles which you can do in Sweden but you can't do in this country showed increases in white cell counts, peripheral white cell counts within hours of exposure.

The Monica(?) study in Germany showed increases in C-reactive protein which is an acute phase inflammatory

marker which again turns out to be a terrific predictor of your risk of dying of a heart attack, much better than any of the lipid measurements, HDL, LDL ratio, you name it, C-reactive protein does a better job and it goes up when the air pollution goes up.

Again, there have been epidemiology studies showing increases in white cells as well as controlled studies and a recent controlled human exposure study showing increases in endothelin-1 which affects the vascular reactivity of the peripheral arteries so that we may be seeing changes in arterial reactivity similar to the kinds of things that are seen in diabetes.

Now, given that it is not surprising that we see in actually quite a number of papers increases in hospital admissions of the elderly for heart disease.

We had a study a couple of years ago looking at 15 US cities and in each city we saw correlations between day-to-day changes in particles and hospital admissions for heart disease. There was just a parallel study done in European cities. There are a number of other studies out there.

The myocardial infarction onset study which is the

study that publishes all that depression stuff about you know if you have sex your risk of heart attack goes up for the next couple of hours. Well, it is not just sex, it is also, PM 2.5 that couple of hours ago that increases your risk of having a heart attack which I am more willing to do without.

(Laughter.)

DR. SCHWARTZ: There are increases in cardiac deaths. There are studies in literally hundreds of cities showing that day-to-day changes in particles are associated with day-to-day changes in mortality and most of those excess deaths are in fact cardiovascular deaths, not respiratory deaths.

Let me show you a little more detail about one of these studies. We got data from Medicare because if you are over 65 your hospital admission was covered. So, we didn't have to beg at every single hospital at every town. We could get it in a centralized location, and we looked at hospital admissions for permanent residents of these 14 cities over the years 1985 to 1994 and what we saw, we put in air pollution the same day, the day before, 2 days before out to 5 days before simultaneously to see well, what lag is there

and for heart disease the biggest effect is the same day. It seems like it is a triggering phenomenon which is something that certainly occurs with myocardial infarction and you can also produce rapid decompensation of heart failure over a relatively short period of time.

There is still a significant association at lag one but the magnitude is way down and then we are down to zero after that.

So, the effect occurs relatively quickly. It is not confounded by sulfur dioxide, ozone or carbon monoxide which is not to say that we don't also see associations with carbon monoxide but they are independent of the particle association but they are an additional thing.

Now, we have tried to go on and learn some more about this, and we focused on two different issues. One are there differential toxicities of different kinds of combustion particles and two, what are the things that convey susceptibility?

So, here is an example. This is a picture from the 14 cities that we studied and what I have plotted is the regression coefficient which is not something that means a great deal to you, but the measure of how big the effect is

in each city versus the percent of the particles in that city that come from guess what? Traffic, okay? And this is a bubble plot. Most of you are used to seeing these nice error bar plots and the problem with them is a lot of interesting psychological studies that show that your eyes zoom right in on those points with the really big error bars, right? Well, they are not telling you anything. That is what those really big error bars say. They say, "I don't know," and the points with the little tiny error bars you just skip right over them.

So, the idea is why don't we invert that process and so the size of these circles is proportional to one over the standard error so that your eyes get going to the circles that have more information instead of the ones that have less. So, every city isn't the same size. Some of these numbers are very noisy but there is a significant increase in the magnitude of the effect as you go to town where more of the particles come from traffic similar to what we saw with the defibrillator discharge suggesting that those may be worse for the cardiovascular system.

We then focused on four of the biggest cities that we looked at and we stratified the daily counts of how many

people were hospitalized into four groups, the younger elderly, the older elderly and with and without a secondary diagnosis of diabetes because changes in C-reactive protein, changes in heart rate variability, increased white cell count, changes in the performance of the vascular system, these are all hallmarks of diabetes and if those look like they are mechanisms whereby particles are having their effects on the cardiovascular system maybe there is an interaction and what we found was this is the percent increase in admission for a 10-microgram increase in PM-10 and it is about .9 percent and these are the confidence intervals. They are all significant for people in the younger elderly group without diabetes but they essentially doubled in the same age group if you are looking at diabetics. They are higher in the people over 75 and again higher still in the people over 75 with diabetes. So we are definitely seeing diabetes which is a disease whose prevalence is increasing in this country as a marker of susceptibility in the elderly.

I should also mention that in these studies we also found that respiratory illness was also a predisposing factor in these cities for hospital admissions for heart

disease but I don't have that slide here.

Then we went to Chicago and we got 100,000 people who had been admitted at some point after they turned 65 for heart or lung disease and who subsequently died and we looked at the risk of dying relative to what the air pollution levels were at the time.

So, what we did is called a case crossover design. We matched each death with the pollution at the time of death and the pollution in a control period last week when the person didn't die. Now, by doing that you have matched perfectly on smoking history, blood pressure history, personality. It is the same exact person. So, all these predictors of dying and there are many of them that don't change much over a period of a week have been controlled for by matching but the hypothesis is maybe the exposure was different last week on average than this week when they didn't die, and we took at look at that, and we found that in this population there was an increased risk of death of about 1.2 percent for 10 micrograms which is higher than in the general population but then we put in interaction terms for having been admitted for a heart attack, diabetes, for heart failure, for COPD and for conduction defects and what

we find is that if you have none of those conditions the increase, the slope goes down to .7 percent per 10 micrograms and if you have a heart attack it is 2.7 times higher.

So, we see strong relative effect modification for people who have had heart attacks, for people who have had diabetes but now we are talking about deaths, not subsequent admissions, moderately strong for heart failure and then nothing in fact for COPD.

So, overall diabetes, heart attacks, previously heart attacks and heart failure seem to further increase the already increased risk in the elderly for these cardiovascular events.

Thank you.

(Applause.)

DR. LANDSBERGIS: Thank you.

I would like to next introduce Dr. George Thurston from the New York University School of Medicine who I believe will be focusing on the health effects of air pollution. I think we will find a lot of resonance between the two talks and different studies but very confirmatory, I think.

DR. THURSTON: First of all I would like to point out by listening this morning I really thought as a person who has an engineering degree I liked the fact that he said that engineers have probably saved more lives than physicians in New York because of getting rid of cholera and things like that, but I think really a good point to bring from that is that public health measures are very effective. Prevention is a great way to avoid problems and I think that air pollution is one of the examples and water pollution as well that an ounce of prevention is worth a pound of cure.

So, I am going to talk about the susceptibility of older individuals and I am going to start out a little more general I think because I have a little more general talk but then I will get into some specific studies and you know, past air pollution episodes as Joel pointed out and recent epidemiological and toxicological studies have indicated that air pollutants and in particular particulate matter and ozone can cause significant adverse health effects, and I am going to talk about some studies of those two pollutants and I will briefly review the evidence and discuss the evidence indicating that older adults are especially at risk.

Some of the things that Joel talked about that air pollution can cause reduced lung function in children and adults, lung airway inflammation, asthma exacerbations, asthma attacks, increased hospital emergency room visit risk and admission risk and even increased mortality. When we are talking about particulate matter I think many of you here are familiar with that but perhaps not all the people on the webcast.

There are really two types of particulate matter particles. There are primary particles emitted directly from air pollution sources such as soot that comes from diesel buses and then there are secondary particles that are formed in the atmosphere from gaseous air pollutants such as sulfur dioxide from powerplants and you can see the primary pollutants coming out of these sources and then the secondary particles that are formed in the United States really the dominant source of secondary particles especially in the East is from sulfur oxides which form sulfuric acid and other sulfates in the atmosphere that are responsible for acid rain and also our sulfate air pollution, lots of the fine particles, and the majority of that is from coal-fired powerplants and the majority of the emissions from

coal-fired powerplants are from plants that were built before the Clean Air Act was implemented and were temporarily grandfathered from the provisions and the deal was that once they upgraded the plants then they would have to clean up, put modern emission controls on them and I guess the Bush Administration now is putting forth a plan where they will be permanently grandfathered in so that even if they modernize and upgrade they still can pollute as much as they have in the past.

So, I don't see in the near future this source being reduced as much as we had expected. Those fine particles, here is a picture from New Jersey Palisades looking over to the Washington Bridge and a lot of people say, "Oh, that is water," but really that wouldn't be there except for the fine particles that are sucking up the moisture. The relative humidity on that day was probably about 50 percent. So, you really wouldn't see this unless there were particles there to be the nuclei and form that pollution that causes the haze, the white milky haze we see all summer long, and the dark, you can see here the filter. This is a filter after a day's collection. The fine particles as shown here are deposited deep in the lungs.

This is the percent deposition and this is size of the particle.

So, the larger particles are caught in the upper airways. The smaller particles are the ones that get deep in the lung and are deposited. That is why we are so concerned about the fine particles although in our work at the World Trade Center the dust there 99 percent or more was up in this large fraction which was caught in people's noses and throats and didn't get deep in the lungs which is a good thing, but it caused them to have this World Trade Center cough that was so prevalent.

So, if it is very alkaline as those particles were you can still have health effects from very large particles. Ozone, I think most of us are familiar with it. It is an invisible irritant gas formed in the air in the presence of sunlight from precursor pollutants that are put directly out of cars and powerplants and the like from nitrogen oxides and hydrocarbons and then a secondary pollutant formed in the atmosphere.

So, who is most affected? Well, as we have been discussing today children, especially those with asthma are strongly affected and infants. More and more studies are

coming out showing neonatal infants are especially at risk, healthy adults who work or exercise outdoors. I have done studies myself of runners and find that whereas on a normal day their lung function would improve by going running that improvement is greatly diminished if they run on a high-pollution day.

People with inadequate health care such as the poor and the working poor, we have done some studies in New York and a lot of the air pollution effects are focused on the poor who have poor nutrition, poor health care who really don't understand and they also tend to get larger exposures as well.

Then older adults, the focus of this meeting and people with pre-existing respiratory disease and I think actually there is a confluence there that I will talk a little bit about, that there certainly is a higher rate of disease in older adults and that may be a big part of the dynamics with why older adults are so much at risk.

As Joel mentioned, 50 years ago the 1952 London fog episode clearly demonstrated air pollution's effect. I know that this wasn't painted in 1952, but it I am sure looked a lot like this. This is a Monet. This is the

artistic portion of our afternoon here but he went there and pointed these really beautiful scenes, but they are also very dangerous pollution. They burned high-sulfur coal in people's homes and the like and so it caused these fogs to occur which now no longer occur because they have banned those fuels, and as Joel showed you on the days of just 50 years ago as the pollution levels jumped the death rate jumped as well and then dropped off after the pollution levels dropped off.

Now, I think this is a very interesting slide looking at the same data but overall. What we have here is by age group. This is less than 1 month of age, 1 to 12 months of age, then 1 to 14 years, 15 to 44, 45 to 64, 65 to 74 and then 75 and older and then here is the deaths the week before the episode in London and then the week after the episode and then basically the relative risk of death and as you can see the highest numbers of deaths are in older adults. Okay, so they have an underlying high attributable risk. They are already at high risk of dying and then on top of that they had the highest relative risk. So, the percentage on top of the higher initial risk, the percentage increase, you know, is much higher, an almost 200

percent increase over what the rate was the week before and I think it is interesting to note, also, that the highest relative, second highest is among under 1 year of age. So, there is that U-shaped curve where the biggest effects are in the older adults.

So, there is really sort of a double whammy for the elderly because they are already at a high risk and then their relative risk, the percent increase is even higher for them.

Here are some studies sort of similar. This is actually one of Joe's slides showing that even today looking at modern levels of air pollution we still see relative risks consistently above one. If there is no effect of air pollution the relative risk should be one.

Well, consistently throughout the world and many different researchers looking at different cities we see relative risks above one significantly such that it is clear that air pollution and particulate matter in this case is causing an increased risk of dying.

Here is a similar plot for ozone where we see a relatively risk and here we have added in another pollutant with particulate matter in there. So, this is ozone alone

and then with particulate matter. Basically we see that it is an independent effect that both of these have an effect on mortality and that they don't confound each other.

Here are some results of a study that I was principal investigator on that was published earlier this year in the Journal of the American Medical Association in a cohort of over 1 million people, the American Cancer Society study that has been going on since the early eighties through today and their purpose of course in doing the study was to look at what is causing people to get cancer. So, they collected a great deal of information about these people and so what Arden Pope and other researchers including myself have done here is said, "Okay, well, you have collected all this information, and we can control for things like smoking and alcohol use and nutrition and all these things and then after controlling for all those things does air pollution still explain mortality differences from place to place?" So, we have the individuals and we have the air pollution levels of people living in cities where we had air pollution records of fine particle pollution for about half a million of those people and basically what we saw was an increased risk.

As the pollution levels go up the risk of dying goes up. For cardiopulmonary, for lung cancer we saw significant risk but for all others we saw basically no increased risk. So, this really makes sense with the cardiopulmonary region and of course over long exposures an increase in the risk of lung cancer, and basically the estimate that comes from this lung cancer is that of the risk of dying of lung cancer from living in a polluted city is about the same risk you take if you are a non-smoker living with a smoker except you have a choice whether or not to live with a smoker, but if you are living in a big city like Washington or New York then you are getting exposed to levels that give you a similar risk and as I was pointing out before and Joel has talked about there is a whole pyramid of effects. Mortality is just the tip of the iceberg and we have lots of morbidity effects. You get greater numbers as you go to less severe impacts and you know one of the examples is hospital admissions. Here is a study that was done in Southern Ontario looking at sulfate fine particle levels and hospital admissions and what we see is that there is basically a monotonic increase even down to very low levels.

What I did actually for this talk I put together some results. We did some new runs for the ACS database which we have. Rick Burnette did these runs for me and we looked at the ACS data set and divided it up as a function of age, asked them to look at 75 and older and then less than 75 and we have a study that was submitted for New York City where we have done the same thing. We have looked at in an acute sense, that is for a period of 1985 to 1994. So, it is about 10 years of data looking in New York daily deaths. So, we have looked at the air pollution effects on a long-term study, prospective study of a large population and then an acute study looking at the effects of chronic exposure and acute exposure.

For the ACS study what we found was that for persons 75 years and older the relative risk of cardiopulmonary disease was roughly doubled. You got double the risk. This is about a 5 percent increase and about a 10 percent increase for a 10-microgram-per-meter-cubed increase in the exposure level of the population.

So, in our original publication in JAMA we just looked at one overall risk which is obviously between these two but when you look by age you see a much higher risk in

older adults.

Similarly when we look at New York City it is kind of interesting, we look at people less than 75 and 75 years and older and what we saw was that without respiratory disease there really wasn't that much of a difference in the relative risk and it was significant but it was not very different between less than 75, but when you look at people with respiratory disease listed on their death certificate the risk for the elderly is much higher for the 75 and older so that it does seem that to get this higher risk in the older group it is associated with pre-existing disease which sort of fits in with the things that Joel was talking about.

We saw the same effect for both cancer and for the circulatory where you see the total without and with. Now, there have been also animal tests looking at older animals and they find kind of similar things, very supportive things. This is some work that is not yet published but was done at NYU for older rats showing that arrhythmias are increased by exposure to the, this is for air and then this is with PM and so you see a big jump in the effect on arrhythmias by the exposure to particulate matter in older

animals.

There have been a series of studies done that have been published in the literature looking at models of compromised health animals, compromised host situations. One of the ways they do that is to expose the animals to monocrotalene(?) and that gives a model of COPD, chronic obstructive pulmonary disease and in these animals they find greater responses to air pollution than in animals that haven't been pre-exposed, normal animals, and I just list a couple of studies here by Constant and Andrea, the people at EPA down in North Carolina who found that particulate matter affects inflammation and death in the monocortalene-exposed rats but not in the healthy rats and another study that exposure inhibited macrophage chemotaxis and particle clearance in the lungs of compromised rats and that diminished their defenses.

So, that is perhaps one of the mechanisms by which COPD could increase the risk of these particles. If they are not cleared out, if the body can't defend against them and they remain there a longer time then they can have a greater effect and other studies have shown very similar, you know, not every study in every case but generally speaking these

studies indicate that diseased animals are affected much more by air pollution than healthy animals so very similar to things that Joel was talking about and this is a model that actually we worked up at an ATS, American Thoracic Society meeting looking at a hypothetical model of illness and air pollution susceptibility. That sort of fits in with these results. So, I thought I would include that in the talk and you start out with healthy or less affected individuals and then there are long-term risk modifiers like diet, chronic disease, medications and then there are individuals with diminished health status. You get short-term risk decrease or short-term risk increase. So, in other words they can move into a significantly diminished reserve.

You can have long-term things that move them into somewhat diminished and then a short-term risk increase like increased illness episode, whatever, stress and that pushes them into this individuals with significantly diminished reserves and then an acute air pollution exposure can come along and they can have very severe outcome but they would move back in as that illness passes. They would have abatement of disease, stress, whatever, and they would move back down to a lower risk category.

Now, it may be that older people spend much more time in this increased susceptibility or very diminished health reserves such that they have this higher relative risk. They are at risk a longer percentage and if they have a chronic disease it is going to be there almost every day.

So, overall the conclusions that I draw here are that historical episodes and recent chronic and acute epidemiologic studies as well as experimental studies all indicate a greater risk of air pollution effects among older individuals and this is apparently due to both their higher underlying risk of disease and also the higher relative risk from air pollution exposure and it does seem that the higher air pollution relative risk may be due to an increased risk from a higher rate of pre-existing disease rather than age per se.

So, I think that is an area that we really want to look into is the interaction of age and disease and what is driving this greater susceptibility in there.

Thank you.

(Applause.)

DR. LANDSBERGIS: Okay, thank you.

The next scheduled speaker, Thomas Guilarte I was

told unfortunately because of the weather was not able to attend the meeting but just to be safe, let me ask if he has arrived recently?

Okay, then let me introduce Dr. Peter Spencer from the School of Medicine, Oregon Health and Science University.

DR. SPENCER: It is from the School of Medicine but more particularly it is from the Center for Research on Occupational and Environmental Toxicology of the Oregon Health and Science University in Portland.

I was asked to speak about the neurology of aging and simply stated the good news is that we will live longer than we ever dreamed. The bad news is that we will not remember why we wanted to.

This amusing statement of course reflects the tragedy of neurodegenerative disease and we have heard plenty over the past decade or so about the burgeoning problem of Alzheimer's disease and other neurodegenerative disorders, stroke-related disorders among the elderly and I am not going to speak about these at all because my charge as I understood it was to try to understand how the nervous system ages in the absence of overt disease.

It may well be that this is an entirely artificial distinction between the deterioration associated with aging and the onset of clinical disease but I am going to try to make that separation guided by the reviews of Katzman and Terry my former chairs at the Albert Einstein College of Medicine who have written excellent reviews on the subject and on my own research with Jose Ochoa on the neurology of aging of the peripheral nervous system.

The central idea that emerges from this work is that the nervous system has more anatomy and physiology than is required for normal function, that is it has a great reserve of anatomical structure and function that must be pared down before there is any overt expression of clinical disease.

There is a safety factor if you like built in and it seems to last pretty well for 50 years or so but then it may be overcome by disease in the later years possibly because homo sapiens were not in fact designed to live beyond the age of 50 since the reproductive years terminate just prior to that.

What can we learn from the previous studies of the aging brain and the aging nervous system? The studies are

not systematic but they can be summarized in this single slide.

As Bernie Weiss mentioned there is really no change in the overall store of information that we have acquired over life. We do become wiser as we age. There are certainly decreased in learning speed and recall ability especially for recently acquired information and there is unquestionably slower central processing of new data, slower reaction to external stimuli. If you ever ask the parkinsonian patient for example, a question or ask them to choose a menu item in a restaurant you know it takes a long time.

There is certainly reduced sensory and special sensory function. There is decreased motor strength and efficiency. There are changes in cerebral blood flow in the electroencephalogram and evoked responses and as Bernie pointed out there is regional loss of nerve cells and their processes in parts of the central nervous system.

There are, also, regressive changes in the dendritic arborization a reduction in the number of synapses which undoubtedly is the key to the eventual cognitive decline that is associated with extreme old age. Now, let us

break this down a little bit.

Let us look at the brain in terms of its anatomical changes. Well, simply the brain weight may change, may decrease but there is a large variability here. Certainly cortical atrophy is common, mostly in the forebrain, again associated with subclinical dementia or overt dementia in the disease state.

Cortical layers 3 and 4 tend to shrink as a reflection of neuronal changes in those layers relative to other layers of the cerebral cortex.

There is an overall enlargement on average of the brain's ventricles and inspection of arterioles and venules demonstrates that there are accumulating changes with age in the form of a coarsening of venules and coiling and looping and so on. Regional neuronal loss affects certain regions very substantially such as the substantia nigra, the locus ceruleus, putamen, cerebellum, etc.

On the neurochemical side there has certainly been documentation of reduced neurotransmitter function. Any number of transmitter markers have been looked at, nothing really systematically but affecting all of the key neurotransmitter systems in the brain and in the spinal

cord, dopaminergic in terms of nigra striatal problems and pre-parkinsonian states, serotonergic, cholinergic, GABA-ergic, etc.

A very early observation was that there was an increase in the amount of cellular lipofuscin. These are intracellular particles which accumulate differentially in certain regions of the brain with age and it is a very reliable biomarker of aging in those certain regions. It probably represents in a very simple statement the garbage can of the cell.

Other pathological structures which are commonly associated with Alzheimer's disease may accumulate as a consequence of advanced age especially in the neocortex and hippocampus although their presence does not indicate a diagnosis of Alzheimer's disease.

I wish I had bolded the third bullet because this is one contribution that I would like to bring before you namely that there are certain populations which show marked early brain aging and the one that I would particularly draw to your attention is the Chamorros population of Guam, the indigenous population of Guam that has over the past 50 years shown a spectacularly tragic I might say high

incidence of amyotrophic lateral sclerosis, parkinsonism, progressive dementia and the neuropathology underlying that dementia being remarkably similar to Alzheimer's disease but I said I wasn't going to talk about disease states and the point I want to mention is this. A study of some 302 brains of Chamorros who died of road traffic accidents in what was said to be an otherwise clinically normal state prior to the accident, no dementia, no recognized clinical disease that some 60 percent of these individuals who were under the age of 50 showed evidence of significant neuropathology which we associate with brain aging and we associate with the neurodegenerative diseases. The bottom line is that for some reason the Chammoros population of Guam ages in terms of its brain much more rapidly than the rest of us.

The specific question of age-related acceleration as it apparently is in that population has not been carefully studied but indeed 50 years of effort has been invested in trying to understand the etiology of the high incidence of neurodegenerative disease.

It is quite clear in that population that environmental factors are dominant, that genetic factors appear to be minimal if present at all and it is also clear

that genetically distinct populations in New Guinea and in a small part of Japan also show a very high incidence of the neurodegenerative diseases that are found on Guam.

It is clear that this is a non-transmissible and therefore non-viral or prion-related environmental factor and in fact the leading etiologic suspect, agent for this disease is a highly toxic plant which has been used for food and/or medicine in Guam and in the other two high-incidence regions where this disease has occurred.

I mention this because the entire focus so far today has been on synthetic chemicals. Please we should not forget that nature has been much smarter in devising nasty chemicals which might appear in our food supply and while I realize that this is not the mandate of EPA to regulate natural chemicals don't let us fool ourselves into believing that natural chemicals have no role in triggering disease and in potentially advancing the normal effects of aging.

The neurologic changes associated with normal aging affect posture, admittedly may be associated with osteologic problems or arthritic problems but in fact it is reminiscent of the parkinsonian posture. The shuffling gait is typical of parkinsonism but in the disease state it

occurs with rigidity and/or tremor or both and in normal aging, quote, unquote rigidity and tremor seem to be lacking.

One can do a variety of neurologic tests such as standing on one leg and show how there is a progressive impairment of the ability to do this with the advance of age.

More elaborate studies, looking, for example at cerebral blood flow, CBF, show that differentially from white matter to gray matter there is a selective blood flow decrease with age in gray matter, not good news at all and correlates of course with differential oxygen uptake by the brain which was shown earlier by one of the speakers, changes in EEG and invoked responses and also changes in the autonomic nervous system both central and peripheral components and it has been argued by Katzman and Terry that really advanced age is really a state of sympathetic nervous system over reactivity, a hyperadrenergic state and that indeed this may interfere with cognitive performance as well as being reflective in changes such as blood pressure, cardiovascular function, etc., impotence, bladder function.

Best studied and somewhat outside of my area of

expertise and very firmly within Bernie Weiss's area of expertise are psychological functions. As he mentioned overall intellectual performance, crystallized memory is retailed throughout the seventies. However, performance on timed tasks declines both because of reduced central processing, brain processing and also changes in motor function. Both contribute to this it is believed.

The good news is that verbal skills may be preserved and may even be improved with the advance of age at least up until the age of 70. The bad news is that simple reaction time increases and choice reaction time increases to a greater degree because when confronted with a complex task there is a need for greater central processing and this interferes with the performance.

Relatively unchanged is the ability to recall data such as a series of digits. The immediate recall may be relatively unchanged as also retrieval of long-term memory and also an aged individual who is asked to over learn, repeatedly learn particular phrases, this retrieval is pretty good as is semantic idea based memory.

The bad news again is that a consistent change but not always a universal change is that the short-term memory

function declines and recall of short-term memory is progressively poorer. There may be difficulty with verbal and visual memory as well.

On top of all this I remind you that the brain is doing a variety of other things, clearly the most important organ in the body and while certainly every component of the body merits close attention in relationship to changes with aging I would encourage the committee to focus carefully on issues relating to the nervous system, sleep changes. There are changes in behavior of sleep patterns and there is early wakening. Earlier to bed is a phase of that. It is again a brain-driven phenomenon. There are changes in audition, visual function, olfaction, gustation and they all decline.

Not commonly thought about is core temperature, the regulation of core temperature by the nervous system becomes progressively failed with the advance of age and individuals are subject both to hypo as well as hyperthermic illness, hypothermic illness on a day such as this, hyperthermic illness perhaps in relationship to drugs which may, medications which may tend towards hypothermic responses.

I am not sure if the last one really is true. This

was data from the pre-Viagra era but when total tumescence time during REM sleep is measured the good news is that the total time and number of episodes is constant between the age of 50 to 79, but in fact one is asleep during the time.

(Laughter.)

DR. SPENCER: Peripheral nervous system function often ignored, in fact, has been extremely well studied. On the somatosensory side there is clear-cut loss of DRG, dorsal root ganglion sensory neurons and also at the other end of the neuron the mechanoreceptor function decreases. The density may decrease as well.

There is a spectacular pathology seen in a number of species which develops in the spinal roots, in the sensory spinal roots and on the motor side and this undoubtedly requires more attention in terms of causation.

On the motor side and here we are talking about the lower motor neuron and the anterior horn cell in the spinal cord there is a progressive loss of lower motor neurons and pronounced neurofiber pathology may be in attendance. There may also be changes in neuromuscular function. There are changes and there may be primary changes in muscle function per se and this means then that the

elderly subject is going to be differentially susceptible to a number of factors that we haven't considered here, for example, ability to detect pain is decreased.

Certainly in London when I was a child we used to have open radiant fires and a large number of elderly people would burn themselves by sitting too close because their pain perception perhaps was declining. You ability to detect vibration is dramatically reduced as a consequence of aging but your ability to detect touch and two-point discrimination is relatively well preserved.

Now, age is not different then from earlier life as long as you are sitting down and the previous two slides really get at that issue. It is the combination of changes in the sensory and motor function of the peripheral nervous system combined with spinal cord and age changes in the brain which makes things difficult quite apart from the co-existent factors of arthritic change and osteologic change and so on.

I would like to end on this slide because again I want to bring forward a point which has not been mentioned here and is gleaned from clinical experience with clinical neurotoxicity and while I am not a clinician, I have the

task of editing a very large textbook on experimental and clinical neurotoxicology with my colleague Herb Shamberg. We found it necessary to include a very large number of therapeutic drugs within that textbook of neurotoxicity and neurotoxicology in addition to the environmental and occupational toxicants and other agents, drugs of abuse, etc.

My point is this, that medications taken in prescribed quantities in this country are a major cause of neurotoxicity, indeed, not only neurotoxicity but morbidity generally and even mortality.

While this is clearly not an area that EPA is going to have to worry about, I would urge the committee that addresses this issue to look at the side effects of drug literature because within that literature you will find some very well established parameters of why aged subjects are more susceptible to chemical exposure in the form of medications.

Broadly speaking it is attributed to factors such as reduced body mass, non-optimal nutrition, absolutely key reduced hepatic metabolism or altered hepatic metabolism and absolutely key again is impaired renal excretion. None of

this has been discussed today but often as not that is why the elderly subject in the clinic is more susceptible to the neurotoxic effects of chemicals to which the individual is exposed for the purposes of medication and there is nothing special about medication. They are chemicals, chemicals, chemicals.

It is certainly aggravated by the tendency for polypharmacy and perhaps although we don't have good data on this by the increasing use of non-traditional,non-regulated medicine usage.

I don't know how often the aged go to their health food store but certainly it is something worth looking into.

Thank you.

(Applause.)

DR. LANDSBERGIS: Okay, thank you.

Also, unfortunately, Dr. Bingham is not able to attend the meeting this afternoon because of the weather. So, what I would like to do now is take a break. It is three-fifteen and we will start the session again at three-thirty-five.

(Brief recess.)

DR. LANDSBERGIS: Okay, I would like to start this

afternoon's final session of the program. I would like to introduce Dr. Frederick de Serres from the Board of Directors of the Alpha-1 Foundation who will be talking about evidence for a large susceptible subgroup of the aged population.

DR. DE SERRES: It is a pleasure to be here, and it is nice to see that I can still walk up one flight of stairs. I am going to talk to you about a disease, a rare disease genetically determined that you may have heard about or you may not have heard about. If you have heard about it I am going to drastically change your perception of who has it, where they are located, how many people are affected and all kinds of adverse effects of this population at whatever age and particularly when they are older.

As a prologue I was treated for 16 years at Chapel Hill and at Duke for asthma and allergy and during that 16-year period I was tested for everything imaginable, everything you can think of, very good yearly workups, physical exams, everything you can think of.

I retired in 1996, when I was 66 years old and in July 1960, July 1997, I am sorry, it was 1996 when I retired and 1997, when I got pneumonia or I thought I had pneumonia

and I couldn't get in to see the regular physician at Duke. It was July. The earliest appointment I could get was September and I couldn't convince the nurse that I would be dead by then. So, I called up Harold Pillsbury at UNC who was my daughter's mentor when she was in medical school, and I said, "Hap, I think I am in real trouble, and I can't get to see anybody," He said, "You get your butt right in here because you have a problem," and he took a chest x-ray and sure enough I had pneumonia but at the bottom of my lungs was emphysema and this is not his major area. He is an eye, ear, nose and throat kind of person. He said, "This is very unuusal. You are not supposed to have emphysema in the lower lobes of your lungs, but I have a pulmonary physician over in another part of the medical school and I want you to go right over there and see Dr.Jim Donohue." Jim Donohue looked at the chest x-ray. Sure enough Fred had pneumonia and he looked at the emphysema and he said, "Fred, I think you have a hereditary disease that is very rare." Within 24 hours I knew that I was a ZZ homozygote for Alpha-1 antitrypsin deficiency.

Well, what a wonderful way to start your retirement. Why me? I immediately wondered well, how many

people have this rare disease; why have I got it and what is the prognosis? What have I got to look forward to in my old age, and are there ways that I can prevent the onset of any adverse health effects that might come with this disease?

Well, when I got into the literature very briefly I found out that people who have Alpha-1 present with allergies, asthma, chronic bronchitis, things that have plagued me for years and the reason I am telling you that is that the disease is believed to be so rare that people who know about it don't test for it. Why bother because the probability of this patient having the disease is so small you know that they don't want to test for it.

Obviously this was a turning point in my life. I am trained as a research person. I have done research in many different areas. So, I said, "Okay, it looks like I am going to get in my retirement to explore a totally new frontier."

Going into the literature Mark Brantley at NIH had a small bibliography of Alpha-1 papers and I systematically went back to 1965. The disease was discovered in 1963, and combed PubMed(?) Web of Science(?) and built a bibliography

of 13,000 references and it was obvious to me that there was one helluva lot of information there about Alpha-1 that nobody had bothered to put together, tabulate, catalog and so forth.

I discovered that there is more information there than I will probably ever be able to collate and write up in my whole lifetime, and I have started the process.

I have a paper that was just published in Chest in the November issue which discusses the worldwide racial and ethnic distribution of Alpha-1 antitrypsin deficiency in 58 countries all over the world and I recently completed, and it is just an overview, it is not the kind of thing you usually do but the impact on the standards of care are so dramatic with the facts in that paper that I just decided to do the summary before I wrote all the details. So, now, i am doing the follow-up publication on all of the control cohorts in every single one of those 58 countries.

So, what I want to talk about is is there evidence that there are genetically determined susceptible subgroups in the elderly population of the United States of America.

Now, if I can remember how to forward, Alpha-1 antitrypsin deficiency is a genetically determined disease

that is a major health problem for the aged population worldwide and particularly the population in the United States of America, and I am going in the wrong direction.

This is me. I am lecturing today as a director of the Board of Directors of the Alpha-1 Foundation. I am also a member of the Molecular Toxicology Group at the National Institutes of Environmental Health Sciences in North Carolina but this is an Alpha-1 lecture and it is going to be for the Alpha-1 Foundation.

This is working in reverse. Okay so the recent publication is the worldwide racial and ethnic distribution of Alpha-1 antitrypsin deficiency and it is a summary of the analysis of published genetic epidemiological surveys. It is all everybody else's work and it is just Fred putting it all together to try to make sense out of it.

The reference is Chest, Volume 122, Issue No. 5, and it just came out. Where I started was this is a genetic disease that is widely thought to be a disease of Caucasians or whites in Northern Europe. There is a lot of work that has been done I found on the molecular biology. The gene locus is located on the long arm of chromosome 14 and it has been mapped to a particular position and that is all well

known. It has been cloned and sequenced and about 100 different variants have been identified and the most common are PIS and PIZ. I have the Z allele. The enzyme that I make is only about 15 percent active. The S allele is considerably higher, and those that have the disease are at a high risk for liver or lung disease and a wide range of adverse health effects that I will enumerate later.

Here they are. These include abdominal and intracranial aneurysms. I have had four abdominal aneurysms so far. I have asthma, bronchiectasis, COPD, liver disease, multiple sclerosis, panniculitis which is a terrible skin disease, peripheral neuropathy, I, also, have. My feet hurt all the time, rheumatoid arthritis, systemic vesiculitis, uveitis. I am working with a guy at Rand who is doing a very bid study on uveitis and Wegener's granulomatosis. This is just a brief summary of some of the adverse health effects that actually are in the literature. There are more.

Well, the concerns for the adverse health effects on an aged population are due to the fact that both lung and liver function decrease with age and cause increased susceptibility to exposure of chemical and physical environmental agents and why is that? As the people who

have Alpha-1 get older they have reduced lung function. The emphysema progresses. You don't clear particulates. You don't clear chemicals as rapidly you know as younger people that have this disease or normal people. So, you are at increased susceptibility to pollutants that are in the air.

What happens in the liver of people, and this is variable from person to person, of people that are ZZ homozygotes make the defective enzyme that doesn't leave the liver. It just stays in the liver and accumulates in the liver. So, you have eventually even if you don't realize you have a liver problem the Danish data would show that autopsy data that all ZZ homozygotes have cirrhosis of the liver. So, it is important to avoid alcohol and a variety of other things that require a lipid metabolism.

So, the point that I am trying to make is that in the aged population that have Alpha-1 you have a decreased ability because of loss of liver function to detoxify things that normal people can.

Okay, we have five phenotypic classes that are believed to be affected and this is again an area of great controversy. Most physicians who know anything about alpha-1 talk about the ZZ homozygotes and they totally ignore the

other four phenotypic classes. These people don't have problems. They don't believe they have problems and sometimes they don't even tell their patients that they are carriers or they are SS or STs even though there is extensive literature to the contrary.

So, the environmental agent exposures of concern in the populations at risk are chemical substances, toxic fumes, organic wastes or particulates, germs and infectious diseases.

This is an interesting list of professions that I don't think most people would have even thought about. I know I certainly didn't until I started to put all this together. For chemical substances, what kind of people, you know, are exposed to chemicals, painters, welders, fumigators, chemical plant workers, toxic fumes, cab and bus and truck drivers, airport personnel, factory workers, dry cleaners, industrial and household cleaners, organic wastes and particulates, miners, textile workers, farmers, other agricultural workers, dental workers; germs and infectious diseases, schoolteachers, doctors, nurses, other health care professionals, sales personnel, restaurant and hotel wait staff. It is a really interesting list of people you know

that would be at risk if they have Alpha-1.

The experimental approach that I used to estimate those at risk for Alpha-1 was to collect control cohorts from genetic epidemiological studies on individual countries worldwide and there was a paper by Duncan Hutchinson that appeared in 1998, that I decided to emulate. He had all the criteria for acceptance, how many people had to be in the cohort and all kinds of really good criteria.

His paper was solely about Europe and what he showed in that paper, and it was a prevalence study that in the northern countries in Europe if you have the Z allele predominantly and as you moved south into Italy and Spain and Portugal and those countries there was a decreasing prevalence of Z whereas the S allele is very prominent in Southern Europe and decreases dramatically as you move north.

So, it was only prevalence data that appeared in that paper and I was trained at NIEHS in the Office of the Director and I knew that if you wanted to impress people you know with how serious a problem you had you have to have numbers and they can't be guesses. They have to be hard numbers and they have to be fully documented.

So, Fred decided okay I want to know how many people in Spain or how many people in Denmark are carriers and how many people you know have the deficiency allele combinations for S and Z, and that was my motivation. So, here we go.

This is the number of carriers for the S allele or the Z allele worldwide. There is no data for South America. All I could find in the literature was data on four different indian tribes, two in Brazil and two in Venezuela but no data in Central America or South America but in Australia and New Zealand and here you can see the numbers are so big they wouldn't fit on the bottom of the screen. So, we are talking about millions and billions of the Z allele carriers and the S allele carriers and you can see that in Northern Europe where the disease is supposed to be a disease of Northern Europeans you probably have close to the smallest number of carriers and the largest number of carriers are in lo and behold Central and South Africa. Blacks have this disease. North America, well we well know that the disease should be in the United States and Canada because most of us come form Northern Europe or Southern Europe and so those data are of no surprise, but the

surprise is that data in Central Asia, Afghanistan, Izbekistan(?) Tajizkistan(?), Far East Asia, that is South Korea but not China or Japan. So, there are some really interesting surprises there and the next slide you have the number of the deficiency allele combinations worldwide. That little tiny bar is the frequency of the Z homozygotes and you can see that in places where you wouldn't have expected and places where you do expect there is a very high frequency of the S allele.

So, this is a numbers game and this is the first time and you are getting to see it for the first time how many people worldwide are affected by this disease and the numbers are big.

So the conclusion is Alpha-1 antitrypsin deficiency is found in African blacks, Arabs and Jews in the Middle East, whites in Australia, New Zealand, Europe and North America and in Central, Far East and Southeast Asia and in the survey of the 58 countries that I performed on there was a total population of 4.4 billion people affected in the 58 countries surveyed. I mean that was the number of people surveyed. That is a typo. There were 4.4 billion people surveyed in 58 countries and in that number there

were 117 million carriers for S and Z and 3.4 million deficiency allele combinations.

The conclusion then is that Alpha-1 is not just a disease of whites in Northern Europe. It affects individuals in all racial subgroups worldwide and it may be one of the most common serious hereditary disorders in the world and that is mind boggling in terms of you know where we started a couple of years ago.

For the purposes of this presentation I thought you might be interested in the United States. The data show that one person out of 11 in the United States is affected by this disease. There is one out of 17 S carrier, one out of 37 Z carriers, one out of 983 for SS, and one out of 1110 for SZ and the ZZ's which most people worry about is one out of 5000 and the actual numbers, the total number at risk in the United States for this disease are 25 million and there you have numbers for those that, and I have 95 percent confidence intervals in all of these numbers. I didn't put them on the slides because it makes them too complicated but in the papers that I am writing you will get confidence intervals and the confidence intervals are small because I have very large numbers of cohorts in the United States.

So, these are numbers that, I mean for example, the 56,249 that I came up with is a number that other people have tried to derive by a different technique and the numbers are in total agreement with other methods of analysis.

So, what have we learned about the aged Alpha-1 deficiency population of the United States? The total numbers are at risk in each of the five phenotypic classes. Those are the numbers I just showed you but the complication is that the population of the United States is comprised of at least five distinct racial subgroups and each subgroup has a different allele frequency for these three different alleles and so the critical information for evaluating the differential susceptibility of the aged ATT population you have to know the numbers of individuals at risk, the size of each racial subgroup, the allele frequencies in each subgroup, the adverse health effects associated with each of the five phenotypic classes and is there comparable susceptibility in each racial subgroup. What a load of interesting questions.

What do we need to know? The numbers in each of the five phenotypic classes for each racial subgroup?

Definitely. The age distribution in each of the five phenotypic classes? I would love to know that but I don't know how to do it, but I do know how to determine how many people there are in each of the major racial subgroups in the United States. You can go to the Internet and find this information very easily and because I have cohorts that are Asians or blacks or Hispanics or Mexicans or whites in the United States it is very easy to determine the different gene frequencies for M, S and Z and you can clearly see that the Asians don't have the S allele or don't have the Z allele or the population of Asians that were tested don't have it and obviously there were no South Koreans in that cohort.

Blacks do have the S allele, do have the Z allele. Hispanics, a much higher frequency of the S allele, and I have already told you that and usually a low frequency of the Z allele. The Mexicans who are a mixture of Metzitos(?) as well as Spaniards have the S allele as you might expect and no detectable Z allele in the cohorts that I was able to find and in the whites again both the S and Z allele are present and then if you total up all the numbers that is a total population of the United States, 281 million and that

is a mean frequency for the whole population.

So, then you can come up with the numbers of people in each one of those racial subgroups that carry the S allele, the Z allele, SS homozygotes, SZs or ZZs and you can see that the Asians basically are home free. The blacks have significant numbers of carriers as well as SS, SZs and ZZs and so forth down the list, and this is the way you begin the process of trying to figure out how to approach the fact that different racial subgroups have very different frequencies of carriers or deficiency allele combinations and with that information it is a very important beginning.

So, the current programs of the Alpha-1 Foundation involve a patient registry in Charleston, South Carolina and a laboratory headed up by Mark Brantly who was instrumental in my diagnosis in Gainesville, Florida where he does phenotyping and genotyping and he has a tissue bank where he collects tissues from as many people that are willing to donate them so we can get an understanding of this disease and we have 53 clinical resource centers in 24 states around the country in the United States that are all interested in working on this problem.

The current screening detection program to try

to,now that we know that we have large numbers of people affected, we have started with COPD patients in Florida. A lot of older people go down to Florida. A lot of them have COPD and the issue is do a lot of them have Alpha-1 antitrypsin deficiency and briefly there is a higher frequency in the COPD population than in the normal population and that program is intended to serve as a prototype for screening and detection programs nationwide.

Our objective is to have such a program going on in the general population of every single state in this country. So, the critical issue what are the adverse health effects associated with each of the five phenotypic classes of one deficiency and the approach that I am doing and I am working with colleagues in Spain on this is to do research data summaries in the peer reviewed literature on the adverse health effects associated with each of the five phenotypes. What diseases do MS's have? What diseases do MS's have and on and on and you know there are tremendous numbers. It is a lot of work and there are hundreds of papers that have to be systematically reviewed and catalogued but the point that I am trying to make is the information is all there and nobody every bothered to do

anything with it. So, this is the value of being a patient that is committed to trying to do something about this disease.

So, the approach then and there you have got the five phenotypic classes in different colors and you see we are going to prepare five reports for publication in the peer-reviewed literature. It will just simply be a tabulation of the adverse health effects associated with each one of those five phenotypes and then we are going to try to get together expert committees to review all the data one phenotype at a time and produce a report so that you can document fully that MS's are subject to this, this and this and MZ's you know and so forth.

It is kind of a complicated process because we know already that there are a large series of modifying genes and so MS's that are black people might be very different from MS's that are white and this is the intriguing aspect of you know the whole problem which makes it especially difficult, but there are people working on it already. There is a sib pair study where my sister and I who are both ZZ homozygotes have donated tissue to Ed Silverman at Harvard, and he is trying to find out what modifiers my

sister has that I don't have because she doesn't have the problems that I do.

She got the good genes. I got the bad genes. So, we will find out from these kinds of studies what the modifiers are and why people who have the same genotype have very different expressions, sometimes in the very same family.

The critical issues are what are the health effects associated with each phenotype; is there a difference in the health effects in different racial subgroups; does the spectrum of health effects change with increasing age and as I told you before because of reduction in liver function and lung function we already know that it changes with age.

So, the follow-up screening detection program is a nationwide, I told you about that, enrollment of new patients in the registry in Charleston and collection of as many DNA samples as we possibly can.

So, the conclusion and I have already gotten rid of the slide and don't know how to get it back again, the conclusion was I think that there is no doubt that Alpha-1 Antitrypsin deficiency is a major health problem in this

country and there are very large numbers of people affected and it is a great research problem for those of you that are interested and a really interesting genetic disease, and I am sorry I am so emotional, but it is important.

Thank you.

(Applause.)

DR. LANDSBERGIS: Thank you very much, Dr. De Serris.

I would now like to introduce Darrell Abernethy from the National Institute on Aging who will be speaking on the impact of aging pathophysiology on drug responses.

DR. ABERNETHY: Thanks very much. It is a pleasure to be here and this has been a most illuminating day. What I would like to talk to you today about has to do with an area of research interest we have had for a good many years. We will be focusing on cardiovascular drug effects simply because that is where the data that we and some others have generated and also where there are markers that allow for one to draw inference from information that one can gain from clinical studies.

I will start with a case that I think for particularly the physicians in the group illuminates kind

of the problem of the interface of aging, illness and attempted therapeutic maneuvers with illness.

This is an 88-year-old woman who comes with multiple diagnoses, very typical sorts of diagnosis for someone in this age group and on multiple medications and worthy of note I think are that really each of these medications is indicated for a variety of ailments that the lady has, the meturpralol(?) and analopril(?) for congestive heart failure as well as hypertension, the hydrochlorothiazide, the allendronate(?) for the osteoporosis, the ameprozol(?) for the esophageal reflux disease and so that it is very hard to criticize the multiple medications that the aged patient is frequently taking because they are administered for very appropriate indications and the efficacy for those indications has been well demonstrated particularly in a case such as this.

This is looking then at physical examination of this lady who is of slightly increased body weight, blood pressure 176/74, laying down, 146/68 standing up for a couple of minutes with a heart rate unchanged with the postural change and then we can see the rest of the examination which again is very typical for a patient in

this age range and the laboratory data as you can see offers the further kinds of information that one would expect and the issue really is in a patient such as this is that with this rather dramatic change in blood pressure with posture than at the same time with systolic hypertension that is a systolic blood pressure of over 160 while supine what is the appropriate course of action for the physician for this patient; does this patient require more therapy or is the patient already on excessive therapy for the blood pressure and how best to approach this because here is a patient who has a clinical picture that literature would tell the physician perhaps needs even more therapeutic intervention. However, at the same time another set of the literature would suggest that this patient is at high risk for the potential of adverse drug effects.

I am not going to tell you the answer because I don't think there is an answer in that patient. This becomes a very individualized sort of therapeutic decision making between the patient and the physician but what I am going to show you now are some data that I think help us understand the pathophysiology of the aged patient particularly with regard to the cardiovascular system and how that impacts on

drug effects and what the interface between cardiovascular drug therapy and this pathophysiology may be.

To begin this is looking at some data from some years ago. There has been a belief out there that there is an increased incidence of adverse drug effect in aged individuals and so on your left panel you will see that if we look at, this is an outpatient study, the percent of patient who have a documentable adverse drug effect and we will discuss in a few minutes what those drug effects might be, we can see an age-related increase in the likelihood of the patient having some sort of adverse drug outcome when on therapy.

However, then when we divide by the number of medications that the patient is taking as you can see on the right panel it looks like at least a big part of that change in incidence of adverse drug outcome or effect is really related to just the numbers of medications the patient is being exposed to.

Now, what are these kinds of side effects? This is from that same study and this is showing that these are meaningful adverse drug effects that are being documented, cognitive impairment or what are the sequelae of cognitive

impairment. Loss of balance, falls and hip fracture, orthostatic hypotension as we were looking at with the patient that we discussed a few moments ago, a very common sort of adverse effect documented when it is looked for clinically in the aged patient and what are the clinical sequelae of orthostatic hypotension, again, when the patient assumes the upright posture. Fainting, falling and breaking hip. Acute renal failure, metabolic abnormalities, we can see then with decreasing frequency but the point to be made is that in this outpatient population that the adverse effects that could be documented are clinically really quite meaningful.

Now, these are data from Mark Biers when he was at Los Angeles because a real question would be how many old people do take multiple medications. This is a nursing home population. This is looking at 12 nursing homes in the Los Angeles area about a decade ago and I can tell you that more recently data suggest that these numbers have not changed appreciably. The mean number of drugs per resident across nursing homes and we can see six to eight drugs for an individual patient so that the drug burden is in fact quite high in the aged individual.

Now, let us move away from that epidemiologic data for a moment and think about the changes in the cardiovascular system with aging that may impact on the likelihood of an adverse drug effect.

This is a listing that has come from a whole variety of studies that I think we would agree can be confirmed across study populations. So, what are the important features here? Decreased reflex sensitivity, when the aged individual sits up or assumes and upright posture the incapacity, the increased heart rate, increased cardiac output to maintain blood pressure, increased blood pressure variability, increased peripheral vascular resistance, these are some of the concomitants that we will look at in a few minutes that we believe impact on drug pharmacodynamics.

Now, this is a picture taken from Robert O'Rourke's text in which it is making the point that an important sequela of aging is decreased compliance of the large blood vessels. Now, if we look at the data on the left side we will see in the quote normal aorta a blood pressure of 130/80, so the pulse wave velocity, the rate of speed of the pulse wave after systolic contraction being a certain number and then as that pulsed wave is distributed there is

a reflected wave and we can see there with the arterial wave form under No. 4 that this reflected wave occurs after the end of systole such that in fact that is a physiologically very useful sort of pressure augmentation during diastole or heart relaxation to help with coronary artery filling.

We can see in the aged individual with the decreased compliance of the large blood vessels that this pulsed wave velocity is markedly increased and so that then the reflected wave occurs much earlier causing the broader pulsed pressure, the greater difference between systolic and diastolic blood pressure and perhaps even more importantly this reflected wave now coming back and actually increasing systolic pressure rather than having the beneficial effects during diastole.

Now, this decreased large vessel compliance occurs as best can be told in the absence of evident cardiovascular disease and is probably accentuated in the presence of cardiovascular disease such as atherosclerosis although it is very difficult to separate those two factors out and as one speaker earlier today said, probably importantly it doesn't make much difference. The aged individual comes with the disease they have and so that is really the individual

that receives the exposure.

Now, these are data that Bob Vestal will look at somewhat fondly from earlier in his career and this is to demonstrate a second important component with regard to aging and cardiovascular function.

This is looking at beta adrenergic responsiveness as a function of increasing age so that isoproterenol, a beta adrenergic agonist is administered to individual to a dose that increases their heart rate 25 beats per minute and we can see that a progressively increasing exposure of isoproterenol is required to have the same effect in the aged individual as compared to the younger individual and that if then we look in the heart we can see the same sort of phenomenon and this would be looking at the maximal activation of adenylyl(?) cyclase with isoproterenol in the heart as a function of increasing age suggesting that this impairment in beta adrenergic function is present and this has been replicated in many studies and is really one of the most well supported features of cardiovascular aging.

This is then more recent data that asks the question about other affecter systems and aging and this is looking at alpha adrenergic responsiveness and in this case

the question would be in younger versus older patients, individuals and these are individuals that have been screened as best as possible to rule out concomitant cardiovascular disease what is the decrease in blood flow with an administered pressor tyramine, a drug which causes release of nor-epinephrine and we can see in the older individual less decrease in blood flow than in the younger individual and at the same time that is with a greater release of nor-epinephrine or greater release of the affecter.

So, it would appear from these data that there is an uncoupling, that a larger amount of circulating nor-epinephrine is causing a lesser response to the pressor hormone.

Then this is looking at administration of finlefrin(?) an alpha-1 adrenergic agonist and we see approximately the same thing and that would be that the older individual would appear to have less fenlefrin mediated vasoconstriction, decrease in formed blood flow than the younger individual.

This is then looking at the other side of the coin and that is if alpha adrenergic responses are blocked what

is the effect in the older as compared to the younger individuals and it would appear that with blockade of the alpha adrenergic response that the younger individuals have a greater vasodilation than do the older individuals.

Now, what is the pharmacodynamic consequence of these findings? Impaired beta adrenergic responsiveness, apparently some impairment in alpha-1 adrenergic responsiveness. Lobetalol(?) is a drug that is commonly used for the treatment of hypertension and it is an alpha-beta adrenergic blocker. These re data from our own laboratory from some years ago looking at the change in baseline heart rate as a function of exposure to lobetalol, lobetalol plasma concentration in younger and in an older woman and we can see in the younger individual a markedly greater sensitivity to the effects of this alpha-beta blocker on decreasing heart rate than in the older individuals. A much greater drug exposure is required to achieve the same decrease in heart rate in the older individual, perhaps due to the impairment in beta adrenergic responsiveness and then if we look at change in systolic blood pressure in the older as compared to the younger individuals across a study population we can see with the

impaired beta adrenergic responsiveness the aged individual has a much greater drop in systolic blood pressure with exposure to the same amount of drug as does the younger individual.

So, with these changes in aging and apparent sensitivity to this kind of a commonly used pharmacologic intervention with regard to calcium antagonist drugs these are drugs that are commonly used for the treatment of hypertension and are direct-acting vasodilators. An additional pharmacodynamic effect of the calcium antagonist drug is the blockade of atrial ventricular conduction delay, electrical conduction within the heart.

Now, we have known for a long time that as an individual ages the conduction system in the heart becomes increasingly fibrosed and one could make the case that a drug which causes suppression of electrical conduction in the heart, an aged patient might be particularly sensitive to that kind of effect.

These are the data that we found and that would be looking at electrocardiographic PR prolongation, a measure of atrial ventricular conduction that can be made non-invasively as a function of drug exposure in younger, older

and older,much older individuals and we can see to our surprise that it was the opposite. We found the opposite of what we expected and that is in this case it would appear that the older individual is relatively less susceptible to this impairment of cardiac electrical conduction than the younger individual.

Looking at another calcium antagonist drug we see essentially the same thing and that is again looking at electrocardiographic PR interval after diltiazem(?) exposure, another calcium antagonist drug that the younger individual would appear to have a greater impairment in cardiac condition than does the older individual. However, this looks like that the maximal effect if the dose is doubled of drug that the maximal effect is no different, that the older individual simply has a dose response curve shifted to the right. Looking at diltiazem, the calcium antagonist drug which is also a direct vasodilating drug we can see again with the vasodilation a decrease in peripheral vascular resistance, a drop in blood pressure that the older individual has less increase in heart rate to defend the blood pressure if you will therefore a greater decrease in blood pressure consistent with the data that we saw with

lobetalol as well, so that there is a complex array of physiologic and pathophysiologic changes with aging that impact on these drug responses that we see such as some of the responses the aged individual would appear to be more sensitive to and others quite the opposite.

Now, one question that has been increasingly able to be answered is what are the mechanisms for some of these interesting sorts of changes with the aged as compared to the younger heart and blood vessels that may relate to drug response.

There is a lot on this slide but the gist of it would be that with aging the capacity to remove calcium from the cytoplasmic space is impaired and that appears to be impaired on the basis of an impairment in serca(?) a transport process within the cytoplasmic space of the cells and this would appear to be a consistent finding with aging and with younger individuals.

We will look at what the concomitants of this kind of impairment might be in a moment. What is being shown here is that this is in a rat model of aging that in the adult we see a certain expression of this enzyme, in the senescent situation a decrease expression and then if we transfect

back the gene we can see that expression of the enzyme reappears back to the basal level.

Then if we look at functional activity in the adult versus senescent we can see a marked decrease in this enzymatic activity which then is corrected with the transfection back in of the deficient gene and this translates itself into cardiac contractility as well, the capacity of the heart to have a forceful heart beat such that with the transfected enzyme back in that heart contraction is in fact improved and if we look then at the physiologic model of this phenomenon this would be looking pacing the heart at different heart rates and looking in the senescent hearts here in the square boxes so that with increasing heart rate the left ventricular volume and end diastolic pressure increases, a concomitant of a failing heart and contractility is not changed, again, a concomitant of a failing heart.

However, in the younger animal we can see that with increasing heart rate this maintained and the contractility increasing and then with the gene transfected back in the rescue of the senescent cardiac function if you will.

Now, let us move for a moment to another affecter system the vascular endothelium. This would be a representation of a vascular endothelial cell and a vascular smooth muscle cell and then a representation of cross talk between these systems.

Nitric oxide synthase is an enzyme in the vascular endothelium that has been shown to be an important modulator of vascular tone with elaboration when it is activated of nitric oxide causing then vascular smooth muscle relaxation. These are data from our laboratory showing that in older individuals; this is in a group of people characterized as closely as possible as healthy, in older individuals the capacity to have vascular endothelial vascular relaxation is impaired as compared to a younger individual, that is the dose of acetyl choline required to cause 50 percent maximal dilation of the older individual's brachial artery. This is again a finding that appears to be consistent. These are data from another study in the coronary vasculature just looking at maximal increase in coronary blood flow as a function of increasing age with acetyl choline infusion and we can see that in the coronary vasculature as well it would appear that the endothelial mediated vasal relaxation

is impaired as a function of age.

Now, how might this be? This then is asking the question in the age related system or in the aging animal or human why is this endothelial function impaired and a very interesting very recent finding would be that it looks like if we transfect back in a telemerase(?) gene that one rescues this impairment in nitric oxide synthase activity that one sees in senescence suggesting a mechanism and down the road a dream might be a potential therapy for this kind of age-related change.

Now, to briefly summarize the cardiovascular changes of aging that we believe relate to potential changes in drug response this is a listing and these would be drug responses measured and summarized in this case by Ed Lakata's group suggesting that heart rate goes down somewhat, that end diastolic volume of the heart goes up somewhat. We talk about vascular compliance being decreased with an increased rate of reflected wave form. Peripheral vascular resistance may or may not change and then a series of other metabolic functions that change to some extent with increasing age including oxygen consumption, cardiac index, heart rate and then the cardiac function itself.

Now, these age-related changes in cardiovascular function then are the substrate upon which pharmacologic agents are administered. This is one very simplified view of kind of the aging process and then in the younger individual with relatively impact homeostatic systems we believe the capacity to sustain the effects of pharmacologic and other therapies that are administered but as the individual has increasingly impaired homeostatic processes less capacity to sustain the effects of multiple drug therapies or other insults. These are obviously goals of treatment when we are thinking about pharmacotherapy in the aged individuals and I would say goals of treatment with regard to exposure issues as well so that we may end up as Robert Louis Stevenson once said with this kind of conclusion. There are these age-related changes that really create a challenging situation with regard to exposure to pharmacologic and other agents and perhaps a pessimistic view but there is probably also an optimistic view that might be had as well.

Thanks very much.

(Applause.)

DR. LANDSBERGIS: Thank you.

As it turns out the next scheduled speaker, Dr.

Dorman is also a casualty of the weather. So, I would like to move on to the final scheduled speaker, Dr. Larry Branch of the University of South Florida who will be talking on the public health perspective.

DR. BRANCH: Thank you.

What I would like to do during the next 20 minutes is invite us to refocus our perspective and look at the really big picture of the interplay between the environment and aging, and I will do this first by trying to clarify what is the traditional public health perspective as it relates to the interplay between the environment and aging and second what one person's view might be of what the future challenges will look like in the interplay between the environment and aging.

So, first what is the public health perspective; it is probably reasonable to ask that question, and the focus of public health is on whole populations and by analogy and somewhat glibly as it is said that clinical medicine attempts to save lives one patient at a time public health attempts to enhance the health of populations 100,000 at a time.

What is the public health perspective in the

context of this interplay between the environment and aging? We have had extremely insightful presentations today about both aspects of that interplay; concerning the aging part of the equation numerous speakers today have clarified how the senescent individual as well as the senescent organs and subsystems within an individual respond to environmental assaults and the take-home message clearly is that the senescent individual and/or senescent system or function is at increased risk for negative outcomes following environmental exposures compared to younger adults. I got that message.

The mechanisms though they might not be fully and completely understood and agreed upon by all of the researchers nevertheless there are some common explanations not the least of which is a compromised immune system is somewhere going to be in the explanation for the increased risk for older individuals.

Concerning the environmental part of the equation, again, a number of excellent presentations depicting the traditional approach to the environmental aspects, now, the good news here is that when I went and first took chemistry the number of elements were the simple four, earth, fire,

water and air and therefore we can summarize the approach to the environmental aspects that traditionally have been looked at.

We clearly have the water dimension, and we have looked at our drinking water and we have our air factors. We have looked at indoor air, outdoor air, particulate matter, particulate parts per million and their effects. We have looked at another aspect of air namely temperature extremes as it will influence an aging individual.

We have looked at the component of the earth. We have looked at the volatile organic compounds as they might be introduced. We have looked at the inorganic compounds or as I who nearly failed chemistry like to call them the heavy metals.

We have a variety of traditional ways of looking at the environmental stressors but I ask you to look at it from the point of view of where do these stressors come from during this traditional that gave evidence, that give rise to this traditional approach, basically from the secondary and for the sake of discussion say unintended by-product of the process of industrialized production of goods, okay?

And for my next slide, this is very similar to the slide that Dr. Donnelly put up probably comes from the same era. I regenerated this the other day because this is very similar to the pie graph that I put up on the wall in my office in about 1978. To the best of my knowledge I thought that Dorothy Rice and Jack Feldman had produced an article around that time looking at the attributable risk for disease burden in the United States and came up with these factors. I tried to contact Dorothy this past week. We did have several very nice conversations and she said that she wasn't the one who produced this but I told her everything that I thought was an excellent conceptual model from that era had to have stemmed from her. She thanked me for that and she said, "But this one wasn't it," but from the traditional point of view of public health 40 percent of the attributable risk for the disease burden in the United States and let us just say for the sake of discussion in the last quarter or so of the 20th century was attributable to life style factors. Okay, so this is a quiz, and it is relatively easy. So, where do you think public health focused the majority of its efforts in trying to enhance the health status of the population during the last quarter of

the 20th century? On the life style factors, smoking, diet and exercise. All right, now, I did note that Dr. Schwartz had pointed out that the increased risk of cardiovascular mortality attributable to 2.5 parts per million of a specific particulate matter and I didn't catch which one it was equal to the increased risk attributable to the by-product of sexual activity among older individuals. Now, from the public health point of view the individual is in much greater control of the environmental threat related to the sexual activity than they are to the environmental threat generated by the outdoor environment or the 2.5 parts per million.

So, if you are a traditional public health person you are going to go on the attributable risk and look where the control is. However, not everything is as simple as it seems. Public health was, also, the one, the discipline that expanded the outcomes from the simple mortality outcome, alive or dead or diseased or not diseased and did include other outcomes such as quality of life which indeed seemed to have complicated that particular discussion.

In addition let us look at the genetic component. What is the traditional approach here? Now, in public

health it was often captured by the expression in trying to understand the individual's risk of disease how well did you choose your parents. Okay? And that somewhat cynical statement implied a certain degree of fatalism to the acknowledged relatively large component of the attributable risk for disease burden but it indicated that there was very little that could be done which was probably accurate during the last quarter of the twentieth century. However, the tremendous advances in the last decade in genomic mapping have created a tremendous sense of optimism for specific gene therapeutic approaches to disease management that are likely to occur relatively soon and for the sake of discussion let us just say within a decade and so a component that was left relatively alone by public health was pursued vigorously by biologic researchers and geneticists and their achievements have been remarkable and will be translated very soon into the health of the public which leads us then to those other two, the environment and infectious disease vectors.

Now, I do want to say that remember that the traditional ones we have looked at are drinking water, indoor air, outdoor air, polluting particulate matter, most

of which are by-products of a process of industrialization, organic compounds, the heavy metals. I ask you to consider for a moment what is going to be the public health perspective on these issues during the 21st century? September 11, has changed the public health approach to these issues dramatically and we are talking about environmental factors and infectious vectors that don't fit the model that we lived with for quite a long while, namely that their role in the attributable risk for disease in the United States was a secondary by-product of some other action.

Now, there is the distinct possibility that these two components can be the primary by-product of actions of individuals. That changes the public health perspective on the interplay between the environment and older people dramatically. What is the new list of environmental agents and infectious vectors that we have to deal with? Dirty bomb particulate matters, they weren't on the research agenda in the last quarter of the 20th century. They have to be on the research agenda for the next interval. Others, anthrax, smallpox, plague, botulism, viral hemorrhagic fevers. I am not even going to try to pronounce that one

correctly. Once you blow it, go past.

These are the factors that the current students in public health are working on. This happens to be the introduction to a web site that one of our current students, a physician who is in our master's of public health program at the University of South Florida has prepared and she maps the categories of infectious disease, environmental threats and infectious vectors that she as a public health officer at a county level is going to have to deal with and it was very interesting. I went on her web site and I looked at certain things and I thought, oh, my goodness, we really do have to look at our history and understand where we have been but also look at our future and figure out where we are going to have to be.

Let us just take inhalation anthrax for a moment. The conventional wisdom is that the effective dose by aerosol is 8000 to 50,000 spores. Does anyone recall how many spores were estimated that the older woman in Connecticut might have been exposed to through her mail and from which she died of exposure to anthrax? Fewer than 100 and that is the example of the new environmental threat and its interplay on an aging population. That is an N of one

but also think for a moment how many other people were exposed to the same level of anthrax spores in her community in Connecticut and did not succumb because the dose was not sufficient to produce the outcome. I think that is what we are going to have to deal with and so then I just looked at the other column that this student prepared within the last several months, the persistence of the organism when we talk about the environmental exposure. For anthrax spores remain viable in soil for greater than 40 years, for plague for up to 1 year in soil, 9 months in live tissue, botulism for weeks in non-moving water and food, smallpox very stable, Q fever able to withstand heat and drying, persistent in environment for weeks to months.

We are going to be dealing with a different level of environmental threat to the health status of older individuals and I think that the last 25 years I am going to say but that is just my own, you know that is a personal perspective showed tremendous insight and excellent research on the interplay between the environment and health status of populations in the context of environmental threats that were the secondary by-product of the industrialization process.

We have got a layer, a new set of environmental threats on top of that as we consider the interplay between the environment and aging as we go into the 21st century and with that I think I will close and say that I contributed 5 extra minutes to the discussion and hope that this change in perspective will enable us to consider gratefully what we have done in our research but also allow us to consider how we are going to have to do things differently for the future. I would have liked that the new Department of Homeland Security would have been called domestic health and security because I think that is where the public health perspective lies.

We do things. We try to focus on three things, prevention, prevention and prevention, primary, secondary and tertiary but that is where our focus is and that is where it will need to be in this interplay between the environment and aging.

Thank you.

(Applause.)

DR. LANDSBERGIS: I would like to ask this afternoon's speakers to please come up to the stage for the final question and comment period.

Okay, the floor is open if anybody has any questions or comments.

DR. SCHWARTZ: I have some comments I would like to make on public health and there are a few things I would like to say. One is that it seems to me the concept makes no sense when you have interactions between genes and environment because the genetics contribution for example is either 0 or 100 percent depending on how you look at it. So, you can actually make those pie charts in an intelligent way but in any case it seems to me the real issue is what is the modifiable attributable risk because it is nice to say that you know we have got these life style factors and you make your little jokes and have people control their sexual activity but the fact of the matter is that we have made no progress despite a lot of effort in controlling obesity in this country, and that doesn't mean we should give up but it does mean we should notice that we have made no progress whereas putting scrubbers on coal-burning powerplants is something we have done before. We know how to do it and if we did it for all of those powerplants it would raise the price of electricity by 1 percent and the administrator of EPA could do that by issuing the regulation.

You don't have to change the behavior individually of 280 million people to do that. So, that is not going to have as big an impact as eliminating obesity but it might be a lot more achievable and therefore from the point of view of prevention, prevention, prevention that might be a lot easier prevention and the second point has to do with whether the future of the environment is really learning about bioterrorism and things like that and I think that the bad news is that there are people putting things into the air of American cities that will kill people and the good news is that we know who they are and the stuff they are putting in is mostly not anthrax. It is mostly other stuff and we do have better mechanisms for controlling them than we do the anthrax bomber and it is important to note that in 2001 more people died from air pollution in New York City than died in the World Trade Center and in 2002, about the same number died and there wasn't a second World Trade Center.

So, I think we have to remember that there are sudden catastrophic things that happen but the small number of excess deaths that occur every day all over tend to add up to a lot bigger numbers even in the years where you have

the World Trade Center.

DR. BRANCH: I don't disagree with virtually any of the points that you made, Dr. Schwartz. In fact, I would agree that -- the one I might disagree with was the conceptual utility of attributable risk as a way of partitioning effort but I agree with you completely that modifiable risk is where we want to be. I would just point out that I think a case could be made that 25 years ago we had the same information about the benefit to be gained by putting scrubbers in for example and as we do for the benefits of cessation of smoking and the former didn't happen and we did have a 10 percent reduction in the national smoking rate. We are still way too high. I mean I agree with you. I think we are both on the same page. We need to do everything at the same time and I was just trying to offer the argument of why people pick and choose when and where they do things but boy, I would be right behind you for the optimism that seems to exist right now on making a substantial move forward in environmental improvement based on legislative or executive action, right behind you.

DR. SPENCER: I would just like to make a parenthetical comment in regard to this discussion as it

pertains to agents that might be used in chemical and biological warfare. This country under international treaty is about to destroy its stockpiled chemical weapons which reside in I think seven sites in the continental United States.

At least three of those have populations of 30, 40 thousand residents within a stone's throw of these chemical warfare facilities.

The incineration which will be used as a method in most of the sites, the incinerators have been built and will begin activation soon, while it seems very likely that there is minimal risk to public health associated with the proper functioning of the incinerators given that the projected burn efficiency will be a minimum of 99.99 percent, there are very, very great concerns with regard to how you take these weaponized chemical agents out of the igloos where they have resided for the past 50 years and get them safely on transporters to go to the incineration sites. Why I wonder has public health paid absolutely no attention to the fact that tens of thousands of Americans shortly will be exposed to a measurable risk associated with the destruction of these extraordinarily potent chemical weapons on our

soil?

DR. WEGMAN: I have a different type I think of disagreement with the pie chart that I just want to mention. Then I have a question I think for Dr. De Serres but anybody who can think about it would help me. The problem I have with the pie chart is particularly around the area of environmental life styles as if those are so easily distinguishable. Life styles are not always so easily chosen as they are to some extent imposed upon people. One example that I have from a colleague of mine that used to be a steel worker was that when he worked in the shipyards as a non-smoker he never got a break but smoking breaks were allowed. It is a complex business and for us to simply say there is life style; that is for people to figure out how to control and there is environment; that is for the public health community to figure out how to control I think confuses an issue which is more complex and should be more complex.

With regard to the question I have for Dr. De Serres and it relates to sort of the perspective that Dr. Frost had earlier today, it is kind of you have seen this problem in a sense from the outside as a research investigator who was part of that earlier panel and now from

the inside is experiencing it as a disease that you found was remarkably under recognized in its total although rather remarkably recognized in its pieces around the literature and it strikes me that the problem that Dr. Frost called attention to was how we don't think outside of the box enough to try to figure out how to put pictures together that really let us know that problems exist and in fact we reject articles that don't meet our preconceived notions of what truth is.

The question I have with that long preamble is does your experience in trying to do this for Alpha-1 antitrypsin deficiency give you any insights as to how we should advise ourselves or the scientific community or us in our particular efforts with this report on the health and safety needs of older workers, is how to take advantage of the data that are out there and organized in ways that we are not familiar with organizing it to look at questions which we have chosen for one reason or another not to look at?

DR. DE SERRES: I asked a very simple question and basically opened a Pandora's box. I mean I had expected to move in, get some quick answers, you know and get back to my

retirement. Obviously I mean it is a puzzle with thousands of pieces and every single dimension, every single thing you think about you know creates a problem.

Like I said, blacks, you know, have this disease. Which blacks? If they come from Nigeria, if they come from Somalia, if they come from South Africa, if they come from Angola, yes. All other blacks, no.

So, blacks are not blacks. I mean blacks are from Nigeria. It is an extremely complicated, you know, series of questions that I have raised and one of the things that I, I mean I am on the Board of Directors of the Alpha-1 initially the Association and now the Foundation. On the Foundation you have a lot of pulmonary docs, okay? I am a PhD. They are MDs. They have a completely different kind of training. I am trained to do research. They are trained to treat patients and occasionally you will get an MD that also does research but you know the world of the physician is the world of his patients and you know I have never seen an MS that has a problem. I have never seen an MZ that has a problem. You know so these are issues that you have to deal with and as q geneticist I mean I could easily explain you know why an MZ in one population will be different from an MZ in another

population. It is because there are different modifiers and so it is an extremely complicated series of issues that are raised and the methods of resolving them are still not clear and I am sorry but I have just opened the door a little bit. It is just cracked open and I have got enough work to carry me and whoever I can enlist for my whole lifetime and I hope it is a long lifetime because I am fully enjoying this.

DR. SPENCER: But one of the key aspects of your presentation which I think is laudatory is that you took a global view of the problem. You did not consider exclusively that this was a problem restricted to the continental United States. You first of all as I understood it looked at the world-wide distribution of the disease.

So often I think we fail to do that in regard to the health conditions that affect us here. We consider that the rest of the world is perhaps of little relevance. So, I would say that that is one facet of the approach that we could use and gain from this very interesting presentation, that we should take a much broader view of human health not just American health, human health.

DR. DE SERRES: The other thing that drove me was you know, the standards of practice. There is an ATS ERS

document that is coming out right now and it will be published in the near future probably in Chest. It has got all the wrong numbers in it with regard to how many people have this disease. It has got all the wrong information with regard to which of the five phenotypes are susceptible to which diseases. They just haven't done a thorough enough job you know getting together the numbers or getting together the adverse health effects.

It is just something that I because of the background and training I have you go in with an open mind and you just try to put it all together and make a story out of it and that hasn't been done and one of the reasons I published an overview before I published all of the data was because of the impact on the standard of practice.

If a black person comes in your office and they present with allergies or asthma or COPD for God's sake test them for Alpha-1 because they may have a Nigerian background or Somalian and it is very important.

DR. ABERNETHY: If I could make a comment that is on a little different focus I didn't address issues of disposition and aging because the speaker after me was scheduled to do that but I think that those issues are

certainly part of an agenda that needs to go forward.

There has been a substantial literature developed and it was commented on earlier about declines in renal function with age and there is some literature with regard to biotransformations of agents which undergo oxidation with age.

I think that the literature is less informative with regard to the highly lipophilic substances that environmental toxicants frequently are, how distribution of these substances changes with age and how organ exposure may change during the aging process, that that may impact importantly on toxicity.

So, just to comment that this is an area that was expected to be addressed today. I think it is an important area that should remain on the agenda..

PARTICIPANT: My comment or question goes to Dr. De Serres. You said early on you understood the importance of having your facts in order and you came in again with worry about some information coming out that is not quite accurate.

Some of us have been worried for a long time that there seems to be almost no connect between having a lot of

facts about very diverse conditions in our country whether it is obesity or anything else and the will of people with the authority and the capacity to change some of the conditions that make that gap seemingly unbridgeable.

The question I would like to ask one or two members to discuss and maybe we can carry it over onto the dinner is being in charge of such profound and powerful and if you will irrefutable facts, with pie charts notwithstanding with that much information already in your hands where do you as a member of a civil society as more than the scientist, how do you go from having that kind of information to making certain that people, other people have that information and use it to bring about some real reduction in the threats that the elders of our society live with?

DR. DE SERRES; I can tell you about what I am doing. It is the reason I am on the Board of Directors of the Alpha-1 Foundation. One of the immediate objectives is physician education. How do we get doctors to realize this is not a rare disease? It is a disease not just of whites but you know of many racial subgroups.

You have got to somehow make presentations

unemotionally at the right kinds of meetings where you can reach people with the new facts that you know there are very large numbers of people in the United States at risk.

These are new numbers. I mean these are powerful numbers. They are numbers that have never been generated before. Nobody had ever heard of such numbers. We were using numbers like 100,000 based on how many people have cystic fibrosis. Well, it was just a guesstimate and you know in my position in the Office of the Director at NIEHS if Dave Rawl ever asked me to go prepare something for him with a guesstimate of 100,000 I mean he would boot me right out of his office and say, "Fred, get back in there and do more work."

You have to have solid numbers and now that we have got solid numbers the issue is what do we do with them. You have got to start with physician education I think and you have got to educate people to the fact that there are large numbers of people at risk for this particular disease, make them aware of the fact that at whatever age they are they are going to have you know decreased lung function, decreased liver function. So, they are not going to behave like normal people with regard to drugs you may prescribe,

with regard to environmental exposures, with regard to washing your hands, all kinds of stuff that you have got to educate.

So, I mean I am driven by trying to make people aware of the fact that there are large numbers of people who have this disease that have not been diagnosed not only in the United States but all over the world and I am determined to work with the board to try to develop mechanisms to deal with this effectively and to go to whatever agency you know exists in the government that has any kind of interest in this problem, to pharmaceutical companies that you know prescribe prolastin(?) I get every week and it has changed my life dramatically you know and try to get the money and the resources to do what needs to be done, and it takes somebody who is willing to spend the time that has the drive and you know is willing to make that commitment and that is how you make a difference.

You don't make a difference by just sitting around and talking about it. You have got to develop an action plan. It has to be a long-term plan and you just do it methodically one step at a time.

For example, I am working with standards because

there is a very high incidence of the S allele in Spain. I got them to form a Spanish consortium so they can all work together and collect funds together and they are currently planning to go into four different countries in South America as well as Puerto Rico to do tests on the general population No. 1, and then No. 2, COPD, asthma and I have forgotten what the third one is but you know to do targeted screening and detection.

I know from the kind of data that I have already collected that one out of four people in Puerto Rico because they are all of Spanish descent is at risk for Alpha-1 antitrypsin deficiency.

That is a phenomenally high number and in Puerto Rico you have a high incidence of asthma. So, you know you have got to try to get the big picture, tie it all together and then do something about it.

PARTICIPANT: I think another aspect of this, of how to get the word out is less to have people in authority and with command of facts intoning what we should do and actually do what is already under way as part of this or as what this initiative on aging is building on and it is what Governor Whitman hinted at this morning as volunteerism in

the senior community.

There are already as I heard about yesterday groups that get out in their own communities and talk to their peers and have access to their peers where public health officials would otherwise not be welcome but these community self-governed groups, self-motivated groups, groups that identify their own goals and therefore have greater longevity in their volunteers are actually making a difference already in going to groups and going into homes where elderly people live and identifying carbon monoxide risks and risks of volatile organics in the home that are already used, pesticide exposure.

Some of these groups are also actively working in water monitoring and looking at water quality issues in their community and making a big difference already.

So, part of this initiative and these public meetings that are coming up is to get the stakeholders involved, the senior communities themselves and I think when the senior communities themselves can talk to their peers I think that will get the word out for some of these life style changes that will affect environmental exposures in a way that perhaps health advisories from public health

officials would not.

I have another question if I can stand up for a second. Dr. Branch's discussion of outcomes, he mentioned mortality and quality of life. Well, quality of life made me think of my animal testing where we moved away from counting dead animals to looking at other functions, loss of sensory function, changes in behavioral function and in fact our EPA regulations consider precursors to adverse effects as adverse effects themselves.

So, my question is in these studies where we are looking at particulate matter and things like that where we see frank mortality increasing with levels of PM for example, how can we move to address end points that are less drastic than mortality because I think those will be important ones that we will have to consider in deciding where to draw these lines.

DR. THURSTON: I don't think that is directed at me but I think many of the things that we would have to do to prevent the mortality would be the same things to prevent the lesser impacts, larger in numbers I think often those things like work lost days, missed school days, lots of things that we, you know there are lots of effects out there

actually that we do not have studies of yet.

So, there are many actually adverse effects in that pyramid of effects that we don't even know yet from environmental insults like air pollution.

So, you know, I think when one does sort of a cost/benefit analysis we are always looking at the costs of clean up versus the benefits of reducing health effects. We are always underestimating the health benefits because we don't know all the health impact.

We haven't studied everything. We don't know, and so, anyway I am not sure that is exactly what you are asking but I think a lot of the measures to reduce the effects of the more severe outcomes will also reduce the less severe but more numerous health impacts.

You know just to pick up on, well, the question that was being asked earlier and what Joel was saying, we do have to look at the numbers and look at the risks in a realistic way. I think there is a tendency to react to things like, well, people are really afraid of plane crashes, but really they should be afraid of getting in a car and driving because that is where all the deaths are, but the press reports a plane crash and 100 people killed

and this is big news, and people are inordinately afraid of flying when they ought to be more afraid of driving, and where we look at our risks we have to look I think rationally at these risks and the ones, again, things that can be controlled. If we are looking at the model Phil Landrigan presented to us where they had a bill and they took action you have to look at the things that the government can actually do something about. They really can't govern our private behavior, and we wouldn't want them to.

Education, of course, we can do that, but what the government can do is actually regulate and do things like make cars safer and things like that.

So, I do think it is important. You know, as Joel was pointing out, we get sort of inured to things like air pollution. We are used to it, but it is causing tens of thousands of deaths every year and I have to agree with his comparison. I, personally, have a friend who died due to the attack in New York, but if you look at the numbers that risk is much lower as he points out than the definite risk of air pollution that we have every year, year after year after year and that every American risks.

So, we have to put these things in perspective when we look to where the government is going to spend its dollars.

I know I saw an article in some great publication like Time, but anyway they had an article on these dirty bombs that were mentioned, and they showed the cancer rate if one were to blow up right here in Washington on the Mall and the cancer risk that would be, and they had rings of cancer risks, and I looked at those risks, and I said, "Gee, that is about the cancer risk that every American has from air pollution over their life span." So, you know, you would have to have a lot of these dirty bombs going off which I do not want but to have the cumulative kind of effect because they are going to go off, if God forbid one happens, it is going to happen once here and maybe once there or something like that. We have air pollution every day, and we don't have any choice. It is not like water where you can carry around bottled water. No, you have got to breathe whatever air is out there and it is relentless every year.

So, I just sort of want to concur in his absence with some of the points that Dr. Schwartz was making about

putting some of these risks that we have in perspective and putting our dollars and our government efforts on the things that will give us the biggest payback and things we have the most control over and have the largest attributable risks are where we should be looking and not necessarily, you know, we have to look at these things rationally, not emotionally and I am afraid that in some cases that it is not the proper balance. Of course, we have to have national security but when we are talking about public health which is the way this was looked at, from a public health perspective the big payback is really in dealing with some of these pervasive ubiquitous challenges that we face in the environment, like air pollution.

DR. DE SERRES: Which brings us back to the basic issue of education, and I have been really coping with this problem now that I have opened this Pandora's box of what are the most effective ways of educating people when you have made a dramatic discovery that changes the whole frame of reference. Well, traditionally we scientists, we publish in our favored journals.

I mean I just told you that I published in Chest. I am proud to have a paper in a medical journal, but how

many people are going to read it? How many people read Chest? How many people who read Chest are going to read my article? Okay, so that is the overview. Hopefully they will read it and they will understand oh, this is a big problem. I didn't know anything about it, but you know how do you reach other people, you know? So, the follow-up papers I am publishing in as many different journals as I can figure out, Human Genetics, Clinical Genetics, Gene Geography, Respiratory Medicine and the list goes on. I have got to write about 12 or 15 papers and every one is going to go into a different journal, but how do I reach real people? How do I reach the kinds of people who make decisions in government? How do I reach the legislators? What kind of articles do I have to write? Where do I publish them, you know, so that there will be an awareness of the problem of all these people at risk, all the different things that they are at risk for and it is a really challenging issue, and I think that is the focus of the whole meeting here, you know, how do we create an awareness that the elderly population of the United States is at risk for Y, Y and Z and reach the right people? How do we do it? I think it is a really challenging problem, and I think we have got to talk some

more about it. I need help.

DR. WEGMAN: I think that is a great note to finish our discussion today although the discussion I am certain will continue over dinner.

The speakers have been invited to attend a dinner that is being sponsored as part of this event, and I would like to ask all of you to check with Jessica at the table at the rear as you leave just to confirm your attendance if you are planning to join the group for dinner tonight.

Again, thank you, all the speakers for the participation today. It has been very informative. I think each of us is taking away different lessons. Hopefully they will stimulate thoughts that hadn't occurred to us before we came today and stimulate some of the conversation that will go on tomorrow as we continue this workshop and continue exploring the ways in which we can examine the differential susceptibility of older people to environmental toxic materials.

Thank you very much.

(Applause.)

(Thereupon, at 5:25 p.m., a recess was taken until 8:30 a.m., the following day, Friday, December 6, 2002.)