A REVIEW OF THE EFFECTS OF DIETARY IODINE ON CERTAIN THYROID DISORDERS

JULY 1976

Prepared for

DIVISION OF NUTRITION
BUREAU OF FOODS
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D.C. 20204

under

Contract Number FDA 223-75-2090
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by

John M. Talbot, M.D.
Kenneth D. Fisher, Ph.D.
C. Jelleff Carr, Ph.D.

LIFE SCIENCES RESEARCH OFFICE
FEDERATION OF AMERICAN SOCIETIES
FOR EXPERIMENTAL BIOLOGY
9650 Rockville Pike
Bethesda, Maryland 20014
FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB) provides scientific assessments of topics in the biomedical sciences. Reports are based upon comprehensive literature reviews and the scientific opinions of knowledgeable investigators engaged in work in specific areas of biology and medicine.

This technical report was prepared for the Bureau of Foods, Food and Drug Administration (FDA), by the staff of the LSRO, FASEB, in accordance with the provisions of Contract No. 223-75-2090.

The LSRO acknowledges the contributions of the numerous investigators and consultants who have assisted with this study. The report reflects the opinions expressed by participants in an ad hoc study group that met at Beaumont House, FASEB, on February 10, 1976, and other consultants, and a judicious attempt has been made to incorporate the different viewpoints and opinions.

The report has been reviewed by these consultants; however, the listing of their names in Section IX does not imply that they endorse the conclusions of this study. The authors accept responsibility for the contents of the report. The report has been reviewed and approved by the LSRO Advisory Committee, consisting of representatives of each constituent society of FASEB, under authority delegated by the Executive Committee of the Federation Board. Upon completion of these reviews, the report has been approved and transmitted to the FDA by the Executive Director, FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinions of all of the individual members of its constituent societies.

C. Jelleff Carr, Ph.D.
Director
Life Sciences Research Office
SUMMARY

This report reviews possible associations of elevated dietary iodine levels with increasing incidence of Hashimoto's disease and with iodide goiter, iodine-induced thyrotoxicosis (jodbasedow), and thyroid cancer. Data from food surveys in 1974 and 1975 suggest that the levels of iodine in foods consumed by Americans of all ages have increased since 1970 and in some instances may be in excess of 500 μg per day.

The concept that iodine used to prevent endemic goiter may be an etiologic agent in Hashimoto's thyroiditis is based on the following observations: the disease was rarely reported in endemic goiter areas prior to the introduction of iodine prophylaxis, but increased in frequency following such prophylactic measures; essentially no lymphocytic infiltration was present in human and animal thyroid glands in certain Himalayan endemic goiter regions where no iodine prophylaxis programs existed; and lymphocytic thyroiditis may result from administration of excess iodine to experimental animals with artificially-induced thyroid hyperplasia. These three lines of evidence of a causal relationship in man between dietary iodine and Hashimoto's thyroiditis are largely circumstantial, incomplete, and lack epidemiologic specificity and precision.

Hashimoto's thyroiditis, infrequently diagnosed in this country before the early 1950's, is now regarded as a common thyroid disorder of children and adults of both sexes. It is closely associated with Graves' disease and although not proven conclusively, is considered by most experts to be an autoimmune disease. It may be benign, self limiting, or progressive and ultimately associated with hypothyroidism. The question of its possible association with thyroid cancer is equivocal. There is some evidence that the incidence of Hashimoto's thyroiditis has become stable in certain limited populations where it has been studied extensively.

Recent goiter surveys in this country revealed that between 5 and 10 percent of school age children, whose diets contained adequate amounts of iodine, had enlarged thyroid glands and that nodular goiter occurs in about 4 percent of the general population. In 1970, examination of 35,999 Americans yielded an overall goiter rate of 3.1 percent with a higher frequency in females. No data were reported to support the concept that excess dietary iodine may have been a contributing factor.

Although an epidemic of jodbasedow occurred in Tasmania after introduction of bread iodination, no reports document occurrence of the disease in the United States. Jodbasedow resulting from goiter prophylaxis programs in other parts of the world has been described as mild and easily
controlled. The prevailing expert opinion holds that the benefits of iodine prophylaxis against endemic goiter far outweigh the disadvantages of occasional jodbasedow.

Available scientific knowledge pertaining to the cause or causes of Hashimoto's thyroiditis, iodine goiter, jodbasedow, and certain other thyroid disorders is too limited for precise evaluation of possible etiologic factors and mechanisms.

The report concludes that a cause and effect relationship between increasing levels of dietary iodine and occurrence of Hashimoto's disease, iodide goiter, and thyroid cancer in the United States is not supported by data currently available. The report identifies several areas for future research and suggests a continuing need for clinical awareness and periodic surveys of thyroid disorders as well as monitoring of dietary iodine levels.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreword</td>
<td>3</td>
</tr>
<tr>
<td>Summary</td>
<td>4</td>
</tr>
<tr>
<td><strong>I. Introduction</strong></td>
<td></td>
</tr>
<tr>
<td>A. Background</td>
<td>9</td>
</tr>
<tr>
<td>B. Scope</td>
<td>10</td>
</tr>
<tr>
<td><strong>II. Background Information</strong></td>
<td></td>
</tr>
<tr>
<td>A. Estimated Current Daily Iodine Intakes</td>
<td>11</td>
</tr>
<tr>
<td>1. Iodine in Foods</td>
<td>11</td>
</tr>
<tr>
<td>2. Iodine from Other Sources</td>
<td>13</td>
</tr>
<tr>
<td>B. Uptake and Distribution of Iodine</td>
<td>13</td>
</tr>
<tr>
<td>1. Bioavailability of Ingested Iodine</td>
<td>13</td>
</tr>
<tr>
<td>2. Other Sources and Portals of Entry</td>
<td>16</td>
</tr>
<tr>
<td>3. Total Body Pool</td>
<td>17</td>
</tr>
<tr>
<td><strong>III. Hashimoto's Thyroiditis</strong></td>
<td></td>
</tr>
<tr>
<td>A. Excess Iodine as a Possible Etiologic Factor</td>
<td>19</td>
</tr>
<tr>
<td>B. Epidemiology</td>
<td>22</td>
</tr>
<tr>
<td>C. Diagnosis</td>
<td>24</td>
</tr>
<tr>
<td>D. Discussion</td>
<td>25</td>
</tr>
<tr>
<td><strong>IV. Iodine-Induced Thyrotoxicosis (Jodbasedow)</strong></td>
<td>29</td>
</tr>
<tr>
<td><strong>V. Other Thyroid Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>A. Iodine Goiter</td>
<td>31</td>
</tr>
<tr>
<td>B. Neonatal Goiter</td>
<td>32</td>
</tr>
<tr>
<td>C. Malignancies</td>
<td>33</td>
</tr>
<tr>
<td>Section</td>
<td>Page</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>VI. Conclusions</td>
<td>35</td>
</tr>
<tr>
<td>VII. Suggestions for Future Consideration</td>
<td>39</td>
</tr>
<tr>
<td>VIII. Bibliography</td>
<td>41</td>
</tr>
<tr>
<td>IX. Scientific Consultants</td>
<td>55</td>
</tr>
<tr>
<td>B. Other Consultants</td>
<td>57</td>
</tr>
</tbody>
</table>
I. INTRODUCTION

A. BACKGROUND

The Office of the Associate Director for Nutrition and Consumer Sciences, Bureau of Foods, Food and Drug Administration (FDA) has a continuing interest in the iodine* content of the American diet. The office is responsible for evaluating and monitoring the safety of foods, establishing regulations, and providing nutrition information to consumers. It is reviewing the iodine content of the American diet and trends in the prevalence of Hashimoto’s thyroiditis, simple or nontoxic goiter, iodine-induced thyrotoxicosis and other thyroid disorders because there is some evidence to suggest that dietary iodine may have reached levels that could influence the prevalence of these thyroid disorders; this evidence should be precisely documented. If evidence is insufficient that dietary iodine exerts an adverse effect, the necessary studies and appropriate methodology to clarify its role should be identified.

The Life Sciences Research Office was requested by FDA to review scientific information, to obtain the opinions of thyroidologists, clinical investigators and epidemiologists, and to prepare a comprehensive report. To assist in this review an ad hoc study group was convened at Beaumont House, FASEB on February 10, 1976.

The first report prepared by LSRO on the general subject of dietary iodine was entitled Iodine in Foods: Chemical Methodology and Sources of Iodine in the Human Diet (Fisher and Carr, 1974). This report included sources of iodine in animal feeds and human foods, the current status of iodine nutrition, and the analytical methodology used in estimating iodine in foods.

The second report was entitled A Review of the Significance of Untoward Reactions to Iodine in Foods (Talbot et al., 1974). The main conclusion of this study was that idiosyncratic and hypersensitivity reactions to iodine in foods were not significant clinical or public health problems in the United States. However, the increasing prevalence of thyrotoxicosis following the introduction of supplemental dietary iodine in iodine-deficient areas was noted and the need for clinical surveillance of this public health issue was emphasized. While at that time there was no documentation of

*In this report "iodine" is used in the generic sense. The element may be present as iodide or bound to protein complexes in foods, body fluids, and tissues. The oxidation-reduction state may not be known in many instances and is designated only when specifically noted by the authors of reports.
an increase in the prevalence of iodine toxicity or iodine-influenced diseases of the thyroid gland, a continuing need for clinical awareness and periodic surveys of these conditions in this country was suggested.

These reports and subsequent developments provided a background for the present study.

B. SCOPE

This report includes information available since 1974 on the iodine content of foods, a review of other sources of biologically available iodine, and the bioavailability of the various forms of ingested iodine. Attention was directed to the epidemiologic aspects of Hashimoto's thyroiditis, its diagnosis and the possible significance of excess dietary iodine as a causal factor in the increased prevalence of this form of thyroiditis. Similar reviews were conducted for iodine-induced thyrotoxicosis, iodine goiter, neonatal goiter, and thyroid malignancies. Although the nutritional significance of the level of iodine in the diet was not a part of the study, an attempt was made to assess the clinical significance of reports of a causal relationship between excess iodine exposure and Hashimoto's thyroiditis, iodine goiter, iodine-induced thyrotoxicosis, and thyroid cancer.

Sources of information included computerized biomedical literature files of the National Library of Medicine and the comprehensive compilations of the scientific literature from 1920 to 1970 prepared in conjunction with an evaluation of the health aspects of potassium iodide as a food ingredient and a Generally Recognized as Safe (GRAS) substance (Informatics, Inc., 1973). In addition, numerous references were supplied by the consultants who assisted with this study.
II. BACKGROUND INFORMATION

A. ESTIMATED CURRENT DAILY IODINE INTAKES

1. Iodine in Foods

In 1974, the average dietary iodine intake for adults in the United States was estimated to be 450 µg and 382 µg for males and females, respectively (Fisher and Carr, 1974). More recently, data from the Fiscal Year 1974 Selected Minerals in Foods Survey (FDA, 1975) indicated that, with a daily intake of 2800 kcal for adult males, iodine intake exclusive of iodized salt was approximately 600 µg; and at 3900 kcal, it was 900 µg. With iodized salt in the 2800 kcal diet, the estimated daily intake could have reached 1050 µg. Foods used in these studies may not have been completely representative of the American diet because convenience foods and products of "fast food" establishments were not included.

In a subsequent survey, the Food and Drug Administration (FDA, 1976) estimated the average daily iodine intake of young adult males (15 to 20 years old) to be 538 µg in the 2800 kcal diet and 750 µg in the 3900 kcal diet. Because of the limits of the survey method, these data should be regarded as indicators of probable dietary iodine intakes rather than as specific measures; hence the fiscal year '75 figures may or may not be significantly lower than the fiscal year '74 data. However, both sets of data indicate the average daily intake of iodine by young adult males on average size diets could be in excess of 500 µg (Table 1). Corresponding increases in iodine intake from dietary sources may be assumed for adult females as well as school age children and teenagers.

The U.S. Recommended Daily Allowances (USRDA) of iodine for infants (6 months old) and children under 4 years of age are 45 and 70 µg respectively. The fiscal year '75 data contained estimates of average iodine intakes of 840 percent of the USRDA for infants, and for toddlers (2 years old) of 685 percent of the USRDA. The small numbers of diets on which the infant and toddler estimates were based make it impractical to estimate their validity in terms of typical intakes throughout the nation. Nevertheless, they are useful as indicators and are part of the growing data base.

Sales of iodized salt in the United States accounted for 58 percent of salt packaged for home use in 1974-1975 as compared with 55 percent in 1969-1970 (Wood, 1976). This relatively small increase does not account for the larger increase in dietary iodine, but rather suggests that the observed increased average dietary iodine intake levels are probably derived from sources other than iodized salt.
## TABLE 1

**AVERAGE DAILY IODINE INTAKES FOR YOUNG ADULT U.S. MALES**

<table>
<thead>
<tr>
<th>Reference period</th>
<th>Iodine intake µg per day</th>
<th>Energy intake kcal</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960</td>
<td>100-150</td>
<td>-</td>
<td>DeGroot and Stanbury, 1975</td>
</tr>
<tr>
<td>Prior to 1970</td>
<td>454</td>
<td>2400</td>
<td>Fisher and Carr, 1974</td>
</tr>
<tr>
<td>Fiscal year 1974</td>
<td>600&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2800</td>
<td>FDA, 1975</td>
</tr>
<tr>
<td></td>
<td>1050&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2300</td>
<td>FDA, 1975</td>
</tr>
<tr>
<td>Fiscal year 1975</td>
<td>538&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2300</td>
<td>FDA, 1976</td>
</tr>
</tbody>
</table>

<sup>a</sup> Without iodized salt  
<sup>b</sup> Upper limit with iodized salt
2. **Iodine from Other Sources**

Iodine in any part of the human environment is potentially available for biologic uptake; for example, iodinated domestic water supplies (Black *et al.*, 1959; Chang and Morris, 1953; Freund *et al.*, 1966; Thomas *et al.*, 1969), swimming pool water disinfected with iodine (Byrd *et al.*, 1963), therapeutic drugs and industrial chemicals (Fisher and Carr, 1974) and wound disinfectants (Reeve *et al.*, 1971). In a test of an iodinated community water supply in New Mexico, the iodinating process provides a residual of 0.5 mg of elemental iodine per liter (Iodinamics Corporation, 1975). If one assumes an average human water intake of between 1 and 2 liters per day, the potential iodine intake from such a source would be 500 to 1000 μg. The Department of Agriculture Forest Service recently conducted tests of a water iodinating system for remote sites (Cook, 1976). Presently, there is no government standard for iodine in drinking water; however, the Environmental Protection Agency (1972-1973) has a policy stating that while iodination of drinking water is acceptable for short term use, it is not approved for permanent water sources such as municipal water supplies. Iodine is considered a pesticide for water disinfection, and since August, 1975, premarketing registration has been required for pesticide products intended for use in disinfecting swimming pool or drinking water (Office of the Federal Register, 1975a). Guidelines for the registration process have been published (Office of the Federal Register, 1975b). The question of standards of performance for home water treatment systems is under study by the Environmental Protection Agency.

B. **UPTAKE AND DISTRIBUTION OF IODINE**

1. **Bioavailability of Ingested Iodine**

Published information about the bioavailability of the different forms of iodine ingested by animals and man is meager. For this review, bioavailable iodine may be defined as that which could be absorbed from the gastrointestinal tract, trapped, and incorporated into thyroactive hormones by the thyroid gland or otherwise stored in body tissues. Obviously, nutrition surveys such as the FDA Market Basket Survey (FDA, 1975, 1976) determine, as accurately as possible, the available iodine in foods as consumed. However, assessment of bioavailable iodine in foods as consumed requires more sophisticated techniques such as radioactive isotope studies.

Iodine occurs in human foods largely as inorganic iodides; other forms of inorganic iodine in foods are reduced to iodides prior to absorption (Stanbury, 1972; Underwood, 1971). Inorganic iodides are completely absorbed from all levels of the intestine (Cohn, 1932) and very little appears in the feces. For example, all of the iodine in fillets of plaice and haddock was inorganic, and
virtually all of it was absorbed after ingestion by human volunteers (Harrison et al., 1965).

Organic iodine of the thyroid hormones is conjugated in the liver and glucuronate and sulfate conjugates are secreted in the bile. Reabsorption is incomplete and approximately 20 percent of organic iodine is normally lost in the feces (Ingbar and Woeber, 1974). For example, Alexander et al. (1967) cited values of 8 to 20 μg daily fecal loss of organic iodine in euthyroid women. Iodinated thyronines and tyrosines may be absorbed intact by the gastrointestinal tract, but the iodinated tyrosines are largely deiodinated prior to absorption. Such iodinated amino acids are readily absorbed but not as rapidly or completely as iodides per se (Keating and Albert, 1949). It should be noted that Harrison et al. (1965) found no thyronine-like compounds or iodoproteins in fish fillets either before or after cooking.

In animals, many forms of iodine are readily bioavailable. For example, the iodine nutritional needs of cattle may be satisfied by several classes of compounds including sodium and potassium iodides, calcium iodate, and pentacalcium orthoperiodate (Moss and Miller, 1970). Iodine from 3,5-diiodosalicylic acid is absorbed and metabolized by cows, but not as efficiently as iodine from potassium iodide (Miller et al., 1964). In cows, ethylene-diaminedihydriodide is absorbed equally to or better than sodium or potassium iodide and the iodine from this source is retained in most organs and tissues longer than iodine from sodium iodide (Miller and Swanson, 1973).

The major part of iodine in milk occurs as inorganic iodide, and no protein-bound iodine could be found in whey (Van Koetsveld, 1966); the ratio of total iodine to protein-bound iodine in milk samples was approximately 4:1. Kelps incorporate iodine from the sea in the form of iodide and iodates and certain seaweeds are used in human and animal diets. Kelp meal fed to hens increased the iodine content of eggs. Oral administration of kelp to human subjects resulted in marked decrease in radioactive iodine uptake (Iino et al., 1958). It has been reported that 98 to 99 percent of the iodine from brown algal kelp, Laminaria japonica is absorbed from the intestine.

Indirect evidence suggests that some or all of the iodine in iodophors is biologically available if inadvertently introduced into the food supply by their use as sanitizers in the dairy and food processing industries or their use as teat dips. Iodophors liberate elemental iodine, which is converted to iodide in the gastrointestinal tract. In the United States, Conrad and Hemken (1975) reported that an iodophor teat dip used for four milkings prior to sampling increased milk iodine by 48 μg per liter when the teats were washed before milking and 56 μg per liter when not washed. The results were considered statistically insignificant. However, a statistically significant, continuing increase in milk iodine occurred when the iodophor dip was used for one week.
In Sweden, Funke et al. (1975) reported mean iodine levels in bulk milk of 127 μg per liter from herds treated after milking with an iodophor teat dip solution containing 0.5 percent active iodine, and 152 μg per liter from other herds treated with a 0.33 percent active iodine iodophor teat dip solution. Milk from untreated control herds had a mean iodine content of 94 μg per liter. No data were reported on other exogenous sources of iodine such as water and feed. Terplan et al. (1975) reported that iodophor teat dipping practices in Germany produce significant increases in milk iodine only in those areas where the "physiological" iodine content of milk (not defined) is low and that increases in the iodine content of milk from teat dipping with iodophors do not represent a health hazard for the consumer. According to Iwarsson and Eckman (1973), in Sweden the wide-spread use of iodophor teat dips will result in an increase in the iodine intake of the milk consuming population, unless cognizance is taken that adequate pre-milking udder washing is of importance in counteracting contamination of milk (Iwarsson and Ekman, 1974).

Iodophor udder washes under controlled conditions did not raise the level of milk iodides significantly (Cantor and Most, 1976). Iodophor teat dips with 0.25 percent and 1.0 percent complexed iodine caused average milk iodide levels of 43 μg and 63 μg per liter respectively when compared with an average of 37 μg per liter when water was used as a control teat dip. An increase of approximately 50 μg of iodide per liter of milk may result when teats dipped in a 1.0 percent solution of iodophor are not washed prior to milking. The authors concluded that the influence of properly formulated and used iodophor teat dips on milk iodide levels appears to be of limited significance in the total human dietary intake of iodine, and that supplements of iodine in cattle feeds exceed the iodine contribution of iodophor teat dips. They suggested that an important procedure for control of adventitious iodine in milk supplies is adequate premilking udder and teat rinsing as generally required in the U.S. to maintain milk quality. However, adequate premilking udder washing is not routinely practiced on dairy farms in the United States because its importance is not recognized and because of the time and labor involved.

According to Underwood (1971), an important factor is the dietary level of other minerals or nutrients that influence the availability or utilization of the element in question. More than 300 natural or synthetic chemicals have goitrogenic properties, which may have a net effect on iodine bioavailability. Most of these chemicals are derivatives of thioured or analine (Fisher and Carr, 1974; Greer et al., 1964). By various mechanisms, excesses or deficiencies of several inorganic chemicals in the human environment including arsenic, bromide, fluoride, cobalt, manganese, and nitrate may inhibit normal iodine uptake and metabolism. Several univalent ions, e.g., thiocyanate, monofluorosulfonate, difluorophosphate, and
fluoroborate can displace iodine from the readily exchangeable pool, and perchlorate exerts a powerful effect on iodine discharge from and uptake by the thyroid gland (Stanbury, 1972).

Data are insufficient on the effects of food processing and cooking on the availability of iodine in the final, ready-to-eat product. However, iodide in the flesh of plaice and haddock is decreased 50 to 80 percent by boiling, and 10 to 40 percent by frying or grilling (Harrison et al., 1965). In bread doughs containing iodate, baking decomposes the iodate primarily to iodides; however, both forms of iodine are readily bioavailable (Conn et al., 1950; Fisher and Carr, 1974). Since 1974, the use of iodate dough conditioners in the United States is reported to have declined, and both encapsulated and non-encapsulated ascorbic acid or azodicarbonamide are being used more widely (Hepburn, 1976). Of the six major baking companies surveyed in 1974 and 1975, four reported no change in the use of iodate dough conditioners, or further decreased use; one company again reported no use of iodate dough conditioners (Hepburn, 1976). In addition, modifications in flour characteristics have led to reduced need for dough conditioners in bread production.

2. Other Sources and Portals of Entry

Fisher and Carr (1974) reviewed the available scientific data on atmospheric iodine as a possible source of human intake. The amount of iodine normally present in the atmosphere is relatively low and makes little significant contribution to the body pool except possibly along the seacoasts. Human respiratory exposure to iodine in seacoast air has been estimated to be about 4 μg per day (Salter, 1940). However, it is possible that human intake of iodine via the respiratory system is significant in atmospheres polluted with iodine from other sources such as radiiodine from nuclear reactors and nuclear weapons tests, and atmospheric iodine levels elevated by vaporization of iodine-containing sanitizers used in confined spaces and inadequately ventilated buildings. Combustion products of fossil fuels have been suggested also as a possible source of atmospheric iodine (Vought et al., 1970); however, information from the Environmental Protection Agency (Merenda, 1976) indicates that recent analyses of gasoline samples for trace contaminants failed to detect iodine, and that the Agency was unaware of any possible source of iodine emissions from motor vehicles in this country. The United States occupational standard for iodine in air, stated as the highest permissible value, is 0.1 ppm (Christian et al., 1974). More studies are needed on the possible significance of atmospheric iodine as a source of human intake.

Parenterally administered iodine-containing radiopaque dyes for diagnostic studies are well-recognized contributors to total body iodine.
For example, an apparently euthyroid patient with an autonomous thyroid nodule developed hyperthyroidism following administration of organic iodine for intravenous pyelography (Blum et al., 1974). Iodinated dyes taken orally for such roentgenologic procedures as gall bladder visualization are absorbed without deiodination (DeGroot and Stanbury, 1975). Iodine in oils, used in bronchograms, lymphangiograms, and myelograms may remain especially long in the body, and excess body burdens of iodine from these sources may persist for many months to more than a year (Davis, 1966).

Iodine in the traditional tincture is absorbed through the skin (Reeve et al., 1973), as is iodine in the form of sodium iodide (Miller and Selle, 1949). Urinary iodine increased in surgical personnel who used aqueous povidone-iodine in the preoperative scrub (Connolly and Shepherd, 1972). No effect on serum protein-bound iodine or radioactive iodine uptake was detected. When used for preoperative disinfection of the skin, povidone-iodine did not cause significant changes in serum protein-bound iodine levels (Alden et al., 1970; Higgins et al., 1964). Connell and Rousselot (1964) and Lavelle and associates (1975) reported a high absorption of iodine in burn patients treated with topical applications or continuous soak of povidone-iodine.

Vitamin-mineral supplements, cough syrups, and certain artificial colorings used in tablet and capsule coatings contain iodine and add to the human intake (Fisher and Carr, 1974).

3. Total Body Pool

The adult human body normally contains about 9 to 10 mg of iodine of which more than 99 percent is in organic form (DeGroot, 1966; Riggs, 1952). The average amount of organic iodine in the thyroid gland is 8 mg; in the blood and extrathyroidal tissues, 1.2 mg. The mean iodide content of the entire inorganic iodide compartment in the normal human adult is about 75 μg (Riggs, 1952). In the euthyroid individual, this body pool is maintained by absorption and rapid excretion of excess iodine, primarily via the kidneys. Very little inorganic iodide is lost in the feces, sweat, and expired air (Stanbury, 1972). According to Welt and Blythe (1965) human plasma inorganic iodide comprises from 10 to 20 percent of total plasma iodine. However, data from other studies suggest lower inorganic: organic iodide ratios in human plasma; for example, approximately 3 to 7 percent (DeGroot, 1966; Vought et al., 1963). Ordinarily, the concentration of circulating inorganic iodide is about 0.5 μg per 100 ml of blood serum, and the thyroid gland/serum gradient may vary 20 to 50 fold, and in certain physiological conditions, can vary 10 to 500 fold or more (Selenkow and Ingbar, 1970). Astwood (1965), suggested that certain other organs and tissues such as salivary glands, gastric mucosa, part of the small intestine, mammary glands, skin, and placenta maintain concentration gradients 10 to 50 times the serum level. Studies should be conducted to differentiate between iodide concentrated in the cells of these organs and that concentrated in the secretions of these organs.
In summary, all available data suggest that the levels of iodine in foods consumed by Americans of all ages have increased since 1970 and in some instances may exceed 500 μg per day. In addition, the evidence is equivocal as to the contribution to the daily iodine intakes made by various other sources such as sanitizers, atmospheric iodine, medicinals, and water disinfectants.
III. HASHIMOTO'S THYROIDITIS

A. EXCESS IODINE AS A POSSIBLE ETIOLOGIC FACTOR

According to DeGroot and Stanbury (1975), Hashimoto's thyroiditis occurs typically as a "painless, diffuse enlargement of the thyroid gland in a young or middle-aged woman." The thyroid glands of Hashimoto's original four patients had diffuse lymphocytic infiltration, lymphoid follicles, parenchymatous degeneration, and extensive new connective tissue (Hashimoto, 1912; Levitt, 1954). He termed the condition struma lymphomatosa. Since then, the terminology has proliferated, resulting in a variety of synonyms including Hashimoto's struma, chronic thyroiditis, lymphocytic thyroiditis, chronic lymphocytic thyroiditis, lymphadenoid goiter, autoimmune thyroiditis, silent thyroiditis, and other terms. Hazard (1955) emphasized the importance of oxyphilic thyroid epithelium in the differential diagnosis of Hashimoto's struma; however, in recent years, a majority of authors have used less rigid diagnostic criteria. Hashimoto's thyroiditis is the term used in this report.

Most authorities agree that the incidence of Hashimoto's thyroiditis has been increasing in the United States. Although the etiology has not been established, certain investigators are persuaded that an important causal factor is the intake of excess iodine. Beierwaltes (1969) has suggested that endemic iodine deficiency goiter is not associated with lymphocytic thyroiditis, but that the introduction of iodized salt in endemic goiter areas was "accompanied by a constantly increasing incidence and severity of lymphocytic thyroiditis and Hashimoto's struma." Further evidence supporting this thesis noted by Beierwaltes (1969) includes reports of iodine-induced lymphocytic thyroiditis in experimental animals and several clinicopathologic reviews which attempted to associate "preiodine" periods with lack of Hashimoto's thyroiditis, and "postiodine" periods with an increasing frequency of the disease. In addition, he has suggested that an increasing percentage of the goiters in a previously endemic goiter area may be associated with thyroid carcinomas.

Support for the concept that excess iodine intake is an important etiologic factor in generating Hashimoto's thyroiditis, especially among persons previously exposed to iodine deficiency, has been based mainly on data on the frequency of Hashimoto's thyroiditis in once endemic goiter areas of the United States and abroad in which programs of iodine prophylaxis have been instituted.
Surgically obtained thyroid tissues at certain medical centers showed a marked rise in the frequency of Hashimoto's thyroiditis in the decades following introduction of iodized salt for goiter prophylaxis as compared with tissues from sample periods before iodized salt (Gaitan, 1974; McConahey, 1972, Perinetti et al., 1971; Weaver et al., 1966, 1969).

Pathologists at the University of Michigan reviewed all the thyroid surgical pathology slides prepared at that institution before and after the use of iodide (Weaver et al., 1966, 1969). They found few, if any, lymphocytes and no Hashimoto's thyroiditis in any surgical thyroid specimens before, and a constantly rising incidence of both after the introduction of iodized salt licks (as a source of iodine in milk) and human use of iodized salt. More recently, Perinetti et al. (1971) in Mendoza, Argentina used the methods of Weaver et al. (1966, 1969) and reported similar findings before and after establishment of goiter prevention programs with iodized salt. Beierwaltes (1969) believes that these old and more recent observations suggest that thyroid hyperplasia (induced by iodine deficiency) plus iodide repletion or excess may be a causative combination in the genesis of Hashimoto's thyroiditis.

Lymphocytic thyroiditis has been induced in laboratory animals by several techniques including administration of iodine. Six of twenty-four (25 percent) rats given 0.1 percent aqueous thiouracil solution instead of water for 600 days developed chronic thyroiditis morphologically similar to human Hashimoto's thyroiditis and manifested by lymphocytic infiltrates of the thyroid gland and testes (Clausen, 1953). The food for both experimental and the control animals was Purina Laboratory Chow. Thyroiditis was not observed in the controls.

Follis (1959) produced acute inflammation of the thyroid gland and a decrease in follicular colloid in 100 g hamsters with goitrogen-induced thyroid hyperplasia by giving 10 mg potassium iodide per day intraperitoneally for periods up to 2 weeks. Within 24 hours, polymorphonuclear leukocytes appeared in the follicles; after 7 days, the infiltration was more intense and included round cells; interstitial infiltration, primarily round cells, was present. At 14 days, the acute intrafollicular inflammatory reaction had been replaced by a less intense, "more chronic" mononuclear form and the interstitial infiltration persisted. In normal hamsters without the goitrogen, such large doses of iodine did not result in morphologic changes in the thyroid gland. This type of acute inflammatory reaction with polymorphonuclear leukocytes has not been observed in human Hashimoto's thyroiditis at any stage of the disease.

In 1964, Follis reported that this type of thyroiditis could be induced in hamsters with goitrogen-induced hyperplastic thyroid glands by intraperitoneal doses of 76 µg of iodine per day for 6 days, but not by daily doses of 25 µg or less.
Few lymphocytes and no Hashimotos' thyroiditis were observed in mongrel dogs on an iodine-deficient diet in Minnesota (Schlotthauer et al., 1930), before the use of iodized salt, but a high incidence of lymphocytic infiltration and Hashimoto's thyroiditis was observed in a beagle colony on a high dietary iodine intake (Beierwaltes and Nishiyama, 1968). The investigators demonstrated that this Hashimoto's thyroiditis in dogs was identical to that in humans by a variety of tests. Evans et al., (1969) were able to induce Hashimoto's thyroiditis in beagles in 7 months with dietary iodine intake of 2 mg per day and immunization against crude saline extract of dog thyroid gland without Freund's adjuvant. Terplan et al., (1960) could not induce thyroiditis in less than 16 months using the same type of thyroid extract and complete Freund's adjuvant, with normal dietary iodine intake. Only four of their 14 dogs had abnormal lymphocytic infiltration after 3 to 11 months of immunization and the possibility that these abnormalities existed prior to immunization could not be ruled out since no biopsies were performed prior to immunization. In addition, the dogs that developed lymphocytic infiltration had a 1+ or 2+ thyroiditis, while three of the four dogs immunized at the University of Michigan without Freund's adjuvant but on a 2 mg iodine per day intake, developed a 3+ thyroiditis after 7 to 8 months. In addition, there was a striking difference between the thyroid pathology of dogs immunized on a 2 mg per day dietary iodine intake and immunized dogs on a normal iodine intake. The lesions in the latter dogs did not persist after cessation of immunization, and were characterized by a predominance of eosinophiles in the glandular infiltrate and a lack of oxyphilic epithelial cells (Evans et al., 1969; Terplan et al., 1960).

"Spontaneous" thyroiditis in beagles has been reported by several investigators (Beierwaltes and Nishiyama, 1968; Evans et al., 1969; Tucker, 1962). The basic diet in Tucker's series was a commercial dog food supplemented by "adequate" amounts of vitamins, minerals, and protein. Beierwaltes and Nishiyama (1968) noted that 12.5 percent of males and 10.9 percent of females of a large, purebred beagle colony had thyroiditis indistinguishable from human Hashimoto's struma. Among noncolony, purchased beagles at the same facility, only 4 percent of males and 3 percent of females had thyroiditis. They mentioned that conventional kennel diets have a high iodine content; for instance, Purina Dog Chow® provided approximately 200 µg of iodine per day.

Seven of eight beagles that had been fed a low iodine diet for 3 to 5 months were reported to have necrosis of as high as 10 to 20 percent of their thyroid follicular epithelial cells following single oral loads of potassium iodide solution at levels of 0.5 to 2.5 mg iodide per kg body weight (Belshaw and Becker, 1973). No leukocytic infiltrates were observed in these thyroid tissues, which were removed 12 to 14 hours after the oral iodide loading. Belshaw and Becker (1973) noted that the necrosis could be prevented by administration of as little as 0.05 mg iodide per kg 24 hours before the oral iodide loading.
In summary, laboratory animal studies of iodine-induced thyroiditis; the temporal association of goiter prophylaxis programs using iodized salt, with an apparent, or possibly real, increase in the occurrence of Hashimoto's thyroiditis; and the virtual absence of lymphocytic infiltration in endemic goiters in a Himalayan community where no goiter prophylaxis was used are considered by some authorities (Beterwaltes, 1969; Weaver et al., 1966, 1969) as sufficient evidence to justify the conclusion that the introduction of iodized salt prophylaxis into an endemic goiter area results in an increased prevalence of Hashimoto's thyroiditis.

B. EPIDEMIOLOGY

Hashimoto's thyroiditis was infrequently diagnosed in the United States prior to the 1950's. Since then, clinical awareness increased and improved means of diagnosis became available, and it is currently regarded as a common thyroid disorder. Classically, it was said to occur in young or middle-aged women, but it is now considered a frequent cause of childhood and adolescent goiter as well (Hahn et al., 1965; Leboef and Ducharme, 1966; Ling et al., 1973; Monteleone et al., 1973). Forty-three biopsy-confirmed cases of Hashimoto's thyroiditis were diagnosed in a series of 77 adolescent, goitrous children examined during the period 1965 through 1971 (Hung et al., 1973). Rallison et al. (1975) reported a prevalence of chronic lymphocytic thyroiditis of 1.2 percent among 5,179 school children examined in Arizona, New Mexico, and Nevada. The ratio of girls to boys with thyroiditis was approximately 2:1. In a review of 10,000 autopsies, Masi et al. (1965a) found the ratio of Hashimoto's thyroiditis in adult white females and males to be 4:1, respectively.

The incidence of Hashimoto's thyroiditis in the United States is unknown; however, it is thought to be approximately the same as Graves' disease, about 3 to 6 cases per 10,000 population per year (DeGroot and Stanbury, 1975). Investigators tend to agree that it is increasing in frequency (Furszyfer et al., 1970, 1972; Hahn et al., 1965; Kinney and Herrmann, 1962; McConahey, 1972; Weaver et al., 1966). Masi et al. (1965a) listed 19 reports of histopathologic diagnoses of thyroid tissues covering various time intervals between 1919 and 1960, that showed a trend toward higher crude relative frequencies of Hashimoto's thyroiditis from 1950 to 1960 than from 1919 to 1949. Masi et al. (1965a) cautioned against drawing a conclusion about a possible true increase in the occurrence of Hashimoto's disease from the available data which, for the most part, were based on detected cases alone, not epidemiologic surveys of adequate population samples.

In their epidemiologic critique of Hashimoto's disease, Masi et al. (1965a) considered the following theories of etiology: chronic inflammatory
process; endocrine imbalance; epithelial hyperplasia with exhaustion; primary thyroid failure; basement membrane defect; autoimmune disease; or some genetic disorder. They found no compelling evidence in favor of any of the theories. In a study of autopsy material from diagnosed cases and matched controls, Masi et al. (1965b) were unable to confirm the observation of other investigators that Hashimoto's thyroiditis often presents itself in association with other autoimmune diseases. Mulhern et al. (1966) analyzed 170 clinically detected, histologically confirmed cases of Hashimoto's thyroiditis in which they noted a possible association with rheumatoid arthritis, an equivocal association with systemic lupus erythematosus, and no association with other autoimmune diseases.

However, associations between Hashimoto's disease and other diseases which are thought to be of autoimmune origin have been reported by many investigators; for example, pernicious anemia (Doniach et al., 1963; Irvine et al., 1962, 1965); rheumatoid arthritis (Buchanan et al., 1961); systemic lupus erythematosus (White et al., 1961); Addison's disease (Bloodworth et al., 1954); and hepatic cirrhosis (McConkey and Callaghan, 1960). Based on the cumulative evidence, current expert opinion favors the concept that Hashimoto's disease is a genetically conditioned autoimmune disease (Blizzard et al., 1959; DeGroot et al., 1962; Doniach and Roitt, 1957; McConahey, 1972; Roitt et al., 1956; Volpé, 1971; Volpé et al., 1974).

In Michigan, Weaver et al. (1966) found no lymphocytic infiltrates in any surgically removed thyroid tissues prior to 1924; however, starting with thyroid tissues surgically removed in 1925, they reported an increasing frequency of two forms of thyroiditis, which they termed lymphocytic thyroiditis and Hashimoto's thyroiditis, from 0.4 percent in 1925 to 9.3 percent by 1958-1963. McConahey (1972) reported a similar increase in the number of cases of Hashimoto's thyroiditis diagnosed at the Mayo Clinic (Rochester, Minnesota) from less than 5 per year in 1930 to 185 per year in 1959. In 1970, 579 cases of Hashimoto's thyroiditis were diagnosed at the Mayo Clinic. McConahey (1972) noted that the cause of Hashimoto's thyroiditis was still unknown, but it was believed to be an autoimmune disorder, genetically transmitted, and related to Graves' disease.

Chapman (1968) concluded that the increase in the frequency of diagnosis of Hashimoto's thyroiditis reported from surgical series covering the 2 decades starting about 1925 (a year after the introduction of iodized salt for home use in the United States) was probably real but was probably only apparent for the period 1945-1965, and did not signify an increase in the general population for the latter two decades.

Annegers (1976) used data from the Mayo Clinic to determine crude and age adjusted incidence rates for Hashimoto's thyroiditis in females of Rochester, Minnesota, by 5-year sampling periods from 1935 through 1974.
These preliminary data, based on diagnosed cases only, show a steadily rising incidence until 1965, after which the rate appears to have reached a plateau. Because of inherent difficulties of retrospective analysis of medical records, and the frequently asymptomatic and subtle nature of Hashimoto's thyroiditis, as well as other factors that perturb epidemiologic evaluation, Annegers (1976) noted that the increased incidence from 1935 to 1960 and the subsequent apparent leveling of the rate may or may not be true changes in incidence.

According to Matovinovic et al. (1974) the nationwide frequency of thyroidectomies for Hashimoto's thyroiditis did not change between 1960 and 1970.

C. DIAGNOSIS

Most thyroidologists agree that Hashimoto's thyroiditis can ordinarily be diagnosed on the basis of the patient's history, physical, and clinical laboratory examinations, but that difficulties of differential diagnosis sometimes require biopsy for histopathologic examination. The preferred technique for this is the needle biopsy. Laboratory studies may aid in the diagnosis although sometimes they merely add to uncertainty (DeGroot and Stanbury, 1975). In patients with Hashimoto's thyroiditis, significant values of basal metabolic rate, plasma thyroxin, butanol nonextractable iodide, radioactive iodine uptake, circulating thyroglobulin antibodies, and other criteria have been reported by numerous authors; however none is unequivocally diagnostic of Hashimoto's thyroiditis. In the differential diagnosis, it is necessary to distinguish Hashimoto's thyroiditis from nontoxic nodular goiter, adolescent goiters, and colloid goiters and concomitant Graves' disease. In addition, it is vital to rule out malignant tumors, on the basis of the history, physical examination, and laboratory studies usually conducted in the diagnosis of thyroid disorders.

The frequency of diagnosis of Hashimoto's thyroiditis in thyroid glands removed at the University of Michigan Medical Center Hospital during 4 selected 5-year periods was: 0 percent, 1915-1920; 0.4 percent, 1925-1930; 1.3 percent, 1942-1946; and 9.3 percent, 1958-1963 (Weaver et al., 1966). In Michigan, iodized salt for domestic use was introduced in 1924. Gaitan (1975) reported a somewhat similar change in the relative frequency of tissue diagnosis of Hashimoto's thyroiditis at the University Hospital in Cali, Colombia during the period 1953 (1 year before the introduction of iodized salt) to 1973. During these 20 years, the frequency of Hashimoto's thyroiditis in 2,018 thyroidectomy specimens rose from 0.1 percent to 1.3 percent. At the Mayo Clinic, McConahey et al. (1962) observed a change in frequency of Hashimoto's thyroiditis from 0.1 percent in 1930-1934 to a peak
of 13 percent in 1959. Over 77 percent of the diagnoses of Hashimoto's thyroiditis were confirmed microscopically. Prior to the iodized salt period, Wilson and Kendall (1916) did not observe lymphocytic infiltration in 566 surgical thyroid specimens examined at the Mayo Clinic during the year 1914. During their study of Himalayan endemic goiter, Roy et al. (1964) noted that, in a community without a goiter prevention program, the goiters were caused by extremely severe environmental iodine deficiency; lymphocytic infiltration of the goitrous thyroid glands of their series of patients was "conspicuous by its rarity." However, Williamson and Pearse (1925) reported lymphocytic infiltrates of the thyroid glands of patients with iodine deficiency goiters before the introduction of iodized salt in England, and, in Venezuela, an area of endemic iodine deficiency, needle biopsies of goiters frequently reveal Hashimoto's thyroiditis (Ingbar, 1976).

D. DISCUSSION

Certain features of the experiments to induce thyroiditis in laboratory animals need careful consideration before possible extrapolation to human beings is considered. In his experiments with hamsters, Follis (1959) altered the thyroid glands by goitrogens and low-iodine diets followed by massive parenteral doses of iodine. The minimal parenteral daily dose of iodine which was followed by thyroiditis was equal, on a body weight basis, to approximately 46 mg daily for a 60 kg human being. However, in subsequent experiments with hamsters parenteral doses of 76 μg daily for 6 days resulted in the inflammatory response (Follis, 1964). In dogs, Evans and his colleagues (1969) used a combination of active immunization by pooled crude thyroid extract and daily subcutaneous doses of 2 mg of sodium iodide, which compares with approximately 12 mg iodide per day for an adult human being. In the Clausen (1953) study, 25 percent of the rats on small oral intakes of thiouracil in the drinking water and with no supplemental iodine developed chronic thyroiditis. In all these studies it was necessary to induce thyroid hyperplasia artificially in order to produce thyroiditis, and, except for the hamsters (Follis, 1964) the doses of iodine were extremely high to massive in terms of realistic human exposure to exogenous dietary iodine. Caution should be observed in attempting to extrapolate these results to the human.

The evidence of a causal relationship between increasing amounts of dietary iodine including iodized salt, and the apparent increase in the occurrence of Hashimoto's thyroiditis is circumstantial. There is a question of whether or not the increasing frequency of Hashimoto's thyroiditis at certain clinical centers was a real change in incidence. The consensus seems to be that it was real; however, the true incidence of the disease is unknown, and this hinders an accurate estimate of epidemiologic status. Certain difficulties in the diagnosis such as a lack of uniform criteria or adequately matched comparison groups, and inadequate statistical analysis detract from the epidemiologic studies. There are few individual case histories of iodized
salt consumption in the studies showing increased frequency of Hashimoto's thyroiditis following introduction of iodized salt. Consequently, to accept the notion of a causal role for exogenous iodine in Hashimoto's thyroiditis, one need assume that patients with the disease were consumers of iodized salt. The data do not necessarily support this assumption. To quote Gaitan (1975): "Even if these increases (in Hashimoto's disease) are real, there is no scientific evidence to indicate more than a circumstantial relationship between iodine supplementation and lymphocytic thyroiditis."

Iodized salt became available for home use in Michigan in 1924, and this was accompanied by a public health education campaign supporting its use. It was estimated that in 1930, about 80 percent of salt (presumably for domestic use) in Michigan was iodized (McClure, 1934). McClure noted that by 1934, in the absence of continuing public health publicity about the importance of iodized salt, his patients usually did not know if they were using iodized salt. Today, about 58 percent of salt sold for domestic use is iodized (Wood, 1976); hence, it is possible that in Michigan, the estimated 80 percent preference for iodized salt in 1930 has decreased significantly.

Although Broders (1936) suggested compound solution of iodine (Lugol's solution) as a possible cause of chronic thyroiditis observed in surgical specimens at the Mayo Clinic, the more recently reported investigations from this medical center did not ascribe exogenous iodine as a possible etiologic agent. The carefully documented studies of iodine-induced hyperthyroidism in Tasmania are silent on the subject of Hashimoto's thyroiditis (Connolly 1971, 1973; Connolly et al., 1970; Stewart et al., 1971; Vidor et al., 1973). Furthermore, Suzuki et al. (1965) did not mention Hashimoto's thyroiditis in their report of iodine-induced goiter in Hokkaido. Histopathologic examination of the thyroid tissues removed from 7 patients whose data were recorded (see Table 5, Suzuki et al., 1965) revealed no lymphocytic infiltrates (Suzuki, 1976).

Several key concepts concerning Hashimoto's thyroiditis were suggested by the consultants at the February 1976 meeting. If valid, these concepts would support the thesis that excess iodine intake is an etiologic factor in Hashimoto's thyroiditis. Scientific evidence for and against these concepts has been reviewed in the preceding paragraphs, and a summary follows of the various points of view developed during the conference.

1. Where there is iodine deficiency, there is no Hashimoto's thyroiditis. However, some of the consultants pointed out that, while this may be true, the study of this relationship was rarely a primary goal of those investigations; consequently, it has not been adequately documented.
The prevalence of Hashimoto's thyroiditis in areas of severe iodine deficiency may be obscured by the fact that the relatively small, diffuse goiters of Hashimoto's thyroiditis are rarely treated surgically as compared with the large nodular goiters in such endemic areas.

2. Most experts agreed that in geographic areas with adequate or excess iodine intake, there is a definite incidence of Hashimoto's thyroiditis. However, it is difficult to accept that with adequate (normal) iodine intake there is a cause and effect relationship with Hashimoto's thyroiditis. No Hashimoto's thyroiditis has been reported in studies of the goiter endemic in Hokkaido coast dwellers who consume large amounts of iodine in seaweeds (Suzuki, 1976; Suzuki et al., 1965). In addition, few people with iodide goiter exhibit Hashimoto's thyroiditis. However, in studies of patients on long-term iodide treatment, Hall et al. (1966) reported that thyroid autoimmunity occurred more frequently in patients with iodide goiter or "intrinsic" asthma than in controls or patients with "extrinsic" asthma, suggesting to these investigators that patients with thyroid autoantibodies or "intrinsic" asthma had latent Hashimoto's thyroiditis which iodide made manifest and that patients with "extrinsic" asthma had true iodide goiter. Notwithstanding this possible association with medicinal iodine, dietary iodine as a variable has not been established as an etiologic agent in Hashimoto's thyroiditis.

3. During the institution of iodized salt use, a rise in the incidence of Hashimoto's thyroiditis has been observed in several geographic areas; analysis of surgical thyroid specimens shows that it continued to rise until the mid-1960's. Some consultants noted that, while this may be true, the relationship needs better documentation than is available today. The "pre-iodine" data in the Michigan study may be too incomplete for valid representations (see Table 2 on age and sex of patients, Weaver et al., 1966) and the histopathologic diagnoses during the iodized salt prophylaxis period were not correlated with iodine intakes of the patients. The consultants indicated that in the Minnesota study, Furszyfer et al. (1970) lacked data on the incidence of Hashimoto's thyroiditis in Olmsted County, Minnesota prior to the use of iodized salt nor did the investigators correlate the reported incidence of the disease during the 1935-1944 and the 1965-1967 sample periods with iodized salt consumption.

Certain consultants commented that while the histopathologic evidence of lymphocytes in surgical thyroid specimens reviewed in the Michigan and Minnesota studies is sound, extrapolation to an essential correlation with increased iodine is supported only by the time factor; no quantitative data were presented on iodine intake of the population groups involved. They noted that variation in diagnostic criteria for Hashimoto's thyroiditis over the past 50 years made the comparability of reported results questionable. In addition, lack of an experimental equivalent under controlled conditions of dietary iodine intake also detracted from these types of studies in terms of their acceptability as definitive proof of a significant causal relationship.
4. Unpublished data from the Mayo Clinic up to 1975, indicate that, among females in the Rochester, Minnesota area, the incidence of Hashimoto's thyroiditis appears to have stabilized since 1965 (Annegers, 1976). While this may be true, further documentation is desirable.

5. All the consultants concurred that further research is necessary to increase and clarify knowledge of relationships between Hashimoto's thyroiditis and environmental factors as well as possible intrinsic predisposing factors such as heritable defects in immunologic surveillance which may result in autoimmunity, and heritable defects in thyroxine synthesis.
IV. IODINE-INDUCED THYROTOXICOSIS (JODBASEDOW)

The occurrence of iodine-induced thyrotoxicosis has been well documented in patients with iodine deficiency goiter who received pharmacologic doses of iodine (Ek et al., 1963) and in goitrous patients from non-endemic areas (Vagenakis et al., 1972). Two or three cases were found among Argentines and Peruvians who participated in a goiter prevention program, but none among New Guineans in an extensive iodine prophylaxis project (Stanbury et al., 1974). In Ecuador, of 960 persons injected with iodized oil in a goiter prevention program, 3 women over 45 years of age with large nodular goiters developed thyrotoxicosis (Fierro-Benitez et al., 1969).

However, convincing evidence of its occurrence in response to levels of iodine supplements used in goiter prevention did not appear until the reports of Van Leeuwen (1954) and the group of investigators in Tasmania (Connolly, 1971, 1973; Stewart et al., 1971; Vidor et al., 1973). The well-documented epidemic of jodbasedow in Tasmania occurred following the addition of supplementary iodine to bread in 1966 to correct endemic iodine deficiency goiter. Most of the patients were over 50 years old and had longstanding, multinodular goiters. Later, Connolly (1973) reported an increase in incidence of jodbasedow among Tasmanians less than 40 years of age and predicted that either as the prevalence of endemic goiter decreases in adults, the rate of thyrotoxicosis will decline in older persons but will gradually increase in younger members (0-40 years), or that the thyrotoxicosis rate may remain stable in both age groups. Stewart (1975) reported that the usual cause of the increased thyrotoxicosis in patients under 40 years old at the Launceston General Hospital, Tasmania, was Graves' disease, and he suggested that iodine repletion may have "unmasked some hitherto subclinical cases." The possibility that iodophors used on dairy farms in Tasmania may also have contributed to human iodine intake and to the epidemic of jodbasedow was suggested by Stewart and Vidor (1976).

In Tasmania, the iodinated bread contains 32 μg of iodine per ounce; the average daily amounts of supplemental iodine ingested by 50 thyrotoxic patients over 50 years of age were estimated at 124 μg; and 139 μg in 43 patients under age 40 (Vidor et al., 1973). Despite the thyrotoxicosis, the iodination of bread as a public health measure against endemic goiter continues in Tasmania. However, it has been suggested that selective iodine supplementation to exclude persons over 40 years old might be advisable (Vidor et al., 1973).

Savoie et al. (1975) described iodine-induced thyrotoxicosis in ten patients who had received excess iodine in medication and in Lipiodol®
for myelography (one patient). The patients were considered euthyroid with no thyroid abnormalities prior to exposure to iodine-containing drugs, and subsequently, following cessation of exposure, they returned to euthyroid status. No thyroid pathology was observed.

Although several reports of increases in thyrotoxicosis rates were published in the 1920's following introduction of iodized salt in the United States (Jackson, 1925; Kimball, 1925; McClure, 1927), the data are not sufficient to prove any causal role for the increased dietary iodine. There are no published reports from the United States which adequately document jobbasedow as a result of supplemental dietary iodine.

Most consultants in this review agree that the possible hazards of goiter prevention by supplemental iodine are acceptable in view of the substantial benefits achieved and that the recently reported cases of thyrotoxicosis following initiation of iodine prophylaxis have been mild and easily managed.
V. OTHER THYROID DISORDERS

A. IODINE GOITER

Long clinical experience with pharmacologic doses of iodide and other iodine-containing compounds attests to their harmlessness and to the ability of persons with normal thyroid glands to adapt to high intakes of iodine for prolonged periods. However, iodide goiter, sometimes associated with hypothyroidism, occasionally complicates the chronic ingestion of excess iodide or iodide-generating compounds (Braverman et al., 1971; Wolff, 1969).

Wolff (1969) divided iodide goiters into four categories: 1) iodide goiter of the newborn whose mothers were on iodide therapy during pregnancy (see p 32); 2) adult iodide goiter, seen rarely in patients with chronic pulmonary disease on long-term iodide treatment; 3) endemic iodide goiter from excess iodine in the diet; and 4) hypothyroidism in thyrotoxic patients treated with iodide (during the decades when this was the preferred treatment).

Adult iodine goiter and myxedema from pharmacologic use of iodine are outside the scope of this report. Endemic goiters from excess iodine in the diet occur among coast dwellers of Hokkaido, Japan, who consume large amounts of seaweed from which individual daily iodine intakes may amount to approximately 200 mg (Suzuki and Mashimo, 1973; Suzuki et al., 1965; Wolff, 1969). These were described as colloid goiters in euthyroid individuals (Suzuki, 1976). Withdrawal of seaweed from the diet resulted in disappearance of the goiters in a few patients, and Suzuki and Mashimo (1973) reported a decrease in the prevalence of iodide goiter when consumption of kelp was reduced. The reasons for individual susceptibility to this type of goiter have not been established nor has it been proved absolutely that the high iodine content of the seaweeds consumed by these patients is the sole etiologic factor (Suzuki et al., 1965).

Recent surveys in four American cities showed that between 5 and 10 percent of the school age children whose diets contained adequate iodine, had enlarged thyroid glands (Stanbury et al., 1974); no cause for these goiters was found. Nodular goiter occurs in about 4 percent of the population in areas abundantly supplied with iodine. Fisher and Carr (1974) noted that no recent reports document endemic dietary iodine deficiency in North America. Most childhood goiter found in field surveys in the United States is a limited, diffuse enlargement of the thyroid gland, not visible, but detected by palpation. Multinodular goiter is rare in American children (Trowbridge et al., 1975a).
In the Ten-State Nutrition Survey (U.S. Department of Health, Education, and Welfare, 1972), physical examination of the thyroid glands of 35,999 persons yielded an overall goiter frequency of 3.1 percent, with a higher frequency in females than in males. There was no apparent association between goiter and low urinary iodine excretion; instead, the prevalence of goiter was higher among those with elevated urinary iodine excretion (Trowbridge et al., 1975b). The higher urinary iodine excretion found among goitrous children (Trowbridge et al., 1975a) and in the study areas with highest goiter prevalence suggests high iodine intake may be an etiologic agent in some of the goiters. However, Trowbridge et al. (1975a) considered the possible etiologic role of high iodine intake as speculative, noting that the overall difference between urinary iodine levels of the goitrous and nongoitrous children was not statistically significant and that the consumption of iodine-rich foods was essentially the same in all the children. From their survey of the prevalence of goiter in 35,999 American consumers, Trowbridge et al. (1975b) concluded that it was not possible from the available data to assess the exact nature of the relationship between the probable high iodine intakes and the prevalence of goiter.

Eighty-two of the 106 Breathitt County, Kentucky school children who were diagnosed as goitrous (Trowbridge et al., 1975a) were classified by family history of goiter, tested for urinary iodine excretion, serum thyroxine, triiodothyronine, protein-bound iodine, thyrotropin, and thyroid autoantibodies, and compared with matched controls. The study revealed clinical and laboratory findings consistent with a diagnosis of thyroiditis in about 20 percent of children, and unexpected disappearance of goiter in 17 of the original 82 goitrous children versus the appearance of goiter in 22 of the matched controls. The authors concluded that, "evolving thyroiditis is common in Appalachian children but does not explain all goiters in an area with abundant iodine and known familial goiter" (Hollingsworth et al., 1976).

B. NEONATAL GOITER

Iodide goiter in the newborn is uncommon, but it occurs with sufficient frequency to suggest clinical caution whenever pregnant women take pharmacologic doses of iodide as in the treatment of chronic pulmonary disease and hyperthyroidism. Carswell et al. (1970) reported 8 cases of congenital goiter and hypothyroidism seen at the Royal Hospital for Sick Children, Glasgow, between 1955 and 1969 and a few additional case reports have appeared in the literature since then. The most serious consequence of neonatal goiter is asphyxia from compression of the airway. Although neonatal goiter may be complicated by hypothyroidism, it usually is self-limiting and the goiter and hypothyroidism gradually disappear (Wolff, 1969).

The neonatal goiters described in the literature were all associated with chronic ingestion of large amounts of iodine by the mothers. For example, daily doses in some cases ranged from 12 to 2010 mg (Ayromlool, 1972), amounts
considerably in excess of dietary intakes in the United States (see p 11). An accurate estimate of the minimum maternal dose of iodine that will cause neonatal goiter has not been established; however, a majority of the consultants in this review agreed that the amounts of iodine in the diet in this country do not present a risk of neonatal goiter.

Other types of neonatal thyroid disorders should be distinguished from iodide goiter of the newborn; for instance, neonatal hyperthyroidism, a rare disease of newborns whose mothers had hyperthyroidism (Johnson and Senior, 1968), and diffusely hyperplastic goiters of the newborn, presumably related to severe iodine deficiency (Follis, 1958).

C. MALIGNANCIES

No reports were found in this survey that clearly link dietary iodine with thyroid cancer in a cause and effect relationship. First, the suggestion is debatable that a true increase in the incidence of thyroid cancer occurred following the introduction of iodized salt in this country. Chapman (1968) analyzed the U.S. literature published between 1908 and 1966 on the changing frequency of thyroid cancer and Hashimoto's thyroiditis and their correlation with such factors as diagnostic criteria, patient selection, ionizing radiation, and iodized salt. Until about 1930, the reported frequency of thyroid cancer in series of thyroidectomies was between 1 and 2 percent; from 1940 to 1950, it was about 5 percent, and in the early 1960's, between 8.8 and 14.8 percent. However, Chapman (1968) concluded that the reported increases did not necessarily mean an increase of the disease in the general population but probably reflected a marked reduction in surgery for toxic goiter and a substantial increase in operations for nontoxic nodular goiter, which, in turn, resulted from changes in patient selection based on new diagnostic criteria and criteria for thyroid surgery.

Carrol et al. (1964) and Weiss et al. (1967) reported data showing an apparent increase in the incidence of thyroid cancer in the younger age groups (under 55 years) between 1940 and 1960. However, Chapman (1968) suggested that this increase may simply mean that, following the disclosure by Mortensen and associates (1954) of finding many more thyroid cancers by extremely careful diagnostic procedures, malignancies were being diagnosed that may have been missed in the past, or detected in older patients when the tumors were larger and easier to diagnose.

Cutler et al. (1974) reported the incidence of thyroid cancers in the United States at 3.6 per 100,000 population per year. Autopsy series reveal higher figures of approximately 100 per 100,000. However, there is no convincing evidence of an increase in the incidence of thyroid cancer in this country during the past three decades unless one includes "occult" cancers found either at autopsy or incidentally diagnosed in thyroid tissue (DeGroot and Stanbury, 1975).
Several authors reported that the prevalence of thyroid cancer appears to be higher in endemic goiter areas (Cole et al., 1949a, 1949b; Hinton and Slattery, 1953; Mortensen et al., 1955; Scrimshaw, 1964; Wahner et al., 1966; Wynder, 1952). However, the near disappearance of endemic goiter after introduction of iodized salt should have reflected a decrease in prevalence of thyroid cancer in goitrous areas if the reported association were significant. No reports of such a decrease have been found.

The substantial association of radiation therapy of the head, neck, and mediastinum with subsequent thyroid cancer in younger group patients clouds the issue of iodized salt as a contributing factor in thyroid neoplasia. The use of iodized salt in the United States to prevent goiter started when x-irradiation was the preferred treatment for thymic enlargement in infants (Pifer et al., 1963). In addition, x-ray treatment of tonsillitis in young children and facial acne in adolescents became popular early in the iodized salt era. DeGroot and Paloyan (1973) noted that, in their experience, from 50 to 75 percent of children who had thyroid neoplasms had a history of radiation to the neck and that radiation-associated thyroid tumors continue to be a significant clinical problem. Latent periods between radiation exposure and diagnosis of thyroid cancers varied from less than 5 years to 30 years, with the majority in the 20 to 30 year period. In 1974, Favus et al. (1976) examined 1056 persons who had therapeutic irradiation of the upper respiratory tract in the 1940's and 1950's. Over 27 percent had nodular thyroid disease, and of the 182 patients in this series who had the thyroid nodules removed, 60 (33 percent) had thyroid cancer.

Woolner and associates (1959) observed that while cancer of the thyroid can coexist with Hashimoto's thyroiditis, this combination is rare, amounting to 18 cases, or a 3 percent association rate in their 605 patients seen at the Mayo Clinic over a 27 year period. Although thyroid cancer was not an objective of their study, Mulhern et al. (1966) in a search for associated disorders in 170 clinically detected cases of Hashimoto's thyroiditis, found the frequency of associated malignancies (all types) no different from that in matched controls who did not have Hashimoto's thyroiditis.

On the other hand, a number of reports indicate relatively high rates of association of thyroid cancer and chronic thyroiditis; for example, 11.6 percent (Lindsay et al., 1952); 11.5 percent (Pollock and Sprong, 1960); 6.9 to 8.7 percent (Schlicke et al., 1960). The significance of these reported associations in terms of epidemiologic trends is not clear but patient selection has been suggested as a contributing factor. If additional data establish that excess dietary iodine has a role in the etiology of Hashimoto's thyroiditis, and if future epidemiological studies demonstrate an association between Hashimoto's thyroiditis and thyroid cancer, then the effects of dietary iodine on the pathogenesis of thyroid cancer would need critical examination.
VI. CONCLUSIONS

Data derived from food surveys in the United States during 1974 and 1975 suggest that levels of iodine in foods consumed by adults as well as infants and toddlers increased since 1970. Continued determination of dietary iodine is required to establish a data base for assessment of the significance of future changes in dietary iodine levels.

It is generally accepted that most iodine-containing compounds that enter the food chain are readily bioavailable after ingestion. However, information to estimate the iodine bioavailability of specific iodine compounds is meager as are the available data on the effects of cooking and food processing on the bioavailability of iodine in foods as consumed.

Currently, the role of iodophors in dairy sanitation as a source of iodine in the human diet is equivocal. Iodine from iodophors can enter the human food chain by this route; however, there are insufficient data to assess the quantitative aspects of this subject, and additional studies should be made.

Iodine as a disinfectant in drinking water has certain advantages over other agents. Although interest in this method of treatment of potable water appears limited at present, it may be expected to increase. The establishment of a federal standard for iodine in potable water supplies appears desirable.

While it is generally believed that atmospheric iodine is of little practical biological consequence, data are limited with which to estimate levels and biological significance in open or closed spaces in situations that favor elevated iodine levels.

Hashimoto's thyroiditis, infrequently diagnosed in the United States prior to 1950, is now regarded as a common thyroid disorder of children and adults of both sexes. It may also be a transient phenomenon in children.

During the period 1925 to 1945, a real increase in incidence of Hashimoto's thyroiditis is believed to have occurred. However, the increased incidence reported since about 1945 is apparent and may be related to greater clinical awareness, more definitive diagnosis, and patient selection. Since 1965, the incidence among females of the carefully studied Rochester, Minnesota area has apparently stabilized.

The concept that supplemental iodine used to prevent endemic goiter may be an etiologic agent in Hashimoto's thyroiditis is based on three main observations: 1) Hashimoto's disease was rarely reported in endemic goiter
areas prior to the introduction of iodine prophylaxis, but increased in frequency following such prophylactic measures; 2) essentially no lymphocytic infiltrates were reported in human and animal thyroid specimens in certain Himalayan endemic goiter regions where there were no iodine prophylaxis programs; and 3) the demonstration that a form of lymphocytic thyroiditis may result from administration of excess iodine to experimental animals with artificially-induced thyroid hyperplasia. The evidence in support of the concept is incomplete, lacks epidemiologic specificity, and is largely circumstantial. Thus, a cause and effect relationship between the use of prophylactic iodine in endemic goiter areas and the prevalence of Hashimoto's thyroiditis cannot be established with the available information. Most thyroidologists agree that the etiology of Hashimoto's thyroiditis remains obscure, but that the disease is a genetically conditioned, autoimmune disorder.

Carefully conducted clinical and epidemiological investigations have established that supplemental iodine used to prevent goiter in areas of significant endemicity contributes to the development of thyrotoxicosis (jodbasedow) in susceptible persons. In Tasmania, where the phenomenon is the best documented, the advantages of the goiter prevention program override the disadvantages of an occasional case of jodbasedow. In the United States, no cases of thyrotoxicosis induced by dietary iodine including iodized salt have been reported.

No recent reports document endemic dietary iodine deficiency in this country. Although iodine deficiency goiter is occasionally reported, it is apparently restricted to a few geographically isolated populations.

Recent goiter surveys in this country revealed that between 5 and 10 percent of school age children in four sample cities had enlarged thyroid glands and that nodular goiter occurs in about four percent of the general population. Dietary iodine was adequate in the sample population, and no data were reported to support the notion that excess dietary iodine may have been a contributing factor.

Iodine-induced goiter in the newborn is a rare complication of treatment of pregnant women for chronic pulmonary disease using pharmacologic doses of iodide. No cases of neonatal goiter from dietary iodine have been documented, and a majority of the consultants in this review agreed that the amounts of iodine in the diet in this country do not present a risk of neonatal goiter.

The true etiologies of Hashimoto's thyroiditis, iodide goiter, and jodbasedow are undoubtedly complex and may involve species-specific, genetic, immunologic, sex, age, and other factors such as high iodine intakes. Despite similar iodine intakes in population groups, the natural history of these diseases may be sporadic, familial, congenital, of late-onset, self-limiting, progressive, clinically mild or debilitating.
Reports of an association of chronic thyroiditis and thyroid cancer are conflicting. If excess dietary iodine were established as a contributing factor in Hashimoto's thyroiditis, its possible significance in thyroid cancer would demand immediate emphasis. At present, there is no convincing scientific evidence of such a cause and effect relationship with dietary iodine.
VII. SUGGESTIONS FOR FUTURE CONSIDERATION

SOURCES OF IODINE

- Continued analysis of iodine in various foods as in the Food and Drug Administration's Market Basket Survey is essential to establish baseline data and trends in potential dietary intake. In addition, actual iodine intakes should be determined throughout the United States. Improvement in the survey techniques would enhance the reliability of the results as indices of iodine consumption of Americans of all ages and representative geographic areas.

- It would be useful to determine if regional geographic differences in iodine availability exist and, if so, if they are associated with patterns of incidence of goiter, Hashimoto's thyroiditis, and thyrotoxicosis.

- There is a lack of information on the effects of food processing and cooking on the net available iodine in ready-to-eat and processed foods.

- Inasmuch as iodination of drinking water may be used to a greater degree in the future for water disinfection, more data on the biologic effects of iodinated water would be valuable.

- Information on the sources and levels of iodine in the air is needed to assess this environmental component of the total bioavailable iodine.

HASHIMOTO'S THYROIDITIS AND OTHER THYROID DISORDERS

- Published data on the exact causes of Hashimoto's thyroiditis are inconclusive although the weight of evidence favors an etiology involving autoimmune mechanisms. Resolution of this question would facilitate a definition of a possible accessory role of excess iodine in Hashimoto's thyroiditis.

- In view of the many synonyms for Hashimoto's thyroiditis and the resulting confusion of terms, standardization of the diagnostic criteria and nomenclature of the lymphocytic thyroiditides is desirable.

- Most thyroidologists consider the diagnosis of Hashimoto's thyroiditis relatively easy; however, improved and simpler means of diagnosis by clinicians other than endocrinologists would be valuable.
• There is a need for factual data on the equivocal matter of the occurrence of Hashimoto's thyroiditis and other forms of lymphocytic thyroiditis in iodine-deficient areas of the world. Biopsy studies should be done on goitrous thyroid glands in subjects known to be iodine-deficient.

• There is a need to establish the true incidence of Hashimoto's thyroiditis, iodine-induced thyrotoxicosis, and other thyroid disorders in the United States.

• Sustained funding support should be provided for research to clarify the etiologies of these thyroid disorders.

• The search for a better laboratory animal model for the study of the etiology of thyroid disorders including genetic influences and such environmental factors as microorganisms, exogenous iodine, and other goitrogens should be continued.

• The demonstration that iodine prophylaxis against goiter sometimes results in thyrotoxicosis (jodbasedow), in Tasmania and the Netherlands, requires careful clinical attention to this possibility in the United States. Evaluation of iodine consumption in patients with thyrotoxicosis is particularly desirable and the possible influence of route, dose, and duration of iodine supplementation on the frequency of jodbasedow should be investigated. In goiter prevention programs, does iodine supplementation create a single cohort of thyrotoxic patients or is an increased incidence of hyperthyroidism likely to persist?

• Methods should be developed for clinical identification of the so-called "preconditioned" individual who is susceptible to adverse effects of "excess" iodine on the thyroid gland. An approach to this might be longitudinal studies of children with goiter, in a small, well-defined population sample where iodine supplementation is recommended. Such studies should include serial needle biopsies, urinary iodine excretion, thyroid autoantibodies, and family history of thyroid disorders. In addition, more sophisticated $^{131}$I kinetic studies should be done in a small group of subjects, with and without goiter, on high iodine intake.

• The fact that high levels of iodine in foods cannot be ruled out as a possible contributing factor in the etiology of certain thyroid diseases such as Hashimoto's disease, thyrotoxicosis, and iodine goiter, emphasizes the need for continuing research and epidemiologic investigations of these associations and the factors that influence individual susceptibility (preconditioning factors) to an adverse effect of excess iodine on the thyroid gland.
VIII. BIBLIOGRAPHY

Documents marked with an asterisk (*) are unpublished material available from the Life Sciences Research Office, Federation of American Societies for Experimental Biology, 9650 Rockville Pike, Bethesda, Maryland 20014.


IX. SCIENTIFIC CONSULTANTS

A REVIEW OF THE EFFECTS OF DIETARY IODINE ON CERTAIN THYROID DISORDERS

A. ATTENDEES, AD HOC CONFERENCE, FEBRUARY 10, 1976

CHAIRMAN

C. Jelleff Carr, Ph. D.
Director
Life Sciences Research Office
Federation of American Societies
for Experimental Biology
Bethesda, Maryland 20014

CONSULTANTS

John F. Annegers, Ph.D.
Research Assistant
Department of Epidemiology and
Medical Statistics
Mayo Clinic
Rochester, Minnesota 55901

Dorothy R. Hollingsworth, M.D.
Professor of Pediatrics
Department of Pediatrics
University of Kentucky
Lexington, Kentucky 40506

William H. Beierwaltes, M.D.
Professor of Medicine
Physician-in-Charge
Section of Nuclear Medicine
University of Michigan Medical Center
University Hospital
Ann Arbor, Michigan 48104

Josip Matovinovic, M.D.
Professor of Medicine
Nuclear Medicine Section
University of Michigan Medical Center
University Hospital
Ann Arbor, Michigan 48104

Roy Hertz, M.D., Ph.D.
Department of Pharmacology
George Washington University
School of Medicine
Washington, D.C. 20037

William M. McConahey, M.D.
President
The American Thyroid Association
Mayo Clinic
Rochester, Minnesota 55901
James A. Pittman, Jr., M.D.
Dean and Professor of Medicine
University of Alabama School
of Medicine
Birmingham, Alabama 35294

John B. Stanbury, M.D.
Professor of Experimental Medicine
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Jan Wolff, M.D., Ph.D.
Associate Chief, Clinical Endocrinology
Branch
National Institute of Arthritis,
Metabolism, and Digestive Diseases
National Institutes of Health
Bethesda, Maryland 20014

FDA

E. Martin Blendermann, M.Ph.
Nutrition Advisory Group
Nutrition & Consumer Sciences

Richard Jacobs, Ph.D.
Mineral Section
Division of Nutrition
Nutrition & Consumer Sciences

J. William Boehne
Assistant Associate Director for
Nutrition & Consumer Sciences

Paul C. Rambaut, Sc.D.
Assistant to the Associate Director
for Nutrition & Consumer Sciences

Joginder G. Chopra, M.D.
Special Assistant for Medical Affairs
Nutrition & Consumer Sciences

Samuel I. Shibko, Ph.D.
Special Assistant to the Director
Division of Toxicology

Allan L. Forbes, M.D.
Acting Associate Director for
Nutrition & Consumer Sciences

Ralph Stafko
Paralegal Assistant
Regulations Staff

M.R.S. Fox, Ph.D.
Chief, Mineral Section
Division of Nutrition
Nutrition & Consumer Sciences

John E. Vanderveen, Ph.D.
Director
Division of Nutrition
Nutrition & Consumer Sciences
LIFE SCIENCES RESEARCH OFFICE

Kenneth D. Fisher, Ph.D.
Associate Director

Kazuo K. Kimura, M.D., Ph.D.
Medical Consultant

John M. Talbot, M.D.
Medical Consultant

Evelyn Volkman
Assistant to the Director

B. OTHER CONSULTANTS

Lewis E. Braverman, M.D.
St. Elizabeth's Hospital
736 Cambridge Street
Boston, Massachusetts 02135

Sidney H. Ingbar, M.D.
Thorndike Laboratory
Beth Israel Hospital
330 Brookline Avenue
Boston, Massachusetts 02115

Sylvia Most, Ph.D.
West Chemical Products, Inc.
42-16 West Street
Long Island City, New York 11101

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