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Medical Effects Of Iodine:
Proceedings Of NASA/JSC Conference

Medical Operations Branch
Medical Sciences Division
Space and Life Sciences

March 1998



National Aeronautics and
Space Administration

Lyndon B. Johnson Space Center
Houston, Texas

[illegible]

MEDICAL EFFECTS OF IODINE: PROCEEDINGS OF NASA/JSC CONFERENCE

Prepared by: Kathleen A. McMonigal, M.D.
SD27/ Medical Operations Branch

March 1998

Approved by: Roger C. Billica 6/3/98

SD2/ Roger C. Billica, M.D. Date
Chief, Medical Operations Branch

4 Jun 98

SA/ Sam L. Pool, M.D. Date
Assistant to the Director for Space Medicine
Space and Life Sciences Directorate

MEDICAL EFFECTS OF IODINE: PROCEEDINGS OF NASA/JSC CONFERENCE

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1.0 INTRODUCTION

The purpose of this document is to provide a written record of the NASA conference "Iodine and Thyroid Function in the United States Space Program", held January 14, 1998 at the Johnson Space Center in Houston, Texas. This document includes the background, agenda, panelists, recommendations, viewgraphs, and transcript of the proceedings.

The meeting was held to review the effects of excess iodine on thyroid function and to determine if there is a relationship between the abnormal thyroid function identified in individual astronauts and their prior consumption of iodinated water on space flights. The panelists were asked to make recommendations regarding the maximum daily iodine intake in space flight crew and to provide guidance for thyroid health screening of astronauts. The recommendations for reducing iodine in the drinking water are for the Space Shuttle and for the International Space Station.

1.1 Background on Iodine in the Space Program

For the past 25 years, iodine has been used as the biocide in the potable water systems for U.S spacecraft. The iodine is added via an anion exchange resin as a triiodide (iodine plus iodide), at a ratio of ~ 3 parts iodine/ 1 part iodide, yielding ~ 4 mg/L total iodine (iodine plus iodide) in the potable water. This level of iodination has been adequate for microbial control throughout the missions.

Recently, the issue of thyroid dysfunction in association with the use of excess iodine has been raised. In space shuttle flights, astronauts consume approximately 2 liters of iodinated water per day for missions as long as 17 days in duration (~ 8 mg/day iodine). In general, individuals are euthyroid upon admission to the astronaut corps; however, most of these individuals have not been screened for anti-thyroid antibodies. A recent review of the data base of astronaut heath records (Longitudinal Study of Astronaut Health) suggests a prevalence of thyroid dysfunction that is greater than the prevalence of thyroid dysfunction in the general population.

NASA has conducted a series of ground based tests to evaluate long duration operation of closed loop life support systems. These tests involved four crewmembers for whom the air, water, and waste was continuously recycled by the life support systems. Iodine was used in the potable water system, at 5 mg/L total iodine. After completion of a 60-day study, one of the male test subjects developed laboratory evidence of mild hypothyroidism and a 15 pound weight gain. [redacted]. The thyroid functions of this crew were normal upon entry (TSH ranges 0.8-1.9); however, when their thyroid functions were evaluated at 30 days after the test began, all 4 crewmembers showed a 2-4 fold increase in TSH and decrease in T4. They had consumed 2-4 L/day of iodinated water (10-20 mg/day iodine).

The following conclusions have been made on the basis of review of the medical literature and consultations with several recognized authorities on iodine related thyroid disorders:

1. Most people who ingest excess iodine will show transient effects but will revert to normal following cessation of excess iodine intake.
2. Susceptible individuals may develop Hashimoto's thyroiditis, hypothyroidism, iodide goiter, or hypothyroidism from excess iodine ingestion.
3. Individual susceptibility to excess iodine cannot always be determined in advance.
4. The safe limit of iodine varies, but in some individuals adverse effects may be seen at 0.5 mg/day.
5. The incidence and magnitude of adverse effects is related to the level of iodine that is ingested.

NASA Medical Operations Branch made an official recommendation that the total amount of iodine ingested by crewmembers should be limited to a maximum of 0.5 mg/24 hrs. This limit includes iodine from all sources including dietary intake and potable water consumption.

The water quality engineering division was directed to devise a method of removing the iodine from chamber water prior to use. They installed an iodine removal cartridge (an anion exchange resin) and a 0.2 micron filter just proximal to the use port. This change has reduced the iodine level to < 0.05 mg/L . Microbial counts from the deiodinated galley use port have been <20 cfu/100 ml (with most counts <1 cfu/100 ml). A similar iodine removal cartridge was temporarily installed on the Space Shuttle, which launched on November 19. The engineering division is currently working to develop a resin system that efficiently reduces iodine to a level that has no physiological effect but still provides effective biocidal control.

2.0 Questions and Agenda

2.1 Questions to be Addresses at Panel Discussion

1. What are the acute effects of iodine on thyroid function?

2. During space flight, TSH values have often increased to levels that have exceeded the normal range. What physiological/pathological changes can occur during this period of abnormal TSH?

3. Does duration of exposure to excess iodine affect the ability of thyroid function to revert to normal following elimination of excess iodine? What about the cumulative effects of repeated exposure?

4. Can we quantify the risks? Is there evidence of a higher incidence of permanent hypothyroidism later in life?

5. We have recommended a maximum of 0.5 mg/day iodine to minimize the risk of adverse effects. What would be an appropriate level to avoid any serious health effects? Is there a no-effect level?

6. We understand that susceptibility can be identified in some individuals by screening for anti-thyroid antibodies, ultrasound, and using a narrow range for TSH. Would you discuss these and recommend any other prescreening measures?

7. Can excess iodine, either for sufficient duration or at a high dose, precipitate Hashimoto's thyroiditis or hypothyroidism in individuals who are not genetically predisposed to these diseases? Can other factors known to affect thyroid function, such as stress and shifts in circadian rhythm, act in concert with the iodine to cause disease?

8. Do we accelerate or otherwise provoke the appearance of these diseases in susceptible individuals by administering excess iodine? Can we reverse this problem if the iodine is stopped?

9. Is there a potential causal association between iodine intake and thyroid dysfunction in our population? How would you follow individuals who have anti-thyroid antibodies and variable borderline elevations of TSH?

10. Some individuals have subclinical hypothyroidism. Does the presence or absence of signs and symptoms alter your approach to treatment?

11. The international space station will be composed of a diversity of peoples from all over the world. Discuss the potential adverse effects of excess iodine on racial, ethnic, and gender diverse groups.

2.2 Agenda

Agenda: Iodine and its effects on thyroid function in the United States space program Wednesday, January 14, 1998

07:30 - 07:40	Introductory Remarks	Sam Pool, M.D., Chief Medical Sciences Division
07:40 - 08:00	Background on Effects of Excess Iodine	Kathleen McMonigal, M.D.
08:00 - 08:25	History of U.S. Spacecraft Potable Water Disinfection	Richard Sauer, P.E., M.S.
08:25 - 08:50	Longitudinal Study of Astronaut Health Data	Mary Wear, M.P.H.
08:50 - 09:00	Break	
09:00 - 10:50	Discussion	All
10:50 - 11:00	Break	
11:00 - 11:50	Panelists Develop Recommendations	
11:50 - 12:00	Break	
12:00 - 01:00	Lunch	
01:00 - 02:45	Summary and Recommendations by Panelists	
03:00 - 04:30	NASA tour for panelists (optional)	

Panelists:

Lewis Braverman, M.D.
Professor, University of Massachusetts, Worcester
Professor, Brigham and Women's Hospital, Boston

John T. Dunn, M.D.
Professor, University of Virginia, Charlottesville

John Stanbury, M.D.
Professor, Harvard University (emeritus)
Professor, Massachusetts Institute of Technology (emeritus)

3.0 Panelists' Summary and Recommendations

Summary and Recommendations from Panelists at Iodine and Thyroid Function in United States Space Program. January 14, 1998

1. The optimal target for maximum daily iodine intake in space flight crew is 0.15 - 0.25 mg. This limit includes iodine from all sources, including dietary intake and potable water consumption.

2. Before defining a maximum allowable iodine concentration in the drinking water, the iodine content of all foods consumed by crewmembers during space flight must be determined by **assay**.

3. The goal for the engineering division is to reduce the iodine in the drinking water of the Shuttle and the International Space Station to undetectable levels, while still maintaining disinfection within the galley tubing. While developing methods to meet this goal, total iodine concentrations of up to 0.25 mg/L could be considered to be tolerable in space craft potable water supplies. Total iodine intake from water may be up to 0.5 mg/day. The combined maximum daily iodine intake from food and water could be as high as 1.0 mg/day, in the interim.

4. Avoid iodized salt in crew food. Any multivitamin/mineral supplementation is to be free of iodine. Foods containing high concentrations of iodine should be avoided.

5. Urinary iodine levels must be obtained periodically during flights to insure that crewmembers are consuming iodine in amounts that do not exceed allowable maximum daily iodine intake.

6. Based on available data, there is no conclusive evidence of serious harm to astronauts from the iodine consumed in space flight. There is, however, a possible causal association between excess iodine intake and thyroid dysfunction in the astronaut population, since it is known that iodine can provoke the types of thyroid disorders that have been found in the astronaut population.

7. Following their selection as astronauts, the initial thyroid health screening of astronauts should include routine thyroid function tests and tests for thyroid autoantibodies. A consensus regarding the need for thyroid ultrasound examination was not determined. Some participants thought that it would be prudent to obtain ultrasound examinations of the thyroid at the initial examination, and subsequently as clinically indicated. If the thyroid autoantibody tests are negative, rescreening for autoantibodies every 5 years is appropriate. If thyroid autoantibody tests are positive, then individuals should be followed more closely and monitored for early signs of

thyroid failure. Routine thyroid function tests should be obtained for all astronauts on an annual basis.

8. Most individuals with elevated TSH on 2 or more occasions should be placed on thyroid replacement hormones, particularly if autoantibodies are present.

9. International astronauts merit special consideration. Since many of these individuals come from iodine deficient regions of the world, they may be especially sensitive to even small increases in the amount of iodine that is consumed. Thyroid autoantibodies and thyroid ultrasonography should be obtained on international astronauts. Urinary iodine levels should be determined, with 0.1 mg/L being considered as the lower limit of normal. Levels that fall beneath this suggest significant iodine deficiency and may indicate that the individual is at risk for iodine-induced hyperthyroidism if supplemental iodine is initiated at levels greater than 0.25 mg/day.

Compiled: K. A. McMonigal, M.D., February 3, 1998

3.1 Panelists

Lewis E. Braverman, M.D.
Brigham and Women's Hospital
Richardson-Fuller Building, Room #157
221 Longwood Ave.
Boston, Massachusetts, 02115
[redacted]

John T. Dunn, M.D.
University of Virginia
Box 511 HSC, Room #1229 Jordan Hall
Charlottesville, Virginia 22908
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John B. Stanbury, M.D.
[redacted]

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FROM: Denise Patterson

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COMMENTS:

Dr. McMonigal

Attached are the copies of Dr. Braverman, Dr. Dunn, and Dr. Stanbury CV's.

Thanks,
Denise Patterson

If you do not receive all the referenced pages, please call [redacted] and ask to speak to the person who transmitted the FAX.

CURRICULUM VITAE

Name: Lewis E. Braverman, M.D.
Address: [redacted]
Date of Birth:
Place of Birth:

Education:

1947	Milton Academy (cum laude)
1951	Harvard College (cum laude), A.B.
1955	Johns Hopkins University School of Medicine, M.D.

Postdoctoral Training:

Internship and Residencies:

1955-56	Medical Intern, Beth Israel Hospital, Boston
1958-60	Resident in Medicine, II-IV (Harvard) Medical Services, Boston City Hospital

Research Fellowships:

1960-1962	Research Fellow in Endocrinology, Harvard Medical Medical School, (Thorndike Memorial Laboratory) Boston City Hospital

Military Service:

1956-58	Captain, U.S. Army

Licensure and Certification:

1955	Maryland License Registration No. D00844
1955	Massachusetts License Registration No. 25746
1963	American Board of Internal Medicine, Certificate No. 20590
1972	American Board of Nuclear Medicine, Certificate No. 02255

Academic Appointments:

1959-60	Assistant in Medicine, Harvard Medical School
1960-62	Research Fellow in Medicine, Harvard Medical School
1962-64	Clinical Assistant in Medicine, II-IV (Harvard) Medical Services, Boston City Hospital
1962-63	Instructor in Medicine, Tufts Medical School
1963-64	Senior Instructor in Medicine, Tufts Medical School
1964-72	Instructor in Medicine, Harvard Medical School
1964-68	Assistant Professor of Medicine, Tufts Medical School

1968-71	Associate Professor of Medicine, Tufts Medical School
1971-75	Professor of Medicine, Tufts Medical School
1975-	Professor of Medicine, UMass Medical School
1975-	Professor of Nuclear Medicine, UMass Medical School
1977-	Professor of Physiology, UMass Medical School
1977-	Lecturer on Medicine, Harvard Medical School

Hospital Appointments:

1962-68	Assistant in Medicine, Beth Israel Hospital
1963-	Assistant Visiting Physician, St. Elisabeth's Hospital
1975-	Assistant Visiting Physician, Boston City Hospital
1975-	Consulting Physician: Memorial Hospital, Worcester Worcester City Hospital, Quincy City Hospital, Jordan Hospital, Plymouth Cape Cod Hospital, Hyannis
1975-	Assistant in Medicine, Beth Israel Hospital

Other Professional Positions and Major Visiting Appointments:

1983	Visiting Professor of Medicine, Royal Perth Hospital, University of Perth, Western Australia
1983	Professor of Endocrinology, University of Pisa Medical School, Pisa, Italy (Sabbatical)

Awards and Honors:

1963	Recipient of the Van Meter Essay Award of American Thyroid Association
1970,72-75	Recipient of Faculty Teaching Award, Tufts Medical School
1983	Recipient, Hamburger Prize Award, Technion University School of Medicine, Haifa, Israel
1987	William H. Resnick Lecturer in Medicine, Stamford Hospital and New York Medical College
1987	Distinguished Service Awardee, American Thyroid Association
1988	Sidney C. Werner Lecturer, Columbia University College of Physicians and Surgeons
1988	Paul Starr Memorial Award, American Thyroid Association
1989	Jack H. Mostow Memorial Lectureship, Northeastern Ohio College of Medicine
1990	Boris Catz Thyroid Professor, Cedars Sinai Medical Center, UCLA School of Medicine
1990	Paschkis Lecturer, Philadelphia Endocrine Society, Philadelphia, PA
1990	Sidney H. Ingbar Memorial Lecturer, American Thyroid Association
1991	Rosenberg Lecturer, Framingham Union Hospital Framingham, MA
1993	Eleventh Annual Neil Auerbach Memorial Lecture, Norwalk Hospital, Norwalk, CT

1993	Thomas T. Amatruda Lecturer, Waterbury Hospital, Waterbury, CT
1994	Berthold Prize, German Endocrine Society Wurzburg, Germany
1994	Paschkis Distinguished Lecturer, Philadelphia Endocrine Society, Philadelphia, PA
1994	Beverly Todd Towery Distinguished Lecturer, University of Louisville, Louisville, KY
1994	400 Best Doctors Award, Better Homes & Gardens
1995	Johnson & Johnson Clinical Diagnostics Award, National Academy of Biochemistry
1996	The Twentieth Annual Lectureship of the Internal Medicine Group, New Orleans, LA
1996	1000 Best Specialist in U.S., American Health Magazine
1996	Richard S. Benua Award, Memorial Sloan-Kettering Cancer Center, NY, NY
1997	Honorary Doctorate in Medicine and Surgery, University of Parma, Parma, Italy

Major Committee Assignments:

National and Regional

1973-77	Member, Endocrinology Study Section, NIH
1978-81	Member, Veterans Administration Merit Review Board for Endocrinology
1978-80	Member, Task Force in Endocrinology, NIH
1978	Ad Hoc Reviewer for Endocrinology Study Section, NIH
1978	Ad Hoc Reviewer for Canadian National Research Council
1981	Ad Hoc Reviewer for Veterans Administration Merit Review Board for Endocrinology Council
1985-89	Member, Medical Test Committee for Part II of National Boards
1985-	Member, International Council for the Control Iodine Deficiency Disorders
1988-	Senior Advisor, International Council for the Control of Iodine Deficiency Disorders
1984	Ad Hoc Member, Endocrinology Study Section, NIH
1985-89	Member, Subcommittee B (DDK-B) Study Section, NIH
1987-89	Chairman, Subcommittee B (DDK-B) Study Section, NIH
1992-	Member, National Diabetes Advisory Board
1993	Panelist, Concensus Development Conference "Detection and Management of Lipid Disorders in Diabetes", Am. Diab. Assoc.

School and Hospital:

1975-	Executive Council, School
1975-1989	Radiation Safety Committee, Chairman
1977-80	Scientific Council
1978-82	Graduate School Council

1977-79	Hospital Management Board
1977-79	Executive Committee, Group Practice
1977-	Advisory Board, Group Practice
1977-	Executive Committee, Hospital
1992	Chair, Search Committee, Director Hospital Laboratories
1992	Chair, Search Committee, Director Cancer Program

Editorial Boards:

1973-76	Editorial Board, Journal of Nuclear Medicine
1974-78	Editorial Board, Journal of Clinical Endocrinology and Metabolism
1979-85	Editorial Board, American Journal of Physiology, Endocrinology and Metabolism
1985-88	Editorial Board, Endocrine Reviews
1986-	Associate Editor, Yearbook of Endocrinology
1986	Co-Editor, The Thyroid--A Fundamental and Clinical Text, J.B. Lippincott, Philadelphia
1988-93	Editor-in-Chief, Journal of Clinical Endocrinology and Metabolism
1991	Co-Editor, The Thyroid--A Fundamental and Clinical Text, J.B. Lippincott, Philadelphia
1994	Co-Editor, Heart and Thyroid Text, Blackwell-MZV, Vienna, Austria
1994	Co-Editor, Endocrine Review Monographs, The Endocrine Society Press, Bethesda, Maryland
1994-	Editorial Board, Endocrine Reviews
1995-	Editorial Board, Am. J. Physiol. Endocrinol. and Metab.
1995-96	Consulting Editor, MERCK Manual for Patients
1995-96	Consulting Editor, MERCK Manual for Physicians
1995	Consulting Editor, Time Life Medical
1996	Co-Editor, The Thyroid--A Fundamental and Clinical Text, J.B. Lippincott, Philadelphia
1997	Editor, Contemporary Endocrinology, Diseases of the Thyroid, Humana Press, Totowa, NJ

Memberships, Offices and Committee Assignments in Professional Societies:

1962	Massachusetts Medical Society
1962	Johns Hopkins Medical and Surgical Society
1963	American Federation for Clinical Research
1965	American Thyroid Association
1966	Fellow, American College of Physicians
1967	Society of Nuclear Medicine
1968	Endocrine Society
1969	American Society for Clinical Investigation
1974	Fellow, American College for Nuclear Physicians
1975	General Secretary, Seventh International Thyroid Conference

1976	European Thyroid Association
1977	Association of American Physicians
1977-83	Secretary, American Thyroid Association
1978	Program Committee, Endocrine Society
1977-82	Program Committee, Society of Nuclear Medicine
1976	Program Committee, American Thyroid Association
1983-86	Council, Endocrine Society
1983-84	President, Elect, American Thyroid Association
1984-85	President American Thyroid Association
1986-88	Chairman, Development Committee, Endocrine Society
1989	Chairman, Development Committee, American Thyroid Association
1989	American Clinical & Climatological Association
1993-95	Standards of Care Committee, American Thyroid Associations
1994-	Member, American Association of Clincial Endocrinologists
1994-	Society of Obstetric Medicine
1995-1997	Member, Endocrine Society Nominating Committee

Major Research Interests:

1. Thyroid Physiology and Pathophysiology
2. General Endocrinology

Teaching Experience:

1962-75	Formal Lectures in Endocrinology, Tufts Medical School
1962-75	Preceptor in Clinical Elective in Endocrinology, Tufts Medical School
1975-	Formal Lectures in Endocrinology, University Massachusetts Medical School
1975-	Preceptor in Clinical Elective in Endocrinology University of Massachusetts Medical School

Principal Clinical and Hospital Service Responsibilities:

1963-75	Director, Endocrine Division, St. Elizabeth's Hospital
1975-	Director, Division of Endocrinology and Metabolism, University of Massachusetts Medical School
1975-86	Acting Chairman, Department of Nuclear Medicine, University of Massachusetts Medical School
1986-	Chairman, Department of Nuclear Medicine, University of Massachusetts Medical School
1992	Chair, Search Committee, Director Hospital Laboratories
1992	Chair, Search Committee, Director Cancer Program

Bibliography: See Enclosure

416. Colzani, R., Fang, S.L., Alex,S. and Braverman, L.E.: The effect of nicotine on thyroid function in rats. Metabolism, (In Press), 1997.

417. Ferling, J., and Braverman, L.E.: My health is feeble: John Adam's health reconsidered. William and Mary Quarterly, (In Press), 1998.

418. Brown, R.S., Cohen III, J.H., Braverman, L.E.:Successful treatment of massive acute thyroid hormone poisoning with iopanoic acid. J. Pediatrics, (In Press), 1998.

419. Simkin, P.H., and Braverman, L.E.:Thyroid and other endocrine disorders in Woman's Imaging, eds, K.L. Reuter, E.E. Mendelson, M. Bohm-Velez, E. Rubin, Mosby Yearbook, Inc., St. Louis, MO, (In Press), 1998.

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423. Minelli, R., Braverman, L.E., Valli,M.A., Schianchi, C., Pedrazzoni, M., Fiaccadori, F., Salvi, M., Magotti, M.G., and Roti, E.: Recombinant interferon α (rIFN-α) does not potentiate the effect of iodine excess on the development of thyroid abnormalities in patients with HCV chronic active hepatitis. Clin. Endocrinol., (Submitted), 1998.

December 1997

CURRICULUM VITAE

JOHN THORNTON DUNN, M.D. [redacted]

Address: [redacted]

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E-mail: [redacted]

Birthdate: [redacted]

Spouse: [redacted]

Education: Princeton University, Princeton, NJ, Biology, A.B., September 1950 - June 1954

Duke University, Durham, NC, Medicine, M.D., September 1954 - June 1958

Training:

1. Intern in Medicine, New York Hospital, Cornell University, New York City, July 1958 - June 1959
2. Assistant Resident in Medicine, University of Utah Hospital, Salt Lake City, Utah, July 1959 - June 1961
3. Clinical and Research Fellow in Medicine (Thyroid Unit), Massachusetts General Hospital and Harvard Medicine School, July 1961 - June 1962
4. Surgeon, USPHS, Division of Radiological Health, assigned to Thyrotoxicosis Follow-up Program, July 1962 - July 1964; concurrent appointments as Clinical and Research Fellow at Thyroid Unit, Columbia University College of Physicians and Surgeons, Presbyterian Hospital (July 1962 - July 1963) and at Thyroid Unit, Massachusetts General Hospital and Harvard Medical School (July 1963 - July 1964)
5. Research Fellow, Department of Biochemistry, Harvard Medical School, July 1964 - August 1966 - research on glycoprotein structure

Academic Positions: Division of Endocrinology, Department of Internal Medicine, University of Virginia Hospital, Charlottesville, VA:

Assistant Professor, August 1966 - 1970
Associate Professor, 1970 - 1976
Associate Chair for Research, 1988-1997
PROFESSOR OF MEDICINE, 1976 - present

Protein and Nucleic Acid Research Facility Oversight Committee, 1988 - 1996 (Chairman)

Associate Director, General Clinical Research Center, University of Virginia, 1986 - 1992

Attending Physician, University Hospital, 1966 - present

Consulting Physician, Salem VA Hospital

Visiting Scientist, Division of Endocrinology, Scripps Clinic and Research Foundation, La Jolla, CA (sabbatical leave 1975 - 1976)

International Council for Control of Iodine Deficiency Disorders (ICCIDD) - Secretary, member of Executive Committee, and Editor, IDD Newsletter, 1985 - present

Honors:

1. Sigma XI, High Honors in Biology, Princeton University
2. Van Meter Prize, American Thyroid Association (for outstanding young investigator, 1968)
3. Research Career Development Award, N.I.H., 1971 - 1976
4. Paul Starr Award, American Thyroid Association (for outstanding contribution to clinical thyroidology, 1997)

Professional Societies:

American Thyroid Association (Public Health Committee 1981-84 (Chairman), 1988-1990, 1995-present) (Chairman), Council, 1990-1994; Awards Committee, 1984-1988)
Endocrine Society
American Society of Biological Chemists
Association of American Physicians
American Federation for Clinical Research
The Southern Society for Clinical Investigation
Peruvian Society for Endocrinology
Society for Experimental Biology and Medicine
Albemarle County Medical Society
American Institute of Nutrition

Areas of Professional Interest:

Thyroid biochemistry and physiology
Clinical thyroid disease
Endemic goiter and nutritional deficiency of iodine

Consultancies (partial list):

Consultant on Iodine Deficiency Disorders, Pan American Health Organization, World Health Organization, UNICEF, World Bank, Canadian International Development Agency, USAID, others, 1970 - present

Consultant missions on iodine nutrition to about 23 developing countries; additional consultancies by telephone or mail with representatives of governments, multilateral organizations, and NGO's.

NIH ad hoc Endocrinology Study Section, various times.

Institute of Medicine, National Academy of Sciences, Committee on Prevention of Micronutrient Deficiencies (member, 1996-97)

Professional Journals:

Editorial Boards:
Thyroid, 1990 - present
Journal of Clinical Endocrinology and Metabolism, 1992 - 1995
IDD Newsletter (Editor), 1985 - present

Manuscript Referee (partial list):
Journal of Clinical Endocrinology and Metabolism, Endocrinology, New England Journal of Medicine, Journal of the American Medical Association, Journal of Biological Chemistry, Thyroid, Clinical Chemistry, European Journal of Endocrinology, Journal of Clinical Investigation

CURRICULUM VITAE

JOHN B. STANBURY, M.D.

Personal

[redacted]

Education

Duke University, Durham, North Carolina	1935	A.B.
Harvard Medical School, Boston, Massachusetts	1939	M.D.

Academic Appointments and Positions

Massachusetts General Hospital, House Officer in Medicine	1940
U.S. Navy, Medical Officer on Active Duty (Lt.(j.G.) to Cmdr.	1941-45
Massachusetts General Hospital, Resident in Medicine	1946-47
Massachusetts General Hospital, Graduate Assistant, Department of medicine	1947-48
Massachusetts General Hospital, Chief Resident in Medicine	1948-49
Massachusetts General Hospital, Assistant in Medicine	1949-50
Massachusetts General Hospital, Chief of Thyroid Clinic and Laboratory	1949-66
Massachusetts General Hospital, Assistant Physician	1950-52
Massachusetts General Hospital, Associate Physician	1956-62
Harvard Medical School, Assistant in Medicine	1946-47
Harvard Medical School, Research Fellow in Pharmacology	1947-48
Harvard Medical School, Assistant in Medicine	1948-49
Harvard Medical School, Instructor in Medicine	1949-50
Harvard Medical School, Associate in Medicine	1950-56
Harvard Medical School, Assistant Professor of Medicine	1056-60
Harvard Medical School, Associate Clinical Professor of Medicine	1960-66
Massachusetts General Hospital, Physician	1962-66
Massachusetts General Hospital, Honorary Physician	1966-
Massachesetts General Hospital, Senior Physician	1982-86
Harvard Medical School, Lecturer in Medicine	1966-
Massachusetts Institute of Technology, Professor of Experimental Medicine	1966-78
Massachusetts Institute of Technology, Professor of Experimental Medicine (emeritus)	1978-
Harvard University-Massachusetts Institute of Technology Program in Health Sciences and Technology, faculty	1972-
University of Leiden, The Netherlands: M.D. (hon)	1975
Executive Vice President, The Pathfinder Fund	1976-78
Massachusetts Institute of Technology, Senior Lecturer	1978-
International Council for the Control of Iodine Deficiency Disorders, Chairman	1986-

Appendix A

Viewgraphs for Background on Medical Effects of Excess Iodine

presented by Kathleen A. McMonigal, M.D.

Medical Effects of Excess Iodine

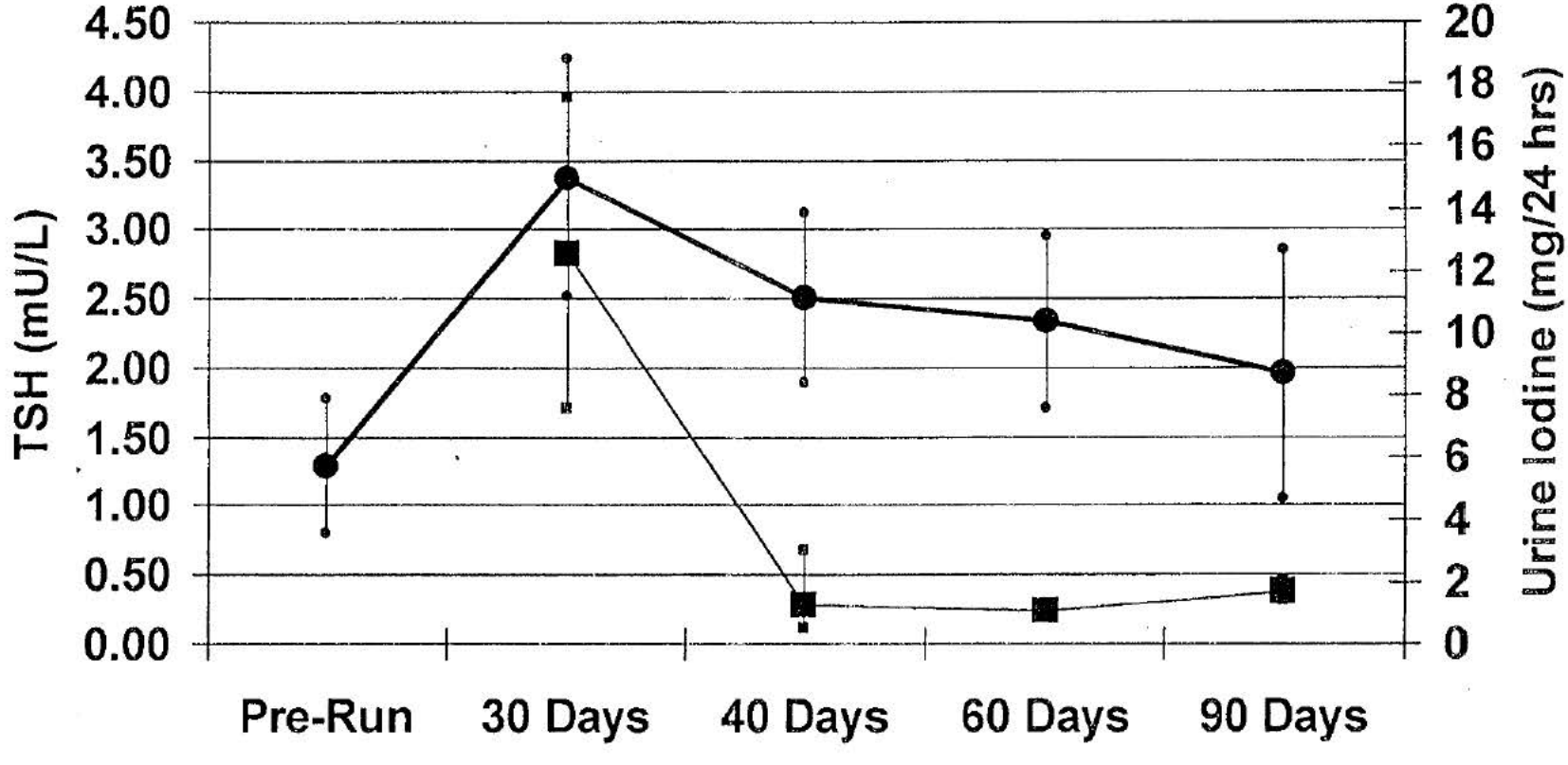
- **Case Reports**
  - Phase IIa Lunar Mars Life Support Test Project
    - crewmember exhibits hypothyroidism following 60 day test
  - [redacted]
    - [redacted]
      - [redacted]

Epidemiology Section

MEDICAL OPERATIONS BRANCH

January 1998

Mean TSH and Urine Iodine Values Prior to, During and After the [redacted] Study



N=4 (except at 90 days for urine iodine where N=2)
Iodine was removed from drinking water on Day 30

- Mean TSH (mU/L) ± 1 SD
- Mean Urine Iodine (mg/24 hours) ± 1 SD

Normal Range = 0.10-0.46 mg/24 hours

Lyndon B. Johnson Space Center

Medical Effects of Excess Iodine

Iodine intake from Shuttle/Chamber Water compared to Recommended Dietary Allowance (RDA)

RDA	0.15 mg/day
avg. US diet	0.2 to 0.7 mg/day
toxicity appears in susceptible persons	0.5 to 1.0 mg/day
Skylab water > 6mg/Liter	12 to 24 mg/day*
Shuttle water 4 mg/Liter	8 to 16 mg/day*
Chamber water 5 mg/Liter	10 to 20 mg/day*

* based on 2 to 4 Liter/day water consumption



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Medical Effects of Excess Iodine

Approach to the Problem

1. Medical Literature Review

2. Biomedical Results from Skylab

3. Consultations with leading endocrinologists, recognized as authorities in thyroid diseases and iodine

4. Longitudinal Study of Astronaut Health

Skylab Results

- SL 2 (28 days)
  - all 3 crewmembers had elevated TSH at completion of mission, but reverted to normal by R+4
- SL 3 (59 days)
  - all 3 crewmembers had elevated TSH at completion of mission and at 14 days
  - 1 crewmember has chronic thyroid dysfunction (chronic thyroiditis)
- SL 4 (84 days)
  - 2 of 3 crewmembers had elevated TSH at completion of mission and at R+14 but normal by next annual PE

Longitudinal Study of Astronaut Health

- selected, pre-screened population
- 270 Astronauts (234male, 36 female)
- 19 total cases of thyroid disorders

  15 male = 6.4%

  4 female = 11.1%

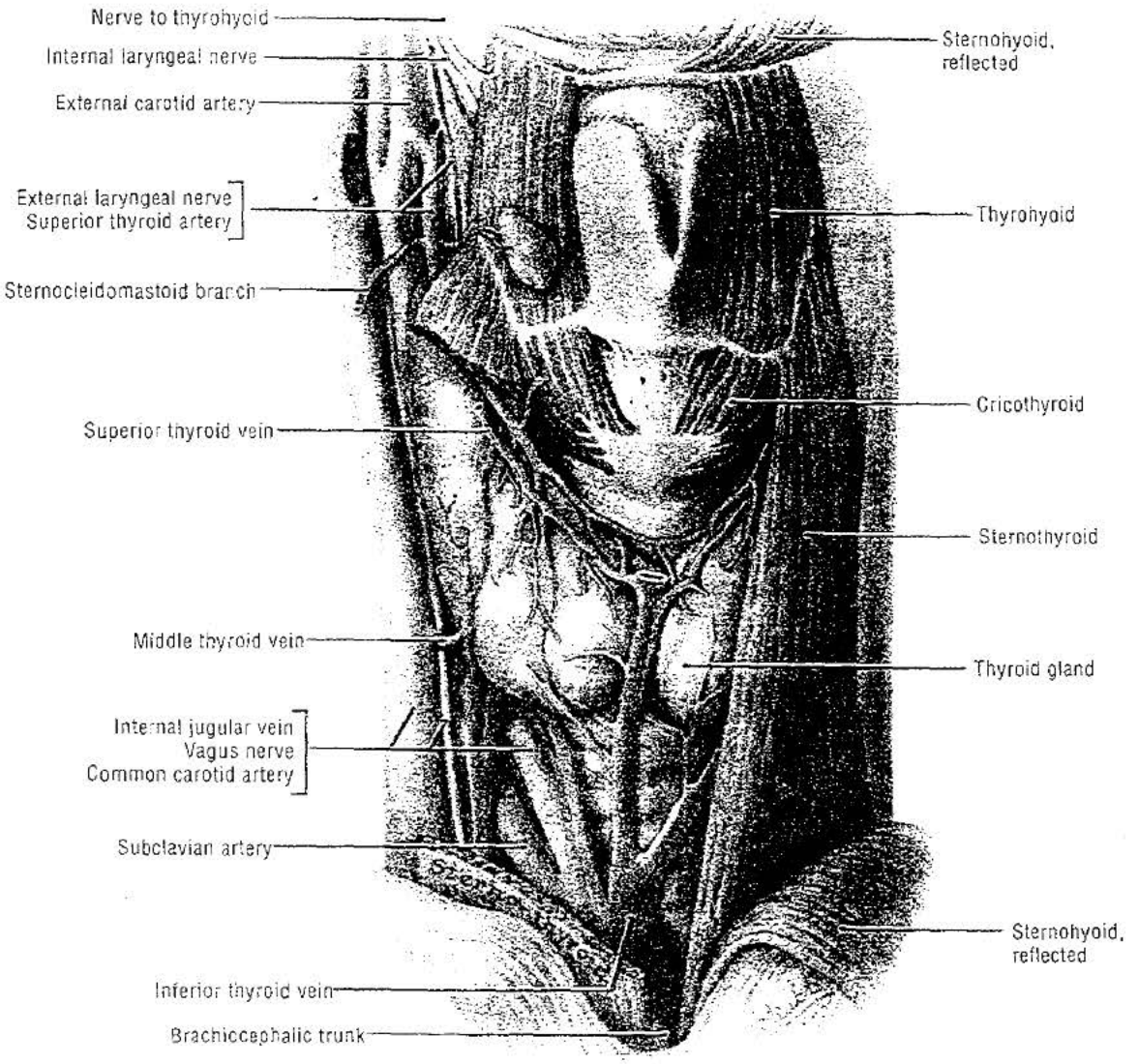

Figure 8-36. Dissection of the anterior aspect of the neck. In this specimen there is an accessory thyroid gland on the right, lying on the thyrohyoid muscle, lateral to the thyroid cartilage.

Medical Effects of Excess Iodine

- **Thyroid Anatomy**
  - located at base of neck
- **Thyroid Physiology**
  - regulated by TSH that is secreted by pituitary
    - feedback loop exists between pituitary and thyroid
  - concentrates iodine
  - synthesizes and secretes thyroid hormones
  - thyroid hormones act at multiple sites, regulating metabolic processes



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Medical Effects of Excess Iodine

Medical Conditions Resulting from Excess Iodine

- **Hashimoto's thyroiditis**
  - autoimmune thyroiditis (Antibody pos or neg)
    - clearly associated with excess iodine
    - female/male ratio is 10:1 in general population
    - commonly progresses to chronic hypothyroidism
- **Hypothyroidism** - decrease in basal metabolic rate
    - symptoms = fatigue, lethargy, cold intolerance, difficulty in concentrating
    - associated with excess iodine intake in individuals who normally have adequate dietary iodine intake
- **Hyperthyroidism** - hypermetabolic state
    - symptoms = nervousness, rapid heart rate, heat intolerance, tremor, fatigue
    - associated with excess iodine intake in individuals who have been chronically iodine deficient

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Medical Effects of Excess Iodine

Conclusions:

1 Most people who are exposed to excess iodine will show transient effects which revert to normal after cessation of excess iodine intake.

2. Susceptible individuals may develop Hashimoto's thyroiditis, hypothyroidism, iodide goiter, or hyperthyroidism from excess iodine.

3. Individual susceptibility to excess iodine cannot always be determined in advance.

4. The safe limit of iodine varies, but in some individuals adverse effects may be seen at 0.5 mg/day.

NASA Medical Operations Requirement Statement

On average, the total amount of iodine ingested by space flight crewmembers per 24 hour period should be limited to a maximum of 0.5 mg. This limit includes iodine from all sources including dietary intake and potable water consumption.

Appendix B

Viewgraphs for History of U. S. Spacecraft Potable Water Disinfection

presented by Richard Sauer, P.E., M.S.

History of US Spacecraft Porable Water Disinfection

Vehicle	Disinfectant	Results
Mercury	Tap Water	Unknown
Gemini	Chlorine Quat	Not Effective Adverse Tastes
Apollo CM	Chlorine	Manual Addition Adverse Tastes Effective
Apollo LM	Iodine	Preflight Addition Effective
Skylab	Iodine	Manual Addition Effective
Shuttle	Iodine	MCV Addition Effective
Mir	Silver + Pasteurization Silver Alone	Effective Not Effective
Space Station	Iodine	Planned

Alternate Spacecraft Disinfectants Considered

Filtration

- No residual activity
- Physical blockage potential
- "Grow-thru" phenomenon
- Single point application

Chlorine

- Lack of automatic, reliable addition system
- Difficulty in maintaining residual
- Potential of forming trihalomethanes (THMs):
  Potential Carcinogenes

Others

- Ozone, Hydrogen peroxide, UV/Sonication

Alternate Spacecraft Disinfectants Considered

Silver

- Considered for Skylab and Shuttle
- Discarded
  - No reliable simple method of addition
  - Methods of detection are difficult
    - Not adaptable for flight
  - Rapid development of bactericidal resistance
  - Maintenance of residual not predictable

Ultraviolet (UV)

- No residual activity in distribution system
- Single point application: Microbial growth/biofilm formation and attendent contamination from microbial byproducts
- Power requirement
- Fouling of optical windows

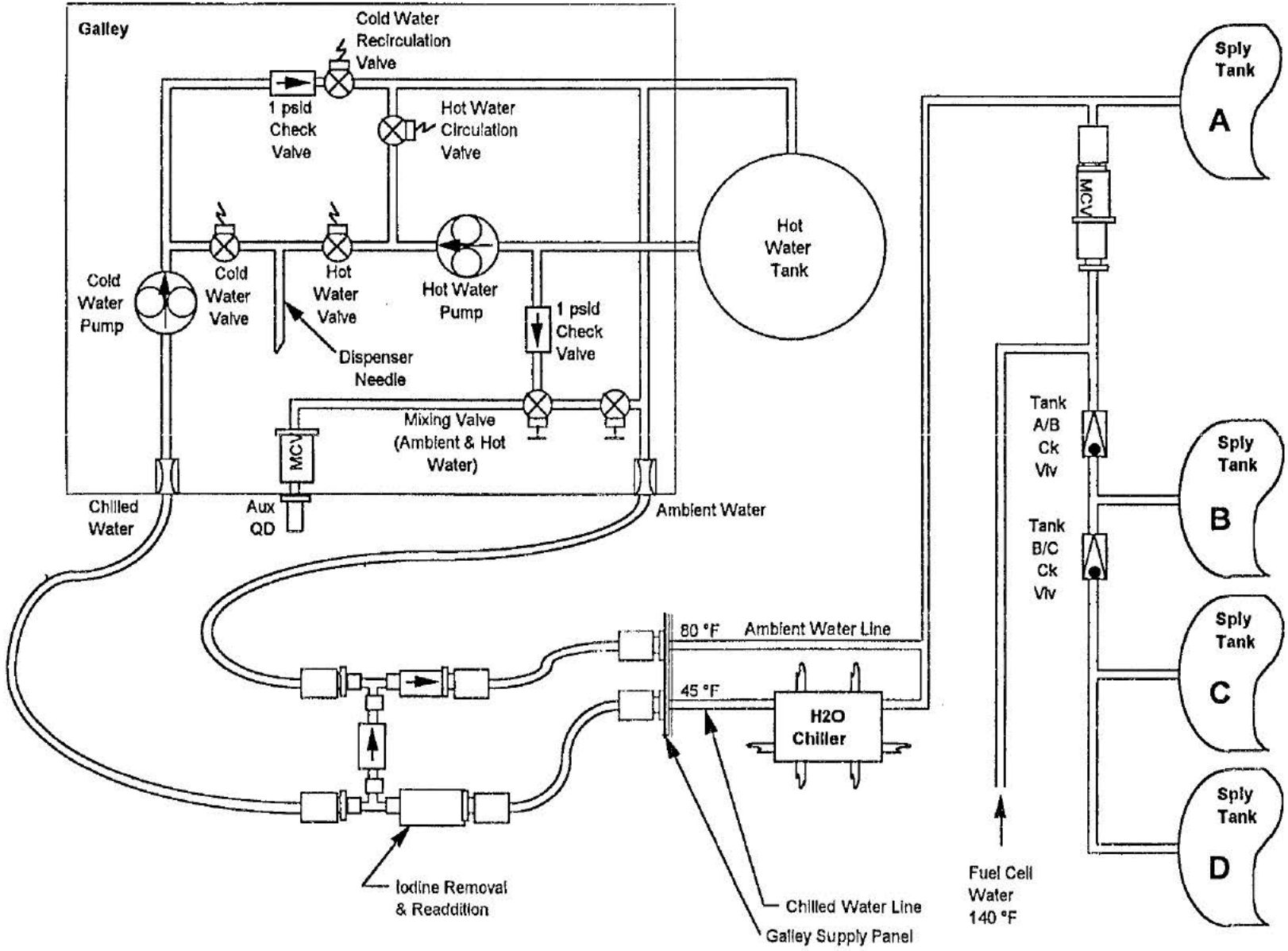
POTABLE WATER DISINFECTION

IN

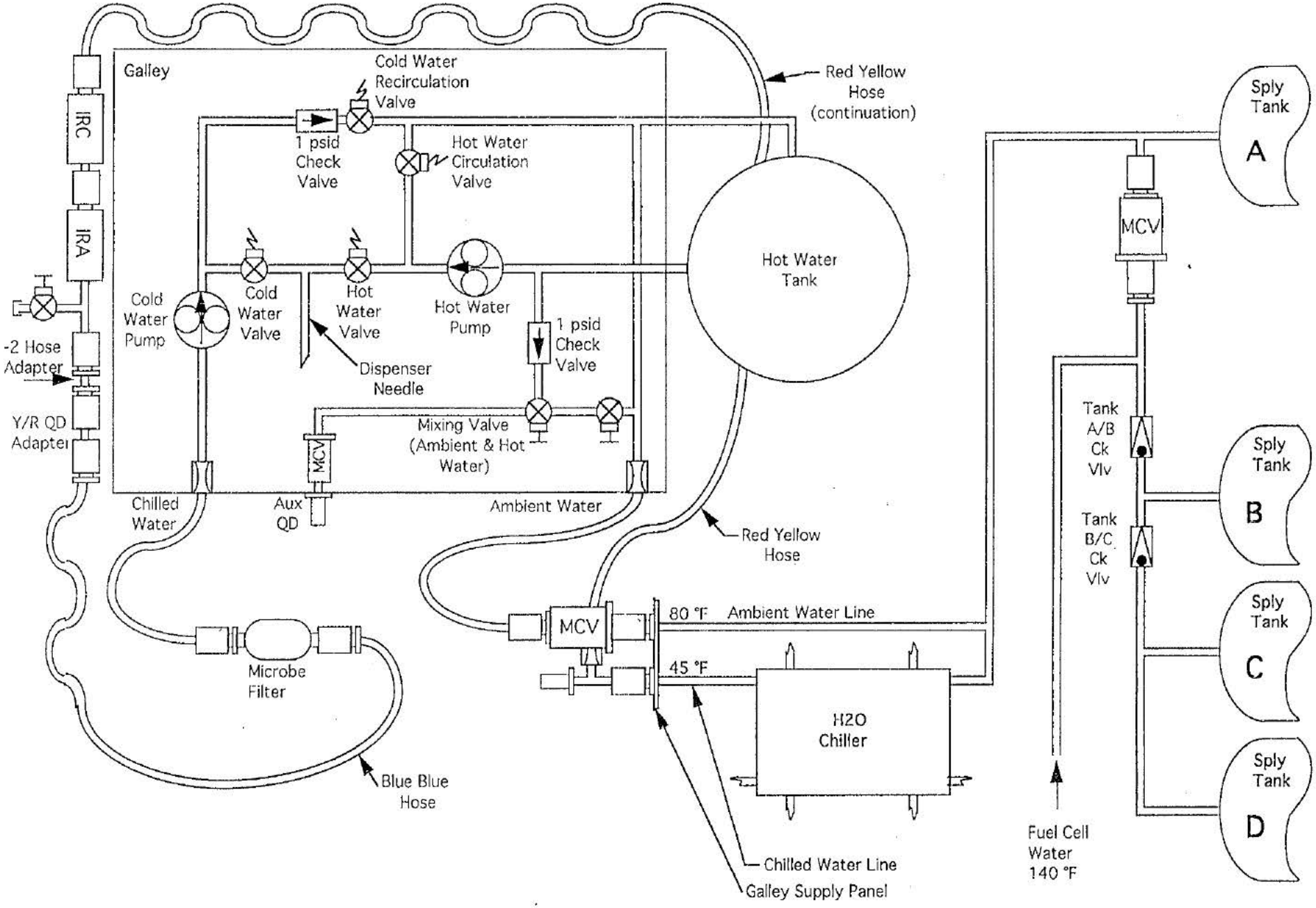
SPACECRAFT

Dick Sauer

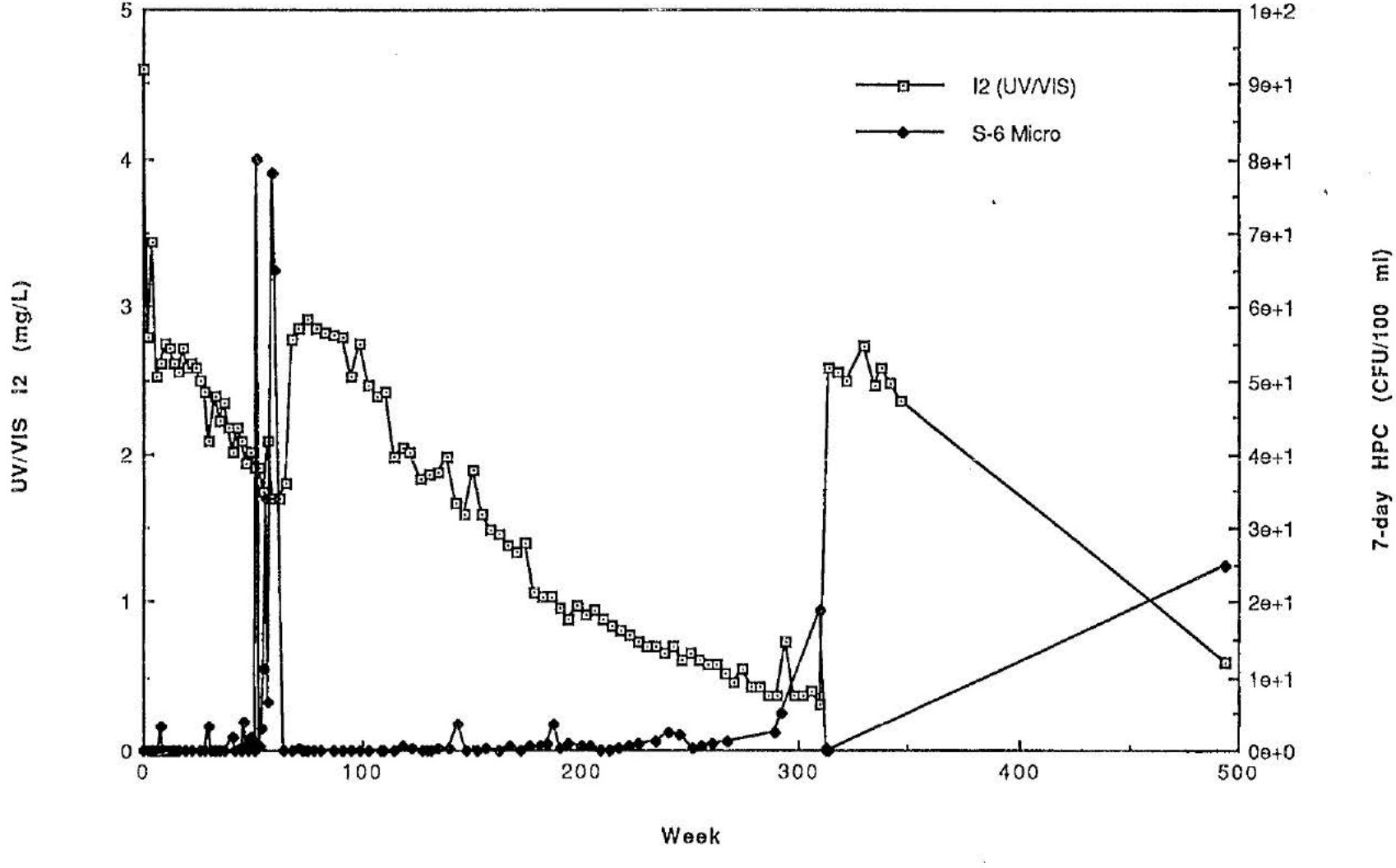
Shuttle Potable Water Iodine Removal Option



Galley With Option #3 Iodine Removal Equipment Installed (STS 87)



Long-Term Biofilm Control Test
Iodine and Bacterial Levels at Port S-6



Shuttle Current Plans

- STS-87:
  - IRMIS deiodinator placed between chilled water outlet & Galley with microbe filter added
    - IRMIS used to deiodinate water transferred to *Mir*
  - Microbial Check Valve (MCV) placed in ambient line
  - Flight Sample Results

	Total Iodine (mgl)	
	Day 0	Day 14
Cold Water	0.12	N.D.
Hot Water	1.51	0.17*

**Suspect Container Incompatibility*

- STS-89
  - Will use same system as STS-87 with mods for CWC servicing

Conclusion

- Active disinfectant level in water systems required to prevent microbial growth.
- Iodine is an effective method for water disinfection and its use should be continued.
- Technology is available to reduce total Iodine to medically acceptable levels.

Recommendation

- Continue treatment of water with Iodine
- Iodine Reduction:

  Short Term: Reduce Iodine to acceptable level using existing hardware depending on required acceptable Iodine level

  Long Term: Develop a resin system, used prior to water consumption, that efficiently removes Iodine to a level that has no physiological effect but provides effective biocidal control

Appendix C

Viewgraphs for Longitudinal Study of Astronaut Health Data

presented by Mary Wear, M.P.H.



Epidemiology Section

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January 1998

Epidemiology Section

Thyroid Disease and Exposure to Iodine During Space Flight

The Longitudinal Study of Astronaut Health (LSAH)

Primary Hypotheses:

- Astronauts have a different risk of total mortality than do ground-based employees

- Astronauts have different risks of total morbidity than do ground-based employees



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Other Objectives

- To examine the mortality and morbidity rates of both the astronauts and the civil service employees in comparison to the general population
- To determine the rate of illness and accidents which require medical care and/or the use of medical equipment and supplies during space travel
- To establish a comprehensive database which will facilitate investigations of health issues as related to specific occupational exposures and health issues in this study population
- To describe the astronaut population



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Study Design

Exposure to the space environment is rare. A cohort study design was chosen to accommodate this constraint. Case comparison studies are nested within this cohort study to examine those research questions where a case comparison study design is appropriate.



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Population

Astronauts

All astronauts selected for the manned space program are followed from selection throughout their life spans.

Comparisons

The primary comparison group comprises JSC employees who received a routine physical examination in the JSC Occupational Medicine Clinic during an astronaut selection year. These employees were group matched to the astronaut classes at a 3:1 ratio by age, sex, and body mass index at baseline.

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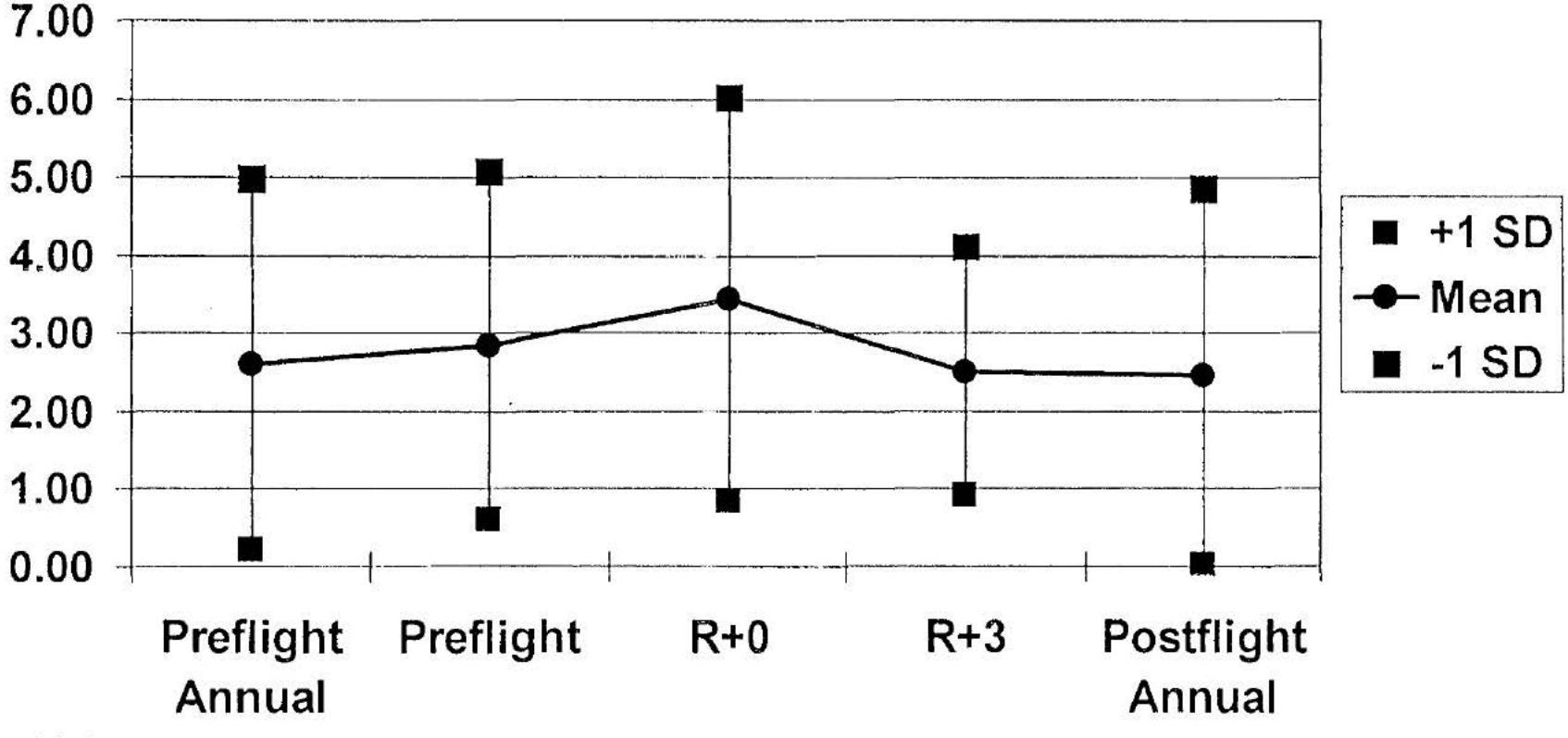
Mean TSH Values at Preflight, Postflight, and Annual Examinations



N=134

Mean TSH at R+0 is significantly different from all other examinations (paired t-test, $p<0.001$)

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Ascertainment of Clinical Thyroid Disease Among Astronauts and Comparisons

- Based on diagnoses documented in JSC clinic medical records from date of selection into astronaut corps (astronauts) or date of selection into LSAH (comparisons) to present
- ICD coding completed for all astronaut physical examinations and private consultant reports
- ICD coding completed for all comparison private consultant reports; a large portion of historical comparison physical examinations have not been data entered or coded



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ICD Codes Used to Identify Cases of Clinical Thyroid Disease

193	Malignant neoplasm of thyroid gland
226	Benign neoplasm of thyroid gland
240	Simple goiter
241	Nontoxic nodular goiter
242	Thyrotoxicosis
244	Acquired hypothyroidism
245	Thyroiditis
V12.2	Personal history of endocrine, metabolic, and immunity disorders

Epidemiology Section

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Frequency of ICD Codes for 39 Cases of Clinical Thyroid Disease

Frequency *	Code	Description
1	193	Malignant neoplasm of thyroid gland
2	226	Benign neoplasm of thyroid gland
8	240.9	Goiter, unspecified
6	241.0	Nontoxic uninodular goiter
2	241.9	Unspecified nontoxic nodular goiter
1	242.2	Toxic uninodular goiter
1	244.0	Acute thyroiditis
1	244.8	Other specified acquired hypothyroidism
8	244.9	Unspecified hypothyroidism
1	245.1	Subacute thyroiditis
4	245.2	Chronic lymphocytic thyroiditis
8	V12.2	Personal history of endocrine, metabolic, and immunity disorders

* Some cases had more than one ICD code



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Ascertainment of Subclinical Thyroid Disease Among Astronauts

- Astronauts who ever had two or more TSH values greater than 4.5 were identified (N=92).
- For these astronauts, all laboratory records were reviewed manually to identify individuals with persistently elevated TSH.
- Subclinical thyroid disease was defined as elevated TSH values (greater than 4.5) on 3 or more annual physical examinations from 1991 to the present.
- Based on the above criteria, 7 astronauts (6 males and 1 female) were identified as cases of subclinical thyroid disease and combined with the 12 cases of clinical thyroid disease for the following analyses.

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Incidence of Clinical Thyroid Disease Among Astronauts and LSAH Comparisons

	Cases	Noncases	Totals
Astronauts	12 (4.4%)	258	270
Comparisons	27 (3.2%)	808	835
Totals	39 (3.5%)	1066	1105

Odds Ratio = 1.39 (95% CI = 0.69,2.78)

Chi-Square Probability = 0.349

Epidemiology Section

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Incidence of Clinical Thyroid Disease Among Astronauts and LSAH Comparisons

	Cases	Noncases	Totals
Astronauts	12	258	270
Males	9 (3.8%)	225	234
Females	3 (8.3%)	33	36
Comparisons	27	808	835
Males	18 (2.5%)	702	720
Females	9 (7.8%)	106	115
Totals	39	1066	1105

Odds Ratios for comparison of males = 1.56 (95% CI = 0.67, 3.63)
Odds Ratios for comparison of females = 1.07 (95% CI = 0.27, 4.18)

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Incidence of Clinical and Subclinical Thyroid Disease Among Astronauts by Sex

	Cases	Noncases	Totals
Males	15 (6.4%)	219	234
Females	4 (11.1%)	32	36
Totals	19 (7.0%)	251	270

Odds Ratio = 0.548 (95% CI = 0.171, 1.755)
Chi-Square Probability = 0.305

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Incidence of Clinical and Subclinical Thyroid Disease Among Astronaut Pilots and Mission Specialists

	Cases	Non-cases	Totals
Pilots	12 (9.2%)	118	130
Mission Specialists	7 (5.0%)	133	140
Totals	19 (7.0%)	251	270

Odds Ratio = 1.932 (95% CI = 0.737, 5.068)
Chi-Square Probability = 0.174

Epidemiology Section

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Incidence of Clinical and Subclinical Thyroid Disease Among Astronaut Pilots and Mission Specialists by Sex

	Cases	Noncases	Totals
Pilots	12 (9.2%)	118	130
Males	12 (9.4%)	115	127
Females	0 (0%)	3	3
Mission Specialists	7 (5.0%)	133	140
Males	3 (2.8%)	104	107
Females	4 (12.1%)	29	33
Totals	19 (7.0%)	251	270

OR for male pilots vs male mission specialists =3.617 (95% CI=0.994, 13.17), p=0.0512
OR for male mission specialists vs female mission specialists= 0.209 (95% CI=0.044, 0.987), p=0.0482

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Incidence of Clinical and Subclinical Thyroid Disease Among Astronauts by Number of Space Flights

	Number of Space Flights							
	0	1	2	3	4	5	6	Totals
Case	5 (7.7%)	4 (6.6%)	4 (6.8%)	2 (4.2%)	3 (10.3%)	1 (16.7%)	0 (0%)	19 (7.0%)
Noncase	60	57	55	46	26	5	2	251
Totals	65	61	59	48	29	6	2	270

Odds Ratio by univariate Logistic Regression = 1.032 with Chi-Square Probability = 0.8488



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Estimation of Astronaut Exposure to Iodine During Space Flight

- Total iodine (mg/L) based on measured and estimated iodine and iodide levels in the water
- Daily intake of water based on average of 1.915 L/day
- Days of exposure based on mission duration or number of days that water supply contained iodine
- Average total iodine consumption per mission (mg) calculated by:

  Total iodine mg/L x 1.915 L/day x days of exposure
- Cumulative exposure for each astronaut equals sum of mission exposures

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Exposure to Iodine During Space Flight

Missions	Exposure Days Mean (Range)	Iodine (mg/L) Mean (Range)	Mission Intake (mg) Mean (Range)
Mercury 3 to Apollo 10	0	0	0
Apollo 11 to Apollo 17	2.1 (0.7-3.4)	11.28 (9.60-13.00)	45.11 (15.32-75.32)
Skylab 2 to Skylab 4	57.2 (28-84)	26.24 (20.81-31.27)	3060.95 (1115.83-5032.59)
STS-1 to STS-51L	6.34 (2.3-10.3)	5.89 (1.41-8.25)	72.09 (18.90-162.60)
STS-26 to STS-87	9.48 (4.0-17.6)	3.85 (1.90-11.90)	67.25 (17.59-139.99)
MIR-18 to MM-6	9.56 (7.9-10.4)	3.32 (2.62-4.18)	60.83 (45.78-83.38)

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Incidence of Clinical and Subclinical Thyroid Disease Among Astronauts By Estimated Categorical Intake of Iodine

	None	< 1000 mg	≥ 1000 mg	Totals
Case	7 (8.1%)	11 (6.3%)	1 (11.1%)	19 (7.0%)
Noncase	79	164	8	258
Totals	86	175	9	270

Odds Ratio by univariate Logistic Regression = 0.886 with Chi-Square Probability = 0.7903

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Relationship Between Time of Diagnosis, Selection, and Flight

Sex	# of Flights	# of Flights Prior to Dx	Years After Selection	Years After First Flight
M	0	0	-2.6	NA
F	2	0	-0.2	-6.8
M	4	0	0.4	-5.3
M	4	0	0.9	-3.7
M	2	0	1.2	-6.0
M	2	1	4.6	2.5
M	4	1	7.1	1.5
F	3	1	12.0	4.7
F	4	3	14.2	8.3
M	5	4	15.1	5.9
M	4	2	16.7	7.4
M	2	2	31.7	25.5

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Odds Ratios of Selected Risk Factors for Clinical and Subclinical Thyroid Disease Among Astronauts

Explanatory Variables:	Odds Ratio	Probability
Exposure to Iodine (Yes=1,No=0)	0.657	0.5523
Sex (Male=1, Female=0)	0.320	0.0981
Number of Flights (0-6)	1.140	0.5653
Position (Pilot=1, MS=0)	2.613	0.0954

Odds Ratios and Chi-Square Probability from Logistic Regression

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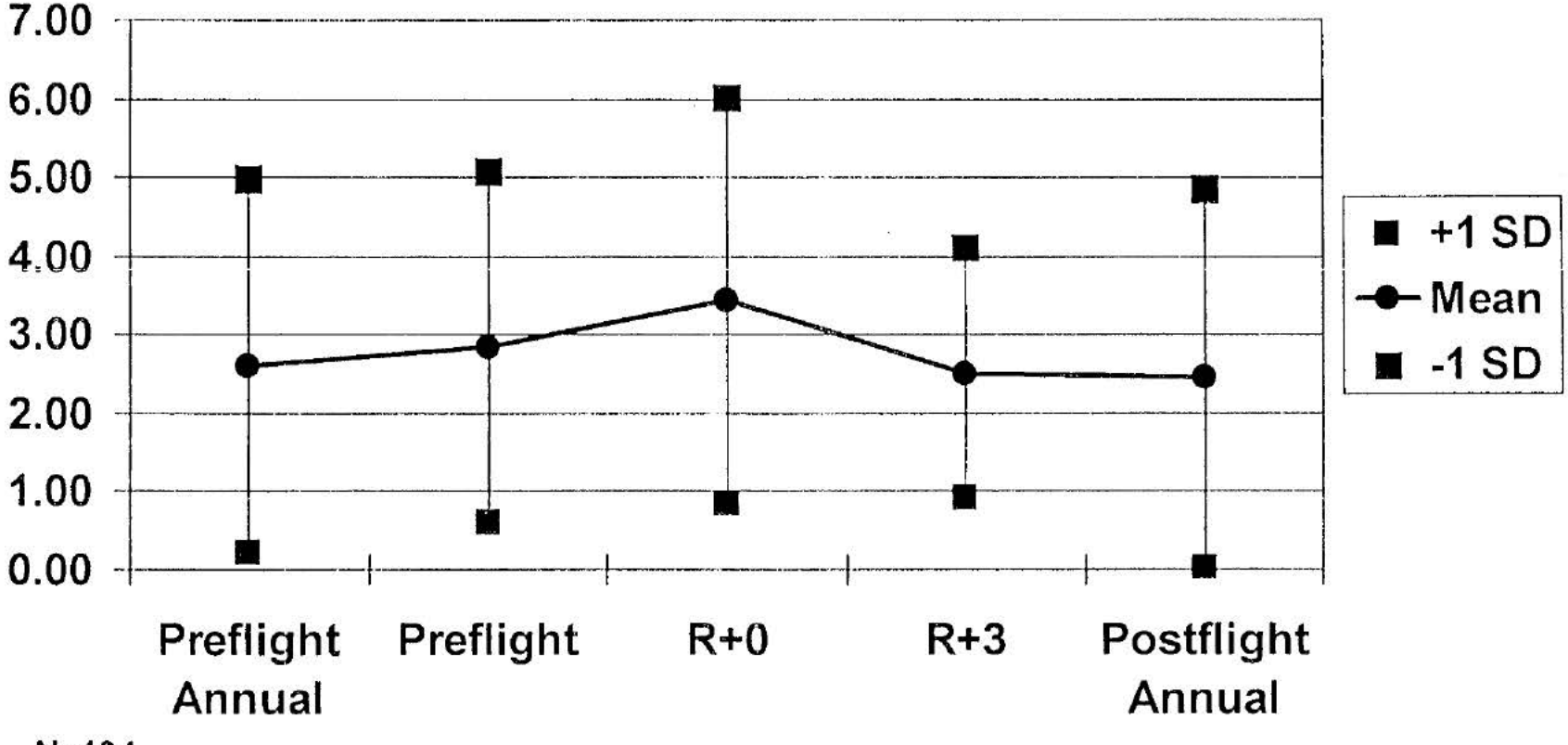
Mean TSH Values at Preflight, Postflight, and Annual Examinations



N=134

Mean TSH at R+0 significantly different from all other examinations (paired t-test, $p<0.001$)

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Mean TSH Values at Preflight, Postflight, and Annual Examinations

	Mean ± 1 SD	Minimum	Maximum
Preflight Annual	2.60 ± 2.39	0.40	17.40
Preflight	2.84 ± 2.24	0.40	19.00
R+0 *	3.43 ± 2.59	0.50	17.00
R+3	2.51 ± 1.60	0.40	13.30
Postflight Annual	2.45 ± 2.42	0.50	22.70

N=134

* Mean TSH at R+0 significantly different from all other examinations (paired t-test, $p<0.001$)

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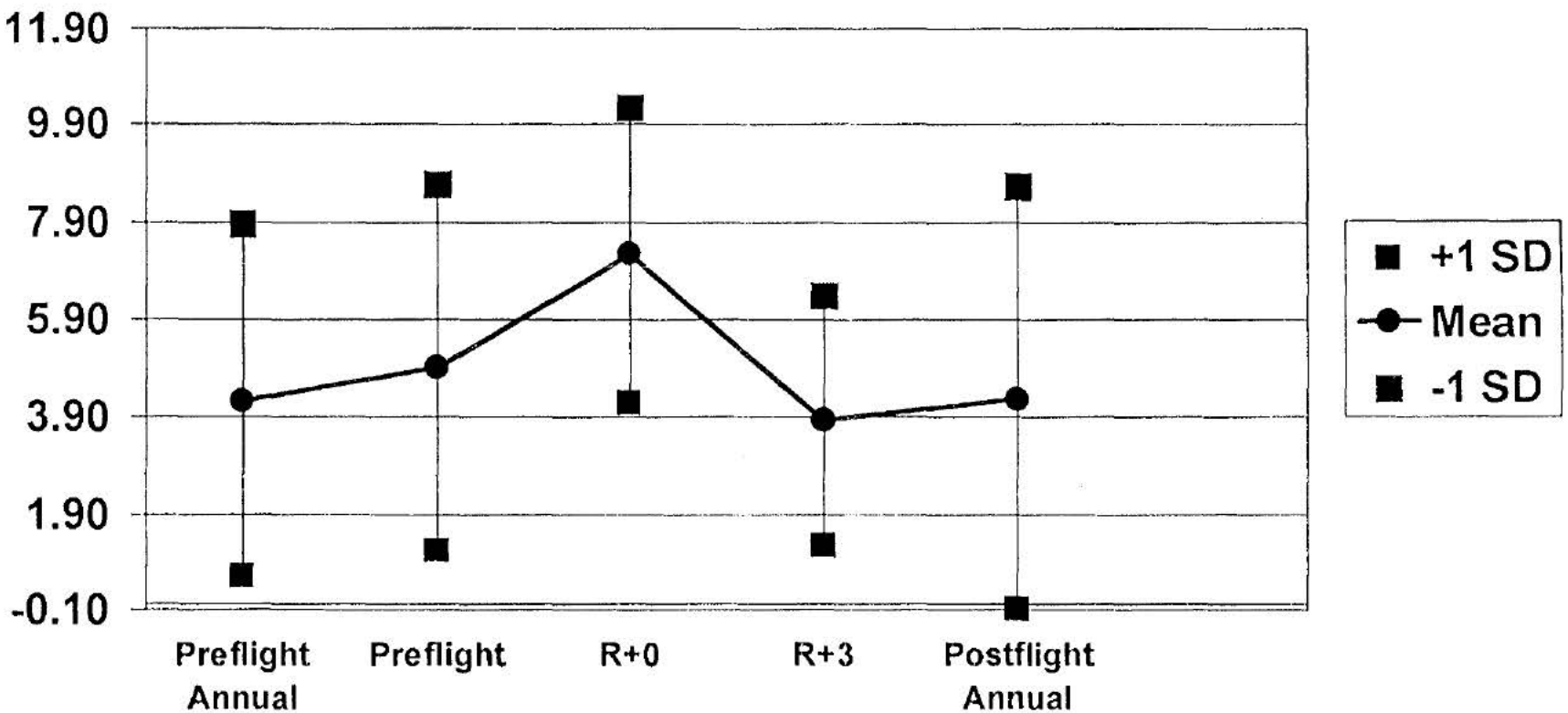
Mean TSH Values at Preflight, Postflight, and Annual Examinations for Astronauts with TSH > 4.5 at R+0 Examination



N=29

Mean TSH at R+0 significantly different from all other examinations (paired t-test, $p<0.001$)

Epidemiology Section

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Mean TSH Values at Preflight, Postflight, and Annual Examinations for Astronauts with TSH > 4.5 at R+0 Examination

	Mean ± 1 SD	Minimum	Maximum
Preflight Annual	4.21 ± 3.62	0.40	17.40
Preflight	4.90 ± 3.76	1.00	19.00
R+0 *	7.23 ± 3.04	4.60	17.00
R+3	3.82 ± 2.59	0.40	13.30
Postflight Annual	4.25 ± 4.35	0.50	22.70

N=29

* Mean TSH at R+0 significantly different from all other examinations (paired t-test, $p<0.001$)

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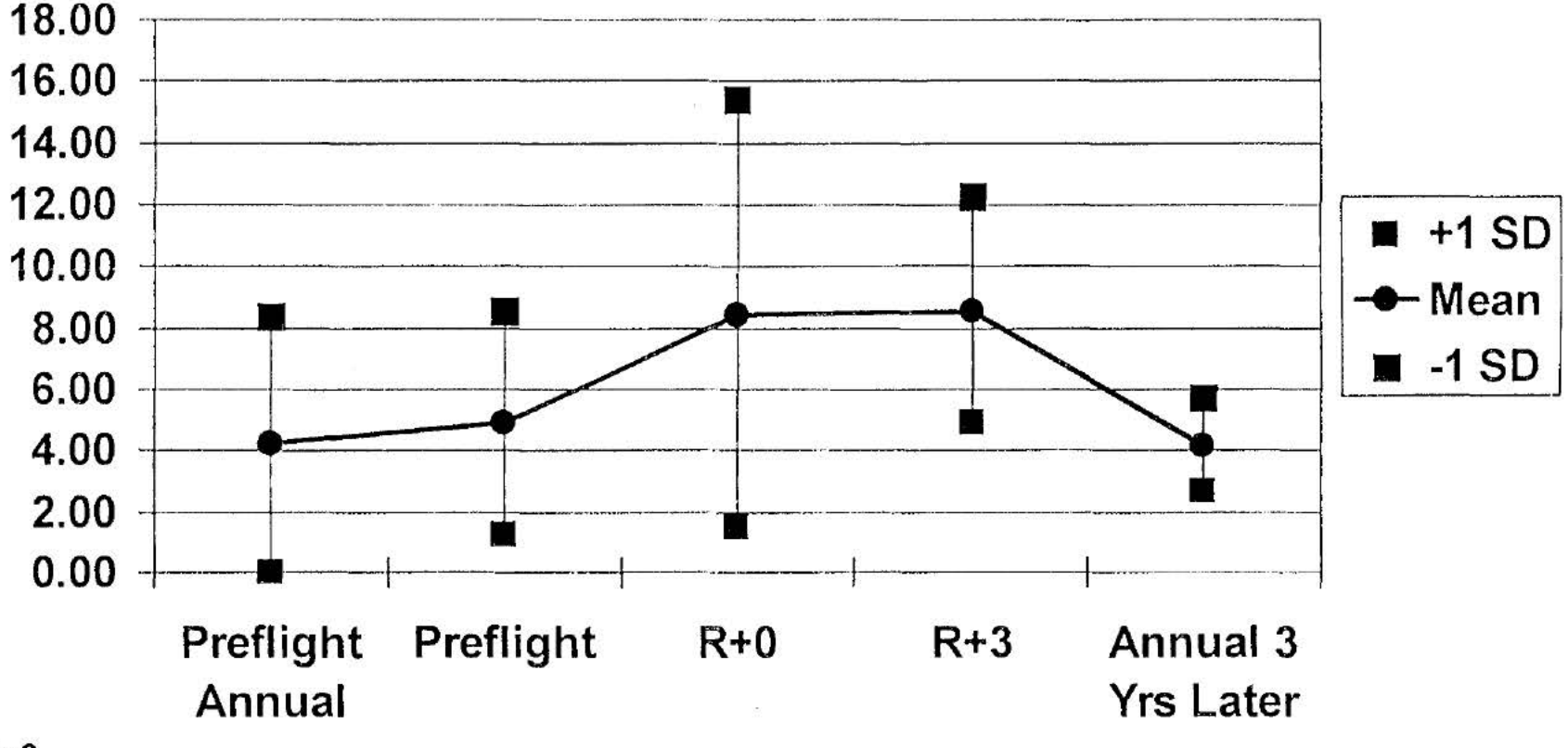
Mean TSH Values at Preflight, Postflight, and Annual Examinations SKYLAB



N=9

Mean TSH at R+3 significantly different from all examinations except R+0 (paired t-test, $p<0.05$)

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Mean TSH Values at Preflight, Postflight, and Annual Examinations SKYLAB

	Mean ± 1 SD	Minimum	Maximum
Preflight Annual	4.19 ± 4.18	1.00	11.50
Preflight	4.89 ± 3.65	1.00	13.50
R+0	8.44 ± 6.94	2.00	25.00
R+3	8.56 ± 3.70	4.00	14.60
Annual 3 Yrs Later	4.17 ± 1.51	3.00	7.80

N=9

Mean TSH at R+3 significantly different from all examinations except R+0 (paired t-test, $p<0.05$)

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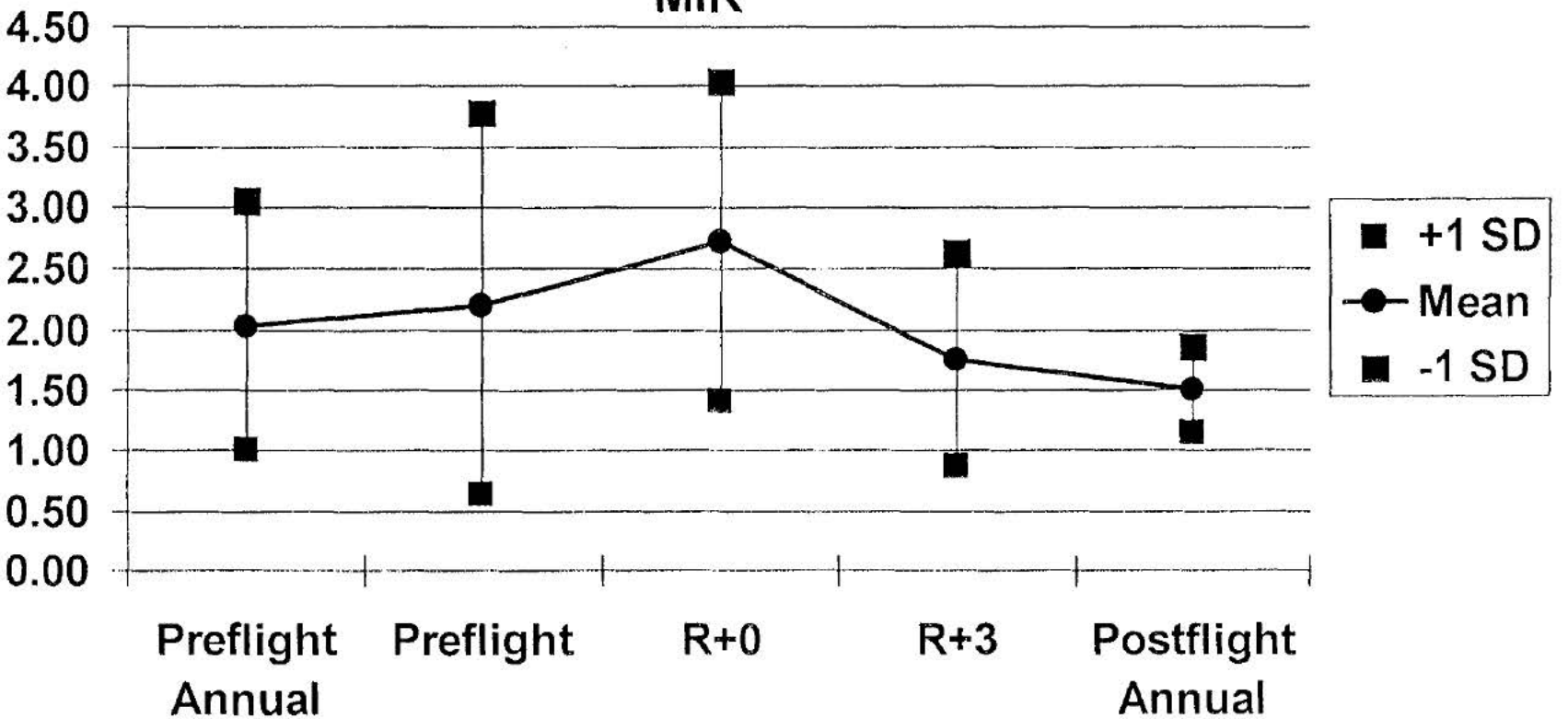
Mean TSH Values at Preflight, Postflight, and Annual Examinations

MIR



N ranges from 3-6

No statistically significant differences in mean TSH between examinations

Epidemiology Section

MEDICAL OPERATIONS BRANCH

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Mean TSH Values at Preflight, Postflight, and Annual Examinations MIR

	Mean ± 1 SD	Minimum	Maximum
Preflight Annual	2.03 ± 1.02	0.80	3.30
Preflight	2.20 ± 1.57	1.10	4.00
R+0	2.72 ± 1.32	1.18	4.60
R+3	1.75 ± 0.88	0.90	2.60
Postflight Annual	1.50 ± 0.36	1.10	1.80

N ranges from 3-6
No statistically significant differences in mean TSH between examinations



Epidemiology Section

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CONCLUSIONS

- There appears to be a transient elevation in TSH values on R+0. On R+3, TSH values are in the process of returning to normal. By the next annual physical examination, TSH values have returned to preflight ranges.
- Astronauts are not at increased risk of developing thyroid disease compared to the LSAH comparison population.

Appendix D

Iodine Conference Highlights

Summarized by Kathleen A. McMonigal, M.D.

Iodine Conference Highlights---January 14, 1998

summarized by Kathleen McMonigal, M.D. February 3, 1998

PANELISTS: Lewis Braverman, M.D.
Professor, University of Massachusetts, Worcester

John T. Dunn, M.D.
Professor, University of Virginia, Charlottesville

John Stanbury, M.D.
Professor, Harvard University, (emeritus)
Professor, Massachusetts Institute of Technology (emeritus)

Morning Session---Presentations

The conference began with a review of the medical effects of iodine on thyroid function by Kathleen McMonigal, M.D. Following the presentation of the index case, she briefly reviewed the history of the ground-based chamber studies. She discussed the alterations in the thyroid function of the test subjects participating in the most recent study that prompted the Medical Division at NASA to recommend that (1) iodine be removed from the chamber drinking water and (2) the use of iodine in the space program be reviewed. Iodine consumption in the water for various types of missions (Skylab [48 -96 mg/day], Space Shuttle [8 - 16 mg/day], and ground-based chamber Tests [10 - 20 mg/day]) was compared with the recommended daily intake formulated by the Food and Drug Administration (0.15 mg/day) and the World Health Organization (0.1 -0.3 mg/day). She reviewed the medical literature, the biomedical results from Skylab, opinions from consultations with leading endocrinologists, and the initial review of the Longitudinal Study of Astronaut Health (LSAH). A brief review of thyroid physiology and of the medical conditions resulting from excess iodine formed the remainder of her discussion. She drew 4 conclusions which were as follows: (1) Most people who are exposed to excess iodine will show transient effects which revert to normal after cessation of excess iodine intake. (2) Susceptible individuals who have underlying thyroid disease such as Hashimoto's thyroiditis or diffuse or nodular goiter may develop hypothyroidism, iodide goiter, or hyperthyroidism from excess iodine. (3) Individual susceptibility to excess iodine cannot always be determined in advance. (4) The safe limit varies but in some individuals adverse effects may be seen at 0.5 mg/day. She ended with the NASA Medical Operations Requirement Statement, drawn up in November 1997: "On average, the total amount of iodine ingested by space flight crewmembers per 24 hour period should be limited to a maximum of 0.5 mg. This limit includes iodine from all sources including dietary intake and potable water consumption."

Discussion with the panelists and audience participants included a number of questions regarding the iodine content of the food consumed by the chamber subjects and Shuttle astronauts. NASA nutritional analysis of food has not included iodine measurements. The panelists emphasized that the iodine content of all foods consumed by crewmembers must be determined by assay.

During the presentation, general discussions of thyroid diseases, including how they are defined, detected, and their incidences occurred during interchanges between the panelists and members of the audience.

The history of U.S. Spacecraft potable water disinfection was presented by Mr. Dick Sauer. After beginning with photographs of the various U.S. Spacecraft, he then briefly discussed the development of the water systems from Mercury and Gemini to Apollo and the Lunar module (where iodine was first used for water potability). He reviewed the water system on Skylab, detailing the iodination and technique of measuring iodine levels in space. Then he focused on the Space Shuttle water system and reviewed the microbial check valve hardware, which automatically iodinates the water. He completed the first portion of his presentation with the plans for recycling of the water aboard the International Space Station. After processing, this water is returned to the potable water system. The second part of the presentation began with discussion of alternate Spacecraft disinfectants, including silver, ultraviolet, filtration, chlorine, ozone, and their disadvantages. The schematic of the Shuttle water system was reviewed in detail, delineating the circulation for the chilled and hot water sides. He then explained the hardware changes made to the STS-87 water system, recounting the original development of the device for the Shuttle/Mir program to remove all iodine from the Shuttle water prior to transfer to the Mir water tanks. He drew the following conclusions: (1) Active disinfectant level in water systems is required to prevent microbial growth. (2) Iodine is an effective method for water disinfection and its use should be continued. (3) Technology is available to reduce iodine to medically acceptable levels. He recommended (1) to continue treatment of water with iodine, (2) for the short term, to reduce iodine to acceptable level using existing hardware depending on required acceptable iodine level, (3) for the long term, to develop a resin system, used prior to water consumption, that efficiently removes iodine to a level that has no physiological effect but provides effective biocidal control.

Discussion with the panelists and Joseph Kerwin, M.D., former astronaut on Skylab, included methods of iodine addition on Skylab and the possibility of using stored frozen urine to determine urine iodine levels and using stored frozen serum to measure thyroid function tests.

Points of clarification were made regarding the recycled water system on the Space Station, including purity levels and the removal of all iodine from the

recycled water after processing. There was also discussion regarding the use of alternative disinfectants.

Some time was spent clarifying how the modification in the STS-87 water system worked. Specific points were emphasized including the fact that the drinking water sat for only a few seconds to a few minutes without iodine and that the storage tank could maintains 2 -3 mg/L iodine and be scrubbed prior to use. The panelists and engineers also discussed the possible design of a water system that will reduce the distance between the iodine scrubber and the use port, which the engineers thought was feasible.

The third presentation, by Mary Wear, M.P.H., consisted of an epidemiological review of the Longitudinal Study of Astronaut Health (LSAH) data. She began by providing background information on the population database of astronauts and comparison subjects, study design, and the hypothesis that astronauts have a different risk of total morbidity and mortality than do ground-based employees. After describing the various types of thyroid disorders diagnosed by review of the medical records, she systematically compared astronauts with the comparison subjects with respect to incidence of previously diagnosed thyroid disease, with breakdowns by sex. The incidence in astronauts was not significantly different from the comparison group. As expected, the incidence in females is significantly higher than the incidence in males in both groups. In a comparison of position within the astronaut corps (pilot vs. mission specialist), male pilots had thyroid disease more often than male mission specialists, with an odds ratio that approached statistical significance (P=.0512). She also examined the data on astronauts for the total amount of iodine consumed, for the total number of space flights, and for the relationship between time of diagnosis, selection, and flight, but again the differences were not statistically significant. In a population of 270 Astronauts, (234 males and 36 females), there were 19 total cases of thyroid disorders, occurring in 15 males (6.4%) and 4 females (11.1%). She then showed graphs of mean TSH values at preflight, postflight, and annual examinations bracketing the flight related values, and showed statistically significant increases in TSH on landing day. This pattern was similar for Shuttle crews, for Skylab crews, and for the specific subset of Astronauts who had elevated TSH values (>4.5) on landing day. She concluded with the following: (1) There appears to be a transient elevation in TSH values on R+0. On R+3, TSH values are in the process of returning to normal. By the next annual physical examination, TSH values have returned to preflight ranges. (2) Astronauts are not at increased risk of developing thyroid disease compared to the comparison subjects.

The discussions that accompanied this presentation were wide-ranging. The first points clarified the time of day during which TSH was measured (the R+0 blood draw may occur at a different time than the remainder of the other

measurements) and the changes in the methodology of TSH measurements (which were accounted for in the data analysis). The panelists commented on the difficulty of comparing cases with such a wide variety of diagnoses. Both the panelists and physicians in the audience remarked on the varying abilities of physicians to detect thyroid gland abnormalities. When the use of ultrasound to detect thyroid gland abnormalities was raised, an animated discussion of the pros and cons of screening by ultrasound ensued. No consensus was reached on screening of American astronauts, since one panelist strongly favored its use, a second panelist was strongly opposed, and the third panelist cheerfully stated each view had points in its favor.

Upon hearing the countries of origin of the international astronauts who will be living aboard the Space Station, the panelists reminded the audience that people from Europe and Russia, who are iodine deficient, are at greater risk than Americans from excess iodine, and more likely to run into trouble at levels greater than 0.25 mg/day. While both the Russians and the Americans will have their own water systems beginning in 2002, audience participants pointed out that everyone will eat and live on the U.S. module. Dr. Pool commented that the space station water should be configured so that it is safe for everyone. In the case of international astronauts, the panelists agreed that they should be screened by ultrasound. This was accompanied by other specific recommendations for the international astronauts later in the conference.

In a consideration of acute vs. chronic exposure to iodine, the panelists were asked to weigh the distinction, if any, that should be drawn between two week missions and longer missions lasting 4-6 months, or even up to a year.

The necessity of measuring the iodine content of foods was again emphasized. The use of vitamin supplements on Mir and other spaceflights was discussed, since each multi-vitamin usually contains 0.15 mg of iodine.

Dr. Kerwin asked whether high levels of iodine could confound the results of experiments of the functions of other systems, such as calcium balance, etc. The panelists responded that either hypo- or hyperthyroidism could influence general metabolism, the balance of various analytes such as calcium and phosphorus, and affect other parameters, particularly lipid metabolism and the cardiovascular system.

Executive session

Regarding permissible iodine levels in the water:

1. Dr. Stanbury: "I think the total should be below 250 mcg/day [0.25 mg per day]."

2. Dr. Dunn: "The upper limit is very hard to define because some people get into trouble. Most people won't. Probably the least you need is something like 100 mcg/day [0.1 mg/day]. So, I guess the point John is making is why go higher if you don't have to. Then the question is: 'Do you have to and how much higher?'"
3. Dr. Braverman: "But we don't know what is in the food....I think one of the things that must be done is to analyze the dried food before they add the water. What they take up there, the food, ought to be analyzed for iodine content."
4. Dr. Dunn: "We should be looking at total iodine intake from all sources."
5. Dr. Dunn: "We would agree that...the most optimal would be somewhere between 150 and 250 mcg/day [0.15 - 0.25 mg/day], but probably up to 500 mcg/day [0.5 mg/day] is almost perfectly safe. The [higher levels] are probably safe for many people, but you perhaps start getting into [some trouble] that you are not certain about."
6. Dr. Braverman: "I think we are all comfortable with that. I wouldn't have much problem with 500 mcg/day [0.5 mg/day]..That's what I think, but my colleagues might differ."
7. Dr. Dunn: "If you say 250 mcg/day [0.25 mg/day] is optimal, but up to 500 mcg/day [0.5 mg/day] total iodine intake [is almost certainly safe]."
8. Dr. Braverman: "I'm saying that up to 1000 mcg/day [1.0 mg/day] may be safe for the majority."

Regarding astronaut health:

1. Dr. Braverman: "The measurement of [thyroid auto-]antibodies is critical."
2. Dr. Dunn: "[Perform autoantibodies] Once. If they are negative, repeat them five years later,... particularly for women."
3. Dr. Dunn: "I would do ultrasound...and of course, use clinical judgment. But I was asking about the medical-legal aspects of it....you always run the risk of someone saying that 'I developed papillary thyroid cancer because you sent me up there.'"
4. Dr. Stanbury: "You are going to get a difference of opinion here. My opinion is, you don't do ultrasound."
5. Dr. Braverman: "I'm in the middle. In my gut, I would agree with John Stanbury. The other part of me says I would agree with John Dunn. I like them both."
6. Dr. Braverman and Dr. Dunn: "Those who are auto-antibody positive should be told to have a TSH every year."

Regarding iodine levels in the water after Mr. Sauer comes to "plead a case":

1. Dr. Braverman: "Until we know what the food iodine content is, we can give no recommendations for [Mr. Sauer]."
2. Dr. Dunn: "What is the minimal amount of iodine you are comfortable with?"
3. Mr. Sauer: "I think somewhere about 250 mcg/L [0.25 mg/L]."
4. Dr. Braverman: "Is that the cold water or the hot water?"

5. Mr. Sauer: "That would be both."
6. Dr. Braverman: "Then you are talking about 500 mcg/day [0.5 mg/day] from the water alone. Suppose the food has 300 mcg [0.3 mg] in it. Then you are talking 800 [0.8 mg/day]."
7. Dr. Dunn: "There is every reason to think that for the period of time that you are dealing with it, that is very close to safe. On the Shuttle, and even if you are talking about 6 months to a year for the vast majority of people [on ISS]. It is a trade off. We can tell you ideally what we would like to see from the thyroid point of view, and you can tell us what you ideally want to have."
8. Dr. Braverman: "250 mcg [0.25 mg/day], ideal, but 500 mcg [0.5 mg/day] we don't see any real problem."
9. Dr. Dunn: "And we could say, we think it is probably reasonable as much as 500 mcg/day [0.5 mg/day] from the water. It is unlikely to cause significant problems for the duration you are talking about. Can you live with that John?"
10. Dr. Stanbury: "I can live with that. I would prefer it to be lower, but that's okay."
11. Dr. Braverman: "But we have to know what is in the food...if it already has 1000 mcg/day [1.0 mg/day], then that changes things."
12. Dr. Braverman: "You should look at urinary iodine while they are up there too. I think until you get some quantitative data, our recommendations will be meaningless if the food is high ...If urinary iodine levels are 1500 mcg/day [1.5 mg/day] up there, that means they are getting their iodine from somewhere. We have to get that data."

Regarding treatment of sub-clinical hypothyroidism:

1. Dr. Dunn: "I have a very low threshold for treating people who are hypothyroid. If somebody has an elevated TSH, unless I see a good reason not to, I treat them."
2. Dr. Stanbury: "Sure."
3. Dr. Braverman: "I would agree with my colleagues here ...I would do it unequivocally with positive antibodies."

Regarding whether there is a potential causal association between iodine intake and thyroid dysfunction in our population:

1. Dr. Dunn: "I think it is pretty clear that with increased iodine in populations there is more thyroiditis, particularly auto-immune thyroid disease....[it is in the astronaut population] because they are part of the American population."
2. Dr. Braverman: "Like another question submitted 'Is there a long term effect after short term extra iodine?' I can't see that....But I think continuous high iodine intake would probably increase the incidence of Hashimoto's. Over prolonged periods....of months to years."

[One question is] whether excess iodine for a sufficient duration, or at a sufficiently high dose precipitate Hashimoto's or hypothyroidism in individuals who are not genetically susceptible:

1. Dr. Stanbury: "I think so."
2. Dr. Dunn: "It is like seizures, ultimately, we are genetically predisposed to seizures, but the threshold is different."

Afternoon session summarizing the information and recommendations of the panelists

Regarding iodine in the food and water:

1. Dr. Braverman: "Before any recommendation can be made of how much iodine should be in the water, you have to know what they are eating and how much iodine is in that....You are doing a lot of different things to that food from what you told me. You have no idea what has been lost. What should be measured is what they take up there."
2. Dr. Lane: "There are only about 100 foods that need to be measured."
3. Dr. Braverman: "Why don't we say that 250 to 500 mcg/day [0.25 - 0.5 mg/day] would be [optimum], up to 1000 mcg or 1.0 mg/day....in astronauts who are iodine sufficient to begin with."
4. Dr. Stanbury: "I don't see why you can't engineer a length of tubing that you can remove with a stopcock and sterilize it."
5. Dr. Pool: "He is suggesting that you keep the iodine concentration high until just short of delivery, and he makes a good point. You could probably rig up or think up some way to keep that clean, either with pasteurization from time to time or taking if off and substituting another. That is probably do-able. You won't have the biofilms forming because behind that you could keep the system pretty well dosed with iodine."
6. Mr. Sauer: "I think if the committee is comfortable with no more than 1.0 mg/day total intake, and it will be incumbent on us, to minimize the amount of iodine intake down to an optimum level, where we will design a system that will do that. Whatever is involved in doing that, we will do that."

Regarding astronaut health screening:

1. Dr. Pool: "I would do it [ultrasound] as a baseline once they are selected."
2. Dr. Billica: That [ultrasound] is to be a baseline for future reference?"
3. Dr. Dunn: "And to pick up any problem. You can very often recognize auto-immune disease from the ultrasound."
4. Dr. Braverman: "You have got to put in there that for ultrasound it was a split decision. There was one yes, one no, and one maybe."

Regarding urine iodine measurements:

1. Dr. Dunn: "It [Urine iodine levels] can be spot samples."

2. Dr. Braverman: "We are trying to monitor how much iodine they are getting...I would suggest that if you think you are down to 500 mcg/day [0.5 mg/day], I think you have to prove that you are down there, and the only way you are going to prove that is to measure it."
3. Cr. Billica: "So, it would be, when we think we have the system in place, to deliver a certain amount of iodine, to actually go and confirm what the actual intake of iodine is that the crew is getting."

Regarding international astronauts:
1. Dr. Dunn: "Back to ultrasound. On these people [international astronauts}, for example, I would be pretty interested if they had a nodular thyroid because these are people who may have a greater risk of becoming hyperthyroid."
2. Dr. Braverman: "I would strongly advise you to measure urinary iodine excretion. You will know. That will tell you.
3. Dr. Dunn: "the one [threshold] we have standardized with WHO is 100 mcg/L urine iodine. That is the lower limit of normal. A lot of the people in your program may be people who, in, fact, paid a lot more attention to their iodine, so even though they live in an iodine deficient country, they are getting enough."

Regarding vitamins and other supplements:
1. Dr. Dunn: "We would recommend against including iodine in your vitamins and minerals preparation...recommend against eating a lot of iodine from other sources, like chewing kelp."

Regarding whether excess iodine, either for sufficient duration or at a high dose, can precipitate Hashimoto's thyroiditis or hypothyroidism in individuals who are not genetically predisposed to these diseases:
1. Dr. Dunn: "That is really hard. Probably all of us are ultimately to some degree susceptible.
2. Dr. Braverman: "I would agree. If you took 10 mg of iodine for the rest of your life, you may very well get into trouble....The only way you can pick those at risk is if you know that they have positive antibodies to begin with, or they have a strong family history of Hashimoto's or they have a constellation of other auto-immune disorders."

Regarding the cumulative effects of repeated exposure to iodine and whether it increased the risk of thyroid disease:
1. Dr. Dunn: "It may, I think it is of reasonable concern...It probably contributes but not a lot. I could not say it does not."
2. Dr. Braverman: "There is no evidence that it does or it doesn't."
3. Dr. Dunn: "Just to expand a little bit. I think you could say the longer you are exposed to a higher amount of iodine, the greater your chance, I think, in a population basis at least, of seeing more auto-immune thyroid disease, like

Hashimoto's. Is there a threshold? And then, if so, how many days or months or years? That is very hard to say. But probably, overall there is some increased risk here. Where it starts and how much it takes, it's very hard to say. "

Regarding whether administering excess iodine can accelerate or otherwise provoke the appearance of these diseases in susceptible individuals:

1. Dr. Dunn: "I would say probably yes."
2. Dr. Stanbury: "Yes."
3. Dr. Braverman: "Yes...can we reverse [it by eliminating iodine]."
4. Dr. Dunn: "Probably you have the underlying tendency, and you bring it out. When you remove the iodine, it may go back down. Probably these people have a life-long concern [susceptibility] about having auto-immune thyroid disease and possibly [will show]some of the effects of it.

Appendix E

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