A REVIEW OF THE SIGNIFICANCE OF UNTOWARD REACTIONS TO IODINE IN FOODS

SEPTEMBER, 1974

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

Under
Contract Number FDA 71-294

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

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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 Division of Nutrition, Bureau of Foods, Food and Drug Administration (FDA), by the staff of the LSRO, FASEB, in accordance with the provisions of Contract No. 71-294.

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 May 14, 1974 and other consultants. A judicious attempt has been made to incorporate the different viewpoints and opinions.

The report has been reviewed by these consultants; however, the authors accept responsibility for the contents of the report. The listing of the consultants' names in Section VIII does not imply that they endorse the conclusions of this study. The report has been reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures the report has been approved and transmitted to 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 opinion of all of the individual members of its constituent societies.

C. Jelleff Carr, Ph. D.
Director
LSRO

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SUMMARY

This study was initiated because of concern for possible untoward reactions to dietary iodine. The concern was based on accumulating evidence that dietary iodine intake in North America has increased in recent years and is generally in excess of amounts recognized as necessary for adequate nutrition. A review of the literature and the opinions of experts in allergy, dermatology, endocrinology, and related specialties indicated that adverse reactions to iodine in foods are not a significant clinical or public health problem in the United States.

The untoward effects of iodine include toxic, idiosyncratic and hypersensitivity reactions. There is no unanimity of opinion on the role of the immune system and nonimmunologic mechanisms in untoward reactions to iodine. While untoward effects of excess iodine from drugs and iodine-containing x-ray contrast media are well recognized, similar effects from excess dietary iodine are not well established. There is some laboratory and clinical evidence supporting the concept that iodine and iodine-containing substances in drugs and foods may be haptenic; however, this subject remains controversial. Currently there are no generally available laboratory methods for diagnosing iodine hypersensitivity. Additional laboratory and clinical research should be conducted to develop improved, practical diagnostic methods for iodine hypersensitivity determination.

Except for transient disturbances in thyroid function, adverse reactions reported since 1911 that were allegedly caused by iodine in foods or food supplements such as iodized salt have been rare. The majority of these cases involved acne and iododerma. Although the reporting clinicians were convinced, scientific proof of the etiologic role of dietary iodine or iodized salt in these cases was lacking. Because medical reporting of nonlife-threatening reactions to foods and drugs is generally incomplete, it should be recognized that a number of cases of idiosyncratic and allergic reactions to iodized salt or iodine in foods have not been documented.

There is no convincing evidence that iodized salt or iodine in foods causes acne; however, it is possible that iodine from these sources may aggravate acne and cause an increase in cyst formation and scarring. Carefully planned and conducted studies are needed to elucidate the possible influence of iodine on acne.

Increased prevalence of thyrotoxicosis has been reported from the United States, the Netherlands, and Tasmania following the introduction of supplemental dietary iodine in iodine-deficient areas. The Tasmanian experience is well documented and points up the need for careful epidemiological
and clinical surveillance in areas of known iodine deficiency with abnormally high goiter prevalence when prophylactic programs of iodine supplementation are contemplated or established.

Iodide goiter, with or without hypothyroidism, occasionally develops in patients on prolonged treatment with iodide or iodide-generating compounds and can occur in otherwise normal individuals whose diets contain excessive amounts of iodine. For this reason and because iodine-induced thyrotoxicosis from ingestion of excess iodine may occur in persons somehow predisposed to this effect, the amounts of iodine in the North American diet should be periodically reevaluated. While there are no current reports that document an increase in the prevalence of iodine toxicity, hypersensitivity reactions, or iodine-influenced diseases of the thyroid gland, this report suggests a continuing need for clinical awareness and periodic surveys of these conditions in this country.
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I. INTRODUCTION

A. BACKGROUND

The Division of Nutrition, Bureau of Foods, Food and Drug Administration has a continuing interest in the iodine content of the American diet because the agency is responsible for evaluating the safety of foods and establishing food-labeling regulations. If the claims of idiosyncratic or allergic reactions to iodine in foods made by some consumers and physicians are real and clinically significant, appropriate regulatory approaches may be necessary. A thorough understanding of the validity and nature of idiosyncratic and allergic reactions to iodine is desirable. In addition, it would be helpful to identify those conditions or diseases in which it is appropriate or essential to restrict iodine intake.

The Life Sciences Research Office was requested by the Division of Nutrition to review current scientific information on idiosyncratic, allergic, and other untoward reactions related to naturally occurring, adventitious or added inorganic and organic iodine in foods. The first undertaking in this review has been the preparation of a comprehensive report entitled Iodine in Foods: Chemical Methodology and Sources of Iodine in the Human Diet (Fisher and Carr, 1974). This report discussed the analytical methodology used in estimating the iodine in foods, documented sources of iodine in animal feeds and human foods, and assessed the current status of iodine nutrition.

Reliable information about the prevalence and the existence of adverse reactions to supplemental iodine in foods is essential. Interest in this subject has been heightened by the knowledge that endemic goiter is still a public health concern in the United States, and by the accumulating evidence that in recent years the amounts of iodine entering the American food supply have increased substantially. To assist the consumer in identifying iodized and uniodized table salt marketed for home consumption, the FDA proposed and enacted regulations stipulating label statements for the two forms of table salt (Edwards, 1971). Whether or not all table salt in this country should be iodized remains controversial.

Supplementation of the diet by the use of iodized table salt on a voluntary basis began in the early 1920's in Michigan (Matovinovic and McGanity, 1970; Scrimshaw, 1970). Its availability for optional use ultimately became widespread in the United States. Recognition of the feasibility and importance of endemic goiter prevention by supplemental iodine prophylaxis has been growing throughout the world (World Health
Organization, 1972). A survey in 1965 showed that 28 countries supported public health programs in endemic goiter prevention by supplementing the diet with iodine. In 23 of these nations the programs were supported by legislation (Lowenstein, 1967). The FDA announcement of January 26, 1972 concerning labels for iodized and noniodized table salt contained the statement: "In addition there is general agreement that it would be desirable to have greatly increased human consumption of iodized salt" (Edwards, 1972).

All these developments highlighted the two concerns: endemic goiter prevention via dietary iodine supplementation, and the possibility of untoward reactions to iodine in foods in view of documented evidence of significantly increasing amounts of iodine in the diet.

B. SCOPE

This review was conducted to determine the prevalence of untoward reactions to inorganic and organic iodine-containing constituents in foods; to identify allergic as contrasted with other types of reactions; to examine the validity of claims by consumers and some physicians that the use of iodized salt causes allergic and idiosyncratic reactions; to reach conclusions on the extent and clinical significance of the various untoward effects identified; and to point out noteworthy gaps of knowledge in this field.

Literature published since 1900 was reviewed including references that documented historical reports on untoward reactions to iodine. Sources of information were 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).

Information was provided also by consultants in this study and by letters from individual experts in clinical and investigative medicine. A request for information on clinical experiences with iodine sensitivity in patients was published in the Annals of Allergy (Carr, 1974). Published reports of untoward reactions to iodine consumed with foods and, for comparison, reactions to iodine taken therapeutically and diagnostically were reviewed. A synopsis of iodine metabolism was included in the prior report (Fisher and Carr, 1974), and is not repeated in this review. The nutritional significance of increased iodine in the diet was not a part of the study.
II. SOURCES OF IODINE IN FOODS

Iodine occurs naturally in soil, water, air, plants, animals, and especially marine life. The iodine in the atmosphere and that subsequently deposited on land by precipitation are derived from iodine in seawater (approximately 50 μg/kg). Lower concentrations of iodine occur in fresh water and most soils (Altman and Dittmer, 1966; Informatics, Inc., 1973; Underwood, 1973). Food and water are the major sources of the small quantities of iodine* needed for adequate growth and nutrition.

In documenting the amount of iodine in foods, Fisher and Carr (1974) surveyed sources of iodine in animal nutrition and the significance of dairy practices and modern food processing that lead to an increase in iodine in foods for man. The total iodine intake of domesticated animals is increasing as a result of the iodine added in mineral supplements to feeds, supplied in iodized salt blocks, or present in veterinary medications. These are more significant sources of iodine than those naturally occurring in forage and feed grains. In addition to iodine naturally present in foods of plant origin and in water, an increasing amount of iodine is entering the human diet from meat, eggs, and dairy products obtained from animals receiving iodine supplemented rations or veterinary medications. Iodine from iodized salt, sanitizing agents, food additives, coloring substances, and medicinals increases the total iodine intake of the North American population. In addition, there is evidence that iodine introduced during food processing as well as atmospheric iodine may be significant sources of iodine in urban North America.

The average human dietary iodine intake in North America has increased in recent years. Measurements of actual dietary iodine and estimates based on food consumption suggest that intake levels are generally in excess of amounts recognized as necessary for adequate nutrition. In addition, the elevation of observed and calculated estimates is consistent with indirect measurements of iodine intake including iodine excretion studies and clinical tests of radioactive iodine uptake by the thyroid gland.

Most authorities agree that the daily iodine requirement for goiter prevention in adults is approximately 50 to 75 μg or 1 μg per kg per day.

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*In this report "iodine" is used in a 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.
(National Research Council, Committee on Food Protection, 1970). Actual daily intakes of 100 to 300 μg are recommended as adequate to meet the known nutritional needs of practically all healthy adults although adult intake levels of 100 to 1000 μg per day are considered safe (National Research Council, Food and Nutrition Board, 1974). According to the data reviewed by Fisher and Carr (1974), the mean adult intake levels currently range from 380 to 450 μg per person per day. The use of iodized salt alone would supply approximately 150 μg per day, an amount well within the suggested intake levels.

In the normal individual, excess iodine is excreted primarily via the kidney, although some organic iodides are lost via feces. Additional iodine excretion occurs via sweat and milk (Welt and Blythe, 1970). It is logical to suggest that untoward reactions may occur in individuals when excretory processes do not eliminate excess iodine or when tissue tolerance of bound and unbound iodides is limited.
III. GENERAL CHARACTERISTICS OF UNTOWARD REACTIONS

A. DEFINITION OF TERMS

Untoward reactions to normally innocuous food ingredients may include toxic, idiosyncratic, and hypersensitivity reactions. While a specific search for documented cases of hypersensitivity reactions to iodine in foods received emphasis in this study, it is important to recognize that certain signs and symptoms which are classical examples of the allergic response may sometimes occur without a demonstrable immune response. This may help to explain why few proven cases of hypersensitivity reactions to iodine were found despite reports of a number of patients with allergic type signs and symptoms. Nonimmunologic mechanisms which may be associated with adverse reactions to foods and food chemicals include enzymatic deficiencies as in disaccharide and gluten intolerance; chemical irritation of the gastrointestinal tract by such foods as cabbage, onions, and spices; toxic reactions from tainted foods including improperly preserved fish and shellfish, which may develop a high histamine content; untoward reactions to food contaminated by bacteria and their products; and toxic effects of naturally occurring or added chemicals in foods.

Toxic effects occur when the amount of toxic material exceeds the tolerance and these reactions are independent of the immune response. Reactions of certain individuals are often termed idiosyncratic in cases where the exact nature is unknown but genetically determined factors are suspected. Untoward idiosyncratic reactions may be mediated by either immune or nonimmune mechanisms and may be precipitated by minute amounts of the eliciting substance. The clinical signs and symptoms of toxic reactions are generally distinguishable from those of hypersensitivity and idiosyncrasy; however, differentiation between idiosyncrasy and hypersensitivity solely on the basis of clinical signs and symptoms is not feasible.

Most, but not all, authorities agree that hypersensitivity reactions to normally innocuous substances are mediated by the immune system. With respect to iodine, the interaction of exogenous or endogenous iodine, directly or indirectly with humoral antibodies or specifically sensitized lymphocytes, is assumed to be a necessary part of the phenomenon. When the effects of the immune response are beneficial to the host, they are called "immunity"; when detrimental, they are variously known as "hypersensitivity," "allergy," or "sensitivity." Hypersensitivity may be defined in terms of four types of reactions (Lakin, 1972):
Type I - anaphylactic reactions  
Type II - cytotoxic reactions
Type III - toxic-complex reactions  
Type IV - cellular hypersensitivity

Some distinguishing features of these reactions are listed in Table I.

Many authorities prefer to use the traditional immediate and delayed classification of hypersensitivity (Austen, 1970; Gordon and Ford, 1971a; White and Timbury, 1973a). Immediate hypersensitivity depends upon circulating antibodies and includes all the allergic responses that begin within minutes or a few hours of any antigen-antibody interaction. Among these are anaphylaxis, the Arthus reaction, and responses such as the hemolytic blood transfusion reaction caused by antibodies acting against cell or tissue antigens.

Delayed or cell-mediated hypersensitivity typically manifests itself in inflammatory reactions which require from 12 to 48 hours to develop and which feature local accumulations of mixed cells, particularly lymphocytes and macrophages. Examples are the positive tuberculin skin test, the well-known rejection of homografts, and the contact or eczematous dermatitides. Delayed hypersensitivity reactions do not result from antigenic interactions with circulating antibodies; instead, the reaction to the local application of antigens is mediated by nucleated cells of the peripheral blood. These cells, thymus-controlled small lymphocytes (T cells) are able to react with specific antigens and, in some way, influence macrophages to participate in the reaction (Austen, 1970; White and Timbury, 1973b).

It is recognized that these and other classifications of hypersensitivity may be expected to change as new knowledge is developed. However, in this report "hypersensitivity" is used as the term of choice to designate reactions to iodine presumed to involve an immune response.

B. TECHNIQUES FOR DIAGNOSING FOOD HYPERSENSITIVITY

Despite some ingenious developments in test methodology, most authorities agree that for diagnosing food and drug allergies the safest and most dependable procedure presently available is elimination of the suspected food or drug, observation for disappearance of symptoms, and provocative reintroduction of the offending substance. Thorough medical histories and expert clinical judgment are essential parts of this method (Almy, 1967; Bronsky and Ellis, 1972; DeSwarte, 1972; Golbert, 1972; Rosenoer, 1968; and Thomas, 1967). The term "provocative reintroduction" should not be
<table>
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<th>Major Types of Hypersensitivity</th>
<th>Reaction</th>
<th>Example of Reaction Site</th>
<th>Example of Cells Involved</th>
<th>Cytolytic Activity</th>
<th>Membrane Lysis</th>
<th>Secondary Complex</th>
<th>Bound Antibody</th>
<th>Immediate</th>
<th>Mediated by</th>
<th>Antaphylactic Anaphylaxis (Antibody or Aropy)</th>
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<td>I. Contact Dermatitis</td>
<td>Allergic Reaction</td>
<td>Urticaria, urticarial rash, urticarial dermatitis</td>
<td>Skin, periphery</td>
<td>Localized, small</td>
<td>Immediate</td>
<td>Secondary complex</td>
<td>Bound antibody</td>
<td>Immediate</td>
<td>Mediated by</td>
<td>Anaphylactic anaphylaxis (antibody or Aropy)</td>
</tr>
<tr>
<td>II. Type I Reactions</td>
<td>Immediate</td>
<td>Multiple tissue sites</td>
<td>Smooth muscle of bronchi and arteries, tissue</td>
<td>Immediate</td>
<td>Mediated by</td>
<td>Cytokinetic activity</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>III. Type II Reactions</td>
<td>Time</td>
<td>Membrane of mast cells</td>
<td>Mast cells</td>
<td>Immediate</td>
<td>Mediated by</td>
<td>Cytokinetic activity</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>IV. Type IV Reactions</td>
<td>Delayed</td>
<td>Delayed hypersensitivity</td>
<td>Skin, mucosa, airways, etc.</td>
<td>Delayed</td>
<td>Mediated by</td>
<td>Cytokinetic activity</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>V. Type V Reactions</td>
<td>Delayed</td>
<td>Delayed hypersensitivity</td>
<td>Skin, mucosa, airways, etc.</td>
<td>Delayed</td>
<td>Mediated by</td>
<td>Cytokinetic activity</td>
<td></td>
<td></td>
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</table>

**Table 1**
confused with "provocative subcutaneous food test technique," a proposed method of detecting food allergy whose possible merits are still controversial (Caplin, 1974; Sharp, 1974; Willoughby and Sharp, 1974).

The mucous membrane sensitivity tests and the various cutaneous tests have shortcomings that impair their usefulness as practical clinical procedures. Among the detracting aspects are false positive and false negative responses. The intravenous sensitivity test for drugs and the intradermal skin tests may induce severe hypersensitivity reactions as well as provoke false results. The passive transfer test in a human subject incurs the risk of passing along serum hepatitis. Recently a radioallergosorbent test (RAST) which is a method for in vitro radioassay of allergen-specific immunoglobulin E antibody, has been reported as promising in the diagnosis of food allergy (Hoffman and Haddad, 1974). However, because of certain technical problems involved in its use, the RAST apparently requires development and clinical testing to demonstrate its potential as a diagnostic aid in suspected food allergy. Other methods including determination of circulating antibody, lymphocyte transformation, basophil degranulation and leukocyte histamine release, while promising in terms of possible practical tests, are primarily investigational at present.

C. IODINE AS A HAPTEN

According to Gordon and Ford (1971b), a hapten is any substance not of itself capable of provoking an immune response, but able to serve as a part of an antigen when bound to another substance, usually of high molecular weight, which is denoted as a carrier molecule. For example, they cite nickel as a hapten when combined with structural proteins of the skin. This nickel-protein complex can provoke an immune response. Individuals thus sensitized by the nickel-protein complex will produce antibodies capable of reacting with the complex, the carrier protein alone, and the uncoupled nickel (hapten) alone.

The haptenic activity of free iodine and the iodide ion has been studied by several investigators. Jacobs (1932) showed that guinea pigs can be anaphylactically sensitized by a mixture of iodine and guinea pig serum. He stated: "The fact that definite sensitization can be set up with homologous serum iodinated by the addition of Lugol's solution under conditions comparable to those obtained in iodine antisepsis indicates the possibility that this type of reaction may be present in cases of human idiosyncrasy."

Jacob et al. (1964) reported a patient with fever, swelling of the submandibular glands, and an extreme degree of eosinophilia (white blood cells 70,000 with 85% eosinophiles). The patient had been taking potassium
iodide for bronchitis; subsequently he took an iodide-containing cough syrup and tetracycline for chronic cough. Using a skin-window technique, they found that the exudation of eosinophiles into a prepared skin area was specific for the suspected allergen (isotonic potassium iodide solution injected into the prepared skin area). They concluded that the eosinophilia was a manifestation of a hypersensitivity reaction to iodine.

Horn and Kabins (1972) reported that three patients who exhibited high fever, rigor, and leukocytosis, had iodide sensitivity reactions although the clinical pattern mimicked bacterial infection. They distinguished between dose-related toxic reactions to iodides and hypersensitivity and noted that most immunologic studies have employed proteins treated with iodine as antigens. Treatment of tyrosine with iodine alters the serologic specificity and antigenicity of tyrosine; the resultant antigen may stimulate antibody formation and, in the susceptible person, the development of the hypersensitive state. A periarteritis nodosa type of hypersensitivity angitis reaction clinically characterized by rash, eosinophilia, lymphadenopathy, arthralgia, and submucosal hemorrhages has been attributed to antigen-antibody complexes damaging small blood vessels.

Rosenberg et al. (1972) concluded that vegetating iododerma in one of their patients was a manifestation of an allergic hypersensitivity reaction in which potassium iodide taken in an asthma remedy acted as a hapten by combining with a serum protein. They cited the work of Halpern et al. (1967) who reported the in vitro demonstration of allergy to iodine by means of the lymphocyte transformation test. These investigators found positive tests in four patients who had previously experienced immediate hypersensitivity-type reactions to iodine.
IV. REPORTS OF UNTOWARD REACTIONS TO IODINE

A. DRUGS AND X-RAY CONTRAST MEDIA

Coindet in the early nineteenth century recognized that goiter could be treated with iodine, but stressed that excessive use could cause untoward reactions; he reported a case of iodism (Elmer, 1938). Stengel (1902) reported the iodine-induced symptom complex of purpura, mucous membrane hemorrhages, metallic taste, swollen tender gums, increased salivation, bronchorrhea, coryza, nausea, vomiting, arthralgia, and fever. Reports of adverse reactions were associated in most cases with use of iodine preparations in treatment of goiter or proprietary preparations containing iodine salts. The signs, symptoms, syndromes and diseases in which iodine has been causally related by numerous authors over the past 75 years are listed in Table II. Many of these authors allude to hypersensitivity or allergic reactions to iodine.

Reactions to iodine-containing urographic contrast media have become frequently reported types of adverse reactions. Coleman et al. (1964), in a review of 10,000 patients who had intravenous urographies, found 853 cases of untoward reactions of which 168 had allergic reactions (dermal, nasal, conjunctival, asthmatic, and/or shock manifestations) to iodine-containing contrast media. Most of the allergic reactions were described as urticaria or angioneurotic edema. The remainder were classified as non-allergic reactions (nausea, vomiting, local pain, faintness). They concluded that there was little or no correlation between reactions to intravenous urography and response to iodides administered by other routes for other purposes. In addition, of the allergic group, 21 subsequently had intravenous urographies and experienced no significant reactions.

Peacock and Davison (1957) reviewed 502 case histories of asthmatic patients on prolonged iodide therapy. The regimen included Fowler's solution (potassium arsenite solution); however the authors attributed the adverse reactions to the toxicity of iodide. Approximately 16 percent of the patients had sufficient reactions to inorganic iodides to warrant discontinuance or sharp reduction of medication. In most patients, signs and symptoms were considered toxic or physiologic and resulted from acute or chronic overdosage. Included were iodine taste, ptyalism, swollen salivary glands, rhinorrhea, conjunctival injection, edema of the lids, frontal headache, gastric upsets, and acneform skin lesions. The authors recognized what they regarded as true hypersensitivity reactions to iodide in 19 cases described in the literature, but concluded that none of the 502 asthmatic patients they studied exhibited this type of reaction.
<table>
<thead>
<tr>
<th>Effect</th>
<th>Reference²</th>
<th>Effect</th>
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<td>pharyngitis</td>
<td>12</td>
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<tr>
<td>larynx, lips, tongue, tonsils</td>
<td>3,81</td>
<td>proteinuria</td>
<td>44</td>
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<tr>
<td>pulmonary</td>
<td>44</td>
<td>psoriasis, pustular, generalized</td>
<td>76</td>
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<td>eosinophilia</td>
<td>3,12,44</td>
<td>ptyalism</td>
<td>66</td>
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<tr>
<td>eruption:</td>
<td></td>
<td>purpura</td>
<td>44,66</td>
</tr>
<tr>
<td>acneform³</td>
<td>3,29,66</td>
<td>purpura, thrombocytopenic³</td>
<td>26</td>
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<tr>
<td>bullous³</td>
<td>6,29</td>
<td>purpura, hypothyroidism³</td>
<td>12</td>
</tr>
<tr>
<td>fixed</td>
<td>6</td>
<td>purpura, hyperthyroidism³</td>
<td>3,12</td>
</tr>
<tr>
<td>fungating</td>
<td>3,66</td>
<td>purpura, hypothyroidism³</td>
<td>44,66,69</td>
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<td>verrucose</td>
<td>3</td>
<td>purpura, hypothyroidism³</td>
<td>44,66,69</td>
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<td>xanthenmatic</td>
<td>44</td>
<td>purpura, hypothyroidism³</td>
<td>44,66,69</td>
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<td>erythema</td>
<td>3</td>
<td>purpura, hypothyroidism³</td>
<td>44,66,69</td>
</tr>
<tr>
<td>erythema multiforme</td>
<td>80</td>
<td>purpura, hypothyroidism³</td>
<td>44,66,69</td>
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<tr>
<td>erythema nodosum</td>
<td>29,80</td>
<td>purpura, hypothyroidism³</td>
<td>44,66,69</td>
</tr>
<tr>
<td>fever</td>
<td>7,12,29,42,80</td>
<td>purpura, hypothyroidism³</td>
<td>44,66,69</td>
</tr>
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<td>fever, iodide</td>
<td>7,44</td>
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<td>44,66,69</td>
</tr>
<tr>
<td>fever, persistent and wasting</td>
<td>3</td>
<td>purpura, hypothyroidism³</td>
<td>44,66,69</td>
</tr>
<tr>
<td>gangrene</td>
<td>80</td>
<td>purpura, hypothyroidism³</td>
<td>44,66,69</td>
</tr>
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<td>gingivitis</td>
<td>12</td>
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<td>44,66,69</td>
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<tr>
<td>glands, salivary, enlarged</td>
<td>3,12,42,66</td>
<td>purpura, hypothyroidism³</td>
<td>44,66,69</td>
</tr>
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<td>12,29,66</td>
<td>purpura, hypothyroidism³</td>
<td>44,66,69</td>
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<td>goiter, toxic³</td>
<td>21</td>
<td>purpura, hypothyroidism³</td>
<td>44,66,69</td>
</tr>
<tr>
<td>growths, popular, nodular, tumor-like</td>
<td>80</td>
<td>purpura, hypothyroidism³</td>
<td>44,66,69</td>
</tr>
<tr>
<td>hair, thinning, diffuse</td>
<td>16</td>
<td>purpura, hypothyroidism³</td>
<td>44,66,69</td>
</tr>
</tbody>
</table>

1 Taken from the literature citations where the author implicated iodine as a causative or predisposing factor. In some of the references, the effects were quoted by the authors from other sources.

2 See Bibliography for complete references.

3 Considered by some authorities to be caused by iodine in foods.
Iodide goiter, with or without hypothyroidism, occasionally occurs in patients on prolonged treatment with iodide or iodide-generating compounds and in otherwise normal individuals whose diets contain excessive amounts of iodine (Braverman et al., 1971; Wolff, 1969). Wolff divided iodide goiters into four classes: (1) adult iodide goiter, experienced primarily by asthmatic patients on prolonged iodide therapy; (2) iodide goiter of the newborn, whose mothers were on iodide therapy; (3) endemic iodide goiter from excess iodine in the diet; and (4) hypothyroidism in thyrotoxic patients being treated with iodide. Although a great deal has been learned about iodide-induced goiter, the responsible mechanisms have not been fully clarified (Nagataki, 1974).

Another untoward effect of excess iodine, which has been recognized for many years, is iodide-induced thyrotoxicosis (iodbasedow). Almost all reported cases have followed administration of iodine to patients living in iodine-deficient areas. However, Vagenakis et al. (1972) reported the development of thyrotoxicosis following oral administration of 180 mg of potassium iodide daily for eight to ten weeks in four out of eight nontoxic goiter patients who had always lived in the Boston, Massachusetts area where there was sufficient dietary iodine. The authors concluded from this and their earlier studies (Braverman et al., 1971) that large doses of iodine should not be given to patients with goiter or to patients with any underlying thyroid disease except in cases of known iodine deficiency or when iodine is given for control of preexisting thyrotoxicosis.

Iodine thyroiditis, a transitory, harmless, but sometimes painful enlargement of the thyroid gland, has been described as a complication of iodine therapy of goiter (Matovinovic and Ramlingaswami, 1960).

Despite occasional undesirable reactions including iodism, iododerma, and disturbed thyroid function, the prolonged use of iodides for asthma and other pulmonary disorders continues to be a recognized method of treatment. There is little evidence that hypersensitivity reactions to inorganic iodides constitute a significant medical problem in the treatment of these disorders. Many cases of long-term, continuous consumption of the iodine medications are described in the literature. For example, Begg and Hall (1963) observed that thyroid disorders usually become evident after three and up to eight years of medication. Some patients had assiduously consumed their asthmatic powder daily for 20 years, but only a specific search revealed evidence of iodide goiter. In most instances, these patients do not seek medical advice and one might conclude that any symptoms resulting from iodine ingestion were not distressing.

A search of the files of the Division of Epidemiology and Drug Experience, Office of Scientific Coordination, Bureau of Drugs, Food and Drug Administration, revealed that over one-half of the reported adverse reactions to inorganic iodides were listed as "rash." A total of 62 patients
were reported as having experienced adverse reactions to inorganic iodides in the period from October, 1969 to March, 1974.

It should be noted that excess iodine in the diet may influence the level of protein-bound iodine in blood serum and the uptake of $^{131}I$ by the thyroid (London et al., 1965). While this should not necessarily be considered an adverse effect of dietary iodine, it is obviously very important in terms of standards for and reliability of clinical laboratory estimations of thyroid function (Ghahremani et al., 1971; Pittman et al., 1969; Sachs et al., 1972).

B. DIETARY IODINE

1. Literature Review

Cases of adverse reactions to dietary iodine reported in the literature reviewed in this study covering the period from 1911 to date are summarized in Table III. In all cases, these patients were seen in clinical practice primarily by dermatologists. The etiologic relationship of iodine to the reactions is probable; however, definite proof is lacking. None of the case reports includes adequately controlled studies. In three of the patients who had been using iodized salt for months or years, the reactions occurred shortly after taking small amounts of therapeutic iodine. It is significant that only 21 cases of alleged dietary iodine sensitivity have been reported in the past 63 years.

It is recognized that many cases of allergy such as food hypersensitivity are diagnosed; however, they are not likely to be reported in the scientific literature unless the conditions have unique features. Therefore it is possible that a larger number of cases actually do occur but are not recorded. However, the numbers of cases reported lead to the conclusion that the prevalence of adverse reactions to iodine in foods has been inconsequential from an epidemiologic point of view.

Adverse effects of dietary iodine on thyroid function are summarized in Table IV. Whether or not iodine-induced thyrotoxicosis, iodine-induced nontoxic goiter (with or without hypothyroidism), and iodine-influenced lymphocytic thyroiditis should be considered sensitivity reactions to excess iodine may be debated. Regardless of this, the public health importance of the thyroid-reactions listed in Table IV is clear.

The occurrence of hyperthyroidism after increase in iodine intake is usually referred to as jodbasedow or iodine-induced thyrotoxicosis. Generally, it is confined to individuals in areas of iodine deficiency. Connolly
### TABLE III

**UPTOWARD REACTIONS TO IODINE IN FOODS**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Vertebral Case</th>
<th>Source</th>
<th>Type of Reaction/Circumstances</th>
</tr>
</thead>
<tbody>
<tr>
<td>09</td>
<td>No</td>
<td>I</td>
<td>Iodized salt</td>
</tr>
<tr>
<td>10</td>
<td>No</td>
<td>I</td>
<td>Iodized salt</td>
</tr>
<tr>
<td>10</td>
<td>Yes</td>
<td>I</td>
<td>Iodized salt, KI</td>
</tr>
<tr>
<td>06</td>
<td>No</td>
<td>I</td>
<td>Iodized salt</td>
</tr>
<tr>
<td>09</td>
<td>No</td>
<td>I</td>
<td>Iodized salt</td>
</tr>
<tr>
<td>10</td>
<td>Yes</td>
<td>I</td>
<td>Iodized salt, KI</td>
</tr>
<tr>
<td>06</td>
<td>No</td>
<td>I</td>
<td>Iodized salt</td>
</tr>
<tr>
<td>09</td>
<td>No</td>
<td>I</td>
<td>Iodized salt</td>
</tr>
<tr>
<td>06</td>
<td>No</td>
<td>I</td>
<td>Iodized salt</td>
</tr>
<tr>
<td>09</td>
<td>No</td>
<td>I</td>
<td>Iodized salt, KI</td>
</tr>
<tr>
<td>27</td>
<td>2</td>
<td>I</td>
<td>Mother's milk</td>
</tr>
<tr>
<td>77</td>
<td>2</td>
<td>I</td>
<td>Iodized salt</td>
</tr>
<tr>
<td>68</td>
<td>2</td>
<td>I</td>
<td>Iodized salt</td>
</tr>
</tbody>
</table>

- Dermatosis of lip
- Pervitis, thromboocytopenia, thrombotic
- Diphtheria (pneumonia, secondary)
- Iododermatitis, bullosus, acute (presumptive)
- Iododermatitis, panniculitis, chronic
- KI cough, max 4 days
- Iododermatitis, bullosus (iodized salt for years)
- Acne, severe, adult
- Uticaria, chronic
- Acne, severe, adult
- For 2 days
- Salts 2 months; none 12 months: KI + colloid
- Iododermatitis, panniculitis, severe (iodized salt)
- For months; 6 - 1 week
- Iododermatitis, bullosus, severe (iodized salt)
- For years; therapeutic KI for 4 months
- Iododermia, focal (iodized salt)
- Acne, severe, adult
- Iododermia, focal (mother on iodine?)
### TABLE IV

**ADVERSE EFFECTS OF SUPPLEMENTAL DIETARY IODINE ON THYROID FUNCTION**

<table>
<thead>
<tr>
<th>Type of reaction/circumstances</th>
<th>Iodine source</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>hyperthyroidism (6 cases with histories of long-standing goiters)</td>
<td>iodized salt</td>
<td>49</td>
</tr>
<tr>
<td>goiter, nodular, toxic (USA, temporary increase in prevalence, 1920's)</td>
<td>iodized salt</td>
<td>40, 58</td>
</tr>
<tr>
<td>hyperthyroidism (Holland, I-deficient areas)</td>
<td>iodized bread</td>
<td>86</td>
</tr>
<tr>
<td>goiter, non-toxic (Hokkaido coast dwellers)</td>
<td>seaweed</td>
<td>82</td>
</tr>
<tr>
<td>goiter, lymphocytic (USA, compares &quot;pre-iodine&quot; and &quot;iodine&quot; eras)</td>
<td>iodized salt and/or therapeutic iodine</td>
<td>89, 90</td>
</tr>
<tr>
<td>thyrotoxicosis (Tasmania, iodine-induced)</td>
<td>iodized bread</td>
<td>20, 21, 79</td>
</tr>
</tbody>
</table>
(1971, 1973), Stewart et al. (1971) and Vidor et al. (1973) have reported on an epidemic of iodine-induced thyrotoxicosis in Tasmania. Iodine supplementation of bread was initiated in 1966 to correct moderate iodine deficiency and subsequently the prevalence of thyrotoxicosis increased (Connolly, 1971; Stewart et al., 1971). These investigators found that the increase in disease incidence involved primarily middle-aged to older individuals who lived in iodine deficient sections of Tasmania and who had histories of long standing nodular goiters.

Vidor et al. (1973) have postulated that the iodine-induced thyrotoxicosis can be explained by the presence of autonomous thyroid tissue in ostensibly euthyroid older persons. They suggested that iodine is a regulator of thyroxine production in the autonomous tissues and that increased dietary intake results in increased hormonal production and jobasedow. Vidor et al. (1973) concluded that because development of autonomous tissue is correlated with aging, a population with a significant number of individuals 40 to 50 years old or older could be at risk of epidemic thyrotoxicosis if iodine intake increased. They questioned the need for dietary iodine supplementation in persons over 40 years old.

In a further study of this issue, Connolly (1973) has reported an increase in iodine-induced thyrotoxicosis among individuals less than 40 years old in Tasmania. He concluded that thyrotoxicosis incidence increased after 1966 primarily in older persons; however, he noted that the incidence of disease in individuals under 40 years old has remained relatively constant since the peak incidence in 1967. Connolly (1973) suggested that either as endemic goiter diminishes in the adult population, the incidence of thyrotoxicosis will decline in older persons but will increase slowly in younger (0-40) persons, or, the disease incidence will remain essentially stable in both age groups. He called for additional epidemiological studies of this population over the next several years.

In Michigan, Miller and Block (1970) studied thyroid function in 70 subjects with large, multinodular goiters. Subjects considered hyperthyroid averaged 63 years of age; those with suppressible goiter, 47 years; and those with autonomous thyroid tissue, but euthyroid, 55 years. They suggested that gradual increase in autonomous tissues led to a transition from the euthyroid to the hyperthyroid state. Possible differences in dietary iodine or therapeutic use of iodine among the subjects was not included in this study. The studies of Vagenakis et al. (1972) on iodine-induced thyrotoxicosis in patients living in the Boston, Massachusetts area were noted previously (see p 21).

The prevalence of dietary iodine-induced goiter (so-called "coast goiter") was 6 to 12 percent among coast dwellers in certain parts of Hokkaido, Japan's north island (Wolff, 1969). Diets included large amounts
of iodine-rich seaweeds. All persons surveyed who exhibited this form of endemic iodide goiter were euthyroid, and, except for the cosmetic effect, Japanese authorities did not consider the goiters a public health problem (Suzuki et al., 1965).

Wartofsky (1973) reviewed the history of 44 patients with diffuse toxic goiter who were treated with antithyroid drugs and among whom the rate of remission was "disappointingly low." Among the possible factors involved, he considered that there may be an inverse relationship between the increasing average daily dietary intake of iodine and the remission rate that may be anticipated after antithyroid drug therapy.

Freund et al. (1966) studied the effects of the ingestion of iodinated drinking water on a controlled population. The water contained 1 mg iodine per liter and was used over a period of nine months. Radioactive iodine uptake decreased markedly in the test population; protein-bound iodine values changed relatively little until the iodine content of the water was increased to 5 mg per liter. No hypersensitivity or other adverse effects of iodine were reported by the subjects or detected by the investigators during the study.

It has been postulated that individuals whose diets contain excessive amounts of iodine and who have either Hashimoto's thyroiditis or thyroid glands that are oversensitive to the thyroid inhibitory effect of large quantities of iodine may be prone to the development of goiter and hypothyroidism. Fisher and Carr (1974), after reviewing the available literature, concluded that in spite of an increase in ingestion and excretion of iodine by the American population, there are no reports that document a corresponding increase in the incidence of iodine toxicity or hypersensitivity; in addition, there is no evidence that the prevalence of metabolic diseases induced by excess iodine has changed.

Because ingested iodine has been cited by many authors as a causative factor in acne, this subject received special scrutiny. For example, Bechet (1947) treated 240 cases of acne in a two-year period; 92 of these patients gave a history of iodized salt ingestion for long periods. They showed no improvement with x-ray therapy; however after oral or intravenous treatment with sodium chloride and discontinuance of iodized salt, all improved rapidly.

There have been no scientifically reliable studies which prove that supplemental dietary iodine causes acne. Nine adult patients with acne (Table III) were considered to have reactions to dietary iodine; however, no proof of a causal relationship was reported. In a three-year study on the influence of oral iodine on acne vulgaris, Gaul and Underwood (1948) concluded that iodized salt does not have an unfavorable effect on the course of the disease.
Hitch and Greenberg (1961) studied 1060 adolescent students in North Carolina to determine the prevalence and severity of acne in relation to estimated amounts of iodine ingested with their food, water, and salt. No influence of iodine on prevalence of acne was shown; however, a slight increase in the amount of scarring and cyst formation was observed.

2. Consultants' Opinions

The Life Sciences Research Office convened an ad hoc group of experts to review the question of adverse reactions to dietary iodine (see Section VIII). A summary of the views and opinions expressed by the conferees is reported in the following paragraphs.

Apparently hypersensitivity reactions to iodine in foods are either extremely rare or are not detected. Approximately 20,000 allergic children examined at a large southeastern medical center from 1953 to 1974 revealed no case diagnosed as a hypersensitivity reaction to iodine in foods. In addition, no cases of food iodine sensitivity had been diagnosed in the adult allergy department. Six allergists in different parts of the United States were asked the number of cases they had observed of hypersensitivity reactions to iodine in foods. None could recall having seen such a case. An examination of 15 standard texts on allergy revealed only one mention of a true allergic reaction to iodine in food.

Pediatric allergists have rarely observed patients with reactions to iodine taken therapeutically as in expectorants for asthma; in addition, hypersensitivity reactions to dietary iodine were not evident. Asthmatic children, as a group, are characteristically allergic to numerous substances yet few if any appear to exhibit hypersensitivity to iodine in expectorants given to treat asthma or to dietary iodine per se ingested over a prolonged time period.

From an informal survey of four allergists and a review of the meager scientific literature, an experienced toxicologist concluded that there were no documented cases of untoward effects from the use of iodized salt or from iodine in foods.

A majority of the clinical allergists agreed that there is little evidence in the literature to document the existence of individuals with circulating antibodies to iodide or iodine-containing compounds or for cases of food allergy that could be causally related to dietary iodine. Despite identical symptoms and demonstrated histamine release, the reactions observed in some patients following administration of iodine-containing x-ray contrast media cannot be considered as allergic because circulating antibodies to these materials were not demonstrated. The scientifically rigorous studies that are needed to prove the existence of true hypersensitivity to iodine have
not been done. However, immunologic techniques have now reached the point that such studies are feasible.

A minority of clinical allergists expressed the opinion that it is not necessary to demonstrate immune system response in order to diagnose food or iodine allergy. They agreed that iodine allergy is not a major problem in the practice of allergy, but hold that iodine in foods may cause an allergic response. Once identified, the allergy can be controlled by avoidance of the source, usually iodized salt or sea foods.

Some research endocrinologists were of the opinion that a type of sensitivity to food iodine does exist and cited as an example the people in Tasmania who developed thyrotoxicosis following the introduction of iodinated bread. However, they noted that those people were unusually sensitive because they had preexisting iodine deficiency and concomitant, long-standing enlargement of their thyroid glands. Presumably some of the foci or areas in their thyroid glands had become autonomous. It is noteworthy that the amount of supplemental iodine ingestion was estimated to be from 50 to 270 μg per day. In reviewing the question of whether or not the amount of iodine in the American diet today is harmful, these consultants observed that while evidence is inconclusive, it is possible that the reported increased prevalence of lymphocytic infiltration of the thyroid could be a result of the increased amounts of iodine in the American diet.

An observation of special interest was that the incidence of papillary carcinoma of the thyroid is higher among the Japanese and the Icelanders than in the U.S. population, and that because of the substantial consumption of sea fish and seaweed in Japan and Iceland, the dietary iodine intake is relatively high. However, the etiological relationship of dietary iodine to thyroid papillary carcinoma has remained highly speculative. Recently the opinion has been expressed that the prevalence of papillary thyroid carcinoma in the United States is related to radiation exposure rather than to excessive iodine intake (DeGroot and Paloyan, 1973; McClintock, 1974; McDougall, 1974) although this conclusion is not universally accepted (Jackson, 1974).

The conferees did not consider acne a hypersensitivity reaction. In pediatric allergy practice, cases of acne related to iodine have been observed; however, none has been severe nor clearly related to dietary iodine. Some experts have noted that high doses of iodine can influence the severity and complications of acne, but that the levels of iodine present in the diet probably do not affect acne.

Possible mechanisms by which iodine might be allergenic were discussed. The concept that certain iodine-containing substances can act as haptenes was generally accepted although it was considered that
scientific demonstration of hapten-carrier protein complexes in patients is limited by present-day techniques. Doubt was expressed that free iodide can act as a hapten. Experiments have shown that granulocytes can oxidize iodide to iodine and induce a variety of iodinated products from tyrosines including iodinated proteins (Klebanoff, 1967; Rasmussen, 1955). If the iodinated protein is released during lysis of the granulocyte at an inflammatory site, in effect, a foreign protein is liberated and could act as an antigen with iodine specificity.

A minority of consultants agreed that while iodine allergy is a real phenomenon, they dispute the evidence supporting the conclusion that iodine allergy is an immunologic phenomenon. They suggested that data supporting the assumption of haptenic activity are inconclusive. For example, in vitro studies using the leukocytes of patients with adverse reactions to iodine-containing contrast media have failed to demonstrate hypersensitivity reactions (Miller et al., 1974). In these experiments, each patient's leukocytes were treated with the dye (contrast medium) alone and with the dye plus the patient's serum. The presence of serum did not influence the amount of histamine released. Part of the objective was either to find preformed antibody or, by combining the dye with the appropriate serum proteins, to discern the appropriate antigen; neither was demonstrated. The investigators could not transfer sensitivity to normals with the patient's serum, could not demonstrate antibody and were unable to get a specific reaction from the incubated mixture of patient's leukocytes and serum. All leukocytes from both the patients and control subjects released some histamine which is indicative of a nonspecific reaction.

A recent request for information on clinical experience with iodine hypersensitivity published in the Annals of Allergy did not elicit any response (Carr, 1974). Although not unanimous, the consultants agreed that the level of dietary iodine currently available in the United States does not cause sufficient numbers of adverse reactions that are recognizable by currently available diagnostic means to represent a significant clinical or public health problem.
V. EVIDENCE FOR CURTAILMENT OR REDUCTION OF DIETARY IODINE

The scarcity of well-documented instances of harmful effects from iodine in the diet makes it impossible to compile a complete list of contraindications. The most creditable exceptions are the rare individuals with a demonstrated idiosyncrasy to iodine or iodine-containing substances and the possible occasional case of a true allergic reaction to iodine. The precise diagnosis of iodine idiosyncrasy and iodine allergy is thwarted by the lack of knowledge of the mechanisms involved and of an accurate method for the immunologic demonstration of iodine hypersensitivity suitable to the typical clinical laboratory.

There is some evidence that dietary iodine or iodized salt may aggravate acne, with a tendency for increased residual cyst formation and scarring. However, this conclusion should be regarded as tentative until more scientific evidence becomes available.

Because dietary iodine has been related to an increased prevalence of hyperthyroidism in certain geographic areas, particular alertness for cases of disturbed thyroid function should be the rule for clinicians and public health personnel in areas of natural iodine deficiency where iodine supplementation has been introduced to prevent endemic goiter. Special attention should be given to identify persons with histories of nontoxic nodular goiter, Hashimoto's thyroiditis, thyrotoxicosis previously treated with radioiodine, and patients with other thyroid gland dysfunctions. In some goiter prevention programs, the need for prophylactic dietary iodine in persons over 40 years of age has been questioned.

Occasionally, patients with severe cardiac and/or renal diseases have shown an increased susceptibility to therapeutic amounts of iodides in terms of serious adverse reactions such as bullous iododerma. However, no instances of such reactions from iodine in foods or from supplemental dietary iodine were found in this review.

Wolff (1969) reported that the prolonged ingestion of iodide or iodide-generating organic compounds in amounts ten or more times the daily requirement led to iodide goiter in certain subjects. Fetal and neonatal thyroid disturbances have been reported in cases of pregnant women taking iodide in therapeutic amounts. There are no reports which show that supplemental dietary iodine and iodine in foods have been involved in such reactions.

Leprosy and tuberculosis have been mentioned as diseases in which therapeutic doses of iodide are inadvisable, presumably on the theory that iodide resolution of granulomas may extend the infections. However, no information is available about the possible effects of dietary iodine on the course of these diseases.
VI. CONCLUSIONS

Untoward reactions to iodine were recognized in 1811, several years after the element was identified. Relatively few toxic, idiosyncratic, and hypersensitivity-type reactions to iodine and its compounds used for diagnosis and treatment have been found in the scientific literature. Symptoms range from trivial to severe, and occasionally fatal; however, most are mild to moderate, and rarely life-threatening. Scientifically documented information about hypersensitivity and idiosyncratic reactions to either naturally occurring or supplemental dietary iodine is scanty.

Clinically recognized and proved untoward reactions are extremely rare except for relatively few cases of disturbed thyroid function in certain endemic goiter regions of the world. Review of the scientific literature since 1911 revealed only 21 case reports of nonthyroid adverse reactions allegedly caused by dietary iodine.

A current Life Sciences Research Office report documented the fact that the amount of iodine available in the North American diet has increased substantially in recent years. There was no evidence of an accompanying increase of untoward reactions to dietary iodine; however, the normal ranges of protein-bound iodine and $^{131}$I uptake have changed and therefore require periodic reevaluation.

As a cause of morbidity, dietary iodine has excited only sporadic medical interest in the United States since 1947. An ad hoc group of experts convened to review this subject agreed that conceivably cases of dietary iodine-induced hypersensitivity and idiosyncrasy in the United States may occur, but they are evidently extremely rare. They recognized the potential of dietary iodine for inducing thyroid gland dysfunctions as exemplified by recent reports of thyrotoxicosis from iodinated bread in parts of Tasmania and of nontoxic goiter among coast and island dwellers in Japan whose diets included large amounts of iodine-rich seaweeds.

While some evidence suggests a causal relationship between increasing prevalence of lymphocytic thyroiditis and increasing dietary iodine, insufficient data exist to prove this concept. With regard to dietary iodine-induced toxic goiter, such as has been reported in Tasmania, more information is needed regarding predictability of responses to prophylactic iodine among people of all age groups living in endemic goiter areas.

There is no scientific proof that dietary iodine evokes attacks of acne vulgaris; however, limited evidence suggests that it may aggravate acne sequelae such as cysts and scarring. Carefully planned and adequately
controlled studies are required to elucidate the possible influence of iodine on acne.

The world scientific literature contains abundant evidence to support the basic harmlessness of iodine compounds in long-term use in goiter-prevention programs, treatment of bronchial asthma and other pulmonary diseases and certain thyroid dysfunctions and in x-ray contrast media. Untoward reaction rates in such regimens are generally so low that the risk-benefit ratio is entirely acceptable.

Knowledge regarding the mechanisms of untoward reactions to iodine is incomplete. It is generally accepted that organic iodine can act as a hapten; however, most attempts to demonstrate circulating antibody to iodine in human patients have failed. Some allergists believe that iodine hypersensitivity has been amply demonstrated on the basis of history, clinical signs, symptoms, and therapeutic results, but most experts consider that true hypersensitivity to iodine requires proof of an immune response mechanism. Laboratory tests to identify weakly antigenic substances are at the threshold of practical application. The development of convenient and efficient laboratory procedures to identify iodine hypersensitivity will aid in diagnosis and determination of the true prevalence of hypersensitivity to dietary iodine.
VII. BIBLIOGRAPHY


VIII. SCIENTIFIC CONSULTANTS

ON

A REVIEW OF THE SIGNIFICANCE OF UNTOWARD REACTIONS TO IODINE IN FOODS

A. ATTENDEES, AD HOC STUDY GROUP MEETING, MAY 14, 1974

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