OAK RIDGE RESERVATION HEALTH EFFECTS SUBCOMMITTEE

CENTERS FOR DISEASE CONTROL AND PREVENTION AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

Detailed Proceedings of the December 3, 2002 Subcommittee meeting

Orientation for New ORRHES Subcommittee Members 10:00 to 11:30 AM

ATSDR conducted a special session for the benefit of new members of the ORRHES, prior to the start of the December 3, 2002 ORRHES meeting. This special session is intended to help new Subcommittee members learn what has been accomplished by the ORRHES and the status of the ATSDR PHA process.

The attendees present at this time were:

La Freta Dalton, DFO, ATSDR
Bob Craig, ORRHES member
James Lewis, ORRHES member
Donna Mosby, ORRHES member
Peggy Adkins, ORRHES member
Anthony Malinauskas, ORRHES member
George Gartseff, ORRHES member
Don Box, ORRHES member
Jerry Pereira, ATSDR
Sandy Isaacs, ATSDR
Burt Cooper, ATSDR
Paul Charp, ATSDR
Jack Hanley, ATSDR
Tim Joseph, Oak Ridge Office, Department of Energy (DOE)
Theresa Nesmith, ATSDR
Lorine Spencer, ATSDR
Yahya Muhammad, ERG
The recorders are Ken Ladrach and Amylane Duncan, Auxier & Associates, Inc.
The meeting was called to order at approximately 10:20 am.

Welcome and Introductions

La Freta Dalton welcomed everyone on behalf of Kowetha Davidson, Chair of ORRHES, and ATSDR. Representatives from ATSDR and some of the ORRHES Workgroup chairpersons were present to discuss and answer questions on ongoing public health activities concerning the Oak Ridge Reservation site. Jerry Pereira is the site project manager. Sandy Isaacs is the chief of federal facilities branch. Burt Cooper is the chief of energy section B of the federal facilities branch. Jack Hanley is the site team leader. Lorine Spencer is the community involvement representative. Yahya Muhammad is a member of the support team. Paul Charp is the health physicist on staff.
Bob Craig is representing the PHA Workgroup. James Lewis and Donna Mosby are co-chairs of the Health Needs Assessment Workgroup. James Lewis is chair of the Communications and Outreach Workgroup.

Barbara Sonnenburg is the chair of the Agenda Workgroup. Karen Galloway is chair of Guidelines and Procedures Workgroup who were unable to attend, however information was provided by La Freta Dalton.

Overview of ATSDR Public Health Activities and the Establishment of ORRHES

ORRHES is chartered under the Citizens Advisory Committee and Public Health Service Activities and Research at the Department of Energy (DOE) sites. Note that ORRHES is one of several Subcommittees that are under CDC and ATSDR. Of the initial Subcommittees that were chartered there are: ORRHES, Fernald (completed), INEL, Savannah River Plant, Hanford, and NTS.

ORRHES was established to improve coordination of public health activities associated with the Oak Ridge site and improve communications with the communities.

The role of the Subcommittee in the charter is to provide advice and recommendations to the director of CDC, and the administrator of ATSDR on public health activities and research at the DOE site.

James Lewis asked the difference between ORRHES and the SSAB (Site Specific Advisory Board). Jerry Pereira explained that these groups have different focus. Jack Hanley added that the primary focus of the SSAB is waste management and other Superfund activities.

La Freta Dalton highlighted a flowchart showing the sharing of information in the ATSDR process. (E.g. ORRHES provides recommendation to ATSDR and ATSDR provides ORRHES information about the site.) La Freta Dalton highlighted a timeline, beginning in 1990, of all of the activities that CDC and ATSDR have been involved in. ORRHES was established in the year 2000. The terms of the current Subcommittee members end in December 2004.

James Lewis asked for an explanation about the selection of ORRHES members and the diversity of the Subcommittee. La Freta Dalton referred to the bylaws of the Subcommittee, which discuss membership. The objective is to have a balanced representation of the community in terms of gender, expertise and ethnicity. Jack Hanley also referred to Appendix A of the bylaws, which explains the process of obtaining members. Initial member solicitation activities took place in 3 individual Public Health Work Group meetings in Oak Ridge. The attendees at the first meeting determined that a public forum was needed. The second meeting considered options of setting up a form (e.g.. FACA, etc.). The third meeting involved small group discussions about member criteria. The outcome of these 3 meetings was used to develop the Subcommittee.

James Lewis added that the Subcommittee subsequently decided to involve a member that was an ill worker. La Freta Dalton commented that there is not a physician representative, and that it is difficult to retain persons of that expertise. At the beginning

of the year when the budget has been solidly determined they will look further into filling that position. Jerry Pereira emphasized that a physician or any representative on the Subcommittee must contribute to the group. There is a level of expectation to participate and involve themselves in the actions of the Subcommittee. The criteria for involvement must not be overlooked. James Lewis commented that many valuable members have been lost, which has hurt the group. Jerry Pereira stated that goals and milestones must be met. If there are diversions the added time to meet goals must be justified.

James Lewis commented that, to the credit of CDC, a lot of efforts in the local community has been expended, by CDC (and EPA) to examine health concerns (e.g. in children in the Scarboro community) of members of the local community. However, sadly, at the end of these efforts few members of the public appeared at public meetings to show an interest in the results of those efforts. CDC has responded well in the past to the health needs of the community.

Discussion with ORRHES Work Groups – Activities and Accomplishments

There are 5 Work Groups.

Agenda Work Group
Chaired by Barbara Sonnenburg. The Agenda Work Group is tasked with developing ORRHES meeting agenda. Many of the agenda items are pulled from work group discussions.

Guidelines and Procedures Work Group
Chaired by Karen Galloway. Guidelines and Procedures Work Group is tasked with reviewing by-laws and making adjustments that facilitate the business process of ORRHES. They also developed the mission statement, goal, and objectives of ORRHES.

Communications and Outreach Work Group
Chaired by James Lewis. The Communications and Outreach Work Group handles issues of community involvement and outreach to the local communities as they relate to the ATSDR PHA process.

James Lewis highlighted the establishment of the ATSDR field office, which is a considerable accomplishment for the community. In addition, the work groups are a form of outreach to the community as are the Subcommittee members as individual members of the community.

However, the Subcommittee needs to do a better job of communicating with the community. James Lewis also highlighted the need to continue to pursue capturing community concerns raised by the public, continuing to improve the ORRHES web site and getting meeting/event schedules on the web site in a more timely manner. James Lewis encouraged Subcommittee members to act individually to get into the community and give presentations about the PHA, and to try to view and present the PHA process

from a layperson's point of view. There is a need for more effective communications about the PHA so that in the future there is less need to explain past efforts.

Bob Craig commented that the communication and outreach efforts have been good, and asked how it could be improved. James Lewis responded that measuring effectiveness is necessary. Output of information alone is not adequate, steps must be taken to ensure that the public becomes actively involved. Information must be taken out into the community. Conversely, Bob Craig noted that there is a lack of interest in the community rather than poor communication. Jerry Pereira added that Lorine Spencer of ATSDR will become heavily involved in community involvement issues in Oak Ridge. Methods are available that can be used to increase community involvement. ex. Explaining one topic in order to enable people to focus on one set of information. La Freta Dalton added that work groups have had some discussions about how to develop more proactive community involvement and that Subcommittee members will have to become more involved, with ATSDR, in those ongoing efforts.

Peggy Adkins commented that communication is a two-way process, the receiver must be listening. There is perhaps too much mistrust of the agency process in the minds of the public. A first step to better communication would be to re-build trust.

Health Education Needs Assessment Work Group

Chaired by Donna Mosby and James Lewis. Oversees the Needs Assessment portion of the PHA process and brings related reports and recommendations to the Subcommittee.

Theresa Nesmith presented a fact sheet on the AOEC clinics, other handouts summarizing the Needs Assessment, and a table about qualitative versus quantitative needs assessment research. Theresa Nesmith highlighted the Needs Assessment process, what it is, why it is performed, what kind of information needs to be circulated, and how is it best circulated. George Washington University was chosen to implement the Needs Assessment. The lead on the Needs Assessment is Rebecca Parkin of George Washington University. Theresa Nesmith detailed the steps of the Needs Assessment process, the status of each step in the process, and activities underway/planned to finish the process. The Needs Assessment is currently in step 6, focus group implementation. These focus groups should occur in January 2003. The Needs Assessment report is scheduled to be in draft in the spring of 2003 and will be a qualitative research work product.

Public Health Assessment Work Group

Chaired by Bob Craig. The Public Health Assessment Work Group provides in-depth analysis of information and data related to the PHA and provides advice and recommendations to the Subcommittee about what ought to be recommended to ATSDR.

James Lewis distributed a list of key individual Subcommittee members that have been involved in various work tasks.

New ORRHES Member Comment/Issues

Jack Hanley presented a handout "Topics and Issues for the ORRHES Orientation Meeting", and discussed 15-20 items/issues raised by the new members in the handout.

1. Clear statement of ORRHES mission
2. Accomplishments
3. What is to be accomplished/scope of the PHA
4. What is the focus of Needs Assessment Work Groups
5. Timeline of ORRHES evolution and progress
6. Original and total funding for ORRHES
7. Community's principle ORR-related health concerns
8. 1998 Dose Reconstruction Report for Oak Ridge - release estimates
9. ORRHES areas of concern and health issues not in the ORRHES charter
10. Balancing the weight of stakeholders/selection of Subcommittee members
11. Policies regarding examination of toxic releases
12. Trust in AOEC clinics
13. Why does CDC refer ill persons to AOEC clinics
14. Needs of sick workers facing reluctant doctors/clinics
15. Limited resources of ill persons
16. What pressures are keeping people silent
17. Why doesn't CDC dig into Oak ridge issues as it does other hazards

Wrap up

A copy of the binder of information provided to new Subcommittee members for the orientation meeting will be kept in the ATSDR field office as a source of information documenting the work performed under the Subcommittee.

The new member orientation meeting ended at 11:50 AM.

Call to Order/ Opening Remarks

The Oak Ridge Reservation Health Effects Subcommittee (ORRHES) convened on December 3, 2002 at the YWCA at 1660 Oak Ridge Turnpike, Oak Ridge, Tennessee. Chairperson Kowetha Davidson called the meeting to order at 12:30 PM, welcoming all attendees.

Introduction of Subcommittee Members

Kowetha Davidson asked the attendees to introduce themselves. The attendees present at this time were:

Kowetha Davidson, Chairperson, ORRHES
La Freta Dalton, DFO, ATSDR
Chudi Nwangwa, Tennessee Department of Environment and Conservation
Jeff Crane, Environmental Protection Agency (EPA)
Bob Craig, ORRHES member
James Lewis, ORRHES member
Don Creasia, ORRHES member
LC Manley, ORRHES member
Jeff Hill, ORRHES member
Barbara Sonnenburg, ORRHES member
Donna Mosby, ORRHES member
Charles Washington, ORRHES member
Peggy Adkins, ORRHES member
Anthony Malinauskas, ORRHES member
George Gartseff, ORRHES member
Don Box, ORRHES member
Herman Cember, ORRHES member
Jerry Pereira, ATSDR
Sandy Isaacs, ATSDR
Burt Cooper, ATSDR
Paul Charp, ATSDR
Jack Hanley, ATSDR
Bill Murray, ATSDR
Elizabeth Howze, ATSDR
Lorine Spencer, ATSDR
Jean Shaakir-Ali

Tim Joseph, Oak Ridge Office, Department of Energy (DOE)
The recorders are Ken Ladrach and Amylane Duncan, Auxier & Associates, Inc.

Agenda Review, Correspondence, and Announcements

Agenda Review
Kowetha Davidson reviewed highlights of the agenda dated November 19, 2002. At 1:45 PM is the presentation on thyroid disorders by Dr. Jerome Hershman of UCLA Medical School. The public comment period is at 3:45 PM. Work group recommendations session is at 4:15 PM. Jeff Crane will present an update on the status of the EPA Scarboro soil-sampling project.

Correspondence
No correspondence has been received since the October 22, 2002 ORRHES meeting.

Announcements
Bill Murray has coordinated an optional tour for the new members of the Subcommittee on December 4, 2002. Members need to meet at the Oak Ridge ATSDR field office at 8:30 AM. The tour will be by van. The tour will visit ETTP, Y-12, ORNL, Scarboro, and other areas of interest to the Subcommittee members. The tour will last for 3 to 3.5 hours.

La Freta Dalton reminded Subcommittee members that there is an annual requirement for Subcommittee members to complete the financial disclosure reports (form 450). If the information is not received and processed Subcommittee members cannot vote during a meeting.

Approval of October 22, 2002 ORRHES Meeting Minutes

A motion to approve the minutes of the October 22, 2002 ORRHES meeting was received and seconded. The minutes of the October 22, 2002 ORRHES meeting were approved by voice vote with none opposed.

Status of Action items – list provided

The list of action items and recommendations was reviewed by the Subcommittee. La Freta Dalton highlighted that the action items concerning the ORRHES web site from the August 27, 2002 ORRHES meeting have been completed.

ORR Project Update

Jerry Pereira reported that Lorine Spencer will be working, primarily, with the Communications and Outreach Work Group on Oak Ridge activities, as a senior health communications specialist (approximately 50% of her time). Lorine Spencer will be working only on community involvement (CI) activities in order to develop fact sheets and perhaps onsite availability sessions to present specific information about the PHA to members of the community.

The administrative assistant for the field office in Oak Ridge, Gayla Cutler, will unfortunately will be leaving within the next couple of weeks for personal reasons. She expressed concerns about the work hours and being out at night during winter months. Jerry Pereira will find out the next step in the process of trying to obtain a replacement person.

Jerry Pereira presented the Subcommittee with ATSDR's ORR PHA Project Management Plan Overview, the project Gantt chart, and contaminants of concern sheet. The Gantt chart covers the entire PHA process, with the last item, the executive summary, scheduled for completion in the second quarter of 2005. All PHA activities are scheduled for completion by fourth quarter 2004. The Gantt chart detail shows that the focused PHA for Y-12 uranium releases has been accelerated in the schedule. The Gantt chart symbols show percentage of completion for each individual work task. Sandy Isaacs took the time to assemble and construct the Gantt chart in all of its detail. Subcommittee member comments on the Gantt chart should be submitted to ATSDR at any time and concerns should not be delayed until the next Subcommittee meeting. Examination of the Gantt chart reveals that many tasks will occur simultaneously, and it will require major effort from ORRHES and ATSDR staff in order to maintain and complete the schedule as indicated. Jerry Pereira will have to justify causes to ATSDR management if schedule slippage occur.

James Lewis asked for indication on the Gantt chart of where ORRHES needs to concentrate its effort. Jerry Pereira responded that the Gantt chart schedule lists, for example, PHA Work Group actions which would be an ORRHES action item. Kowetha

Davidson added that any PHA Work Group work items listed on the schedule will be examples of actions that will be brought to the Subcommittee.

George Gartseff asked to what extent the Gantt chart schedule reflects the Subcommittee's meeting schedule. The concern would be that ORRHES meeting schedule might be a cause for a schedule delay. Jerry Pereira replied that if a potential for a schedule delay appears ATSDR and the work groups will need to work together to adjust meeting schedules to accomplish the required deliverables.

James Lewis commented that a plan needs to be developed within ORRHES to understand what has to be accomplished by ORRHES by what time point. Bob Craig commented that the schedule software can easily produce a resource report for an individual group, such as PHA Work Group, that will assist with keeping up on the schedule.

Sandy Isaacs commented that the schedule includes two built-in PHA Work Group meetings for every focused public health assessment. There is a printout of the PHA Work Group resource report that can be given to the Subcommittee.

Kowetha Davidson added that there may be some occasions when additional PHA Work Group meetings may need to be added.

Jerry Pereira announced that Dr. Elizabeth Howze of ATSDR (Division Director of the Division of Health Education and Promotion) is in attendance at the meeting.

Presentation on the Status of the EPA Soil Sampling Effort in the Scarboro Community

Jeff Crane of EPA Region IV (substituting for Elmer Akin) presented the Draft Sampling Report for the Scarboro Community. Connie Jones is the EPA project manager for the Scarboro project.

Project Background:

- Oak Ridge NAACP requested EPA to conduct sampling in Scarboro
- DOE is defined as "lead agency" for conducting Comprehensive Environmental Response Compensation and Liabilities Act (CERCLA) investigations.
- CERCLA investigations can include "off the Oak Ridge Reservation" environmental activities
- In September 1998 DOE presented a report on its Scarboro Community Project, which primarily addressed radionuclide contaminants.
- Additional concerns of EPA recognized that other potential contaminants had not been addressed. Work plan developed in 1999, sampling conducted in 2001.

Project Activities:

- EPA draft report posted for public review and comment in September 24, 2002. www.epa.gov/region4/waste/fedfac
- EPA held 2 public availability sessions in November 2002.
- Final report will be available in late January 2003.

EPA Analytical Conclusions:

- There were no site-related radionuclides that exceeded both the PRGs (preliminary remediation goals) and their background levels in the samples or the walkover survey
- Exceedance of the PRGs without comparing to background would lead to false assumptions that the levels are excessive or site-related
- Some chemicals had high detection limits or slightly exceeded PRGs, but none are known to be site-related
- EPAs analysis identified no date above regulatory health level of concern
- Project results compare similarly with Department of Energy's results (no significant differences were noted)

General Website Addresses:

EPA's home web site: www.epa.gov

Radionuclide PRGs: www.epa-prgs.ornl.gov/radionuclides/

Chemical PRGs: www.epa.gov/region09/waste/sfund/prg/index.htm

Summary:

Based on EPA's analysis of the data:

- EPA findings are consistent with DOE conclusions
- There are no elevated chemicals, metals, or radionuclides above a regulatory health level of concern
- Scarboro residents are not currently exposed to substances that warrant an EPA response for more sampling
- Scarboro is safe for residents

Path Forward:

- Final EPA report scheduled for issuance in January 2003
- Future off-site evaluations (Oak Ridge-wide) will be coordinated with the ATSDR PHA report:
  - Should address ORR Health Effect Subcommittee recommendations to Agency for Toxic Substances and Disease Registry (ATSDR)
  - ATSDR is the principle federal public health agency with responsibility to evaluate human health effects

- After ATSDR PHA report is issued, DOE, TDEC, and EPA will scope offsite assessment activities with stakeholder involvement

Herman Cember asked, concerning the draft EPA Scarboro soil sampling report, whether the uranium MCL in drinking water (30 micrograms/L)listed in the report refers to natural uranium. Jeff Crane responded that his understanding was that the MCL represents total uranium (all isotopes).

LC Manley asked what additional contaminants did EPA sample and analyze for that the DOE effort did not include. Jeff Crane responded that additional analyses included organic compounds and metals.

James Lewis asked what specific additional compounds were analyzed and why EPA was prompted to perform those additional analyses. Jeff Crane responded that the EPA preferred to include a more complete list of analytes simply because the DOE effort focused primarily on radionuclides.

Bob Craig commented that the uranium data appear to have the same distribution as uranium in background soil samples, suggesting that no uranium got to the community from the nearby Y-12 plant. Jeff Crane agreed that this is the conclusion of the EPA sampling effort.

Work Group Sessions

AGENDA WORK GROUP PRESENTATION

Barbara Sonnenburg reported that future subjects for discussion before the Subcommittee should be presented to the Agenda Work Group before future ORRHES meetings.

GUIDELINES AND PROCEDURES WORK GROUP

Karen Galloway was not present. Kowetha Davidson noted that the Subcommittee had not given any tasks to the Guidelines and Procedures Work Group.

HEALTH EDUCATION NEEDS ASSESSMENT WORK GROUP

Donna Mosby reported that Theresa Nesmith would present update information regarding the focus groups of the Needs Assessment. Donna Mosby reported that the work group itself had not met since the last ORRHES meeting.

Theresa Nesmith reported on the identities of the categories for the focus groups of the Needs Assessment. A copy of an e-mail concerning the input compiled from the work group on categories of focus groups was distributed. The e-mail discusses the reasons for choosing the focus group categories. Information was taken from the phone surveys, key resource interviews, and information from the work group. The data collected did not support inclusion of some of the focus group categories originally proposed by the work group. However, the categories selected will likely capture the persons who would have been in those categories. The titles for the focus groups are vague, due to confidentiality concerns, but should answer Subcommittee questions. The focus groups are due to be held in January. The categories of focus groups are:

- Midlife women
- Long-term elderly residents
- People who have respiratory diseases
- People who have cancer
- People who have heart disease
- Ill workers (people who have worked or who are working at ORR)
- And 3 general resident groups (distinctly different groups based on the study evidence)

Theresa Nesmith pointed out that a Needs Assessment is performed at all DOE and DOD facilities addressed by an ATSDR PHA process. Needs Assessment reports are available for each of those sites.

Barbara Sonnenberg asked why the focus group labels cannot be given more specifically. Theresa Nesmith stated that the categories are generalized in order to allow as many people as possible to take part in the focus groups and avoid biasing the membership in the categories too narrowly.

Don Creasia asked whether the ill worker category and the respiratory disease category were redundant. Theresa Nesmith explained that, while there could be overlap, the screening process will distinguish between ill workers and other people who have respiratory diseases.

Peggy Adkins asked for clarification on the 3 general resident focus groups. Theresa Nesmith responded that the screening process helps enable persons with certain health concerns to be placed into a specific focus group. Peggy Adkins requested that persons with neurological autoimmune diseases, endocrine disorders, fibromyalgia, multiple sclerosis, and lupus be specifically included in a focus group(s). Theresa Nesmith responded that people with those illnesses may be captured within the existing focus groups but she does not know if that is true.

Kowetha Davidson asked if everyone who calls in to be included in a focus group will indeed be put in a focus group. Theresa Nesmith responded that the only way a person will be turned away and not included in any focus group is if all the focus groups are full. The likelihood that the focus groups will be full and volunteers will have to be turned away is low.

Herman Cember asked how a person with multiple health concerns would be selected for one focus group rather than another. The concern being creation of confounding factors in the statistical analysis of the data when persons could be placed in more than one category. Theresa Nesmith replied that even though a person may qualify for more than one group they would only participate in one focus group.

Tony Malinauskas inquired how solicitations would cover a large geographic area, such as Roane County, if advertisements were limited to the Oak Ridger. Theresa Nesmith stated that the Roane County News was used to carry advertisements as well, and other resources, such as college students handing out fliers, were used. The suggestions of the work group to solve this issue were very helpful.

James Lewis requested that the Subcommittee be given an example report of a Needs Assessment that has been completed for a site. James Lewis asked about the definition of the term "priority health issues" in the Needs Assessment Project Summary dated March 19, 2001, where is the list of priority health issues, will it be presented, and will it be incorporated into the PHA community concerns database. Theresa Nesmith stated that this kind of information was currently being collected, that is exactly one of the reasons for performing the Needs Assessment. James Lewis also asked if assistance could be provided for effectively communicating in the community the information collected and put in the final Needs Assessment report. Can the information be sequenced in order for the Subcommittee to know what communication approach to take with the community, to reach people.

Don Box asked if persons with cancers in remission are disqualified them from participating in a focus group (i.e., because their cancer may be in the past or "cured"). Theresa Nesmith replied that there would be no such disqualification.

COMMUNICATIONS AND OUTREACH WORK GROUP

James Lewis reported that he has had discussions with Lorine Spencer about potential community involvement plans, and asked that Lorine Spencer introduce herself to the Subcommittee. James Lewis repeated his request that Theresa Nesmith provide a copy of a Needs Assessment report prepared for another site for the Subcommittee to review.

Lorine Spencer introduced herself and stated that she has assembled ideas for community involvement activities based on the ATSDR PHA project plan. Lorine Spencer encouraged suggestions for community involvement activities that would involve the

community in the ORR area. The goal is to make the effort to involve as may people as possible, so that members of the local community feel that they are part of the process.

Kowetha Davidson asked that the Communications and Outreach Work Group work closely with Lorine Spencer to develop specific strategies for the ideas for enhancing community involvement. Perhaps a presentation of strategies could be made at the next ORRHES meeting.

Bob Craig recalled that at the last ORRHES meeting there was agreement that Kathy Daniels of the Oak Ridger would be invited to meet with ORRHES, re-establish the Subcommittee's relationship with the Oak Ridger. James Lewis has met with Kathy Daniels previously and will talk with her again.

La Freta Dalton noted that the existing communication strategy should be revisited in light of the new project plan that is available at this time.

PUBLIC HEALTH ASSESSMENT WORK GROUP

Bob Craig reported that good working meetings have taken place recently and the PHA Work Group is identifying the data they would propose request from the State of Tennessee cancer registry. The work group will likely have a recommendation for the Subcommittee at the next ORRHES meeting on that issue.

Jerry Pereira took a moment to distribute to the Subcommittee a printed resource report from the scheduling software (for the PHA Work Group), listing who is responsible for what task completions and when.

Presentation and Discussion: Thyroid Disorders – Nodular Diseases and Cancer

Presentation by Dr. Jerome Hershman, M.D., M.S., Associate Chief, Endocrinology and Diabetes, West Los Angeles Veterans Administration Medical Center. Dr. Hershman is here to make his presentation because issues of thyroid disease and I-131 exposures are significant issues to the Subcommittee.

Outline of Material:

- Thyroid Physiology – Background on How Thyroid Works
- Thyroid Function Tests - How Thyroid Is Evaluated
- Hypothyroidism - Underactive Thyroid Gland
- Hyperthyroidism - Overactive Thyroid Gland

- Thyroid Nodules - Common Condition That Can Result from Radiation Exposure to Thyroid
- Thyroid Cancer

Thyroid Physiology – Background on How Thyroid Works:

The thyroid lies in front of the neck and trachea, and weighs about 15-20 grams in a normal adult. It is composed of units called follicles, balls of cells. The colloid - center of follicles is filled with a storage protein (colliglobulin). The thyroid secretes thyroxine (T4), & triiodothyronine (T3) that exert effects on peripheral tissues exerting the actions of thyroid hormone. The pituitary gland produces thyroid stimulating hormone (TSH) that goes into the blood stream to activate thyroid cells, which then secrete T3 and T4 into the peripheral tissues. The hypothalamus secretes a small peptide called Thyroid Releasing Hormone.

The thyroid hormone exerts negative feedback on cells that produce TSH, causing them to shut down production. The pituitary senses there is too much hormone production and is shut off. When it senses not enough thyroid hormone circulating it produces more TSH.

T4 has four atoms of iodine on phenol rings. It is metabolized so one iodine atom is removed to produce T3 – about 10 times as active as T4 in binding to a receptor that exerts the action as receptor to the thyroid hormone. If taken by mouth T3 is 3 to 4 times as active as T4. When T4 is converted to T3 it produces the more active thyroid hormone and activates the pathway.

T4 can be deiodinated to lose an atom of iodine of the inner ring to produce reverse-T3, which has no metabolic activity. It is an inactivating pathway. On a portion of thyroid cell facing the blood stream there is a protein called sodium iodine symporter that transports iodine into the thyroid cell. It is a very active transport due to the need to produce thyroid hormone. The iodine is what the cells need to make the thyroid hormone.

In the normal U.S. diet, iodine intake is about 250 micrograms or ¼ milligram (mg) of iodine per day, which goes into the thyroid cells and is incorporated into amino acids called tyrosine (in a large thyroglobulin molecule). Two amino acids combine to form T4 and T3 production. The thyroid gland secretes about 8 micrograms of T3/day, but 40 micrograms of T3 is made overall. The additional 32 micrograms is the result of T4 to T3 conversion by the deiodinase enzyme, located in almost all tissues of the body, mainly the liver. The iodine on those hormones is removed as urinary iodine. The iodine intake per day is used to study deficiencies by urine iodine measurement.

The iodine hormone exerts its action on receptors on the nucleus in cells. T3 binds to the nuclear receptor (TR) and combines with another receptor (RXR) then combines with a receptor element on DNA. It binds on the DNA, exerting an effect on DNA to regulate

the synthesis of proteins regulated by DNA. The action of thyroid hormone is on the nucleus, which is true for a lot of hormones.

Actions of Thyroid Hormone:

- Regulates growth and development
- Regulates energy metabolism, fat metabolism, protein synthesis
- Regulates cholesterol uptake
- Affects function of brain, heart, muscles, liver, bones, and other organs

The action of hormones are transduced by regulating the synthesis of proteins (5% of proteins in the body are regulated by thyroid hormone). The actual number is unknown. These proteins regulate growth and development. With no thyroid hormone an infant becomes a cretin, having poor intellectual development, and is short. Underactive thyroids are hopefully diagnosed at birth. The thyroid hormone regulates energy and fat metabolism and protein synthesis by regulating different enzymes that are involved in those processes. It regulates the serum cholesterol level by influencing the level of cholesterol uptake into cells. It regulates the receptor for cholesterol, takes it out of the blood stream and puts it into the cells. It is not the only thing that does that.

<u>Thyroid Function Tests - How Thyroid Is Evaluated</u>:

- TSH
- FREE T4 (or FREE T4 INDEX)
- T3 or FREE T3
- Thyroid Radioiodine Uptake –This test is no longer performed. A trace amount of radioactive iodine is given, now I-123 is used, and measured in 24 hours. Patients with hyperthyroidism have a high level of radioactive iodine uptake. Patients with hypothyroidism have a low level of radioiodine uptake.

Herman Cember asked when an uptake study is done, what is the order of magnitude of the radiation doses to the thyroid for a person who is hypothyroid or euthyroid?
Dr. Hershman responded that in years past I-131 was used in larger doses for uptakes of 25-50 microcuries (microCi). The radiation dose to the thyroid was several rads to 100 rads. Now I-123 is used. An uptake could be done with 1 microCi of I-123. Now I-123 is used and the radiation to the thyroid is negligible, far less than 1 rad.

Examples of thyroid scans shown:

- normal thyroid,
- overactive thyroid,
- nodule of thyroid that takes up all of the radioiodine,
- right lower part of thyroid that does not take up any of the radioiodine.

Thyroid function tests commonly used are the measurement of serum TSH, measurement of thyroid hormone in the blood (99.97% of the T4 is bound to proteins, plasma proteins). The unbound fraction is what enters cells and transduces the action of thyroid hormone. That is only 0.02 to 0.03%. That can be measured now by sensitive techniques called the Free T4. The total T3 concentration is measured, the Free T3 and radioiodine uptake are very seldom used.

Graph of TSH versus Free T4 relationship shown:
It takes a long time for equilibration in the pituitary gland from oral daily doses of TSH as reflected by the serum TSH dose that the patient is getting. There are a lot of people who have a normal TSH who are on doses of thyroxine, and then when thy are followed their TSH goes up. It could be, of course, that the patient is forgetful, and doesn't take their medicine; noncompliance. Or years ago there were ineffective generic preparations. Now, the FDA has made the requirements for making thyroid hormone and selling it very stringent, so that only big, substantial companies can make it. So, the small, generic companies may have been driven out of business who may have made ineffective preparations.

There are a number of drugs which will bind thyroxine and prevent it's absorption And it turns out that calcium carbonate, which a lot of people take to avoid osteoporosis, a lot of women take that, prevents thyroxine from being absorbed if they are taken together. If you separate them it is probably okay. Iron, ferrous sulfate, will do that too. Some medicines for ulcer conditions, sucralfate, or just aluminum hydroxide will do that also. Resins for treating hypocholesterolemia that aren't used much will do that. There are some drugs, which will increase the metabolism, and, if a person taking thyroxine then goes on Dilantion for a seizure disorder the need for thyroxine increases. It turns out those women who might have hypothyroidism and are on thyroxine, and everything is just right, then take estrogen, and the need for thyroxine increases. Hashimoto's disease, which is the most common cause of hypothyroidism, is progressive, so the thyroid is progressively wiped out and the requirement for thyroxine can go up. That means that the patient has to have measurement of the TSH, and the effect of the thyroid hormone, on probably an annual basis. Even people who have had Hashimoto's disease for a long time.

Herman Cember asked once there has been a great reduction in hormone replacement therapy what effect is it having on the thyroid. Dr. Hershman responded that it would make the dose a little on the high side. The woman would need to be retitrated in a sense if she goes off estrogen and was taking thyroxine with it.

<u>Hypothyroidism - Underactive Thyroid Gland:</u>

Referring to the graph of TSH versus Free T4:
The X-axis shows the Free T4 (thyroxine) and the Y-axis shows the TSH, on a log scale. The rectangle in this plot encloses the normal values for the T4 and TSH.

A small change in the Free T4 will result in a bigger change in TSH because TSH is on a log scale.

There are different disorders defined on the plot as well. The elevated TSH and low Free T4 defines hypothyroidism. Not enough circulating thyroid hormone in the blood causes the pituitary to send lots of TSH to the thyroid. If the Free thyroxin is high and TSH is low on a log scale it is hyperthyroidism. There are also 2 variations of the thyroid dysfunction. There are patients who have a normal free thyroxin with elevated TSH. It is very common. It is called mild or subclinical hypothyroidism. It means that patients usually do not have clinical features of hypothyroidism.

Then there are patients who have a low TSH and a normal free thyroxine. This is called mild or subclinical hyperthyroidism. The numbers of dots shown here do not represent the frequency in population, but is a representation of data points collected.

Picture of a patient shown:
This is a tired-looking, depressed lady who has severe hypothyroidism who also has nexadema. She has to furrow her brow to keep her eyelids open, and she complains of severe fatigue and she wants to sleep all of the time, and is very cold. So she has advanced, severe hypothyroidism that we seldom see today. The hypothyroidism is common in the population. It is estimated that 10 million Americans are affected by it. It is more common in women, although perhaps it has been overestimated in the past. It increases in frequency with age.

Epidemiology of Hypothyroidism:

- >10 million Americans affected
- 5-10 times more common in women than men
- Increased risk among women >40 years of age
- Elevated thyroid stimulating hormone (TSH) in 9.6% of women between ages 45-54, and 6.9% of men between ages 54-74
- Elevated TSH in approximately 12% of women older than 60

Etiology of Hypothyroidism:

- Hashimoto's thyroiditis
- Thyroid ablation
    - Surgery
    - Following I-131 therapy of hyperthyroidism
    - Radiation of cervical neoplasms
- Drugs
    - Iodine, inorganic or organic (amiodarone)
    - Lithium, Interferon-alpha, Bexarotene
- Hypopituitarism or hypothalamic disease
- Congenital: dysgenesis, biosynthetic defects

There are a number of causes of hypothyroidism. The most common is a condition which is an autoimmune disease, which is an autoimmune inflammation called "chronic", because it is there all of the time when you get it. It is a lymphocitic disease. There are white cells that are called lymphocytes that infiltrate the thyroid (Thyroiditis). This disease is named by a Japanese pathologist named Hashimoto, so it is called Hashimoto's lymphocytic thyroiditis. If the thyroid is surgically removed that will cause hypothyroidism, or if a patient with an overactive thyroid is treated with I-131 a lot of people develop hypothyroidism afterwards. Or the thyroid could be radiated in patients receiving radiation for cancer, cancer of the larynx or Hodgkin's disease for example. That high dose of radiation will cause hypothyroidism in a portion of the people who receive high-dose therapeutic radiation for a cancer. Then there are a number of drugs which will interfere with thyroid function. Any large amount of iodine given chronically will do that. The only drug given now that will do that with a lot of iodine in it that is given chronically is amnioderonis given for cardiac arrhythmia. If the pituitary doesn't work, and there is not enough TSH produced you can get hypothyroidism. In that case the TSH in the blood would be low and the Free T4 would be low, this happens in about 1% of the patients.

There are newborns with hypothyroidism, which usually occurs from an anatomic development disorder. In other words the thyroid just doesn't develop at birth. Or it could occur because there is a defect in the synthesis of the thyroid hormone or an abnormality in one of the enzymes for making thyroid hormone.

Features of Hypothyroidism:

- Most common symptoms: none, fatigue, mental slowing, depression, menorrhagia, dry skin, cool feeling, weight gain, etc.
- Goiter of Hashimoto’s disease
- Family history of autoimmune thyroid disease

Patients with hypothyroidism have a number of features, which are common in the hypothyroid population, but non-specific. And these symptoms include fatigue, mental slowing, and depression, heavy or light menstrual periods, dry skin, feeling cold or weight gain. Those are very common in the population and can occur from many other conditions, so they are not specific.

Patients with Hashimoto's disease, particularly younger women will often have a goiter. And older men with it, like I see sometimes at the VA, the thyroid is shrunken, it's atrophied. And then I think of it in patients who have a family history of autoimmune thyroid disease because it runs in families.

Diagnosis of Primary Hypothyroidism:

- Elevated TSH and reduced Free T4
- Screening shows prevalence increases with age, 1 / 4,000 in newborns, 10-15% in elderly
- Female/male = 4/1

The diagnosis of hypothyroidism is very straightforward. The TSH is high; the Free T4 (thyroxine) in the blood is low. Screening for it shows a prevalence of 1 per 4,000. In newborns it is mandatory to screen for it in all of the states in the United States, and in almost all of the developed countries in the world. On the other hand, at the other end of the age spectrum, in elderly people the incidence is 10 -15%, and in some of the nursing homes that have been studied 20%. And male to female ratio has probably been overestimated, but I will show it to you. It is probably more like 2:1 rather than 4:1.

Herman Cember asked if there is a geographical variation associated with the 1 per 4,000-incidence rate. Dr. Hershman replied that there has been some minor variation, but thinks that the incidence is so low that it may just be sampling variation.

In some countries hypothyroidism prevalence has been reported to be 1 per 5,000 and in others 1 per 3,000. Most of them are 1 per 4,000. If you looked in a country with severe iodine deficiency, as occurred many years ago in the Republic of the Congo, severe iodine deficiency probably caused hypothyroidism in 5% of the newborns because of extremely severe iodine deficiency. By and large in developed countries with adequate iodine intake prevalence is 1 per 4,000 without a lot of variation.

Question asked about prevalence in newborns (inaudible):
Dr. Hershman stated that it seems to be steady. This screening has been going on for 25 years. California, he's proud to say, was the first state. It was actually started in Canada because of a combination of a Canadian from Montreal and someone named del Fischer in California who started this. There are about 25 years of data, roughly. Not aware of a big change in frequency and believes they do a good job in screening. What is diagnosed is mild hypothyroidism, and the children are immediately treated. What has changed some is that it used to be thought you could make everybody normal, but as it turns out, in-utero if a very severe iodine deficiency occurs while the baby is growing in late pregnancy you still wind up with children who probably do not attain normal intellectual achievement or IQs.

Don Box asked if there were any data that go back far enough to see an effect of the nuclear age. Dr. Hershman responded that he was not aware of any. There was the Chernobyl problem where children took up the iodine through the thyroid. The thyroid develops at 12 weeks of pregnancy, so after that the baby's thyroid makes the thyroid hormone for the remainder of the 40 weeks. So that the baby in-utero, the fetus, can take up iodine that the mother has ingested. And that was responsible for cancers in children

who were not even born. The cancers from radioiodine uptake were developed at 3 to 4 years of age.

Management of Hypothyroidism:

- Usual Rx is synthetic levothyroxine = T4
- Young and middle-aged: 1.5-2.0 mcg/kg T4/day. Usual daily doses are 100-150 mcg. Start with ½ dose for 1-2 weeks.
- Elderly +CAD: Start with 12.5-25 mcg/day and increase 12.5-25 mcg q 4-6 weeks

Concerning the management of hypothyroidism, the usual treatment is synthetic levothyroxine. There are several brands that are good. The usual dose in young and middle-aged people is 1.5 to 2 microgrrams per kg so the common doses are 100-150 micrograms of thyroxine/day. In younger people you can give nearly the full amount to start with. In older people they might have a coronary condition so that it is dangerous to raise their metabolic rate up too quickly. So it is best to start with a smaller dose and go slowly and bring them up to a normal serum TSH. At the endpoint of the treatment, not only does a patient feel better, but it brings the serum TSH into the mid-normal range, about 1-2 mUnits/L. As doctors make a change in the dose it takes about 6 weeks for the change to result in a TSH which has equilibrated. The TSH level equilibrates very slowly.

Endpoint of Therapy:

- Titrate dose of T4 to achieve serum TSH in the normal range, preferably 1-2 mU/L
- It takes 6 weeks for TSH to equilibrate to a given oral daily dose

Explanations for rise of TSH in patient on same dose of T4:

- Noncompliance = drug holiday
- Ineffective generic preparation
- Drug-induced malabsorption:
    - Calcium carbonate
    - Ferrous sulfate
    - Sucralfate, Aluminum hydroxide
    - Cholestyramine, colestipol

Explanations for rise of TSH in patient on same dose of T4:

- Accelerated metabolism
    - Dilantin, Tegretol, Rifampin
    - Zoloft (sertraline)

- Estrogen replacement
- Worsening of thyroid failure

Subclinical Hypothyroidism:

- Same etiology as primary hypothyroidism
- Several studies show patients benefit in regard to mood, lipid profile
- Rotterdam study: independent risk factor for coronary disease (Ann Int Med., 2/15/00)
- Review: DS Cooper, NEJM, 7/26/01

Subclinical hypothyroidism, high TSH with the normal free thyroxine, has the same causes as the hypothyroidism just discussed. It is a milder disorder, and there has been a lot of debate on the part of evidence-based medical specialists. Is it really causing elevation in TSH? There are some studies showing that it is an independent risk factor for coronary disease, and may alter mood and lipid profile.

Hypothyroidism:

- 44-year-old white female noted fatigue for 6 months, depression for 1 month, occasional muscle cramps, reduced memory. Bowel function, skin, weight, and temperature preference had not changed.
- She was slender, pulse 68, blood pressure 98/62. Thyroid slightly enlarged with prominent isthmus. DTR and other exam normal.

A patient I saw a couple of years ago, a 44 year old lady, noted fatigue for 6 months, depression for 1 month, occassional muscle cramps, and reduced memory. She had been entirely well before that, and did not have any other features of hypothyroidism. She was a slender woman who did not look hypothyroid, did not look like the previous photo of the patient. Her thyroid was a little enlarged, and had margins that felt very sharply defined like what is found in patient's with Hashimoto's Disease. The rest of the examination was normal.

Patient's Lab Tests:

- 2 years previous: TSH 4.2
- 1 year ago: TSH 7.0, FT4 1.2 (N1 .8-2.1)
- 1 month ago: TSH 12.5, FT4 0.8
- Anti-TPO >6800 U/ml

The doctor who had referred the patient had measured her TSH level 2 years before, which was within the normal limit, but in the high end. One year before it had risen from 4.2 up to 7, but the Free thyroxin was still normal. One month before I saw her, when she was symptomatic, her TSH had gone up higher – 12.5 and the Free thyroxin had gone lower than normal. And the antiperoxides antibody was 6800 units/ml, indicating that

she had Hashimoto's disease as the cause of her mild hypothyroidism. I treated her with 75 micrograms of levothyroxine.

Response to Treatment:

- Given 75 mcg levothyroxine
- 2 months later she reported that depression disappeared, fatigue disappeared, and she felt normal. TSH 4.5, FT4 1.0
- Dose increased to 100 mcg T4

When I saw her 2 months later her depression had disappeared, her fatigue disappeared, and she really felt normal. At that point her TSH was 4.5, so it was very slightly elevated for our UCLA assay. Her Free thyroxine was now normal, but I increased her dose to 100 microg. Her TSH 2 months later was 2, and she did not feel any better than she did on the slightly lower dose.

Progression of Mild Thyroid Failure:

So, the 75 microgram dose had gotten rid of all of her symptoms. So she illustrates the progression of mild thyroid failure, going from euthyroid, or normal state, to a state with just elevated TSH where the thyroxine is normal, to what is called overt hypothyroidism, or more significant clinical hypothyrioidism, with a high TSH and a low thyroxine. It is a progressive disorder in most people. Now, there have been studies on what causes the progression, if the TSH is more than 12. In one Swiss study within a 10-year period, ¾ of the patients, who are all women, within that study got biochemical hypothyroidism, low free thyroxine. So, it is a progressive disorder.

Colorado Thyroid Disease Prevalence Study of 25, 682 people at state health fair.

Prevalence of Thyroid Dysfunction:

- Euthyroid 90.1%
- Hypothyroid 0.4%; Subclinical 8.5%
- Hyperthyroid 0.1%; Subclinical 0.9%
- Taking thyroid Rx 1525 = 6%
    - High TSH 8.9%
    - Low TSH 1%

There was a study of thyroid function at a Colorado health fair in which over 25,000 people answered a questionnaire about symptoms of thyroid dysfunction, over or under-active thyroid conditions, and also had blood measured for TSH and T4. It turns out that out of those 25,000 people, over 1500 were taking thyroid hormone. That is about 6% of that population, who were people in an age spectrum of 20 to 70 years old who were sampled at the Health Fair. And of those people on thyroxine, almost 9% still had a high TSH, and weren't taking enough. Some had a low TSH, and were taking too much. Of the rest of the population 94% - 90.1% of that were euthyroid, but 0.4% were

hypothyroid and the subclinical hypothyroidism was twenty times as common at 8.5%. Hyperthyroidism accounted for 0.1%, and the subclinical hyperthyroidism was at 0.9%. The point is that subclinical mild disorders are common in the population compared with the more severe overt disorders. The Colorado study shows the prevalence of high TSH levels, you can see with increasing age, age 18 to 24, up to greater than 74 that there is an increase in both women and men. And the ratio is not 2:1 at all, the ratio is older men catch up to women in regard to developing hypothyroidism due to autoimmune thyroiditis. That Colorado study also reported symptoms. These are some of the symptoms of hypothyroidism. The most prevalent was dry skin, 30%, but poor memory, slower thinking, weaker muscles, more tired, muscle cramps, feeling colder, puffier eyes, deep voice, constipation, hoarse voice, more constipation than before, hoarser voice, and changes in the voice were also reported.

The people with normal TSH show symptoms almost as common. Because of the huge number of people, on statistical grounds the symptoms of hypothyroidism were more prevalent in the people with the high TSH. I want to point out that these are nonspecific symptoms that people without hypothyroidism have almost as commonly as people do with hypothyroidism.

Why Treat Patients with Mild Thyroid Failure with L-Thyroxine?

- Prevent progression to overt hypothyroidism
- Alleviate symptoms
- Normalize serum lipids
- Normalize cardiac function
- May help depression

There have been arguments about treating people with mild thyroid failure. Once you begin treatment further progression is prevented. The thyroid can get more disease, but you're going to stop hypothyroidism in its tracks. Some people will have symptoms and you make them feel better. You can lower the cholesterol of a person who has high cholesterol and it is shown in some studies that cardiac function and depression are improved. Most endocrinologists will treat people who have mild hypothyroidism, particularly if the TSH is more than 10. Between 5 to 10 there is a big argument if a patient has symptoms such as have been described. Most endocrinologists, internists, family doctors would be inclined to treat, but there are some people who say "show me the proof that, looking at a whole population, did you do any good with that treatment?"

<u>Hyperthyroidism - Overactive Thyroid Gland</u>:

There is a lady I saw about 10 years ago who had this wide-eyed stare. She has an enlarged thyroid. She was complaining of severe fatigue, nervousness, anxiety, pounding heart, losing weight, weakness, and really felt terrible from her overactive thyroid gland. Her thyroid gland was enlarged. Her eyes are prominent because she has Graves' disease

with the eyes being affected significantly, which occurs in about 5% of patients with overactive thyroid due to Grave's disease. In patients with Graves' disease there is a thyroid stimulating antibody, it's an autoimmune disorder in which an antibody is made that binds to the TSH receptor and stimulates thyroid gland much like TSH does. And why it is produced is a mystery.

Causes of Hyperthyroidism:

- Graves' disease
- Hyperfunctioning solitary thyroid adenoma ("hot" nodule)
- "Toxic" multinodular goiter
- Lymphocytic thyroiditis with low thyroid radioiodine uptake
- Subacute (granulomatous) thyroiditis (early phase)
- Ingestion of excessive amount of thyroid hormone
- Iodine-induced (amiodarone)

Grave's disease accounts for about 90% of the hyperthyroid patients in our population. The next most common cause is an overactive multi-nodular goiter. The third most common cause is a "hot" nodule of the thyroid. You can get it from thyroiditis where the gland is just releasing thyroid hormone in a disordered manner. There are a lot of other causes, which are rare, and I'm not going to spend the time going over them.

Rare Causes of Hyperthyroidism:

- Excess HCG secretion
- TSH-producing pituitary adenoma
- Pituitary resistance to suppressive effect of thyroid hormone due to a mutation in the T3 receptor
- Follicular thyroid carcinoma with widespread metastases
- Struma ovarii (ovarian teratoma with thyroid elements)

Diagnosis of Hyperthyroidism:

- Increased Free T4 and Free T3, low TSH
- Thyroid-stimulating IgG or TSH-Receptor antibody not routinely measured
- Thyroid uptake: low in thyroiditis, high with hyperfunction
- Radioiodine scan: Shows Graves' (uniform uptake), multinodular goiter, hot nodule

For hyperthyroid diagnosis, the TSH is low and circulating thyroid hormone levels, T4 and T3, are all increased. The thyroid stimulating immuno-globulin can be measured, but it is a kind of expensive and it is not done regularly. That test shows Grave's Disease as the cause for hyperthyroidism. The thyroid uptake is high if the gland is hyperfunctioning like Graves' Disease, but if there is a viral thyroiditis, which causes a

tender thyroid, then thyroid uptake of radioidide is very low. The gland is very sick. It is leaking thyroid hormone. It is a very uncommon cause of hyperthyroidism. And the radioidine scan shows it is uniform distribution as illustrated earlier. In Grave's Disease and multi-nodular goiters, there is a patchy uptake and a single nodule takes up all of the radioiodine in that disorder.

Clinical Features of Hyperthyroidism:

- Most common: nervousness, weakness, fatigue, heat intolerance, tachycardia, weight loss, tremor
- Depression or altered behavior
- Goiter
- Graves' eye disease

The clinical features of hyperthyroidism that are most common are a little non-specific: nervousness, fatigue, heat intolerance, rapid heartbeat palpitation, weight loss (with the same appetite and food ingestion in younger people or even increase in intake; older people usually lose their appetite), and then a tremor.

Even though we think of the hyperthyroid patient as someone slightly agitated, and sometimes "high", a lot of patients with hyperthyroidism will be depressed, just like people with hypothyroidism. And it can alter behavior. There are some instances where people have resorted to criminal behavior due to hyperthyroidism in part. It causes an enlarged thyroid, a goiter, and also Graves' eye disease.

Management of Hyperthyroidism:

- Radioiodine-131
- Antithyroid Drugs
- Surgical thyroidectomy
- Beta-adrenergic blockers
    - Propranolol
    - Atenolol

The management of hyperthyroidism consists of 1 of 3 modalities. One that is used most often now is Radioiodine-131. That has been used for 50 years. The second is antithyroid drugs, that have also been used for the last 50 years. The drugs control the production of thyroid hormone, and in that way bring the patient to a normal function thyroid state. When you stop the drug treatments there is a high relapse rate. That is the disadvantage of the drugs. They control the condition, but about ½ the people will have a recurrence or relapse when they stop the medicine. For the other ½ it is good because it produces a long-term cure. The earliest treatment was to remove the thyroid gland. That is more drastic, and you can, in a sense, remove it with radioactive iodine. To reduce the symptoms, drugs that inhibit the adrenergic nervous system are used such as Propranolol,

so-called beta-blockers. They stop the shaking, lower the heart rate, reduce the feeling of being too warm, sweating, improve muscle strength, but they have only a temporary effect while you give them. As far as which of these treatments is used in a woman with a typical condition, in a survey of American thyroid specialists (what would they do for this 40 year old woman who had a couple of children and mild to moderate Graves' disease causing hyperthyroidism) only 1% chose surgical treatment, about 70% said that they would use Radioiodine as their preferred treatment. I was in the 30% that said, "let's use antithyroid drugs to treat the condition".

Subclinical Thyrotoxicosis:

- A.D. Toft, NEJM, August 16, 2001
- Parle JV et al. Lancet 9/15/01, 2 – 3 fold increased mortality in patients aged > 60 with low TSH.

There is a mild hyperthyroidism, subclinical thyrotoxicosis, or subclinical hyperthyroidism. In one study in England looking at people over age 60 with a low TSH, and then comparing them with people who had a normal TSH over age 60, and looking at death certificates, in England they were able to track them nicely. It turned out that people with a low TSH had a 2 to 3 fold increased mortality over a 10 year period due mainly to cardiovascular disease. So there is some hazard to having a low TSH, meaning that you have too much thyroid hormone circulating around, which can cause some damage.

Autoimmune Thyroiditis = Hashimoto's Disease:

- Very common, mainly women
- Causes goiter, hypothyroidism, thyroid atrophy, rarely hyperthyroidism, especially postpartum
- Markers: Anti-TPO, Anti-thyroglobulin antibodies
- Biopsy: lymphocytes, etc.

Old Anti-Microsomal Ab versus new TPO Ab Test:

Hashimoto's disease is very common, mainly in women. It causes a goiter, hypothyroidism, thyroid atrophy, can flare up after pregnancy. The marker is the antiperoxidase antibody, and we used to diagnosis it with an antibody measurement called anti-microsomal antibody. It was only positive in about 70% of patients with Hashimoto's thyroiditis, but now we can measure an antibody called thyroidperoxidase antibody. That is the protein that is in this microsomal fraction of the thyroid, and with the radioimmuno-assay of that protein, 90% of patients with Hashimoto's disease have a positive test. So it is a very sensitive test. I would venture to say that probably 20% of Hashimoto's patients, at least 10% and probably 20%, have this antibody in their blood. It does not mean that you are hyperthyroid. It turns out, in middle aged women

particularly, about 30% will have this antiperoxidase antibody, but only about 1/3 will have an underactive thyroid from that condition. So the tendency for Hashimoto's disease is present by having the antibody, but no hypothyroidism, a very prevalent disorder.

Clinical Course of Silent, Postpartum, and Subacute Thyroiditis:

Now, once in a while patients with Hashimoto's thyroiditis, especially postpartum, will have a high circulating thyroid hormone level, and be hyperthyroid, and then over a period of time the TSH will be low, then it will rise during this period when they can be hyperthyroid. They go from hyperthyroidism to hypothyroidism, then straighten out. And that occurs in some postpartum women.

<u>Thyroid Nodules - Common Condition That Can Result from Radiation Exposure to Thyroid</u>:

Frequency of Thyroid Nodules:

- 4.2 % in Framingham
- 3.2% in Whickham
- 58% Mayo Clinic Autopsies in 1955
- 13% military autopsies, ages 18-39

Picture of patient with very large thyroid nodules shown:
This picture shows that thyroid nodules have been around for a long time. This woodcut from the Middle Ages shows that the musician here has big thyroid nodules, very unsightly nodules. Nodular thyroid conditions have been around probably as long as mankind has been around, much more prevalent in areas of iodine deficiency, but caused by other disorders as well.

Concerning the frequency of thyroid nodules occurring in our population, there was a survey in Framingham. Those people in Framingham were followed mainly for cardiovascular disease, but as a part of that study in the health of the adult population the thyroid was also examined. By feeling the thyroid, 4.2% of the adults in Framingham had a thyroid nodule. Over a 15 year period 1.5% developed a thyroid nodule by feeling the thyroid. About 5.7% were reported in a paper.

In the town of Whickham, England 3.2% of the adult population were surveyed and had a thyroid nodule. All of them were surveyed, 3.2% had a thyroid nodule. In a study of autopsies in the Mayo Clinic in 1955, when the thyroid gland of people who had died from all sorts of causes were carefully examined, thyroid nodules were found in 58%. So, thyroid nodules are common and increase in frequency with age. In military autopsies of men aged 18-39, 13% had thyroid nodules. So this is not just restricted to older people.

Thyroid Ultrasound Surveys:

- 67% at Cedars-Sinai
- 40% patients with hyperparathyroidism
- One-half those with palpable nodule have additional nodules detected by ultrasound

Detection by ultrasound examination of thyroid nodules is common. One study carried out at a sister hospital of UCLA, Cedar-Sinai, in Los Angeles, did a survey by putting out a notice – if you want to have your thyroid examined by ultrasound, come and see us. They got 100 people, examined them by palpation, and found nodules in 20%, which is on the high side. It makes me think that people who volunteered may have been worried about their thyroid for one reason or another. By the ultrasound, 67% had thyroid nodules, about 22% had a solitary, a single, thyroid nodule (that is a little more worrisome), and 45% had multiple nodules, by ultrasound, which is very sensitive.

Thyroid Incidentalomas-an Epidemic:

- Ultrasound
- CT
- MRI
- PET

In a study of patients who underwent ultrasound for a different disorder, hyperparathyroidism, in the Mayo Clinic, in the 1980's, 40% who were middle aged and older in the population had thyroid nodules. Of those people who have a palpable nodule, when you do an ultrasound, about half of them will have additional nodules, because the ultrasound is so sensitive. So there has been this epidemic of incidentally discovered thyroid nodules, called thyroid incidentalomas - that is just medical jargon. And these nodules are found by ultrasound, which is performed most often now to measure blood flow, look for corroded arteries, lesions that could cause strokes. Nodules are also found by CT scans of the neck or by MRI, PET Scans. When the thyroid gland is examined and the imaging modality is ordered for something else, thyroid nodules are found commonly in our population. They are very common.

Prevalence of Occult Thyroid Cancer:

- In USA, 0.45-13%, average 3.6%
- In Spain, 5.3% visible, 22% on fine microscopic sections
- Microcarcinomas are <2mm

At autopsy, when the thyroid is very carefully examined, there is an incidence of incidentally discovered cancer, in people who are not known to have a thyroid cancer. Thyroid cancer incidence varies in the studies in the U.S. from 0.45 to 13% with an

average of 3.6% that a colleague of mine studied. There was a study of thyroids in Spain, carefully sectioned at autopsy. Autopsies revealed that 5.3% of the people had visible nodules that were cancers. And when they studies them very carefully, sectioned them carefully, they found 22% were cancers. These extra cancers were 2mm cancers, little tiny cancers, and papillary carcinomas.

Bob Craig inquired whether these studies were performed on bodies of people who died of something else. Dr. Hershman confirmed that the studies concerned people, who had died of something other than cancer, and microscopic thyroid cancer was found, and they had had no idea that they had thyroid cancer. If you study older men who die of something else, say prostate cancer, and you look at the thyroid you find some microscopic thyroid cancers.

Pictures of sectioned thyroid tissues shown:
This is a classification of goiter, it is either enlarged under the entire thyroid, the fusegoiter, or a nodular goiter, meaning a thyroid nodule or more than one nodule. The most common cause of the condition we still do not understand, and it is called 'colloid goiter'. You can have Hashimoto's thyroiditis causing an enlargement of the entire thyroid, or Graves' disease, or iodine deficiency will do that. Thyroid nodules can be caused by, as mentioned, colloid goiter, Hashimoto's thyroiditis, can present as a nodule, or a viral inflammation of the thyroid called subacute viral subacute viral granulomus thyroiditis, thyroid cysts that are filled with fluid, or benign thyroid tumors called adenomas or thyroid cancers. So, a thyroid nodule could represent one of a number of different lesions that can be a thyroid nodule.

Pictures of patients with thyroid nodule shown:
A man I saw a number of years ago had found a lump in his neck when he was shaving. It didn't bother him, and he denied any symptoms of hyperthyroidism. He was on a beta-blocker, he lost 10 pounds, and he was worried about his wife who had breast cancer, but by doing blood tests we found that he was really hyperthyroid. His Free thyroxin was very high, his TSH level was very low. So we did a radioiodine scan and all of the radioactive iodine concentrated in that nodule, so that was what was called a "hot nodule". He was treated for hyperthyroidism with radioactive iodine that removed the nodule and cured his overactive nodule.

Picture of a patient with thyroid nodules shown:
Another patient, a lady with a really large neck, had multinodular goiter, which she had had all of her adult life. It didn't bother her breathing, did not prevent her from eating, nor did she have obstructive symptoms, and it didn't bother her. She came to see me because she would have bouts of palpitations and shortness of breath at night. Her son was a cardiologist who performed an electrocardiogram. She had atriofibrulation, a real rapid heartbeat, because her thyroid was overactive. Not all of it was overactive, or she would really be sick, but probably little regions of it, as illustrated on a scan as patchy areas of increased uptake and some areas of reduced uptake. When this patient had a multinodular goiter removed the dark scan regions are where the radioactive Iodine was taken up by those active follicles, and the other follicles, groups of cells, are underactive.

It is conceptualized as underactive and overactive follicles, and when there are enough overactive follicles in a multinodular goiter you can get hyperthyroidism, like my patient had.

Best Diagnostic Test is Fine Needle Aspiration Biopsy:

- TSH, FT4
- Anti-TPO
- Then refer for FNA
- Ultrasound good to quantitate size, but may not give dx (determination) of benign vs malignant
- Radioiodine scan is non-specific –only valuable to indicate a "hot nodule"

In regard to the thyroid nodules, the ones that we worry about are the solitary thyroid nodules. The best diagnostic test is to do a biopsy, a fine-needle aspiration biopsy. It is worthwhile to do thyroid function tests first because that will give you some idea whether it is underactive thyroid, Hashimoto's thyroiditis, or an overactive thyroid – like an overactive or "hot" nodule. Sometimes the thyroid nodules are cystic. When fluid is aspirated there can be this water-clear fluid which is very rare, from a parathyroid cyst. Most of the time the fluid looks like a tan color, or can be blood-tinged with a cyst. Cysts make up about 10% of the thyroid nodules. Or there can be a thyroid carcinoma. A thyroid papillary cancer, the most common type of cancer, can be diagnosed by fine-needle aspiration biopsy.

Thyroid FNA Diagnoses –18,000 biopsies in 7 series:

Cytology	Percent
Benign	69
Malignant	3.5
Suspicious	10
Unsatisfactory/non-diagnostic	17

A group at the Mayo Clinic did 18,000 biopsies in 7 different series. About 10,000 out of the 18,000 biopsies were from the Mayo Clinic. The results were that 69% were benign cytology. Mostly variations of colloid goiter. About 17% of the biopsies were undiagnostic, meaning there were not enough thyroid cells on that biopsy to make a diagnosis. So biopsy is not a 100% method. When that happens you just have to go back and do it again. A malignancy was diagnosed 3.5% of the time in this group of 18,000 biopsies, and the suspicious category was 10%. That suspicious category shows normal thyroid cells, but there are clusters of them that are a little worrisome. If the cells all look normal everything is good, but if there are cells that look abnormal or worrisome often doctors will say, "well, if it is suspicious you had better have it operated on." When that was done 25%, or ¼ of this 10%, (2.5%) were malignant. If you have 2.5 to 3.5% counted then there were 6% actual cancers. So 6% out of the 18,000 biopsies turn out to have thyroid cancer. In the nodules that are not cancer, the single best predictive clinical feature for thyroid cancer is the thyroid nodule. Many years ago doctors would

recommend removing them all, but now we know that only 6% of them are actual cancers. So we try to make a diagnosis of cancer and get patients to surgery who are likely to have cancer, and if it's benign, then we do not generally recommend surgery.

Thyroxine Suppression of TSH to Suppress Size and Growth of Nodules

One form of treatment for patients who do not go to surgery is to give thyroxine to lower TSH and that will shrink the nodule in many instances. Summarizing a study series at the Mayo Clinic, patients were either given a placebo or thyroxine. The patients didn't know what they got nor did the doctors know what the patients got. It was a double-blind study. The first one done at the Mayo Clinic showed no benefit from giving thyroxine, the placebo gave the same results. But other studies showed that the thyroxine was very beneficial. Another study was interpreted as showing that thyroxine wasn't beneficial, but there was a recent study from a French group showing that by giving thyroxine the nodule would be shrunk by 50%. It was also a double-blind placebo control study. When you put them all together the data are overwhelming, thyroxine has an effect on about ½ the patients of reducing the size of the nodule. I think that it is useful and the one study at the Mayo Clinic made people think that it wasn't useful at all, so there is a lot of controversy.

Thyroxine Suppression of Nodules:

- A recent survey of American thyroid specialists showed that 47% used suppression therapy for solitary thyroid nodules. (Bennedbaek FN, Hegedus L. Management of the solitary thyroid nodule: results of a North American survey. J Clin Endocrinol Metab 85:2493-9, 2000).

In a survey done of American thyroid specialists by a Danish group they showed that 47% of American specialists used thyroxine suppression treatment for treatment of solitary thyroid nodules.

Another study was performed in patients who had had the nodule removed. half of them were given thyroxine to prevent a regrowth of a thyroid nodule, which usually occurs in patients with multinodular goiter, and half of them were given nothing. So it wasn't placebo controlled. This is going out 10 years at this point. By 10 years the group who were on thyroxine had a lower recurrence rate. This is looking at percent remaining free of thyroid enlargement after surgery. And by 10 years it looks like there is a real separation in these two groups. The author, Dr. Hegedis, said that he doesn't see any benefit to giving thyroixine, but I do because if you look at the data over a long period of time those who took thyroxine were less likely to have a recurrence of the nodular goiter compared to the other group. So I recommend to patients who have surgery for thyroid nodules to take thyroxine, but it is a contentious area. If enough thyroid is left the patient may have normal thyroid function without taking the thyroxine. If not enough thyroid tissue is left then the patient has to take the thyroid hormone after surgery.

Another study involving treatment of people with large, nodular thyroids was a Dutch study in which they compared giving radioactive iodine to people with multinodular goiters. These goiters were 60 grams. The solitary nodules are more like 3grams, so this is big time nodular disease. The patients receiving radioiodine had some significant shrinkage when the thyroid was measured carefully by ultrasound, whereas the group getting thyroxine had only a little bit of shrinkage in instances, but not significantly. Most of the time people with big multinodular goiters that are causing some trouble wind up getting surgery in the U.S., but they could be treated with radioactive iodine. Thyroxine treatment is unlikely to make a difference there if there is big, multinodular goiter.

Terry Lewis asked if Dr. Hershman had run across instances where the TSH test shows normal, but someone has all sorts of problems. Dr. Hershman responded that he had seen this, but that the problems are from other conditions. Sometimes the TSH is very slightly elevated, and when they are treated they benefit. There is a lot of argument on treating people whose TSH is within the normal range. Some doctors do recommend it in a patient, but as far as diagnosing hypothyroidism with a normal TSH and normal Free Thyroxine, they are on very treacherous grounds.

Terry Lewis stated that all of her tests had been normal, until her family doctor ran an ultrasound, which found all sorts of problems, and since that time she has run into many people in the Oak Ridge area who experience the same situation. Tests are normal until they insist on additional testing, and probably ½ of them had cancer. Dr. Hershman responded that the vast majority of patients, nearly all, have normal thyroid function. That is to say that cancer usually occupies a small part of the thyroid, and the rest of the thyroid functions normally, yet a cancer can be present. So a thyroid nodule can contain a cancer, but the function of the thyroid gland is normal, and that it probably the case in more than 95 to 98% of thyroid cancer cases. Terry Lewis inquired whether the case was the same with people who have Hashimoto's disease, having normal TSH. Dr. Hershman responded that the vast majority of patients who have Hashimoto's disease, who have a positive antibody, have normal functioning thyroids. Only about 1/3 will have abnormal functioning thyroids. If you look at the younger population more than 2/3 will have normal thyroid function, but I'm guessing that in women in their 50's or 60's you could have the antibody present, but the thyroid function be normal. In 1/3 patients, the thyroid function will be abnormal in patients who have the tendency for Hashimoto's disease. If you biopsy some that have Hashimoto's disease the thyroid function could be normal. It takes more significant Hashimoto's disease to develop an underactive thyroid.

Terry Lewis stated that she personally knows 37 people who went through 3 to 4 years of having something wrong, that was undiagnosed, because their thyroid tests kept coming back normal, and then when further tests were done, such as ultrasound and biopsies, they had major thyroid problems. Dr. Hershman stated that the nodules, as he tried to point out, are very common, so that 2/3, or at least half of adults, will have thyroid nodules. The nodules, probably 95% of them, are benign, not cancerous. Terry Lewis asked if the TSH test is supposed to show if something is wrong with the thyroid. Dr. Hershman clarified that it will not show if something is wrong with the nodule, it will not

show that there is a cancer. The patient can have a bad thyroid cancer and a normal TSH. The thyroid cancer occurs most of the time in people who have normal thyroid function. Well over 90% of patients who have thyroid cancer have normal thyroid function until they are operated on, and the thyroid is removed.

Charles Washington asked if you could measure the ratio of TSH to Free thyroxine. Dr. Hershman stated that you could calculate a ratio, but it is not used clinically like calculating ratios for cholesterol, high-density cholesterol. It is better to look at the levels individually, then consider them together, instead of looking at ratios. You could certainly calculate ratios, however there is not a calculated ratio that is clinically used.

Charles Washington inquired when you look at women 40 and older, how do you distinguish that this isn't the normal process? Dr. Hershman clarified, "you mean having the TSH go up with age?" It turns out that if you look at the young adult population and then an older adult population (people 50, 60, 70 years of age) that the serum TSH levels are about the same. On the other hand, there are a lot of patients with Hashimoto's thyroiditis, so if their TSH is high we have to exclude them. People with positive antibodies may also be excluded. I did a study of populations looking at a group who were age 30 to 50 compared with a group age 60 and up in the Framingham population. The TSH was the same in these two groups of adults, the youngest were age 40. They were the original Framingham study people and their children. The TSH's were not different between those two groups. Charles Washington asked if Dr. Hershman would advise women with the onset of menopause to have thyroid testing. Dr. Hershman stated that he thinks that there is so much hypothyroidism in the population that it is worth screening, but it is not an official recommendation of any group. It is more worthwhile to screen women than men for hypothyroidism by measuring TSH. It is a good screening test, but then there are arguments about the cost. Maybe when the cost is $1 or a nickel we will do it without thinking about it, but the medical insurance people sometime worry about the cost of it. Cost is probably coming down. There was a study done by a fellow from Johns Hopkins University that Paul Avison published in the Journal of the American Medical Association about 10 years ago looking at cost effectiveness. He calculated that it was cost effective to measure TSH in women over 35, and I think he recommended men over age 60, but that recommendation was not based on the kinds of calculations he did for the women.

Thyroid Cancer:

- Epidemiology of Thyroid Cancer in 2002:
- Estimate 21,700 new cases in U.S. in 2002.
    - Female/male = 3.2
    - 1.5% of new cancers.
- Comparisons: Ovary 23,300, Testis 7,500, Hodgkin's 7,000
- Prevalence: About 220,000 cases in U.S
- Thyroid cancer deaths = 1300, Female/male = 1.6

Classification of Thyroid Cancer:

Type	% of Type	Etiological Factors
Papillary	81	Radiation; ret oncogene rearrangement
Follicular	13	ras oncogene; Mutation
Medullary	3	ret oncogene
Anaplasic	2	p53 mutation
Lymphoma	1	Telomerase mutation

In regard to thyroid cancer, it is estimated that in the current year there will be about 21,000 new cases of thyroid cancer in the U.S. It is more common in women, 3:1 female to male ratio. It makes up 1 ½ % of new cancers. In comparison it is almost as common as cancer of the ovary, and is about 3 times as common as testicular cancer or Hodgkin's disease. The number of people with thyroid cancer in the U.S. is about 220,000. This year it is estimated that there will be about 1300 deaths from thyroid cancer. There are different classes, different histologic types, of thyroid cancer. In a study of 5583 cases of thyroid cancer in 1996, which were reported to a Registry of the American College of Surgeons, 81% were papillary cancer, 13% were follicular cancer, 3% were medullar, that is a cancer of the parafollicular cells that make the hormone calcitonin, 2% were a very terrible type called anaplastic, and 1% were probably thyroid lymphomas, they did not report them but in other series lymphomas originating in the thyroid have been reported, so I put it in there. Those are not treated surgically. They are treated with radiation and chemotherapy, and are completely curable. Without treatment they are 100% fatal. So it is an important diagnosis to make.

Papillary cancers are the ones that are induced by radiation. They often will have an oncogene that is thought to have a role in causing the cancer.

Clinical Features Suggesting Malignant Nature of a Thyroid Nodule:

- History
  - Thyroid irradiation during childhood (Chernobyl 1986)
  - Familial history of thyroid cancer
  - Age <20 or >60 years

- Thyroid nodule
  - Gradual increase in size, especially during T4 therapy
  - Firm, hard, or fixed to soft tissues

- Others
  - Cervical lymphadenopathy
  - Hoarseness, dysphagia

The clinical features that suggest the malignant nature of a thyroid nodule are a history of thyroid irradiation during childhood. The most recent outbreak of that was the Chernobyl

reactor explosion in 1986. That released a huge amount of radioiodine. The thyroid cancer outbreak was in children who were 4 to 5 years old from that area, the northern part of Ukraine and the Southern part of Belarus. It was a consequence of that reactor. The population, feeling that Russia had misled them, those countries, in a way, separated from Russia. It played a role in the revolution there. Children 4 and 5 years old developed thyroid cancer. Lumps in their thyroid were eventually treated surgically. The Russian/Ukrainian surgeons were not very good initially, but they got training from developed countries and improved. So there was an outbreak of papillary cancer in children where it was almost unheard of. From I-131 it was hard to estimate the amounts, but this reactor explosion released 150 million curies. It was a gigantic explosion compared with reactor releases elsewhere, and it was all at once. There was contamination of the soil, it got into the food, and children ingested milk that was contaminated. They were exposed in-utero, as I mentioned earlier. So that was a real epidemic increase in thyroid cancer in children that was estimated as 100-fold increase. The most vulnerable group was children aged 0, meaning they were in-utero, and up to 6 years of age. There probably was some thyroid cancer induced in adults, but that is a little less clear. There was an increase in thyroid cancer in adults.

I want to point out that I-131 has only about ¼ as much predisposition to causing thyroid cancer as does external radiation. Most studies done in the U.S. regarding radiation exposure and thyroid cancer concerned external radiation given to children with enlarged tonsils and adenoids, particularly in Chicago. Coincident radiation exposure of the thyroid also occurred. That stopped in 1962, and those children were followed at the Michael Reese Hospital. Initially they turned out to have thyroid cancer in 6% of the children who received radiation at age 2 or 3. Now that figure has gone up to 12% as more and more have been followed. Many more nodules than thyroid cancers are induced by external radiation. So the thyroid is radiosensitive, more so to external radiation, per rad or centigray than to internal radiation, but both cause thyroid nodules and thyroid cancer. So if a patient has a history of radiation in childhood we worry about it. A Russian immigrant, who lived in the Chernobyl area, we worry about it.

Indications for Surgical Removal of a Thyroid Nodule:

- Strong suspicion of malignancy by clinical judgment
- FNA biopsy indicative of carcinoma
- Recent rapid growth that is not hemorrhage into a cyst
- Elevated calcitonin or ret oncogene mutation with MEN2 background
- Obstructive symptoms
- Cosmetic deformity
- Growth of nodule during T4 suppression

Some thyroid cancer is familial, so that if there is a family history it is worrisome. If there is a nodule in a younger person that is a little more worrisome, or a nodule in an older person because, even though they are more common in older persons, if they are significant in size we worry because thyroid cancers in older people are much more

aggressive. If the thyroxine treatment is being used and the nodule grows, then that is a little worrisome, and such a patient probably should go to surgery if it is one of these indeterminant nodules. Of course if the nodule on the first exam is really firm and fixed, and you can't move it, it is stuck to the neck, then that suggests cancer. If there are a lot of lymph nodes with the nodule in children, that would suggest a cancer.

Herman Cember commented, going back to the children of Chernobyl, he had heard that general areas had been iodine deficient, what role would uptake of iodine have played, especially in in-utero exposure? Dr. Hershman replied that he thinks that the area was iodine deficient. Unfortunately at the time of Chernobyl there were no surveys of iodine deficiency, but before Chernobyl there was iodine deficiency. After Chernobyl surveys have been done, and there is iodine deficiency. It just turns out that at that time there weren't studies showing iodine deficiency of the population. I visited the Chernobyl areas to review a USAID study, and with the fall of communism the health of the public has deteriorated. There had been people that would go around and survey the schools, and that had kind of fallen off in recent years. If they found a lot they would determine the incidence of goiter in school children, but the surveys weren't being done, and the iodization of salt was not being pushed as much. Distribution to school children and the population is very poor, so even though iodized salt is cheap, the people are really poor and they do not use it. They do not buy it. So now I think that there is iodine deficiency in that population. What effect would it have? The fetal thyroid is very active and it would take up whatever iodine it could get from the mother. So if the mother has radioactive iodine in her blood that fetus is going to be taking it up. I think that the fractional uptake is higher with iodine deficiency. If there is iodine deficiency that will cause some thyroid enlargement, so then you have a problem of calculating, since there is more thyroid tissue, is the radiation per gram or milligram higher? I suspect that it would be. So I think that iodine deficiency would contribute to taking up more of this radioactive iodine that can cause thyroid cancer.

A hoarseness or severe alteration in voice suggests that the nerve controlling the voice is involved with thyroid cancer. That is always worrisome in a patient with thyroid nodule; probably ought to look at the vocal cords in that sense, for that condition. There are various indications for surgical removal of a thyroid nodule, if it is suspected to be malignant by clinical judgement, if biopsy shows cancer, if there is recent rapid growth, if it is not bleeding in a cyst, if the patient had a family history of this medullary cancer, which can be studied by a measurement of a gene that is abnormal, and if the patient has obstructive symptoms and compression of the trachea or esophagus. Sometimes women think that the thyroid nodule is unsightly if it is easily visible, and they would rather have it removed and trade it for a scar. If it grows during the thyroxine suppression treatment it is an indication for surgical removal.

Complications of Surgery:

- Near-total or total thyroidectomy constituted the dominant surgical treatment
- Hypocalcemia occurred in 10% of cases

- Recurrent laryngeal nerve injury in 1.3% of cases
- Complications were most frequently associated with total thyroidectomy combined with lymph node dissection
- Thirty-day mortality was 0.2% excluding anaplastic cancer.

In the study of the 5583 people in 1996, the surgery was to remove all of the thyroid gland, or nearly all, in almost all of the patients. When there is surgery of a thyroid cancer the surgeon does not attempt to leave enough thyroid tissue for normal thyroid function. The parathyroid glands are 4 little thyroid glands located behind the thyroid. They regulate the serum calcium in the blood. They can be damaged by an extensive thyroidectomy. So about 10% of the people had low-blood calcium and required additional medical treatment for that. The nerve controlling the vocal cord was damaged in 1.3% and these complications were more frequent in patients who had had extensive surgery because they probably had more extensive cancers. There was a mortality of 0.2% excluding the anaplastic cancers that have a very high mortality.

Graph of cancer survival shown:
A study of the 100% survival over a 10-year period of 53,856 cases from that same registry in the preceding 10-year interval was performed. Of the patients with the anaplastic cancer that I just mentioned, only 20% of them survived in one year. So that is a terrible condition that is fortunately just 2% of cancers, in older people, of rapidly growing thyroid masses. The papillary cancer, that was the 81%, has very good survival, so that it is more than 90% in 10 years. Follicular cancer is not quite as good. The Hrudle-cell cancer, which may be different from follicular, had survival like the medullar cancers.

Graph of papillary cancer survival shown:
Because over 80% are papillary let's look at the papillary in regards to stage. Stage 4 means it is a medistatic tumor at the time of the diagnosis. Stage 1 are small tumors in young people within the thyroid gland, stages 2 and 3 are in between. Stage 1 patients with papillary cancer have a very good survivial. No reduction of age adjusted survival rate. This is only over 5 years. The Mayo Clinic goes out to 20 years and shows the same thing. On the other hand, people with Stages 2 or 3 have some reduced survival. Stage 4 is relatively poor survival at 5 years in people with metastatic disease. It turns out that because papillary thyroid cancer is the most common type that it accounts for most of the deaths from thyroid cancers. Not anplastic, it's papillary just because there is so much more of it.

Outcome: Cumulative Percent Recurrence & Cancer Death After Initial Therapy

Graph of cancer recurrences shown:
Recurrences of thyroid cancer are much more common than deaths, based on a study of 1355 patients followed by Dr. Mazzaferri at Ohio State. Going out to 40 years, there are about 10% deaths in 40 years overall in this group. Recurrences are at about 30%. So recurrences are about 3 times as common deaths, with their treatment, so the people don't die from their treatment.

I-131 Therapy for Thyroid Cancer:

A. Ablation of remnants after thyroidectomy
B. Treatment of recurrences and distant metastases.

One treatment for thyroid cancer, after it is removed surgically, is to give radioactive I-131 to get rid of any residual normal thyroid tissue and thyroid cancer. I like to divide it into getting rid of remnants from the thyroidectomy, which is normal tissue, and treatment of recurrences and distant metastases.

Indications for I-131 Remnant Ablation:

- Distant metastases
- Incomplete excision of tumor
- Stage 3 or 4: age >45; big tumor, +lymph nodes
- More aggressive tumor: tall cell variant, insular cancer, follicular cancer, Hurthle-cell cancer

The indications for giving I-131 treatment are used for distant metastases. It shouldn't be given to somebody after an incomplete surgery. However, if the tumor is a larger tumor or goes through the thyroid gland, Stages 3 or 4, then certainly radioiodine should be given. There are some variations of papillary carcinoma that are more aggressive or for follicular cancers, which are more aggressive or Hurdle-cell cancers, then I-131 should be given after surgery.

Lack of Indication for I-131 Remnant Ablation:

- Small papillary thyroid cancer: <1.5cm, encapsulated, no nodes, age <40 years
- Such patients have excellent prognosis

If it is a little, tiny tumor , less than 1.5 cm, and it is all within the thyroid, and the lymph nodes are negative for cancer, then there is no evidence of benefits in the use of I-131 afterwards, routinely.

Patient scan shown:

Now let me show a patient that I saw over 20 years ago who was, at that time, 34. Here is a chest x-ray 3 months after she had a baby. It was ordered because doctors found out that she had a history of papillary thyroid cancer when she was 15. She was treated with surgery and radioactive iodine at a hospital in Los Angeles. She moved to Northern

California and went about her life taking her thyroid hormone. And both, she, and probably her mother, decided to deny the disorder. She skiied and was a very happy, functional person. But the doctor got that history, and referred her to an endocrinologist who took her off thyroid hormone and did a radioiodine scan, and there was diffuse uptake of the radioiodine, in her lungs, with some uptake in one lobe of the thyroid that had regrown. So she had pulmonary metasteses, microscopic and diffuse. She was treated with 140 millicuries of I-131 which localized in the pulmonary metastases. What doesn't get into thyroid tissue or cancer in this instance is excreted through the kidneys. And then she had a follow-up scan seven months later, a diagnostic scan, showing there was no uptake in her lungs. So it looked like she was cured. Unfortunately, a couple of years later, her lung scan was positive again. And she got another treatment. This went on for about 4 cycles, then she started developing some grossly visible nodules in her lungs, and they wouldn't take up any radioactive iodine.

About 15 years after I first saw her she died a pulmonary death of a metastatic thyroid cancer, papillary cancer. The papillary cancer had not stayed the same, it just undergoes differentiation. The cells that survive no longer take up radioiodine. That's bad.
A marker that we use for thyroid cancer is the protein called thyroglobulin made by normal thyroid tissue and also made by the differentiated cancers. If you take out all of the normal thyroid tissue and you find thyroglobulin in the blood, in a patient with thyroid cancer, that suggests the patient has residual cancer. By doing this measurement is has reduced the need to do a recurrence scan.

Graph of serum thyroglobulin shown:
Data of thyroglobulin measurements in patients who had thyroid cancer or are taking thyroid hormone are shown. When the level is under 2 that is generally a good sign, no cancer.

Serum Thyroglobulin is a Tumor Marker for Differentiated Thyroid Cancer:

- Made by normal thyroid tissue
- Stimulated by TSH, suppressed by T4 suppression of TSH
- Measurement of Thyroglobulin has reduced the need for routine thyroid scans

If you take people off their thyroid hormone their serum TSH goes high, because they don't have a thyroid gland, so the pituitary makes lots of TSH. You increase the serum thyroglobulin in some of the patients, it goes up way high, showing there is residual thyroid tissue, presumably cancer. Such patients are all symptomatic of hypothyroidism. If you give recompetent human TSH, 2 shots of that, $1200 worth, unfortunately, that will raise the thyroglobulin also, and show there is residual thyroid tissue. That can be done while the patient continues to take their thyroxine treatment, so that they don't undergo symptomatic hypothyroidism.

Imaging Techniques for Recurrent Thyroid Cancer:

- I-131 scans after withdrawal of T4 (T3) to elevate TSH or after rhTSH

- Ultrasonography of the neck
- Thallium scans
- Sestamibi scans or Tetrafosmin
- CT scans or chest x-rays
- MRI
- PET scans –labeled glucose

If the thyroglobulin is high you follow it to where it is coming from. That can be done with the radioactive iodine scan. Sometimes people will have negative scans, but high thyroglobulin; either baseline or stimulated. Such patients can be studied by other means. One way of routinely following people with thyroid cancer is to do ultrasonography and see if there are any recurrences in the lymph nodes in the neck. They show up very well in ultrasound examinations of the neck. It will also show recurrences of thyroid cancer in the neck. Then there are some other radioactive agents: thallium scans, sestamibi scans, tetrafosmin, which are used for following people in Europe primarily. You can do CT scans, which are more sensitive than chest x-rays, or an MRI. The latest technique for following people is PET scans.

Patient X-ray shown:
Shown here is lady at the Sloane Kettering Hospital in New York. She is a 60 year old woman who had follicular cancer with lung nodules on the chest x-ray, and a very high thyroglobulin, more than 6,000, which shows that she had big-time metastatic disease, of course, it was in the lung. She had a radioiodine scan that was negative. That follicular thyroid cancer doesn't have the iodine transport anymore. Then she had a PET scan that showed localization in 3 areas, including one that was a mass indenting her trachea. That was recurrent from thyroid cancer.

Summary of Key Points (for nodules and cancer)

- Thyroid nodules are common and the vast majority are benign
- Fine needle aspiration biopsy is the best diagnostic procedure to determine whether a nodule is malignant
- Patients with thyroid cancer are managed by teams of endocrinologists, surgeons, and nuclear medicine specialists.

To summarize the key points for nodules and cancer, thyroid nodules are very common in our population, particularly increasing with age. The vast majority are benign. The best test to diagnose what causes a thyroid nodule, whether there is a cancer, is a fine need aspiration biopsy, so-called FNA. And then patients with thyroid cancer are managed by teams of endocrinologists, surgeons, and nuclear medicine specialists.

<u>Discussion</u>:

Herman Cember asked, in the case where someone receives an acute radiation dose, such as might have happened from Chernobyl, what is the best estimate of the latent period

until termination of the possible cancer risk from the radiation, based on the data that we have from the atomic bomb survivors, children who were exposed, etc.

Dr. Hershman responded that the latency for external radiation, based for example on the atomic bomb survivor risks, results in a minimum latency of 10 yearrs on up to 30 to 40 years. However, the children exposed from Chernobyl showed a latency period of only 4 to 5 years, a very short latency. Those children had very big lumps. There continue to be some case occurring among those exposed from Chernobyl.

Peggy Adkins asked has there been significant research on lower rates of exposure over long periods of time, and also has there been research on transmittal/passage of risk from parents to children. Dr. Hershman responded, regarding the question of passage of risk from parents to children, that there are familial papillary thyroid cancers but the gene for these cancers has not been identified, and there is not a basis for thinking that a radiation-induced thyroid cancer in a parent results in an altered gene that predisposes their children to thyroid cancer. Regarding research about long term low exposure rate effects, the government has for many years supported studies of low level radiation exposure, say reactor leaks, there are not data to show increased thyroid cancers in adults, but in very young children (< age 1) there may be some effect. The studies show that the effect is usually greater from an amount of radiation delivered as a single exposure rather than delivered as several separate smaller exposures.

Terry Lewis commented that she has lived in Oak Ridge since birth, her mother was the first woman to work at Y-12 and worked with the calutrons, many family members came to work in Oak Ridge over the years. Now, many family members have developed thyroid problems, nodules, cysts, Hashimoto's disease. Terry Lewis said that no one in previous generations of her family had thyroid problems. Has there been any research or documentation on thyroid diseases in second generation Oak Ridgers that worked at the plants or whose parents worked at the plants? Dr. Hershman responded that he has seen a study of thyroid cancer incidence in Oak Ridge showing that only children exposed at age less than 1 year who had high exposure from eating local goat's milk or cow's milk were considerably vulnerable to thyroid cancer or nodules. The nodules with radiation exposure are more frequent, 5-10, nodules are very common in the population even without radiation exposure. Autoimmune thyroid disorders, such as Hashimoto's disease are familial, but the genetic mechanism has not been discovered. It could come from either side of the family.

Don Creasia asked if someone gets an acute dose of I-131 and half of the thyroid is depleted, does it regenerate. Dr. Hershman replied that there is minimal effect from a small dose of I-131 (fraction of a millicurie), which could not damage the thyroid, unless it is a full millicurie, which could cause the thyroid to become hypothyroid. If part of the thyroid is surgically removed, what is left may grow a little and would function as the entire thyroid.

Bob Craig commented that women from the 1940-50's seem to have had their thyroids removed. Dr. Hershman stated that ½ a decade ago thyroids which were discovered to have nodules, and were not necessarily cancerous, were surgically removed due to the possibility that they were cancerous. It could have also depended on local medical practices at the time. Surgery is much less common today, as it is limited to those who may be of high risk for cancerous nodules. I think in the 1950's and 60s, prior to current diagnostic tests, nodules were surgically removed after a diagnosis by radioiodine scan. They were regarded as potentially cancerous. The incidence of cancer once the nodules had been surgically removed was about 6%.

Kowetha Davidson asked about the Mayo Clinic study of autopsied patients in which 58% had nodules in 1955, before the global fall-out on iodine. The ultrasound survey found nodules in 67%. The number of nodules found in the population does not appear to have gone up as a local or global fall-out. Dr. Hershman responded that that is probably true. The populations who were surveyed by ultrasound were 30-60 years old, and the autopsied individuals were people over 50, 60, 70, or 80. The two studied populations need to be age-matched. In general, I agree, with the commenter's point of view.

Public Comment

Bill Murray asked about the dosage received to the parathyroid when the thyroid received radiation doses to treat cancer, and if there was any damage to the parathyroid gland. In addition, what other tissues in the body does iodine go to besides the thyroid? Dr. Hershman stated that parathyroid damage does not occur after radioiodine treatment for thyroid cancer. It is very resistant, and only a very few cases have been reported. As for the second questions salivary glands may experience damage or loss of salivary function from the radioiodine treatment. There is the same function in the lining of the stomach also has iodine transport, but there has never been any damage or cancers reported.

Theresa Chen stated that recently she was diagnosed with Hashimoto's disease and asked for brief summary of what this disease is. Dr. Hershman responded that it is a chronic autoimmune inflammation of the thyroid that is common in the population and occurs more frequently with age.

Peggy Adkins stated that Terry Lewis' case seemed very similar to some people she knew in this area years ago. In 1963-64 doctors were referring young girls to a doctor in Crossville, Tennessee for underactive thyroids. There was no family history of those diseases. Is there any connection between estrogen and these diagnoses in multiple families? Dr. Hershman stated that the most vulnerable group for Hashimoto's disease today is adolescent girls, aged 12-14. In regions of moderate iodine deficiency the most vulnerable population are adolescent girls. It may be estrogen-related, but the data is

very weak. Peggy Adkins noted that the mothers of these adolescent girls developed diseases like Lupus and MS at menopause, and asked if there was any study that looks at the relation of disease, estrogen, and thyroid? Dr. Hershman stated that he knew of one study showing that a very high proportion of women who had Lupus also had Hashimoto's disease. If you examine Hashimoto's patients only a small percentage have Lupus. It could be a family related tendency. Peggy Adkins asked if there is information on research on thyroid effects from exposures to a multitude of contaminants. Dr. Hershman responded that there is some interest now in environmental toxins and how they could affect the thyroid. I have a colleague, Gregory Brent, who is on a national committee studying the effects of environmental toxins on the thyroid.

Kowetha Davidson asked if there was a connection between post-partum depression and post partum hypothyroidism. Dr. Hershman responded that there has been a connection between post-partum depression and post partum thyroiditis with hypothyroidism. The majority of post partum depression is unrelated to post partum hypothyroidism.

Break

Break.

Work Group Recommendations

AGENDA WORK GROUP

Barbara Sonnenburg was no longer present, but asked for suggestions for the agenda from the Subcommittee.

GUIDELINES AND PROCEDURES WORK GROUP

Karen Galloway was not present, and there was no task assigned to this Work Group at this time.

COMMUNICATIONS AND OUTREACH WORK GROUP

James Lewis asked that Theresa Nesmith submit a Needs Assessment report from another site's Needs Assessment so that the Subcommittee with have an example work product to become familiar with.

HEALTH EDUCATION NEEDS ASSESSMENT WORK GROUP

Donna Mosby reported that there were no recommendations at this time.

PUBLIC HEALTH ASSESSMENT WORK GROUP

Bob Craig reported that there are no recommendations at this time, but mentioned that Tony Malinauskas has agreed to lead the public health assessment on uranium releases from Y-12. There will a recommendation from the Work Group at the next ORRHES meeting regarding cancer data to request from the State of Tennessee.

James Lewis commented on the there is low attendance at the Work Group meetings, which may leave some Subcommittee people under-informed as public health issues are addressed (i.e. The cancer registry data request). Bob Craig encouraged that anyone who would like to be considered for, or provide input to, the Work Group looking at the cancer registry data to contact Pete Malmquist, Tony Malinauskas, James Lewis, or George Gartseff.

Kowetha Davidson suggested a brief summary of Work Group topics during the Work Group meetings to inform everyone of what is going on.

James Lewis commented that some recommendations from the Public Health Assessment Work Group, October 22, 2002 ORRHES meeting, did not pass and there was some question as to if they should be revisited. The Subcommittee needs to be aware of the importance of some recommendations, even if the do pass a vote of the Subcommittee. Bob Craig suggested that the recommendations be resubmitted for discussion during the Work Group meeting. Donna Mosby stated that the PHAWG recommendation did not have support material to make a decision on, and that there needed to be material to review in order for members to make a decision, and asked what the task of the Cancer Registry Group is. Kowetha Davidson explained that in the last Subcommittee meeting there was a request that Toni Bounds provide incidence rate data for certain cancers in our 8 county area. This group will be deciding specifically which cancer rates in the area will be requested. Currently the maps show all cancers, and the Subcommittee needs to be selective in deciding which information is going to be useful, and will be presented to the Subcommittee in a way that shows the relationship to what we are doing. They are going to narrow down the list of what specific types of cancer will be included (e.g. thyroid). Bob Craig confirmed that the Public Health Assessment Work Group will have a recommendation concerning cancer registry data requests at the February 10 ORRHES meeting. The PHAWG has 3 meeting scheduled before the February 10 meeting at which the recommendation will be developed. Paul Charp has made a thorough presentation on the screening dose (MRL) at the October 22 meeting that contained sufficient information for Subcommittee members to make an informed decision.

Kowetha Davidson stated that it is the responsibility of the PHAWG to decided whether or not, and how to, present the issue again to the Subcommittee. James Lewis emphasized that certain public health issues, such as the screening level, need to be condensed for the

benefit of lay-people and Subcommittee members. Kowetha Davidson replied that it is the responsibility of the PHAWG working with Paul Charp. Jerry Pereira reminded Subcommittee members that it is incumbent on work groups to bring that information to ORRHES for decision-making. It is also incumbent that each Subcommittee member to ask for clarification on issues that need it. Work groups are an entity that is necessary in regards to the volume of information to digest and present to the Subcommittee. If the Work Groups do not succeed in bringing clear understanding of issues to the Subcommittee, the Subcommittee will be unable to present it to the community in a manner that is logical. Kowetha Davidson: action item for the PHAWG is to study the issue of the screening level for radiation and to bring a report back to the Subcommittee at the next meeting and make a decision on how they want to handle it.

Unfinished Business/New Business/Issues/Concerns

Peggy Adkins requested additional information from Dr. Hershman concerning any available research on the effects of multiple exposures, including I-131, on the thyroid. Also, requested the contact information of Dr. Gregory Brent, a colleague of Dr. Hershman, who is an expert on how environmental toxins effect the thyroid. There was much discussion about whether this information should be requested of Dr. Hershman directly by Peggy Adkins or an appointed source from the Subcommittee. The information will be provided to Peggy Adkins as requested.

Identification of Action Items

ACTION 1: Theresa Nesmith will provide the ORRHES with a copy of a representative ATSDR Needs Assessment prepared for another site.

ACTION 2: The Communications and Outreach Work Group will work closely with Lorine Spencer of ATSDR to develop CI (community involvement) aspects of the work of the ORRHES.

ACTION 3: The chair of the Communications and Outreach Work Group will schedule a workgroup meeting.

ACTION 4: The Public Health Assessment Work Group (PHAWG) will determine whether there is a need and the best way to present again to the ORRHES

the recommendation that the PHAWG made to the ORRHES on October 22, 2002 regarding the magnitude of the ATSDR screening level for radiation exposure.

The recommendation presented by the PHAWG to the ORRHES on October 22, 2002 is reproduced below:

> RECOMMENDATION:
>
> Bob Craig reported the following recommendation from the Public Health Assessment Work Group.
>
> The Subcommittee should remain silent on the issue of the magnitude of the ATSDR screening level for radiation exposure.
>
> This recommendation received a motion, was seconded, and was not passed by the Subcommittee by a vote count of 8 in favor and 7 opposed.

Housekeeping Issues and Closing Comments

The next ORRHES meeting is February 10, 2003.

The meeting was adjourned at 5:00 PM.